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COVID-19: The Need of Non-traditional Techniques to Screen for the Virus

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Abstract

BACKGROUND: At the present moment, the etiological diagnosis of SARS-CoV-2 is based on the polymerase chain reaction (PCR). False negative cases are increasingly reported in several studies using reverse transcription-PCR (RT-PCR). For example, the positive rate of RT-PCR for throat swabs was reported to be about 60% in early stage of COVID-19.

AIM: We aimed to present metagenomic next-generation sequencing (mNGS) as a potential tool to detect pathogens.

METHODS: In the recent year, mNGS is shown the potential to detect pathogens without the need of hypothesis guided approach and is proven to be highly effective.

RESULTS: A recent prospective study in the United States compared the diagnostic performance of routine diagnostic tests with mNGS and showed that mNGS detected a bacteria or virus in the CSF of 13 of 58 patients presenting with meningoencephalitis who were negative for or not assessed with routine diagnostic test including PCR. NGS also has the advantage to cover entire viral genomes.

CONCLUSION: As viral metagenomics has significantly improved in recent years and become more cost effective, we think that a change in the approach toward a shot-gun metagenomic testing should be explored and could potentially aid the diagnosis of COVID-19 cases and the management of this pandemic.

Dear editor,

We, along with the international community, are gravely concerned by the recent international outbreak of the coronavirus SARS-CoV-2 (coronavirus disease 2019; previously 2019-nCoV). SARS-CoV-2 was declared a pandemic by the World Health Organization (WHO) on March 13, 2020, following spread from the Hubei Province of the People's Republic of China. Europe has now overtaken China, becoming the epicenter of the infection and the incidence of new cases plus deaths from COVID-19 in Italy is now greater than in China. To date, 19 genomic strains of the virus have been identified in infected patients [1].

The WHO recommends a combination of measures to tackle spread of the virus including rapid diagnosis, immediate isolation of cases, rigorous tracking, and precautionary self-isolation of close contacts [2]. Rapid diagnosis has been key in managing this pandemic and has worked effectively in many countries such as South Korea and in China which have seen a decline in the number of new infections. However, many individuals with SARS-CoV-2 infection remain undiagnosed because testing efforts are currently ineffective or not widely available. At the present moment, the etiological diagnosis of SARS-CoV-2 is based on the polymerase chain reaction (PCR). Both the WHO and the US centers for disease control and prevention, along with other national and international scientific organizations, have released detailed information for in-house development of reverse transcription-PCR (RT-PCR) tests. These are being implemented by many reference laboratories worldwide and are undergoing clearance by many regulatory agencies. Unfortunately, false negative cases are increasingly reported in several studies using RT-PCR [3]. For example, the positive rate of RT-PCR for throat swabs was reported to be about 60% in the early stage of COVID-19. This is an area of major concern and has huge impacts on the efficacy of testing and isolation processes. False negative RT-PCR patients are less likely isolate, propagating viral spread and means the results of RT-PCR should be interpreted with caution [4].

However, an alternative to RT-PCR may already exist. In the recent year, metagenomic next-generation sequencing (mNGS) is shown the potential to detect pathogens without the need of hypothesis guided approach [5] and is proven to be highly effective [5], [6], [7]. As an example, a recent prospective study in the United States compared the diagnostic performance of routine diagnostic tests with mNGS and showed that mNGS detected a bacteria or virus in the CSF of 13 of 58 patients presenting with meningoencephalitis who were negative for or not assessed with routine diagnostic test including PCR. NGS also has the advantage to cover entire viral genomes. This carries the added benefit of helping to understand if individual mutations or strain may be responsible for the variable pattern of spread and illness we are witnessing worldwide.

As viral metagenomics has significantly improved in recent years and becomes more cost effective, we think that a change in the approach toward a shot-gun metagenomic testing should be explored and could potentially aid the diagnosis of COVID-19 cases and the management of this pandemic.

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Common Phobias among Egyptian Primary Schoolchildren: An Emergency Trigger for Panic Disorder due to Corona Pandemic

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Abstract

BACKGROUND: In the wake of the adverse situation we are currently facing globally due to the coronavirus pandemic outbreak, it is normal to feel stressed, confused, and scared but what is abnormal is to turn this to panic. Phobias are more pronounced than fears. They develop when a person has an exaggerated or unrealistic sense of danger that may be evolved to experience panic attacks.

AIM: Our objective was to identify the prevalence of most common phobias as well as panic disorder (PD) due to the coronavirus pandemic among Egyptian primary schoolchildren and their determinants.

METHODS: A cross-sectional study was conducted among 2015 schoolchildren from 3 to 6 grades in three governorates of Egypt. Seven types of phobias were investigated: Agoraphobia, phobias from darkness, animal, untreatable illness (mainly coronavirus), insects, height, and social phobia. The child's self-reported PD symptoms were assessed using DSM-IV with psychiatric diagnoses.

RESULTS: Almost two-thirds of the surveyed primary schoolchildren have phobias of the low score (<9) versus one-third who had high phobias score (61.% vs. 35%, respectively) with highly significant difference (p < 0.001). The most prevalent phobias were from heights (66.5%) followed by darkness (60.0%). The important predictors of phobias were: Being a male child, living in an urban area, and studying at governmental school at fifth or sixth-grade residence. The prevalence of PD due to the corona epidemic is very high, it is reported by almost half of the surveyed primary schoolchildren. Fear of losing any of their family members, especially grandparents, was reported to be the highest PD symptom (97%).

CONCLUSION: Phobia from heights and darkness was the most common. The prevalence of PD due to the coronavirus epidemic is reported to be very high. Calming down children who might be experienced with a phobia that is triggering their PD is recommended.

Introduction

A phobia is defined by being a debilitating, massive, and persistent fear. It is triggered by the presence of a situation, animal, heights, illness, etc. If a phobia becomes very severe, it causes restricting of the day-to-day life and a lot of distress. As well as, the person will avoid the thing that causing phobia [1], [2].

To consider phobia in children, the identified fear must last at least 6 months. Types of common phobias seen in children include specific phobia (e.g., fear from darkness, animal, insect, or heights), agoraphobia (e.g., fear of crowded places or narrow places), social phobia (as phobia when entering a place where people are gathered and talking for fear of embarrassing yourself and being humiliated in public), and medical phobia (afraid of illness) [1], [2], [3], [4].

Phobia is common in all ages, with 25% of children and adolescents suffering from phobia during their lifetime, making it one of the most prevalent and chronic psychological disorders [2].

Specific phobia is considered one of the most common phobias. Recent studies show that the lifetime prevalence of specific phobias around the world ranges from 3% to 15% and the most common types are heights and animals. These studies confirm the high prevalence of specific phobias in the general population, especially in children.7-8. The National Institute of Mental Health estimates approximately 7–9% of children have been estimated to have a specific phobia [5], [6], [7], [8]. Moreover, younger individuals showed the highest rates of social phobia. It usually first appears at age 8 years [9], [10].

The prevalence rates and types of phobia in children differ in nature due to different cultural and ethnic groups. Traditions, values, and beliefs may play a role [5], [11].

Phobia might act as a triggering factor for Panic. Recent researches indicated that panic disorder (PD) has been documented not only among adolescents but also many primary school-aged children experienced this disorder nowadays [12], [13], [14].

Coronavirus (COVID-19) is a lower respiratory tract infection and it is considered by the World Health Organization as a pandemic disease because it causes more than 430,000 cases and almost 20,000 deaths worldwide [15], [16].

In the wake of the adverse situation we are currently facing globally due to the COVID-19 outbreak; the whole nations are confronted with a pandemic for which all government agencies are doing their best to control. Meanwhile, to fight this pandemic efficiently, the majority of nations have reinstated a work-from-home policy to help in flattening the COVID transmission curve. All parents are working under extreme pressure at this time that is also reflected in their children. To enable parents to work optimally from home, it is necessary to create an enabling environment that is free from any phobia or panic. This is also necessitated to calm down children who might be experienced with a phobia that is triggering their PD.

To assist in these potential crisis moments and achieve our target with resilience and compassion, we assessed the prevalence of phobia among primary school-aged children as a trigger for PD due to Corona Pandemic. We assessed the prevalence of phobia among primary school-aged children as a trigger for PD due to the corona pandemic. When it comes to PD due to the coronavirus epidemic, it is essential to measure PD among children. The experienced panic illness usually accompanied by decreased resistance and more susceptibility to diseases [17], [18], [19].

The aim of this study was to identify the prevalence of most common phobias among the studied Egyptian primary school-aged children and determine the prevalence of different types of phobia and their determinants according to certain demographic characteristics. The study also will focus on the prevalence of PD due to the coronavirus pandemic and detect the dominance of its symptoms.

Methods

Study design and study setting

The study was a cross-sectional that was conducted in three governorates, one representing Lower Egypt (Behara governorate), one representing the Coastal region (Damietta governorate), and one representing Upper Egypt (Al Fayoum governorate).

Sampling frame and sampling unit; three sampling frames were chosen: The first sampling frame used was based on stratification of the served rural governorates into three strata representing rural Lower Egypt, Coastal region, and Upper Egypt governorates. The second sampling frame was based on a comprehensive list of the governorates as per regions. The third sampling frame was the stratification of listing the units to be sampled (governmental primary schoolchildren). For the third sampling frame, a logical order was used for schools and then a cluster of schools was chosen with probability proportion to size from that listing. This ensured that the units were evenly distributed within the listing and avoided the possibility that, due to chance, one type of school ends up being under-represented.

Governorates that matched the inclusion criteria and randomly selected were Al Fayoum, Damietta, and Behara governorates representing Lower Egypt, Coastal region, and Upper Egypt governorates, respectively.

Sample size and sampling technique

Confidence intervals for one proportion – Numeric results for two-sided confidence intervals for one proportion.

Confidence interval formula: Exact (Clopper-Pearson).

Sample Confidence level	Size (n)	Target width	Actual width	Proportion (p)	Lower limit	Upper limit	Width if p=0.5
0.970	1921	0.050	0.050	0.500	0.475	0.525	0.050

Summary statements

A sample size of 1921 produces a two-sided 97% confidence interval with a width equal to 0.050 when the sample proportion is 0.500. This sample is the minimum sample to ensure the accuracy of the results with.05 margin of error and 97% confidence [20].

Study population

The choice of subjects was in the form of clusters (4 clusters/each school); each cluster was formed from 17 students from each grade with a total of 68 children/each primary schoolchildren. The actual total number of the randomly surveyed schools was 30 schools distributed along 16 districts within three governorates with average 1–3 schools/district and 10–12 schools/each of the selected governorates according to the number of schools per district. The total number of children was rounded to 2040. Of the expected 2040 children, 2015, children completed the questionnaire. These schoolchildren were in the age group 8–12 years, studying at primary levels in governmental and private schools in some rural and urban areas of three governorates of Egypt.

Inclusion criteria

Boys and girls in the primary schools from grade 3 to grade 6. The primary schoolchildren are aged 8–12 years so that they could express their feelings properly. The study included both private and governmental schools as well as schools in rural and urban areas.

Exclusion criteria

Students proved to have any mental disorder, visual or auditory impairment, or chronic disease were excluded from the study.

Data collection types and tools

The questionnaire was designed and distributed to the parents of the studied schoolchildren studying at primary levels and living in both urban and rural areas of Egypt. The designed questionnaire was completed by the primary schoolchildren.

Seven types of phobias were investigated: Agoraphobia, phobia from darkness, phobia from animal, phobia from untreatable illness (mainly coronavirus), phobia from insect, phobia from height, and social phobia. The questionnaire consisted of some sociodemographic data (age, gender, residence, school type, and school level) and 20 questions related to different types of phobia. Students' parents were asked to answer the questions by indicating "yes" or "no." Questions evaluate the levels of phobia were scored from zero to ≥10 where 0 means no phobia, 1–9 means a low level of phobia, however, the score of a high level of phobia ranges from 10 to more.

Children completed self-report rating scale [21].

Two child psychiatrists made psychiatric diagnoses through a systematic review of the symptoms.

DSM-IV panic symptoms were used for the child self-reported PD symptoms.

Data management analysis

The collected data were revised, coded, entered, and verified with proofreading data, where one researcher checked the data entered against the original document. Data analysis was done using Statistical Package for the Social Science 18 for windows. Descriptive statistics in the form of frequency and percentage were used for data summarization. Diagrams and figures were used to illustrate the other simple information. Qualitative data were presented in frequencies and percentages. Chi-square test was used for measuring differences; meanwhile, odds ratio and 95% confidence interval were computed to assess the degree of association. The analysis was also done using Z test between two proportions [22]. Multivariate logistic analysis was done to predict risk factors significantly affecting phobia. $p < 0.05$ was considered significant and $p < 0.001$ was considered highly significant.

Results

Of 2015 studied schoolchildren in the age group 8–12 years, 52% were female. The majority of the sample was studying at primary levels in private schools and was from rural areas of Egypt (61.3% and 62.5%, respectively). About one-third of the participants were studying in primary five (30.3%), around one-quarter of them were studying in primary three and another was studying in primary six (24% both), and 21.5% were studying in primary four.

Table 1 reveals the distribution of the most common phobias among the studied schoolchildren. Feeling of falling down from high places (66.5%), phobia from dark places (60.0%), phobia from going bathroom when it is dark (57.1%), and phobia from untreatable illness (44.2%) were the most common phobias found among the studied schoolchildren. Other types of phobias such as phobia when entering a place where people are gathered and talking (19.4%) were found less commonly. The table also shows that low and high scores of phobia accounted for 60.9% and 35.2%, respectively, with a highly significant difference and there is a highly significant difference between certain types of phobia ($p < 0.001$). More than 5% of the studied schoolchildren had from 5 to 12 types of phobia (Figure 1).

Table 1: Distribution of different types of phobia among the studied schoolchildren

Type of phobia	Total n=2015 n (%)	p-value
Total score of phobia		
No (0)	79 (3.9)	<0.001
Low 1–9	1227 (60.9)*	
High 10 or more	709 (35.2)*	
Agoraphobia		
Phobia from narrow places	714 (35.4)	<0.001
Phobia from train or bus even they are not crowded	545 (27.0)*	
Phobia from crowded places	752 (37.3)*	
Phobia from darkness		
Phobia from dark places while he is in	1208 (60.0)	<0.001
Imagine that somebody is talking to him while he is in darkness	750 (37.2)	
Phobia from going alone to bed at night	658 (32.7)*	
Feeling shudder when he is in darkness	984 (48.8)	
Imagine in darkness that somebody on the wall	930 (46.2)	
Phobia from sitting in dark room	1044 (51.8)	
Phobia from going bathroom when it is dark	1151 (57.1)*	
Phobia from animal		
Feeling dizzy and shudder when he sees a dog or cat	572 (28.4)*	<0.001
Runaway and be tachycardia when seeing a dog or cat	790 (39.2)	
Phobia from rats and be tachycardia on seeing a rat	1031 (51.2)*	
Phobia from snacks even if he saw them in TV or pictures	893 (44.3)	
Phobia from untreatable illness (like corona)	890 (44.2%)	
Phobia from insect		
Phobia from cockroach and become tachycardia on viewing a cockroach	690 (34.2)	
Phobia from height		
Phobia from heights	1034 (51.3)	<0.001
Feeling that he will fall down while he is in high places	1340 (66.5)	
Social phobia		
Phobia from something or people he knows they are harmless	514 (25.5)	<0.001
Phobia when entering place where people are gathered and talking	390 (19.4)	

*p<0.001.

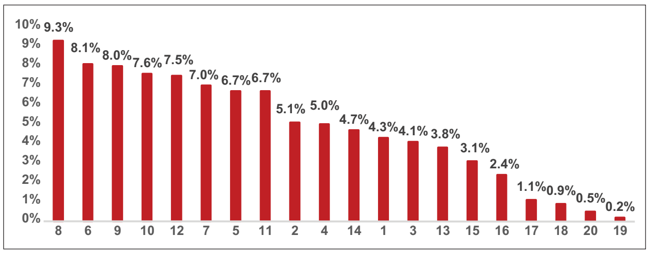

Figure 1: Percent distribution of different no. of phobias among the studied schoolchildren

The low score of phobia was more among the studied female schoolchildren (63.5%), while the high score of phobia was more among the studied male schoolchildren (71.8%). As regards low versus high scores of phobia, males were 4.4 times with highly significant (p < 0.001). There is a highly significant difference between rural and urban areas regarding no phobia versus high scores of phobia with odds ratio 3.5 (95% CI 2.1–5.7). Governmental schools were almost two times likely than private schools regarding low versus high scores of phobia with a highly significant difference (p < 0.001). Fifth graders scored higher than other graders, for low scores versus high scores of phobia with highly significant difference (p < 0.001) Table 2.

Table 2: Prevalence of phobia among the studied schoolchildren according to certain characteristics

Variable	Phobia			
	Total n=2015	No (0) (n=79) n (%)	Low (1–9) (n=1227) n (%)	High (10 or more) (n=709) n (%)
Gender				
Males	967	10 (12.7)	448 (36.5)	509 (71.8)
Females®	1048	69 (87.3)	779 (63.5)	200 (28.2)
OR (CI) between: No versus low=4.0 (2.0–7.8)**, no versus high=17.6 (8.9–34.8)**, low versus high=4.4 (3.6–5.4)**				
Residence				
Rural	1259	28 (35.4)	765 (62.3)	466 (65.7)
Urban®	756	51 (64.6)	462 (37.7)	243 (34.3)
OR (CI) between: No versus low=3.0 (1.9–4.9)**, no versus high=3.5 (2.1–5.7)**, low versus high=1.2 (1.0–1.4)				
Type of school				
Governmental	780	17 (21.5)	425 (34.6)	338 (47.7)
Private®	1235	62 (78.5)	802 (65.4)	371 (52.3)
OR (CI) between: No versus low=1.9 (1.1–3.3)*, no versus high=3.3 (1.9–5.8)**, low versus high=1.7 (1.4–2.1)**				
School level/grade**				
Primary three	483	27 (34.2)	309 (25.2)	147 (20.7)
Primary four	434	11 (13.9)	264 (21.5)	159 (22.4)
Primary five	611	30 (38.0)	371 (30.2)	210 (29.7)
Primary six	487	11 (13.9)	283 (23.1)	193 (27.2)

*p<0.05, **p<0.001, OR: Odds ratio; CI: Confidence interval.

Table 3 illustrates the prevalence of different types of phobia among the studied schoolchildren according to certain characteristics. Prevalence of different types of phobia was more frequent in males than females with significant differences (agoraphobia [p = 0.008], phobia from darkness [p < 0.001], animal phobia [p = 0.035]). The frequency of different types of phobia was increased in rural areas than urban areas with significant difference (agoraphobia [p < 0.001], phobia from darkness [p = 0.043], animal phobia [p < 0.001]). In addition, private schools demonstrated higher percent than governmental schools in almost all types of phobia with significant difference (phobia from darkness [p = 0.029], animal phobia [p = 0.001]). The studied fifth graders (about one third) show the highest percentage for almost all types of phobia, whereas phobia from untreatable illness was more common in third and fourth grades students (27.6% and 27.0%, respectively).

Figure 2 with regard to PD symptoms due to coronavirus pandemic, somatic symptoms were not common; the most common somatic complaints were in order: Shortness of breath of children (40%), chest pain, palpitations, nausea, trembling, sweating, and choking. Meanwhile, fear of losing family members was the most common (97%), then the fear of the unknown consequences of the corona (78%) and fear of dying (68%) with a highly significant difference (p < 0.001).

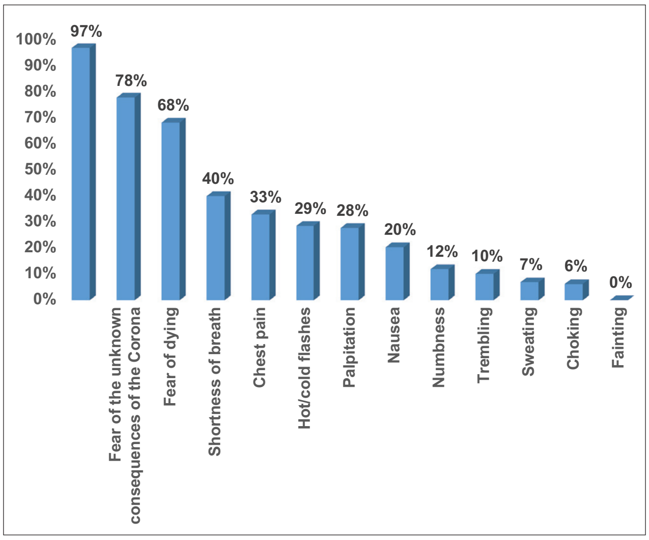

Figure 2: Prevalence of panic disorder's symptoms from catching coronavirus among the studied schoolchildren according to certain characteristics, p < 0.001

Table 4 presents the logistic regression analysis for investigating factors affecting phobia among studied schoolchildren. It was carried out using a type of school, residence, gender, and school level/grade in the model. It revealed that male studied schoolchildren, urban areas, and governmental schools were highly significant predicting factors for phobia regarding low score of phobia versus high score of phobia, no phobia versus high scores of phobia, and no phobia versus low scores of phobia, p < 0.001.

Discussion

Phobias are the most common anxiety disorder. It is characterized by the overwhelming and constant fear of specific objects or situations that present little or no real threat causing distress and impairment to the child's life [11], [23], [24]. If phobias are not treated and continue into adulthood, they will become chronic, causing a marked reduction in

Table 3: Prevalence of agoraphobia, phobia from darkness, animal, illness, insect, height, and social phobia among the studied schoolchildren according to certain characteristics

Variable	Gender		Residence		Type of School		School level/primary grade			
	Males	Females	Rural	Urban	Govern-mental	Private	Three	Four	Five	Six
Phobia from narrow places n=714	445 (62.3)	269 (37. 7)	522 (73.1)	192 (26.9)	318 (44.5)	396 (55.5)	160 (22.4)	155 (21.7)	223 (31.2)	176 (24.6)
Phobia from train or bus even they are not crowded n=545	294 (53.9)	251 (46.1)	387 (71.0)	158 (29.0)	228 (41.8)	317 (58.2)	133 (24.4)	130 (23.9)	164 (30.1)	118 (21.7)
Phobia from crowded places n=752	453 (60.2)	299 (39.8)	482 (64.1)	270 (35.9)	345 (45.9)	407 (54.1)	165 (21.9)	172 (22.9)	245 (32.6)	170 (22.6)
p-value	0.008		<0.001		0.347		0.744			
Phobia from dark places while he is in n=1208	743 (61.5)	465 (38.5)	737 (61.0)	471 (39.0)	508 (42.1)	700 (57.9)	255 (21.1)	242 (20.0)	380 (31.5)	331 (27.4)
Imagine that somebody is talking to him while he is in darkness n=750	425 (56.7)	325 (43.3)	468 (62.4)	282 (37.6)	369 (49.2)	381 (50.8)	168 (22.4)	127 (16.9)	250 (33.3)	205 (27.3)
Phobia from going alone to bed at night n=658	431 (65.5)	227 (34.5)	418 (63.5)	240 (36.5)	293 (44.5)	365 (55.5)	138 (21.0)	142 (21.6)	208 (31.6)	170 (25.8)
Feeling shudder when he is in darkness n=984	562 (57.1)	422 (42.9)	627 (63.7)	357 (36.3)	442 (44.9)	542 (55.1)	211 (21.4)	207 (21.0)	304 (30.9)	262 (26.6)
Imagine in darkness that somebody on the wall n=930	543 (58.4)	387 (41.6)	635 (68.3)	295 (31.7)	402 (43.2)	528 (56.8)	245 (26.3)	179 (19.2)	283 (30.4)	223 (24.0)
Phobia from sitting in dark room n=1044	662 (63.4)	382 (36.6)	657 (62.9)	387 (37.1)	458 (43.9)	586 (56.1)	225 (21.6)	227 (21.7)	329 (31.5)	263 (25.2)
Phobia from going bathroom when it is dark n=1151	677 (58.8)	474 (41.2)	727 (63.2)	424 (36.8)	546 (47.4)	605 (52.6)	252 (21.9)	214 (18.6)	353 (30.7)	332 (28.8)
p-value	<0.001		0.043		0.029		0.153			
Feeling dizzy and shudder when he sees a dog or cat n=572	368 (64.3)	204 (35.7)	340 (59.4)	232 (40.6)	251 (43.9)	321 (56.1)	93 (16.3)	136 (23.8)	205 (35.8)	138 (24.1)
Runaway and be tachycardia when seeing a dog or cat N=790	498 (63.0)	292 (37.0)	462 (58.5)	328 (41.5)	311 (39.4)	479 (60.6)	174 (22.0)	159 (20.1)	250 (31.6)	207 (26.2)
Phobia from rats and be tachycardia on seeing a rat n=1031	690 (66.9)	341 (33.1)	601 (58.3)	430 (41.7)	368 (35.7)	663 (64.3)	214 (20.8)	256 (24.8)	301 (29.2)	260 (25.2)
Phobia from snacks even if he saw them in TV or pictures n=893	541 (60.6)	352 (39.4)	636 (71.2)	257 (28.8)	388 (43.4)	505 (56.6)	169 (18.9)	183 (20.5)	298 (33.4)	243 (27.2)
p-value	0.035		<0.001		0.001		0.017			
Phobia from untreatable illness (like corona) n=890	564 (63.4)	326 (36.7)	630 (70.8)	260 (29.2)	392 (44.0)	498 (56.0)	246 (27.6)	240 (27.0)	176 (19.8)	228 (25.6)
Phobia from cockroach and become tachycardia on viewing a cockroach n=690	473 (68.6)	217 (31.4)	458 (66.4)	232 (33.6)	215 (31.2)	475 (68.8)	181 (26.2)	157 (22.8)	190 (27.5)	162 (23.5)
Phobia from heights n=1034	550 (53.2)	484 (46.8)	679 (65.7)	355 (34.3)	440 (42.6)	594 (57.4)	201 (19.4)	266 (25.7)	323 (31.2)	244 (23.6)
Feeling that he will fall down while he is in high places n=1340	748 (55.8)	592 (44.2)	856 (63.9)	484 (36.1)	568 (42.4)	772 (57.6)	290 (21.6)	276 (20.6)	431 (32.2)	343 (25.6)
p-value	0.217		0.244		0.969		0.027			
Phobia from something or people he knows they are harmless n=514	305 (59.3)	209 (40.7)	372 (72.4)	142 (27.6)	238 (46.3)	276 (53.7)	126 (24.5)	112 (21.8)	154 (30.0)	122 (23.7)
Phobia when entering place where people are gathered and talking n=390	242 (62.0)	148 (38.0)	286 (73.3)	104 (26.7)	196 (50.3)	194 (49.7)	92 (23.6)	90 (23.1)	118 (30.3)	90 (23.1)
p-value	0.449		0.806		0.267		0.962			

Table 4: Logistic regression of factors affecting phobia

Variables	B	p	OR	95% CI of OR	
				Lower	Upper
Low versus high					
Type of school*	–0.485	<0.001	0.615	0.501	0.757
Residence*	0.321	0.003	1.379	1.115	1.706
Gender*	–1.478	<0.001	0.228	0.186	0.279
School level/grade	0.076	0.106	1.079	0.984	1.183
No versus low					
Type of school*	–0.798	0.006	0.450	0.255	0.796
Residence*	1.423	<0.001	4.148	2.525	6.816
Gender*	–1.458	<0.001	0.233	0.117	0.462
School level/grade	0.209	0.070	1.232	0.983	1.545
No versus high					
Type of school*	–1.389	<0.001	0.249	0.130	0.479
Residence*	1.388	<0.001	4.005	2.297	6.985
Gender*	–2.816	<0.001	0.060	0.030	0.120
School level/grade	0.118	0.396	1.125	0.857	1.476

Variables entered in the model: Type of school, residence, gender, and school level/grade. B: Regression co-efficient; OR: Odds ratio; CI: Confidence interval.

quality of life and disability in young populations. Thus, early diagnosis may help in the prevention of severe psychiatric symptoms [5], [23], [25].

Therefore, the present study discussed two major observations: First, identify the prevalence of most common phobias in the studied Egyptian primary schoolchildren, and second, determine the prevalence of different types of phobia according to certain characteristics. Most importantly, determine the influence of phobia from diseases on the occurrence of PD due to the corona pandemic.

Phobia consists of many types as a specific phobia (e.g., fear from darkness, animal, insect, or heights), agoraphobia (e.g., fear of crowded or narrow places), as well as, social phobia (as phobia when entering a place where people are gathered and talking for fear of embarrassing yourself and being humiliated in public), and medical phobia (afraid of illness). The results suggest that the most commonly reported phobias among the studied Egyptian schoolchildren were certain types of specific phobia (falling down from high places, phobia from dark places, and phobia from going bathroom when it is dark). Our study is aligned with others showing that the specific phobias were more common in children versus adults and adolescents, making it the most common anxiety disorder and one of the most common psychiatric disorders among children [25], [26]. This is explained by many stressors as parental overprotectiveness, physical abuse, parental separation or loss, death of a close relative, physical health, genetic vulnerability, etc. [26]. In contrast, social phobia was found to be more common among children by other studies [5], [27], [28], [29], [30]. Certain risk factors causing increase prevalence of social phobia as environmental and biological changes, family type, physical activity, meditation, etc. [5], [29].

The present study demonstrated that more than 5% of the studied schoolchildren had more than 5 types of phobia. This finding is supported by a study done by de Vries *et al.*, 2019, who found that 8% of children reported four or more phobias [31]. The present study also scored the phobia into the low score (1–9) and high score (≥10) which accounted for 60.9% and 35.2%, respectively, of the studied participants. In this respect, the study carried out by Archana *et al*., 2017, described that mild and severe phobia accounted for 24.1% and 1.6%, respectively [29]. Different levels of phobia may be due to the underlying influence of paternal and maternal factors on child development starting early after childbirth [32], [33], [34].

Gender differences in different phobias were explored in the current study which clarified that the different types of phobia were more prevalent in males than females with a significant difference. This is because boys are more susceptible to stress and neuropsychiatric disorders, so they need more care and support from their mothers [35] and maybe due to the way of the child-rearing with overprotectiveness of boys than girls especially in Egyptian rural communities which were more in this study. Moreover, the phobia was increased in rural areas than urban areas with a significant difference because of firm social controls by these communities [36]. However, other studies who were inconsistent with the current study finding and reported that phobias were more prevalent in female students than in males [5], [25], [27], [37], [38]. In addition, the problem of phobia is varying in rural and urban populations based on multiple issues [29].

Most of the phobias generally appear in early childhood, the studied fifth or sixth graders (9–12 years) showed the highest percentage for almost all types of phobia because older children are more susceptible to phobia than younger children. With respect to phobias, our results are in agreement with Bener *et al*., 2011; Varughese and Peteru, 2019; and de Vries *et al*., 2019 suggesting that phobias were common in the age group 6–11 years [5], [26], [31]. Results of other studies were somewhat different from those found in our sample, two studies suggested that the average age of onset of phobias symptoms at approximately 8 years [11], [37]. While one study found that the onset of phobias symptoms was more in the age group of 11-13 years [29]. This variation may be due to different socioenvironmental stresses.

Because phobia can spread quickly, so it has played an important role in coronavirus spread and the fear of catching the virus expressed by panic, stress, unhappiness, avoiding public places, psychosomatic diseases, etc. The most important thing that we have to fear is fear itself [39], [40], [41], [42]. Regarding PD due to the corona pandemic, the study reported 44.2% prevalence which could be considered as the highest prevalence worldwide. PD is likely to be increased with increased number of infected persons with coronavirus and number of deaths and expected to reach almost all people (80% or 90%) if it is surveyed at this time. The highest PD symptoms were fear of losing any of the family members, especially grandparents (97%), fear of the unknown consequences of the corona (78%), and fear of dying because it has not a treatment yet (68%). The observed somatic complaints such as shortness of breath of children, chest pain, palpitations, nausea, trembling, sweating, and choking often misdiagnosed as anxiety or mood disorders. Such diagnosis often masks the presence of PD in primary schoolchildren. The majority of Egyptian studies among primary school-aged groups seldom considered PD for such symptoms or studied its effect on cognitive and psychosocial development [42], [43], [44], [45], [46], [47]. These somatic symptoms were slightly higher in this study due to fear from corona and its complications more than symptoms caused by the disease itself.

Furthermore, our results indicate that the studied male schoolchildren, urban areas, and governmental schools were highly significant predicting factors for phobia regarding low score of phobia versus high score of phobia, no phobia versus high scores of phobia, and no phobia versus low scores of phobia, $p < 0.001$.

It was notable that even with the high percentages of different types of phobia and with PD, no child who was diagnosed or had been referred to seek advice, further evaluation or treatment, indicating a very low level of awareness. It is really recommended to encourage community-based awareness programs to raise awareness of parents about phobia and how to manage. Such programs in Egypt are proved to be effective in many health settings resulted in the empowerment of the communities and in mitigation of many health problems [48], [49], [50], [51], [52], [53], [54].

Strengths of the study

Up to date, the majority of studies for phobia and PD has both small sample size and was done in a clinical setting such as hospitals or clinics. Our study is characterized by being a community based one. It is the first one in Egypt to study common and specific phobia as well as a PD due to the corona pandemic among primary school-aged children with a very large sample size (2015 children), with a high confidence level of 97% and low two-sided margin of error (0.05).

Limitation of the study

As this study was limited to investigate different forms of specific phobia without studying the symptoms of the specific phobia and without studying the sociodemographic implication. Moreover, self-reported symptoms of being panic due to the corona pandemic were the focus of the study without studying the comorbidity between PD and internalizing and externalizing disorders. Another limitation is that children were assessed by a self-reported questionnaire rather than with the use of structured diagnostic interviews that tend to be lengthy. Meanwhile, the cognitive capabilities of school-aged children are below what is required to fill in these questionnaires. Although the role of the paternal and maternal parameters on child development is well evident in many Egyptian studies [32], [33], [34] starting early after childbirth, yet the current study also obscured exploring such influence as underlying factors for the variation of the widespread of specific phobia.

Conclusion and Recommendation

Although our sample is not representative of the whole Egyptian schoolchildren, yet it represents the opinion of primary schoolchildren of different geographical and socioeconomic levels. Phobia from heights and darkness was the most common with a higher frequency in the 9–12 years old age group (fifth or sixth graders). Boys had higher rates of all phobic disorders than girls. The important determinants of phobias were the type of school, residence, gender, and school-level/grade.

The prevalence of PD due to the corona epidemic is very high, it is reported by almost half of the surveyed primary schoolchildren. Fear of losing any of their family members, especially grandparents, fear of the unknown consequences of the corona, and fear of death were reported to be the highest PD symptoms. The prevalence of PD due to the coronavirus epidemic is reported to be very high.

It is important to assure fearful children and their parents that during lockdown, they should be optimistic. They should know that mental and spiritual wellbeing are linked and important during the crisis to decrease their suitability to diseases. To enable parents to work optimally from home, it is necessary to create an enabling environment that is free from any phobia or panic. This is also necessitated to calm down children who might be experienced with a phobia that is triggering their PD.

We believe our responsibility lies in catalyzing the process of helping people seamlessly to be engaged and motivated on ways to make their work from home “business as usual” safe, smart, and swift. This will be achieved by assuring their children and reducing their PDs.

Ethics Approval and Consent to Participate

The study complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects. Written consent was obtained from parents of all participants after ensuring their full understanding of the research. Information obtained at the individual level was kept strictly confidential.

Approval of the Ministry of Education before starting the research was taken. The study ethical approval was obtained from the Medical Research Ethics Committee of the National Research Centre with the ethical approval number of 19068.

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Authors’ Contributions

AMM and HE conceived and designed the study. MME, EE, and AE conducted field visits and data collection. AMM, HE GAA, and NAI oversaw the implementation. GAA did the statistical analyses and interpreted the data. GAA and MME drafted the paper. AMM and LE reviewed the manuscript. GAA submitted the manuscript. All authors provided input into the manuscript and approved the final version.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Subcorneal Pustular Dermatosis with Temporary Autoimmune Features during COVID-19 Pandemic

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Abstract

Subcorneal pustular dermatosis, Sneddon-Wilkinson, is an uncommon neutrophilic dermatosis of unknown etiology. We report on a 51-year-old woman who presented with multiple superficial erythematous erosions surrounded by annular arranged sterile pustules concentrated on the trunk, the neck, and the proximal extremities during the coronavirus disease-19 pandemic. Larges pustules and flaccid bullae showed a hypopyon. There were no fever and no pruritus, general health was unaffected. Laboratory investigations revealed leukocytosis, neutrophilia, lymphopenia, and increased C-reactive protein. Initially, antinuclear antibodies, pemphigoid antibodies, and antibodies to BP 230 were positive, but negative 5 days later. Nasopharyngeal swabs were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA tested by real-time reverse-transcriptase-polymerase chain reaction. A diagnostic skin biopsy showed epidermal spongiotic vesiculation and subcorneal pustulation with acantholysis and an inflammatory infiltrate composed of neutrophils and lymphocytes. The confirmed diagnosis was subcorneal pustular dermatosis Sneddon-Wilkinson. She was treated by dapsone and corticosteroids with the latter tempered down. Clinical response was rapid. We suggest that the autoimmune features seen on admission may be due to an undefined viral infection, but not SARS-CoV-2.

Introduction

Neutrophilic dermatoses are a heterogeneous group of chronic inflammatory disorders characterized by the presence of a sterile cutaneous infiltrate of mature neutrophilic leukocytes. Cutaneous presentation can be variable including pustules, papules, plaques, nodules, and ulcerations. Histological examination of skin lesions demonstrates a strong epidermal, dermal, or hypodermal infiltrate composed of neutrophils without any evidence of infection or primary vasculitis. Other important features of neutrophilic dermatoses are the potential occurrence of extracutaneous neutrophilic infiltrates, a frequent association with some systemic diseases, and a possible overlap between several neutrophilic or autoinflammatory disorders [1].

One of the more uncommon neutrophilic dermatoses is subcorneal pustular dermatosis Sneddon-Wilkinson [2]. We report a case during the recent coronavirus disease-19 (COVID-19) pandemic with initially uncommon immunologic findings and discuss the differential diagnosis and treatment.

A 51-year-old woman presented with a rapidly spreading disseminated dermatosis that started 3 days ago. She had no history of fever, infection, or medical drugs. There was no known allergy. She did not use medical drugs and had no chronic disorder. Her family history was negative for skin disease and atopic disease. She was overweight but not obese.

On examination, we observed multiple superficial erythematous erosions surrounded by annular arranged numerous tiny pustules concentrated on the trunk, in particular in the submammary region, the neck, and the proximal extremities. Pustules were asymptomatic and distributed arciform surrounded by an annular erythema (Figure 1).

On the upper extremities, several larger pustules and small flaccid bullae (up to 1 cm in diameter) were observed showing a hypopyon (Figure 2).

Oral and genital mucosa, head, and palmoplantar skin remained unaffected. There was no nail involvement.

She reported no pruritus or pain, but some burning sensations on the erosions. The general health was unaffected.

Laboratory: Leukocytosis of 16.96 Gpt/l (normal range 3.8–11.8), neutrophilia of 13.60 Gpt/l (1.8–7.6), lymphopenia of 10% (25–45), and mild monocytosis of 1.20 Gpt/l (0–1.0). C-reactive protein was 42.7 mg/l (<5). Autoantibodies:antinuclear antibodies (ANAs) 1:160, pemphigus antibodies negative, pemphigoid antibodies initially 1:40, a control 5 days later was negative, antibodies to desmoglein 1 and 3, IgG and IgA antibodies to gliadin and tissue transglutaminase were negative. Antibodies to BP 180 were negative, while antibodies to BP 230 were positive on admission, but negative 5 days later. No other laboratory abnormalities including protein electrophoresis were noted. Swabs from pustules were sterile. Swabs from erosions, pustules, and nasal mucosa were negative for methicillin-resistant *Staphylococcus aureus*. Nasopharyngeal swabs were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA tested by real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) assay.

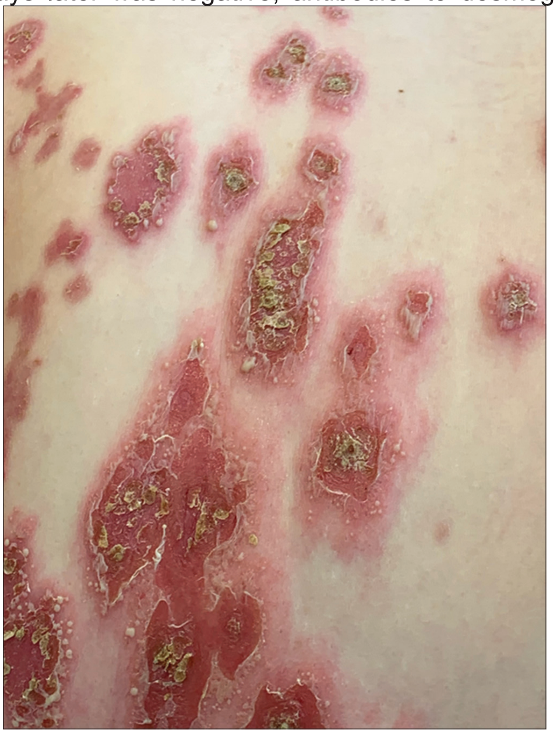

Figure 1: Erythematous erosions surrounded by tiny sterile pustules

Figure 2: Flaccid pustules and small bullae with hypopyon

A diagnostic skin biopsy was performed from the right upper arm with hypopyon-positive bullae for histopathology and direct immunofluorescence. We performed hematoxylin-eosin, Giemsa, iron, and periodic acid-Schiff stain on formalin-fixed tissue. The orthokeratotic epidermis showed spongiotic vesiculation and centrally subcorneal pustulation with acantholysis. There was a massive subepidermal edema with vesiculation. The upper corium and the stratum papillare demonstrated an inflammatory infiltrate composed of neutrophils and lymphocytes. Some eosinophils were intermingled. The iron reaction remained negative.

Direct immunofluorescence showed an IgG-positive intercellular reaction in the upper epidermis, but remained negative for IgA, IgM, and C3.

The primary differential diagnoses were dermatitis herpetiformis Duhring, pemphigus foliaceus, acute generalized exanthematic pustulosis (AGEP), and subcorneal pustular dermatosis Sneddon-Wilkinson.

Clinical picture, course, laboratory investigations, and histopathology confirmed the diagnosis of Sneddon-Wilkinson disease, probably triggered by an undefined viral infection with pronounced lymphopenia.

We started initially with 100 mg prednisolone per day with minimal improvement but switched to 3 mg × 50 mg dapsone/d after laboratory test revealed a normal level of glucose-6-phosphate dehydrogenase. With 24 h after initiation of dapsone, almost all pustules disappeared, and the redness of the erosions diminished remarkable (Figures 3 and 4). No new pustules developed thereafter. Systemic corticosteroids were tapered down to zero.

Discussion

Subcorneal pustulosis Sneddon-Wilkinson first described in 1956 is a rare, chronic inflammatory neutrophilic, pseudo-bullous disorder [2]. Middle-aged women are mainly affected, but rare cases from children and elderly people have also been reported [3], [4].

The etiology is unknown, but infections, autoimmune diseases, neoplasia, and blood dyscrasias in patients have been documented with Sneddon-Wilkinson disease. In the present patient, a possible

Figure 3: Dramatic improvement within 24 h of dapsone treatment

viral infection may have been the trigger since we observed a temporary lymphopenia. The most obvious finding is a massive activation of neutrophils in skin and peripheral blood [3].

Figure 4: Detail of the skin biopsy area. Most pustules cleared and the inflammation diminished

The differential diagnosis of Sneddon-Wilkinson disease included AGEP, pustular psoriasis, impetigo, and autoimmune bullous disorders including dermatitis herpetiformis Duhring. The hypopyon is seen mainly in Sneddon-Wilkinson disease and Duhring disease [5]. In Duhring disease, however, autoantibodies to gliadin and transglutaminase are present and the cutaneous lesions are extremely pruritic [6].

IgA pemphigus is an important differential diagnosis, where epidermal intercellular IgA and autoantibodies to desmocollin 1, 2, and 3 can be demonstrated [7], [8]. IgA deposits, however, could not be detected in the present case.

The initial intercellular IgG staining of upper epidermis and BP 230 autoantibodies suggested pemphigus foliaceus, but clinical presentation and course argued against. ANAs were positive, but clinically there was no hint for an autoimmune connective tissue disorder. Pemphigoid antibodies were positive, but no clinical signs of this disease, which often affects elderly people, were present. Desmoglein antibodies could not be detected, what is typical in Sneddon-Wilkinson disease [9].

Temporary presence of autoantibodies has been observed in viral infections including HIV, with reduction after decrease of viral load [10], [11]. We suggest that the temporary presence of ANA, pemphigoid and BP 230 autoantibodies, and epidermal intercellular IgG in direct immunofluorescence could be explained by a viral infection. In case of COVID-19 pandemic, we screened for SARS-CoV-2 RNA by RT-PCR, which was negative. The initially observed lymphopenia, however, would be in favor of an (unidentified) viral infection. Within 5 days, all autoimmune features disappeared.

The treatment of choice of Sneddon-Wilkinson disease is oral dapsone. Absolute contraindications for dapsone are hypersensitivity to dapsone or its derivatives including agranulocytosis and hypersensitivity syndrome and glucose-6-phosphate deficiency. The drug needs a regular complete blood count with differential every week for 4 weeks, then every 2 weeks until week 12, then every 3–4 months, a reticulocyte count as needed, and liver function tests and renal function tests every 3–4 months. The methemoglobin level should be measured as clinically indicated [12].

In dapsone-resistant patients or patients with impaired function of glucose-6-phosphate dehydrogenase, therapeutic alternatives include acitretin, psoralen-ultraviolet A photochemotherapy (PUVA), retinoids with PUVA (Re-PUVA), narrowband UVB, and systemic corticosteroids. Anecdotal uses of colchicine, pentoxifylline, ketoconazole, azithromycin, tetracyclines, Vitamin E, ciclosporin, nicotinamide, tumor necrosis-alpha inhibitors, mycophenolate mofetil, and intravenous immunoglobulin have all been reported [3].

Conclusion

Unusual autoimmune phenomena have been observed in Sneddon-Wilkinson disease during the COVID-19 pandemic. Although an infection with SARS-CoV-2 could be excluded another, unidentified viral infection may have caused these temporary laboratory symptoms, lymphopenia, and triggered the onset of subcorneal pustular dermatosis.

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Clinical Features of Patients with Probable 2019 Novel Coronavirus Infected Pneumonia in Rasht, Iran: A Retrospective Case Series

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Abstract

BACKGROUND: Coronavirus disease-19 (COVID-19) is the first pandemic infectious disease caused by a novel coronavirus. Viral pneumonia is a severe complication of COVID-19.

AIM: Due to the high prevalence of this disease globally, especially in Iran, the aim of this study was to determine the clinical features of seven patients with probable COVID-19 infected pneumonia in Rasht, North Iran.

MATERIALS AND METHODS: In this retrospective case series study, we described the clinical, laboratory, and radiological features of seven patients with probable COVID-19 infected pneumonia at Razi Hospital, Rasht, north of Iran, from February 27 to March 16, 2020.

RESULTS: In this study, the most common clinical symptoms during hospitalization in patients with COVID-19 were poor appetite (seven cases), dehydration (seven cases), cough (six cases), dyspnea (six cases), fatigue (six cases), fever above 38°C (five cases), myalgia (five cases), Chills (five cases), feeling fever (five cases), sore throat (five cases), and nausea (five cases), respectively. The average body temperature in these patients was 39.32°C. In laboratory findings, erythrocyte sedimentation rate was elevated in three patients. Contrary to most of the evidence, C-reactive protein was not elevated in five patients. All patients received antibiotic and antiviral medications and received symptomatic treatment. Finally, four patients responded to the treatments and were discharged from the hospital; two patients were still hospitalized and only one patient died.

CONCLUSION: Patients with COVID-19 associated pneumonia can be treated by evaluating and implementing appropriate therapeutic management. However, at the moment the disease progression for patients with COVID-19 cannot be accurately predicted.

Introduction

Concerns have been raised about a new outbreak in the world since December 8, 2019, in Wuhan, Hubei Province, China, following reports of pneumonia with unknown etiology. These patients mostly lived or worked in the wholesale markets of Huawei seafood (the buying and selling of live animals) [1], [2]. Following the identification of the new coronavirus by the Chinese Centers for Disease Control and Prevention (China CDC), the disease has named Coronavirus Disease 2019 by the World Health Organization (WHO) [3], [4], [5]. Since January 2020, the spread of the disease has increased first in China and then in other countries [3] and by February 10, 2020, a total of 40,261 cases have been diagnosed in China, with 909 deaths [1], [6]. The disease is transmitted from person to person [4] and according to the latest WHO report, COVID-19 affected up to 179,111 individuals globally by March 17, 2020, of which 7426 people have died [7]. The Iranian Ministry of Health and Medical Education also reported 14,991 cases of COVID-19 in Iran by March 17, 2020, of which 853 cases have died [8].

According to the previous studies, symptoms such as fever, cough, myalgia, fatigue, diarrhea, shortness of breath, lymphopenia, and lung parenchymal opacity were detected in COVID-19 patients [9], [10]. The disease was associated with serious complications including acute respiratory distress syndrome (ARDS), shock, acute cardiac, and kidney injury and consequently, death. Clinically, patients with COVID-19 develop rapidly and eventually severe respiratory failure [1]. Epidemiological studies indicated that the overall risk of mortality in affected critically ill patients is high. Older age, male sex, history of immunodeficiency disorders, smoking, and underlying diseases are major risk factors for developing severe symptoms of COVID-19 [11], [12]. However, we have little information on clinical features in patients with OVID-19 infected pneumonia.

Due to the high prevalence of COVID-19 and lack of sufficient details regarding underlying mechanism of disease, and its clinical presentation or treatment in these patients, the aim of this study was to determine the clinical features of seven cases with probable COVID-19 infected pneumonia to take a step to discover the unknowns of the disease caused by SARS-CoV-2.

Case Presentation

This study aimed to determine the clinical features of patients with COVID-19 infected pneumonia since February 27 to March 16, 2020, on seven cases referred to Razi Hospital in Rasht, Guilan Province, Iran. This hospital is the main center for the treatment of COVID-19 patients in Rasht. In this study, patients with suspected diagnosis of COVID-19 infected pneumonia were examined through clinical and radiological findings. Due to restricted access to reverse transcription polymerase chain reaction (RT-PCR) laboratory kits, in this study, the diagnosis of COVID-19 pneumonia was based on the results of chest computed tomography (CT) scan imaging findings, according to the criteria developed by Iranian Radiologic Consultant Group [13].

We extracted information from patient records and interviews using pre-designed researcher-made checklist. This checklist includes demographic and clinical characteristics including age, sex, occupation, residency location, underlying disease history, history of immunosuppressive illness, history of contact to COVID-19 patient, history of travel to the China, disease symptoms, radiological findings, and factors associated with the disease. Consent form was filled out by all of the patients, or their family member, anonymously to use their medical records, and treatment plan.

In this case series, seven patients with COVID-19 pneumonia referred to the Razi Hospital in Rasht, Iran, were studied since February 27, 2010, to March 16, 2020. After early diagnosis, treatment and follow-up were performed for them. To protect patients' privacy, only purpose-related data were reported. There was no material or spiritual burden on the patients and their companions.

Case 1

The patient was a 79-year-old housewife. She was complaining about cough, loss of appetite and fatigue, which led her to the hospital. She had a history of hypertension and cardiovascular disease. She was under treatment with metoprolol and losartan. She did not have a history of travel or contact with a confirmed COVID-19 patient. The vital signs of the patient were BP =160/90, T = 37.3, SPO_2 = 84%, HR =90, and RR =18. Oxygen therapy was performed immediately with mask (8L/min). Chest x-ray (CXR) and CT scan findings have showed bilateral pneumonia. Laboratory findings showed that patient alkaline phosphatase (336 U/L) were in high range. The patient treatments were symptomatic and included with antibiotic drugs, such as levofloxacin (750 mg, daily) and meropenem (1 g, 3 times a day), as well as antiviral drugs, such as oseltamivir (75 mg, Twice daily) and hydroxychloroquine (200 mg, twice daily). The patient was discharged from the hospital after 11 days with complete recovery (Figure 1).

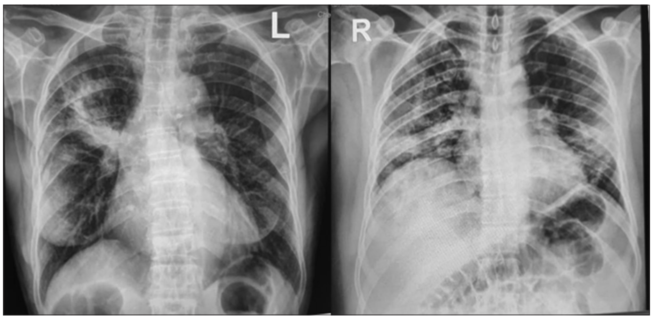

Figure 1: Chest X-Ray imaging from Patient 1 (Left) and Patient four (Right)

Case 2

The patient was a 51-year-old housewife who was referred to the hospital with her daughter with complaint of dry cough and shortness of breath, sore throat, and periodic fever (39.5°C) and chills. On further examination, the patient also reported symptoms, such as chest pain, headache, and diarrhea. The patient did not mention any previous history of the disease. She had attended a ceremony about 2 weeks ago and had contact with a person whose COVID-19 RT-PCR test was positive. The patient symptoms were treated by antibiotic therapy and the antiviral drugs, such as oseltamivir (75 mg, twice daily) and hydroxychloroquine (200 mg, twice daily). On the physical examination, the patient was observed with dehydration, myalgia, and fever. The vital signs of the patient were BP =135/80, T = 39.5, SPO_2 = 86%, HR =83, and RR =16. Oxygen therapy was performed immediately with mask (8 L/min). CXR and CT-scan findings indicated bilateral pneumonia. The patient was discharged after 12 days of care.

Case 3

The patient was a 68-year-old female, with symptoms of fever (39.4°C), cough, sore throat, and shortness of breath, who had been hospitalized for several days, and had been referred to Razi Hospital through a pre-hospital emergency medical service. In the initial examination, the patient had temporary symptoms of anorexia, nausea, dehydration, and chest pain. She had no previous history of the disease. She did not have a history of travel to China or contact with a positive COVID-19 patient. The patient participated in school ceremony for 14 days before admission and hospitalization. The patient treatments were symptomatic and included with antibiotics, such as levofloxacin

(750 mg, daily) and meropenem (1 g, 3 times a day), as well as antiviral drugs, such as oseltamivir (75 mg, twice daily) and hydroxychloroquine (200 mg, twice daily). The vital signs of the patient were BP =100/60, T = 37.2, SPO_2 = 75%, HR =88, and RR =18. Oxygen therapy was performed immediately with mask (8 L/min) to improve the patient’s condition. CXR and chest CT-scan imaging findings have indicated a unilateral pneumonia. Laboratory findings showed the high levels of erythrocyte sedimentation rate (ESR) and negative C-reactive protein (CRP). In laboratory tests, the patient had leukocytosis and hypernatremia. She was discharged after 14 days of care and improvement of clinical symptoms.

Case 4

The patient was a 40 years old, a teacher, who was referred to the emergency department with complaints of cough, sore throat, shortness of breath, nausea, vomiting, and diarrhea. On initial examination, the patient had symptoms of fatigue, anorexia, fever (39°C), chills, and dehydration. There was no previous underlying disease. Due to exacerbation of condition and SPO_2 = 29.9%, the patient was transferred to the intensive care unit (ICU) and subjected to intubation and underwent mechanical ventilation with synchronized intermittent mandatory ventilation mode. The patient has had a history of attending school for the past 14 days. The patient’s treatment was symptomatic, using antibiotic and antiviral drugs. CXR and chest CT-scan results indicated a bilateral pneumonia. In the study of the patient’s laboratory findings, creatine phosphokinase, creatine phosphokinase-MB, and ESR showed an increase of 271, 103, and 64, respectively. The patient died after 4 days of intubation in the ICU due to severe pulmonary involvement and respiratory distress syndrome (Figure 1).

Case 5

The patient was a 65-year-old, retired, who was referred to emergency department of the hospital with complaints of shortness of breath, fatigue, and abdominal pain. In the skin turgor examination, patient had dehydration. The patient had no fever (T = 37.5), but gastrointestinal symptoms such as anorexia, nausea, vomiting, and diarrhea were observed for 3 days. The patient has not been in any meeting for the past 14 days. He had a history of diabetes and hypertension. Initially, the patient received oxygen (6 L/min), levofloxacin (750 mg, daily), as well as oseltamivir (75 mg, twice daily), and hydroxychloroquine (200 mg, twice daily). CXR and chest CT-scan imaging results showed a unilateral pneumonia. Laboratory results were as follows: LDH =952 (elevated), creatine phosphokinase=54 (elevated), and BS =438. After 11 days of symptomatic care, antibiotics and antiviral therapy, the patient was discharged with improved clinical symptoms.

Case 6

The patient was 58-year-old man who has been referred to emergency department by ambulance. The patient’s chief complaints were high fever (39.5°C), chills, dry cough, sore throat, and shortness of breath. On initial examination, the patient was suffering from chest pain, fatigue, and loss of appetite. He had been smoking a pack of cigarettes daily for the past 20 years. He had no history of underlying disease. He did not have a history of travel to China or contact with a positive COVID-19 patient. Initially, oxygen therapy (9 L/min) was performed for symptomatic treatment, but on the 2^{nd} day of hospitalization after reduction in arterial blood oxygen level (O_2sat =72%), the patient was intubated and treated with bi-level positive airway pressure (BiPAP). Antibiotic therapy with levofloxacin (750 mg, daily), as well as antiviral therapy with oseltamivir (75 mg, twice daily) and hydroxychloroquine (200 mg, twice daily) were administered to the patient. CXR and chest CT-scan results were also evaluated and bilateral pneumonia was observed. In the last follow-up after 19 days, he was hospitalized and received treatment.

Case 7

The patient was a 65-year-old man, who was presented to the hospital complaining of cough, sore throat, fever, chills, and night sweats. On further examination, the patient’s appetite has decreased and he was suffering from fatigue, headache, and dehydration. The patient’s initial temperature was 38°C, which peaked at 39.2°C after 4 days. From day 5, a decreasing trend was found and finally reached at 37.8°C on day 10. The patient had a history of diabetes. On the other hand, he had traveled to Tehran in the past 14 days. The patient receives antibiotic and antiviral treatments with levofloxacin (750 mg, daily) and oseltamivir (75 mg, twice daily). CXR and chest CT-scan imaging results were also reviewed and bilateral pneumonia was observed. The patient’s LDH level was high (821 U/L). The patient is currently in hospital and undergoing treatment (Figure 2).

Additional results

The mean age of the patients was 60.85 years ranged from 40 to 79 years old. Four of the patients were male and three were female. All patients were residents of Rasht and were indirectly exposed and affected due to the widespread prevalence of this disease in this city. None of the patients had a close relationship with the history of traveling to China or with people who had traveled there. The patients’ symptoms included: Poor appetite (seven cases), dehydration (seven cases), cough (six cases), dyspnea (six cases), fatigue (six cases), fever (five cases), myalgia (five cases), chills (five cases), feeling febrile (five cases), sore throat (five cases), nausea (five cases), vomiting

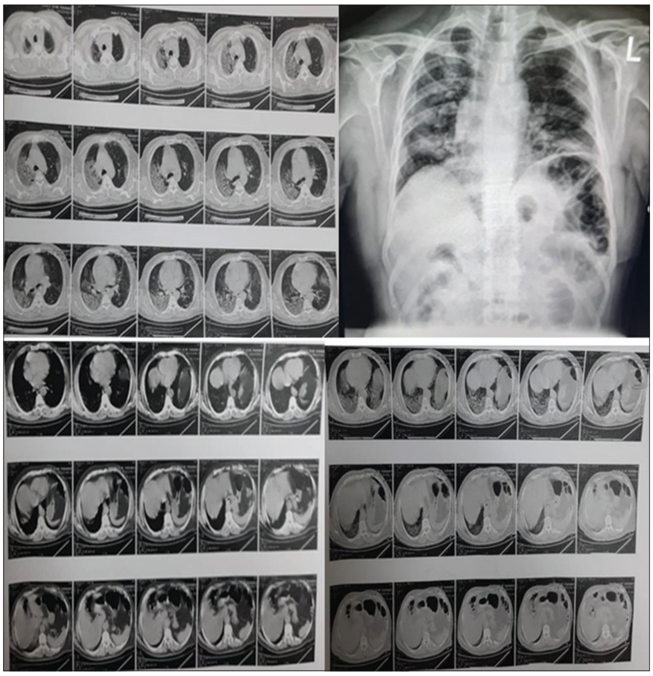

Figure 2: Transversal chest CT-scan and Chest X-Ray imaging from Patient seven

(four cases), headache (three cases), chest pain (three cases), diarrhea (three cases), and wheezing (one case). Body temperature higher than 38°C was observed in five patients with a mean of 39.32°C (from 39°C to 39.5°C). The results of chest radiography revealed four cases with bilateral pneumonia, two cases of unilateral pneumonia with right lung involvement, and one case of unilateral pneumonia with left lung involvement. Furthermore, unilateral multiple mottling and ground glass opacity were observed in three cases. All patients received antibiotics and received symptomatic treatment, and three were intubated due to low O_2 saturation. For all patients, medications such as: Oseltamivir capsule (75 mg, twice daily), hydroxychloroquine tablets (200 mg, twice daily), diphenhydramine (10 ml, four times a day before meals), intravenous ranitidine (25 mg/ml, twice daily), acetaminophen tablets in case of pain, ondansetron tablets in case of nausea, salbutamol, and ipratropium spray (two puffs in case of shortness of breath; 4 times a day), ceftriaxone (1 g, twice daily), meropenem (1 g, twice daily), vancomycin (1 g, twice daily), and oxygen therapy (in case of shortness of breath). A total of four patients responded appropriately to treatments and were discharged, two patients were still hospitalized and one patient expired. More detailed information is shown in Table 1. Furthermore, the patients' all laboratory data are presented in Table 2.

Discussion

Coronavirus is one of the major pathogens causing respiratory infections in humans. Two types of this pathogen including SARS-CoV and MERS-CoV are highly pathogenic, causing severe respiratory syndrome in humans [1]. Initial and major outbreaks of SARS-CoV between 2002 and 2003 leads to a total of 8422 confirmed infected cases in 29 countries [14]. MERS-CoV appeared in 2012 in Asia and the Middle East [15]. The SARS-CoV mortality rate was more than 10% and MERS-CoV was more than 35% [16].

This study was conducted in Rasht, the capital city of Guilan Province, north of Iran, due to the high prevalence of the disease and the establishment of an epidemic area. None of patients in this study had a history of traveling to China, or contacts with people who came from China in the past 2 weeks. It seems that these patients had contact with suspected COVID19 patients, which was similar to Li *et al*. [3], but in the study of Chen *et al*., all patients were from individuals associated with the Chinese seafood market [1], which may be attributed to the study's location.

The most common clinical manifestations of patients with COVID 19 infected pneumonia in this study were poor appetite and dehydration (all patients), cough, sore throat, dyspnea, fatigue, fever higher than 38°C, chills, and myalgia, respectively. However, a study by Chen *et al*. reported that fever, cough, and dyspnea were the most common symptoms in these patients [1]. Ethnicity and having underlying disease are the possible reasons for this difference. In a similar study, Wei Xu *et al.*, in Wuhan, China, reported that the most common clinical symptoms of the patients were fatigue, myalgia, headache, diarrhea, and vertigo, respectively [3], [17]. According to the results of our study, about half of patients had underlying diseases, such as hypertension, diabetes mellitus, and cardiovascular disease. Badawi *et al.* reported that about half of MERS-CoV patients had underlying diseases, such as diabetes mellitus, hypertension, and heart disease [18]. Furthermore, in this study, similar to other studies, the majority of patients had older age, people with underlying diseases and reduced immune systems were more likely to be affected [1], [19].

According to the results of our study, unlike the study by Chen *et al*., the levels of lymphocytes and white blood cells were within the normal range [1]. Moreover, in our investigation, CRP were negative in most cases (71.42%), which was consistent with the study by Wang *et al*. study [20]. It has been previously reported a 75–93% of elevated levels of CRP in COVID-19 patients [1], [13], [21], [22], [23]. This might be related to underlying diseases and other characteristics of infected patients. There has been shown an inverse association between the underlying diseases such as diabetes mellitus, hypertension and kidney and liver disease and higher CRP level in patients with acute or chronic illnesses [2], [24], [25]. In our study, the serum levels of other biomarkers such as LDH and ESR were increased significantly in COVID 19 patients, that is in line with study of Chen *et al*. (85% increase in ESR) [1]. The previous studies showed the increases

Table 1: Clinical features among COVID-19 infected in Rasht, Iran

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Basic information							
Admission date (2020)	March 5	March 6	March 6	February 28	March 5	February 27	March 2
Age (years)	79	51	68	40	65	58	65
Sex	Female	Female	Female	Male	Male	Male	Male
Occupation	Housewife	Housewife	Housewife	Teacher	Retired	farmer	Freelance
Epidemiological history							
Contact with index case directly	Unknown	Yes	Unknown	Unknown	Unknown	Unknown	Unknown
Current smoking	No	No	No	No	No	Yes	No
Hypertension	Yes	No	No	No	Yes	No	No
Diabetes	No	No	No	No	Yes	No	Yes
Cardiovascular disease	Yes	No	No	No	No	No	No
Coronary artery disease	Yes	No	No	No	No	No	No
Clinical characteristics							
Peak of fever (°C)	Afebrile	39.5	39.4	39	afebrile	39.5	39.2
Duration of fever (days)	--	7	2	6	--	2	3
Cough	Yes	Yes	Yes	Yes	No	Yes	Yes
Sore throat	No	Yes	Yes	Yes	No	Yes	Yes
Dyspnea	No	Yes	Yes	Yes	Yes	Yes	Yes
wheezing	No	No	No	No	Yes	No	No
Diarrhea	No	Yes	No	Yes	Yes	No	No
Nausea	No	Yes	Yes	Yes	Yes	Yes	No
Vomit	No	No	No	Yes	Yes	Yes	Yes
Abdominal pain	No	No	No	No	Yes	No	Yes
Poor appetite	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fatigue	Yes	No	Yes	Yes	Yes	Yes	Yes
Dehydration	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Myalgia	No	Yes	Yes	Yes	No	Yes	Yes
Feeling fever	No	Yes	Yes	Yes	No	Yes	Yes
Chills	No	Yes	Yes	Yes	No	Yes	Yes
Headache	No	Yes	No	No	No	Yes	Yes
Chest pain	No	Yes	No	No	No	Yes	Yes
Treatment							
Symptomatic treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Antibiotic	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Antivirus	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Oxygen therapy	No	Yes	Yes	Yes	Yes	Yes	Yes
Intubation	No	No	No	Yes	No	Yes	Yes
Chest X-ray and CT-scan findings							
Bilateral or unilateral pneumonia	Unilateral right lung	Bilateral	Unilateral left lung	Bilateral	Unilateral right lung	Bilateral	Bilateral
Multiple mottling and GGO	No	No	No	Yes	No	Yes	Yes
Affected lobe	2	3	2	5	2	4	4
Clinical outcome	Discharged	Discharged	Discharged	Died	Discharged	Remained in hospital	Remained in hospital

Table 2: Laboratory values of all patients

White blood cell count (×10□ /L); (normal range 4–11)	8.7	3.3↓	12.7↑	6	7.1	7.7	6.9
Red blood cell count	3.13	3.76	4.4	4.15	4.89	5.53	4.77
Hemoglobin (g/dL)	9.1	10.7	11.3	11.9	14.9	14.7	13.8
Hematocrit (%)	29	31.7	36.9	35.3	43.2	44.6	44.6
Mean corpuscular volume (F.L)	92.7	84.3	83.9	85.1	88.3	80.7	93.5
Neutrophil count (%)	NA	NA	NA	NA	70	NA	NA
Lymphocyte count (%)	NA	NA	NA	NA	27	NA	NA
Platelet count (×10□ /L)	330	249	362	236	247	258	203
Erythrocyte sedimentation rate 1 h (mm/h)	NA	114↑	92↑	64↑	NA	NA	NA
Blood Sugar (mg/dL)	141 ↑	186	NA	109	438	162	349
BUN (mg/dL)	28↑	10	21↑	20	36↑	28↑	13
Creatinine (mg/dL)	1.3	0.9	1.2	1.3	1.2	1.1	0.9
eGFR (U/L)	40.85	≥60	44.72	≥60	≥60	≥60	≥60
Aspartate aminotransferase (U/L)	16	28	NA	NA	27	NA	42↑
Alanine aminotransferase (U/L)	18	30	NA	NA	30	NA	31
Alkaline phosphatase (U/L)	336↑	226	NA	NA	253	NA	177
Lactate dehydrogenase (U/L)	382	1048↑	1237↑	NA	952↑	NA	821↑
Creatine phosphokinase (U/L)	64	168	296↑	1788↑	271↑	193	NA
Creatine phosphokinase-MB (U/L)	21	39↑	NA	54↑	103↑	135↑	NA
Ca (mg/dL)	9.2	8.2↓	NA	NA	9	NA	8.5↓
Phosphorus (mg/dL)	4.4	2.0↓	NA	NA	3	NA	3.1
Na (mEq/L)	137	135	131↓	134↓	130↓	130↓	134↓
K (mEq/L)	4.2	3.7	3.7	4.7	4.3	5	4
C-reactive protein (mg/L)	3	Negative	Negative	Negative	Negative	Negative	1
Arterial blood gas							
PH	NA	NA	7.361	7.36	NA	NA	NA
Pco_2 (mmHg)	NA	NA	32.5	44	NA	NA	NA
Po_2 (mmHg)	NA	NA	50.2	20.4	NA	NA	NA
Hco_3 (mEq/L)	NA	NA	18	24.3	NA	NA	NA
O_2 Sat (%); (normal range 95–100)	NA	NA	82.8↓	29.9↓	NA	NA	NA
BE (mmol/L)	NA	NA	−6.2↓	−1.2	NA	NA	NA
BB (mmol/L)	NA	NA	41.7	46.7	NA	NA	NA

BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, BE: Base excess, BB: Buffer base.

approximately 69–92% in serum LDH level in patients with COVID 19 patients, which was consistent with our findings [2], [22]. But unlike to our study, in the Xu *et al*. study, LDH levels increased in 27% of patients [17].

According to the results of our study, the results of chest radiography and CT scan, in most patients showed bilateral pneumonia that was consistent with the results of studies by Liu *et al*., Chen *et al*., and Chang *et al.* [1], [26], [27]. In another study, almost all patients had bilateral pneumonia [3], which may be attributed to the deterioration of their patients’ conditions.

In our study, supportive treatments such as oxygen therapy, antibiotics, and antivirals medications were used for all patients. Antibiotic and antiviral medications such as ceftriaxone, meropenem, vancomycin, oseltamivir, and hydroxychloroquine were used for patients, if needed. The previous studies have also used these drugs [1], [26] However, it has been shown that despite using these medications, they were effective only in the treatment of SARS-CoV and MERS-CoV [28] and reported that there is no strong evidence for the effective drug treatment of COVID19 [26]. However, the majority of our patients received these medications with a positive response.

Conclusion

Patients with COVID-19 associated pneumonia can be treated by evaluating and implementing appropriate therapeutic management. However, at the moment the disease progression for patients with COVID-19 cannot be accurately predicted. Prompt diagnosis, effective treatment, and use of chest CT-scan are essential for appropriate management and surveillance for disease features.

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COVID-19 in Children: A Narrative Review

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Abstract

BACKGROUND: In December 2019, coronavirus (CoV) disease 2019 (COVID-19) was detected in Wuhan, China, which is known as severe acute respiratory syndrome CoV 2 (Severe acute respiratory syndrome [SARS]-CoV-2).

AIM: This study attempted a narrative review of the researches about COVID-19 in children.

METHODS: We searched all articles between 2000 and April 2020 in PubMed, Scopus, and ScienceDirect related to COVID-19 in children, using the following terms: "COVID-19," "coronavirus," "SARS-CoV-2" in combination with "pediatrics," or "children."

RESULTS: The most common method of transmitting the disease to children was through close contact with family members through respiratory droplets. Coinfection is common in pediatric with COVID-19 infection. One of the most important transmission routes is oral feces. The severity of the disease was mild or asymptomatic in most children. The most common clinical symptoms were fever and cough, and gastrointestinal symptoms were more common in children than in adults. Infants and preschoolers had more severe clinical symptoms than older children. The most common radiographic findings from the lungs were bilateral ground-glass opacity. Increased procalcitonin and lactate dehydrogenase should be considered in children. The use of intravenous immunoglobulin, lopinavir/ritonavir, and oseltamivir, along with oxygen therapy, had the greatest effect on improving children's conditions.

CONCLUSIONS: The most important way to prevent this disease in children is to follow the health tips of family members. Although the number of children with the disease is low, children are vulnerable to infection. Antiviral medications along with the use of muscle relaxants and oxygen therapy have a great impact on children's condition.

Introduction

Coronaviruses (CoV) were discovered in 1965 and continued to be studied until the mid-1980s. Corona's history of human viruses began in 1965 when Tyrrell and Bynoe discovered that they could pass a virus called B814. The virus was found in the human embryonic trachea that was obtained from the respiratory tract of an adult with a cold. In the late 1960s, Tyrrell, along with a team of virologists working on human and animal strains of many viruses, found that a group of viruses, including infectious bronchitis virus, mouse hepatitis virus, and transmissible gastroenteritis virus of swine, they are similar in morphology. This new group of viruses was called CoV (the crown because of the crown-like appearance on the surface) and was later formally accepted as the new genus of viruses [1]. CoVs are a large family of viruses and a subset of the coronaviridae belonging to the nidovirales order in the realm riboviria that range from the common cold virus to the more severe causes of diseases such as severe acute respiratory syndrome CoV (severe acute respiratory syndrome [SARS]), middle east respiratory syndrome (MERS), and CoV disease 2019 (COVID19). CoVs are a group of viruses that cause diseases in mammals and birds. In December 2019, COVID-19 was detected in Wuhan, China. It has a very high transmission capacity and is known as severe acute respiratory syndrome CoV 2 (SARS-CoV-2) [2], [3].

Search Strategy

This is a narrative review. According to its nature as "narrative," we did not graduate the articles, but we chose the most relevant contributions to the matter. This article is a narrative review study and an attempt to gather information on all aspects of COVID-19 in children. These aspects include virology and genetics, physiopathology, epidemiology, clinical manifestations, diagnosis, and treatment. The search was conducted using five keywords "COVID-19," "coronavirus," "SARS-CoV-2" in combination with "pediatrics," or "children" in PubMed, Scopus, and ScienceDirect among articles between 2000 and April 2020. We focused on publications post-year 2000, with emphasis on the past 10 years, but we did not exclude commonly referenced, relevant, and influential older publications. The clinical trial, case–control, review, and a meta-analysis study of 20 years; 2000–2020 articles, case series, cohort, and cross-sectional studies were reviewed. We also reviewed the references of each article to include further other studies or reports not identified by the search. We excluded articles considering the expert viewpoints and letters to the editor, which was only one article. A total of 85 articles were obtained that resulted in a decrease of 64 in the selection of English articles and articles on human research.

Virology

All viruses in the *Nidovirales* order are ribonucleic acid (RNA) viruses which are enveloped, non-segmented positive-sense RNA viruses. These viruses have very large genomes for RNA viruses, and Coronavirinae is the largest known RNA genome and contains approximately 30 kb genomes [2]. The genome of these viruses includes a 5’ cap structure with a 3’ poly (A) tail, authorizing it to act as messenger RNA (mRNA) to translate replicase polyproteins. The replicase gene that encodes nonstructural proteins, unlike structural and accessory proteins, which make up only about 10 kb of the viral genome, makes up two-thirds of the genome, about 20 kb [4]. The CoV is specified by club-like spikes from its surface [5]. Proteins that contribute to the overall structure of all CoVs are the spike (S), envelope (E), membrane (M), and nucleocapsid (N), all of which are encoded within the 3′ end of the viral genome. In the specific case of the SARS CoV, a defined receptor-binding domain on S mediates the attachment of the virus to its cellular receptor, angiotensin-converting enzyme 2 (ACE2) [6]. Some CoVs (specifically the members of beta-CoV subgroup A) also have a shorter spike-like protein called hemagglutinin esterase (HE) [7]. CoVs can be divided into four genera: Alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans [8]. So far seven types of CoV have been found in humans: HCoV-229E, human CoV OC43 (HCoV-OC43), HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV, and the SARS-CoV-2 or novel CoV (2019-nCoV) [9]. SARS-CoV-2 belongs to the CoV strain associated with severe acute respiratory syndrome (SARSr-CoV) and from the genus beta-CoV [10]. Recent studies have shown that SARS-CoV-2, known as a novel virus, can share 79.5% of its genetic sequence with SARS-CoV and 96.2% is homologous to bat CoV genome named RaTG13. Still, the synonymous mutation also results in increased T: C transition. This mutation may be due to the loss of RNA 3’-to-5’ exoribonuclease function. 2019-nCoV shares an ACE2-like entry cell receptor with SARS-CoV-2, which indicates that SARS-CoV-2 may be more infectious to humans than SARS-CoV [11], [12].

Physiopathology

Epithelial cells are the first cells of the human body to be infected by CoVs. *In vitro* studies show that CoVs spread from a particular part of these polar cells, and this polar spread may be important for the spread of infection *in vivo*. In epithelial cells, CoVs are located between the rough endoplasmic reticulum and the Golgi body. After the replication of viral particles with inverse genetic systems, viruses are transmitted to the plasma membrane through the secretory pathway and released by exocytosis [13]. As mentioned, CoVs can use a number of factors to promote pathogenesis. The CoV has four major structural proteins that are: Pike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. S glycoprotein is a Class I fusion protein that mediates binding to the host epithelial cell receptor. M protein enhances membrane curvature and attaches to the nucleocapsid and determines the shape of the virus. E protein facilitates virus assembly and release but has other functions such as ion channel activity in the SARS-CoV E protein for pathogenesis. N protein helps to bind the viral genome to the replicase-transcription complex and wraps the encapsulated genome into the viral particles. HE binds sialic acid to surface glycoproteins with its acetylesterase activity. These activities are thought to increase the entry of S protein into the cell and the virus to enter the mucosa [2], [14]. It is possible that SARS-CoV-2 is entered to host cells through the binding of spike glycoprotein to the enzyme two ACE2, sialic acid receptor, transmembrane 2 serine proteinase (TMPRSS2), and extracellular slow cell matrix metalloproteinase (CD147). This condition which causes endothelial dysfunction is exacerbated by hypoxia and causes thrombosis by increasing blood viscosity as well as the signaling pathway associated with the hypoxia transcription factor [15].

Epidemiology

On December 31, 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province, China. This virus was referred to as SARS-CoV-2 and the associated disease as COVID-19. As of January 5, 2020, 9692 cases were identified in China, of which 213 died. Most children with COVID-19 have a mild clinical presentation. Few may progress to the lower respiratory infections [16]. The incidence of this disease in patients under 18 is low (2.4% of total reported) [17]. Since the first report of COVID-19 cases from Wuhan to the end of February 2020, 87,137 people have been diagnosed with the disease [18]. The disease is highly contagious, with the pandemic reported in the 51st WHO Status Report on March 11, 2020 [19]. On April 3, the WHO announced that 972,303 people had contracted the disease and 50,321 had died from the disease [20]. In the first major report from China Centers for Disease Control and Prevention, which approved 44,672 COVID-19 cases, only one death occurred in people under 19 and about 80% of deaths in adults over 60 years of age [21]. The first report of United Stats results among patients with COVID-19 shows that 80% of deaths occur in adults over the age of 65, with the highest percentage of severe consequences among people aged 85 and no casualties observed in people under 19 [22]. In Italy, only 1.1% of reported primary deaths occurred in people <50 years of age, none of whom were children [23].

Current calculations show the incubation period of COVID-19 ranging from 1 to 14 days with an average of 5–6 days. However, some studies suggest that incubation may take up to 24 days, which is higher than the WHO statistics. The number of reproductions (R0) for SARS-CoV-2 is estimated by current studies between 2 and 3, indicating that the epidemic potential of this disease is higher than SARS with R0 = 0.8 and MERS with R0 = 0.69 [24], [25], [26]. Recent data suggest that COVID-19 has a mortality rate of between 2.3 and 3 [18], [27]. We need to be careful in calculating the case fatality rate of COVID-19 (currently at a global rate of up to 5%), authenticating that these rates will be lower after setting the denominator to reflect the exact number of individuals who acquired the infection [26].

Infection sources

The CoV reservoir is different for its variants. For SARS, cats were the reservoir of infection, for MERS camels, but COVID-19 is still unclear [11]. Given that human SARS-CoV-2 has a unique retinoic acid receptor recognize motif in S protein, the idea that human SARS-CoV-2 is directly from pangolins is partially rejected [28]. Some recent studies have suggested that pangolins and snakes are likely to host SARS-CoV-2 mediators [29], [30].

Transmission route

It is thought that CoVs are transmitted from person to person by sneezing and coughing through airborne droplets to the nasal mucosa [31], [32]. So far, no evidence has been found that COVID-19 is transmitted through the air. Still, it has shown that respiratory droplets containing the virus, which disperse on surfaces, may be responsible for transmitting the virus. These surfaces can be as small as the vents [33]. In a study by Seyedi *et al*., it was suggested that the virus might also be transmitted through the oral-fecal route [34]. Due to the presence of the virus in the feces, there is particular concern about the transmission of fecal-oral feces, especially for infants and children who are not trained in the toilet. Prolonged ejaculation of nasal and fecal secretions has important implications for community development in childcare centers, schools, and homes [35].

In Qiu *et al*.'s study, which conducted on 36 children infected with COVID-19, the transmission route was through close contact with family members (32 [89%]) and a history of exposure to the epidemic zone (12 [%33]). Eight cases (22%) both had exposure [36]. In a study by Chang *et al*., according to the data collected, most infected children (75%) had a home contact history [37]. In Xia *et al*. study, 13 patients in children (13.20%, 65%) had a history of close contact with family members with COVID-19. Given that most reports of the disease have been passed onto children through close contact at home with family members, it is recommended that family members, especially parents, follow the health tips. Coinfection (8/20, 40%) is common in pediatric with COVID-19 infection [38]. At present, there is no evidence of vertical transmission in infants born to mothers with COVID-19 [37], [39] but some previous reports have also shown that babies are infected in the first few hours after birth [40], [41], [42].

Clinical Characteristics

Clinical presentations

At present, COVID-19 is classified according to symptom severity into four levels: Mild, moderate, severe, and critical. Mild patients have mild symptoms, no symptoms, and no clear radiographic features. Patients with severe symptoms have one of three criteria: (1) Shortness of breath, respiratory rate (RR) >30 times per minute, (2) oxygen saturation <93% in ambient air, and (3) partial pressure of oxygen/fractional inspired oxygen <300 mmHg. Critically, ill patients have one of three criteria: (1) Respiratory failure, (2) septic shock, and (3) multiple organ failure [28]. Most children with COVID-19 infection are asymptomatic or have mild symptoms, no fever, or pneumonia [43], [44]. The range of manifestations described in 171 children (1 day–15 years) infected with SARS-CoV-2 treated at Wuhan Children's Hospital showed that the most common symptoms included cough (in 48.5% of cases), pharyngeal erythema (46.2%), and fever (41.5%). Less common symptoms were present in <10% of children: Diarrhea, fatigue, rhinorrhea, and nasal congestion. It was observed in 28.7% of children with tachypnea and in 2.2% of children with hypoxemia (oxygen saturation

<92% during hospitalization) [45]. In a study of 2214 children suspected of COVID-19, Dong *et al*., of which 731 children were diagnosed with the disease, 94 (12.9%), 315 (43.1%), and 300 (41%). They were placed in asymptomatic, mild, or moderate cases, respectively, accounting for 97% of the confirmed cases. The proportions of children classified as severe and critical were 2.5% and 0.6%, respectively, significantly lower than those observed in adults with COVID-19. The point of this study was that infants and preschoolers had more severe clinical symptoms than older children [46]. In a study by Chang *et al*., the severity of the disease was mostly mild to moderate (98%). Only two children (2%) received intensive care. Fever occurred in 59% of patients with cough in 46%. Gastrointestinal symptoms (12%) were not common. About 26% of children are asymptomatic [37]. In a study by Qiu *et al*., 19 (53%) infected children had a moderate clinical type with pneumonia; 17 (47%) had a mild clinical type, and either was asymptomatic (ten [28%]) or had acute upper respiratory symptoms (seven [19%]). Common symptoms on admission were fever (13 [36%]) and dry cough (seven [19%]). Of those with fever, four (11%) had a body temperature of 38·5°C or higher, and nine (25%) had a body temperature of 37.5–38.5°C [36]. Dong *et al*. study showed the intensity of illness by age, and it disclosed that young children, particularly infants, were vulnerable to 2019-nCoV infection. The content of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1%, and 3.0% for the age group of <1, 1–5, 6–10, 11–15, and ≥16 years, respectively [46]. In Ludvigsson’s study, studies have shown that children have so far accounted for 1–5% of COVID-19 cases, which are often milder than in adults, and that mortality is very rare among them. Diagnostic findings are similar to those of adults, and fever and respiratory symptoms are common, but fewer children appear to have severe pneumonia [39]. In Xia *et al*.’s study, fever (12/20, 60%) and cough (13/20, 65%) were the most common symptoms [38].

In another study, children with COVID-19 usually develop fever, fatigue, and cough at the onset of the disease, which may be companioned by nasal congestion, runny nose, expectoration, diarrhea, headache, and so on. Most children had low to moderate fever and no fever. Dyspnea of breath, cyanosis, and other symptoms was concomitant with systemic toxic symptoms, such as weakness or restlessness, malnutrition, poor appetite, and less activity after 1 week and may develop to respiratory failure. Septic shock, metabolic acidosis, and irreversible bleeding and coagulation dysfunction may occur in these severe cases. Characteristics and features of rapid RR for the diagnosis of pneumonia in children are 60 times per minute for <2 months; 50 times per minute for 2–12 months, 40 times per minute for 5 years, 30 times/min for >5 years (after dismissing the effects of fever and crying) [47]. According to recent reports, children usually have a good prognosis for the disease and improve after 1–2 weeks after the onset of mild symptoms. The reason for this can be attributed to the decrease in ACE2 expression in the lung with increasing age. ACE2 plays a role in lung-protective mechanisms [48], but it is not clear why children with COVID-19 have a milder condition. Adults may be more sensitive to conditions such as high blood pressure, diabetes, heart disease, or smoking, which can reduce their ability to prevent infections. Adults may also be more likely to develop an immune overdrive that leads to acute respiratory distress syndrome (ARDS). Mild or asymptomatic presentation in children may be effective in controlling the infection because it can be eliminated with existing monitoring.

Laboratory examination

Laboratory samples were taken from nasopharyngeal in children with COVID-19 demonstrated lymphopenia, leukopenia, and decreased hepatic and myoglobin enzymes in the first phase. Thrombocytopenia may occur [49]. It has been shown that lactate dehydrogenase and C-reactive protein (CRP) levels increase and decrease in children more than adults, respectively, especially in severe cases [44], [49]. Elevated erythrocyte sedimentation rate and CRP in the second phase, and increased dimerization and severe lymphopenia in children with severe symptoms can be seen. Procalcitonin (PCT) is normal in most cases (PCT<0.5) [16], [47]. In a study by Qiu *et al*., common abnormal laboratory findings in children were an increase in creatine kinase MB (11 [31%]), decreased lymphocytes (11 [31%]), leukopenia (seven [19%]), and elevated PCT (six [17%]). The variables that were significantly associated with COVID-19 intensity were decreased lymphocytes, elevated body temperature, and high levels of PCT, D-dimer, and creatine kinase MB [36]. In Ludvigsson’s study, high inflammatory markers were less common in children, and lymphocytopenia was rare. Newborn babies have developed COVID-19 [39]. In a study by Xia *et al*., it was suggested that laboratory findings in children should be noted for an increase in PCT (16/20, 80%), which is not common in adults [38].

Imaging features

Chest X-ray (CXR) can also be used to diagnose the disease. The most common findings for CXR were bilateral ground-glass opacities with or without consolidation in the lung periphery. In children with severe infection, there have been numerous lobar lesions in both lungs [16]. In a study by Li *et al*., it was reported that children had similar but fewer pulmonary abnormalities in computed tomography (CT) than adults [50]. In a study by Lu *et al*., the most common radiological finding was bilateral ground-glass opacity, which was observed in one-third of cases [45]. In another study, the most common radiographic findings were ground-glass opacities (48%) [37]. In the study by Xia *et al*. had a total of sxi patients with unilateral lung lesions (6/20, 30%), ten people with bilateral lung lesions (10/20, 50%), and four cases with no chest CT abnormality (4/20, 20%). Consolidation with surrounding halo sign was observed in ten patients (10/20, 50%), ground-glass opacities were observed in 12 patients (12/20, 60%), fine mesh shadow was observed in four patients (4/20, 20%), and tiny nodules were observed in three patients (3/20, 15%) [38].

Diagnosis

For those who are suspected of having COVID-19 disease, we must review the epidemiological and clinical criteria. Epidemiological criteria are based on the presence of the person in the areas infected with the virus and clinical criteria are based on clinical symptoms, laboratory findings, and radiography [47]. To diagnose COVID-19 infection in infants, all of the following criteria must be met: (1) At least one of the clinical symptoms, including unstable body temperature, low activity or poor nutrition, or dyspnea, (2) visualization of abnormality in chest radiography including bilateral ground-glass opacities, (3) diagnosis of infection in the patient's family or companions, and (4) close contact with people who may have or definitively have the disease, patients with pneumonia without any specific cause or close contact with wild animals [41]. Types of samples include upper airway specimens (pharynx, nasal swabs, and nasopharyngeal secretions), inferior airway specimens (sputum, air ducts, and bronchoalveolar lavage fluid), blood, stool, urine, and conjunctival secretions. Sputum and other lower respiratory tract specimens are highly positive for nucleic acids and should preferably be collected from them. Combined testing with respiratory, fecal, blood, and other specimens is useful to improve the diagnostic sensitivity of suspected cases, monitor the effectiveness of treatment, and manage post-discharge isolation measures [35]. Gene sequencing is one way to survey and diagnose COVID-19. RT-PCR, based on the S and N genes, is now used to detect viral RNA and is known as the gold standard [10], [28], [51], [52].

Treatment

There is no specific antiviral treatment recommended for children with COVID-19, but general treatment strategies for children include bed rest and supportive therapies. Affected children should get enough calories and water. Preservation of water and electrolytes, homeostasis, and strengthening of psychotherapy in older children should be performed if necessary [43], [39]. In one study of serine protease TMPRSS2, which is required for protein S priming, it was suggested that camostat mesylate as a protease serase inhibitor could prevent COVID-19 from entering the lung cell [53]. Children with COVID-19 who breathe through a ventilator often need sedatives, painkillers, and even muscle relaxants to prevent lung damage caused by the ventilator. Note that, antibiotics and corticosteroids should be avoided except in some cases. Corticosteroids can be used in limited cases, such as the occurrence of ARDS on CXR, septic shock, encephalopathy, and hemophagocytic syndrome. Some studies recommended drug and dose is intravenous methylprednisolone (1–2 mg/kg/day) for only 3–5 days [16], [47]. In the study of Shen ibuprofen was used orally at a dose of 5–10 mg/kg and acetaminophen orally at a dose of 10–15 mg/kg [16]. In Ludvigsson's study, the proposed treatment included oxygen supply, inhalation, nutritional support, and fluid retention, and electrolyte balance [39].

Therapeutics and drugs

Antiviral therapy

Numerous studies have been conducted on drugs that affect the treatment of COVID-19 in children, but so far, no antiviral drug has led to definitive treatment. In a study by Chen *et al*. as well as Shen and Yang study, some effective antiviral drugs to improve the condition of children with the disease include interferon-α2b nebulization 100,000–200,000 IU/kg for mild cases, and 200,000–400,000 IU/kg for severe cases, 2 times/day for 5–7 days [16], [47]. Lopinavir/ritonavir (200 mg/50 mg), the recommended doses: Weight 7–15 kg, 12 mg/3 mg/kg; weight 15–40 kg, 10 mg/2.5 mg/kg; and weight >40 kg, 400 mg/100 mg as an adult each time, twice a day for 1–2 weeks [47], [54]. In Wang *et al*. study, food and drug administration-approved antiviral drugs *in vitro*, especially remdesivir and chloroquine, have been effective in controlling COVID-19 infection *in vitro* [55]. In Tang *et al*. study, medicines for treating infected children include oseltamivir, ribavirin, interferon, Kaletra, and traditional Chinese medicine [56]. In the study by See *et al*., none of the children needed antiviral therapy [57]. In the study of Liu *et al*., in six children, ribavirin was used in two patients and oseltamivir in six children [44]. In a study of nine children by Rahimzadeh *et al*., oseltamivir, lopinavir, and ritonavir were used for treatment, with the role of oseltamivir being very pronounced. However, there was no use of ribavirin [17]. In the study of Shen *et al*., arbidol and oseltamivir were used [16]. In Qiu *et al*. study, all children received interferon alpha twice daily by aerosolization and 14 (39%) infected children received twice daily lopinavir-ritonavir syrup [36]. In another study, double-stranded RNA activated caspase oligomerizer (DRACO) and immucillin-A, which inhibit RNA synthesis, have been suggested as antiviral drugs for the treatment of this disease (Table 1) [49].

Antibody therapy

Intravenous immunoglobulin can be used in severe cases, but the effect should be further investigated. The recommended dose is 1.0 g/kg for 2 days or 400 mg/kg for 5 days [14], [16], [17], [44], [56]. It has been shown that monoclonal antibodies (from human brain plasma, animal, or manufactured plasma) affect glycoprotein S, inhibiting the penetration of CoVs into human cells and reducing mortality in patients infected with SARS-CoV-2 (Table 1) [58].

Antibacterial therapy

In Rahimzadeh *et al*. study, meropenem, vancomycin, and chloroquine were used as an antibacterial therapy [17]. In the Lu *et al*. study, the combination of sirolimus plus dactinomycin in pediatric treatment has been suggested [40]. In a study by Zimmermann and Curtis, it was noted that the use of chloroquine *in vitro* is effective against SARS-CoV-2, but further studies have been recommended *in vivo* (Table 1) [58].

Other drugs

In Lu *et al*. study, two-drug combinations (mercaptopurine plus melatonin, and toremifene plus emodin) are the drugs suggested for pediatric treatment [40]. Scutellariae Radix, Armeniacae Semen and Coicis Semen have been suggested in a study examining herbal medicines used to treat COVID-19 in children (Table 1) [59].

Oxygen therapy

In hypoxia in children, an oxygen mask or nasal catheter should be used immediately to adjust the oxygen concentration. In many studies, using oxygen therapy or mechanical ventilators have been effective in improving patients' well-being [16], [17], [36], [44], [47]. In Lu *et al*. study, infants with ARDS, high-dose pulmonary surfactant, inhaled nitric oxide, high-frequency oscillatory ventilation, and extracorporeal membrane lung may be highly recommended (Table 1) [40].

Plasma therapy

Studies that show that serums from COVID-19 improved patients may be useful for the treatment of COVID-19 infection [40].

Conclusions

The current prevalence of COVID-19 is widespread in the world and the WHO has identified it as one of the public health concerns. The disease is highly contagious because most children with COVID-19 have close contact with family members, including their parents, increasing public health information and following these tips can have a significant impact on reducing children's susceptibility to the disease. Although the number of children with the disease is low, children are vulnerable to infection. Antiviral medications for the treatment of children Along with the use of pain relievers, muscle relaxants, and oxygen therapy have a great impact on children's condition. The role of serum therapy should also be taken seriously in future COVID-19 treatment.

Table 1: Different types of treatments of children with COVID-19 according to various studies

Studies	Treatments					
	Antibacterial therapy	Antiviral therapy	Antibody therapy	Oxygen therapy	Plasma therapy	Other medications
Shen *et al*. [16]	No	Arbidol, oseltamivir, interferon-α nebulization, interferon-α2b nebulization	Yes (Intravenous immunoglobulin)	Yes	No	Ibuprofen, acetaminophen, intravenous methylprednisolone
Rahimzadeh *et al*. [17]	Meropenem, vancomycin, chloroquine	Lopinavir, oseltamivir, ritonavir	No	Yes	No	No
Liu *et al*. [44]	Yes	Ribavirin, oseltamivir	Yes (Intravenous immunoglobulin)	Yes	No	Glucocorticoids
Chen *et al*. [47]	No	Interferon-α2b nebulization, lopinavir/ritonavir	Yes (Intravenous immunoglobulin)	Yes	No	Intravenous methylprednisolone
Zimmermann and Curtis [49]	Chloroquine	Lopinavir/ritonavir, DRACO, and immucillin-A	Yes (Intravenous immunoglobulin)	Yes	Yes	No
Tang *et al*. [56]	No	Ribavirin, oseltamivir, interferon-α2b nebulization, lopinavir/ritonavir	No	No	No	Traditional Chinese medicines
Lu and Shi [40]	Combination of sirolimus and dactinomycin	No	Yes	Yes	Yes	Mercaptopurine plus melatonin, toremifene plus emodin, and inhaled nitric oxide
Qiu *et al*. [36]	No	Interferon alpha twice daily by aerosolization and twice-daily lopinavir-ritonavir syrup	No	Yes	No	No
Ang *et al*. [59]	No	No	No	No	No	Scutellariae Radix, Armeniacae Semen and Coicis Semen

COVID-2019: Coronavirus disease 2019.

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Author's contributions

AR analyzed the data and were a major contributor in writing the manuscript. HJ and LS searched and collected data. LD and AR designed the review and were responsible for communicating the work. All authors read and approved the final manuscript.

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Do we Trust the Polymerase Chain Reaction Test Result in Children to Diagnose COVID-19? A Case Report of COVID-19

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Abstract

BACKGROUND: Coronavirus disease-19 (COVID-19) resulted in widespread concern in global public health and has a bad prognosis despite drug therapy.

CASE REPORT: The patient was an 11-year-old girl referred to a children hospital with a dry cough, fever, and headache symptoms, without comorbidity. She was hospitalized following the results of high-resolution computed tomography (HRCT). The patient was treated with ceftriaxone 1 g every 12 h and the oseltamivir capsule 45 mg every 12 h and azithromycin 250 mg tablet once daily and 200 mg hydroxychloroquine tablet every 12 h for a total of 5 days. After 5 days, the patient had suitable chest status and then was discharged. Azithromycin for 5 days and hydroxychloroquine for 10 days were prescribed for the patient to take at home. The patient's polymerase chain reaction (PCR) was negative at baseline through the nasopharyngeal swap, but HRCT of the patient's was completely consistent with COVID-19 accompanied by consolidation and ground-glass opacity in the left lower and right upper lobes.

CONCLUSION: The numerous technical errors in taking the nasopharyngeal swap were the main reasons for the negative PCR. The main lesson from this case report is the high sensitivity and specificity of HRCT compared to the PCR.

Introduction

Coronavirus disease-19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV2) and is a causative agent of a potentially fatal disease that has caused widespread concern in the global public health. Coronavirus is one of the largest pathogens that mainly target the human respiratory tract, which has a bad prognosis despite drug therapy [1], [2].

Moreover, SARS-COV2 results in multi-organ failure, such as renal and liver failure [3], [4]. Regarding prevalence, these patients were associated with a wholesale market for seafood and wet animals in Wuhan, Hubei Province, China [5], [6]. Preliminary reports predicted the launch of a potential coronavirus epidemic with a basic *reproduction* number (*R0)* varying from 2.24 to 3.58 [7]. A study by Wang *et al*. showed that the ratio of male-to-female mortality was 3.25 to 1, the median age of death was 75 years, the median time from the first symptoms to death was 14 days, and the median time from the initial symptoms to death above 70 years was shorter (11.5 days) than in people under 70 years of age (20 days). These findings suggest that the disease may progress more rapidly in adults than in young people [8].

Li *et al*. reported the mean age of 59 years for coronavirus-positive patients, of which 56% were men, the mean incubation period was 2.5 days, and almost half of the adult patients were 60 years and older [9]. The treatment of coronavirus in most cases is unnecessary because most patients have mild or moderate symptoms. However, it may be necessary to identify an etiological factor in epidemiological studies, especially during epidemic outbreaks. Since the novel coronavirus-2019 has not been found in humans before, no specific vaccine or treatment has been provided. In the current state of emergency, the number of cases is rapidly increasing. Therefore, it is important to diagnose all suspected cases as soon as possible and to remove them quickly to cutoff the source of the infection. New diagnostic solutions, including reverse transcription PCR and microscopic-based measurements, may be effective in monitoring epidemiological measures, along with preventive measures [10]. Coronavirus Novin-2019 nucleic acids can be detected in samples such as nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, and feces [11], [12]. Therefore, we present a case report of different radiologic findings apart from PCR results.

Case Presentation

The patient was an 11-year-old girl referred to a children hospital with a dry cough, fever, and headache symptoms, without comorbidity, and with a history of adenoidectomy and ventilation tube implantation in both ears 9 months ago. She was hospitalized following the results of high-resolution computed tomography (HRCT) and imaging due to the aggravation of coughs. At the time of admission, height, weight, Spo_2, respiratory rate, heart rate, and axillary temperature were 145 cm, 24 kg, 97% (on room air), 17 breaths/min, 97 beats/min, and 38.5°C, respectively. Laboratory results were as following:

C-reaction protein = +1, white blood cell (WBC): 5200/mm^3, lymph: 17%, neut: 75%, platelet) = 216,000, hemoglobin: 12.5 mg/dl, aspartate aminotransferase (*AST*) = 30 Iu/l, alanine transaminase (*ALT*) = 35 IU/l, alkaline *phosphatase* = 135 IU/l, prothrombin time = 13 s, partial thromboplastin time = 45 s, international normalized ratio = 1.1, serum calcium (Ca) = 8.8 mg/dl, 25 (oH) Vitamin D level = 52 ng/ml, blood urea nitrogen = 8 mg/dl, creatinine (Cr) = 0.6 mg/dl, erythrocyte sedimentation rate = 30 mm/hand, and lactate dehydrogenase = 461 IU/L.

The patient was treated with ceftriaxone 1 g every 12 h and the oseltamivir capsule 45 mg every 12 h and azithromycin 250 mg tablet once daily and 200 mg hydroxychloroquine tablet every 12 h for a total of 5 days. After 5 days, the patient had suitable chest status and then was discharged. Azithromycin for 5 days and hydroxychloroquine for 10 days were prescribed for the patient to take at home.

The patient's PCR was negative at baseline through the nasopharyngeal swap. HRCT of the patient's, which was reported by two radiologists, was completely consistent with COVID-19.

In Iran, there is no kit to detect coronavirus antibodies (IgM and IgG). The patient had previously been visited by an otorhinolaryngologist and had no upper airway problems and most of the symptoms were in the lower airway.

Due to the absence of respiratory distress and Spo_2 above 94%, blood gas was not taken from the patient. Due to the good general condition, the PCR test was not taken after discharge and was quarantined for only 2 weeks. Due to a large number of false negatives in the nasopharyngeal swab sample and the failure to obtain the correct sample or CT scan based on COVID19, which was reported by two radiologists, the PCR test and CT were not performed again.

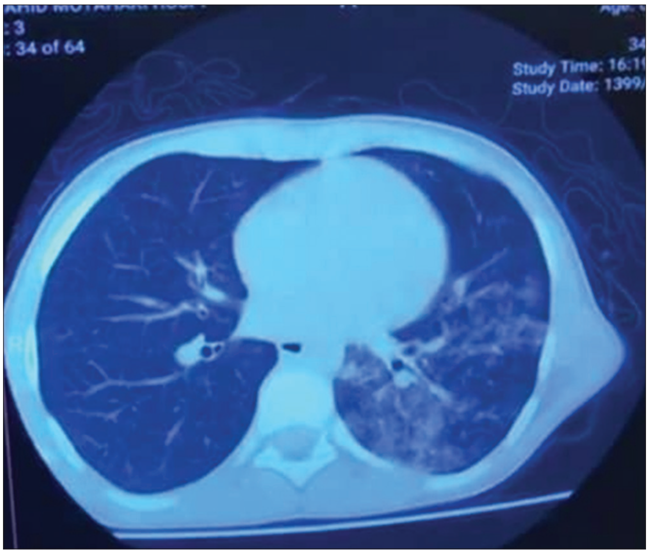

Figure 1: Consolidation and ground-glass opacity in the left lower lobe in high-resolution computed tomography

Figure 1 represents a consolidation and ground-glass opacity (GGO) in the left lower lobe. Figure 2 represents consolidation and GGO in the right upper lobe. Figure 3 shows no significant findings in the chest-X ray.

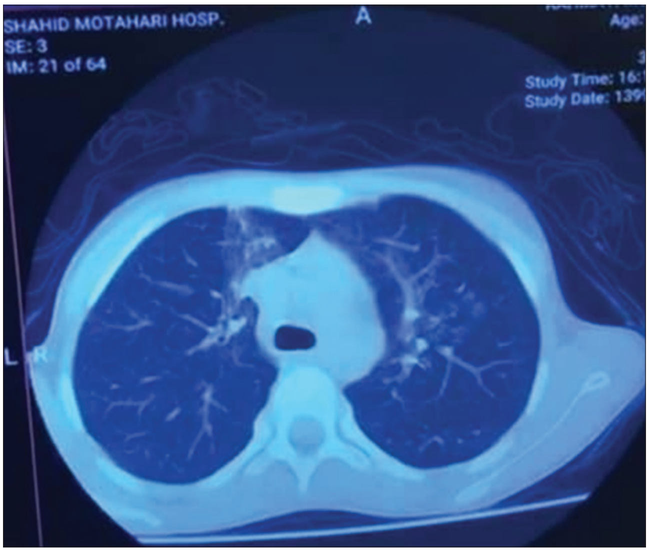

Figure 2: Consolidation and ground-glass opacity in the right upper lobe in high-resolution computed tomography

Discussion

Guan *et al.* reported 1099 cases of the novel 2019 coronavirus infection. They found that fever (78.9%) and cough (67.7%) were the most common symptoms. Abnormalities in CT images of the chest were observed in 96% of patients infected with the novel coronavirus-2019,

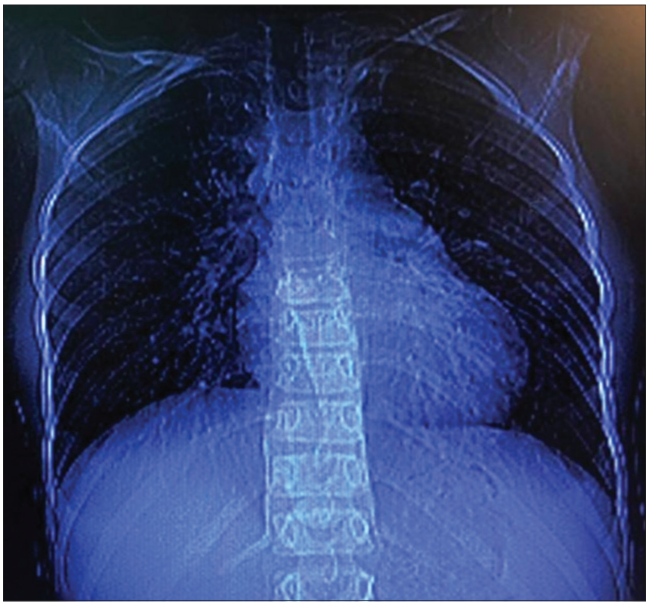

Figure 3: Normal chest-X ray of the patient

and lymphocytopenia was recorded in 82.1% of them [9]. Our case was the same indicating that dry cough and fever can be common in the children too. WBC of 5200/mm^3, lymph of 17%, and neut of 75% showed lymphocytopenia of our case. In some studies, it has been reported that chest X-rays do not have enough sensitivity and specificity; thus, CT scans should be done like our case [13], [14], [15]. In the present case, chest X-ray was normal and could not detect COVID-19; then, we had no choice to check the CT scan of the patients. In the assessment of HRCT, we found that the lung had consolidation and GGO in the right upper and left lower lobes. In spite of the negative result of PCR, the radiologic findings approved COVID-19. Therefore, clinicians should check CT to approve the definite diagnosis of COVID-19. Hence, the majority of patients infected with the novel coronavirus-2019 can be diagnosed by CT. The fact that "children are not very susceptible" may jeopardize their health. Children should be prevented to have a close contact with the epidemic area and people [16], [17].

Huang *et al*. found that 98% of patients with COVID-19 had a fever. They reported that 76% of patients had a cough with dyspnea. Furthermore, a small number of patients had expectoration sputum. Laboratory tests showed that 25% of infected patients had leukopenia and 64% had lymphocytopenia. AST levels were elevated in 37% of patients. Abnormalities in chest CT images were observed in 100% of patients. GGO and consolidation areas were found in 37% of the lungs on both sides of infected patients [18]. The findings of CT of the present case were consistent with the study of Huang *et al*. In the present case, liver function tests were normal (*AST*=30 Iu/l, *ALT*= 35IU/l, and ALO=135 IU/l), in such a way that was inconsistent with the study by Huang *et al*. [18].

Conclusion

The number and severity of pulmonary involvement in children are lower than adults based on Chinese and the previous articles. In our case, the severity of the symptoms was mild, and the numerous technical errors in taking the nasopharyngeal swap were the main reasons for the negative PCR, but HRCT apparently showed COVID-19. The main lesson from this case report is the high sensitivity and specificity of HRCT compared to the PCR.

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General Anxiety Disorder-Related Coronavirus Disease-19 Outbreak in Indonesia: A Case Report

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Abstract

BACKGROUND: The outbreak of coronavirus disease-19 (COVID-19) which is now a pandemic has become a problem that occurs in every area of life. Coronaphobia, a new term in the psychiatry literature referring to excessive fear of being infected by SARS-COV2 or COVID 19. Infected by influenza, having close relatives or friends with this fatal virus, and strong fear of infection have been reported as important predictors of stress posttrauma. We report a case report-related COVID-19 in Indonesia.

CASE PRESENTATION: A 23-year-old female, dentistry student living in a boarding house in East Java, Indonesia, along with her friend and coming from a middle-up income family background, came to psychiatric consultation with complaints of difficulty of breathing for 1 month ago. This anxiety began to get heavy, especially since the severe acute respiratory syndrome coronavirus 2 (COVID 19) outbreak appeared in Indonesia. In addition, she also recently experienced a failure in her final examination so that her study period as a dentistry student must be extended. Exploration of history revealed that the patient initially experience a feeling of heaviness in the chest, difficulty breathing, palpitation, and sometimes feeling sad due to her failure before. She was then given pharmacological interventions in the form of fluoxetine and clobazam and psychotherapy and progressive muscular relaxation through online.

CONCLUSION: General anxiety disorder, especially due to the COVID-19 outbreak, should be managed appropriately and comprehensively. The pandemic situation and widespread spread of the disease cause psychotherapy to be modified in such a way that assistance can be carried out online.

Background

Since December 2019, the world was shocked by a new outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) or better known as coronavirus disease-19 (COVID-19). This virus is feared due to the symptoms that are quite heavy on immunocompromised individuals and very massive spread [1], [2]. The prevention efforts in the form of social distancing, maintaining cleanliness of the body and hands repeatedly, and government-supported policies in the form of "stay at home, work from home, and school from home," make very significant changes in all areas of human life. People who are accustomed to directly socializing (physically) become distant for fear of spreading the virus through physical contact. This turned out to cause a stressful situation for some people, especially people who had previously experienced anxiety disorders. We report cases of general anxiety disorder-related to the COVID-19 outbreak in Indonesia.

Case Presentation

Miss A, a 23-year-old female, 1st in birth order, a dentistry student living in a boarding house in East Java, Indonesia, along with her friend and coming from a middle-up income family background, came to psychiatric consultation with complaints of difficulty of breathing for 1 month ago. The patient claimed to experience anxiety so severe that she was unable to move as usual. This anxiety began to get worsen, especially since the SARS CoV-2 (COVID 19) outbreak appeared in Indonesia. In addition, she also recently experienced a failure in her final examination so that her study period as a dentistry student must be extended. Exploration of history revealed that the patient initially experience a feeling of heaviness in the chest, difficulty breathing, palpitation, and sometimes feeling sad due to her failure before. All of these complaints were felt by the patient, especially when they heard that there was a COVID 19 patient who died or there were new patients who were confirmed to be positive. Examination of the cardiovascular and respiratory system shows that the organ is functioning properly, and there are no abnormalities.

Due to the disturbance experienced by the patient, she was unable to do daily activities. The government's call for citizens to remain at home during the outbreak makes patients more stressed because she cannot go home to meet their parents.

On further psychiatric examination, there were afraid of death preoccupation, fears of contracting SARS-CoV2 (COVID-19), and preoccupation with thoughts that disappointed her parents. At this time, she also began to experience symptoms of depression in the form of pervasive sadness, feelings of anhedonia, despair, and low self-esteem and felt himself useless and disappointing. There is no history of suicidal ideation, delusions, or hallucinations. There is no specific fear of a particular object.

Family history shows a dysfunctional family, where her father is authoritarian, while the mother treats the patient permissively. She also said and she had seen her father threatening her mother abusively and often angry excessively in front of her children. However, no history of physical trauma or sexual abuse was found during development.

On the mental status examination, the patient was alert and oriented, with a preoccupation with the fear of contracted an illness and was afraid of disappointing his parents. There are symptoms of moderate depression that accompany patient complaints. Insight was preserved, for example, she was sure that her fear was irrational, illogical, and caused by psychological disorders, and the patient agreed to be treated. A diagnosis of general anxiety disorder was considered. She was started on fluoxetine 20 mg/day and clobazam 5 mg/day. Personality assessment using Millon Clinical Multiaxial Inventory IV shows that the dominant patient's personality is narcissistic, histrionic, and turbulent type, which is accompanied by clinical depression, anxiety, tension, insomnia, and fatigue that have no apparent cause. The graphic test with a house tree person shows that the patient experienced extreme anxiety and had past psychological trauma. The degree of patient anxiety measured by the Hamilton Anxiety Rating Scale (HARS) is 26 (severe anxiety).

Patients agreed to undergo psychotherapy in the form of cognitive-behavioral therapy through teleconference plus a gradual exercise of muscle progression relaxation. Patients are asked to identify situations that make patients anxious and give a rating on what situations; most patients feel anxious. Patients are also asked to keep a daily journal, and notes in the journal will be discussed with the psychiatrist. Patients are also asked to reduce exposure to news about COVID-19 and reduce the intensity of using social media such as Instagram, WhatsApp, and others.

After six sessions of psychotherapy online and progressive muscular relaxation exercises, the patient's anxiety begins to decrease (HARS 13). Patients began to like a new hobby in the form of aerobic exercise as a substitute for their internet browsing habits and social media. The patient claimed to be more passionate about living life and ready to complete her education as a dentist.

Discussion

The SARS-COV2 or COVID-19 pandemic is increasing the attention of specialists around the world, including psychiatrists. In this pandemic outbreak, it is estimated that there will be an increase in mental health disorders during and after the pandemic.

Individuals who previously have personality disorders or psychiatric disorders will be prone to experience exacerbations or worsening in symptoms during a pandemic. Studies show generalized anxiety disorder that may be caused by genetic and non-genetic factors. This non-genetic factor, in the form of stressful events faced by patients, is thought to trigger anxiety symptoms in patients. Several neurotransmitter systems, including norepinephrine, GABAergic, and the serotonergic system in the frontal lobe and limbic system, are thought to play a role in mediating this disorder [3], [4].

The main psychological burdens such as anxiety [5], generalized anxiety disorder, and panic attack can worsen shortness of breath; aggressive behavior which results in patient disobedience and anxiety of medical personnel and obsessive behavior that can cause people, including medical personnel dysfunction, depression, and sleep disorders which are common psychological reactions. Coronaphobia, a new term in the psychiatry literature referring to excessive fear of being infected by SARS-COV2 or COVID 19 [6]. Being Infected by influenza, having close relatives or friends with this fatal virus, and strong fear of infection have been reported as important predictors of stress posttrauma [7], [8].

In this case, a pharmacological intervention was carried out in the form of a selective serotonin reuptake inhibitor agent, fluoxetine, and benzodiazepines (clobazam) to reduce the somatic symptoms experienced by the patient. After the anxiety symptoms decrease, psychotherapy intervention in the form of cognitive behavior therapy and online progressive muscular relaxation training assistance was started, and continued to give transfer of stimulus in the form of reducing exposure to COVID 19 news on electronic media and social media. And given the transfer of stimulus in the form of reducing exposure to COVID-19 news on electronic media and social media. This has been proven to reduce symptoms of anxiety and depression gradually in patients. This is in line with a review of published research that has shown that telepsychiatry is an efficient intervention in emergency settings [8], [9], [10], [11]. However, obstacles such as the use of the internet and adequate collaboration must be overcome [12], [13], [14]. In a situation like the current coronavirus pandemic which prohibits people from gathering, this is a very important issue in preventing COVID-19 spreading.

Conclusion

General anxiety disorder, especially due to the COVID-19 outbreak, should be managed appropriately and comprehensively. The pandemic situation and widespread spread of the disease cause psychotherapy to be modified in such a way that assistance can be carried out online.

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Coronavirus Disease-19 and Cardiovascular Disease

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Abstract

We are facing serious coronavirus disease-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2. Among infected individuals, there is a higher prevalence of the cardiovascular disease, which leads to their poor prognosis. Myocardial injury is present in more than 15% of critical ill patients in the form of acute myocardial dysfunction or subsequent myocardial injury that develops as disease severity. This new virus pandemic is a global challenge for health-care system which was we still have much to learn.

Introduction

The coronavirus disease 19 (COVID-19) pandemic has opened up several serious challenges to the world. It changed our lives in several ways. The pandemic has put enormous pressure on health-care systems worldwide. Changes in the medical system with unchanged and insufficient financial and medical resources were unexpected. Hospitals in China, Italy, Spain, and now the United States as the most affected countries have faced huge numbers of critically ill patients with COVID-19, which leads to the reduction of hospital resources, infection of medical personnel, and shortages of vital resources especially in intensive care units [1]. The experiences and numbers coming from those regions have put developing countries in the position of serious alerts and even more fear of the final health and economic impact of the COVID-19 pandemic. There are many unknown puzzles the virus imposes to us as medical professionals. Each day we are gaining new information's concerning the clinical expressions and course of the disease that significantly influence the actual therapy we use. Most data we have come from China, Italy, France, and recently the USA and management is guided by the expert opinion. We do not have randomized studies due to recent infection or control groups of patients due to ethical reasons. We learn every day on the virus that forces us to change our health and social directions.

Methods

The investigators review and summarize the latest and evolving scientific data regarding evidence linking COVID-19 with increased cardiovascular morbidity and mortality. The authors conducted a search of the relevant articles from various databases, namely, PubMed and SCOPUS science, direct for the latest published papers. We also search for expert opinions important for the review paper.

Global burden of COVID-19 pandemic

COVID-19 is now a global pandemic. Outbreak of pneumonia caused by a new coronavirus occurred in Wuhan in December 2019 and has rapidly spread throughout China and the rest of the world [2], [3]. After virus identification and isolation, the pathogen for this pneumonia was originally called 2019 novel coronavirus (2019-nCoV) but has been officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO). On January 30, 2020, the WHO declared the outbreak of SARS-CoV-2. On February 11, 2020, the WHO announces "COVID-19" as the name of new disease [3], [4]. Before December 2019, the virus was unknown to science. As of April 12, 2020, there were more than 1.846.983 cases worldwide, with nearly 113.885 case-fatalities in a total of 210 countries. Although COVID-19 predominantly affects lung function, it affects the cardiovascular system on multiple levels, increasing morbidity in patients with underlying cardiovascular disease (CVD) and provoking myocardial injury and dysfunction [5]. Patients with established heart disease constitute a particularly challenging group, as many of them have conditions that may be life-threatening if intervention is inadequately delayed. Even with the treatment evidence we have today, those patients have increased risk for complications and unfavorable disease courses.

COVID-19 case fatality rate (CFR, number of deaths/numbers of those diagnosed) is significantly different around the world. The original reports from China are referring a CFR of 2.3% with lower symptomatic case fatality risk of 1.4%, which is much different from influenza (0.1%), Middle East respiratory syndrome (34%), and SARS (10%) [6]. Based on reported data from April 12, 2020, the global number of COVID-19 cases is 1.846.983, with 113.885 deaths and 421.898 patients recovered. The CFR varies significantly by country: China reported 4.4% death rate (82,052 cases), Italy 8.5% (156,363 cases), Spain 8.9% (116,127 cases), Germany 6.9% (127,57 cases), and the United States 30% (557,217 cases) [7]. The CFR rises rapidly with increasing age. The CFR is <1% for individuals under 50 years of age, rising to 3.6% for 60 years old and up to 14.8% for octogenarians. In addition, the CFR increases with disease severity, with CFR of around 50% among critical patients. Patients with several comorbidities have significantly increased CFR: 10.5% for CVD; 7.3% for diabetes mellitus; 6.3% for chronic obstructive pulmonary disease; 6% for hypertension; and 5.6% for patients with cancer [8]. The mortality numbers have region and time differences and are influenced by the volume of testing, the quality of healthcare system, disease treatment, time since initial outbreak, and population characteristics such as age, sex, and population health (Figure 1).

COVID-19 in humans: Virus spread, signs, and symptoms

The novel COVID-19 virus is a singe-stranded enveloped RNA virus, the seventh so far known human coronavirus (Figure 2). It is assumed to have originated from bats, then moved from bats to an intermediate host and then to humans [9]. Coronaviruses have capacity for rapid mutation and recombination.

COVID-19 is spreading mostly through respiratory droplets but also can be aerosolized or detected in the stool. There is a high viral load in both symptomatic and asymptomatic patients, meaning the asymptomatic spread between person to person is likely, with secondary infection rates ranging up to 5%. The incubation period is believed to be between 2 and 14 days and up to 98% of individuals will experience symptoms within 11.5 days of exposure [10]. The virus has been demonstrated to remain stable for up to 3 h in the aerosolized form, up to 24 h on cardboard and up to 72 h on plastic or stainless steel. Compared with an outbreak of SARS in 2003, caused by the SARS-CoV, COVID-19 has a stronger transmission capacity [11].

What we currently know is that COVID-19 shows a wide range of manifestations and severity of the disease. Infection usually causes mild upper respiratory infections in younger individuals but may lead to hospitalization in elderly patients with underlying cardiac and lung disease. Initially predominantly affecting older individuals, now we are increasingly facing the spread of the disease among the younger population, with often unpredictable course of the disease, assumed to be caused by the individual immune response to the virus. The most common symptoms are fever (88%) and dry cough (67.7%), as in many other viral syndromes. Rhinorrhea (4.8%) and gastrointestinal symptoms (diarrhea 4–14%, nausea/emesis 5%) appear to be less frequent with COVID-19. In addition, reported symptoms are loss of smell and taste [12].

Reports we have from China shows that a significant majority of patients (81%) had mild symptoms (no pneumonia or mild pneumonia). Among those with more significant symptoms, 14% experienced severe symptoms and 5% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction) [12].

COVID-19 and cardiovascular system

Published data about disease manifestation and progression showed that patients with underlying CVD are among the highest risk individuals for severe disease and death. In a series of 44 672 confirmed patients with COVID-19 from China, 14.2% were reported to have CVD [13]. About 22.7% of all deaths were in patients with underlying CVD [13].

It is even of a greater concern that COVID-19 can cause cardiac injury in patients without underlying heart condition. Understanding the damage caused by COVID-19 to the cardiovascular system and the underlying mechanisms is of the greatest importance. This will allow timely and effective treatment of patients, meaning reduction of mortality.

A place of attachment of COVID-19 is believed to be angiotensin converting-enzyme 2 (ACE-2), a membrane-linked aminopeptidase and receptor through which the virus can potentially attach to the epithelial cells in the lungs, or to the myocardial cells and mediate tissue injury [14]. The expression level of ACE-2 is probably higher in diabetic and hypertensive individuals, which makes them prone to the infection with COVID-19.

Cardiac injury – elevated cardiac troponin

The data from published studies showed that patients with myocardial injury (elevated cardiac troponin) have higher hospital mortality, up to 3 times [15]. About 50% of fatal cases have increased high-sensitivity cardiac troponin I during hospitalization, as shown in Table 1 [8]. Troponin elevation goes parallel to the elevation of N-terminal pro-B-type natriuretic peptide and C-reactive protein. It is obvious that troponin rise in the same time with the rise of other inflammatory biomarkers (D-dimer, ferritin, interleukin-6, and lactate dehydrogenase) speaks against isolated myocardial injury mediated through ACE-2. It might be a reflection of cytokine storm or secondary hemophagocytic lymphohistiocytosis.

Temporal changes in troponin levels show slow elevation of values first 2 weeks, and steep elevation 3rd week in patients with a severe and critical form of the disease. During follow-up, the median hs- troponin I among survivors did not change significantly [8].

Cases of ST elevation (STEMI like) without coronary obstruction were published [16], [17] and explained as viral myocarditis or stress cardiomyopathy. However, until now, no signs of direct virus infiltration of the myocardium were published. The scientific data we have point towards inflammation as one of the mechanisms of the multi-organ damage in the course of the COVID-19 disease. Sporadic autopsy cases suggest infiltration of myocardium by interstitial mononuclear inflammatory cells [18].

The use of cardiac magnetic resonance imaging or endomyocardial biopsy may give more answers to these questions.

There is still no evidence of impaired heart function due to myocardial injury in patients who recover from COVID-19. They rather have normal heart function after full recovery. According to that, we may see the myocardial injury and troponin level as a marker of disease severity, related to cytokine storm, hypoxia, vasopressors, and coagulation disturbances. Monitoring and managing a myocardial injury is of utmost importance in severe and critically ill patients [15].

Troponin elevation in the context of COVID-19 infection, in the absence of other signs and symptoms, suggesting acute coronary syndrome, should not a priority lead to invasive diagnostic procedures.

Heart failure

It is a challenge for every physician to make differential diagnoses between decompensated heart failure, often complicated with pulmonary infection and COVID-19 infection, before laboratory-confirmation. And more than that, chest computed tomography images of patients with decompensated heart failure are very similar to those with infection of COVID-19 [22]. Ground-glass opacity and thickening of interlobular septa are present in both cases, but patients with heart failure have a higher ratio of central versus gradient distribution [22].

Extreme elevations in natriuretic peptides with the cause of death attributed to cardiac failure and arrest are reported in up to 25% of case-fatality rates [8], [23]. In a large cohort from China, heart failure was reported in 23% of infected patients and the prevalence was significantly higher among non-survivors (52% vs. 12%, $p < 0.0001$) [8].

It is clear that patients with previous heart failure will have a more complicated pulmonary disease of any kind. However, during COVID-19 pandemic, fulminant myocarditis or cardiomyopathy presentations are observed. A hypothesis is proposed that underlying structural heart disease in early-stage (like heart failure with preserved ejection fraction) in the context of pulmonary complications and later in the form of acute systolic heart failure develops as a response to the cytokine phase of COVID-19.

Elderly patients with heart failure may have left ventricular hypertrophy, diastolic dysfunction, or systolic dysfunction. These patients are prone to higher pulmonary vascular pressure in the typical critical care scenario of overload with fluid infusions to maintain blood pressure as well as the administration of parenteral medications. The use of non-steroid anti-inflammatory drugs as well as secretagogues in diabetic patients, alter salt and water balance and may worsen cardiac function.

Coronary artery disease

Patients with coronary artery disease, stable, or unstable are prone to complications during COVID-19 infection, due to coronary plaque rupture or stent-thrombosis secondary to pro-coagulant effects of systemic inflammation.

The first autopsy of a 53-year-old woman with chronic renal failure in Jinyintan Hospital showed acute myocardial infarction [8]. About 5.8% of patients with severe/critical clinical presentation have a history of coronary heart disease, in comparison with 1.8% of those with non-severe illness [9].

It is important to emphasize that many COVID-19 infected patients were presented to the doctor with heart palpitations and chest tightness, instead of fever and cough. Accompanied by ECG changes suggestive of ischemia, represent a trap for the doctors, to reduce cautions toward self-protection. Coronary arteries without coronary obstruction on angiography will raise the first suspicion of infection with COVID-19. However, elevated troponin during COVID-19 infection, if coupled with symptoms and signs of myocardial infarction, should lead to guideline-directed interventions, fibrinolysis, or coronary angioplasty in designated hospitals [24].

Treatment in the light of CVD

Regarding the treatment of the COVID-19 infection until the beginning of April 2020, more than

Table 1: Comparison of hs-troponin I levels in severe/critically ill patients and non-critically ill patients

Authors	No. of pts	Acute cardiac injury (high troponin level) in severe/critical form of disease (ICU pts)	Acute cardiac injury (high troponin level) in non-ICU pts	p-value
Huang *et al*. [12]	41 pts	31%	4%	p<0.01
Wang *et al*. [19]	138 pts	22,2%	2%	p<0.01
		Acute cardiac injury (high troponin level) in fatal cases	Acute cardiac injury (high troponin level) in survivors	
Zhou *et al*. [8]	191 pts	59%	1%	p<0.01
He *et al*. [20]	54 pts	60.9%	25.8%	p<0.0013
Shi *et al*. [21]	416 pts	51.2%	4.5%	p<0.01

ICU: Intensive care unit

300 clinical trials are ongoing. In the absence of proven effective therapy, supportive care, starting from symptomatic measures, up to complete intensive care support is recommended [25].

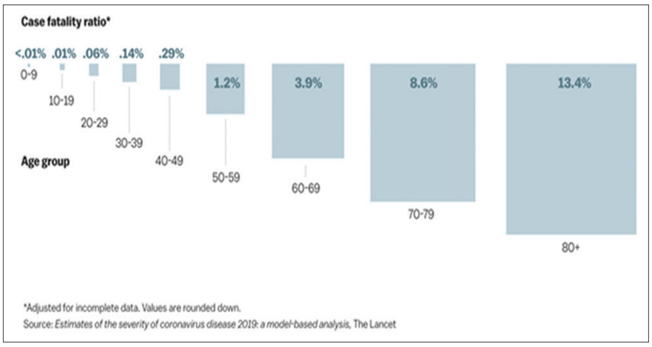

Figure 1: Covid-19's case fatality rate increases with age based on China's data Robert Verity, Lancet Infect Dis. 2020 Mar 30. pii: S1473-3099(20)30243-7. doi: 10.1016/S1473-3099(20)30243-7

The role of the pharmacologic renin-angiotensin-aldosterone blockade, in patients with CVD and COVID-19 infection, needs more research, because the relationship seems to be very complex. Up to date, major health institutions and cardiology societies do not recommend discontinuation of ACE inhibitors or angiotensin II receptor (ARB) medications for all patients taking those medications for another cardiology indication. There is no evidence showing an increased risk of infection or worse clinical course in patients using these medications. However, there are strong warnings that discontinuation of drugs, proven to decrease mortality in patients with CVD, may lead to excess mortality due to cardiovascular reasons.

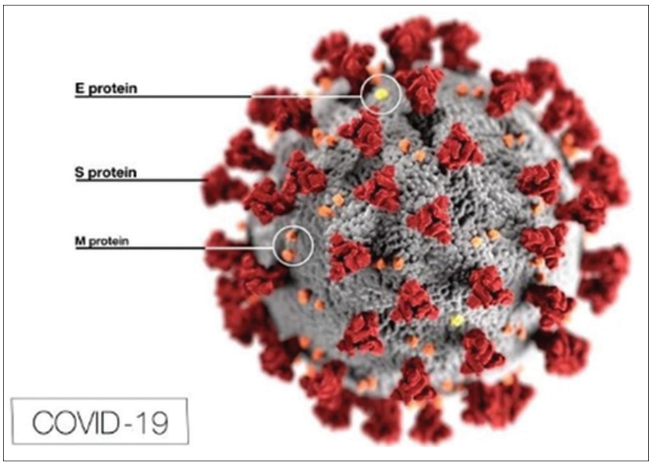

Figure 2: COVID-19 structure https://www.amercrystalassn.org/

In patients with heart failure, excessive fluid use and drugs that may alter salt and water balance, such as NSAID, should be avoided. Management of advanced heart failure should be guided by the cardiologist, having into consideration the hyper-inflammation phase of the infection.

In patients with coronary artery disease and COVID-19 infection, use of plaque stabilizing agents (aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors) has been suggested as a possible therapeutic strategy [26]. Unnecessary diagnostic tests (cardiac troponin and echocardiography) should be minimized, or in some cases, avoided [27], [28], [29]. These tests should be used in the circumstances in which they could add to the management of patients with COVID-19.

Special care should be taken about the potential cardiovascular side-effects of various therapies used for treating the viral infection: Antiretroviral drugs, hydroxychloroquine, azithromycin, etc. Daily electrocardiographic monitoring of the QT interval is suggested [29].

Knowledge gaps and future directions

The pathobiology, clinical characteristics, and prognosis of the infection are still being studied. An early signal of myocardial injury (cardiac troponin elevation) and new heart failure as a consequence of it is recognized as a bad prognostic marker of the disease. Special caution should be taken in therapeutic management, drug interactions, and proarrhythmogenic potentials in some antiviral protocols.

The current evidence of the association between renin-angiotensin-aldosterone medications and ACE-2 levels with clinical outcome in COVID-19 infection is insufficient. More information needs to be generated.

COVID-19 has emerged as a new disease only a few months ago and it is impossible to discuss the long-term outcome in patients recovering from the infection. There is still no evidence of impaired heart function due to myocardial damage in the acute phase. Follow-up studies and more data are needed to make conclusions.

Conclusion

Preexisting CVD is common in patients with COVID-19 and those patients are at higher risk of morbidity and mortality. Myocardial injury is present in more than 15% of severely ill patients. Several promising treatments are under investigation, but so far none with the proven clinical efficacy. The continuation of clinically indicated ACEi or ARB therapy is recommended by many heart associations, based on the currently available evidence. We hope the near future will answer the remaining questions and prove the force we make each day to fight the virus.

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One-month Progress of COVID-19 Cases in East Kalimantan, Indonesia

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Abstract

BACKGROUND: East Kalimantan, Indonesia, will play a significant geopolitical role as the province has been selected as the location of the future capital city of Indonesia. As a buffer zone to the capital city, there is urgent attention on the preparedness of the cities and regencies in East Kalimantan to respond to emergent infectious disease events such as coronavirus disease-19 (COVID-19).

AIM: The aim of the present study was to descriptively convey information about COVID-19 cases in East Kalimantan during the period of March 18, 2020–April 18, 2020, in terms of the isolation, testing, and tracing mechanisms used.

METHODS: The initial distribution of COVID-19 was identified in 5 of 10 districts and is now present in almost all districts except for one very remote regency.

RESULTS: The tracing performance of the fast response teams in East Kalimantan during this period was considered satisfactory with a mean of 0.7% of people under observation testing positive for severe acute respiratory syndrome coronavirus 2, and a mean of 14.4% patients under investigations testing positive. The use of rapid tests since March 30, 2020 has improved the detection ability, with confirmed positive cases as a percentage of confirmed negatives increasing from 20.2% to 31.8%. The use of the COVID-19 rapid test was cross-checked with a dengue rapid test to prevent false-positive identification. Confirmed clusters were announced to the public, urging people to respond and report.

CONCLUSION: The 1-month progress of COVID-19 cases in East Kalimantan showed a total case fatality rate (CFR) of 1.85%, a closed CFR of 8.3% and a closed case recovery rate of 91.7%.

Introduction

Coronavirus disease 2019 (COVID-19), a disease which causes by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started as reported cases of respiratory illnesses from Wuhan, China by the end of 2019 and eventually spread all over the world in the following months, which forced World Health Organization (WHO) to declare it as pandemic by March 11, 2020 [1], [2]. To curb the spread of SARS-CoV-2, many countries implemented several measures such as limiting to closing border movements, community-wide isolation, and preventing the gathering of people [3], [4], [5].

Indonesia officially confirmed its first COVID-19 case on March 02, 2020. In the announcement by the President of the Republic of Indonesia, the first cluster was identified as a dance class [6]. In this cluster, 13 people were later positively identified as COVID-19 cases [7]. Three major activities which occurred between February 26, 2020 and February 28, 2020 were identified as clusters of COVID-19 transmission: The Seminar *Sinode* Bogor, Seminar *Anti Riba* Bogor, and Seminar *Kerohanian* Lembang [8]. Participants in these events came from all regions of Indonesia, including East Kalimantan. On March 18–20, 2020, East Kalimantan confirmed nine COVID-19 patients, the majority of them coming from the two main clusters: The Seminar *Sinode* Bogor, Indonesia and Seminar *Anti Riba* Bogor, Indonesia. There was a confirmed positive patient from another cluster, the General Election Commission meeting in Jakarta [9].

East Kalimantan has been selected as the location for the new capital of the Republic of Indonesia [10]. Consequently, the flow of people in and out of East Kalimantan has increased rapidly. Despite this, health-care facilities in East Kalimantan are still limited compared to similar facilities on the island of Java. For this reason, the spread of COVID-19 needs special attention, given the nature of rapid transmission and the need for significant intensive care unit facilities [11]. Management of infectious diseases such as COVID-19 requires special arrangements such as negative pressure isolation rooms, personal protective equipment with a level three biosafety standard, and ventilators to help critical patients [12]. Therefore, the provincial government set several measures in place to flatten the curve of the COVID-19 infection rate and to prevent health services from being overloaded.

Recording the events surrounding the COVID-19 pandemic is needed as a future learning effort for similar outbreaks that might occur in East Kalimantan. The purpose of the present study was to descriptively convey information about COVID-19 cases in East Kalimantan during the period from March 18, 2020, to April 18, 2020.

Materials and Methods

Data collection

Timeline information on the COVID-19 cases in East Kalimantan was tracked from broadcasts and announcements from the East Kalimantan Provincial Health Office [13], Samarinda City Health Office [14], and Balikpapan City Health Office [15] news channels based on official announcements and reportage, interviews, and communication with field workers at health offices in East Kalimantan, Hospitals, and Emergency Reporting Task Force 112.

Data processing

Official data collected from the Provincial Health Office, Samarinda City Health Office, and Balikpapan City Health Office were collated in a database and analyzed using Microsoft Office Excel software.

Statistical analysis

Statistical analysis was performed by Microsoft Office Excel 365 (Microsoft, Redmond, Washington, USA).

Ethics statement

The laboratory and diagnostic procedures of this study were approved by the Health Research Ethics Committee of the Faculty of Medicine, Mulawarman University, Samarinda, East Kalimantan, Indonesia (Jl. Kerayan Kampus Gunung Kelua, Samarinda, East Kalimantan, Indonesia).

Results and Discussion

Progress of COVID-19 cases

COVID-19 cases were first reported in Jakarta, Indonesia since March 02, 2020, and following that, the first case in East Kalimantan province was detected on March 18, 2020. The timeline of COVID-19 progression in East Kalimantan Province can be seen in Table 1.

Tracing and Isolation before the use of rapid tests

The WHO has established procedures for handling infectious diseases with four main steps: Isolate, test, treat, and trace [16]. The implementation of this handling procedure has varied by country. For example, South Korea initiated a large scale use of rapid tests [17], China implemented strict lockdown procedures in affected provinces [18], India has used force to curb dissidents in lockdown [19], and Indonesia has established large-scale social restrictions [20].

In Indonesia, there have been differences between regions in the way that people under observation (PUO) and patients under investigation (PUI) have been determined [21]. East Kalimantan, for example, with a population of about 3.7 million, has more PUO than other more populated provinces [22]. The determination of PUO, in general, is based on a history of trips to an area with the local transmission or overseas travel [23]. In East Kalimantan, the community's compliance in reporting themselves to the hotline number 112 or 119 in Samarinda and Balikpapan was good, and the performance of the hotline team was also satisfactory. The mean daily tracing performance from March 20, 2020, to April 18, 2020, was one positive confirmed for every 14.3 PUO and one positive confirmed for every 6.9 PUIs. In addition, 48% of the PUIs were confirmed negative.

The Samarinda and Balikpapan fast response teams quickly disseminated information on the initially identified clusters such as the Seminar *Sinode* Bogor, Seminar *Anti Riba* Bogor, General Election Commission meetings, and other trips or meetings in areas with local transmission. This information was widely disseminated through social media channels in one or several posts which were easy to read and understand [24]. The return of participants from *Ijtima Gowa* was considered as a very challenging tracing activity, due to the sheer number of people and their locations.

The performance of the tracing can be calculated based on daily published data by the East Kalimantan Health Office. For example, on March 19, 2020, the first publicly available data, there were 208 PUOs, 39 PUIs, three positives and 11 negatives [13]. This means COVID-19 positive individuals as a percentage of total PUO and PUI at that time were 1.4% and 7.7%, respectively. The highest percentage of COVID-19 positive of PUO and PUI occurred on March 28, 2020, with 21.0% and 0.7%, respectively. On a monthly mean, the percentage of COVID-19 positive of PUO and PUI was 14.4% and 0.7%, respectively.

Before the COVID-19 rapid test kit was received by the East Kalimantan Health Office, the procedure for determining PUI status was based on the Pedoman Pencegahan dan Pengendalian COVID-19 which had been revised 3 times by the Ministry of Health of the Republic of Indonesia [11]. PUI was determined

Table 1: COVID-19 timeline in East Kalimantan, Indonesia

Date	Event
March 18, 2020	Announcement of the first confirmed COVID-19 patient in East Kalimantan from a cluster of religious activities in Bogor. A total of 35 patients under investigation were identified in East Kalimantan from 31 January to March 18, 2020. Ten of them had been declared negative, one positive, and 24 other patients under investigations were still waiting for laboratory results
	Thermal scanners started operating at APT Pranoto Airport Samarinda and SAMS Sepinggan Airport Balikpapan
March 19, 2020	Announcement of second and third confirmed COVID-19 patients in East Kalimantan from a cluster of sharia business activities in Bogor
March 20, 2020	The addition of six new positive cases in Balikpapan and Kutai Kartanegara (total cases: 9)
March 23, 2020	The addition of two new positive cases in Bontang and East Kutai (total cases: 11)
March 26, 2020	KM Lambelu, a passenger vessel carrying around 1500 participants from *Ijtima Gowa* religious activities from East Kalimantan and South Kalimantan, docked in Balikpapan. Around 600 people immediately registered and were declared people under observation
	COVID-19 positive patients from the Jakarta travel cluster and the General Election Commission meeting were confirmed
	The first batch of shipments of medical personal protective equipment arrived in East Kalimantan.
March 27, 2020	The Indonesian Ulama Council in East Kalimantan issued a circular for Friday and as a result, congregational prayers were not carried out, instead replaced with prayers at home during the COVID-19 pandemic
March 28, 2020	The addition of six new positive cases in Balikpapan (total cases: 17)
March 29, 2020	Official announcement of the first death case. A participant of the religious event *Ijtima Gowa* died as patients under investigation. The person arrived in Balikpapan on a transit flight trip to Banjarmasin from Makassar on March 22, 2020, and tested positive for COVID-19 in the following days
	A trial was started on the use of rapid tests in East Kalimantan, and from this point, the determination of patients under investigation has been with rapid tests
March 30, 2020	A patient under investigation from a new cluster (Makassar city cluster) was identified by rapid test in Samarinda; the patient under investigation was then isolated and tested positive for COVID-19 about a week afterward
	Balikpapan was declared as a local transmission area of COVID-19 by the Ministry of Health
	An agreement to check access between cities was put in place by two cities in East Kalimantan (Balikpapan and Samarinda). They implemented restriction to main road sections
March 31, 2020	The addition of three new positive cases in Balikpapan (total cases: 20)
April 01, 2020	The addition of one new positive case in Kutai Kartanegara (total cases: 21)
April 02, 2020	The addition of one new positive case in Samarinda (total cases: 22)
April 04, 2020	The addition of two new positive cases in Samarinda and East Kutai (total cases: 24)
	Two first cases of recovery in Bontang and Kutai Kartanegara
April 05, 2020	The addition of one new positive case in Samarinda (total cases: 25)
	KM Queen Soya, a passenger ship from Pare-pare, docked at Samarinda Harbor. Thermal scanning and brief interviews related to travel history were carried out and 200 people under observations were determined. Based on tracing data, KM Queen Soya brought 541 passengers from Pare-Pare on March 28, 2020, and 284 people on April 04, 2020. Another passenger vessel, KM Aditya, sailed with 297 people on March 29, 2020, and 104 people on April 05, 2020. The total number of ship passengers who had arrived in Samarinda since March 28, 2020, was 1,226.
April 06, 2020	The addition of six new positive cases in Penajam Paser Utara and Balikpapan (total cases: 31)
April 07, 2020	One patient recovered in East Kutai, to a total of three recovered cases
April 08, 2020	The addition of one new positive case in East Kutai (total cases: 32)
	Three patients recovered in Balikpapan, to a total of six recovered cases
April 09, 2020	Airlines decided to reduce 95% air traffic from and to East Kalimantan
April 10, 2020	The use of the C19 rapid test coupled with NS1 rapid test as a false positive cross-check against dengue hemorrhagic fever started
	The addition of three new positive cases in Samarinda, Balikpapan, and Berau (total cases: 35)
April 12, 2020	The prohibition of *mudik* (the tradition of going home during religious holidays) was issued by the Government of East Kalimantan
April 13, 2020	A total of 1264 rapid tests had been carried out, with 43 patients under investigations reactive to rapid tests
April 15, 2020	A total of 1637 rapid tests had been carried out, with 65 patients under investigations reactive to rapid tests
April 16, 2020	The addition of nine new positive cases in Berau, West Kutai, and Balikpapan (total cases: 44)
	At least five burials using the COVID-19 protocol in East Kalimantan, although three of them had been confirmed negative
April 17, 2020	Another cluster was established, namely, a trip to Sangatta, East Kutai
	Of 151 crew of KM Lambelu, 92 were confirmed positive for COVID-19
	The increase of patients under investigation since the rapid test started was 4.09 persons per day
April 18, 2020	The addition of ten new positive cases in Penajam Paser Utara, Paser, and Balikpapan (total cases: 54). Of all the regencies in East Kalimantan, only Mahakam Ulu has not been affected by this stage
	Eleven patients recovered (case fatality rate total cases 1.85%; case fatality rate closed cases 8.3%, recovered closed cases 91.7%)
	Tracing performance from March 20, 2020, to April 18, 2020, was an average of one positive confirmed for every 14.3 people under observations and one positive confirmed for every 6.9 patients under investigations, with 48% of the patients under investigations confirmed negative

COVID-19: Coronavirus disease-19.

based on contact with positive confirmed COVID-19 or travel to areas that had been designated as local transmission and/or the patient had shown symptoms consistent with COVID-19. The main symptoms are fever (≥38°C) accompanied by dry cough, shortness of breath, body weakness, or diarrhea. As of March 30, 2020, 169 PUIs had been established, 84 of which were declared negative and 17 confirmed positive, with 68 PUIs waiting for confirmation of test results.

Confirmed COVID-19 patients were isolated in a hospital in the nearest city. Patients with a history of contact or travel to areas with local transmission of COVID-19 and show symptoms resembling COVID-19 were isolated. A part from these categories, all PUO and PUI were urged to carry out independent isolation for at least 14 days in their homes [23].

Use of rapid test in determination of PUI

The use of finger prick antibody-based rapid tests for the determination of the status of a person suspected of having COVID-19 has been carried out in several countries [25]. Several rapid tests have been recommended by health authorities [26]. The accuracy rate of rapid test detection is expected at 70–90%, depending on the sensitivity of the kit produced by each manufacturer. These tests use a blood sample to detect antibodies (IgG and/or IgM) as the host response to COVID-19 infection [27].

On March 26, 2020, the Government of the Republic of Indonesia, through its Pedoman Pencegahan dan Pengendalian COVID-19 4th revision, established the procedures for establishing the PUI by rapid test [11]. This device was distributed throughout Indonesia, and East Kalimantan was allocated with 2 400 units of rapid tests. This device arrived on March 27, 2020 and was subsequently distributed to all District Health Offices in East Kalimantan. The use of rapid tests in Samarinda City was first recorded on March 29, 2020. The first result of rapid tests was announced on March 30, 2020. After being screened with rapid test, 175 PUIs had been subjected to the more accurate swab tests, of which 35 PUI swabs were waiting for the swab results (Figure 1). There were 120 confirmed negative PUIs and 20 PUIs confirmed positive for COVID-19.

The use of rapid tests since March 30, 2020, helped the tracing team to identify PUIs. For example, on March 30, 2020, of 169 PUIs, 84 were negative for COVID-19 and 17 of them were positive using swab test, and positive cases as a percentage of confirmed negatives were 20.2%. On April 18, 2020, from 352 PUIs were registered, 170 were negative, and 54 were positive cases. Hence, positive cases as a percentage of confirmed negatives were 31.8%. Therefore, it was concluded that the use of the rapid test had increased the screening capability of the tracing team.

The increase in PUIs with the establishment of rapid tests was 4.09 people per day since March 30, 2020 (Figure 1). On April 16, 2020, a rate of 442 rapid tests and 95.13 swabs per 1 million populations was reported. The number of rapid tests performed on a national scale was not available. However, the rate of swab tests for East Kalimantan was considered slightly lower than the national rate of 156.36 swabs per 1 million populations. As of April 18, 2020, there was a cumulative total of 352 PUIs, with 128 people waiting for the results of the swab test. About 170 people were negative and 54 people were positive for COVID-19 [13].

As an important note, the use of rapid tests in Indonesia may be accompanied by other rapid tests. Since Indonesia is a country with endemic Dengue hemorrhagic fever (DHF), some positive blood-based rapid test PUIs were cross-checked with the NS1 rapid test designed for DHF. The use of cross-checking with NS1 kits has never been reported in publications in sub-tropical countries because DHF is endemic to tropical countries [28].

Distribution of COVID-19 to regencies in East Kalimantan

The dynamics of the spread of COVID-19 are still being elucidated, but a Basic Reproduction Number (R0) of 2.2–5.7 has been reported in the literature [1]. Awareness of the rapid spread of COVID-19 needs to be improved. Trips between regions or cities with public transport are considered to be the main contagion vector. The focus of attention is preventing an outbreak of cases in areas with limited health facilities such as the communities in distant and remote areas that are abundant in East Kalimantan [29].

The COVID-19 patients were first confirmed in Samarinda city on March 18, 2020 (Figure 2). Within a week, the spread of confirmed COVID-19 patients expanded to five other regencies. Penajam Paser Utara and Berau recorded positive COVID-19 patients, comprising 11% and 3%, respectively, of the total confirmed cases in East Kalimantan on April 10, 2020. The confirmed number of COVID-19 cases increased to 54, of which 11 were declared cured as reported on April 18, 2020. The spread of COVID-19 has also reached areas distant from

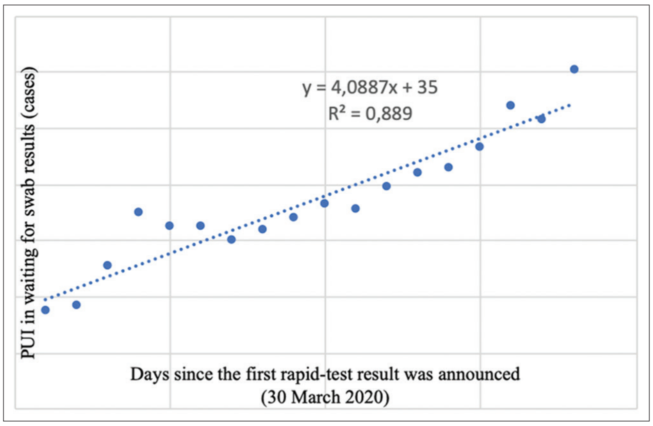

Figure 1: Development of patients under investigation with positive rapid tests since March 30, 2020

airports and main harbors such as the West Kutai and Paser Regency. The highest increase in COVID-19 confirmed that patients were in Penajam Paser Utara Regency [13].

Determination of the distribution cluster

Tracing of the main clusters of COVID-19 distribution was based on a travel history interview or contact by the PUI. COVID-19 patients would confirm their travel history or contact data and were then be submitted to the surveillance teams. After the data were confirmed, the surveillance teams conducted contact tracing based on the information obtained [23]. The main confirmed clusters were subsequently announced in a daily broadcast by the Provincial Health Office. Announcement of the main clusters of the spread of COVID-19 increases community awareness through self-reporting and community reporting through community leaders, heads of villages, and neighborhood units. This is especially important for people without symptoms who have contact with PUI or have a history of travel to areas with local transmission.

Conclusion

During the month since the first case of East Kalimantan was announced on March 18, 2020, an initial spread of COVID-19 was identified in five regencies and has subsequently reached nine regencies in East Kalimantan. The tracing performance of the 112 teams in East Kalimantan can be considered satisfactory during the 1-month observation period, with a mean of 0.7% of PUO and 14.4% of PUI confirmed as COVID-19 positive. The use of rapid tests since March 30, 2020, has increased the detection ability of the tracing team from 20.2% to 31.8%, expressed as confirmed positive PUI as a percentage of confirmed negative PUI. The

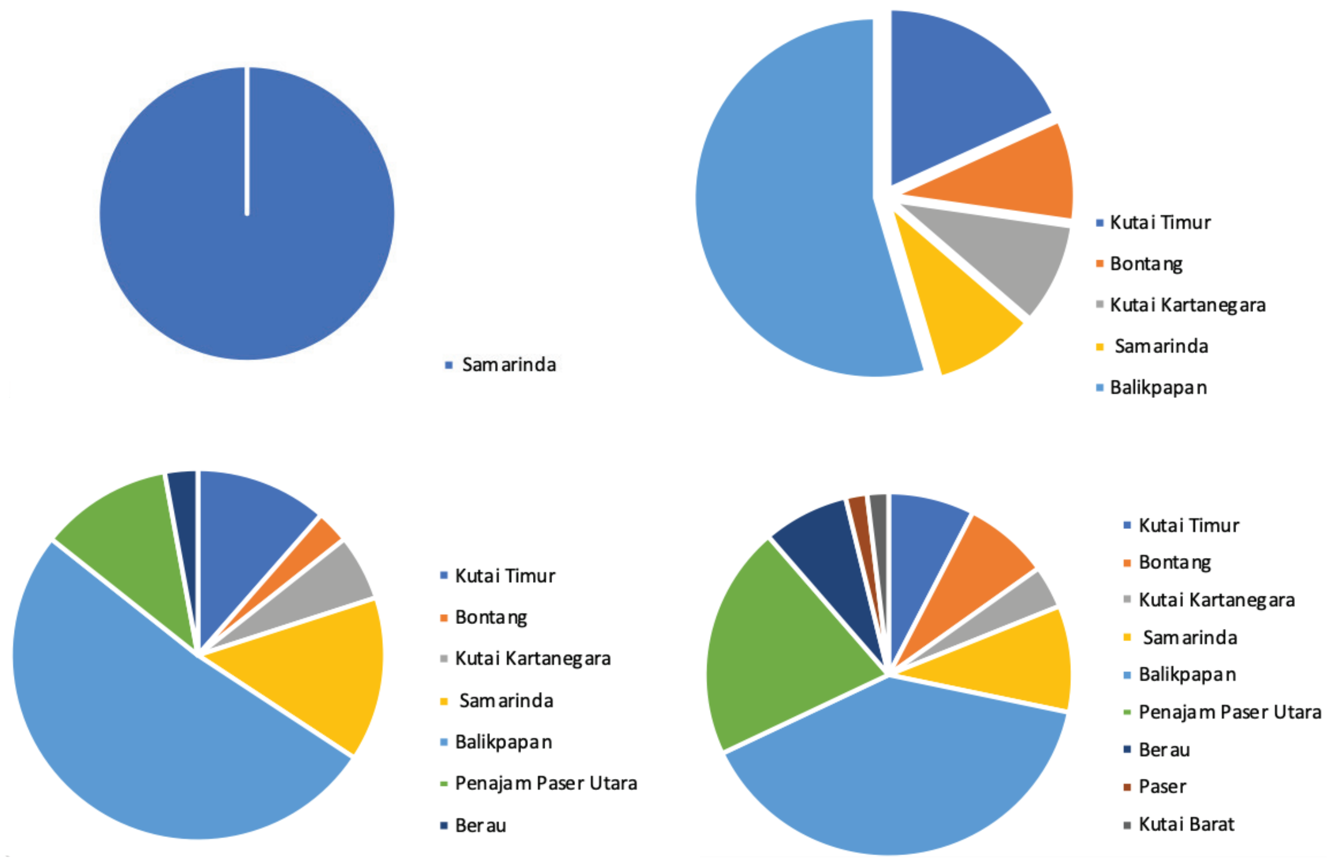

Figure 2: Snapshot of coronavirus disease-19 East Kalimantan cases

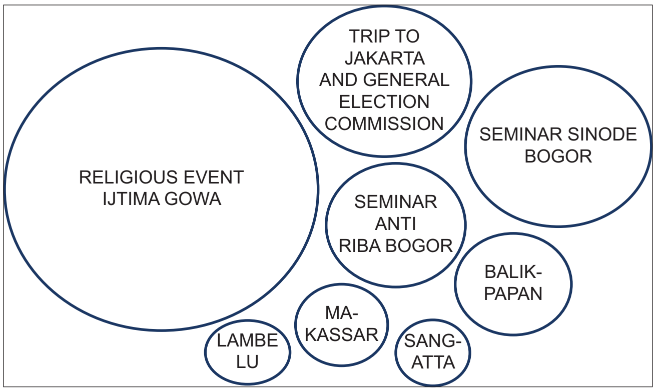

Figure 3: Origin of the East Kalimantan coronavirus disease-19 cluster

use of the COVID-19 rapid test can be cross-checked with a DHF rapid test. Precautions for the spread of COVID-19 should be increased in districts with larger areas and more limited health facilities than in urban areas. Confirmed clusters need to be announced to the public to increase the effectiveness of community self-reporting. In 1 month since the first confirmed patient, 54 cases were confirmed, 11 patients recovered, and one confirmed COVID-19 patient died. The total case fatality rate (CFR) was 1.85%, closed case CFR was 8.3%, while the closed case recovery rate was 91.7%. Tracing of the main clusters of COVID-19 distribution was based on a travel history interview or contact by the PUI (Figure 3). COVID-19 patients would confirm their travel history or contact.

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COVID-19 from a Perspective of Neuromuscular Diseases: Meeting the Challenges

Dear editor,

The new severe acute respiratory syndrome coronavirus 2 epidemic is imposing immense strain on the health systems in several countries. The growth of the epidemic has led the WHO to declare the 2019-nCoV disease as a global pandemic [1]. Coronavirus disease 2019 (COVID-19) pandemic has the potential to affect patients with neuromuscular diseases. The evaluation of the overall risk of COVID-19 in patients with neuromuscular diseases depends on several factors: The specificity of the neuromuscular disease, the general condition, the presence of other comorbidities, age, and the type of immunosuppressive treatment they receive. It is important to emphasize the fact that most patients with neuromuscular disease are not expected to suffer from severe complications due to coronavirus infection. Corona infections can affect certain myopathies. In a recent study published in China, related to COVID-19 is shown that hospitalized patients experienced fatigue and myalgia (44–70%) and increased creatine kinase (33%) in the serum [2]. Apart from this, a third of hospitalized patients infected with the coronavirus had rhabdomyolysis [3]. All of this point to the fact that coronavirus infection may be responsible for viral myositis. In addition, is the finding that some of the critical cases have developed polyneuropathy or myopathy [4]. On the other hand, it is well known that infection is a trigger for exacerbation of certain neuromuscular diseases. There are no data that measured the risk of exacerbation as a result of coronaviruses infection for neuromuscular disorders. However, in one retrospective study, COVID-19 infection was a leading reason for the exacerbation of myasthenia gravis [5]. As a result of this, an increased incidence of exacerbations of certain neuromuscular diseases should be expected, as well as the appearance of new clinical presentations during this pandemic. It is important to note that there are still no neuromuscular disease-specific recommendations for patients who are infected with the coronavirus. Observation is recommended in patients at high and medium risk, especially in those patients where there is a possibility of a decrease in respiratory function. Last but not least, we would like to emphasize the need for reorganization of clinical care for these patients [6]. The goal is to reduce exposure of patients to areas where the coronavirus could be found. Moreover, non-urgent or outpatient care is remarkably reduced. In conclusion, we must learn to apply our clinical practices to reduce the complications that may occur in patients with neuromuscular disease due to COVID-19. The primary goal is to develop evidence-based medical practices to reduce morbidity and mortality. Collaboration among institutions worldwide will be able to give us the data needed for planning management for neuromuscular disorders with COVID-19 and maintain clinical research against strong challenges.

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Gastrointestinal Aspects of COVID-19: A Review

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Abstract

Coronaviruses commonly cause mild infections, but recently severe acute respiratory syndrome-coronavirus (SARS-CoV)-2 caused a pandemic of coronavirus disease 2019 (COVID-19). A total of 3,181,642 cases were confirmed globally. Gastrointestinal tract may be involved in COVID-19 due to the presence of angiotensin converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) in small intestine and colon which are mandatory for SARS-CoV-2 invasion. A proportion of patients with COVID-19 had gastrointestinal manifestation without respiratory symptoms. Viable virus can also be isolated from feces of patients. Fecal-oral transmission should be considered in controlling disease spreading. Fecal examination may also be considered to diagnose COVID-19, especially in areas with limited personal protective equipment.

Introduction

Coronavirus is enveloped non-segmented positive-sense RNA virus from Coronaviridae family and Nidovirales order. The virus is commonly found in several mammals, including bats [1]. Most of coronavirus infections are mild, but there were several epidemics due to the infection such as severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle-East respiratory syndrome-coronavirus (MERS-CoV). Both epidemics had high mortality rates with MERS-CoV as the highest (37%) [2]. Recently, an outbreak of coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 occurred at the end of 2019. It started in Wuhan, Hubei, China, and now, it spreads globally, affecting 199 countries [2], [3], [4], [5]. On March 11, 2020, the World Health Organization (WHO) declared it as a pandemic [1].

Epidemiology

On May 1st 2020, there was a total of 3,181,642 confirmed cases of COVID-19 worldwide with 224,301 death cases. Europe was the region with highest prevalence rate (1,461,404 cases) while the USA was the highest prevalence country with 1,035,353 cases [6]. Most of patients were male with underlying diseases such as diabetes, hypertension, and cardiovascular diseases [2] [7] [8]. The median age of infected patients was 49.0 years [2]. Other study stated that mean age of the patients was 46.14 years and 10.8% of them had pre-existing liver disease [9]. The most common death leading complication was acute respiratory distress syndrome. The death rate reported from a study by Huang *et al*. was 15% [2].

Pathophysiology

The virus mainly infects respiratory epithelial cells and spreads from human to human through respiratory tract [7]. Gastrointestinal tract is also affected in COVID-19, similar with SARS-CoV and MERS-CoV, but the manifestations are uncommon [1], [3], [10]. Lin *et al*. found that SARS-CoV-2 could be detected in esophagus, stomach, duodenum, and rectum. The virus was also present in 52.4% of patients' feces [11]. SARS-CoV-2 needs angiotensin-converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) to enter host cells [1], [2], [3], [7], [8], [12], [13]. Both are highly expressed in small intestine and colon, but not in esophagus. This raises probability that the virus can invade through digestive tract. The invasion causes the development of gastrointestinal manifestations [3], [7]. After binding with ACE2, the virus enters host cell. Viral RNA then integrates into host cell DNA. This process initiates viral protein synthesis and assembly of new viruses. This new viruses may invade other cells or released into body fluid in respiratory and gastrointestinal tract [7]. As the role of ACE2 is to mediate inflammation, the infection causes damage in ACE2 receptor, increases in inflammation, damages in mucosa, and triggers diarrhea [12], [14]. In addition, viral invasion causes inflammatory response and imbalance of intestinal microorganism which further damages the digestive system and manifested as gastrointestinal symptoms [8], [13]. The effect of gut–lung axis is also suspected to play an important role in the interaction between respiratory and gastrointestinal manifestations through the common mucosal immune system [8]. A study by Xiao *et al*. proved that gastrointestinal epithelium of patients with COVID-19 suffered from damage based on endoscopy findings. The damage was observed in esophagus, stomach, duodenum, and rectum. Viral RNA was found in esophageal mucosa but not viral nucleocapsid, indicating that the viral invasion was absent in esophagus due to the absence of ACE2 [7]. ACE2 is also detected in hepatocytes and cholangiocytes so it is possible that liver is involved with SARS-CoV-2 infection. However, the effect of medications, including antibiotic and experimental antiviral, must also be in concern as the aggravating factors of liver damage along with other underlying comorbidities. However, the binding efficiency is thought to be stronger for SARS-CoV-2 compared to other coronavirus. A literature stated that binding affinity of SARS-CoV-2 is 73% stronger than SARS-CoV. This explains the high transmission rate of SARS-CoV-2 [12] [13].

Clinical manifestations

Classical manifestations of COVID-19 are fever, cough, dyspnea, and myalgia which indicate droplet as the main mode of transmission of the disease [2], [3], [5], [8], 10], [13]. In MERS-CoV or SARS-CoV infections, gastrointestinal manifestations were found in 20%–25% of patients [2], [10], [12]. Cheung *et al*. reported a cumulative prevalence of gastrointestinal manifestation in COVID-19 patients as much as 17.6% while Pan *et al*. reported a higher rate (20.5%) [1], [8]. Diarrhea was found in 1–3.8% of patients with COVID-19 while nausea and vomiting were found in 10.1% and 3.6% of patients, respectively [3]. Other study reported that anorexia was the most common gastrointestinal manifestation (26.8%) followed by diarrhea (12.5%) and nausea/vomiting (10.2%) [1]. In a study by Pan *et al*., anorexia was the most common gastrointestinal symptom (78.6%), followed by diarrhea (34%), vomiting (3.9%), and abdominal pain (1.9%) [8].

Jin *et al*. reported that gastrointestinal manifestations were found in 11.4% of patients with COVID-19 and 28% of patients with gastrointestinal manifestations did not have respiratory symptoms. Furthermore, they had more severe disease course compared to those without gastrointestinal manifestations [9]. Another study reported a higher rate of gastrointestinal manifestations in COVID-19 patients. A total of 61.1% of patients had gastrointestinal manifestations which consisted of diarrhea (24.2%), nausea (17.9%), vomiting (42.2%), and impaired liver function (32.6%) [11]. Various degrees of liver damage had been reported in COVID-19 patients. Total bilirubin level raised in 10% of patients while ALT level rose in 16%–35% of patients. Elevated AST was observed in 21% of patients and alkaline phosphatase was generally normal [12].

Auxiliary examinations

Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swab is used to confirm the diagnosis of COVID-19 [4], [5]. Other specimens also showed positive result with bronchoalveolar lavage fluid held the highest positive rate (93%), followed by sputum (72%), nasal swabs (63%), fibrobronchoscope brush biopsy (46%), pharyngeal swab (32%), feces (29%), and blood (1%) [4]. A meta-analysis reported that the prevalence of positive stool viral RNA was 48.1% [1]. The accuracy of SARS-CoV-2 detection from feces is comparable with nasopharyngeal swab. It can be suggested that the diagnosis of COVID-19 can be performed from fecal specimen, particularly in areas with limited personal protective equipment [5], [15]. From chest computed tomography, one can find ground-glass opacity [2], [5], while X-rays showed bilateral lung involvement in 98% of patients. From laboratory examination, 45% had white blood cell count between 4000 and 10,000/mL, 69% had procalcitonin level of <0.1 ng/mL, and more than a half patients had lymphopenia. Critical patients showed elevated pro-inflammatory cytokines, leading to a condition called cytokine storm [2]. The virus might be found in feces from day 1 to 12 of infection [7]. The potential of fecal-oral transmission is present since SARS-CoV-2 is still detected in feces even after the virus has been cleared from respiratory tract [1], [3], [7], [13]. The presence of viable virus in feces makes it possible for the disease to spread through stool contaminated hand, food, and water. It is in concordance with the viability of virus in several environments [5], [12], [15]. The virus was still found in feces for a mean of 27.9 days after first symptom onset compared to 16.7 days in respiratory samples [15]. However, the presence of virus in feces was not associated with gastrointestinal manifestations, disease severity, and antiviral treatment [4], [5], [15]. Prevention of fecal-oral transmission should be taken into consideration to prevent further spreading of the disease [7], [10].

Conclusion

COVID-19 is now a pandemic with increasing prevalence and mortality rates. The presence of ACE2 and TMPRSS2 in gastrointestinal tract makes it possible for SARS-CoV-2 to invade through gastrointestinal tract and elicits manifestations. Anorexia and diarrhea are the most common gastrointestinal tract in COVID-19 patients. Viable virus is also detected in feces of patients even though it has been cleared from respiratory tract. Fecal examination can be a candidate of diagnostic testing, especially in area with limited personal protective equipment. Further, consideration is mandatory regarding fecal-oral transmission of COVID-19.

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A Survey of the Knowledge of Surveillance Officers and Outbreak Investigation Team toward COVID-19 in North Sumatera Province, Indonesia

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Abstract

BACKGROUND: Our world is now facing the public health emergency situation. Since early December 2019, COVID-19 emerged the Wuhan City, Hubei Province, China. The disease is still continuing spread to more than 200 countries and territories globally.

AIM: This study aimed to assess the knowledge of COVID-19 among the surveillance officers and outbreak investigation team in North Sumatera, Indonesia.

METHODS: A cross-sectional study was performed between March 5, 2020 and April 20, 2020, among the surveillance officers and outbreak investigation team in North Sumatera province, Indonesia. A set of validated, pre-tested questionnaire was used to measure knowledge regarding COVID-19 infection and to collect a range of explanatory variables. Data were collected through a self-administered questionnaire. A two-step logistic regression analysis was employed to assess the association of participants' demographic data, level of education, surveillance training, length of work, and location of workplace with the knowledge.

RESULTS: A total of 246 participants were collected. We found that 109 out of 246 (44.3%) participants were good knowledge of COVID-19. Multivariate model revealed that surveillance training was the most associated variable with knowledge of COVID-19 (OR = 2.15, 95% CI = 1.09–4.27). In addition, as much as 27 participants (79.4%) have good knowledge and also have received surveillance training expressed a willingness to conduct surveillance (OR = 4.75, 95% CI = 1.98–11.39).

CONCLUSIONS: The knowledge of surveillance officers and outbreak investigation team in North Sumatera regarding COVID-19 is relatively low. Participants who have good knowledge and have received surveillance training expressed a willingness to conduct surveillance of COVID-19 in the community. Therefore, training for surveillance and outbreak investigation team to improve the understanding and skill is a must.

Introduction

Our world is now facing the public health emergency situation. Since early December 2019, unknown etiology of pneumonia disease emerged the Wuhan City, Hubei Province, China [1] The disease rapidly spread throughout China. On January 7, 2020, China identified the disease caused by a new type of coronavirus [2], [3]. Coronavirus (CoV) is a large family of viruses that cause diseases ranging from mild to severe symptoms. At least two types of coronavirus are known to cause diseases that can cause severe symptoms such as Middle-East respiratory syndrome and severe acute respiratory syndrome (SARS) [1], [3], [4]. Coronavirus disease 2019 (COVID-19) is a new type of infectious disease that has never been identified before in humans. Clinical manifestations usually appear within 2 days–14 days after exposure. Common signs and symptoms of coronavirus infection include symptoms of acute respiratory disorders such as fever, coughing, and shortness of breath. In severe cases, the disease can cause pneumonia, acute respiratory syndrome, kidney failure, and even death [4], [5].

On January 30, 2020, the WHO has designated the COVID-19 as Public Health Emergency of International Concern (PHEIC) [1], [6], [7] As of March 11, 2020, the WHO has declared that COVID-19 as a global pandemic [6], [8], [9]. The increase number of COVID-19 cases took place quite quickly and there has been a spread outside the Wuhan and other countries. The disease is still continuing spread to more than 200 countries and territories globally [1], [7]. As of May 7, 2020, there were 3,634,172 confirmed cases of COVID-19 globally including 251,446 deaths (CFR = 6.92%) [7].

The first confirmed case of COVID-19 in Indonesia was reported on March 2, 2020 [10], [11]. On April 13, 2020, the President of Indonesia has declared that COVID-19 as national disaster [12], [13]. As of April 10, 2020, all provinces in Indonesia have already reported the COVID-19 cases [14], [15] As of May 7, 2020, there were 12,776 confirmed cases of COVID-19 including 930 deaths (CFR = 7.28%) in Indonesia [16]. The COVID-19 confirmed cases have been reported throughout all the Indonesian archipelago. Local transmissions occurring mainly in the island of Java, specifically in the capital city of Indonesia: Jakarta and other provinces in Java island such as West Java, Banten, Central Java, and East Java. North Sumatera province is one of the provinces outside of Java island that reported local transmission of COVID-19 [16], [17] On March 18, 2020, North Sumatera Province reported the first confirmed case of COVID-19 [18]. The case was a man who had traveled to Jerusalem and Italy a few couple days before. As of April 23, there were 111 cases including 12 deaths (CFR = 10.81%) in North Sumatera. The battle against COVID-19 is still continuing in North Sumatera [19].

In addition, during the public health emergencies like COVID-19, it is important to implement good surveillance [20], [21]. Surveillance activities are needed to identify risk factors, measure the impact of disease, detect changes in trends, determine action items, prioritize the use of public health resources, and the target of interventions [22]. The surveillance officers as the front liner officer play a critical role to prevent the spread of COVID-19. A good knowledge about the disease is needed for the surveillance officers and outbreak investigation team in carrying out these surveillance actions. Therefore, the purpose of the study was to assess the knowledge of COVID-19 among the surveillance officers and outbreak investigation team in North Sumatera, Indonesia.

Methods

Study design and setting

This cross-sectional survey was conducted from March 5, 2020, to April 20, 2020. The online survey was designed by Google Forms and then the survey’s link shared to the surveillance *WhatsApp* groups in North Sumatera and the districts. Each member of the *WhatsApp* group was invited to answer the survey and requested to forward the survey link to others. It required 7–10 min to complete the survey.

Data collection

The questionnaire consisted of two parts: Demographics and knowledge section. Demographic section included age, gender, level of education, length of work, and surveillance training experience variables. To measure the knowledge regarding the surveillance of COVID-19, the questions according to guideline of prevention and control of COVID-19 by the Ministry of Health of Indonesia [5]. In the last part of questionnaire, we ask about willingness to conduct surveillance and outbreak investigation of COVID-19 in their work area.

Statistical analysis

The respondent’s knowledge score about COVID-19 was calculated as the sum of the response scores. The number of questions regarding the respondent’s knowledge was 24 questions. Each correct respondent’s answer will get a score of 1 and 0 for each incorrect/unknown answer. The minimum score of the respondent is 0 and 24 for the maximum score. The level of knowledge was grouped into “good” and “poor” based on the 80% cutoff point. The Cronbach’s alpha coefficient of the knowledge questionnaire was 0.73 in our sample, indicating acceptable internal con]. A two-step logistic regression was employed to assess the association of participants’ demographic data and other potential variables with the knowledge of participants. All variables with $p \leq 0.25$ in the univariate analysis were included in the multivariate model. Odds ratio (OR) was used to determine the potential variables. The estimated crude OR of the univariate analyses and the adjusted OR (aOR) of the multivariate analyses were calculated together with 95% confidence interval (CI).

Ethical consideration

The study was approved by the Research Ethics Committee of University of Prima Indonesia (No: 005/KEPK/UNPRI/III/2020). We conducted the survey with agreement of the respondents. All personal information of the respondents involved in the survey have been kept confidential.

Results

Characteristics of participants

A total of 246 participants were collected during the study period. Most of participants were female 193 (78.5%), there were only 57 (23.2%) participants who had surveillance training, the highest age group was 31–40 years (48.0%), level of education was bachelor degree (61.4%), and length of work was higher than 5 years (71.5%) (Table 1).

Knowledge of COVID-19

We found that 109 out of 246 (44.3%) participants were good knowledge on COVID-19.

Table 1: Univariate logistic regression analysis of knowledge on COVID-19 (n = 246)

Variable	n (%)	Good knowledge	Univariate		Multivariate	
		n (%)	P	OR (95% CI)	P	OR (95% CI)
Age group						
<30*	34 (13.8)	11 (32.4)		1		1
31–40	118 (48.0)	60 (50.8)	0.41	1.42 (0.62–3.25)	0.74	1.16 (0.49–2.76)
>40	94 (38.2)	38 (40.4)	0.13	0.66 (0.38–1.13)	0.08	0.60 (0.34–1.07)
Gender						
Male*	53 (21.5)	26 (49.1)				
Female	193 (78.5)	83 (43.0)	0.44	1.28 (0.69–2.35)	0.99	1.01 (0.49–2.06)
Level of education						
Diploma degree*	61 (24.8)	21 (34.4)		1		1
Bachelor degree	151 (61.4)	71 (47.0)	0.04	1.51 (1.81–4.48)	0.07	1.05 (0.41–2.73)
Master degree	34 (13.8)	17 (50.0)	0.75	1.13 (0.54–2.37)	0.59	0.79 (0.35–1.82)
Surveillance training						
Yes*	57 (23.2)	35 (59.3)	0.004	2.47 (1.35–4.54)	0.028	2.15 (1.09–4.27)
No	189 (76.8)	74 (39.6)				
Length of work (year)						
<1*	53 (21.5)	24 (45.3)		1		1
1–3	5 (2.1)	1 (20.0)	0.96	0.98 (0.53–1.82)	0.81	0.92 (0.46–1.82)
>3–5	12 (4.9)	5 (41.7)	0.29	3.26 (0.36–29.74)	0.46	2.33 (0.25–21.68)
>5	176 (71.5)	79 (44.9)	0.04	1.14 (1.35–3.73)	0.95	1.05 0.29–3.72)
Location of workplace						
Subdistrict*	143 (58.1)	55 (38.5)		1		1
District/regency	70 (28.5)	34 (48.6)	0.02	2.46 (1.13–5.35)	0.14	1.88 (0.82–4.29)
Province	33 (13.4)	20 (60.6)	0.03	1.63 (1.70–3.78)	0.46	1.40 (0.58–3.42)

P: *P* value, OR: Odds ratio, CI: Confidence interval, *: Reference group

Almost all of participants (99.6%) know that COVID-19 caused by coronavirus. All participants reported that they have heard of COVID-19 before the survey was conducted. As much as, 83.5% of participants first heard of COVID-19 through social media followed by television (81.1%) and health worker/health-care providers (66.3%). Most of participants (96.3%) reported that they know about the COVID-19 guidelines, but only 52.4% of participants have good understanding of the guidelines (Table 2).

Table 2: Participants' general knowledge of COVID-19 and examining of COVID-19 guidelines

Questions	n (%)	χ^2	P
Source of information			
Social media	208 (83.5)	2.132	0.555
Television	202 (81.1)	2.141	0.678
Health worker/health-care provider	165 (66.3)	1.831	0.877
Online newspaper	97 (39)		0.794
COVID-19 caused by			
Virus	245 (99.6)	0.799	0.371
Bacteria	1 (0.4)		
COVID-19 more danger than MERS-CoV and SARS			
Yes	126 (51.2)	43.042	<0.001
No	120 (48.8)		
Main clinical symptoms of COVID-19: Fever, fatigue, dry cough, myalgia, and influenza			
Yes	241 (97.9)		
No	5 (2.1)		
Transmission of COVID-19 through droplets			
Yes	219 (89)	0.224	0.636
No	27 (11)		
Not all persons with COVID-19 will develop to severe cases			
Yes	182 (73.9)	1.573	0.21
No	64 (26.1)		
Persons who do not show clinical symptoms can infected others			
Yes	209 (84.9)	0.09	0.764
No	37 (15.1)		
COVID-19 can be prevented			
Yes	225 (91.5)	0.04	0.948
No	21 (8.5)		
Know about COVID-19 guideline			
Yes	237 (96.3)	80.974	<0.001
No	9 (3.7)		
Understanding of COVID-19 guideline			
Good	129 (52.4)	73.426	<0.001
Poor	117 (47.6)		

MERS: Middle-East respiratory syndrome

Associated factors with knowledge of COVID-19

The univariate logistic regression analysis resulted that level of education (bachelor degree) has received surveillance training, length of work (more than 5 years) and location of workplace (district/regency and province) were associated with knowledge of COVID-19 (Table 1). However, the multivariate model resulted that only surveillance training was the most associated variable with knowledge of COVID-19 (Table 1). Participants who have received surveillance training were 2.15 times more likely to have good knowledge compared to participants who have not received surveillance training.

Willingness to conduct investigation and contact tracing

The study found that participants who have good knowledge and who have received surveillance training were the significant factors of willingness to conduct surveillance and outbreak investigation of COVID-19 in North Sumatera, Indonesia. Participants who have good knowledge were 2.45 times more likely to be willing to conduct surveillance rather than they who do not have good knowledge (95% CI= 1.44-41.17). In addition, participants who have received surveillance training were 2.08 times more likely to be willing to conduct surveillance rather than they who not received surveillance training (Table 3).

Table 3: Predictors of willingness to conduct surveillance and outbreak investigation of COVID-19

Variable	Willing to conduct surveillance n (%)	p value	OR (95% CI)
Knowledge			
Good*	69 (63.3)	0.001	2.45 (1.44–4.17)
Poor	53 (38.7)		
Training			
Yes*	38 (66.7)	0.036	2.08 (1.44–4.17)
No	84 (44.4)		
Level of education			
Diploma degree*	25 (41)		1
Bachelor degree	74 (49)	0.089	2.26 (0.88–5.77)
Master degree	23 (67.6)	0.125	1.95 (0.83–4.54)
Length of work (year)			
<1*	26 (49.1)		1
1–3	2 (40)	0.783	0.91 (0.47–1.78)
>3–5	5 (41.7)	0.951	1.1 (0.17–6.81)
>5	89 (50.6)	0.751	1.22 (0.34–4.14)

P value, OR: Odds ratio, CI: Confidence interval, *: Reference group

Discussion

Knowledge is a logical prerequisite to the intentional performance of health-related behaviors, prevention beliefs, individual’s cognition, and positive behaviors [24]. Good knowledge will enhance self-confidence in carrying out competent actions. The previous studies have explored the knowledge of COVID-19 among health care workers [25], [26], [27], but our study aimed to determine the knowledge of surveillance officer and outbreak investigation team. The findings of the study showed that a poor level of knowledge toward the COVID-19 among surveillance officer and outbreak investigation team in North Sumatera. We identified that surveillance training was the most associated variable to the poor level of participants’ knowledge.

Surveillance is playing a critical role in preventing and controlling the public health emergencies situation like COVID-19 [20], [28]. Our study revealed that participants who have received any surveillance training have good knowledge about COVID-19 (59.3%). We identified significant knowledge gaps between those who have received surveillance training and those who have not received surveillance training. For instance, as much as, 59.3% those who have received surveillance training have good knowledge of COVID-19 rather than those who have not received surveillance training (39.6%). Although COVID-19 is a new emerging infectious disease, participants who have received surveillance training showed a good level of knowledge. This can be explained because the topic-related prevention and control including surveillance, outbreak investigation, and response of new emerging infectious diseases were included in the curriculum of the training. Not surprisingly, participants who have received surveillance training were 2.15 times more likely to be have good knowledge than they who not received training (95%CI: 1.09–4.27). Training is a key component to strengthen the capacity for public health surveillance and response [21].

The study also found that only 122 out of 246 participants (49.6%) expressed a willingness to conduct investigation and contact tracing of COVID-19 in the community. In addition, as much as, 27 participants (79.4%) who have good knowledge and also have received surveillance training expressed a willingness to conduct surveillance. There were two main reasons that participant unwilling to conduct surveillance because of shortage of personal protective equipment (PPE) and fear of COVID-19 (57.3% and 25%, respectively). Shortage of PPE occurs not only in North Sumatera but also in Indonesia [29], [30]. An appropriate PPE increases the confidence of the surveillance officers in conducting surveillance and outbreak investigation in the community [31], [32]. As COVID-19 is a new emerging disease and the most devastating effects globally, its emergence and rapid spread causes confusion, anxiety, and fear not only in the general public but also in health care workers’ perspective [33], [34], [35].

Another important finding was that social media as the most predominant source of information related to COVID-19. Nowadays, social media has increasingly become a popular and important source of health information by connecting people with health contents, experts, support, and latest news. The social media can be used to improve professional networking and education, public health programs, sharing of health information, and also online surveillance training [36], [37]. Finally, we are now facing the unpredictable public health emergencies situation [38], [39]. Surveillance has responsibilities to prevent, detect, and respond it. Policy-makers should consider the perspectives of surveillance systems as the core effort of public health. Therefore, it is a crucial need to conduct surveillance training to all surveillance officers to enhance their knowledge and willingness to conduct surveillance and outbreak investigations in the next future [20], [21], [40].

Strength and limitation

To the best of our knowledge, this is the first study examining the knowledge toward COVID-19 among surveillance officers and outbreak investigation team in Indonesia. The survey provides direct information about the knowledge of COVID-19, and the result determines the importance of surveillance training. However, the survey was conducted in only one province in Indonesia, the results may not be generalizable to other provinces. In addition, the measurement of knowledge may be imprecise due to the limited number of items. Further study is needed to expand upon and resolve these issues.

Conclusions

The knowledge of surveillance officers and outbreak investigation team of COVID-19 in North Sumatera is relative low. Participants who have good knowledge and have received surveillance training expressed a willingness to conduct surveillance of COVID-19 in the community. There is a clear need of training for surveillance and outbreak investigation team to improve the understanding and skill to prevent the public health emergencies situation and preparedness the emergencies situation in the next future.

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Public Eye toward COVID-19: A Systematic Review

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Abstract

BACKGROUND: The general public has an important role in controlling the spread of infectious diseases by pursuing prophylactic measures.

AIM: The aim of the present systematic review was to describe public perceptions, knowledge, attitudes, and behaviors toward COVID-19.

METHODS: In this review, articles were extracted from the Google Scholar, Embase, Scopus, Web of Science, and PubMed search engines. The main keywords for the search were coronavirus, COVID-19, public perceptions, knowledge, attitudes, and behaviors.

RESULTS: The knowledge level toward novel coronavirus in different countries was generally high, and it had an increasing pattern during the pandemic phase. Furthermore, the insight self-efficacy, perceived severity of the COVID-19, and intention to meet the needs of preventive measures have increased notably. Furthermore, there are several misconceptions and unconfirmed beliefs in the general public in the case of preventive measures recommended, in particular.

CONCLUSIONS: Health authorities and other disease control centers should monitor public misconceptions and perceptions continuously and manage a trusting platform to be presented to the public, especially in the case of a novel disease outbreak.

Introduction

In late 2019, a new strain of coronavirus (COVID-19) spread rapidly around the world and it led to the second global pandemic in the 21st century. The "early phase" began in December 2019 with the outbreak of the disease in Wuhan, China. Later, other cases of the disease were reported in other countries such as Korea, Japan, Italy, Japan, Iran, and the United States [1]. On January 30, 2020, the World Health Organization (WHO) declared it as a "Health Emergency of International Concern" and on 11 March, WHO defined COVID-19 as a pandemic [2].

As of April 20, 2020, a total of 2,428,274 cases, 166,126 deaths, and 636,723 recovered in the worldwide have been reported [3]. The clinical and epidemiological characteristics revealed that 18.5% of the patients with SARA developed to the severe phase, which is defined by acute respiratory distress syndrome, dyspnea, and coagulation dysfunction [4], [5]. Initially, with the aim of limiting the prevalence of coronavirus, measures were taken according to the strategy of most countries to contain/delay it. This strategy included preventing close contact, isolating cases, and quarantining. Most countries also focused on a reduction strategy aimed at minimizing the effects of the disease. Due to the fact that antiviral drugs have no effect and yet there is no vaccine for this disease; therefore, the emphasis is on strict personal hygiene, frequent handwashing, covering the mouth when coughing, social distancing (maintaining a distance of at least one meter), and avoiding crowded places. The general public has a key role in controlling the disease during and after the pandemic by adopting government-recommended prophylactic measures. The protection motivation theory, as a theoretical model, has declared that behavioral manner may be influenced by public perceptions of personal susceptibility to the disease, disease severity, effectiveness of recommended measures, and self-efficacy (confidence in the ability to perform the recommended measures) [6]. Furthermore, knowledge, attitudes, and practices (KAP) of peoples have an important role in successful control and fighting against COVID-19 [7], [8]. Social behavior may also be impressed by the knowledge and more affective factors, like the feeling of anxiety is of importance [9], [10]. Intuition into behaviors and public perceptions during a pandemic can provide useful information for risk relevance. The COVID-19 pandemic was specified by changes in risk, propaganda, and recommended measures during the different phases. This situation is an opportunity to gain insight into behaviors and public perceptions in the world. The aim of the present systematic review was to describe public perceptions, knowledge, attitudes, and behaviors toward COVID-19.

Methods

Search strategy and criteria

A narrative-systematic search in the scientific literature to find studies on KAP, public perceptions, and behaviors during the COVID-19 pandemic was performed on April 29 in 2020. PubMed, SCOPUS, Web of Science, Embase, and Google Scholar databases were searched with predefined online search terms. The terms which were used represented public perceptions of risk (perceived vulnerability and disease severity), KAP, willingness to take preventive measures, and actual behavior.

Inclusion criteria contained these items: Original research studies which were centered on public perceptions, behaviors, knowledge, and attitudes during the COVID-19 pandemic. Furthermore, only articles published in the English language were selected.

The excluded studies were as follows: The studies regarding pregnant women, diabetics' patients and dialyzed patients, editorials, meta-analysis, and systematic reviews. However, the reference lists were searched for relevant papers. Further, a manual search was conducted with the first authors' reference database. This study focused on the description of studies, results, their application, and limitations in qualitative composition, not on the meta-analysis.

The PRISMA guidelines for the literature search and preparation of the article were used [11].

The first author (BF) could gather 234 articles. In the primary evaluation on the basis of title and abstract, 187 records were excluded from the study. Then, the full-text articles (n = 47) were screened independently by the first author (BF) and the third author (LI). Any case of disagreement was discussed fully and further study and evaluation with the help of other authors were used to resolve data mining differences.

Results

Figure 1 presents the study flow diagram. Table 1 represents the characteristics of the studies included in this narrative review. The studies were conducted in China (n = 2), Iran (n = 2), the United States, and United Kingdom (n = 1), and the data had gathered during the coronavirus pandemic phase.

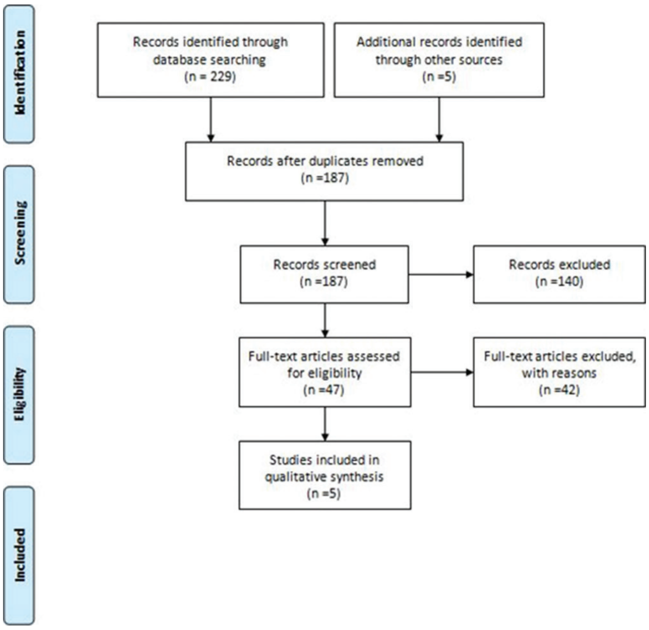

Figure 1: Systematic review process

Zhong *et al*. surveyed KAP toward COVID-19 in China. The data were collected with the aim of an online KAP questionnaire (containing 12 questions for knowledge, 2 questions for attitudes, and 2 questions for practices). A total of 6910 participants were included in the study. The results revealed that public knowledge has a high level about the novel coronavirus. Moreover, this subject was highlighted in women groups and high level educated participants. Furthermore, holding an optimistic attitude, more than 90% of participants believed that the coronavirus will finally be successfully controlled. In short, they suggested that health education programs can be helpful in improving COVID-19 knowledge, encouraging an optimistic attitude, and maintaining safe personal hygiene practices [12]. Furthermore, Taghrir *et al*. studied knowledge, preventive behaviors, and risk perception of SARS-CoV-2 in medical students in Iran. The data were gathered by an online questionnaire that had 26 items (15 questions about knowledge, 9 questions regarding preventive measures, and 2 questions about COVID-19 risk perception). Two hundred forty questionnaires were fully completed by

Table 1: The characteristics of the studies included in this review

Study	n (missed)	Country	Survey method	Study design*	Content of questionnaire	Gender	Age ranges	Occupation
Zhong *et al.* [12]	6919 (9)	China	Online	CS	KAP	F, M	16-50$^+$	PL, S, U, ML
Taghrir *et al.* [13]	240 (0)	Iran	Online	CS	K and PB and RP	F, M	20-30	MS
Nemati *et al.* [14]	85 (0)	Iran	Online	CS	A and K	F, M	23–40$^+$	HCW
Geldsetzer [15]	6000 (24)	US and UK	Online	CS	K and PB and RP	F, M	18–58$^+$	HCW, O
Zhou *et al.* [16]	1375 (0)	China	Online	CS	KAP	F, M	none	HCW

AQ7

*CS indicates cross-sectional, D: Demographic, KAP: Knowledge, attitudes and practices, PB: *Preventive behaviors*, RP: Risk perception, A: Anxiety, F: Female, M: Male, HCW: Health care worker, MS: Medical student, S: Student, PL: Physical labor, U: Unemployed, ML: Mental labor, O: Other.

students. The knowledge and related knowledge about COVID-19 showed high levels. Furthermore, the mean rate of practicing preventive behaviors and performance in preventive behaviors was high. However, the participants' risk perception was in the moderate range and it had a negative relation with preventive behaviors. Risk perception was different between groups with varying educational levels and also in gender sub-groups. The female groups had a lower range of risk perception [13]. In another study, Nemati *et al*. assessed knowledge and anxiety toward COVID-19 among nurses in Iran. A total of 85 nurses were enrolled in the study and answered the questions through a self-administered questionnaire. The results illustrated that the anxiety level toward novel coronavirus among nurses was reported to be high. Furthermore, their awareness in relation to infectious disease was well. Moreover, more than 50% of the participants had good knowledge about the disease. Most of them rated their information as a high level. However, despite this stated high level of knowledge, more information is still needed to be provided by the World Health Organization and the National Iranian Ministry of Health [14]. Furthermore, Geldsetzer reported the results of a rapid online survey on public perception toward COVID-19 in the United States and the United Kingdom. The total number of participants who completed the questionnaires was 5974 (2986 from the US and 2988 from the UK). The knowledge level in participants in both countries was well. Furthermore, the results showed that most of the participants believed that common surgical masks are highly effective in preventing infection with COVID-19. Regardless of the reported high level of information, about 25% of participants stated a need to seek more information on SARS-CoV-2 from health-care staff. However, a large proportion of participants had misconceptions about how to prevent an infection disease and how to seek medical care [15]. In addition, Zhou *et al*. studied the KAP of healthcare workers regarding COVID-19 in China. The data were collected by a questionnaire. One thousand three hundred fifty-seven of healthcare workers from 10 hospitals collaborated in the study. The results showed that 89% of healthcare workers had satisfactory knowledge of COVID-19, more than 85% feared self-infection with the novel coronavirus, and 89.7% followed correct practices toward SARS-Cov-2. Furthermore, the knowledge level and some other risk factors, including job category and work experience, affected health workers' attitudes, and practice concerning new coronavirus. Steps need to be taken to protect healthcare workers from risks related to working hours, work experience, job category, educational achievement, and front line healthcare workers [16].

Discussion

In this population-based narrative- systematic review, the results revealed that the knowledge level toward novel coronavirus in different countries was generally high, and it had an increasing pattern during the pandemic phase. The public information in case of preventing virus transmission was estimated to be well [12], [13], [14], [15], [16]. Similar results have been found in case of other epidemic or pandemic diseases such as flu, SARS, and MERS [17], [18], [19]. The discerned self-efficacy, perceived severity of the COVID-19, and intention to meet the needs of preventive measures have increased notably [12], [13], [14], [15], [16]. Furthermore, during the pandemic, the amount of trust in different forms of media experienced a dramatic change; the trust in social network media decreased due to fake news and exaggerations in mortality of COVID-19 [20]. Therefore, the discerned reliability of information from the governmental authorities such as ministry of health increased. On the other hand, in healthcare workers feeling of anxiety increased, especially for their family to be infected by COVID-19 [14], [21]. During the pandemic phase, the discerned vulnerability had increased and undertakers did most of the cautionary measures [15], [16]. This was in line with the fact that the number of infected people and the number of fatalities increased rapidly. A similar finding is reported in other epidemics (flu, SARS) [22], [23]. On the contrary, there are several misconceptions and unconfirmed beliefs in the general public in the case of preventive measures recommended, in particular. In this regard, such misconceptions are reported during H1N1 flu epidemic [24], [25]. In addition, most respondents believed that it was less likely for themselves to become infected to COVID-19 than other people at the peak of the pandemic. A similar misconception was observed in other studies on the flu epidemic [22], [23]. Since, during the pandemic, the public in different countries felt unrealistically optimistic regarding the risk of being infected by the virus. This optimism bias could stem from the belief that the illness is not as severe and fatal as it is spoken of in the media and people are able to protect themselves by taking hygienic preventive measures. Considering this fact that the present review has focused on the published papers on COVID-19 pandemic which is a hot topic in past 4 months, the number of studies which were found is not large; so, the small number of articles being reviewed here is the result of the coronavirus tide is not over yet. Despite this limitation, the findings of this review present useful information for further research on knowledge, attitudes, practices, perception, behavior, and anxiety of general public in case of COVID-19 infectious diseases, which can pave the way to achieve successful changes in public behavior that reduce the spread and fatality of the disease. Furthermore, better ways of risk communication could be applied to remove misconceptions and misperceptions in the general public. It is recommended that a risk communication policy should be established to conduct research on behavioral responses and risk perception of the general public during and after the pandemic. Furthermore, it is recommended to use health behavior theories in further studies so that new insight into basic perceptions and behaviors could be achieved.

Conclusion

Regarding the unstable nature of public understanding and behaviors' health authorities and other disease control centers should monitor public misconceptions and perceptions continuously and manage a trusting platform to be presented to the public, especially in the case a novel disease outbreak.

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Possible Mechanism and Current Recommendation of Thromboembolism in COVID-19

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Abstract

The coronavirus disease (COVID-19) has become a global pandemic with a high mortality rate. There has been emerging evidence regarding the presence of thrombosis in patients with severe COVID-19 infection. In addition, prognosis of COVID patients, once they are complicated with DVT or fatal pulmonary emboli, will also significantly decline. Hence, understanding the pathomechanism and prompt treatment of thromboembolism is important in improving the outcome in COVID-19 patients. Prophylaxis anticoagulant was proposed for all hospitalized COVID-19 patients. The aim of this article is to review the current literature regarding pathomechanism, risk assessment, diagnosis, and management of VTE.

Introduction

The coronavirus disease (COVID-19) has become a global pandemic. Since December 2019, the total number worldwide of confirmed cases is 2,356,414 with mortality rate 6.8% involving 213 countries all over the world (WHO data April 21, 2020) [1]. The first two COVID-19 patients in Indonesia were reported on March 2, 2020. As per April 21, 2020, the total cases of COVID-19 reached 6760 positive cases, of which 590 had died. The mortality rate in Indonesia was as much as 8.7%, and it was the highest rate in Southeast Asia [2].

Study of epidemiology and clinical characteristics of COVID-19 patients have started to unfold. On the other hand, the mortality risk factors and the exact clinical course of disease, including shedding of the coronavirus, have not been well described. The clinical spectrum of COVID-19 ranges from mild to critically ill cases. The clinical spectrum of COVID-19 consists of mild to critical illness. The previous studies revealed that old age, increased SOFA scores, greater d-dimers level more than 1000 ng/mL, and those who have pre-existing comorbidities are more likely to have a poor prognosis [3], [4]. Patient with COVID-19 who fell into severe or critical condition is exposed to venous thromboembolism potential risk factors such as infection, immobilization, respiratory failure, hypoxia, mechanical ventilation, and use of central venous catheter (CVC) [5].

Three cases in China showed antiphospholipid autoimmune response in patients with COVID-19. These findings give rise to coagulopathy roles in extensive thromboembolism in patients with COVID-19 [6]. The prognosis of COVID patients, once they are complicated with DVT or fatal pulmonary emboli, will significantly decline [5], [7], [8].

This article was aimed to summarize the current literature of mechanism and recommendation in thromboembolism related COVID-19 patients.

Epidemiology

Venous thromboembolic events (VTE) discussed in this article include deep vein thrombosis (DVT) and pulmonary embolism (PE). Epidemiology data regarding these events in COVID-19 were still very limited. The prevalence of VTE, particularly in critically ill/severe patients suffering from COVID-19, was reported as much as 25–27%. A study from three Dutch hospitals showed a 27% incidence of VTE, including PE and DVT [5]. Another data from China hospital revealed 25% (25/81) patients with severe COVID-19 pneumonia developed lower extremity venous thrombosis [8]. In a study by Xie *et al*. in Tongji Hospitals, 40% (10/25) COVID-19 pneumonia confirmed patients who underwent computed tomography pulmonary angiography scans (CTPA) were found to be acute PE positive [9].

Pathomechanism

COVID-19 may put the patient susceptible to both arterial and venous thromboembolism due to hypoxia, immobilization, disseminated intravascular coagulation (DIC), and excessive inflammation [5]. Systemic pro-inflammatory cytokine responses, including interleukin-1 and interleukin-6, are mediators of atherosclerosis, directly contributing to plaque rupture through local inflammation and hemodynamic changes. These responses also induce procoagulant factors, which predispose to ischemia and thrombosis [4]. Patient with COVID-19 who fell into severe or critical condition is also exposed to other potential risk factors for VTE such as mechanical ventilation, respiratory failure, and use of CVC [5].

Cell entry is an important component for cross-species transmission, particularly for beta-coronavirus. Spikes, surface glycoproteins encoded by all coronaviruses which bind to host cell receptors, mediate the entry of viruses. For beta-coronaviruses, the receptor-binding domain, a single region of spike protein, mediates interactions with receptors of host cell. After binding to the receptor, protease of the adjacent host cuts the spike, which liberates fusion peptides in spike, facilitating the entry of the virus. Familiar host receptors for beta-coronavirus include dipeptidyl peptidase-4 for MERS-CoV and angiotensin-converting enzyme 2 (ACE2) for SARS-CoV. In addition, ACE2, which is also the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells. The dysfunction of vascular endothelial cells is one of the mechanisms of thrombus formation [10].

Endothelial cell dysfunction caused by infection results in excess thrombin production and cessation of fibrinolysis, which indicates a state of hypercoagulability in patients with infections such as COVID-19. In addition, hypoxia found in severe COVID-19 can induce thrombosis by increasing not only viscosity of blood but also signaling pathways that depend on transcription factors induced by hypoxia [11].

Study by Chen *et al*. revealed index of biochemical examination of 99 patients with COVID-19 pneumonia, and also reported an abnormal biochemical indexes phenomenon related to patients' hemoglobin. This report shows that the number of neutrophils and hemoglobin in most patients decreased, while the rate of erythrocyte sedimentation, serum ferritin, albumin, C-reactive protein, and lactate dehydrogenase in many patients increased significantly [12].

Whenzong and Hualan hypothesize a possible involvement of hemoglobin in the pathogenesis of COVID-19 [13]. When hemoglobin decreases, and heme increases, the body will accumulate too much dangerous iron ions, which will induce inflammation and increase albumin and C-reactive protein. Cells react to stress due to inflammation, creating large amounts of serum ferritin to bind to free iron to reduce destruction [13]. The previous study stated that iron ion might cause endothelial dysfunction, including vascular endothelial. A study by Zhu concludes that intravascular nanoparticles of iron oxide may provoke inflammation and dysfunction of endothelial cells [14]. However, that proposed pathogenesis of hemoglobin in COVID-19 by Whenzong and Hualan has received critical commentary by Read *et al*. due to the lack of experimental evidence to support any of their conclusions and their claiming the therapeutic effect of drugs that are only just entering clinical trials [15].

The presence of antiphospholipid (aPL) antibodies might also eventually cause thrombosis. Anticardiolipin IgA antibodies, as well as anti-β2-glycoprotein I IgA and IgG antibodies, were found in COVID-19 patients [6]. Antiphospholipid antibodies target phospholipid protein abnormally, and the presence of these antibodies is important in antiphospholipid syndrome diagnosis. Still, these antibodies can also increase temporarily in patients with critical diseases and various infections. In critical patients such as thrombotic microangiopathy, heparin-induced thrombocytopenia, and disseminated intravascular coagulation, the appearance of these antibodies may rarely cause thrombotic events that are difficult to distinguish from other causes of multifocal thrombosis [6]. The main antigenic target of the aPL antibody is known as β2-glycoprotein I (β2GPI), mediating the binding of aPL antibodies to target cells, including monocyte, endothelial cells, trophoblast, and platelet, which lead to pro-inflammatory and prothrombotic changes that subsequently result in thrombosis [16].

The net results of those mechanisms may induce the development of subclinical thrombosis in patients suffering from COVID-19. Increased D-dimer, a sign of excessive coagulation activation and hyperfibrinolysis, may explain the result of those pathomechanisms. D-dimer is often used to identify active thrombus with high sensitivity but low specificity. Patients with COVID-19 have an increase of the D-dimer level. After undergoing therapeutic anticoagulation, D-dimer level decreases continuously, which means D-dimer can predict not only thrombosis but also monitor anticoagulant's effectiveness [7]. Another evidence, histopathology study on lung biopsy of critical patients with COVID-19, revealed the presence of occlusion and microthrombosis formation in pulmonary small vessels [17].

Risk assessment and diagnosis

It is important to identify which patients with COVID-19 are at increased risk of VTE. Current clinical recommendation state that thromboprophylaxis should be given to all acute patient with high risk of VTE. Modified IMPROVE-VTE risk score is a scoring system that combines D-Dimer level with other VTE clinical predictors to identify patients with high-risk VTE who are eligible for thromboprophylaxis medication (Table 1). Marker for higher VTE risk is a total score of 4 or 2–3 with D-dimer level at the time of screening is more than twice the upper limit of normal range [18].

Table 1: Modified IMPROVE VTE risk score

VTE risk factor	VTE risk score
Previous VTE	3
Known thrombophilia[a]	2
Current lower limb paralysis or paresis[b]	2
History of cancer[c]	2
ICU/CCU stay	1
Complete immobilization[d] ≥ 1 day	1
Age ≥ 60 years	1

CCU: Cardiac care unit, ICU: Intensive care unit, IMPROVE: International Medical Prevention Registry on Venous Thromboembolism, NIH: National Institutes of Health, VTE: Venous thromboembolism. [a]A congenital or acquired condition that causes the risk of excessive thrombosis (e.g., factor C or S deficiency, lupus anticoagulant, Leiden Factor V). [b]Feet falls into bed 5 s but has an effort against gravity (taken from the NIH stroke scale). [c]Cancer (not including non-melanoma skin cancer) at any time in the past 5 years (cancer must be in remission to meet eligibility criteria). [d]Immobilization is limited to beds or chairs with or without bathroom privileges.

Risk of pulmonary embolism

The clinical manifestation of acute PE is not specific. Symptoms include chest pain, dyspnea, hemoptysis, and syncope. COVID-19 may exhibit symptoms that bear a misleading resemblance to acute PE. This generates a diagnostic challenge for clinician treating patient with COVID-19. Identifying the presence of risk factors of VTE is vital to determine disease clinical probability. Revised Geneva Rule and Wells Score are often used as prediction rules. They combine symptoms, clinical findings, and risk factors to classify patients with suspected PE into specific category, separating them from the others. Acute thrombosis will activate coagulation and fibrinolysis, leading to increase serum D-dimer. D-dimer has high negative predictive value in diagnosing acute PE. If D-dimer level is normal, then the diagnosis of acute PE is unlikely. Meanwhile, the positive predictive value of high D-dimer is low. Making it less meaningful to confirm the presence of acute PE [19].

Several studies reported that increased D-dimer levels (>1000 ng/mL) are a potential predictor for mortality. D-dimer level has low specificity value, making it unfavorable as a screening tool. Relying D-Dimer as screening tool might cause overutilization of CTPA if applied in patients with acute kidney injury [20].

Prompt diagnosis of PE for patient presenting with respiratory distress, desaturation, and hypotension is crucial to improve the clinical outcomes. Despite the lack of evidence, assessment of serial D-dimer alongside imaging modalities such as bedside echocardiography or Doppler ultrasound will provide valuable information to determine the presence of PE in patients with COVID-19 infection [21]. A recent study examining 25 patients suspected of PE showed that D-dimer levels in patients with confirmed PE had values higher than 7000 ng/mL, significantly higher than those without PE [9], [21].

Risk of deep vein thrombosis

The initial step in the diagnostic algorithm of DVT suspicion is using two levels modified wells score. It will classify DVT suspected patients into two categories (DVT unlikely or likely). For DVT-unlikely, D-dimer examination is established. Normal D-dimer renders DVT unlikely. In patients with DVT-likely, D-Dimer testing is not required, but imaging is required. If not contraindicated, anticoagulation therapy must be started in patients with DVT-likely until imaging. First-line imaging modality of DVT is venous ultrasonography [22].

Elevated serum D-dimer level

Study by Cui, *et al.* revealed that one-fourth of COVID-19 patients developed VTE. VTE was strongly correlated with elevated serum D-dimer level, as shown in Table 2. The authors subsequently tested several D-dimer cutoff value to predict VTE occurrence (Table 3). The best cutoff of D-Dimer value was 1500 ng/ml (85% sensitivity and 89% specificity). This supports the concept of empiric anticoagulation for patients with markedly elevated D-dimers (particularly in situations where frequent CT angiography and Doppler Ultrasound is impossible due to logistic restraints) [8].

Table 2: Characteristics between the VTE and non-VTE groups (*n* = 81)

Characteristics	Normal range	VTE (*n* = 20)	Non-VTE (*n* = 61)	p-value
Age (years)	-	68.4 ± 9.1	57.1 ± 14.3	0.001
Leukocytes (×109/L)	3.5–9.5	7.8 ± 3.1	6.6 ± 2.6	0.120
Lymphocytes (×109/L)	1.1–3.2	0.8 ± 0.4	1.3 ± 0.6	<0.001
Platelets (×109/L)	125.0–350.0	246.6 ± 110.6	248.8 ± 111.7	0.938
Hemoglobin (g/L)	115.0–150.0	123.2 ± 16.5	125.3 ± 16.7	0.633
APTT (s)	27.0–45.0	39.9 ± 6.4	35.6 ± 4.5	0.001
Prothrombin time (s)	11.0–16.0	15.4 ± 1.0	15.6 ± 1.0	0.465
D-dimer (ug/mL)	0.0–0.5	5.2 ± 3.0	0.8 ± 1.2	<0.001

Due to current limited studies, initiating full dose of anticoagulation based on D-dimer value will remain controversial. For now, these decisions may be judged on a patient-by-patient basis, considering both risks of thrombosis and hemorrhage. Among patients without risk factors for hemorrhage, empiric anticoagulation may be reasonable for patients with D-dimer levels above ~1500 ng/ml [8].

Table 3: Sensitivity, specificity, positive predictive value, and negative predictive value of different D-dimer cutoff levels for predicting VTE in COVID-19 patients

Cutoff (µg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1.0	85.0	77.0	54.8	94.0
1.5	85.0	88.5	70.8	94.7
2.0	80.0	90.2	72.7	93.2
2.5	70.0	93.4	77.8	90.5
3.0	70.0	96.7	87.5	90.8
3.5	65.0	96.7	86.7	89.4

PPV: Positive predictive value, NPV: Negative predictive value

In conclusion, modified IMPROVE-VTE risk score and serum D-Dimer level are valuable tools to help identify COVID-19 patients at increased risk of VTE. Increased D-Dimer level above 1500 ng/ml has the best sensitivity and specificity value for predicting the VTE events in COVID-19 patients. The diagnosis of PE and DVT require imaging modality such as bedside echocardiography or Doppler ultrasound.

Management

Anticoagulant

Most patients with COVID-19 may have excessive activation of coagulation and will consequently have microthrombi [17]. Hence, several interim guidelines and health-care center protocols agreed that all hospitalized COVID-19 patients must all be in some form of anticoagulation, whether it is confirmed VTE or not [23], [24], [25], [26], [27].

Heparin, including LMWH or its synthetic form, is commonly used as an anticoagulant to prevent DIC and VTE in patients with infection due to its anti-inflammatory effects. As well as preventing thrombosis, heparin has its property to lower cytokine levels and prevents cytokine storm in patients with COVID-19 [23], [28], [29]. American Society of Hematology (ASH) recommends LMWH or Fondaparinux over UFH for all hospitalized patients unless increased bleeding risk is present. While in patients with heparin-induced thrombocytopenia history, it is recommended to use fondaparinux. If anticoagulants are not available or contraindicated, then mechanical thromboprophylaxis is advised (e.g., pneumatic compression device) [24], [30].

A retrospective analysis by Tang *et al.* comparing 28-day mortality between heparin users and non-users of 449 consecutive patients with severe COVID-19 was done in China. Ninety-nine patients had received heparin for 7 days or longer. They found no significant difference in 28-day mortality between heparin users and non-users (30.3% vs. 29.7% p = 0.910). However, in patients with sepsis-induced coagulopathy (SIC) score ≥4 (Table 4), mortality was significantly reduced by anticoagulant medication (p = 0.029). In patients with D-dimers >3000 ng/mL (6 times of the normal upper limit), anticoagulation results in a 20% mortality reduction (p = 0.017) [11].

Table 4: ISTH SIC scoring system [11]

Item	Score	Range
Platelet count (×109/L)	1	100–150
	2	<100
PT-INR	1	1.2–1.4
	2	>1.4
SOFA score	1	1
	2	≥2
Total score for SIC	4	

INR: International normalized ratio, ISTH: The International Society on Thrombosis and Hemostasis, SIC: Sepsis-induced coagulopathy, SOFA: Sequential organ failure assessment

The International Society of Thrombosis and Hemostasis (ISTH)

The interim guidance delivers risk stratification of coagulopathy at admission for patients with COVID-19 and coagulopathy management (Figure 1) [23]. Their recommendations including:

1. Patients with high D-dimers (e.g., arbitrarily defined as 3–4 times increase) will need to be hospitalized.
2. Monitoring the reduction in fibrinogen levels later in the course of the disease (e.g., days 10–14) can help in determining whether the patient has progressed to DIC.
3. LMWH should be considered in all patients (including those who are not critical) who need to be hospitalized for COVID-19, if there are no contraindications:
   - Active hemorrhage
   - Platelet count <25 × 10^9/L
   - Monitoring recommended for severe renal impairment
   - Abnormal PT or aPTT is not a contraindication
4. LMWH might carry anti-inflammatory properties that provide added benefits in COVID-19 infection.

Prophylactic anticoagulant

Brigham and Women's Hospital guideline recommendation of standard prophylactic anticoagulation for thrombotic disease management in all hospitalized COVID-19 is as follows [27]:

1. If GFR >30 mL/min: Enoxaparin 40 mg subcutaneous (SC) daily
2. If GFR <30 mL/min or acute kidney injury: Unfractionated heparin (UFH) 5000 units SC q8hr
3. Hold if platelets <30,000 or bleeding, start thromboembolic deterrent stockings, and sequential compression devices.

Klok *et al.* reported that in spite of prophylaxis anticoagulant administration, 27% of patients had later developed VTE, and 4% had an incidence of arterial thromboembolism (which may be underestimated, due to the lack of systematic screening for this event and the interrupted observation period in some patients). As a result, they recommend doubling the conventional dose of heparin prophylaxis (e.g., Enoxaparin 40 mg twice a day, rather than once a day) [5]. Prophylactic doses higher than standard doses can also be considered in patients with elevated D-dimers (e.g., 500–1500 ng/mL) [31]:

GFR > 30 mL/min: Enoxaparin 0.5 mg/kg q12hr. Check anti-Xa level 4 h after the third dose, with a target level of 0.5–0.8 IU/ml.

1. GFR < 30 mL/min: UFH 7500 units q8hr (consider dose adjustment for atypical weight patients).

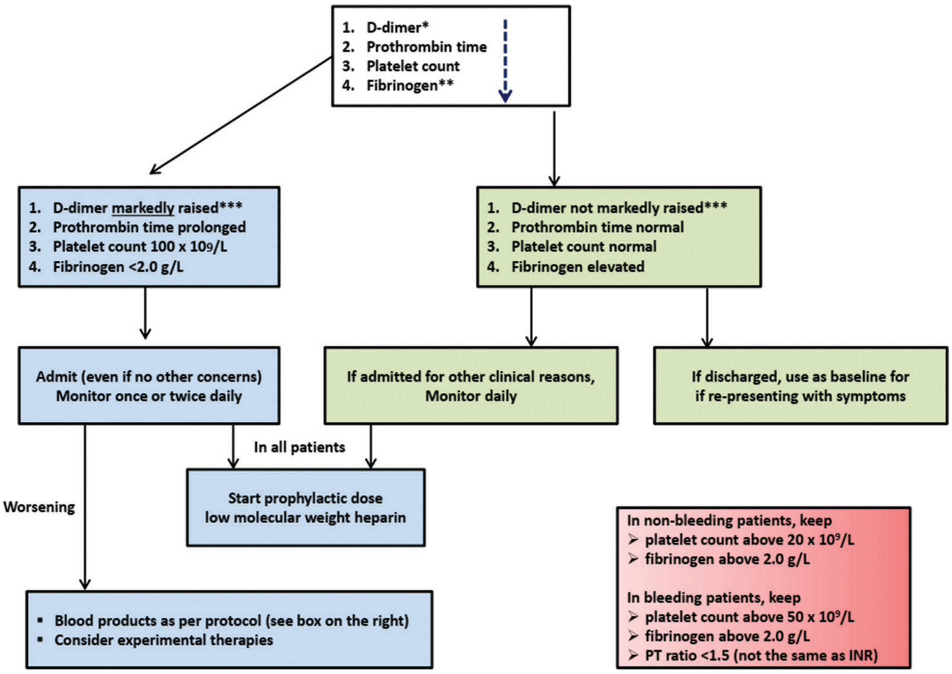

*Figure 1: Algorithm of coagulopathy management in COVID-19 build on simple laboratory parameters. *The list of parameters is written in descending order of importance. **Taking a fibrinogen test may not be available in some laboratories, but monitoring levels can be helpful after hospitalization. ***Even though the specific cutoff cannot be defined, an increase in D-dimer 3-4-fold can be considered significant. One of the values in this table can be considered significant [23]*

Therapeutic anticoagulant

Therapeutic anticoagulation with heparin has been proposed for patients with D-dimers level greater than 2000 ng/ml, but this has not been proven [11], [32]. At present, therapeutic anticoagulation was limited to COVID-19 patients with documented acute VTE, and pre-hospital management with therapeutic anticoagulation (such as for recurrent VTE, certain mechanical heart valves, and atrial fibrillation). In general, the recommendation for VTE therapeutic as follows [23], [25], [26], [27], [33]:

1. If the patient uses direct oral anticoagulant (DOAC) or warfarin for Afib or VTE, switch to the full dose of anticoagulant (LMWH or UFH, according to indications based on kidney function or clinical conditions; LMWH is preferred over UFH to reduce blood drawing in monitoring PTT because of more possible interactions with COVID 19).
2. If the patient has confirmed acute PE or DVT or is undergoing anticoagulant therapy before being hospitalized and is now converted to parenteral, the following guidelines are recommended:
   a. LMWH is preferred to minimize blood drawing and has superior efficacy in critical care population [26].
   b. Patients who need to use UFH (not LMWH) should be monitored with anti-Xa levels (in contrast to PTT given that the increases in COVID-19 patients who are severe and can make PTT unreliable) [26].
3. Consult with a hematologist to discuss specific guidelines if coagulopathy in the patient appears to be deteriorating or to discuss an escalated or modified treatment approach, as some hematologic disorder such as thrombocytopenia increased risk of severity and mortality in COVID-19 [34].
4. Farkas proposed a possible approach to empiric anticoagulation with a limit of D-dimer above 1000–2000 ng/ml, fibrinogen level, thromboelastography (TEG) as guidance, as shown in Figure 2. This author states that this approach has not yet been supported by any high-level evidence, and the decision to provide anticoagulants should preferably be individualized, so this is only intended as an approach scheme in the management of patients. In the case of very advanced stages, severe disease may be characterized by low fibrinogen levels, which can produce hemorrhagic clinics, where anticoagulation can theoretically be dangerous in that condition [31].

Yale-New Haven Hospital (YNHH) and Massachusetts General Hospital (MGH) issued a local protocol of anticoagulation dosing guidelines including LMWH, heparin, fondaparinux, and DOAC (apixaban, rivaroxaban, and dabigatran) in prophylaxis and therapeutic management of VTE, as shown in Table 5.

Direct oral anticoagulant (DOAC)

Because of possible drug interactions between DOAC and combinations of antiviral (especially

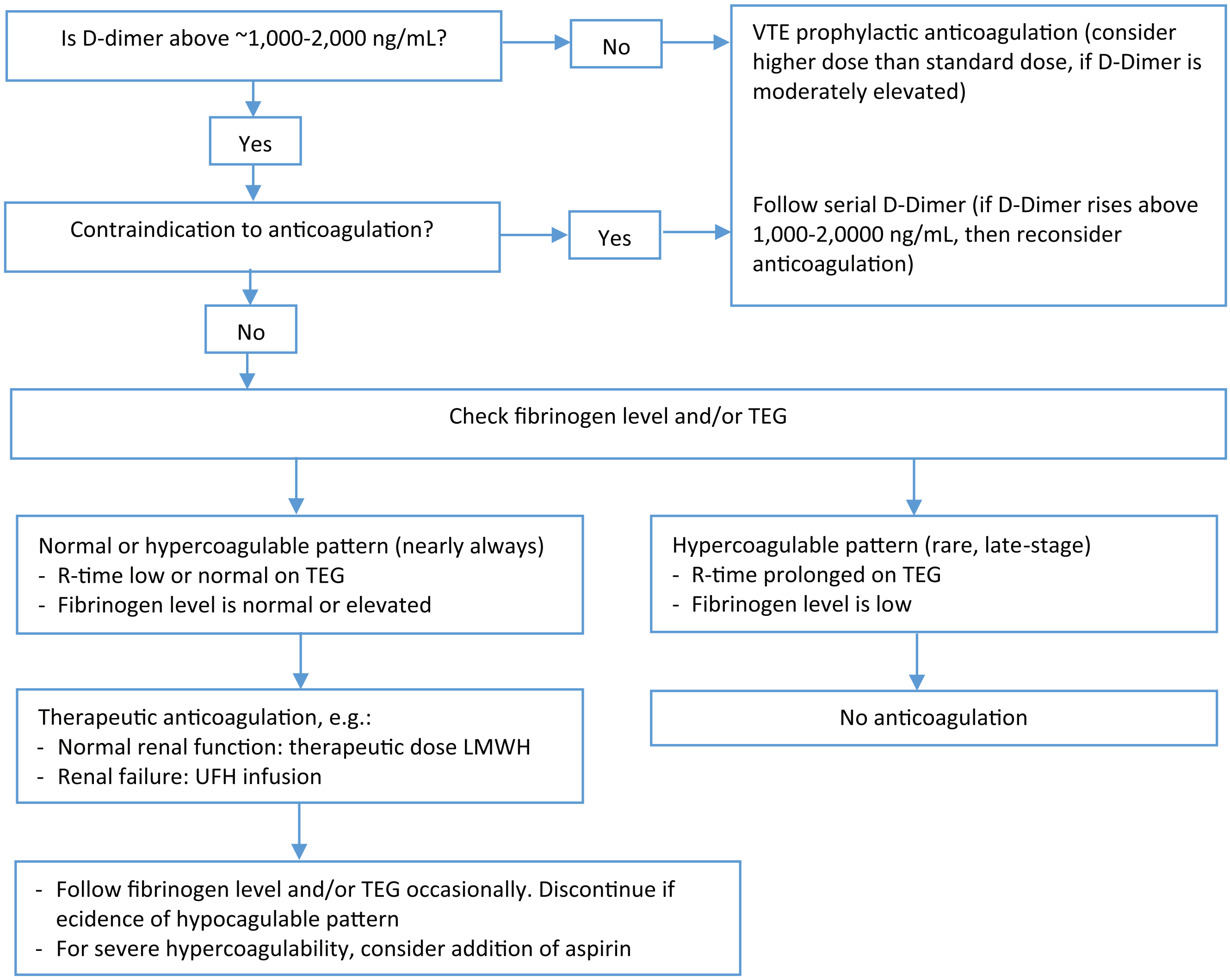

Figure 2: Possible approach to empiric anticoagulation in COVID-19 (adapted from Farkas, 2020) [31]. LMWH: Low molecular weight heparin, TEG: Thromboelastography, UFH: Unfractionated heparin.

anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin), LMWH or UFH should be preferred over DOAC. Such antiviral and antibacterial therapy interferes with the CYP3A4 and/or P-GP pathways, which can increase the risk of bleeding or reduce the antithrombotic effect in the case of DOAC use [19].

Fibrinolytic

At present, there are not enough data suggesting the use of more advanced therapies such as tissue plasminogen activator/tPA or to increase the dose of prophylactic anticoagulation in VTE associated with critically ill COVID-19 patients. There is evidence in animals and humans that fibrinolytic in acute lung injury and acute respiratory distress syndrome (ARDS) improves survival. This evidence also shows fibrin deposition in pulmonary microvasculature as the main cause of ARDS and is expected to be found in ARDS patients and a concurrent diagnosis of DIC seen in laboratory parameters, as observed in more than 70% of patients who died from COVID-19 [35]. Wang *et al.* reported three cases of intravenous tPA off-label (Alteplase) in COVID-19 patients with ARDS and respiratory failure. In all cases, patients showed an initial increase in the P/F ratio. However, the observed increase was temporary and disappeared over time in all three patients after completing their tPA infusion. They also mentioned that larger bolus tPA doses (50 mg or 100 mg bolus) without retaining anticoagulants are worth further considering and research to prevent the recurrence of suspected thrombosis of pulmonary microvascular that underlies ARDS in COVID-19 [35].

In conclusion, it is reasonable to give anticoagulant for prophylaxis treatment to all admitted patient with COVID-19. Heparin is the preferred anticoagulant for patients with COVID-19 because of its anti-inflammation property. Therapeutic anticoagulant should be given to patient with confirmed VTE or has high suspicion of developing VTE. The decision to give anticoagulation should be judged on patient-by-patient basis, considering both risks of thrombosis and hemorrhage.

Table 5: Prophylactic and therapeutic dosing of anticoagulation in VTE management

D-dimer	Brigham and Women's Hospital (BWH)	Yale-New Haven Hospital (YNHH)	Massachusetts General Hospital (MGH)
<500 ng/mL: Prophylactic dose	GFR > 30 ml/min: Enoxaparin 40 mg SC q24h GFR < 30 ml/min: UFH 5000 units SC q8h	BMI < 40 kg/m^2 GFR ≥ 30: Enoxaparin 40 mg SC q24h GFR < 30: Enoxaparin 30 mg SC q24h UFH 5000 units SC q12h BMI ≥ 40 kg/m^2 GFR ≥ 30: Enoxaparin 40 mg SC q12h GFR < 30: Enoxaparin 40 mg SC q24h Heparin 7500 units SC q12h	Standard dose UFH: 5000 units SC q12h Enoxaparin: 40 mg SC q24h Fondaparinux: 2.5 mg SC q24h Apixaban: 2.5 mg PO q12h Rivaroxaban: 10 mg PO q24h Dabigatran: 110 mg followed by 220 mg q24h BMI ≥ 40 kg/m^2 UFH: 5000 units SC q8h Enoxaparin: GFR ≥ 30: 40 mg SC q12h GFR < 30: 40 mg SC q24h
≥500 ng/mL: Intermediate prophylactic dose	Recommended higher prophylactic dose by Klok *et al.* and Farkas. GFR > 30 ml/min: Enoxaparin 0.5 mg/kg q12h. Check an Xa level four hours after the third dose, targeting a level of ~0.5–0.8 IU/ml. GFR < 30 ml/min: UFH 7,500 units q8hr (consider dose adjustment for atypical weight patients).	BMI < 40 kg/m^2 GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban UFH 7500 units SC q12h BMI ≥ 40 kg/m^2 GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban UFH 7500 units SC q12h Apixaban: 5 mg PO q12h regardless of renal function	n/a
Confirmed VTE or high clinical suspicion: Therapeutic dose	n/a	BMI < 40 kg/m^2 GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban Therapeutic UFH BMI ≥ 40 kg/m^2 GFR ≥ 30: Enoxaparin 0,5 mg/kg SC q12h Apixaban GFR < 30: Enoxaparin 1 mg/kg SC q24h Apixaban Therapeutic UFH Apixaban: 10 mg PO q12h × 7 days followed by 5 mg PO q12h	Standard dose: UFH: 80 unit/kg bolus + 18 units/kg/hr infusion Enoxaparin: 1 mg/kg SC q12h Fondaparinux: <50 kg: 5 mg SC q24h 50–100 kg: 7.5 mg 124h >100 kg: 10 mg q24h BMI ≥ 40 kg/m^2 Enoxaparin: GFR ≥ 30: 0.75 mg/kg q12h GFR < 30: 0.75 mg/kg q24h

n/a: Not available, BMI: Body mass index, GFR: Glomerular filtration rate, SC: Subcutaneously, UFH: Unfractionated heparin, VTE: Venous thromboembolism

Prognosis

Several studies proved the role of increased D-dimers as a predictor of mortality. Higher levels of D-dimer and fibrin degradation products showed to have associated with multi-organ dysfunction syndrome and worse prognosis [4], [7]. Huang *et al.* showed that the level of D-dimer at admission was higher in patients who needed critical care support (median [range] D-dimer level 2400 ng/mL [600–14.400]) compared to patients who did not need it (median [range]] D-dimer level 0.5 ng/mL [300–800], p=0.0042) [29]. Tang *et al*. reported DIC development on the 4th day in 71.4% of patients who did not survive compared to only one patient (0.6%) who survived. They also reported increased D-dimer and PT levels with decreased levels of fibrinogen in those who did not survive on 10th and 14th days significantly [7].

Sepsis patients are more likely to develop multi-organ failure in the presence of coagulopathy. Giving these patients medication which inhibits thrombin formation will likely aid in reducing mortality [23]. Study by Tang *et al.* proposed that monitoring D-dimers, PT, fibrinogen, and platelet counts can help to determine prognosis in patients with COVID-19. Aggressive critical care support is proposed if these parameters worsen.

Thrombocytopenia at presentation is considered to be a prognostic factor for mortality (OR, 5.1; 95% CI, 1.8–14.6), as stated by Lippi *et al*. [34]. Thus, this study suggests the clinician provide adequate blood product and consider giving more "experimental' therapies" as the data regarding therapies in COVID-19 are still limited [7], [23].

Conclusion

Patients suffering from COVID-19 are at high risk of developing thrombosis, including VTE. Excessive inflammation, hypoxia, immobilization, aPL antibody, and diffuse intravascular coagulation contributes to development of VTE. There has been upcoming evidence regarding the presence of thrombosis in patients with severe COVID-19 infection. Prophylaxis anticoagulant was proposed for all hospitalized COVID-19 patients. However, until additional data are available, when to initiate full therapeutic anticoagulation will remain controversial. For now, these decisions may be judged on a patient-by-patient basis, considering both risks of thrombosis and hemorrhage. Anti-inflammatory effect of LMWH may provide additional benefit in COVID-19 patients.

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When Shall Coronavirus Disease-19 Stop? Review of Literature

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Abstract

In December 2019, a new coronavirus, now labeled as severe acute respiratory syndrome coronavirus 2, induced an episode of acute atypical respiratory illness started in Wuhan, Province of Hubei, China. The illness triggered by this virus was called coronavirus disease-19 (COVID-19). The infection is spread within humans and has triggered a global pandemic. The amount of death tolls continues to increase and a growing number of countries have been driven to create social barriers and lock-ups. The shortage of tailored counseling remains an issue. Epidemiological researches have shown that elderly patients are more vulnerable to serious diseases, while children tend to have milder symptoms. Here, we checked the latest understanding of this disease and found a possible explanation of the potential sequel and the expectations for the future.

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Introduction

On the morning of 1 day, the world will not wake up to a message, phone, or urgent news that the crisis is over and the ponds of the pandemic have all receded in one go [1]. It is essential that no one knows when the ordeal of humanity will end with the emerging coronavirus "coronavirus disease-19 (COVID 19)" with certainty [2]. In spite of the optimistic visions that herald the diminishing fears and decreasing the growing losses currently, other visions and analyses are expecting the worse for a year coming or over [3].

The problem that closes all doors of anticipation is that the current crisis is not a war that could end with a truce or a peace agreement, and not a recession or economic distress that is sufficient for countries to allocate an urgent support and revitalization package [4]. The world is locked in a struggle with an eccentric microscopic organism, for which complete information is not yet available, so it is difficult to surround the stakes of the crisis or to predict the behaviors of the virus, and all we have until now: A map of actions and measures, a list of expectations and possibilities, and an open horizon on hopes, aspirations, and fears that are not completely negative, and it is not guaranteed to reach its positive points in time [5], [6].

Rapid Pandemic and Mysterious Organism

Even now, the picture is not entirely clear, even among specialists from doctors and microbiologists. The most alarming thing about the crisis is that the new coronavirus "COVID 19" has disturbing characteristics in terms of proliferation, infection, and periods of survival outside living cells, and the most disturbing is that the virus is mysterious for us, so what we know about it is much less than what we do not know [6], [7]. Fears are compounded by preliminary weightings from researchers and doctors that involve the possibility that this huge unknown area is dynamic, that is, it is a changing state in terms of characteristics and activity, and not a constant that can build the equation on it and reach a sound solution to it due to the ability to control the variables associated with the pathology or the conditions of transmission and yet infection [7].

On January 2020, the World Health Organization said it had no evidence of transmission of "COVID 19" between humans, indicating that it may differ from the well-known Corona family, including the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome viruses, or that it is closer to the "Hantavirus" family, which is transmitted from rodents to humans, but not between humans and each other [7], [8]. The important thing is that the aforementioned health statement pushed many countries to a state of reassurance and caused the delay in adopting serious measures to confront, to the extent that many parties now accuse the organization of being the reason behind the spread of the epidemic [8].

Political Versus Medical Point of View

The US President announced in his daily briefing that his country decided to suspend its regular support to the World Health Organization (Washington is the largest contributor to the budget of the International Organization), because it provides false information about the emerging epidemic of coronavirus, according to his statement [9]. Beyond the possibilities of political recruitment, whether in his speech, or accusing the organization of bias toward China, or even accusing China itself of blinding and concealing facts, the only thing that is reached is that the current epidemic represents a real danger, first because it is evil and rapidly spreading and second because we are unable to understand and surround it until now, and most importantly, we were not prepared for this type of long-term crisis, and that point alone will cause confusion in plans and prolong the ordeal [10].

Current Precautions versus Curfews and Panic

Actually, we are facing an "INFODEMIC" rather than a pandemic. Previous reports stated that the virulence and infectivity of measles, smallpox, and SARS were more than COVID-19, 15 times, 10 times, and 3 times, respectively. Case fatality in Ebola virus is 6 times higher than COVID 19. Reports stated that many points of weakness in the virus-like inability of the virus to be transmitted and survive in high temperatures, which means a high possibility of cessation in the summer season. Global panic and massive vibrations in social media will only make the problem worse [11].

Prisoning of people at homes and 24 h curfews will not participate in problem solving. On contrary, it may lead to other problems such as depression, anxiety, obesity, suicidal attempts, moreover, the economic and financial crisis at the individual and community level. Like it or not, a day will come, when the international systems will collapse, and the governments will be forced to leave people to confront the virus with simple precautions and personal immunity [12].

Simple precautions and well-cultured people are enough to stop the virus. Handwashing, masks, gloves, and practicing of proper social distancing can safely replace curfews and panic. Governments can prevent the crowd by closing malls and social clubs, not by prisoning people at homes. Prevent the places of crowdedness but not prison people [13].

When does the Epidemic Stop?

Despite touching the level of a million and a half infections, in 4 months, and recording about 85,000 deaths, which exceeds 5.6%, with a spread in more than 212 countries and regions around the world, it cannot be said that we have reached the peak level so far [13]. The World Health Organization says that most countries in the world do not provide true and accurate figures on infections, and Italian press reports indicated that the analysis of the blood of healthy donors in one of the affected towns of the Lombardy region had proven the presence of antibodies to the virus in 70% of them. Whether this information is correct or not, it is certain that the actual infections are more than what the health services calculate around the world [14].

The previous truth may seem reassuring to some when approaching the scene and trying to foresee its future horizons, as the underlying meaning is that the epidemic is not necessarily dangerous and deadly for everyone and that thousands or millions of people crossed it without feeling or feeling their country [15]. However, unlike that optimistic case, the matter is not reassuring, first because we do not know the virus fully, and then we have no evidence that it may not return or that those who recovered from it are immune from its recurrence again and second because we do not know these potential cured patients. So by default, all of us remain in existing danger even for those who were not aware that they were infected and recovered [16].

The most dangerous thing is that even if the real numbers are a 1000 times the numbers currently registered, this does not represent only 20% of the world's population, and the extent of the epidemic is still open to 6 billion people who could be infected in the future near. In practice, the cessation of the epidemic is not related to any precautionary measures. Rather, it could be a reason for the complexity of the crisis in the future [17]. The global economy does not bear the broad and long-term closure, and health institutions cannot work with that operational power and the pace indefinitely, and at some point, everyone may have to reduce the oppressive grip of the epidemic circumstance, which may cause an explosion or an acute wave of infections with a more massive bill because it comes after the economy and state structures have been completely exhausted [18].

The calculations are all complicated, and in a simple way, it can be said that the epidemic stop station is linked to biological inputs that cannot be induced or predicted, and the stage of its decline or its transformation into a transient seasonal disease will not be achieved before acquiring a wide-ranging societal immunity (at least 60% of people) [19]. It means that nearly 5 billion should be infected and recovered from the virus or acquires the virus without infection [20].

The Pessimistic Hypothesis

The optimistic forecasts hope that the crisis will pass within weeks, whether due to high temperatures and droughts during the summer or with metaphysical hopes that the infection will decline, even if the scientific opinion so far has been the opposite [21]. Pessimistic expectations not only indicate the continuation of the epidemic beyond the middle of next year only but augur well for its renewal in fierce epidemiological waves for several years before it subsides and takes a simple seasonal form, just like the current flu [22]. Between the two possibilities, scientists stand without the ability to resolve the matter yet [23].

Almost and approximately every hundred years, the universe has been attacked fiercely by a wave of an influenza pandemic [24], [25]. The last one was the Spanish flu pandemic in 1918, which was responsible for the mortality of 50 million of people over <10 years [26], [27]. Until it has been transformed to what's known nowadays by seasonal influenza, which used to come to everyone every year without significant side effects [28], [29]. This could be due to the adaptation of the human immunity for this virus across human being generations [30], [31]. According to this hypothesis and according to the pessimistic view, the outcome of the previous pandemic will be achieved by the current pandemic, with one difference [32], [33]. The number of mortalities will not reach 50 million in 10 years, but in 30–50 years because of the exaggerated precautions and curfews [34], [35]. This could be like some sort of natural selection [36], [37]. Family of influenza viruses characterized by periodic genetic mutation in the form antigenic shifts, every 10 years, and antigenic drifts every year [38], [39].

What we are going through today is one of the severest antigenic shifts of the influenza virus [40], [41]. Almost a new inscrutable virus not used to be transmitted from human to human [42], [43]. It was only a zoonotic cycle and man is not involved except by viral mutation [44], [45]. Our target is to elicit a natural active immunity in the whole population through allowing of subclinical/clinical infections and herd immunity [46], [47]. From the beginning of the pandemic, the countries which applied strict 24 h curfew have shown no decrease in case numbers on the epidemic curve [48], [49]. After curfew practicing, the cases continued to increase [50], [51]. The number of cases detected as well as fatalities in underdeveloped countries which did not apply any precautions was less than developed countries who applied strict precautions [52], [53]. This may be due to lack of modern diagnostic technology or may be due to the high population immunity or may be due to herd immunity acquired by the spread of subclinical infection all over the nation, no one knows [54], [55].

The Epidemic between, Medicine and Vaccine

To this moment, the SARS Cove 2 mutations or the emerging COVID 19 have not yet been severed [56], [57]. The main host of the virus is the bat that has a huge reservoir of that viral family, but the human infection did not come from a bat [58], [59]. China said that the virus was transmitted to humans from an anteater with a squid ant, but available studies indicated a similarity observation of about 94% with the possible validity of that [60], [61]. The information, however, cannot be confirmed, and until the moment also, information is conflicting about the "zero" case, which was the first human infection, and many Chinese media outlets published reports on more than three people as the first infection [62], [63].

In contrast, studies varied regarding the periods of virus activity outside the host cells and on different surfaces, and some said that it is transmitted in the air, and doctors differed in the clinical symptoms of patients, and the response to health care varied even with the installation of variables of geography, weather, age, and patient history [64], [65]. In short, we do not yet know "COVID 19" as it should, and by default, our predictions about it cannot be completely accurate unless we have more cases, more basic research, and no fear to face [66], [67]. We must give up the dread and have the courage to know more about the virus, not just follow the precautions for fear of infection [68], [69].

Access to an effective drug in the face of clinical symptoms, mitigating the effects of the virus and then curing it can be an important step toward reducing the severity of the epidemic and escaping from its economic, political, and psychological repercussions, and reaching a "vaccine" can lead to a state of reassurance, stability, and ability to restore an aspect of natural daily life, at least in the vital sectors and productive institutions [70]. Contrary to positive expectations committed to logic, or hopes driven by the state of fear and the search for reassurance, even if they are false, the medicine and vaccine will not be the end of the epidemic as some people think, not because they will miss the effectiveness in facing it and restraining it, but because the equations of testing, production, and sufficiency have its pressures, and most importantly, the crisis is not a war that stops its fire completely with armistice or surrender of the virus under the bombing of laboratories and drug factories [71].

Gradual Exit and Extended Effects

At present, world leaders and experts sit inside laboratories and hospitals [72]. Everyone thinks that the crisis will not end far away from epidemiology, microbiology, and pharmacology, but most likely they will move away from a little, not beyond the horizons of scientific solutions, but rather close to the panoramic view and integrated solutions that balance the considerations of science and economics with the lives and lives of people [73]. Decision-makers must leave their offices and go down to the ground to reconsider the planning of streets and squares [74]. Doctors, scientists, and researchers will work on their important path, but others will turn to idle paths, but they are equally important [75].

Many societies will gradually return to life, with strict precautions and a constant level of fear [76]. Perhaps Germany's pathway to conducting immunological examinations and tests and allowing those who are found to be less at risk to return to work and re-pump blood into the arteries of the economy may be adopted [77]. That vision may expand or be circulated temporarily, especially since even with the arrival of a guaranteed drug or an effective vaccine, the crisis will not end immediately, fears will remain, and the potential for risk will be open until the epidemiological freeze is confirmed, to begin the chain of gradual decline associated with the priority of countries and sectors and who are getting on innovative drugs and return to a normal life first [78].

The economic and social effects of the epidemic, the state of panic and psychological fractures that have afflicted millions of people around the world, confirm that the virus sizing or drug suppression station will not be the end of the crisis [79]. It will take months to restore the psyche of those affected and longer months to repair the economic cracks and perhaps years to restore confidence in the existing global system and people return to a full normal life [80]. The first periods will witness confusion in visions, evil demand for goods and services, a sharp rise in prices with diminishing savings and benefits, and the ability of banking institutions to activate the investment machine [81]. Those potential prospects mean that the pace of exiting the repercussions of the crisis may be slower than overcoming the epidemic itself and that we may live as "COVID 19" fears and its effects for years to come, even if we close the epidemic page a year later as pessimists expect, or within weeks as optimists preach [82].

Conclusion

Our vision for the current situation could be summarized in the following points; the most affected categories are diabetic patients and those who were immunocompromized. Most of cases are subclinical infection and the disease transmitted among people by herd immunity. No need for exaggerated or arbitrary measures, just infection control precautions, immunity augmentation, and treatment of diabetes. we recommend the conduction of studies to prove that medical staff who were positive for COVID 19, didn't know about their disease except at the time of study.

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Chest Computed Tomography Findings in COVID-19 Pneumonia from Tehran, Iran

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Abstract

From February 24, 2020, to April 2, 2020, this study presents a preliminary report on the chest computed tomography (CT) findings of COVID-19 pneumonia at Baqiyatallah Hospital, Tehran, Iran. This study performed on 70 patients with a final diagnosis of COVID-19.

Introduction

Unfortunately, as is known, coronavirus disease 19 (COVID-19) with high transmission, extensive concern and challenge in public health the global, is spreading quickly [1], [2]. In parallel, the current diagnostic techniques for recognizing the virus have a great significance in the primary stage [2]. Nevertheless, computed tomography (CT) investigation widely applied in prognostication, monitoring the advance of disease, clinical management, and appraising the therapeutic strategies of COVID-19 pneumonia in worldwide cases [3], [4], [5].

Findings

In our report, CT images were obtained from 70 patients admitted to a Tehran Hospital after symptom onset between February 24, 2020, and April 2, 2020, who had confirmed COVID-19 pneumonia with age range 23–75 years.

In our patients, the typical pattern of CT imaging features of COVID-19 patients comprised predominantly of multifocal subpleural patchy ground-glass opacity (GGO) in 64 cases (bilateral in 28 cases, unilateral in 12 cases, synchronous with patchy consolidation in 18 cases, and patchy GGO with crazy-paving pattern in 6 cases), only multifocal patchy consolidation and alveolar opacities in six cases, dense linear opacities in 16 case, and reverse halo sign in 22 cases (Figure 1). These lesions quickly evolved to become lung bilateral, multifocal, and diffuse with multilobar distribution in most patients (Figure 1).

On the other hand, in our case series, chest CT findings such as pulmonary nodules, masses, calcifications, tree-in-bud appearance, cystic changes, bronchiectasis, cavitation, pleural effusion, and mediastinal lymphadenopathy were not found.

Conclusion

In our case series, chest CT findings such as pulmonary nodules, masses, calcifications, tree-in-bud

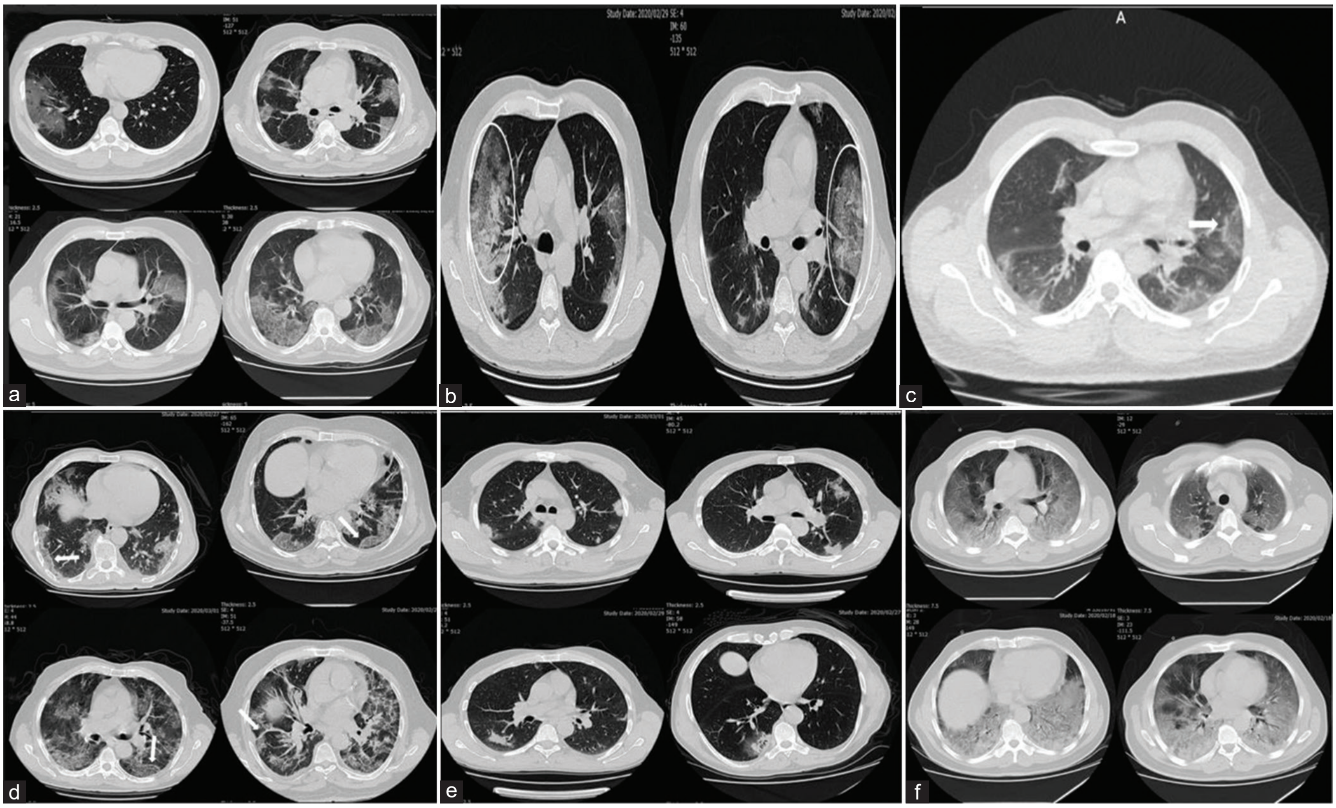

Figure 1: A) Multifocal subpleural patchy ground glass opacities with multilobar distribution on both lungs in multiple patients with confirmed COVID-19 infection. B) Mulifocal subpleural patchy ground glass opacities superimposed with interlobular and intralobular septal thickening compatible with crazy-paving pattern in a 61 year old male with COVID-19 infection. C) Reversed halo sign (white arrows) is a highly suggestive imaging finding for COVID-19 infection. D) Relatively dense linear opacities at boundary of ground glass opacities (white arrows) or in lung parenchyma is a common imaging finding at late stage of COVID-19 infection. E) Multifocal sub pleural patchy alveolar consolidation with multilobar distribution on both lungs in 57 year old male, which was a known case of chronic renal failure and positive PCR test for COVID-19 infection. F) Background of widespread ground glass opacities with an anteroposterior density gradient on both lung fields and consolidation in the most dependent areas compatible with ARDS in a 55 year old male with severe COVID-19 infection

appearance, cystic changes, bronchiectasis, cavitation, pleural effusion, and mediastinal lymphadenopathy were not found.

Consent for publication

Patients gave written informed consent for publication

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Evaluation of Angiotensin-converting Enzyme 2 (ACE2) in COVID-19: A Systematic Review on All Types of Studies for Epidemiologic, Diagnostic, and Therapeutic Purposes

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses the angiotensin-converting enzyme 2 (ACE2) receptor of SARS-CoV for cell entry. We aimed to check the association between ACE2 and COVID-19 (coronavirus disease 2019) in a systematic review. Two databases (PubMed/Medline and Scopus) and bioRxiv were checked for retrieving all types of studies in relation to ACE2 and COVID-19 until March 18, 2020. Forty-one studies were entered to the systematic review. These studies included nineteen original, eight reviews, four letters to the editor, three research papers, one correspondence, one commentary, one mini review, two reports, one opinion, and one perspective. In summary, the results showed that the ACE2 receptor for COVID-19 is similar to that of SARS-CoV. However, its expression was different in various populations as well as in the two genders. ACE2 may be used as a therapeutic target. Patients who take ACE inhibitors may have benefit in severe disease outcomes. Finally, pangolins and snakes and turtles may act as the potential intermediate hosts transmitting disease to humans.

Introduction

COVID-19 or 2019 novel coronavirus epidemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was emerged in late December 2019 in Wuhan, China [1]. This disease has been rapidly expanded in the world with a short time [2] and it is named a COVID-19 pandemic. The COVID-19 strains are genetically correlated to SARS-CoV and Middle-East respiratory syndrome coronavirus (MERS-CoV) [3]. A hypothesis reported that angiotensin II type I receptor (AT1R) inhibitors might be helpful for COVID-19 patients who experience pneumonia and suggested the treatment of COVID-19 patients with AT1R blockers [4]. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor-binding domain for its spike (S) protein glycoproteins [4], [5], [6]. ACE2 is a negative regulator of the renin-angiotensin system and reduces angiotensin II [5]. Mutant S proteins are capable of detecting host receptors within species [6], [7]. Almost all the coronaviruses detect their host cells through S proteins [8], [9]. Each S protein consists of two subunits that the S1 subunit contains a region called the receptor-binding domain (RBD) (targeting receptors in host cells) and the S2 subunit regulates membrane fusion between the virus and the host cells [10]. The single-cell transcriptomes showed that ACE2 and TMPRSS (transmembrane protease and serine) are highly expressed in AT2 (type II alveolar) cells of lung, esophageal upper epithelial cells, and absorptive enterocytes [11]. It was also reported an identity of more than 70% between the S protein sequences of SARS-CoV and SARS-CoV-2 [12]. Different methods of nucleic acid testing, protein testing, and point-of-care testing are on the way along with imaging techniques for better diagnosis [13]. Herein, we aimed to summary the results of all types of studies checking association between ACE2 and COVID-19 in a systematic review for the 1st time.

Search strategy

Two databases, namely, PubMed/Medline and Scopus were comprehensively searched by an author (M.S) to retrieve all relevant references published until March 18, 2020, without restrictions. The searched queries were "2019 novel coronavirus" or "2019-nCoV" or "COVID-19" or "SARS-CoV-2" and "angiotensin" or "angiotensin-converting enzyme 2" or "ACE2". We manually searched the citations (original and review articles and meta-analyses) related to our topics as well as bioRxiv (https://www.biorxiv.org/). We know that we cannot rely solely on bioRxiv preprints and papers due to the absence of peer review. However, we did not omit these articles, not to lose sources of data in a new emerging entity.

Eligibility criteria

Inclusion criteria were as follows: (1) Studies evaluating the correlation ACE2 and COVID-19 and (2) all types of studies.

Study selection and data extraction

Two authors (H.N and M.S) read independently the titles and abstracts of the retrieved studies. Then, the two authors selected the relevant studies, while another author (M.R) retrieved the full texts of the articles. Two authors (M.R and M.S) independently extracted the data from each study for being included in the systematic review. If there was a disagreement between the two authors, the third author (H.N) helped to find a final decision. The data extracted for the systematic review included basic information including the first author, publication year, type of study, and main result(s)/conclusion(s). Other authors (F.N, B.S, and M.N) rechecked independently the extracted data. At last, the disagreement resolved by a discussion between all authors.

Study selection

Out of 52 records retrieved from two databases and 10 studies from bioRxiv, after removing duplicates, 47 records were screened (Figure 1). After that, 6 other

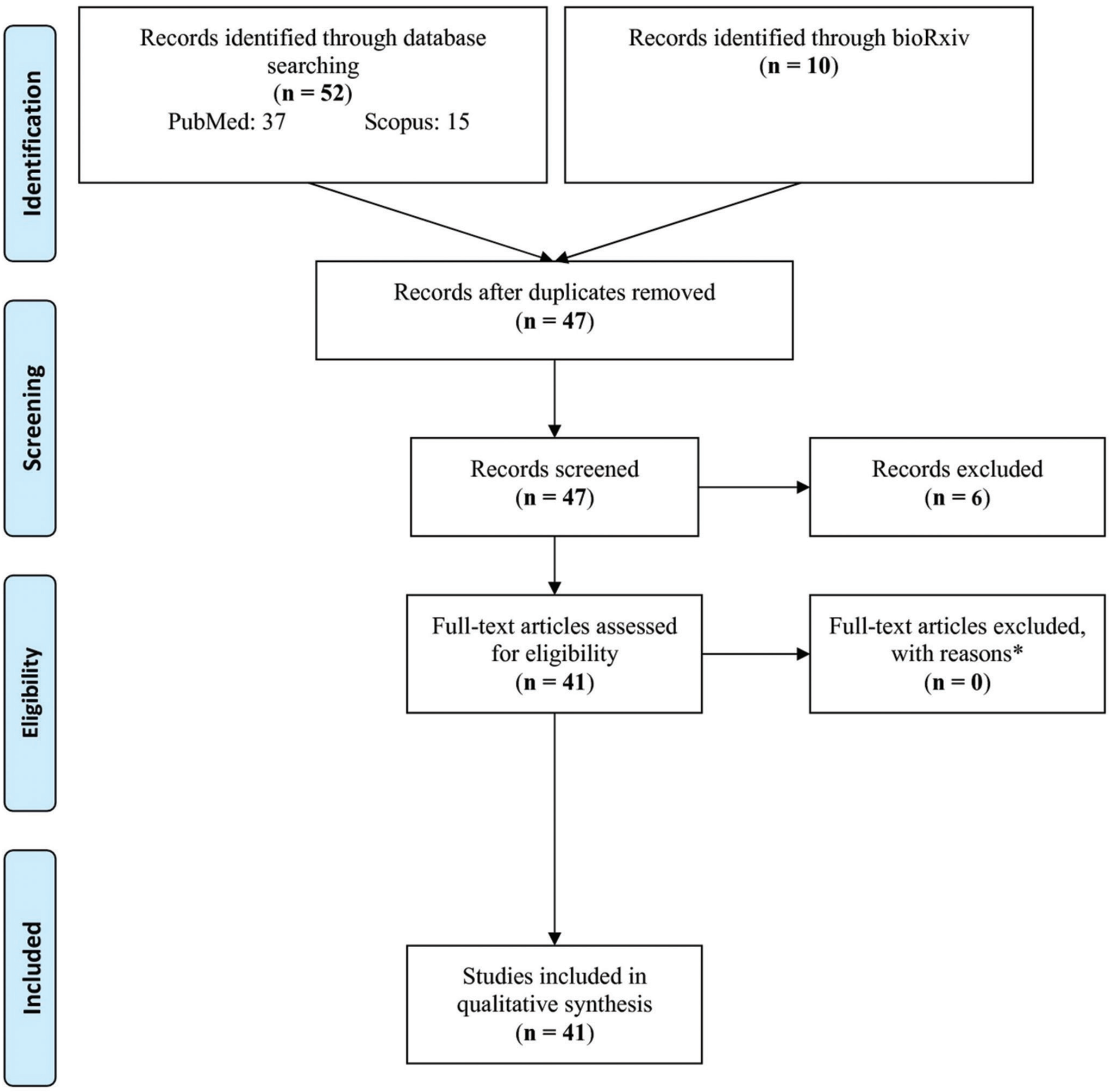

Figure 1: Flowchart of the study selection

studies were removed with further evaluation because they were irrelevant records. At last, 41 full texts met eligibility criteria and all of them were entered to the systematic review.

Characteristics

Table 1 shows the characteristics of 41 studies included in the systematic review [4], [11], [12], [14], [15], [16], [17],[18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29] [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51]. The studies included nineteen original articles [11], [12], [15], [17], [20], [22], [25], [28], [33], [35], [36], [40], [43], [44], [45], [48], [49], [50], [51], eight reviews [14], [19], [23], [29], [34], [37], [38], [47], four letters to the editor [4], [18], [30], [39], three research papers [31], [32], [46], one correspondence [16], one commentary [24], one mini review [26], two reports [21], [41], one opinion [27], and one perspective [42].

Blockers and inhibitors

Host cell entry from SARS-CoV-2 is dependent on the ACE2 receptor of SARS-CoV and may be clinically prevented by a proven inhibitor of TMPRSS2, a cellular serine proteinase used by SARS-CoV-2 for S protein priming. The antibody responses increased against SARS-CoV can at least partially protect

Table 1: Characteristics of studies included in systematic review

First author, publication year	Type of study	Journal	Main result(s)/conclusion(s)
Diaz, 2020 [4]	Letter to the editor	J Travel Med	Patients who take angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be at elevated risk of severe disease outcomes because of SARS-CoV-2.
Zou, 2020 [51]	Original	Front Med	Indicating the vulnerability of different organs to SARS-CoV-2.
Guo, 2020 [23]	Review	Mil Med Res	The ACE2 receptor of SARS-CoV is similar to SARS-CoV and mainly spreads through the respiratory tract.
Baig, 2020 [14]	Review	ACS Chem Neurosci	There was the ACE2 expression in the CNS.
Batlle, 2020 [16]	Correspondence	Clin Sci (Lond)	The association between SARS-CoV, SARS-CoV-2, and ACE2 suggests a rational reason for soluble ACE2 as a potential treatment.
Hoffmann, 2020 [25]	Original	Cell	SARS-CoV-2 uses the ACE2 receptor of SARS-CoV for cell entry.
Kannan, 2020 [26]	Mini review	Eur Rev Med Pharmacol Sci	The ACE2 receptor of SARS-CoV is similar to SARS-CoV.
Sun, 2020 [38]	Review	Int J Environ Res Public Health	SARS-CoV-2 uses the ACE2 receptor of SARS-CoV for cell entry.
Cao, 2020 [18]	Letter to the editor	Cell Discov	High expression of ACE2 in Asian males compared to others.
Yan, 2020 [46]	Research paper	Science	The RBD is identified by the extracellular peptidase domain of ACE2 chiefly through polar residues.
Gurwitz, 2020 [24]	Commentary	Drug Dev Res	Angiotensin II type I receptor (AT1R) blockers are as treatments for decreasing the aggressiveness and mortality from SARS-CoV-2.
Deng, 2020 [21]	Report	Chin Med J (Engl)	ACE2 expression in the human kidney indicated the kidney is a potential target organ of SARS-CoV-2.
Kruse, 2020 [27]	Opinion	F1000 Research	The ACE2-Fc therapy will decrease ACE2 levels in the lungs during infection.
Liu, 2020 [32]	Research paper	J Med Virol	SARS-CoV-2 might also use ACE2 receptor.
Letko, 2020 [28]	Original	Nat Microbiol	The hACE2 is the receptor for the SARS-CoV-2.
Xu, 2020 [45]	Original	Int J Oral Sci	There was ACE2 expression in the mucosa of oral cavity.
Li, 2020 [30]	Letter to the editor	J Infect	Structural studies of human and other ACE2 species in the SARS-CoV-2 S protein complex will help understand the use of cross-receptors for SARS-CoV-2.
Li, 2020 [29]	Review	Microbes Infect	SARS-CoV-2 may have wide host ranges.
Chen, 2020 [20]	Original	Biochem Biophys Res Commun	SARS-CoV-2 RBD has a stronger interaction with ACE2.
Guan, 2020 [22]	Original	Zhonghua Gan Zang Bing Za Zhi	ACE2 expression was in bile duct epithelial cells of normal liver tissues, and very low in hepatocytes in COVID-19 patients.
Wrapp, 2020 [41]	Report	Science	It has reported that the binding capacity of SARS-CoV-2 S protein to ACE2 is much stronger than that of SARS-CoV, which indicts that there are more intermediate hosts for SARS-CoV-2.
Tian, 2020 [39]	Letter to the editor	Emerg Microbes Infect	CR3022 has the potential to be expanded as candidate therapeutics for the SARS-CoV-2 prevention and treatment.
Sun, 2020 [37]	Review	Zhonghua Jie He He Hu Xi Za Zhi	The COVID-19/ACE2 binding resulted in the ACE2 exhaustion, and then, ACE2/Ang/Mas receptor pathway was inhibited.
Liu, 2020 [31]	Research paper	Sci China Life Sci	The angiotensin II plasma level in SARS-CoV-2 patients was significantly increased and linearly associated to viral load and lung injury.
Wu, 2020 [42]	Perspective	Virol Sin	SARS-CoV-2 uses the same cell entry ACE2 receptor similar to SARS-CoV.
Chen, 2020 [19]	Review	Microbes Infect	CoV-NL63 uses the same receptor ACE2 as SARS-CoV-2, but with very different severity of disease.
Morse, 2020 [34]	Review	Chembiochem	Potential drug candidates (an ACE2-based peptide, remdesivir, CLpro-1, and a novel vinylsulfone protease inhibitor) could be used to treat COVID-19 patients.
Zhou, 2020 [50]	Original	Nature	SARS-CoV-2 uses the same cell entry receptor – ACE2 – as SARS-CoV.
Walls, 2020 [40]	Original	Cell	The receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2.
Zhang, 2020 [47]	Review	Intensive Care Med	ACE2 is rationally and scientifically valid therapeutic target for the current COVID-19 epidemic.
Lu, 2020 [12]	Original	Lancet	SARS-CoV-2 might be able to bind to the ACE2 receptor in humans.
Wu, 2020 [43]	Original	bioRxiv	Bat SARS-like CoVs have an evolutionary convergent RBD sequence with SARS-CoV-2 and SARS-CoV may be pre-adapted to hACE2 receptor.
Brielle, 2020 [17]	Original	bioRxiv	Evolution of S protein binding to the ACE2 receptor is similar to the rapid evolution along the antibody-antigen affinity maturation process.
Lukassen, 2020 [33]	Original	bioRxiv	The high rate of human-to-human transmission of SARS-CoV-2 and severe cases of COVID-19 may be caused by additional sites, resulting in a higher binding affinity of ACE2 and/or membrane fusion.
Othman, 2020 [35]	Original	bioRxiv	The S protein RBD might be obtained by SARS-CoV-2 through a complex evolutionary process rather than the accumulation of mutations.
Su, 2020 [36]	Original	bioRxiv	The SARS-CoV-2 S protein mediates its recognition with the human receptor ACE2.
Bao, 2020 [15]	Original	bioRxiv	The mouse model may simplify the therapeutic and vaccine development against SARS-CoV-2.
Zhang, 2020 [48]	Original	bioRxiv	Pangolin-CoV will be useful for tracing the origin and potential host of SARS-CoV-2.
Xie, 2020 [44]	Original	bioRxiv	SARS-CoV-2 and SARS-CoV bind to hACE2 with same affinities and consequently may have same transmissibility.
Meng, 2020 [11]	Original	bioRxiv	The single-cell RNA sequencing showed that high expression of ACE2 in type II alveolar cells (AT2) cells of lung, esophageal upper epithelial cells, and absorptive enterocytes.
Zhao, 2020 [49]	Original	bioRxiv	ACE2 receptor is necessary for the SARS-CoV-2 viral entry.

ACE2: Angiotensin-converting enzyme 2, ACE2-immunoglobulin Fc domain ACE2-Fc, hACE2: Human ACE2, RBD: Receptor-binding domain, S: Spike.

against SARS-CoV-2 [25]. Patients under treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increase the number of ACE2 receptors in their lungs to bind to coronavirus S proteins, thus may be at elevated risk for severe disease outcomes due to SARS-CoV-2 virus. Many patients with cardiovascular disease are treated with ACEIs and ARBs, so their ACE2 receptors are increased. In fact, the patients for cardiovascular diseases should refrain from congestion, mass accidents, ocean cruises, prolonged air travel, and all cases with respiratory illnesses during COVID-19 outbreaks to reduce the risks of infection of SARS-CoV-2 virus [4]. ACE2 is likely to act as the SARS-CoV-2 virus junction [24], [25] and the strain involved in the current COVID-19 epidemic is similar to the SARS-CoV strain in the 2002–2003 SARS epidemic [24]. However paradoxically, AT1R blockers, such as losartan, can be as tentative treatment to decrease the aggressive forms and mortality caused by SARS-CoV-2 virus. Higher expression of ACE2 with losartan protects against lung injury by complementary mechanisms: (1) Blocking the excessive angiotensin-mediated AT1R activation caused by viral infection and (2) upregulating ACE2 culminating in reducing angiotensin production by ACE and increasing angiotensin 1–7 (vasodilator) [24]. Broking the balance of the RAS (renin-angiotensin system) leads to aggravation of severe acute pneumonia. However, it is speculated that ACEI and AT1R inhibitors can be used in COVID-19 pneumonia patients under controlling hypertension and may decrease the pulmonary inflammatory response and mortality [37]. Further research is needed for approving this treatment modality in COVID and side effect of hypotension must be kept in mind [24].

Cell expression

Among 536 COVID-19 patients, 6.7% presented acute kidney injury (AKI) in spite of normal plasma levels of creatinine at the first clinical manifestation, and these patients experienced exceedingly great mortality of up to 91.7% [52]. A report showed ACE2 expression in the human kidney and that the kidney is a possible target organ of SARS-CoV-2 virus [21]. ACE2 expression was established in several other human organs such as the intestines (glandular cells), gallbladder (glandular cells), adrenal gland, lungs, and lung macrophages and the expression was highly in the urogenital, digestive systems, and the proximal tubules. In addition, the single-cell RNA sequencing (scRNA-seq) showed that ACE2 is highly coexpressed in type II alveolar cells of lung, along with esophageal upper epithelial cells and absorptive enterocytes [11]. These results may propose that antibodies or biological inhibitors may target virus proteins such as S protein showing that the ACE2 receptor can be a part of therapeutic guidelines of SARS-CoV-2 virus [21]. Interestingly, this receptor is highly enriched in tongue epithelial cells, and the findings have explained the underlying mechanism that the oral cavity is another potential risk for the SARS-CoV-2 virus [45]. The scRNA-seq data of fetal and adult kidney samples appeared that ACE2 expression was significantly in tubule cells [21] and also in myocardial cells (> 7.5%), ileal epithelial cells (~30%), esophagus epithelial cells (> 1%), kidney proximal tubule (< 1%), and bladder urothelial cells (2.4%) [51]. Therefore, the pattern of ACE2 expression shows other modes of SARS-CoV transmission that may involve the intestine, testis, kidney, and other tissue functions [19].

One study reported the ACE2 expression in neurological tissue that this illustrates a connection between the tissue damage and the morbidity and mortality by SARS-CoV-2 [14]. A mouse model checking acute liver injury with partial hepatectomy showed that ACE2 expression changed after treatment (day 1: Downregulated, day 3: Increased up to twice of the normal level, and day 7 or liver recovering: Returned to the normal level). Based on scRNA-seq data, 77 transcription factors were positively related to the ACE2 expression, which were mainly enriched in the development, differentiation, morphogenesis, and cell proliferation of glandular epithelial cells. This ACE2 expression upregulation in liver tissue induced by compensatory hepatocyte proliferation obtained from bile duct epithelial cells may also be the possible mechanism of liver tissue injury caused by COVID-19 [32]. The ACE2 expression in several cells, such as to lung type II alveolar cells, upper part of esophagus, epithelial cells, and ileum- and colon-absorbing enterocytes, may play to a role of the multitissue infection of SARS-CoV-2 [49]. Around 40% of ACE2-positive transient secretory cells are coexpressing TMPRSS2 proteinase, including FURIN as another proteinase in SARS-CoV-2 entry of the host cell, the percentage of transient secretory cells expressing the ACE2 receptor, both or one of the TMPRSS2 and FURIN proteinases increased by up to 50%. Thus, these cells can be highly vulnerable to SARS-CoV-2 infection [33].

Receptor-binding domain (RBD) and proteins

Human ACE2 (hACE2) is a receptor for different lineage B viruses such as SARS-CoV-2 to gain entry into human cells [28]. The CoV S glycoprotein plays a significant target for therapeutic antibodies, vaccines, and diagnostics [41] that affinity of SARS-CoV-2 S protein bind to ACE2 is more than SARS-CoV S protein. Antibody cross-reactivity is limited between the two RBDs [40]. Glycosylation may impact on interaction of the RBD with ACE2, and therefore, the aim is to test the drugs for their ability to block the RBD/ACE2 interaction. Antibodies and small molecular inhibitors blocking the RBD/ACE2 interaction should be developed to combat the SARS-CoV-2 virus [19]. Checking m396 and CR3014 (SARS-CoV-specific neutralizing antibodies) that target the ACE2 binding site of SARS-CoV, there was no bind to SARS-CoV-2 S protein [38]. RdRp and 3CLpro regions of RBD binding to ACE2 are significantly different between the SARS-CoV and SARS-CoV-2 [11], [34]. This difference effectively rules out the use of previously developed antibodies and therapeutic peptides for the SARS-CoV S RBD [11]. Therefore, the difference in the RBD of between two viruses (SARS-CoV and SARS-CoV-2) shows a critical impact for the antibodies and that it should develop novel monoclonal antibodies that could bind specifically to SARS-CoV-2 RBD. To prevent SARS-CoV-2 and COVID-19 treatment, CR3022 does not overlap with the ACE2 binding site of SARS-CoV-2 RBD, and therefore, CR3022 may be as a candidate treatment, alone or in connection to other neutralizing antibodies [38]. One perspective study [32] checked Asn501 in RBD with the sites 41 and 353 of ACE2 receptor and the result showed that turtles and pangolins as potential expanded hosts of SARS-CoV-2 are closer to humans than bat [32]. Furthermore, the Q493 and P499 amino acid residues of SARS-CoV-2 RBD bind to hACE2 and maintain interface stability, neither of which is likely to interact with SARS-CoV-2 RBD [34]. SARS-CoV-2 and SARS-CoV interfaces include long flexible loops and nine aromatic residues in the interface with ACE2 [16].

Bat SARS-like CoVs have a RBD sequence with high similarity to SARS-CoV-2 [43]. ACE2 is widely expressed with conserved primary structures throughout the animal kingdom from fish, amphibians, reptiles, birds, to mammals. Therefore, it suggests that ACE2 from these animals (possible natural hosts for the virus) can potentially bind SARS-CoV-2 RBD [20]. Antibodies targeting the receptor-binding motif (RBM) regions may have more potential because of their ACE2 blocking activities but cross-protecting antibodies [43]. Another study [48] checking interactions of hACE2 between pangolin-CoV and SARS-CoV-2 showed that the S1 protein of pangolin-CoV was very closely related to SARS-CoV-2 than RaTG13 and this result shows a similar pathogenic potential of pangolin-CoV to SARS-CoV-2, showing pangolin as probable intermediate host of SARS-CoV-2 [29]. The nucleocapsid (N) protein of SARS-CoV-2 has approximately 90% amino acid sequence similar to SARS-CoV that therefore the N protein antibodies of SARS-CoV may cross-react with SARS-CoV-2 but may not provide cross-immunity. The N protein of SARS-CoV-2 may have a significant role in suppressing the RNA interference (RNAi) to overcome the host defense, similar to SARS-CoV [25]. One study [39] reported the striking structural similarity and sequence conservation among the SARS-CoV-2 S and SARS-CoV S glycoproteins emphasize the close correlation between these two viruses that recognize hACE2 to enter target cells [45]. The interaction between the key amino acids of S protein RBD and ACE2 indicated that except for pangolins and snakes, turtles may be as other potential intermediate hosts transmitting SARS-CoV-2 to humans [31].

Mutation

ACE2 sequence and structure from different species alert to potential intermediate translocation of SARS-CoV-2 and provide further monitoring in other animals [30]. Genotype distribution and allele frequencies (AFs) may be involved in further ACE2 research, including its role in lung function and acute lung injury. The AFs in the Eastern Asian people were much higher and associated with higher ACE2 expression in tissues that may propose different susceptibility or response to SARS-CoV-2 among different populations under the same conditions [17]. The distribution of ACE2-expressing cell population in different cohorts showed potentially identifies the susceptible population: Asian donor (male): 2.50% of all cells and African-American donors: 0.47% of all cells [49]. Furthermore, the ACE2 distribution is also more prevalent in male donors than females [49].

Treatment

The less correlation between SARS-CoV-2 and ACE2 can lead to longer incubation time, while still having a relatively higher level of viral concentration in human body [36]. CoV-NL63 uses the same ACE2 receptor as SARS-CoV-2, whereas it creates very different severity of disease [19]. Several studies [16], [23], [26], [38], [42], [50] demonstrate that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and to explain the connection between the SARS-CoV, SARS-CoV-2, ACE2, and the rationale for soluble ACE2 as a potential therapy [16]. Furthermore, checking the sites of interaction between ACE2 and SARS-CoV at the atomic level showed the interaction between ACE2 and SARS-CoV-2 [46]. The ACE2-immunoglobulin Fc domain (ACE2-Fc) protein sequence was investigated and the result showed that the ACE2-Fc therapy would also supplement reduced ACE2 levels in the lungs during infection, thereby directly treating acute respiratory distress pathophysiology as a third mechanism of action before a protective vaccine is administrated and widely available in the coming months to year(s) in the COVID-19 patients [27]. Results have shown that angiotensin II levels in plasma samples from 2019-nCoV-infected patients are significantly correlated linearly with viral load and lung injury, suggesting a number of diagnostic potential biomarkers and ARB drugs for the treatment of 2019-nCoV [31]. Weight loss and virus replication in the lungs were noticed in hACE2 mice infected with SARS-CoV-2 and this event was not established in wild-type mice with SARS-CoV-2. Therefore, the mouse model may make easier the treatment and vaccine development against SARS-CoV-2 [15].

Limitations

COVID-19 is a new emerging disease so the researches for systematic review are limited. Some studies may have lower levels of validity with fast peer review. More time is needed for evaluating the results of clinical trials.

Conclusion

Whatever there were some different residues for ACE2 receptor between SARS-CoV-2 and SARS-CoV, but most studies showed that the ACE2 receptor for SARS-CoV-2 is similar to that of SARS-CoV, and therefore, ACE2 is rationally and scientifically valid therapeutic target for the current COVID-19 pandemic. Therefore, four potential drug candidates (an ACE2-based peptide, remdesivir, CLpro-1, and a novel vinylsulfone protease inhibitor) may use to treat COVID-19 patients. ACE2 expression was found in several human organs introducing new organs such as brain tissue and oral cavity and the expression in various populations was different as well as in the two genders. These data may be used for epidemiologic, diagnostic, and therapeutic purposes. Patients who take ACEIs and ARBs may have benefit in severe disease outcomes due to SARS-CoV-2, but further investigation is necessary. The RBD/ACE2 interaction suggested pangolins and snakes, and turtles may act as the potential intermediate hosts transmitting SARS-CoV-2 to humans.

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Azithromycin in Coronavirus Disease-19: What We Know?

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Abstract

Azithromycin (AZM) is a broad-spectrum antibiotic with anti-inflammatory and immunomodulatory properties. It is particularly used in chronic lung diseases including chronic obstructive pulmonary disease, asthma, interstitial lung diseases, bronchiectasis, and cystic fibrosis. AZM has not approved for the treatment of viral infections, but some study supported its antiviral activity. Recently, few studies are emphasized used AZM in combination with chloroquine/hydroxychloroquine for the treatment of novel coronavirus disease-2019 (COVID-19). The present review highlighted uses, dosage, and adverse effects of AZM in COVID-19 based on available literature.

Introduction

An outbreak of coronavirus disease-2019 occurred in Wuhan, China in the month of December 2019 and rapidly spread across the world [1], [2]. On March 11, 2020, the WHO declared COVID-19 as a pandemic disease [3]. In an early stage, infection is characterized mainly by respiratory symptoms such as cough, sore throat, fever, and fatigue [4]. On later stage, high viral replication, high inflammatory activity, and exacerbated immune response lead to a "cytokine storm," which is responsible for complications, such as severe pneumonia and acute respiratory distress syndrome [5], with increased requirement of ventilatory support and intensive care unit admission [6]. About 80% of patients have mild disease and the overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70–79 years and 14.8% in those aged ≥80 years, but major concern is that number of asymptomatic carriers in the population, and thus, the mortality rate is probably overestimated [7]. Therefore, there is an urgent need for an effective treatment to treat symptomatic patients and decrease the duration of virus carriage to limit the transmission in the community.

Till date, there is no specific treatment which is available to treat COVID-19. However, the backbone of the treatment strategy for COVID-19 is good quality supportive care as in any viral pneumonia. There is no current evidence from randomized controlled trial to recommend any specific anti-COVID-19 treatment for patients with suspected or confirmed COVID-19 infection. The clinicians are using various drugs such as antiviral drugs that include inhibitors against protease, integrase, and polymerase enzymes based on anecdotal data and some recent publications. Moreover, antiviral effects of azithromycin (AZM) have been attracted considerable attention [8].

There are various treatments being used to control COVID-19 based on previous experiences with other viral infections. In the present review, we aim to summarize the uses of AZM in COVID-19.

Materials and Methods

Data sources

We performed thorough literature search on published studies between January 1, 2020, and April 15, 2020. PubMed and Google Scholar databases were used to find articles providing information on the efficacy and safety of AZM in patients with COVID-19. No language restrictions were imposed.

Inclusion and exclusion criteria

The studies which describe used of AZM in COVID-19 and previous epidemic viruses such Ebola, severe acute respiratory syndrome, and Middle-East respiratory syndrome were selected. Meanwhile, studies which (a) duplicate publications, (b) full articles not available, (c) literature reviews, and (d) do not provided sufficient information or support regarding their recommendation of their proposed drugs or treatment process were excluded from the study.

Results

A total of 170 articles initially identified. After removing duplicates, checking title, abstract, and full text 30 were found eligible based on the predetermined exclusion and inclusion criteria for this study. Among these three articles were relevant which showed used of AZM in COVID-19 patients as summarized in Table 1 while rest of all articles were used for basic information.

Discussion

AZM

AZM is a macrolide antibiotic with a 15-membered lactone ring. It is broad-spectrum antibiotics with long serum half-life near about 68 h and large volume of distribution [9]. AZM has excellent tissue penetration. In infected tissues, AZM concentrations are about 300-fold higher than in plasma, due to recruitment of leukocytes at the site of infection [10]. It also has anti-inflammatory activity, decreases pro-inflammatory cytokine and hastening of the macrophages phagocytosis ability [11]. Due to its antibacterial and anti-inflammatory effects, it is used for many chronic lung diseases including chronic obstructive pulmonary disease, asthma, interstitial lung diseases, bronchiectasis, and cystic fibrosis [12].

AZM as antiviral

Azithromycin effective against rhinovirus, respiratory syncytial virus, influenza virus, Zika virus and Ebola viruses [13], [14], [15], [16]. The mechanism is unknown. The multiple mechanisms have been proposed for antiviral activity observed with AZM. The antiviral activity may be mediated by amplification of the host's interferon (IFN) pathway by inducing pattern recognition receptors, IFNs, and IFN-stimulated genes that lead to a reduction of viral replication [17], by directly acting on bronchial epithelial cells which reduce mucus secretion (19). Moreover, a recent quantum mechanical modeling suggests a potential role of AZM in COVID-19 by interfering with viral entry through binding interaction between coronavirus spike protein and host receptor angiotensin-converting enzyme-2 protein; further, experimental work on this is necessary to confirm the model [18].

Clinical study

The symptoms of COVID-19 are similar to those seen in these lung infections; therefore, it is not surprising that AZM treatment was initiated early in the current pandemic of COVID-19. The use of AZM in 25 of 138 patients who were suffer from COVID-19 in Wuhan, China, reported in a recent JAMA article [19].

First French clinical study

A French confirmed COVID-19 positive; 36 patients (n = 20 in treatment group and n = 16 in control group) were enrolled in an open-label non-randomized clinical trial. In the treatment group, 600 mg HCQ daily was given to patients and their viral load in nasopharyngeal swabs was tested daily. On basis of clinical presentation of patients, six patients received AZM (500 mg on day 1 followed by 250 mg/day for the next 4 days) to prevent bacterial superinfection under daily electrocardiogram (ECG) control. Untreated patients from another center and cases refusing the protocol were included as negative controls. The presence and absence of virus at day 6 post-inclusion was considered the end point. The combination of hydroxychloroquine and AZM results in negative PCR results in nasopharyngeal samples was significantly

Table 1: Clinical study of azithromycin in COVID-19

Study population	Sample size	Study design	Treatments	Results	Reference
COVID-19	n=36 Treatment group n=20 Control group n=16	Observational open-label non-randomized clinical trial	HCQ 200 mg, TID×10 days HCQ+AZM (500 mg D1 and 250 mg D2-5)	At day 6 post-inclusion, virologically cured HCQ+AZM: 100% HCQ: 57.1% Control: 12.5% p<0.001	20
COVID-19	n=80	Uncontrolled non-comparative observational	HCQ 200 mg, TID×10 days+AZM (500 mg D1 and 250 mg D2-5)	Nasopharyngeal viral load tested by qPCR; 83% negative at day 7 and 93% at day 8 Virus cultures from patient respiratory samples were negative in 97.5% of patients at day 5	21
Suspected COVID-19; flu-like symptoms	n=636 Treatment group n=412 Control group n=224	Observational open-label non-randomized	HCQ 800 mg on D1 and 400 mg D2-D7+AZM 500 mg D1-D5	HCQ+AZM: 1.9% of patients required hospitalization Control: 5.4% of patients required hospitalization (p<0.0001) Patients treated before versus after day 7 of symptoms required less hospitalization (1.17% and 3.2%, respectively, p<0.001)	22

different between the two groups at days 3-4-5 and 6 post-inclusion. At day 6 post-inclusion, 100% of patients treated with hydroxychloroquine and AZM were virologically cured compared to 57.1% in patients treated with hydroxychloroquine only and 12.5% in the control group ($p < 0.001$). Therefore, addition of AZM to hydroxychloroquine treatment results in significantly viral load reduction/disappearance in COVID-19 patients. The limitations of study are small sample size, limited long-term outcome follow-up, and dropout of six patients from the study [20].

Second French clinical study

Gautret *et al*. conducted an uncontrolled non-comparative observational study in a cohort of 80 confirmed COVID-19 patients. All patients received 600 mg/day oral hydroxychloroquine sulfate for 10 days combined with AZM (500 mg on day 1 followed by 250 mg/day for the next 4 days). Patients with pneumonia and NEWS score ≥5, a broad-spectrum antibiotic (ceftriaxone), were added to hydroxychloroquine and AZM. Twelve-lead ECGs were performed on each patient before treatment and 2 days after treatment began. The median age of patients was 52 years (ranging from 18 to 88 years) and had at least one chronic condition such as hypertension, diabetes, and chronic respiratory disease. About 81.3% of patients had favorable outcome and were discharged from unit while only 15% required oxygen therapy during their stay. A rapid fall of nasopharyngeal viral load tested by quantitative polymerase chain reaction was noted, with 83% negative at day 7 and 93% at day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at day 5. Moreover, patients were able to be rapidly discharged from infectious disease unit with a mean length of stay of 5 days. Therefore, a beneficial effect of coadministration of AZM along with hydroxychloroquine observed in COVID-19 patients [21].

Brazil telemedicine clinical study

A telemedicine study was conducted in Sao Paulo, Brazil, after the pandemic was officially declared in city. Patients with persistent flu-like symptoms (suspected COVID-19 infection), persisting for a period equal to or greater than 2 days, were first evaluated by the telemedicine team or by the emergency department medical doctor. Participants who did not need immediate hospitalization and azithromycin was not contraindications were invited to participate in the study. A total of 636 symptomatic outpatients enrolled in the study. The treatment group (n = 412) received hydroxychloroquine 800 mg on the 1st day and 400 mg for another 6 days and AZM 500 mg once daily for 5 days. A total of 224 patients who refused to medications served as control group. The swab laboratory was not mandatory and chest computed tomography was performed according to medical judgment. All patients were followed daily by telemedicine consultations until the 5th day of symptoms, after that, patients were contacted twice a day until the 14th day of initial symptoms. In the treatment group, 1.9% of patients required hospitalization as compared to 5.4% of patients in the control group ($p < 0.0001$) which indicates 2.8 times greater need for hospitalization compared to those without medication. An absolute risk reduction is 3.5% and a number needed to treat (NNT) is 28 to prevent one hospitalization. The patients treated before versus after day 7 of symptoms required less hospitalization (1.17% and 3.2%, respectively, $p < 0.001$). Comparing the early treatment (< 7 days of symptoms) to those without treatment (control group), the NNT was 23. Therefore, empirical treatment of hydroxychloroquine and AZM for suspected cases of COVID-19 reduces the need for hospitalization [22]. To sum up, Table 1 shows clinical studies of AZM in COVID-19.

Adverse events

Common side effects of AZM include abdominal pain, diarrhea, constipation, nausea, dizziness, headaches, photosensitivity, or a skin rash [23]. Tinnitus and even hearing loss are associated with this medication [24], [25]. It should be avoided in patients with a history of Stevens-Johnson syndrome [26] and other serious skin reactions [27] as well as those with myasthenia gravis. Prolonged cardiac repolarization and prolongation of the QT interval can occur [28]. An ECG should be performed to assess the normal heart rhythm because the medication can cause arrhythmias. Patients with abnormal QT intervals, congenital long QT syndrome, a history of torsades de pointes, bradyarrhythmias, or heart failure may be at risk for fatal QT prolongation [29]. Elderly patients are more at risk. Abnormal liver function tests, hepatitis, hepatic necrosis, cholestatic jaundice, and hepatic failure have been reported with its use. AZM increased levels of theophylline and aminophylline, warfarin, digoxin, phenytoin, and statins. Nelfinavir increases serum concentration of AZM, so those receiving single oral doses need to have liver enzyme tests and hearing monitored [30].

Conclusion

The literature presented here provides a significant role of AZM in COVID-19 when combined with HCQ. It helps to reduce nasopharyngeal viral load, hospitalization and patients were able to be rapidly discharged from infectious disease unit. A well-designed randomized double-blind placebo control clinical trials are needed for further clarity and evidence. Results of near future researches will assess safety data of its use to guide clinical usage during this pandemic.

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Guide to Leading a Patient with Symptoms of an Acute Respiratory Infection during a Coronavirus Pandemic (COVID-19)

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Abstract

BACKGROUND: Over 500 viruses and bacteria primarily cause respiratory infections. During COVID-19 pandemic, these respiratory infections remain; i.e., COVID-19 has no ability to suppress these infections from the circulation. Therefore, it is very important to differentiate respiratory infections from COVID-19. Proving the presence of COVID-19 with polymerase chain reaction (PCR) is not evidence that the disease was caused by this virus. Possible options are: First, a random encounter of the virus in the patient's upper respiratory tract; second, further possible colonization with a coronavirus (or with COVID-19); the third option is to have an infection; and the fourth possibility is to have a disease or COVID-19 upper respiratory infection. Unfortunately, the method with PCR, although it is with high sensitivity and specificity, does not help us to distinguish which of these four possibilities are in question.

AIM: We aimed to present a guide to leading a patient with symptoms of an acute respiratory infection during a coronavirus pandemic (COVID-19).

RESULTS: A pandemic of COVID-19 shows that many patients get primary viral pneumonia, but people with normal immune system have no problem recovering. People with reduced immunity die from COVID-19, as opposed to the pandemic influenza virus. It is indirectly concluded that COVID-19 in itself is not very virulent, but it weakens the immunity of those infected who already have some condition and impaired immunity. The available scientific papers show that there is no strong cytokine response, patients have leukopenia and lymphopenia, some patients have a decrease in CD4 T-lymphocytes. From the results of the autopsies available so far, it is clear that there are very few inflammatory cells in the lungs and a lot of fluid domination. Hence, SARS-Cov-2 only somehow speeds up the decline in immunity. The previously published radiographic findings of COVID-19 patients, gave a characteristic findings of the presence of multifocal nodules, described as milky glass, very often localized in the periphery of the lung. Whether it is typical pneumonia, atypical, viral, mixed-type pneumonia, or mycotic pneumonia, it can progress to severe pneumonia. The pneumonia becomes severe when breathing is over 30/min; diastolic pressure below 60 mmHg; low partial oxygen pressure in the blood (PaO_2/FiO_2 <250 mmHg) (1 mmHg = 0.133 kPa); massive pneumonia, bilateral or multilayered lung X-ray; desorientation; leukopenia; and increased urea.

CONCLUSION: Patients with COVID-19 placed in intensive care units should be led by a team of anesthesiologists with an infectious disease specialist or an anesthesiologist with a pulmonologist. Critical respiratory parameters should be peripheral oxygen saturation <90%, PaO_2/FiO_2 ratio 100 or <100, tachycardia above 110/min.

Introduction

Acute respiratory infections are the most common infections in humans. As many as, two-thirds of all infections are thought to be respiratory infections. Over 500 viruses and bacteria primarily cause respiratory infections. Adults have a respiratory infection 3–5 times a year. At children, that number is much higher. Upper respiratory infections (rhinitis, sinusitis, tonsillopharyngitis, angina, gingivostomatitis, and laryngitis) are much more common than lower respiratory (tracheitis, bronchitis, bronchiolitis, alveolitis, and pneumonia). During COVID-19 pandemic, these respiratory infections remain, i.e., SARS-Cov-2 has no ability to suppress these infections from the circulation. Therefore, it is very important to differentiate respiratory infections from COVID-19. A good demarcation will increase the effectiveness of treating respiratory infections. We are very successful in treating bacterial infections. There are good antiviral drugs for the flu or influenza virus. We must consider about mycotic respiratory infections, and there are effective antifungal drugs for them.

Laboratory biochemical analyzes give us great help in distinguishing viral from bacterial infection and acting correctly in the decision to give an antibiotic. Thus, high sedimentation, leukocytosis with neutrophilia, high C-reactive protein (CRP), and elevated procalcitonin values are in addition to bacterial infection. Normal erythrocyte sedimentation rate, peripheral lymphocyte dominance (blood count), and normal CRP are in addition to viral infection.

Acute rhinitis (cold) – upper respiratory infection that from the 1st day goes with catarrhal symptoms (runny nose, sneezing, burning eyes, and tearing) with signs of general infectious syndrome and temperature up to 37.5°C to be treated as a common cold syndrome (acute rhinitis). The most common causes are rhinoviruses, coronaviruses, influenza type C, parainfluenza, and respiratory syncytial virus (RSV).

Flu – if the patient had a high fever for 2–3 days (37.5–39.5), severe infectious syndrome (headaches, myalgias, arthralgias, bone pain, malaise, and drowsiness), there are no catarrhal signs, and the same occur after 2–3 days, then these patients have the flu and need to seek serological confirmation of influenza virus.

Catarrhus febrilis respiratorius – if the patient has a high fever from the 1st day, accompanied by symptoms of the general infectious syndrome, but from the 1st day, there are catarrhal symptoms (sneezing, runny nose, burning in the eyes, and tearing), then it is a so-called catarrhal febrile respiratory syndrome. This syndrome is most commonly caused by so-called atypical (intracellular) bacteria, primarily *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae,* and adenoviruses from viruses with this clinical picture [1], [2], [3].

Laboratory biochemical analysis will be very helpful in differentiating whether it is a bacterial or a viral infection. Thus, leukocytosis, with a predominance of polymorphonuclear in the peripheral smear, together with high CRP values (above 100 mg/L) and accelerated erythrocyte sedimentation rate (above 20 mm/1 h) goes in favor of bacterial upper respiratory infection and those patients regardless. The obtained microbiological and serological results should be treated with antibiotics and corona infections should be separated. Moderately elevated or normal values of leukocytes, elevated CRP but with values below 50 mg/l, moderately elevated erythrocyte sedimentation rate (10–20 mm/1 h), and clinical picture of catarrhus febrilis respiratorius (1st day temperature and catarrhal signs) atypical bacterial infection (*M. pneumoniae*, so-called Pontiac fever caused by *L. pneumophila* and *C. pneumoniae*) and should be treated with macrolide antibiotics or tetracyclines. If we have a predominance of lymphocytes (regardless of the values of leukocytes), the sedimentation of erythrocytes in normal values 5–10 mm/1 h, and CRP is with normal values of 1–10 mg/l or slightly elevated; then, it is a viral upper respiratory infection, called rhinitis syndrome. Possible causes are rhinoviruses, influenza type C, parainfluenza, and coronaviruses in adults, and in children, the most common causes are RSV, rhinoviruses, influenza type C, parainfluenza, and coronaviruses. If the epidemiological situation in the region goes with the confirmation of many cases with the confirmed presence of COVID-19, then the most likely upper respiratory infection is with a coronavirus. Proving the presence of SARS-Cov-2 with polymerase chain reaction (PCR) is not evidence that the disease was caused by this virus. Possible options are: First, a random encounter of the virus in the patient's upper respiratory tract; second, possible colonization with a coronavirus (or with COVID-19); the third option is to have an infection; and the fourth possibility is to have a disease or COVID-19 upper respiratory infection. Unfortunately, the method with PCR, although it is with high sensitivity and specificity, does not help us to distinguish which of these four possibilities are in question. The infection does not cause any clinical problems, but can be proven by serological tests. Proof of the presence of IgM antibodies to SARS-Cov-2 by serological test is reliable and acceptable evidence that it is an upper respiratory infection caused by COVID-19. Regardless of the etiological cause of rhinitis, or even an upper respiratory infection is with COVID-19, treatment should be symptomatic, i.e., the patient should rest, use more fluids through the mouth (teas, juices), Vitamin C (in high doses), and nothing else. Antibiotics and corticosteroids are contraindicated, and analgesics, antipyretics, immunoglobulins, immunomodulators, etc., may cause harm. Patients with upper respiratory tract infection with COVID-19 should be treated at home [1], [3], [4], [5], [6], [7], [8].

From the epidemiological data so far, about 15% of all COVID-19 patients develop lower respiratory tract infections. These primary viral pneumonias should be treated in a hospital. To increase treatment efficacy, and to reduce mortality, it is necessary to properly differentiate primary viral pneumonia with COVID-19 from other pneumonia. Pneumonia is a serious disease with high mortality. They are the 10th leading cause of death in the world, and in the age group of 65, they are the sixth leading cause of death. There are several divisions of pneumonia, but the most appropriate is the division of hospital-acquired pneumonia and community-acquired pneumonia.

Hospital-acquired pneumonias are common conditions, especially in patients who have been placed on a respirator or have had a diagnostic procedure on the respiratory tract (bronchoscopy and biopsy). Of all intrahospital infections, 13%–18% have nosocomial pneumonia. These pneumonias are sent with a high mortality rate of 33%–50% depending on the cause: *Streptococcus pneumoniae, Staphylococcus aureus, P. aeruginosa, Klebsiella*, and *Acinetobacter* species.

Community-acquired pneumonia – The best results in practice are given by the division of typical and atypical pneumonia. Typical pneumonias have a rich auscultatory finding, the presence of small moist bronchial murmurs (crepitations), and/or impaired breathing in a particular region. This auscultatory finding is confirmed by a rich rentgenogram. Atypical auscultation pneumonia has a normal finding because the inflammation is in the interstitium and the airways are free. However, the X-ray has a rich finding and diagnoses pneumonia. Depending on the size of the lesion, both typical and atypical pneumonias may have small inflammatory foci (bronchopneumonia), segmental, lobular, or occupy multiple lobes, i.e., be multilobar/massive unilateral or bilateral pneumonia. The advantage of this division into typical and atypical is that this division helps for proper antibiotic treatment. Pneumonia mortality is reduced if appropriate antibiotic treatment is started within the first 4–6 h. Typical pneumonia is most commonly caused by pneumococcus (*S. pneumoniae*), *S. aureus,* and *Haemophilus influenzae*. The good part is that all these causes are susceptible to the same groups of antibiotics. Our drug of choice is the third-generation cephalosporin for parenteral use, ceftriaxone in doses of 30–50 mg/kg/bw [1], [3], [8], [9], [10].

Atypical pneumonia is caused by viruses and so-called atypical intracellular causes (*M. pneumoniae, L. pneumophila, Chlamydia pneumoniae,* and *Coxiella burnetii*). The good side is that these intracellular bacteria are sensitive to macrolide antibiotics and tetracyclines. Unlike viral atypical pneumonia, we have a moderate increase in erythrocyte sedimentation rate of 15–30 mm/1h, and moderately elevated CRP, in addition to possible leukocytosis. The drug of choice during pandemic with COVID-19 should be azithromycin 5 mg/kg/bw, preferably intravenously [1].

Another division of community-acquired pneumonia is primary and secondary. Primary pneumonia involves pneumonia caused by any infectious agent and is caused by a primary infection of the same cause. Secondary pneumonia is pneumonia caused by another upper respiratory infection, usually viral. This viral infection is thought to damage the respiratory epithelium, disrupting the defense mechanisms of the respiratory tract, and a secondary bacterial pneumonia develops within a few days to 2 months of the virus infection. These secondary bacterial pneumonias usually present with clinical and etiological presentation of typical pneumonia. Secondary pneumonia is also of fungal etiology (*Cryptococcus neoformans,* Pneumocystis jiroveci*, Histoplasmosis,* and *Candida* spp.). Fungal pneumonia occurs after a serious decline in immunity due to malignancy, severe chronic disease, starvation, treatment with cytostatics, and long-term treatment with antibiotics. These pneumonias are much more common than we think and diagnose and are often the cause of death.

Primary pneumonia can be caused by any cause. Primary pneumonia is usually caused by a bacterium. Viruses rarely give rise to primary pneumonia. Primary viral pneumonia occurs when the virus is highly virulent. As a rule, primary viral pneumonia is difficult to treat and ends in death. Such primary viral pneumonias give many viruses (RSV, varicella, measles*,* and SARS-Cov-1). Influenza virus does not cause primary viral pneumonia during epidemics. However, during pandemics that occur after major, so-called shift antigenic changes, and when there is a population that will first encounter a new subtype of influenza virus, primary viral pneumonia is a common and significant cause of death. During the 1918–1920 pandemic caused by the H1N1 subtype of Influenza A virus, such primary viral pneumonias were given only to people born after 1890, as most of the elderly had contact with the H1N1 subtype that had circulated before. Hence, young people with good and enhanced immunity died of primary viral pneumonia. The autopsy finding is up to 2 L of non-fibrinous fluid in the lungs. Coronaviruses typically present with a mild clinical picture of upper respiratory infection, followed by bacterial secondary pneumonia. No matter how and when the mutation occurred and COVID-19 occurred, it is evident that now in this COVID-19 pandemic, most of the deaths are due to the development of primary viral pneumonia and acute respiratory distress syndrome. During pandemics with influenza pneumonia with high mortality, young people have a good immune response, and the development of pneumonia is due to the virulence of the causative agent itself. A pandemic of COVID-19 shows that many patients get primary viral pneumonia, but people with normal immune system have no problem recovering. People with reduced immunity die from COVID-19, as opposed to the pandemic influenza virus. It is indirectly concluded that COVID-19 in itself is not very virulent, but it weakens the immunity of those infected who already have some condition and impaired immunity. The available scientific papers show that there is no strong cytokine response, patients have leukopenia and lymphopenia, some patients have a decrease in CD4 T-lymphocytes. From the results of the autopsies available so far, it is clear that there are very few inflammatory cells in the lungs and a lot of fluid domination. Hence, COVID-19 only somehow speeds up the decline in immunity [1], [3], [8], [10], [11], [12].

It is necessary to strictly distinguish which patients have developed primary viral pneumonia from COVID-19, from patients who are positive for COVID-19, but for some other reason develop ARDS. These causes may be: The COVID-19 virus itself; other viruses; other infectious agents; holding patients on the respirator for more than 12 h; long-term oxygen delivery; hemodynamic disturbances; and alveolar capillary shunts, some internist notches [1], [3], [8].

X-ray Characteristics of Pneumonia

Lung X-rays certainly confirm the existence of a process in the lungs, but they rarely have specifics that will point us to the etiological cause. However, lobar pleuropneumonia suggests a possible pneumococcal etiology, cotton-like shadows (pneumatocele) of staphylococcal pneumonia, and a clearly limited round shadow of possible coxiellosis. The description of changes in the interstitium suggests that we have atypical bacterial pneumonia or interstitial viral pneumonia. The previously published radiographic findings of COVID-19 patients, gave a characteristic findings of the presence of multifocal nodules, described as milky glass, very often localized in the periphery of the lung. It is this kind of finding of peripheral nodules such as milky glass that has been pathognomonic to Chinese radiologists who have only begun to diagnose primary viral pneumonia with COVID-19 based on this finding. This finding in 80–85% coincided with the positivity of SARS-Cov-2 with PCR [9], [12], [13].

Specialist infectious disease specialists outside the pandemic successfully treat acute respiratory infections. However, during a pandemic due to a large number of patients, general practitioners and physicians with other specialties will be involved in the treatment of patients with COVID-19. A doctrinal approach in the treatment of patients with COVID-19 will give the best results, and there will be the smallest percentage of deaths.

Guide for the Treatment of Patients with Pneumonia

Pneumonia should be treated by an infectious disease specialist or pulmonologist. In conditions of increased number of pneumonias (larger than hospital capacities), the easier forms can be treated by a family doctor or internist.

Typical Pneumonia

If the pneumonia is characterized by typical pneumonia (rich auscultatory findings, radiographic confirmation, and laboratory biochemical analysis in addition to bacterial infection) to be treated doctrinally with third-generation cephalosporin for parenteral use, ceftriaxone 30–50 mg/kg/bw/i.v, once a day if up to 2 g, twice a day if given a maximum dose of 2 g ×2.0 g. The treatment should be in hospital. Mild forms can be treated on an outpatient basis. Intravenous fluids should be kept to a minimum. Do not include oxygen therapy. If the patient is treated on an outpatient basis, see the vital parameters at least once a day and follow the auscultatory findings. This therapy should be given a chance to work for at least 4 days. If there is a withdrawal of the auscultatory finding, a decrease in CRP values, a decrease erythrocyte sedimentation rate, regardless of the values of leukocytes in the blood, continue therapy for 10–12 days. After that control, lung graphics and a set of laboratory biochemical analyze. If after 4 days, there is a worsening of the pulmonary auscultatory finding, and/or a worsening of the condition, the patient should be treated exclusively in hospital. Replacing ceftriaxone with moxifloxacin 400 mg daily/iv (streptococcal pneumonia, the most common cause of typical pneumonia, is most sensitive to moxifloxacin, has a good effect on staphylococcal and anaerobic bacteria), and atypical intracellular bacteria. If there is a good assumption (a valid finding on lung X-ray, furunculosis…) that it is MRSA instead of moxifloxacin, immediately go with vancomycin 25–60 mg/kg/day. If it is assumed that aspiration and/or mixed pneumonia are possible, metronidazole 30 mg/kg/day should be added in two daily doses (clindamycin is a good choice 10–30 mg/kg/day/i.m. or i.v. in two doses). Continue intravenous fluid delivery to a minimum. Oxygen should not be given as support. Avoid expectorants. Give antitussives if there is a persistent irritating cough. Moxifloxacin should be given a chance to be effective again for at least 4 days. If there is no withdrawal of the finding or the patient's condition worsens, after 4 days of moxifloxacin therapy, replace with vancomycin [1], [14].

Atypical Bacterial Pneumonia

Atypical bacterial pneumonia can go into epidemic forms (*M. pneumoniae*, *C. pneumoniae,* and *L. pneumophila*) and can be easily transmitted from person to person. Due to the similar clinical picture and uncharacteristic laboratory biochemical parameters, they make serious differential diagnostic difficulties, i.e., we can hardly distinguish them from atypical pneumonia of viral origin. The drug of choice for atypical bacterial pneumonia (during COVID-19 pandemic) should be azithromycin 5 mg/kg/bw preferably intravenously. Treatment with other macrolide antibiotics or tetracyclines may not work because of the resistance of the primarily *L. pneumophila* to them. Treating these bacterial atypical pneumonias with cephalosporins or other beta-lactam antibiotics is without effect [1], [14].

Primary Viral Pneumonia

Many viruses can cause primary viral pneumonia, but the most common are influenza A virus, influenza B virus, RSV, human metapneumovirus, and adenovirus types 4 and 7. Influenza A viruses are statistically the most common primary pneumonia virus, but this occurs when there is a large shift antigenic change in hemagglutinin and neuraminidase and the appearance of a new circulatory subtype (H2N2). Some variants of circulating influenza subtype H1N1 know how to obtain many virulent features and give primary viral pneumonia. Because the epidemiological situation in the world regarding influenza A virus is calm (there is no new subtype, the variants that are now circulating are not so virulent), in a pandemic with COVID-19, it is expected that most of the primary viral pneumonia will be caused by COVID-19. Leukopenia, a weak immune response, a decrease in CD4 T-lymphocytes in some patients, and a characteristic radiographic finding of peripheral nodules and/or changes described as an opaque glass suggest primary viral pneumonia with COVID-19 [8], [10], [11], [13], [15], [16], [17].

Recommendations for Therapy

Do not do more than possible. It should be borne in mind that in many papers in these patients were given various antiviral drugs, although it is known that they do not act on the virus. Even if there is a presumption that viral pneumonia may be caused by influenza viruses, it is not justified to give oseltamivir which is effective only if therapy is started within the first 36 h of illness (pneumonia occurs secondary after 8 days). Antiretroviral drugs do not work either. Giving such antiviral drugs is only an alibi without scientifically proven support. Giving corticosteroids to most patients (according to studies published in scientific journals) can only reduce the immune response, that is already weak [4], [6], [11], [13], [15], [17], [18]. Giving chloroquine and other and other antiparasitic drugs justified is only if we want to achieve a reduction in the anti-inflammatory response. Because the majority of patients with such primary viral pneumonia with COVID-19 have no problem recovering regardless of the size of the pathological process, it is best to leave the patient's immunity to fight alone. Provide suppurative therapy, give Vitamin C (in high doses), and avoid intravenous fluids. Giving a drug without confirmed scientific proof that the drug is effective only, will do harm regardless of the doctor's intention to do something.

Mycotic Pneumonia

Mycotic pneumonia is a possible etiological cause as a secondary infection in patients with COVID-19. Therefore, in massive bilateral pneumonias with a characteristic X-ray finding for COVID-19 (peripheral nodules and milk glass findings) in which there are medium values of inflammatory markers in the blood (CRP, procalcitonin, and erythrocyte sedimentation rate), antimycotic replacement should be considered for antiparasitic and antiviral drugs that do not act on the COVID-19 [1], [9], [19].

Severe Pneumonia

Whether it is typical pneumonia, atypical, viral, mixed-type pneumonia, or mycotic pneumonia, it can progress to severe pneumonia. The pneumonia becomes severe, when breathing is over 30/min; diastolic pressure below 60 mmHg; low partial oxygen pressure in the blood (PaO_2/FiO_2 <250 mmHg) (1 mmHg = 0.133 kPa); massive pneumonia, bilateral or multilayered lung X-ray; desorientation; leukopenia; and increased urea. When a pneumonia progresses and becomes severe pneumonia, the patient should be transferred to an intensive care unit. (Note: Peripheral oxygen saturation of up to 90% and tachycardia up to 110/min are not in themselves indicative of intensive care treatment). Switching to an intensive care unit does not mean immediately putting the patient on a respirator. Patients with COVID-19 placed in intensive care units should be led by a team of anesthesiologists with an infectious disease specialist or an anesthesiologist with a pulmonologist. Critical respiratory parameters should be peripheral oxygen saturation <90%, PaO_2/FiO_2 ratio 100 or <100, and tachycardia above 110/min. Severe acidosis itself may also be an indication for respiratory placement. Before setting up a respirator, make an operational plan, i.e., clearly set a goal of which parameters will be improved and for how long. Reduce the risks of getting ARDS from the respirator itself, and the risks of getting secondary pneumonia from a respirator [1], [6], [9], [10], [12], [20].

Conclusion

Distinguishing between typical and atypical bacterial pneumonia from atypical viral pneumonia is very important during a pandemic with COVID-19. Distinguishing primary viral pneumonia from secondary bacterial or fungal pneumonia is also important and will yield good results in successfully treating and reducing the percentage of deaths during pandemic with COVID-19. When we separate pneumonia with COVID-19, from other pneumonia, we will be able to analyze them much better and get much more accurate results. This will make it much easier and faster for us to come up with scientific explanations of what is happening to us and how to successfully oppose COVID-19.

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Kidney Diseases and COVID-19 Pandemic – A Review Article

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Abstract

In December 2019, first cases of a novel coronavirus were identified in Wuhan, China. A state of global pandemic was shortly declared among a very rapid contagious spread of the virus. The causative virus was identified as the SARS-CoV-2 viruses and is genetically related to the previous SARS outbreak in 2003. The virus causes a wide clinical spectrum from mild flu-like symptoms to adult respiratory distress syndrome. Kidney involvement has been reported in several reports in patients with various degrees of severity of SARS-CoV-2 infection. As knowledge is evolving, the accurate incidence of acute kidney injury (AKI) is not known. Many questions are yet to be answered regarding the effect of epidemiological variables and comorbidities on the occurrence of AKI. Some reports have observed the occurrence of hematuria and proteinuria in a percentage of infected patients. Moreover, chronic kidney disease has not been found, in some reports to add to the adverse outcomes, an aspect that merits further exploration. Patients on regular hemodialysis may be vulnerable to coronavirus infection due to the lower status of immunity and the need for frequent attendance at health-care facilities. Due to the previous factors, prevention and mitigation of the SARS-CoV-2 virus, in this vulnerable population, constitutes a major challenge.

Introduction

Origin and epidemiology

SARS-CoV-2 is a novel mutant of the coronavirus family that is causing the most recent and ongoing pandemic. The coronavirus is thought to have been transmitted at first instance from bats to humans. A wet wild animal market is likely considered to be the primary focus. The first cases of human infections were then reported in the city of Wuhan, the capital of Hubei Province of China. This was followed by widespread of the pandemic to many countries around the globe. Until the time of writing this paper (April 6, 2020), the number of infected people around the globe exceeded 1,300,000 patients with mortality over 74,000 [1].

Pathogenesis

COVID-19 primarily targets the respiratory system, causing a wide clinical spectrum from mild symptoms to adult respiratory distress syndrome. The pathogenesis is mediated in severe cases through the so-called cytokine storm (Figure 1). This involves the secretion of large amounts of pro-inflammatory cytokines and chemokines including IL8, IL 6, IL9, IL10, and many others. Pathogenic mechanisms in the kidneys are not fully elucidated, but the suggested mechanisms are through attachment of the virus to ACE2 receptors. Excess secretion of cytokines leads to multiorgan failure in a percentage of patients, including acute kidney injury (AKI), through tissue hypoxia [2].

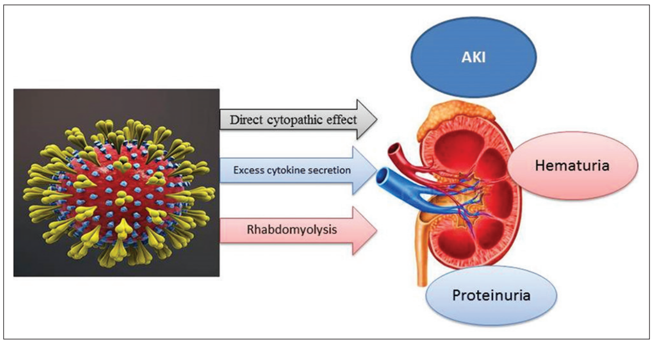

Figure 1: Renal complications of SARS-CoV-2 virus

Chronic kidney disease (CKD) as a predisposing comorbidity in the event of COVID-19

A number of studies have analyzed patients' comorbidities. The prevalence of CKD was variable across studies, ranging from 0.7 to 6.5% [3]. Only one cohort of 710 patients reported that 40% of patients had CKD in the form of deranged kidney function, hematuria, or proteinuria [4]. Most studies that used regression analysis to predict poor outcome have not identified chronic kidney disease as an important prognostic factor [5]. The lack of stratification of CKD among the prognostic factors of SAR-CoV-2 denotes that patients with CKD are not particularly at a higher risk of SAR-CoV-2 infection [3], [5].

Patients with end-stage renal disease (ESRD) on hemodialysis have a lower immunity status to various types of infections. The impact of COVID-19 infection on hemodialysis patients merits further investigation. In a study of 230 patients on hemodialysis in Wuhan, during the COVID-19 outbreak, 37 patients and 4 health-care providers became infected. The clinical features of hemodialysis patients reported in this cohort were mild. Seven deaths occurred among dialysis patients during the outbreak; however, causes of death were not attributed to COVID-19 [6].

AKI as a complication of COVID-19

Acute kidney injury is a common complication of several infections. In the previous SARS-CoV-2 outbreak in 2003, the incidence of AKI was as low as 6% [2], [7]. Nevertheless, AKI case fatality rate was high [8]. As for SARS-CoV-2, the exact incidence of AKI is not well known. Cohorts that reported AKI incidence are summarized in Table 1 [9],[10], [11], [12], [13], [4], [3], [14], [15], [16], [17], [18], [19], [20], [21], [5].

There is heterogeneity among studies regarding the reported incidence of AKI. This may be attributed to inconsistencies in applying AKI definitions or due to genetic variability that merits further studies.

Some reports have shown that the incidence of AKI is significant, while others report that the incidence is marginal. Guan *et al*. have shown, in a large cohort of confirmed COVID-19 cases that the prevalence of AKI was as low as 0.5%. This increased in patients with severe COVID-19 to 2.9% [5]. In other cohorts, the incidence of AKI in confirmed cases of COVID-19 was higher.

In two cohorts, the reported incidence of AKI was notably higher. In a cohort of 193 patients, the overall incidence of AKI was 28% and the incidence in severe cases was 66% [18]. In another cohort of 191 patients, the incidence of AKI in non-survivors was 50% [19]. In the study by Hu *et al*., AKI was present in 17 of all 323 patients (5.3%); however, the incidence of AKI in patients with critical COVID-19 was 38.5%. Furthermore, in this cohort, most patients who had AKI (14 out of 17) had unfavorable outcomes [17].

Interestingly, one retrospective study of 116 patients showed that the changes in kidney function throughout the disease course were subtle [13]; this study included five patients on maintenance hemodialysis, all of whom had severe disease but survived. Despite the subtle changes in kidney function, none of patients in this cohort met the defining criteria for AKI, including seven deaths that were reported [13]. This report concluded that AKI and other kidney diseases are not of paramount clinical significance in patients with COVID-19 [13].

During a previous SARS outbreak in 2003, a study of postmortem kidney biopsies examined using electron transmission microcopy, failed to detect any viral particles in kidney tissues. This finding supports the theory that most of the kidney pathogenesis in the earlier SARS outbreak was in the context of multiorgan failure. The pathogenesis of AKI may be multifactorial. Suggested mechanisms are direct cytopathic effects on kidney tissues, as denoted by the retrieval of the viral RNA from urine samples [4]. The direct cytopathic effect of COVID-19 on kidneys is now more evident, as it has been shown that there is overexpression of both ACE2 receptors and a cleavage spike protein in podocytes and proximal tubular cells [22]. This experimental evidence is of paramount importance and can explain proteinuria in patients with COVID-19. Interestingly, the latter experiment reports variable expression of cleaved S protein such that there is low expression in the Chinese race as compared to Caucasians. Important pathological evidence was reported by Diao *et al*. The pathology team managed to confirm the visualization of the SARS-CoV-2 viral particles in the renal tubular cells of postmortem kidney biopsies [23], [24]. The difference in kidney tropism between SARS-CoV and SARS-CoV-2 may be attributed to the affinity to ACE2 receptors in the kidneys.

Tissue hypoxia, in the context of massive cytokine secretion, is a key renal pathogenic mechanism. Rhabdomyolysis and raised creatinine kinase have been observed in a few cases [5]. It was also noticed in one cohort that AKI occurred later to acute cardiac injury, suggesting a temporal relationship between cardiac injury and AKI and the possible occurrence of cardiorenal syndrome [19]. In a recent single case report, collapsing variant of focal segmental glomerulosclerosis was diagnosed in renal biopsy of African-American woman, who tested positive to COVID-19. The patient presented with confusion and rapidly deteriorating kidney function, she improved markedly with the initiation of dialysis [25].

Hematuria and proteinuria

In the largest prospective cohort of kidney diseases in COVID-19, it was found that hematuria occurred in 26% of patients and proteinuria occurred in about 43% [4]. Large prevalence of proteinuria could be explained by the finding of the above-mentioned experimental study that showed expression of ACE 2 receptors in podocytes and proximal tubular cells [22]. However, quantification of proteinuria, using 24 h urinary collection or protein to creatinine ratio, was not done within the investigation battery. Kidney biopsy has not been attempted in any patient. In this prospective report, the presence of hematuria or proteinuria signaled poor outcome, as measured by in-hospital mortality.

Effect of dialysis modalities on survival in patients infected with COVID-19

Continuous renal replacement therapy (CRRT) is a modality of dialysis that implies increasing the clearance of solutes through convection, diffusion, ultrafiltration,

Table 1: Characterization of renal complications in several cohorts

Author Name	Number of patients	Study design	AKI percentage(all)	AKI percentage (non severe cases)	AKI percentage (severe cases)	significance	CKD at baseline	Baseline BUN (non severe cases)	Baseline BUN (severe cases)	Baseline creatinine (severe cases)	Baseline creatinine (non severe cases)	significance	mean BUN (non severe cases)	mean BUN (severe cases)	mean creatinine (non severe cases)	mean creatinine (severe cases)	significance	comment
Luwen Wand et al	116	retrospective	7/116	Not reported	Not reported	NA	4.3% on CRRT											7 deaths had no AKI 5 patients on CRRT survived
Shijiao Yan et al	168	retrospective	3.6%	0%	8.30%		0.6%						3.6	4.1	62.1	57.3		AKI was the 3rd leading cause of death
Yi Yang	36	retrospective	22.0%	Not reported	Not reported													CRRT made no difference of death at 3 days
Guo-Qing Qian	91	retrospective	3.0%	Not reported	Not reported		Not reported						3.9	5.8	66	81		
Yafei Wang,	110	retrospective											3.93	4.99	55	74	significant	
Zonghao Zhao	75	retrospective	20.0%	Not reported	Not reported	NA	5.3%								67	72.5		significant difference in serum creatinine between patients with severe pneumonia and patients with mild illness
Luwen Wang ***	116	retrospective	7.2%	Not reported	Not reported	NA	4.3%											5 hemodilaysis patients received CRRT and all of them had severe infection but survived
Guan et al***	1099		5% all and 2.9% in severe cases	0.1	2.9	NS	0.7%											
Yichun Cheng	710	Prospective	5.1%				Abnormal kidney function in about 40%											Hematuria(26%) and proteinuria(40%)
Wen Zhao	77	Retrospective	2.6% NS between severe and non severe			NS	6.5%,NS between severe and non severe			68	63	NS						No siginificant difference between severe and non severe cases as regard baseline serum creatinine
Jiatao Lu	577	retrospective	3.0%	2.8	3.3	NS				65.5	64	NS						cutoff value of serum creatinine 77 was associated with 2.9 odds mortality
Huang Huang	125 severe Cases	Retrospective		Not reported	Not reported					64	77.5	NS						Nor AKI or CKD were identified as a prognostic factors
Jianfeng Xie	444	Retrospective								66	85	0.001						There was significant difference in basline creatinine between patients who survived and patients who died
Ling Hu	323	retrospective	5.3%	3.3	38.5	0.007	2.2%											
Zhen Li	193	retrospective	28.0%	9%	66%					73	63							
Fei Zhou	191	retrospective	15.0%		50% in non survivors	Significantly higher in non survivors	1.0%											10 patients had renal replacemnet therapy and they all did not survive
Kun-Long Ma	84 severe cases	retrospective	7.1%	1.60%	25%	0.003	1.2%											

BUN: Blood urea nitrogen, AKI: Acute kidney injury, CRRT: Continuous renal replacement therapy.

and adsorption. The modality has benefits in critically ill patients, including the removal of septic toxins in addition to correction of the uremic status. There is accumulating evidence that critically ill patients who develop AKI may have lower mortality if they are treated using CRRT [26].

As knowledge is evolving about the SARS-CoV-2 virus, the benefit of CRRT in the management of critically ill patients with COVID-19 is much less clear. One retrospective study was conducted in China on 36 confirmed COVID-19 cases who have been admitted to the intensive care unit [10]. All patients were mechanically ventilated; the aim was to compare the effect of CRRT as compared to conventional dialysis. Patients were followed up for an average time of 10.4 days. The mean serum creatinine was slightly higher in patients who received CRRT than in patients who did not receive CRRT (94.5 mmol/L vs. 72 mmol/L, p=0.017). There was a marginally a favorable effect of CRRT in terms of adjusted mortality (54.4% in CRRT group vs. 78% in the conventional hemodialysis group).

On the contrary, another analysis of risk factors and survival in critically ill patients found that non-survivors received more treatment with CRRT than survivors.

Another study of 101 case fatalities in China, five cases had CRRT. Two patients died within 3 days and three patients died after 3 days. The mean baseline serum creatinine was 139.8 μmol/L [27]. In another large retrospective analysis by Guan *et al*., nine patients were treated with CRRT, eight of whom died suggesting that CRRT had no mortality benefit [5]. In a cohort of 191 patients, 10 patients received renal replacement therapy, and all did not survive, suggesting that renal replacement therapy in severe cases of COVID-19 may not have any survival benefit [19].

Renal-specific mortality due to COVID-19

The leading causes of mortality in COVID-19-infected patients are sepsis and ARDS. This has been observed in several cohorts. A large prospective study showed that the development of AKI in patients infected with COVID-19 was associated with four-fold increase in the mortality [4]. In other reports, renal-specific causes were not the most common or the second most common of mortality in COVID-19. In a retrospective study of 101 non-surviving COVID-19 patients, the incidence of AKI was 23%, there was no significant difference between patients who died within 3 days and patients who died later with regard to AKI incidence (25% vs. 21%, p=0.611) [27]. In this cohort, AKI was the 3rd leading cause of death after respiratory and cardiovascular causes. In a single-centered study in China, chronic kidney disease was present in 7 out of 323 patients (2%). Four patients had severe disease while the other three patients had non severe disease. Elevation of BUN > 88 mmol/L was associated with a two-fold increase in the chance of poor clinical outcomes. Baseline serum creatinine of <88 mmol/L was associated with 63% reduction in the development of poor outcomes. In another report of 82 non-surviving patients with confirmed COVID-19, the AKI percentage was 31% [28].

Prevention and mitigation of COVID-19 among dialysis patients

Until the time of writing this paper, there is no consensus or formal approval of any medication for COVID-19. This fact mandates the exhaustion of all measures to prevent the transmission of infection. In this respect, the Centers for Disease Control and Prevention (CDC) has issued an interim guideline for hemodialysis centers. The guideline emphasizes the importance of early recognition and isolation of cases while attending their scheduled sessions [29]. This mandates treating confirmed cases of COVID-19 hemodialysis in designated rooms with droplet infection prevention precautions; patients with confirmed of suspected COVID-19 should be separated by 6 feet distance. The instructions for hemodialysis patients should be centralized around reporting any new symptoms of fever or cough. Patients should be instructed on the proper use of face masks and using tissues when sneezing or coughing to prevent spread of infections [30], [29]. There is an anticipated extraordinary strain on hemodialysis facilities. In parallel, there are a number of suggestions to match the resources. These practical suggestions aim at reduction of the strain on hemodialysis units [29].

Summary and Conclusion

SARS-CoV-2 (COVID-19) virus pandemic constitutes a global health threat. The disease spectrum caused by the virus flu-like symptoms to adult respiratory distress syndrome. Kidney involvement in COVID-19 has been reported in previous cohorts. Acute kidney injury is a complication of COVID-19, either as part of multiorgan failure caused by excess cytokine production or through direct cytopathic effect on renal tissue. Overexpression of ACE2 receptors in podocytes and proximal tubular cells has been observed in patients with COVID-19. Other renal manifestations include proteinuria and hematuria. The true incidence and outcome of AKI in COVID-19 is not entirely clear and merits further studies. Continuous renal replacement therapy (CRRT) benefits in case of AKI are controversial. Patients on hemodialysis may be at increased risk of COVID-19 due to the nature of renal replacement therapy that requires 3 times weekly attendance at dialysis facilities. This necessitates the application of meticulous measures to prevent and mitigate the outbreak in patients on hemodialysis.

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Systematic Review with no Meta-analysis of Coronavirus COVID-19

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Abstract

AIMS: COVID-19 is a new virus which has spread to most countries in the world. Many papers have been published on the clinical manifestations of this virus. This paper concentrates only on the clinical cases and prognosis of COVID-19 presented in the literature.

METHODS: Systematic review is done, and taken into consideration, all published papers in the literature related to COVID-19. Inclusion and exclusion criteria have been applied.

RESULTS: Few papers have been determined after many filtrations of all published papers concerning inclusion and exclusion criteria to assess outcome of existing COVID-19. Most published papers or reports did not provide full details for each case.

CONCLUSION: Most clinical description data in these reports are so limited and missing some of the critical elements such as the date of infection, source of infection, symptoms, diagnostic criteria, incubation of infection, transmission of infection, number of identified cases after contact with infected patients, and health workers are affected or not by treatment of infected patients, patient age, and type of study. No clear evidence of the treatment plan and the prevention and most data in literature depending on personal experience only which is different from country to others.

Introduction

SARS-CoV-2 was identified as the causative factor of outbreak of respiratory disease, now named COVID-19 [1].

The virus did not cause illness in humans before [2]. This virus caused pneumonia of unknown etiology in Wuhan, China [3], [4], 27 out of 41 confirmed cases had direct exposure to the Wuhan seafood market where is believed the animal source of infection [5]. The transmission of COVID-19 from person to person has been confirmed [6]. The infected patients have identified in China, then the infection is spreading to many countries in the world [7]. The number of infected patients is increased daily. There is limited number of publication in literature due to the discovery of this COVID-19 as new virus. The aim of this study is to do systematic review of the available published data of COVID-19, also to highlight the most important clinical data only concerning on COVID to assess the prognosis of this new virus.

Materials and Methods

A literature search using MEDLINE, accessed through the National Library of Medicine, PubMed, EMBASE, and Cochrane systematic review interface, from 2019 to 2020 for articles relating to COVID-19 written in the English language. Various terms were used for the search: Coronavirus; COVID-19.

Inclusion criteria

All published articles or clinical report concerning COVID-19. Only clinical data written in English language will be included such as type of study, place of existing infection, gender, diagnostic criteria to detect COVID-19, number of confirmed cases, symptoms, and management.

Exclusion criteria

Articles includes non-clinical data such as pathogenesis, route of transmission, and other types of

Table 1: Clinical data of case series in selected papers of some patients infected with COVID-19

Authour	Type of study	Country	N of cases	Patient gender	Patient age	Confirmed cases	Clinical features	Outcome
Bordi et al (February 2020)	Case report	Italay	126 patients		Mean age 35 (range 1-85 years)	3 out of 126	Not mention	Not mention
Chen et al (Feburary 2020)	Case report	Jinyintan Hospital, Wuhan, China	99 patients		Mean age 55.5 (range 21-82)	99 confirmed cases	Fever in 83,cough,81 have cough, 31 shortness of breath,11 muscle ache, 9 confusion,8 headache, 5 sore throat, 4 rhinorrhoea,2 chest pain,2 Diarhoea, 1nausea and vomiting	31 discharge, 11 died, all other patients were still in hospital
Stoecklin et al (January 2020)	Case report	France	3 cases		48, 31, 30	3 cases confirmed	First patient complains of fever, headaches and cough, second patient develops of fever, chills, fatigue, conjunctivitis and cough, third patient develops fever, chills, fatigue and cough	Not reported
Patel et al (2020)	Case report	Unted States	11 cases		Range age 20-60	11 confirmed cases	fever, cough, or sore throat	No death reported
National Emergency Response Center, Epidemiology and Case Management Team (2020)	Case report	South Korea	28 cases		Range 20-79	28 confirmed cases	Fever , sore throat, cough,chills,muscle ache	Not reported
Spiteri et al (2020)	Case report	Europe	38 cases		2-81	38 confirmed cases	Fever, cough,weakness,headaches,sore throat, Rhinorrhoea, Shortness of breath	One patient died

coronavirus will be excluded. Duplicated clinical data will be excluded as well.

Results

A total of 984 papers have been identified. We have reviewed the full text of those papers, after many filtration of those papers after reading abstract and full papers, 6 out of 984 were identified and included to be consistent with the inclusion and exclusion criteria.

Table 1 summarizes the clinical data for the selected papers, Bordi *et al*. [1] reported that 126 suspected patients have undergone for COVID-19 test in Rome. They indicated that 3 out of 126 patients had confirmed COVID-19. They mentioned that the positive test of the respiratory pathogens might be related to other virus such as influenza. They advised to use a broad-spectrum molecular diagnostic for fast detection of this new virus.

Chen *et al*. [4] indicated that 99 patients had confirmed COVID-19 in China. COVID-19 was detected in 67 males and 32 females. The mean age was 55.5 years. Fifty (51%) patients had chronic diseases, including cardiovascular endocrine system disease, digestive system disease, respiratory system disease, malignant tumor, and nervous system disease. The most common clinical features are cough and fever in 82% and 83% of patients. All the patients stay in hospital for isolation and 75% had undergone for antiviral treatment. Thirty-one (31%) patients had been discharged, 11 (11%) were died. Two out 11 died patients had no history of chronic disease but they were smokers. Nine out 11 of patients who died, five were older than 60 years, three had hypertension, and one was heavy smoker. They highlighted that the reduction in lymphocytes value in most infected patients indicated that COVID-19 causes damage for the immune cells and blocks the body cellular immune function.

Stoecklin *et al*. [8] reported that three cases confirmed COVID-19 in France. First, the patient complains of fever, headaches, and cough; second, the patient develops of fever, chills, fatigue, conjunctivitis, and cough; and third, the patient develops fever, chills, fatigue, and cough. Patients age was 30-31 and 48 years old.

Patel and Jernigan [9] reported that 11 cases were identified in the USA with COVID-19. The patients age ranges from 20 to 60. Patients complain of fever, cough, or sore throat and no death reported.

National Emergency Response Center, Epidemiology, and Case Management Team [10] indicated to 28 cases detected in South Korea with COVID-19. Patients age ranges from 20 to 79. They complained of fever, sore throat, cough, chills, muscle, and ache.

Spiteri *et al*. [11] reported that 38 cases confirmed with COVID-19. The symptoms were fever, cough, weakness, headaches, sore throat, rhinorrhea, and shortness of breath.

Discussion

COVID-19 is a danger virus which can spread from human to human. The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes [6], [7]. These infected droplets can spread 1–2 m and deposit on surfaces. COVID-19 is transmitted either by inhalation of these droplets or touching surfaces contaminated by patient and touching the nose, mouth, and eyes [2], [6], [7], [12]. Most of the published articles or reports concerning COVID-19 missed many useful information to assess this virus in infected patients. The incubation period of this virus is 14 days [2], [12].

Some patients infected with the COVID-19 virus with mild-to-moderate respiratory illness showed recovery without requiring special treatment [12]. Older people, compromised patients such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to show bad prognosis [2], [3], [12]. In another study, nine pregnant women [13] infected with COVID-19, there was no transmission of COVID-19 to their new born babies. The World Health Organization (WHO) indicates to protect yourself by washing hands and used alcohol based rub frequently and not touching face [7]. The most common symptoms of COVID-19 are fever and cough [3], [4], [10]. Some patients may have aches and pains, nasal congestion, runny nose, sore throat, or diarrhea. You can catch COVID-19 from patients looks not ill or with mild symptoms [7]. It is recommended to keep at least 1 m (3 feet) distance between yourself and anyone who is coughing or sneezing [3], [7]. Also use tissue to cover your eye and nose when you are coughing or sneezing [7]. The WHO is mentioned [7] to avoid contamination of uncooked foods. The recommended method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR [3], [12]. Furthermore, throat swabs test shows positive in the 1st day of infection and by contrast, rectal swabs show positive in the latter period of infection [14]. We declare from our extensive reading in literature that false negative results in detection COVID-19 in some patients although its presence in body. These false negative result due to different reasons such as an improper collection of sputum samples, inhomogeneous sputum, contamination of the collected sample, ignorance of viral load due to the early stages of the infection, inappropriate diagnostic kits, sampling from inappropriate site of the throat in the throat swab, no good training and skills, and poor experience. There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Immunocompromised patients should avoid public exposure. Despite the limitations of this study it highlighted the most critical issues concerning COVID-19. The clinical manifestations of COVID-19, determination of route of transmission for COVID-19, diagnostic tools of COVID-19, prevention and modalities of treatment, following up of infected patients for long term after recovery, are essential points to be considered in any future research in order to obtain more valid results about the nature and behavior of COVID-19.

. There is no clear international plan to stop spreading this virus as it spreads in more than 100 countries in the world. The current available plan is to stay home in all countries specially those which have many patients confirmed COVID-19. Although China has made a great progress in stop this virus and many patients showed a good recovery, this needs follow-up of the previous cases to avoid secondary infection and to do full screening for all healthy people that contact with infected patients. This international pandemic COVID-19 showed that there is lack of education for public to deal with any danger disease-like COVID. The only available data in literature are case series. We believe that the number of infected patients in some countries is not reliable and needs hard work from the WHO to evaluate and confirm the cases number. Most published data on COVID-19 need to differentiate between mild, moderate, and severe cases that need to refer to hospital. We have noticed poor information about the died patients infected with this virus. No long follow-up for patients get recovery. Recurrent cases of COVID-19 should highlight. The WHO should educate the health workers over the world with strict criteria to detect this virus and avoid transmission the virus to them.

Conclusion

This virus outbreak has challenged the economic, medical, and public health infrastructure, of the most countries in the world. Strict procedures should be taken in the near future to avoid outbreak of this virus of zoonotic origin. People over the world are looking for finding new vaccination to avoid this virus and the best treatment to save their life.

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Social Stigma toward Health Workers Associated with Coronavirus Disease 2019

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Abstract

BACKGROUND: The World Health Organization declared the novel coronavirus disease 2019 (COVID-19) a global pandemic, which classifies the outbreak as an international emergency. This disease has been confirmed as the first pandemic in 21st century. Healthcare workers on the front line who are directly involved in the diagnosis, treatment, and care of patients with COVID-19 are at risk of being stigmatized.

AIM: This study was a review.

METHODS: This study was conducted by conducting analytic appraisal using published journals and sources through an electronic database.

RESULTS: From cases in Indonesia and other countries, there's bunch of examples that healthcare workers being negatively stigmatized in case of COVID-19. They lost their rights to have a normal life in this pandemic era.

DISCUSSION: The government itself has actually promoted socialization about COVID-19, including the importance of mutual support and assistance including morally and psychosocially for the sufferers and health workers involved. However, negative stigma for health workers and patients and their families suffering from COVID-19 remains strongly attached until nowadays. Synergy between the central government, regional governments, community leaders, and referral hospital officials are certainly important to overcome this stigma problem, in addition to promoting education in the community.

CONCLUSION: Synergy among the central government, regional governments, community leaders, and referral hospital officials is certainly important to overcome this stigma problem, in addition to promoting education in the community.

Introduction

Stigma is a powerful social process that is characterized by labelling, stereotyping, and separation, leading to loss of status and discrimination, all occurring in the context of power [1]. Stigma also impacts the well-being of the health workforce because healthcare workers may also be living with stigmatized conditions [2]. They may conceal their own health status from colleagues and be reluctant to access and engage in care. Yet, stigma reduction is not a routine part of the way in which health services are delivered or evaluated, nor is it regularly integrated into pre-service and in-service training of all cadres of healthcare workers [3].

Since the end of December 2019, the Chinese city of Wuhan has reported a novel pneumonia caused by coronavirus disease 2019 (COVID-19), which is spreading domestically and internationally [4]. The virus has been named severe acute respiratory syndrome coronavirus 2 [5]. In this report, we will refer to the disease, COVID-19. On January 30, 2020, the World Health Organization (WHO) held an emergency meeting and declared the global COVID-19 outbreak a public health emergency of international concern [6]. Moreover, On March 11, 2020, the WHO declared the novel COVID-19 a global pandemic, which classifies the outbreak as an international emergency [7].

At the time of drafting this editorial, COVID-19 has swept through more than 181 countries, which it means almost all of countries in the world, infected more with around 1,084,000 infected subjects, more than 58,000 death over the world [8]. This disease has been confirmed as the first pandemic in modern days, especially in 21st century.

Facing this critical situation, healthcare workers on the front line who are directly involved in the diagnosis, treatment, and care of patients with COVID-19 are at risk of being stigmatized. This correspondence article explores how stigma is currently being addressed in health facilities across medical conditions, discusses gaps arising from a scan of the literature, and the potential for synergies across disease stigmas that could be harnessed for a joint response to more than one disease stigma. Such stigma may be experienced in all spheres of life; however, stigma in health facilities is particularly egregious, negatively affecting people seeking health services at a time when they are at their most vulnerable.

Synergy is needed for stigma reduction although it needs some effort in large scale and cost and time consuming. However, clearly, interventions must pay attention to specific cultural and socioeconomic contexts and recognize that stigmas are not always experienced in the same way in all settings. An improved understanding of how health condition stigma is currently addressed in health facilities is needed to identify gaps and areas for investment in stigma reduction, as well as to explore the possibility of concurrently addressing more than one health condition stigma with a joint intervention. Thus, this correspondence article takes an explicitly programmatic focus and aims to examine “how” health facility-based stigma reduction interventions are implemented across health condition stigmas.

From social media, it can be seen that support for health workers during the outbreak of the COVID-19 pandemic is huge [9]. This support came from many parties, ranging from ordinary people, community leaders, government officials, artists, musicians, and even to social organizations and businesses. This form of support is also very diverse. This form of support is also very diverse, starting from messages of support, songs, poems, incentives for health workers, to the provision of free food and drinks from businesses and the community. Donations from ordinary people in the form of personal protective equipment and various other needs needed by medical personnel during the pandemic [10].

The messages that have emerged on social media and the mainstream illustrates that health workers are heroes who are struggling on the front lines in the face of this pandemic. They are described as willing to struggle to risk their lives to save others in a pandemic. This large number of messages and real support illustrates that there is a strong positive stigma for health workers in our society. Of course this is very encouraging.

But that does not mean that there is no negative stigma for health workers working in this pandemic situation. Negative stigma as a person who brings disease appears in the community. Although from the news and information that appeared in the media it can be concluded that most of this stigma occurs in people with low education in rural areas whose access to information is still limited, but this also still occurs in the republic’s capital and in front of one of the main referral hospitals for cases COVID-19 in Indonesia, too [11]. People were afraid that medical workers could be at risk of transmitting the virus. Unable to find other places to stay, some medical workers had to stay at the hospital [9].

Even after this news went viral and drew public criticism, it seemed that the stigmatization of the medical staff also did not stop spontaneously. Resident doctors also were at risk. Society tends to discriminate on the grounds of notification from the local government to avoid contact with people suspected of being exposed to the virus in the hospital [12]. The same situation is experienced by health workers in several other regions in Indonesia, although the news is not massive. Mostly, doctors who got stigmatized working on large hospital which is the referral center for respiratory disease and other infectious disease in Indonesia. Even though in the end of the two cases above, the government has intervened, even giving a legal assistance, but this indicates that stigmatization of health workers during the pandemic has not diminished. Stigma is associated being unreasonable fear with infectious disease can be a barrier to adopting healthy behaviors, leading to difficulty controlling infectious disease outbreaks [13].

The government itself has actually promoted socialization about COVID-19, including the importance of mutual support and assistance including morally and psychosocially for the sufferers and health workers involved. This message from the government was included in one of the mental and psychosocial health campaigns launched by the WHO to deal with the COVID-19 pandemic. However, negative stigma for health workers and patients and their families suffering from COVID-19 remains strongly attached. Of course we do not forget cases of rejection of patients and their families in several boarding houses near the hospital where patients were treated, even the refusal to bury COVID-19 patients in various areas that had been viral [14]. The Indonesian government, to this day, continues to face public pressure, even from the central legislature, to promote socialization and make regulations to prevent stigmatization of patients and medical workers affected by COVID-19 so as not to experience the events above. But until now, unfortunately, there is no specific regulation from the government to deal with the complicated situation for health workers. Even so, the government, both central and regional, still continues to try to disseminate information to reduce this stigmatization, even though it is still considered to be not optimal [14], [15].

This is a chore for all of us, not just the government. Synergy between the central government, regional governments, community leaders, and referral hospital officials is certainly important to overcome this stigma problem, in addition to promoting education in the community. Many sources of how to prevent stigma in patients and health workers related to COVID-19 have been published, both by the private sector, government, and even from WHO that we can apply to contribute to changing this condition. Surely, we do not want that in the midst of the struggles of health workers on the front lines with (still) limited means, negative stigma is also attached to them and aggravating their working conditions.

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Effects of Electronic Technology Antenatal Care (E-ANC) on Midwives and Pregnant Women during the COVID-19 Period

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Abstract

BACKGROUND: Pregnant women are considered as a risk group for exposure to COVID-19. Changes in their hormones and immune systems possibly influence their rate of infection by several viruses, including the coronavirus. This stresses the need to observe necessary precautions, by maintaining social distancing, avoiding crowds, and staying at home. Furthermore, the condition also influences the scope of pregnant women's antenatal visits.

AIM: The study aims to determine the effect of COVID-19 on antenatal visits by pregnant women. Furthermore, it seeks to ascertain the effect of electronic technology antenatal care (e-ANC) on the enhanced participation of midwives and pregnant women in antenatal care (ANC) (i.e., counseling, high-risk early detection on pregnancy, and monitoring of Hb and Fe tablets). Therefore, the impact COVID-19 on women's reproductive health during the pandemic is also evaluated.

METHODS: This research involved pre- and post-test experiments on 30 pregnant women and 20 midwives at areas around the Public Health Centers in Tinggiede and Marawola. A purposive sampling technique was adopted, and the results were analyzed using a paired t-test.

RESULTS: The study showed discrepancies in the ANC visits of pregnant women before and after the COVID-19 lockdown period, with $p < 0.00$. Furthermore, there were also differences in midwife participation in counseling by $p < 0.00$, high-risk early detection on pregnancy by $p < 0.001$, Hb monitoring by $p < 0.002$, and provision of Fe tablets by $p < 0.003$ during the pandemic. Moreover, the pregnant women showed variations in the frequency of counseling by $p < 0.00$, high-risk early detection on pregnancy by $p < 0.00$, Hb monitoring by $p < 0.002$, and the provision of Fe tablets by $p < 0.003$. The e-ANC instigated a decline in reproductive health problems before (73.4%) and after (10.0%) the intervention.

CONCLUSION: The lockdown period influences the low antenatal visits of pregnant women. However, e-ANC for midwives and pregnant women is developed as an alternative solution to improve ANC (i.e., counseling, high-risk early detection, and monitoring Hb and Fe tablets). This consequently has an effect on the reduced reproductive health problems of pregnant women during the pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) was first reported in Indonesia on March 2, 2020, with the country originally having two cases. However, data from May 9, 2020, reveal that it already has a total of 13,645 confirmed cases with 959 deaths. Furthermore, the mortality rate was estimated to be at 8.9%. This is the highest in Southeast Asia, resulting from the ability to infect all people, including even pregnant, postpartum, and breastfeeding mothers [1]. This infective prospect instigates the high recommendation of prevention, as a means to minimize the virus exposure. The most common instruction for everyone include social distancing and staying at home [1], [2]. Furthermore, such condition affects the scope of antenatal care (ANC) visits. Based on the data obtained from the Public Health Center of Tinggiede and Marawola during the lockdown period (March 10–April 10), there was a very low percentage (0.1%) ANC visits. The same is true also for home check-ups by midwives, in cases of COVID-19-related complaints. These practices are known to be very important to monitor the pregnancy development of women, to detect possible abnormalities and complications early on Rasmussen *et al*. [3]. In addition, the provision of complete ANC promotes speedy and correct treatment, leading to a reduction in morbidity risks. Such may also reduce the possibility of death of the mother and child during the COVID-19 period [4].

These challenges facilitate the need to identify the alternative means of achieving proper ANC. Therefore, an Android-based electronic technology antenatal care (e-ANC), specifically designed for midwives and pregnant women, is expected to increase online ANC coverage for health counseling, high-risk early detection, Hb monitoring, and the provision of Fe tablets. This relatively new model improves the midwives' ability to monitor pregnancy development. Furthermore, it also aids in their capacity to provide services at any time and any place without physical contact. However, communication and education are needed for both parties to maximize e-ANC features. This is true, especially in obtaining information, counseling, and communicating with health workers [5]. The pregnant women tend to feel more comfortable through their pregnancy, childbirth, and puerperal within the COVID-19 period, subsequently assuring safe delivery and good health of their baby [6].

Research on mobile health technology (m-Health) using Android has been carried out by Haddad *et al*., Feroz *et al*. Schwartz [7], [8], [9]. However, the locus is currently limited to health workers, in conditions unaffected by the COVID-19 pandemic. A study on electronic technology involvement in the COVD-19 pandemic situation for midwives and pregnant women to improve maternal and infant health has never been conducted. This prompts the need to perform applied research on the effects of e-ANC for midwives and pregnant women during the pandemic, as a model for improving ANC. This study, therefore, aims to determine the effect of the COVID-19 pandemic on ANC visits. It also seeks to evaluate the effect of e-ANC on the participation of midwives and pregnant women in counseling, high-risk early detection, monitoring of Hb and Fe tablets, and the impact on their reproductive health.

The e-ANC model has many advantages. First, it provides intensive counseling to pregnant women and midwives regarding maternal and child health, with respect to the COVID-19 pandemic. Second, midwives are able to effectively monitor pregnant women, detect high-risk pregnancies early on, and evaluate Hb and Fe tablets and the development of pregnancy conditions without physical contact, anytime and anywhere. Third, the model is simple, easy to understand, and is cost effective during the pandemic.

Materials and Methods

Research design, place, and sample

This is quasi-experimental study that used pre- and post-tests. The study was conducted in 11 villages within the Public Health Center area of Tinggiede and Marawola, Sigi Regency, Central Sulawesi Province, from February 9, 2020, to May 9, 2020. Moreover, a purposive sampling technique was used to select 30 respondents, based on the inclusion criteria of pregnant women (in their second trimester [>4 months], with willingness to participate, ability to speak Indonesian, and the ability to use an Android device). Meanwhile, 20 midwives were chosen as respondents (on duty at the Tinggiede and Marawola Public Health Center, and the ability to use an Android device).

Data collection technique

Before distributing the e-ANC application, secondary data were obtained from the midwives in the Tinggiede and Marawola Public Health Centers. However, secondary data were obtained from 11 more village midwives online. This information was related to the antenatal coverage before (February 9, 2020–March 9, 2020) and after the lockdown period (March 10, 2020–April 9, 2020). Moreover, midwife services during the pandemic, with regard to counseling, high-risk early detection, and Hb and Fe tablets monitoring were also considered. Data on the reproductive disorders experienced by pregnant women during the lockdown period were also obtained.

In addition, between April 9, 2020, and May 9, 2020, treatment was provided following the e-ANC application distribution. There was also a tutorial on usage of the application's treatment to both midwives and pregnant women. However, any barriers or issues recognized are asked and resolved online. The e-ANC is continuously developed every day based on the first-hand observations, with the help of midwife coordinators and Public Health Center heads. All the data from the respondents were analyzed on May 9, 2020. In addition, the e-ANC is made up of very simple content. These include, among others, a complete ANC, counseling, information on the need for high-risk early detection, Hb and Fe tablets monitoring, information on the danger of pregnancy, healthy living behavior during the pandemic, prevention methods, and the dangers and impact of the COVID-19 pandemic.

Data analysis technique

The differences were analyzed using paired sample t-tests.

Results

Social demographic characteristics of respondent

The respondents' characteristics were based on age, occupation, education, and number of children.

Based on Table 1, majority of the pregnant women were aged 20–35 years (56.7%), indicating that the average respondent was within the ideal childbearing age. Furthermore, 76.7% of the participants were housewives, hence, the absence of a steady income. On the other hand, 56.3% had a last education of senior high school, suggesting the participants' moderate capacity of using Android devices with the e-ANC feature. Moreover, the highest number of children was >3 (60%), showing the non-compliance with the National Family Planning Coordinating Agency recommendation of at most two children. Conversely, 60.0% of the midwives were aged 35–55 years, indicating the presence of a relatively young and productive workforce in both the Public Health Centers. In addition, 49.1% of the midwives have served for ≥5 years, suggesting a relatively high experience level in providing ANC.

Table 1: Distribution of respondents based on their social demographics characteristics

Characteristics	Frequency	Percentage
Pregnant woman		
Age		
<20 years old	12	40.0
20–35 years old	17	56.7
>35 years old	1	3.3
Total	30	100
Occupation		
Employee	4	13.3
Entrepreneur	3	10.0
Housewife	23	76.7
Total	30	100
Education		
Elementary school	7	23.3
Junior high school	7	23.3
Senior high school<	16	53.3
Total	30	100
Number of children		
≥2	14	40.0
>3	16	60.0
Total	30	100
Midwife		
Age		
<35 years old	1	5.0
35–55 years old	12	60.0
>55years old	7	35.0
Total	20	100
Length of work		
<5 years	7	35.0
≥5 years	13	65.0
Total	20	100

Effect of COVID-19 periods on ANC coverage of pregnant women

Based on Table 2, the statistical test results showed an ANC coverage of 0.00 or $p < \alpha$ 0.05. Thus, a significant difference is established between the outcome before (February 9, 2020–March 9, 2020) and after (March 10, 2020–April 9, 2020) the lockdown period.

Table 2: Difference in value of ANC coverage of pregnant women before and after the COVID-19 lockdown period

Variable	Mean	Standard deviation	p-value
Before the COVID-19 lockdown period	−15.433	5.782	0.000
After the COVID-19 lockdown period			

The effects of ANC on the improved midwife participation in counseling, high-risk early detection, Hb monitoring, and the provision of Fe tablets

Based on Table 3, the statistical test results for counseling p = 0.00 or < α 0.05. Thus, a significant difference was established between the values reported before and after the intervention. Similarly, p < 0.00 was recorded for high-risk early detection and p < 0.002 for examination of Hb. Therefore, there was a significant difference between the values before and after the intervention. Furthermore, the provision of Fe tablets was at p < 0.003, which confirms a significant discrepancy between the value estimated before and after the e-ANC.

Table 3: Difference in value of midwife participation in counseling, high-risk early detection, Hb examination, and provision of Fe tablets

Variable	Mean	Standard deviation	p-value
Counseling			
Pre-intervention	−14.500	6.856	0.000
Post-intervention			
High-risk early detection			
Pre-intervention	−17.950	4.718	0.000
Post-intervention			
Hb monitoring			
Pre-intervention	−15.550	4.617	0.002
Post-intervention			
Provision of Fe tablets			
Pre-intervention	−15.250	3.567	0.003
Post-intervention			

Effects of e-ANC on pregnant women for counseling, high-risk early detection, Hb examination, and provision of Fe tablets

Based on Table 4, the statistical test results for counseling showed p = 0.00 or < α 0.05. This shows that there were significant differences in pregnant women participation before and after the e-ANC intervention. Meanwhile, the high-risk early detection was at p < 0.00, while the Hb examination was at p < 0.002. Such indicate significant differences in both parameters, similar for the provision of Fe tablets with p < 0.003.

Table 4: Differences in the value of pregnant women participation in counseling, high-risk early detection, Hb examination, and provision of Fe tablets during the COVID-19 period

Variable	Mean	Standard deviation	p-value
Counseling			
Pre-intervention	−14.167	6.069	0.000
Post-intervention			
High-risk early detection			
Pre-intervention	−18.900	4.318	0.000
Post-intervention			
Hb monitoring			
Pre-intervention	−14.833	5.045	0.002
Post-intervention			
Provision of Fe tablets			
Pre-intervention	−15.400	3.701	0.003
Post-intervention			

Impact of disorders on women's reproductive health

Table 5 shows the reproductive health problems suffered by pregnant women before the provision of ANC. These include dizziness or headache (46.6), fever (10.0%), fetal death (3.3%), miscarriage (3.3%), and bleeding (10.0%). Furthermore, 6.7% decline in dizziness and 3.3% decline in headache and fever were reported after the intervention. However, fetal death, miscarriage, and bleeding were all at 0.0%. However, the incident of no complaints reached 90.0%.

Table 5: Reproductive health problems pre- and post-intervention during the COVID-19 period

Reproductive health problems	Before		After	
	F	%	f	%
Dizziness/headache	14	46.6	2	6.7
Fever	3	10.0	1	3.3
Fetal death	1	3.3	0	0.0
Miscarriage	1	3.3	0	0.0
Bleeding	3	10.0	0	0.0
Number of complaints	22	73.4	3	10
No complaints	8	26.6	27	90.0
Total	30	100	30	100

Discussion

Effect of the COVID-19 lockdown period on the ANC coverage for pregnant women

The analysis showed a significant difference in the antenatal coverage before and after the COVID-19 lockdown period. This was the result of the Indonesian local governments recommending various safety measures against COVID-19 such as staying at home, working from home, social distancing, avoiding direct physical contact, and evading crowds [1], [2]. In addition, the disease has prevented pregnant women and health workers from visiting the Public Health Center, due to the fear of contracting the virus. This condition is congruent with Daw MA [10], where lockdown periods were reported to affect the visiting of pregnant women in health facilities. Meanwhile, midwives tend to perform more home visits on instances where there are complaints. The current study highlighted the service rendered at the Public Health Center to include only childbirth, and this is served according to the COVID-19 protocol [1].

Effects of ANC application on increased midwife participation in counseling, high-risk early detection, monitoring HB, and provision of Fe tablets for pregnant women

The analysis showed a significant difference in the participation of midwives before and after using the e-ANC for counseling, detecting early high-risk pregnancies, measuring Hb, and providing of Fe tablets to pregnant women (Table 3). This is possible because the application automatically modifies the midwives' behavior because communication, counseling, and evaluation are all conducted without direct physical contact with the pregnant women. The e-ANC feature allows for intense detailing about the pregnant women's health condition during the pandemic. Furthermore, there are also a number of questions from pregnant women relating to the ways of preventing, the harm caused, and the overall influence of the COVI-19. This further improves the midwives' knowledge [11], and counseling is now focused on the pregnancy and more on how it may be affected by COVID-19, thus subsequently impacting service improvement [2]. This situation indirectly promotes motivation and activity in providing ANC services [12], [13].

The study results are congruent with Segars *et al.*, [14] where the midwives with knowledge on ANC and COVID-19 effectively conducted ANC according to COVID-19 standards. This expertise is also very useful for counseling, high-risk early detection, and improving overall maternal safety and infant health. In addition, the use of a risk approach in testing is important, especially in high-risk pregnancies [14], because the incidence of anemia ought to be detected very early [15], [16]. Therefore, it is mandatory for midwives to examine Hb and provide Fe tablets while providing ANC during the pandemic [17].

Based on the results, some midwives avoided reporting to the Public Health Centers for the fear of contracting the COVID-19 virus before the e-ANC implementation. This was because one of the criteria for identifying people under surveillance (ODP) includes people working and visiting health facilities involved with treating patients with COVID-19 symptoms [17]. Therefore, the use of e-ANC guarantees the feeling of safety, as services to pregnant women are now made possible without physically visiting the Public Health Center.

Furthermore, some midwives considered the tendency for Hb measurement to increase the duration of contact with pregnant women. However, e-ANC implementation increased the midwife participation in examination, as measurements were conducted at home and the health workers and pregnant women had to wear their personal protective equipment. The results obtained from the evaluation are used as a reference in explaining the benefits of iron tablets and the possible consequences of anemia [18]. This situation is in line with Yan *et al*. [19], where ANC enables the detection of problems faced by pregnant women in need of special services. These challenges include anemia, complications, high fever, and other symptoms with a tendency to endanger the lives of both the mother and child [20]. Therefore, the practice of early treatment saves pregnant women during the COVID-19 pandemic.

Effects of ANC on pregnant women in counseling, high-risk early detection, HB monitoring, and provision of Fe tablets

The results showed that there were significant differences between counseling, high-risk early detection examinations, Hb monitoring, and provision of Fe tablets before and after the e-ANC intervention (Table 4). This occurred possibly because the implementation of the application influences the pregnant women's knowledge about pregnancy and COVID-19. Such is possible because the elements of e-ANC serve as guide for them in describing the actions to perform. Furthermore, the counseling benefits are obtainable at any time and any place without making physical contact with health workers. Moreover, pregnant women are able to personally detect their risk level (high or low). The results are also congruent with Haddad *et al*. and Feroz *et al*. [7], [8], where the use of information technology to serve pregnant women promotes the individuals' knowledge of the progress, because the results of previous examinations are reaccessible.

The most significant improvement after the e-ANC implementation is observed in the domain of counseling and high-risk early detection. Following the counseling instructions, four items were obtained to protect pregnant women against COVID-19. First, pregnant women must practice frequent handwashing with soap and running water for 20 s and use hand sanitizers with at least 70% alcohol content. Second, they must maintain a minimum distance of 1 m from other people and avoid crowded rooms. Third, they must avoid touching their eyes, nose, and mouth. Finally, they need to pay conscious attention to the cleanliness of their breathing, using a mask, especially when coughing or sneezing. In addition, the incidence of fever, cough, or difficulty in breathing requires contacting the nearest health worker or hospital immediately. The results of this study are in accordance with Ministry of Health of the Republic of Indonesia (1), where the COVID-19 protocol for pregnant women includes avoiding touching the eyes, nose, and mouth with unwashed hands, as well as avoiding physical contact with sick people. Furthermore, using a medical mask and staying at home when sick or visiting a suitable health facility immediately, keeping clean, and regularly disinfecting surfaces and frequently touched objects are effective preventive measures. In addition, Yan *et al*. and Lim *et al*. [20], [21], counseling about COVID-19 during pregnancy is very important to maintain the safety of pregnant women.

The e-ANC is an Android-based application, specifically designed for the COVID-19 pandemic. This application is used by pregnant women to personally detect their risk (high or low). Furthermore, health workers including doctors and midwives are able to monitor the development of pregnancy and the fetuses at any time. Clients feel safe and happy as services are provided at any time from home. This is congruent with the outcome of Haddad *et al*. Schwartz [7], [9], relating to the effect of health information technology on the quality of care provided to pregnant women during the pandemic. Furthermore, this is improved by health information technology, especially through reduced negligence in monitoring the pregnancy and fetus development [1], [7], [8].

Impact of ANC on reproductive health problems during in the COVID-19 pandemic

Reproductive health problems before and after the intervention decreased from 55.5% to 3.6% (Table 5). This condition is possibly due to the integration of midwives and pregnant women on a single system, which ensured their regular and continuous communication and education. In addition, the presence of e-ANC improved counseling, high-risk early detection, monitoring Hb levels, and compliance in consuming Fe tablets during the pandemic. The midwives also now possess the knowledge and skills for early detection, needed to ensure timely resolution. This is in accordance with Ministry of Health of the Republic of Indonesia, Firdiiansyah, Saleh, [1], [22], [23], where the education model expected by pregnant women during in the COVID-19 pandemic is comprehensive for determining the pregnancy development.

Furthermore, other health problems, including fever, flu, and cough, similar to COVID-19 symptoms were very low (10%) compared to the findings of Mamar *et al*., [6] where complaints in the form of fever/convulsions, coughing, and spasms were reported by 55% of respondents. This is possible due to the stigma, stereotype, and subsequent marginalization assumed to worsen the health status and recovery rate of pregnant women, hence, the practice of concealing the information. In addition, there is fear of being ostracized by the community, and this greatly affects mental health (fear) and worsens the individuals' immunity. The research results are congruent with Firdiyansyah and Saleh [22], [23], where stigma and stereotyping contributed to the healing process of patients and high mortality rate resulting from the COVID-19 pandemic in Indonesia, for both the patient and the health workers. The issues of rejection of the COVID-19 corpse and patients by some communities prompt the reluctance to report the disease to health institutions, despite the already existing infection [22].

The e-ANC provides information on the current condition of pregnant women, and the midwives are able to provide preventive treatment more quickly. For example, dizziness/headache reported before the intervention was at 45.6%, and this has reduced to 6.7% afterward (Table 5). This is possibly due to the regular checks for body temperature, blood pressure from the beginning, facilitating the early protection against patients with COVID-19 symptoms. Therefore, the use of e-ANC is highly needed. It also plays an important role in reducing reproductive health problems. This also serves as the main supporting tool to anticipate an increase in postnatal pregnancy deaths, due to the minimal contact with health workers. In addition, antenatal care reduces maternal mortality rate during social distancing [1], [24]. This finding is a novelty to complement the research of Haddad *et al*., Feroz *et al*. [7], [8], where the comprehensive use of technology in ANC improved the reproductive health of pregnant women. Furthermore, reduced maternal mortality rate was reported during the pandemic lockdown period, especially in the Central Sulawesi Province of Indonesia.

This study showed no positive cases of COVID-19 for pregnant women and babies born. However, miscarriages and fetal deaths were reported. A convincing relationship was not established between COVID-19 infection and the risk of miscarriage and fetal death in the second trimester. This trend is in line with Infections, Reproduction, Obstetrics, Ginecology and Recommendations in Pregnant Women-Childbirth [24], where no clear data were observed to correlate high fever with disability and fetal death.

Conclusion

The lockdown period during the COVID-19 pandemic led to a low ANC visitation rate for pregnant women. Therefore, e-ANC was introduced as an alternative solution to increase ANC (i.e., counseling, high-risk early detection, monitoring Hb, and provision of Tablet Fe). After the implementation of the application, counseling on maternal-child health and COVID-19, and high-risk early detection were identified as the highest domain in the services provided. Furthermore, e-ANC influenced the decline in the overall reproductive health problems.

Authors' Contributions

Rosmala Nur (conceptualizing and designing the study, preparing the manuscript draft, doing revisions, or providing critique); St. Radiah (sectional scientific management), Ulfa (analyzing and interpreting the data); Rahma Dwi larasati (analyzing and interpreting the data); Nurhaya S. Patui (analyzing and interpreting the data); Elvaria Mantao (analyzing and interpreting the data); Syaiful Hendra (sectional scientific management); Hajra Rasmita Ngemba (data analysis and interpretation); Muh. Rusydi, H (sectional scientific management); and Nenita P. Domingo (sectional scientific management).

Significance Statement

This study identified the effect of COVID-19 lockdown on the low ANC visit of pregnant women. In addition, electronic antenatal care (e-ANC) for midwives and pregnant women is an alternative solution to improve care, due to increased participation in counseling, early detection of high risk, as well as Hb and Fe tablet monitoring. This practice also reduces reproductive health problems.

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Public Health, Socioeconomic Responses, and associated Challenges against Coronavirus Disease 2019 Pandemic in Nigeria

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Abstract

For over 6 months of its emergence, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) pandemic, has resulted to unprecedented global health challenge and economic uncertainties. The pandemic swiftly disseminated to almost all the countries and territories of the world. The index case in Nigeria was imported by an Italian citizen on February 27, 2020. Typical of a novel respiratory tract viral infection, the spread of SARS-CoV-2 in Nigeria was slow in the first few days. However, as at 8:00 AM GMT+1, July 1, 2020, there were 25694 confirmed COVID-19 cases. With the continuous daily rise in the incidence of SARS-CoV-2 infection, enhanced surveillance programs were immediately activated and implemented in all parts of Nigeria. Even though an inadequate number of persons have been tested so far, the government of Nigeria has been activating public health laboratories to scale up its testing capacity. Due to the impact of partial lockdown and curfew in most states of Nigeria, the government has been able to provide some form of palliatives to vulnerable populations. This study aims to review and present the various public health and socioeconomic responses and challenges of the COVID19 pandemic in Nigeria. This reflects the efforts and successful steps taken to minimize the spread of COVID-19 in Nigeria.

Introduction

There are recent scientific controversies over the date and origin of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19). It was initially widely believed to have originated from the Wuhan live animal market in Wuhan city, Hubei Province, China. However, recent reports are suggesting SARS-CoV-2 infection originated from laboratory recombination [1]. The first human-to-human transmission was reported to the World Health Organization (WHO) country office in China on December 31, 2019. But, SARS-CoV-2 was first imported to Nigeria through an Italian Citizen on February 27, 2020 [2].

Based on available data, the transmission dynamics of SARS-CoV-2 continue to improve with the evolution and expansion of the outbreak with time. Epidemiologically, the transmission of SARS-CoV-2 can be broadly categorized into three stages, namely, from being asymptomatic to pre-symptomatic and symptomatic [3]; it is worthy to note that all these categories of people are infected with SARS-CoV-2 [3].

There are various mathematical models and biological investigations which seek to elucidate the transmission dynamics of SARS-CoV-2 [4]. At present, the only available means of controlling the spread of SARS-CoV-2 to previously uninfected locations is through consistent adherence to physical distancing, adequate hygienic practices, and monitored self-isolation of infected persons. Despite all these, the world continues rise in the incidence rates of SARS-CoV-2.

Initially, the spread of SARS-CoV-2 in Nigeria was slow with single digits, mainly at Lagos and Abuja, for 10 days (Figure 1) [5]. However, as at 8:00 AM GMT+1, July 1, 2020, 17 weeks after the first index case, there were 25693 confirmed COVID-19 cases with a case fatality rate of 2.3% [5]. Of these, Lagos ha the highest reported incidence and fatality rates (Table 1). Several observers have attributed the low reported incidence rate of COVID-19 in Nigeria and many African countries to be a cause of underdiagnosis probably because of inadequate molecular diagnostic capacity and few human resources skilled in molecular diagnostic tests [6]. Recently, a more worrisome in Nigeria is the mysterious and rise in the death rate of unknown origin in the ancient Kano city [7].

This study aims to review and present the various public health and socioeconomic responses and challenges of the COVID19 pandemic in Nigeria.

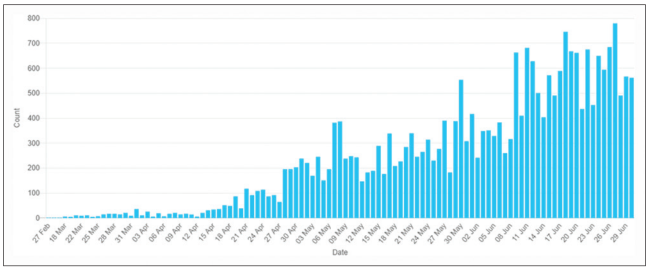

Figure 1: Daily trend of confirmed coronavirus disease 2019 cases in Nigeria [5]

This reflects the efforts and successful steps taken to minimize the spread of COVID-19 in Nigeria.

Table 1: Top 10 states with highest confirmed COVID-19 cases in Nigeria (as of July 1, 2020) [5]

State	Number of confirmed cases	Number of death	Number active COVID-19	State population
Lagos	10510	128	8779	12,550,598
Federal capital territory (Abuja)	1870	33	1267	3,564,126
Oyo	1380	12	672	7,840,864
Kano	1216	52	233	13,076,892
Edo	1105	39	778	4,235,595
Rivers	1056	38	398	7,303,924
Delta	965	23	752	5,663,362
Ogun	826	19	238	5,217,716
Kaduna	766	12	222	8,252,366
Katsina	556	23	249	7,831,319

COVID-19: Coronavirus disease 2019.

Public Health Response against the COVID-19 Pandemic in Nigeria

For about 7 days after the first index (imported) case, there were few infection control measures implemented in Nigeria [5]. However, the evolving nature and spread of the SARS-CoV-2 infection have led to a thorough rejig of initial control measures. Particularly, the geometric increase in new cases of COVID-19 has warranted the Federal Government (FG) to constitute a COVID-19 presidential task force saddled with the responsibilities of containing the spread of SARS-CoV-2 infection and other public health responses [5]. As SARS-COV-2 continued to spread to 35 states and Abuja (the federal capital territory) of Nigeria, a similar task force has been adopted in all state levels with a various state task force which has been constituted with representatives from the government executive arm and members of the health sector [8]. The FG of Nigeria issued public health advisories, which included an initial 2 weeks lockdown of 3 high-risk States, closure of land, and international air borders. In addition, the FG and several state governments (SGs) have put in place other measures such as the opening of isolation centers, inter-state border closure, movement restrictions, and stay-at-home policy to ensure full compliance of physical distancing [5]. Recently, the FG encourages the use of locally-made Personal Protective Equipment (such as face masks), continuous monitoring of institutions that offer essential services to ensure that they maintain a restricted number of guests within their premises and also strategically position temperature devices as well as water and soap for hand hygiene, and the temporary ban on the traditional crowded funerals, religious, weddings, and other social functions [5].

Even though there are over 206 million Nigerians, as of July 1, 2020, the Nigerian Center for Disease Control (NCDC) had only been able to test about 1,34,257 persons across its 37 testing sites [5]. In the past 4 weeks, more efforts such as activation of more laboratories and isolation centers were undertaken by the FG due to the sudden and persistent double-digits reports of new cases of COVID-19 in certain states, which suggested active community transmission. Hence, Abuja and Lagos had embarked on active community case search and testing. This public health response has led to the detection of more asymptomatic cases at the community level.

There is an ongoing plan by the NCDC to activate ≥1 COVID-19 testing center(s) in every State of Nigeria to optimize early case detection, especially in rural and remote settlements [5]. Furthermore, Nigeria plans to adopted house-to-house testing to meet up with the National testing goal. It will enable prompt case detection isolation and avoid further transmission of SARS-CoV-2 infection. As a measure to minimize contraction of SARS-CoV-2 infection, the FG has massively advocated for periodic environmental disinfection exercises be conducted in every community.

At present, a major factor that could facilitate the spread of SARS-CoV-2 infection Nigeria is the densely populated camps of internal displace persons that experienced terrorism crises in the Northeastern part of Nigeria [9]. In these camps, the practice of physical distancing and other infection control and prevention measures cannot be guaranteed [10], [11].

Socioeconomic Impacts and Response to the COVID-19 Pandemic in Nigeria

In view of the hardship and adverse effects due to COVID-19 pandemic on household and home economy, FG and various SGs have begun house-to-house distribution of palliatives in the form of cash transfer and foodstuffs covering urban, semi-urban, and rural residents. However, the selection of eligible citizens was proposed to be based on either having a maximum of 15 US$ (5000 Nigerian Naira) in the bank account and/or maximum airtime expenditures of 0.3

US$ (100 Nigerian Naira) [12]. In addition, FG and some private organizations have made available interest free or very minimal interest-based loans to small-and middle-income enterprises. The later was severely affected by the COVID-19 pandemic (especially the agricultural sector).

Due to the insufficient molecular testing centers, it is necessary SGs provide the enabling environment for epidemiologists, NCDC staff, and appropriate health-care professionals to promptly collect and test samples from suspected cases. Besides, FG and SGs should expand and activate as many laboratories, isolation centers, and COVID-19 frontline workforce. However, not every state has a designated COVID-19 testing laboratory. Even though the FG and some SGs made an upward review of hazard and risk allowances, there is an urgent need to implement health and/or life insurance cover for all frontline healthcare workers. It has become necessary due to the recent report of the rising number of HCWs infected by SARS-CoV-2 from 40 to 113 in 1 week [13].

A major socioeconomic factor which could affect the COVID-19 response in Nigeria is the high level of poverty among infection vulnerable population, especially in crises zones [9]. These humanitarian crises affected persons experience various grades of malnutrition, increase risks of communicable and non-communicable diseases [14]. These may weaken their innate immunity and make them have chances of contracting severe COVID-19 [15].

Despite the palliatives distributed to the vulnerable populations, the reality on the ground is that only a small fraction of the population confirmed to receive the support [16]. Unfortunately, the majority of Nigerian citizens have disobeyed the lockdown order with the plan and hope of earning some money through petty trades and services [16].

Conclusion

Evidently, there is a widespread ongoing community transmission of SARS-CoV-2. Hence, there is an urgent need to scale up testing capacity in Nigeria. Due to the impact of COVID-19 on the global economy, there might be a scarcity of COVID-19 medical equipment and consumables, such as test kits and reagents. Hence, it is recommended that Nigeria and other African countries urgently consider production, evaluation, and validation of SARS-CoV-2 primers and rapid test kits to augment their stockpile. In consideration of the recent report that demonstrated the viability of SARS-CoV-2 in aerosol and fomites [17] and its ability to withstand high temperature [18], people must be restricted from risks of contracting SARS-CoV-2 infection.

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The Coronavirus Disease-19 Infection and the Oral Mucosa

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Abstract

BACKGROUND: The current coronavirus disease (COVID-19) pandemics induced a modification of daily life and clinical practice. Health care workers, particularly dentists and dental hygienists, have been obliged to limit their activity and to establish new operative protocols.

AIM: We aimed to discuss an easy protocol for the prevention of cross-infections in dental settings.

METHODS: We revised literature data about COVID-19 and oral health to establish how to work safely with dental patients.

RESULTS AND CONCLUSION: A few papers are currently available about the effective prevention of COVID-19 during dental procedures. Most of the revised articles report a potential strong effectiveness of povidone-iodine and its safety for both patients and dental professionals.

Introduction

The novel coronavirus (CoV), officially named as severe acute respiratory syndrome (SARS)-CoV-2, is a newly discovered virus, responsible for the so-called CoV infectious disease (COVID)-19, an infection originating in the upper airways. COVID-19 infection occurs mainly by air droplets and after a considerable introduction of viruses particles in closed and poorly ventilated rooms, at close contact with the presumed positive person; also by contact with contaminated objects, where COVID-19 can survive for some hours [1], [2], [3].

Then, it is spread through direct or indirect contact with the oral, the nasal cavity and the eye mucous membranes. At this level, SARS-Cov2 seems to cause chemosensory dysfunction as ageusia and anosmia [2].

The most likely cause for transient hypogeusia and hyposmia in SARS-CoV2-infected patients is a direct contact and interaction of the virus with gustatory receptors or olfactory receptor cells [3]. The oral mucosa could be stimulated by speaking, coughing, and sneezing and viral particles have the ability to become aerosolized; they can stay in the air for 3 or more hours and may spread to contaminate multiple surfaces in the surrounding area [4]. As a consequence, the SARS-CoV-2 became able to interfere with both respiratory and oral environment, also determining temporary (and perhaps permanent) damages of central nervous system [5], [6].

Given the capability of the SARS-CoV-2 of surviving over surfaces for several hours, it is crucial to perform an appropriate disinfection of the oral mucosa before any intervention [7], [8]. Furthermore, arising evidences exist about the positive action of antiviral and anti-allergic drugs in the oral district that seems to be useful in ameliorating the inflammatory status and reducing potential infection transmission. However, at least 10 clinical trials have been started to evaluate the efficacy and potential side effects of other products, including the ones used for oral hygiene [7], [8], [9].

While studies on virucidal activity of povidone-iodine (PVP-I) have not yet been performed specifically on SARS-CoV-2, several *in vitro* studies demonstrated its effectiveness against multiple viruses including related CoVs; for example, Eggers *et al.* examined a diluted PVP-I (0.23%) formulation against SARS-CoV-1, MERS-CoV, and influenza A (H1N1) applied for 15 s and found >99.99% reduction of viral titers [10]. Mouthwash/gargles for 1 min with a solution of PVP-I diluted 1:3 (for 7.5% PVP-I) or 1:4 (for 10% PVP-I) to achieve <3% concentration is safe and may help to reduce the viral load and the potential aerosolization of SARS-CoV-2. It could be effective to reduce viral load from asymptomatic COVID-19 patients, also providing a protective oropharyngeal hygiene measure for the health professionals. Moreover, as suggested by Sampson [11], oral hygiene should be improved during a COVID-19 infection aiming to reduce the bacterial load in the mouth and the risk of a bacterial superinfection. These easy-to-do, cost saving tips may be performed in any dental setting and effective to reduce the risk of severe infections [12], [13], [14]. Our suggestion is to maintain an extremely high level of oral hygiene to avoid any dental emergencies, therefore, patients should wash their teeth at least twice a day, floss daily, and use a PVP-I mouthwash thrice a day. This not only reduce the risk of dental emergencies but the oral viral load also and might, even if there is no evidence, reduce the risk of contaminating the surrounding environment [15], [16], [17].

By the way, based on the current literature, we can use local iodine-based products associated with systemic antiviral and anti-inflammatory drugs to avoid the infection spreading [18], [19], [20].

Conclusion

We must deepen our knowledge about SARS-CoV-2 biology and better understand the oral pathophysiology of COVID-19 to establish specific protocols to prevent its transmission and clinical consequences.

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Tunicamycin Anticancer Drug May Reliable to Treat Coronavirus Disease-19

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Abstract

BACKGROUND: SARS-CoV-2 outbreaks remains a medical and economic challenge, due to the lack of a suitable drug or vaccine. The glycan in some proteins plays an important role in protein folding, sorting, transport, and oligomerization, so the hindering of N-linked glycosylation of glycoproteins will prevent assembly of the virion. Tunicamycin anticancer drug inhibits the N- linked glycan.

AIM: This study aimed to find out the mechanism action of tunicamycin on the viral glycoproteins.

RESULTS: The growth of the virus in the presence of tunicamycin conducted in the production of non-infectious and absence of spike protein (spikeless virions). Tunicamycin inhibits E2, S, and M glycoproteins of coronaviruses. Tunicamycin has also diminished glycosylation of PTMs such as HE, and 8ab of SARS-CoV. Finally,

CONCLUSION: This study recommends using this drug to treat the SARS-CoV-2.

Introduction

Since the last December, a new coronavirus has been a challenge for all of the world. The reason of elevation number of infections and fatality that the researchers failed to find suitable drug or vaccine to stem the outbreaks [1]. A few studies focused on the effect of N- and O-glycosylation through the process of virion assembly. N-linked glycosylation is the attachment of an oligosaccharide (glycan), to a nitrogen atom an asparagine (Asn) residue of a protein. This linkage is important for the structure and function of some eukaryotic proteins. Severe acute respiratory syndrome coronavirus (SARS-CoV) is one of viruses that contain N-linked glycoproteins which are glycosylated by the transfer of core oligosaccharides from a dolichol pyrophosphate carrier to asparagine residues on the polypeptide [2]. O-linked glycosylation is the attachment of a sugar molecule to the oxygen atom on serine (Ser) or threonine (Thr) residues in a protein. O-glycosylation is a post-translational modification (PTM) that occurs after the protein has been synthesized. It occurs either in the endoplasmic reticulum or Golgi apparatus and it influences on the stability and regulation of protein [3]. The main function of O-glycan is allowing recognition of foreign material and controlling cell metabolism. The changes in O-glycosylation are important in many diseases including cancer, diabetes Alzheimer's, as well as some viral infections [4]. Because glycosylation and transport of viral proteins depend on cellular processes, prevention this process depends on the type of the viral protein and the activity of the substrate to diminish it. Coronavirus glycoproteins may be glycosylated by a different mechanism. This glycoproteins serve as a useful model for the study of N- and O-linked glycoproteins [5].

The Role of Tunicamycin (TM)

TM, an antibiotic, was produced by *Streptomyces clavuligerus* and *Streptomyces lysosuperficus* bacteria along with several other species and a proposed biosynthetic pathway was characterized. TM is a white crystalline powder which is soluble in alkaline water, pyridine, and hot methanol, slightly soluble in ethanol and *n*-butanol and insoluble in acetone, ethyl acetate, chloroform, benzene, and acidic water [6].

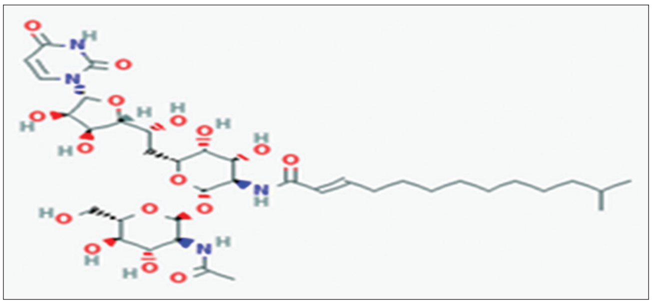

Figure 1: The structure of tunicamycin drugbank

TM, Figure 1, is an analog of UDP-N-acetylglucosamine, interfered with the formation of dolichol pyrophosphate-acetylglucosamine which acts as a carrier for N-glycosidic linkage of core oligosaccharides to asparagine (Asn) residues on glycoproteins. The bacteria utilize the enzymes in the *tun* gene cluster (TunA-N) to make TMs. Several of cellular glycoproteins contain glycosylation linkage such as immunoglobulins, fetuin, thyroglobulin, and proteoglycan. Tunicamycin inhibits the first step in the biosynthesis of N-glycosylation linked in the ER resulting produced many misfolded proteins [7]. When the antibiotic blocks glycosylation of N-glycans, the cell cycle arrests at the G1 phase in human cells. The previous studies suggested that TM may work as a therapeutic drug against cancer cells as it has been shown to sensitize human colon and prostate cancer cells to TRAIL-induced apoptosis. The inhibited glycosylation of the structural glycoproteins was showed in alphaviruses, bunyaviruses, herpesviruses, and myxoviruses and all other viruses possess glycoprotein envelopes. Han *et al.* proposed that inhibition of the N-linked glycan biosynthesis by TM may be a promising therapeutic strategy for enhancing the sensitivity of cancer cells to trastuzumab [8].

Mechanism of Action of TM

TM inhibits the reverse reactions in the first step of the biosynthesis of N-linked oligosaccharides in cells. It prevents the formation of UDP-*N*-acetylglucosamine from *N*-acetylglucosaminylpyrophosphoryl dolichol. The inhibition is increased by pre-incubating the enzyme with antibiotic for up to 5 min before addition the substrate. The addition of phosphatidylcholine at the concentration up to 20 mM does not affect the inhibition regardless of whether it was added during the pre-incubation or at the same time at the substrate. TM binds to the heat denatured microsomal particles of aorta as shown by the fact that pre-incubation of the antibiotic with these particles prevented the inhibition of the *N*-acetylglucosamin-1-phosphate transferase [9].

The Glycosylation of E1 and E2 Glycoproteins of Coronavirus

The transmembrane glycoprotein El composed of three domains: A glycosylated domain projects from the envelope. The second domain lies within the membrane, and the third domain interacts with the nucleocapsid inside the viral envelope. El may be an O-linked glycoprotein [10]. Glycosylation of El appears post-translational event. The glycoprotein E2 forms the large petal-shaped peplomers characteristic of the coronavirus envelope. E2 is a 180 kDa which can be cleaved by trypsin to yield two 90 kDa components. It has been recorded that TM inhibits formation of the E2 glycoprotein but does not prevent synthesis or glycosylation of the glycoprotein El through the formation or releasing of virion from the infected cell. Moreover, the shift from the non-glycosylated 20 kDa form to the glycosylated 23 kDa form does not inhibit by TM [11], [12]. This provides indirect evidence that E1 is not an N-linked glycoprotein but may be an O-linked glycoprotein. Although El glycoproteins are more negatively charged than those of E2, these glycoproteins differ in carbohydrate composition, electrophoretic patterns of glycopeptides, and response to the antibiotic [13]. These data suggested that E1 is an O-linked glycoprotein while E2 is an N-linked glycosylation. In contrast, the effects of TM on the synthesis and glycosylation of the two SARS-CoV-E glycoproteins have permitted tentative assignment of functions to these proteins [14].

The Glycosylation of Coronavirus S Protein

Since the 1980s, the N-linked glycosylation S protein of coronavirus was defined for hepatitis virus MHV. S protein in the rough ER was found to acquire high mannose oligosaccharides. It has been found that the Golgi transport blocker (monensin) inhibited the transport of S protein from trans-Golgi network to the cell surface [15]. Other studies revealed that MHV S protein also modified the N-linked glycosylation of bovine coronavirus BCoV, alpha-coronavirus transmissible gastroenteritis virus (TGEV), and gamma-coronavirus infectious bronchitis virus (IBV). The high mannose oligosaccharides of SARS-CoV S protein were trimerized as early as 30 min post-entry into ER, before the acquisition of complex glycans in the Golgi apparatus using pulse-chase experiments coupled with fractionation. Then, the maturation status of S protein can be monitored by its sensitivity to endoglycosidase H. This enzyme hydrolyzes the high mannose glycans [16]. After that, the structure of N-linked glycosylation of S protein was determined using mass spectrometry. This linked was enriched with high mannose, hybrid and complex glycans with or without bisecting *N*-acetyl-galactosamine (GalNAc), and core fucose. A 12 out of 23 putative glycosylation sites detected of SARS-CoV S protein were actually glycosylated [17].

The SARS-CoV S protein has two domains S1 and S2. When the S1 domain of bovine-CoV S protein was cloned and expressed in insect cells, the mature S protein was glycosylated and bound by neutralizing monoclonal antibodies. On the other hand, the infected cells with TGEV in the presence of TM, the antigenicity of both S and M protein, were significantly reduced [18]. This may confirm that TM is an inhibitor factor of the glycosylation proteins. It has been demonstrated that the inhibition of N-linked glycosylation by TM or removal of N-linked glycans by PNGase F reduced TGEV-induced IFN-α production. Therefore, the N-linked glycans on SARS-CoV S protein may be a pathogen associated molecular pattern recognized by host pattern recognition receptors. These receptors are activated downstream antiviral innate immune response. The growth of coronavirus in the presence inhibitor TM resulted in the production of spikeless, non-infectious virions which were devoid of S protein [19], [20].

The Glycosylation of Coronavirus M Protein

M protein of coronaviruses is the most abundant protein comprising of 220–260 amino acids. It plays a central role of the viral assembly. M protein is a multipass transmembrane protein with a short N-terminal ectodomain, three hydrophobic TM domains, and a large C-terminal endodomain. O-linked glycosylation of the mouse hepatitis virus M protein was first revealed in 1981. It was noted that in the presence of TM, M protein was still normally produced and glycosylated, resulting in the formation of none infectious virions containing normal amounts of N and M protein, but lacking S completely [21], [22].

Distinct from the O-linked glycosylation perceived in the M protein of bovine-coronavirus BCoV, human-coronavirus HCoV-OC43, alpha-coronavirus TGEV, gamma-coronavirus IBV, and turkey enteric coronavirus is all modified by N-linked glycosylation. This linked of M protein is sensitive to endoglycosidase H and can be inhibited by TM. The N-linked glycosylation sites were mapped to N3 and N6 of IBV. M protein of betacoronaviruses in other lineages is also N-linked glycosylated [23]. For example, SARS-CoV M protein contains a single N-glycosylation site at N4. When transiently transfected as a C-terminally FLAG-tagged protein, SARS-CoV M protein was found to obtain high mannose N-glycans and was modified into complex N-glycans in the Golgi. Although the glycosylation of the coronavirus M protein is a strongly conserved feature, this glycosylation is not important for virus assembly or replication [24], [25].

The Glycosylation of Coronavirus Non-structural Proteins nsp3 and nsp4

Some of the luminal domains of nsps coronaviruses proteins undergo N-linked glycosylation in the ER. For instance, MHV nsp3 is inserted into ER cotranslationally and glycosylated at N1525. Glycosylation of nsp4 was detected in IBV at N48 residue while for the nsp4 of MHV, two glycosylation sites were predicted at N176 and N237 residues. Till now, no study supports that TM inhibits N-linked glycans either in nsp3 or nsp4 [26], [27], [28].

The Glycosylation of Coronavirus PTMs Proteins

Coronavirus genome encodes various accessory proteins called apart from the structural and non-structural proteins (PTMs), most of which share no homology to any known proteins. However, some of the PTMs accessory proteins are incorporated in mature virions, others have been concerned in the modulation of host immune response and *in vivo* pathogenesis. One of the PTM proteins is HE protein which is a part of beta-coronaviruses S protein. The HE protein of bovine CoV was also shown to be glycosylated when expressed using human adenovirus vector. Furthermore, HE protein of MHV was found to be modified by N-linked glycosylation and was inhibited by TM but not monensin. The importance of N-linked glycosylation of coronavirus HE protein has not been fully characterized [14], [29].

The O-linked glycosylation of SARS-CoV 3a protein and M shares the same N-exo/C-endo membrane topology. The both proteins contain three TM domains. O-linked glycans of the SARS-CoV protein 3a are resistant to the treatment of PNGase F, and pulse-chase analysis suggested that the oligosaccharides were acquired post-translationally. Protein 3a has been implicated in modulating host immune response [30], [31].

The sgRNA8 of SARS-CoV encodes a single protein 8ab. A 29-nt deletion in the center split open reading frame ORF8 into two smaller frames, encoding proteins 8a and 8b, respectively. The 8ab protein is cotranslationally smuggled into the ER and is N-linked glycosylated at N81. The 8b protein is synthesized in the cytosol and not modified. Both proteins 8b and 8ab were shown to interact and modified by ubiquitination. The glycosylation at N81 stabilized 8ab protein and protected it from proteasomal degradation. Protein 8b is unstable and undergoes rapid proteasomal degradation. The ubiquitinated 8b and 8ab may mediate rapid degradation of IRF3 and regulate host antiviral innate immunity. The inhibition N-linked glycosylation of SARS-CoV 8ab protein by TM is not completely understood [32], [33].

Conclusions

The transmembrane structural proteins S, E, M, nsp3, nsp4, and accessory proteins (HE, 3a, and 8ab) of the most coronavirus family are modified by glycosylation. Although the M proteins of beta-coronavirus adopt the special O-linked glycosylation, the M proteins of the other coronaviruses are modified by N-linked glycosylation. It has been registered that glycosylation of coronavirus S protein is essentially N-linked. The folding and intracellular trafficking N-linked glycans of the coronavirus S protein also constitute a significant part of conformation of mature protein. TM inhibits formation of the coronavirus E2 glycoprotein but does not prevent synthesis or glycosylation of the glycoprotein El. The antigenicity of TGEV S and M protein was significantly reduced in the presence of TM. M protein of the most *Coronaviridae* is sensitive to endoglycosidase H and can be inhibited by TM. Lack information about the effect TM on SARS-CoV N-linked glycans ns3 and ns4. HE and 8ab proteins of SARS-CoV glycosylation are inhibited by TM. Although TM inhibits N-linked glycosylation of coronaviruses glycoproteins, no drug available to inhibit O-linked glycosylation has been identified yet.

We concluded that TM inhibits E2, S, and M glycoproteins of coronaviruses. TM is also diminished glycosylation of PTMs such as HE and 8ab of SARS-CoV. Since TM has long been used as an anticancer and has the ability to inhibit glycoproteins of coronaviruses, we recommend to use this drug to treat the SARS-CoV-2.

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The Role of Social Participation in Controlling and Preventing of Coronavirus 2019 Disease in Iran

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Abstract

BACKGROUND: According to the prevalence of *coronavirus* in the world, health measures will not be accountable to face the disease. As well as the economic, political, and social dimensions of the disease, there will be a lot of pressure on the health system, which may not be able to compensate in its various aspects. Therefore, the participation and cooperation of the society in the form of mobilizing the society with the health system will be effective in controlling and preventing this disease.

AIM: Investigating the role of social participation in the controlling and preventing of Coronavirus 2019 disease (COVID-19) was the aim of this study.

METHODS: In this review study, related English and Persian articles from PubMed, Google Scholar, Irandoc, SID, and Science direct were searched and studied using COVID-19, coronavirus, and social participation keywords.

RESULTS: The opportunity to distribute health knowledge in the community has been created and led to the internal acquisition of mastery in health promoting of preventing and controlling of COVID-19 in the process of participation in health. Furthermore, the percentage of resources has been increased and the cost of government will be decreased and the possibility of accumulating available resources and the access to them will be provided; at the same time, the allocation of resources will be facilitated to the needy. A better understanding of the health and well-being needs of the people and the promotion of health are other benefits of people's participation in controlling COVID-19. Involvement and active participation of the people increases the sense of social responsibility and the feeling of authority and it cause to disappear the dominance of official organizations. All of these outcomes have a positive effect on the health of people and society and ultimately in controlling COVID-19.

CONCLUSION: As for a common goal is formed in social participation, the common motivation to achieve that goal in the light of proper and timely awareness and information can be a stimulus, a comprehensive determination to control coronavirus and lead to effective collective action against this disease.

Introduction

The coronavirus is spreading rapidly around the world these days, and many countries are infected around the world. Coronavirus is actually a large family of viruses that lead to respiratory infections from a simple cold to the severe acute respiratory syndrome (SARS) epidemic which was spread in 2019. And now coronavirus 2019 disease (COVID-19), the newest member of the family known as the Corona in Iran, is expanding rapidly [1], [2].*Corona* pandemics is currently one of the most important health issues in the world [3]. The number of COVID-19 cases in the world has increased significantly compared to SARS and MERS, and it may take some time to reduce the incidence of the disease. This means that control measures must be in place for a longer period of time [4].The health system of Iran and Iranian society has been severely affected by this pandemic [5].

Due to the severity of the disease, the health system has plans to deal with the disease. However, due to the wide dimensions of the disease, there will be a lot of work pressure on the health-care system, which may not be able to compensate for its dimensions in various aspects. Those aspects include economic problems, social anxiety and lack of response of the health system to patients. Therefore, the participation and cooperation of the society in the form of mobilizing the society with the health system will be effective in controlling and preventing this disease.

Social Partnership

Social participation requires the participatory action of all citizens of a neighborhood to achieve control and influence on the determinants of health in that neighborhood, which is one of the important goals in the sustainable development of communities [6]. Social participation is the conscious, voluntary, spontaneous, and purposeful participation of groups and individuals in the processes and social affairs of the society to share and play a role in the work, facilitate and expedite the affairs of the society and exploit their results and help the goals of social development [7]. In today's society, social participation can be divided in the form of five dimensions political, social, economic, physical, and cultural, and the role and presence of the people and local communities are very important at each of its levels. If governments and the health system target the local community and consider citizens with *potential* capabilities and prioritize the discovery and development of their capabilities, we will undoubtedly be able to move forward on the path of development. This form of participations is pursued by local and national governments to coordinate and facilitate neighborhood-based efforts to be followed by innovation, plan, and implementing projects in principled ways to determine the path by the community itself, to organize by the community itself, and to manage the process by the community itself [8], [9].

The result of participation in this area is the development of the local community, which is a kind of approach to development from below. In this view, the development of the local community will be a factor of success and promotion if it is achieved by non-governmental organizations. Therefore, this requires mobilizing the endogenous capabilities of society [10]. In this regard, the use of social participation should be considered as one of the basic capabilities of society in planning. In fact, it is social participation that ensures the formation of a society in the true sense, and forms the concept of social cohesion that restores the amount and quality of interaction and social relations and the strengthening of social networks in society. Thus, participation with a community-based approach takes action in the field of community health in a wide variety of areas, including institutional capacity building, basic skills development, entrepreneurial group formation, poverty reduction programs, reducing risky behaviors and social harms, and education (including people, managers, and facilitators) [11].

The most obvious benefit of social participation, which has been addressed in various sources, is the improving of people's sense of responsibility and awareness toward the individual and collective health. Another advantage is the acquisition of power through the creation of new skills and the power of resource's control. In fact, the participants train themselves and their neighborhood to control their own and their neighborhood's destiny, and provide equal opportunities between themselves and health-care providers [6]. In the process of participation in health, the opportunity of health knowledge distribution in society is created and led the internal acquisition of mastery in promoting public health. Furthermore, the percentage of supply of resources will increase and the cost of spending will decrease and the possibility of accumulating of available resources and access to them will be possible; at the same time, the allocation of resources will be facilitated for the needy. A better understanding of the health and well-being needs of the people and the promotion of health are other benefits of people's participation in health affairs. The involvement and active participation of the local people increases the sense of social responsibility and eliminates the sense of authority and dominance of official organizations. All of these outcomes have a positive effect on the health of people and society [7]. The quality of people behave in an emergency occasions depends on their understanding and their assessment of risk and their vulnerability. In general, the perception of disaster risk is considered as a commensurate behavior in risks so that the negative consequences of disasters are related to low risk perception [5]. Shortly, after the initial shock caused by the coronavirus outbreak in the country, we have witnessed the formation of social participation movements in various forms and methods by people all around the country.

Some example of social participation in COVID-19

Distribution of masks and free health packages among people by donors across the country, voluntary cooperation of people with medical staff, preparation of food packages for families of coronavirus patients by people and donors, installation water faucets and placing handwashing liquid on the side of the street by some shopkeepers for public use, food preparation and accommodation for the staff of the involved hospitals, accepting the cost of training packages to prevent coronavirus, informing best ways to prevent the disease with a free speaker by personal vehicle, and another aspect of social participation is the support of individuals and businesses that are not booming these days due to the current state of emergency.

Non-governmental organizations and associations can take the necessary supportive measures at this time by brainstorming, invitation the support of benefactors, helping to identify the needy, and the financially disadvantaged. Let's not forget that social participation is usually spontaneous during crises such as floods and earthquakes and epidemics such as cholera, it occurs spontaneously at this time. However, all of these actions will be significant along with the efforts of health officials and the concerted efforts of government officials to curb the disease and its effects.

Conclusion

Since a common goal is formed in social participation, a common motivation to achieve that goal can be a stimulus for inclusive determination to curb crises and lead to effective collective action in the light of accurate and timely awareness and informing. Hence, social participation can certainly counteract coronavirus. Concepts such as empathy and social participation have extra meaning today, and out of despair and hopelessness, we can hope to more developments in the field of medical science and service delivery in various fields of health and treatment and attention to the deprived individuals.

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Knowledge, Attitude, and Practice Regarding Coronavirus Disease-19: Population-Based Study in Iraq

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Abstract

INTRODUCTION: In March 2020, the world health organization declared Coronavirus Disease (COVID)-19 a pandemic global communicable disease, there is neither a vaccine nor a treatment for this virus. The aim of the current study was to assess knowledge, attitude, and practice (KAP) of Iraqi population toward COVID-19.

METHODS: A cross-sectional study was conducted among 272 respondents from different states of Iraq using online administered questionnaires. The questions were adopted from the previous study and consist of three parts mainly socio-demographic, KAP.

RESULTS: The majority of the respondents had good knowledge regarding COVID-19 (95.2%). A total of 97.8% of the respondents knew that COVID-19 caused by a virus. Regarding incubation period, 75% of them answer correctly that it is 2–15 days. Higher percept (39%) and 37.9% of participant people considered the disease as a very dangerous and seriously dangerous disease, respectively. The majority (85.3%) of the sample thought that no vaccination available for the disease. More than two-thirds of the sample (76.5%) were wearing face mask sometimes while only 19.5% wearing it all the time. The majority (265) out of 272 was ready to stay home if it required to prevent the spread of the disease. There was a significant association between gender, living state, and COVID-19 knowledge (p = 0.009, <0.0001), respectively.

CONCLUSION: The overall knowledge, practice of respondents was good regarding COVID-19. People need to stay at home to prevent the infection and reduce the number of cases.

Introduction

The new epidemic virus infection 2019-novel coronavirus (nCoV) (now named Severe acute respiratory syndrome [SARS]-CoV-2) that rise in china with about tens of thousands of people infected give worldwide attention and response as it infects people in about 28 countries [1]. The first record of this nCoV was in Wuhan, China, at the end of 2019 [2]. This virus is belonging to a large family of viruses that can infect a wide range of organisms such as birds and mammals, including humans, according to the world health organization (WHO) [3].

For its more pronounce symptom, the new diseases are called the SARS-CoV-2 [4], [5]. The features of the nCoV (2019-nCoV) are summarized as a positive-sense single-stranded RNA virus mainly with respiratory illness. Hence, the new SARS-CoV-2 disease is a contagious in humans it gets attention and the WHO announced it as an ongoing pandemic disease with public health emergency of international concern [6], [7].

Each infection results in 1.4–3.9 new cases according to epidemiological studies when there is no immune previously done and no preventive measures are taken. The primary route of infection of this virus appears related to close contact with infected people and through coughs or sneezes which release a respiratory droplet [8]. After contact, the virus starts to invade the human cells by binding to the angiotensin-converting enzyme receptor 2 [9].

In Iraq, the first CoV disease (COVID)-19 cases was discovered in February 2020. As of August 1, 2020, there are 126,704 confirmed cases with 4805 deaths [10].

No approved SARS-CoV-2 therapy or vaccine is currently available. Primary step to reduce the spread of the virus both in health-care settings and the population is to introduce effective infection controls [11]. Public awareness of the treatment of highly infectious respiratory diseases plays a key role in limiting infection spread, especially in middle and low revenue countries, where health systems at best have moderate capacity to respond to outbreaks. Egypt had over 800 confirmed cases by the beginning of April 2020 and over 50 deaths, with a fast growth trend [12]. The development of vaccines is estimated to take months, and so crisis management mainly depends on adherence of people to the measures recommended. The awareness, perceptions, and behaviors (knowledge, attitude, and practice) of the public have a significant impact on these measures [13].

The aim of the current study was to find out the level of knowledge and practice about COVID-19 among general population in Iraq.

Methods

A cross-sectional study was conducted among 272 adults living in Iraq using internet-based platform. The respondents were chosen using non-probability convenience sampling. The questionnaires link was distributed to respondents through Facebook groups and a Google form was used to host and distribute the questions. After accessing the link, respondent needs to read the consent form carefully and agrees to participate in the study. A full explanation of the study aims, and objectives were written in the introduction part of the questionnaires. All the questionnaires are compulsory to answer. The questionnaires consist of three parts, Part 1 about socio-demographic data (age, gender, educational level, working status, and state), Part 2 about COVID-19 knowledge (transmission method, treatment availability, incubation period, and patient presentation), and Part 3 about practice and attitudes toward COVID-19 (hand washing, hand sanitizer, and home quarantine). The questionnaires were adopted from the previous study [14].

Knowledge questionnaires consist of seven questions and maximum score of 7. Those who answered more than 50% considered to have good knowledge.

The sample size was calculated based on the previous study [13] where good knowledge was 90% and using single population proportion formula.

$N = 1.96^2 \times (0.90\ (1–0.90)/0.05^2) = 139 + 20\%$ non-response rate = 167 the minimum sample size required.

We decided to use internet-based method in data collection due movement restriction and curfew imposed by Iraqi government on March 17, 2020, that make it difficult to use physical data collection methods and also to decrease the contact between people to minimum as much as possible.

Data were analyzed using SPSS software version 24. All respondents filled up a consent form and agreed to participate in the study before proceeding to the questionnaires and ethical approval was taken from International Medical School, Management and Science University.

Results

Table 1 demonstrates the socio-demographic features of the study participants. The mean age for the 272 respondents was 36.35 ± 7.87, with more than half of them (58.1%) were males. Only nine states were involved in answering the survey questions, with a higher percentage in Baghdad city which represents about 182 (66.9%) of the whole sample, followed by 37 persons (13.65%) were from Basra city. The majority (87.5%) of the sample were working at the same period of data collection with 202 (74.3%) of them had postgraduate educational level. The internet and different social media such as Facebook and Instagram were the major source of information about COVID-19 in 130 (47.8%) of the sample, followed by medical doctors in about 30 (25.8%) of the participants. Only 9 (3.3%) of the sample were mentioned as a relative to positive COVID-19 test patients.

Table 1: Socio-demographic characteristics of the respondents

Variables	Min.	Max.	Mean	SD
Age	23.0	65.0	36.35	7.87
	N		%	
Gender				
Male	158		58.1	
Female	114		41.9	
State				
Erbil	6		2.2	
Basra	37		13.6	
Sulaymaniyah	7		2.6	
Mosul	7		2.6	
Baghdad	182		66.9	
Diyala	6		2.2	
Dhi Qar	5		1.8	
Kirkuk	2		0.7	
Wasit	20		7.4	
Currently Working				
No	34		12.5	
Yes	238		87.5	
Educational level				
Secondary	4		1.5	
University degree	66		24.2	
Postgraduate	202		74.3	
Source of information				
Television	49		18.0	
Internet (Facebook, WhatsApp, Instagram)	130		47.8	
Medical doctors	70		25.8	
Radio	23		8.4	
Relatives with COVID-19				
No	263		96.7	
Yes	9		3.3	

Table 2 shows the knowledge of respondents about COVID-19. Most of the sample 266 (97.8%) were aware of the nature of the disease and agreed with the answer (virus) as a cause of the disease. In this study, 250 respondents (91.9%) mentioned infected persons who transmit the disease, while only 15 (5.56%) were mentioned Bats. Two-thirds of the sample (75%) were informed about the true incubation period of COVID-19. Most of the study participants (83.82%) knew that washing hands can be an effective preventive method for the disease rather than covering face while sneezing and vaccination. About patients’

Table 2: Knowledge on COVID-19 among respondents

Knowledge	n (%)
COVID-19 caused by	
Virus	266 (97.8)
I do not know	6 (2.2)
COVID-19 transmitted by	
Camel	7 (2.6)
Bats	15 (5.56)
Infected person	250 (91.9)
COVID-19 Incubation period	
2–10 days	25 (9.2)
2–20 days	33 (12.1)
2–15 days	204 (75.0)
I do not know	10 (3.7)
Patient presentation	
Sore throat, vomiting and diarrhea	19 (6.99)
Fever and body ache	48 (17.65)
I do not know	3 (1.10)
Lower respiratory syndrome (cough and shortness of breath)	183 (67.28)
Upper respiratory syndrome (Runny nose, Sore throat)	19 (6.99)
Prevention possible through	
Vaccine	6 (2.21)
Cover face when sneezing	27 (9.93)
Wash hands regularly	228 (83.82)
No method for prevention	11 (4.04)
COVID-19 treatment	
Supportive at home	91 (33.46)
At hospitals	70 (25.74)
ICU	23 (8.46)
No treatments	88 (32.35)
Most affected areas in the world	
China	257 (94.49)
Iraq	2 (0.74)
USA	13 (4.78)

presentations, 183 (67.28%) persons mentioned lower respiratory symptoms. It was obvious for 257 (94.49%) participants that China is the most affected area in the world. About 33.46% and 32.35% answered the using of a supportive treatment at home and no treatment, respectively, for the treatment of this disease.

In Table 3, about 80.2% of participants mentioned that COVID-19 is a contagious disease and can lead to death, higher percept (39%) and (37.9%) of participant people considered the disease as a very dangerous and seriously dangerous disease, respectively. The majority (85.3%) of the sample thought that no vaccination available for the disease. Regarding the practices performed by the respondents toward COVID-19, Table 3 shows more than that

Table 3: Attitudes and practice regarding COVID-19

Attitude	n (%)
I think COVID-19 is	
Contagious and cannot lead to death	54 (19.8)
Contagious and can lead to death	218 (80.2)
I feel COVID-19 is dangerous	
Dangerous	56 (20.6)
Very dangerous	106 (39.0)
Seriously dangerous	103 (37.9)
Not dangerous	7 (2.6)
There is vaccine for COVID-19	
No	232 (85.3)
Yes	17 (6.2)
I do not know	23 (8.5)
I wear face Mask	
Sometimes	208 (76.5)
All the times	53 (19.5)
No benefit	11 (4.0)
I wear gloves	
Sometimes	184 (67.7)
All the times	81 (29.8)
No benefit	7 (2.5)
I wash my hands	
More than 10 times/day	136 (50.0)
More than 3 times/day	125 (45.0)
1–2 times/day	11 (4.1)
I use hand sanitizer	
No	63 (23.2)
Yes	209 (76.8)
I will stay at home if require	
No	7 (2.6)
Yes	265 (97.4)

two-thirds of the sample (76.5%) were wearing face mask sometimes while only 19.5% wearing it all the time. About a third (29.8%) wears gloves all the time. Very little percent (4.1%) were washing hands <3 times/day, while the majority (76.8%) using hand sanitizer. As mentioned above, the majority 265 out of 272 was ready to stay home if it required to prevent the spread of the disease.

Table 4 demonstrates the association between socio-demographic characteristics and COVID-19 knowledge, there was a significant association between gender, living state, and COVID-19 knowledge (p = 0.009, <0.0001) respectively.

Table 4: Association between socio-demographic characteristics and COVID-19 knowledge

Variables	Knowledge		χ^2	p-value
	Poor	Good		
	n (%)	n (%)		
Gender				
Female	1 (0.9)	113 (99.1)	6.56	0.009[a]
Male	12 (7.6)	146 (92.4)		
Working Status				
No	0 (0)	34 (100.0)	1.95	0.163[a]
Yes	13 (5.5)	225 (94.5)		
Educational level				
Secondary	0 (0)	4 (100.0)	5.16	0.076[b]
University	0 (0)	66 (100.0)		
Postgraduate	13 (6.4)	189 (93.6)		
Living states				
Erbil	6 (100.0)	0 (0)	124.10	<0.001[b]
Basra	0 (0)	37 (100.0)		
Sulaymaniyah	0 (0)	7 (100.0)		
Mosul	0 (0)	7 (100.0)		
Baghdad	7 (3.8)	175 (96.2)		
Diyala	0 (0)	6 (100.0)		
Dhi Qar	0 (0)	5 (100.0)		
Kirkuk	0 (0)	2 (100.0)		
Wasit	0 (0)	20 (100.0)		

[a]Chi-square test was performed, [b]Fisher exact test was performed

Discussion

Our findings suggest that general population in Iraq have good knowledge regarding COVID-19 with good level of practice just few weeks into the global pandemic announced by the WHO of COVID-19 and after declared public health emergency of international concern.

The level of good knowledge in our study was 95.2% which is similar to previous studies done [13]. Regarding the source of information, overall, the internet and social media (Facebook, WhatsApp, and Instagram) account for the main source of information of 47.8% of all other sources, second highest from medical personnel of 25.8% and least through radio 8.4% and that is persistent with another study done in China in year 2020 which found that the internet (93.5%) was the primary health information channel for the general public during the initial stage of COVID-19 epidemic in China [15].

In this study, it was found that the level of knowledge was good overall the major parameters of knowledge and as compared to other study done in mainland China in 2020 it was similar result to us such as COVID-19 knowledge where respondents indicate that droplets (92.1%), infected artifacts (73.7%), and airborne transmission (60.5%) are the most frequently seen transmission path. Nearly all respondents learned of an increase in infected people (98.8%), an increase in deaths (97.8%) and an increase in the number of persons recovered (93.3%). The Web was the most popular source of health information on COVID-19 (93.5%). The majority, 75.1%, were very satisfied with the quantity of available health data [15].

This study showed high knowledge about the transmission mode through infected person 91.9% and that is consistent with the finding of other study which stated human-to-human transmittances for COVID-19 are well-established, with the WHO at present estimated to be 1.4–2.5 for R0 (expected number of secondary cases produced by a single typical) infected population [16].

The present study showed that the respondents had a strong understanding of the Cause-Inductor for the COVID-19, which was the 97.8% CoV, and this was similar to the international findings that a novel beta-CoV now called SARS-CoV-2 causing clinical disease called COVID-19. SARS-CoV-2 shares 79% SARS-CoV sequence identity, which resulted in a major outbreak in 2002–2003 [17], [18], [19].

The respondent's knowledge about the clinical symptoms was mainly toward the lower respiratory syndrome (67.28%) for cough and shortness of breath, and next mentioned fever and body ache (17.65%), and 1.1% stated they know nothing about the symptoms. A research was done in the United Kingdom (UK) mentioned that the most common symptoms being reported are fever, cough or chest tightness, and dyspnea, also added that cases are reported to experience a mild illness course [20].

Another research in the UK found fever (98%), cough (76 %), dyspnea (55%), and myalgia or weakness (44%) to be the most common signs of disease launch. Not least of all, few patients had strong signs of the upper airway tract like coryza and only one patient had diarrhea. Other clinical characteristics include development of sputum (28%), headache (8%), and hemoptysis in two cases [21].

This study has several limitations. Given the limited resources available and time-sensitivity of the COVID-19 outbreak that forced the authors to collect the data virtually through online questionnaires. Bigger study with more participants is needed also need to measure the impact of home stay on people's daily life.

Conclusion

The overall knowledge, practice of respondents was good regarding COVID-19. People need to stay at home and follow the health authorities' instructions to prevent the infection and reduce the number of cases.

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Can Coronavirus Disease-19 Lead to Temporomandibular Joint Disease?

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Abstract

BACKGROUND: The coronavirus disease (COVID-19) has become pandemic spreading globally. The outbreak of COVID-19 has led to psychological problems and compromised the mental health of the people. Temporomandibular disorder (TMD) shows the pain and dysfunction of the masticatory apparatus. History of trauma, stress, psychosocial impairment, drinking alcohol, and catastrophizing are related to the TMD.

AIM: We aimed to present some background information, in which COVID-19 may be correlated with TMD.

METHODS: The outbreak of COVID-19 has led to psychological problems and compromised the mental health of the people.

RESULTS: The outbreak of COVID-19 has led to psychological problems and compromised the mental health of the people, not those only who suffered from coronavirus but also to those in self-isolation, social-distancing, and quarantined. TMD shows the pain and dysfunction of the masticatory apparatus, and one of the major causes of TMD is stress and psychosocial impairment apart from drinking alcohol and history of trauma. Hence, TMD may be correlated with COVID-19. The consequences of anxiety, depression, and stress in people from the outbreak of COVID-19 may lead to TMD.

CONCLUSION: Hence, COVID-19 may be correlated with TMD as one of the major causes of TMD is stress and psychosocial impairment.

The coronavirus disease (COVID-19) has become pandemic spreading globally over 210 countries [1], [2]. At present, many countries are locked down, and people are on self-quarantine to limit the spread of disease. COVID-19 is a respiratory virus showing symptoms such as fever, fatigue, dry cough, and dyspnea. Most infected people show mild-to-moderate respiratory illness and recover. Older people with underlying medical diseases such as diabetes, cardiovascular disease, chronic respiratory disease, and cancer have a higher chance of developing severe illness, causing mortality [2], [3]. The WHO has given details of COVID and mentions that there are no specific vaccines or other therapies developed for COVID-19 till now [2]. However, many ongoing clinical trials are evaluating potential treatments. Improvement in viral metagenomics could potentially aid the diagnosis of COVID-19 cases and the management of this pandemic [4].

The outbreak of COVID-19 has led to psychological problems and compromised the mental health of the people, not those only who suffered from coronavirus but also to those in self-isolation, social-distancing, and quarantined [5], [6]. In addition, people suffer from fear, anxiety, stress, and self-efficacy [7], and this also led COVID-19-suicides [8]. Most vulnerable are those with existing mental health problems such as loneliness, depression, and isolation. Enforced isolation and quarantine interrupted normal social live causing emotional imbalance, economic shutdown, financial and future insecurities, and psychological fear.

Temporomandibular disorder (TMD) shows the pain and dysfunction of the masticatory apparatus and the temporomandibular joint. History of trauma, stress, drinking alcohol, psychosocial impairment, and catastrophizing are related to the TMD [9], [10], [11], [12]. Anxiety, depression, and stress contribute to chronic upregulation of the hypothalamic-pituitary-adrenal axis, which lead to TMD [9]. Hence, TMD may be correlated with COVID-19. The consequences of anxiety, depression, and stress in people from the outbreak of COVID-19 may lead to TMD.

The provision of care and support in people is a high priority service [2]. Work from home, spending time indoors with our families, connect to friends on social media, and engage in mindfulness activities may help to reduce the stress. A multidisciplinary clinical approach, including dentistry, is needed in the diagnosis of TMD and the treatment for this condition through a clinical practice supported by scientific knowledge [13]. Psychological intervention and mental health support are needed to reduce anxiety and stress as a part of the TMD treatment. Psychological counseling is also required to reduce anxiety and stress in severe cases.

Authors' Contributions

DR and SK conceptualized and designed the study. DR drafted the first manuscript. SK reviewed and edited the manuscript. All authors are responsible for the integrity of the data.

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Clinical and Demographic Characteristics of Patients with COVID-19 Who Died in Modarres Hospital

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Abstract

BACKGROUND: Novel coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome-CoV2 as a century concern affecting public health.

AIM: This study aimed to find the clinical and demographic characteristics of the patients died following COVID-19 development at Modarres Hospital, Tehran, Iran.

METHODS: In this descriptive-analytical cross-sectional study, 62 patients died following COVID-19 were studied in terms of age, gender, body mass index, comorbidity, symptoms, liver profile, lipid profile, hemoglobin, platelet, white blood cell, lymphocytes, neutrophils, C-reaction protein, polymerase chain reaction (PCR), creatine phosphokinase, creatinine, blood urea nitrogen (BUN), potassium, magnesium, and sodium.

RESULTS: The results showed that 71% of patients were male and 69.4% had positive PCR test indicating low sensitivity of the test; 90.3% of patients were above 60 years old; 56.5 of patients had lymphocytopenia; the mean age was 67.62 ± 15.07 years; with symptoms lasting 6.24 days. The mean serum creatinine and BUN were 3.18 g/dl and 125.9 mg/dl, respectively, indicating renal involvement. All patients had pulmonary involvement accompanied by other organ involvements. Regarding symptoms, 72% of patients showed fever. Some affected patients had diarrhea, lethargy, and fatigue. A comparison of comorbidities by gender showed no significant differences.

CONCLUSION: According to our results, the majority of patients were overweight. In people who are more than 60 years, multi-organ failure was notable. Fever, cough, and shortness of breath were dominant symptoms like other studies, but neurological complications following COVID-19 as meningoencephalitis is possible that can be used as a differential diagnosis. We did not found differences between male and female regarding comorbidity, symptoms, and mortality rate.

Introduction

Novel coronavirus (CoV) disease (COVID-19) is caused by severe acute respiratory syndrome (SARS)-CoV2 and is a causative agent of a potentially lethal disease resulting in widespread concern in the global public health. CoV is one of the largest pathogens that mainly target the human respiratory tract. Previous outbreaks of CoV have included SARS and Middle East respiratory syndrome, which have long been known to be very threatening to public health. In late December 2019, a number of patients were admitted to hospitals whose initial diagnosis was a side effect of an unknown cause. The affected cases were associated with a wholesale market for seafood and wet animals in Wuhan, Hubei Province, China [1], [2]. Indeed, COVID-19 is a novel zoonotic disease caused by a novel CoV that started from China and bat is the reservoir hosts of novel CoVs [3]. Epidemiological studies of primary cases of CoV pneumoniae-2019 showed that many cases were exposed to the seafood market in Wuhan, China [4]. The basic reproduction number of COVID-19 was reported from 2.24 to 3.58 [5].

The first official COVID-19 case in Iran was announced on February 19, 2020. On March 16, 2020, 4 weeks later, the daily situation report on COVID-19 showed about 5000 confirmed cases [6]. According to the World Health Organization (WHO), total confirmed cases of COVID-19 in Iran are 93,657 cases and show a decline slope so that in the last report, 80 deaths occurred on 30 April 2020 [7].

A study by Wang *et al*. showed that from January 10 to 24, 2019, the number of people infected with the novel coronavirus-2019 in China increased 31.4 times. They estimated the mortality rate of 2.84% for COVID-19. They also found that the male-to-female mortality ratio was 3.25 to 1; the median age of death was 75 years; the median time from the first symptoms to death was 14 days, and the median time from the initial symptoms to death in people aged 70 years and older (11 days) was shorter than people under 70 years (20 days) [8]. A study by Li *et al*. revealed that the mean age of 425 patients infected with novel CoV was 59 years, of which 56% were men; the mean incubation period was 5.2 days, and almost half of the adult patients were 60 years and older. The incubation period for COVID-19 was 14 days after exposure, in which lots of cases occur approximately 4–5 days after exposure [9].

Detection of COVID-19 in most cases is not easy because most patients have mild or moderate syndrome with a strong prognosis. However, it may be necessary to identify an etiological factor in epidemiological studies, especially during epidemic outbreaks. Since the new CoV-2019 has not been found in humans before, no specific vaccine or treatment has been provided. Furthermore, drug therapy did not show optimum results in multiple organ failures [10], [11], [12], [13].

Renal involvement is prominent in this regard and it is recommended to check renal factors such as creatinine at admission [14], [15]. There is more need to conduct further studies in different conditions, for example, pregnant women, because the data of these conditions are sparse. Regarding that, many factors influence the development of any disease, special groups should be careful more [16], [17], [18], [19]. It is important to diagnose all suspected cases as soon as possible and to treat them quickly, to cut off the source of the infection. Conventional diagnostic testing methods, such as assessment to detect antiviral antibodies or viral antigens, have been clinically developed and used. New diagnostic solutions, including real-time polymerase chain reaction (RT-PCR) and microscopic-based measurements, may be effective in monitoring epidemiological measures, along with preventive measures [20], [21].

Like other CoVs, COVID-19 nucleic acids can be detected in samples such as nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, and feces. Clinical signs and graphic findings provide an acceptable diagnosis. It is showed that fever (78.9%) and cough (67.7%) were the most common symptoms. Diarrhea (3.7%) and vomiting (5%) were rare. Abnormalities in computed tomography (CT) images of the chest were observed in 96% of patients infected with novel CoV, and in 82.1% of them, lymphopenia was recorded [22]. In Italy and Bulgaria, the same clinical characteristics of COVID-19 were reported [23], [24], [25]. Furthermore, the mortality of the COVID-19 varies country by country and sometimes city by city [26], [27].

Due to the high mortality of COVID and the WHO's announcement of a pandemic on February 2020, further studies are needed to identify disease symptoms, prognosis, graphical, and paraclinical findings for definitive diagnosis and subsequent treatment. In this study, the clinical and demographic characteristics of the dead patients following COVID-19 development were evaluated.

Methods

In this descriptive-analytical cross-sectional study performed as a retrospective, the total numbers of patients died due to COVID-19 (n = 62) were studied in Modarres Hospital, Tehran. The existing records of patients who died following COVID-19 were examined through census sampling and the variables of age, gender, body mass index (BMI), comorbidity, symptoms, liver profile, lipid profile, hemoglobin, platelet, white blood cell (WBC), lymphocytes, neutrophils, C-reaction protein (CRP), RT-PCR (for partial diagnosis), creatine phosphokinase (CPK), creatinine, blood urea nitrogen, potassium, magnesium, and sodium were examined.

Inclusion criteria were the patients with approved COVID-19 died within April 2020. Exclusion criterion was the illegible file of the patients. Indeed, the method of sampling was census. Regarding the case definition, the approved COVID-19 case was considered as a patient with a positive respiratory sample performed by PCR method (nasopharyngeal swab RT-PCR) with a sensitivity and specificity of 78.2% and 98.8%, respectively [28].

There were 430 hospitalized patients at Modarres Hospital in April 2020, and 62 of whom died this month. The diagnosis was based on radiological chest X-ray, CT scan, PCR test, and initial symptoms of COVID-19 (evidence of extensive pulmonary involvement with tachycardia and respiratory rate above 25 or higher, fever, myalgia, and cough). O_2 saturation was below 93%, requiring hospitalization at the intensive care unit at the beginning of the visit or short-term after admission. These patients underwent treatment protocols based on the respiratory pattern and clinical findings and pulmonary scintigraphy in the middle and severe groups of COVID-19, including hydroxychloroquine with or without Kaletra@ (Lopinavir+Ritonavir) and sometimes oseltamivir. Some patients were given antibiotics and corticosteroids, intravenous immunoglobulin, and Vitamin C ampoules. Depending on the patient's respiratory progression or progression of the disease to acute respiratory distress syndrome (PiO_2/FiO_2 <300) or acute lung injury (PiO_2/FiO_2 <200), or suffering from respiratory distress or severe decrease of O_2 saturation, they needed intubation and mechanical ventilation.

Statistical analysis

Descriptive statistics (frequency, mean, and standard deviation) and analytical statistics were used to analyze the data analysis. All the analysis was conducted using SPSS. The Kolmogorov–Smirnov statistical test demonstrated that the data did not have a normal distribution. Thus, the nonparametric tests were used in order to analyze the data. $p < 0.05$ was considered statistically significant.

Ethical consideration

This research was performed according to the Declaration of Helsinki. Informed written consent was obtained from the patients, and the study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethical code: IR.SBMU.RETECH.REC.1399.034, available at: http://ethics.research.ac.ir/IR.SBMU.RETECH.REC.1399.034).

Results

In this study, 62 patients who died due to confirmed COVID-19 in Modarres Hospital in Tehran. Regarding gender, 71% of patients were male and 69.4% had positive PCR test results, indicating low sensitivity of the test. Regarding age as an effective factor, 90.3% of patients had above 60 years old. Regarding lymphocytopenia, 56.5 of patients had lymphocytopenia. Indeed we used absolute lymphocyte count formula for calculating lymphocytopenia [29]. Thrombocytopenia is divided into three groups: mild (100,000–150,000 platelets/μL), moderate (50,000-100,000 platelets/μL), and sever (<50,000 platelets/μL) (Table 1). In terms of clinical and paraclinical characteristics, patients had a mean BMI of 28.34 kg/m^2 (overweight class). The mean age was 67.62 years, with symptoms lasting 6.24 days, length of hospital stay 6.64 days, and staying in the intensive care unit for 4.70 days. The mean serum creatinine and blood urea were 3.18 g/dl and 125.9 mg/dl, respectively, indicating renal involvement. Other laboratory variables are listed in Table 2. Regarding involvement of organs, 33.9% of patients had solely pulmonary involvement, which was often associated with cardiac involvement and systemic infection (17.7%). However, all patients had pulmonary involvement accompanied by other organ involvements. In 16.16% of cases, pulmonary involvement was associated with renal involvement and 11 patients undergone hemodialysis and 18 patients developed acute kidney injury. One person developed meningoencephalitis (Table 3). Regarding comorbidities, 24.4% of patients had hypertension and heart disease. Some affected patients had diabetes, gastrointestinal diseases, and cancer (Table 4). Regarding symptoms, 19% of patients had fever, cough, and shortness of breath together. However, 72% of patients showed fever. Some affected patients had diarrhea, lethargy, and fatigue (Table 5). A comparison of comorbidities by gender showed no significant differences (Table 6). In patients more than 60 years, the frequency of organ failures was significantly different and 10 patients were involved with renal failure, 13 patients with heart disease, and six patients with systematic infection. Approximately

Table 1: The number of patients by lymphocytopenia, PCR, BMI, age, gender, and platelet patients with COVID-19

Variable	Number of patients	Percent
Gender		
Female	18	29.0
Male	44	71.0
PCR test		
Positive	43	69.4
Negative	19	30.6
Lymphocytopenia		
Yes	35	56.5
No	26	41.9
BMI (kg/m^2)		
18.5–24.9	7	22.6
25–29.9	15	48.4
30–39.9	9	29.0
Platelet (Count per mL)		
100–150	24	40.0
50–100	8	13.3
<50	2	3.3
Age (year)		
28–40	1	1.6
41–60	5	8.1
>60	56	90.3

BMI: Body mass index, PCR: Polymerase chain reaction.

Table 2: Clinical and paraclinical characteristics of patients with COVID-19

Variable	Minimum	Maximum	Mean	Standard deviation	Reference range
Age (year)	28.00	95.00	67.62	15.07	-
BMI (kg/m^2)	21.40	39.50	28.34	4.13	-
Duration of sign (Day)	1.00	20.00	6.24	4.14	-
Duration of admission sign (Day)	1.00	20.00	6.48	4.64	-
Stay in the intensive care unit sign (Day)	1.00	17.00	4.70	4.39	-
Duration of intubation sign (Day)	1.00	17.00	4.34	4.25	
WBC (Count per microliter)	2,700	177,000	15,470	22,330	4500–11,000
Lym (Count per microliter)	2,800	90,000	11,610	15,460	800–5000
Neut (Count per microliter)	5,900	96,000	82,260	18,070	5000–10,000
Plt (Count per microliter)	22,000	249,0000	208,230	312,130	150,000–450,000
Hb (mg/dl)	6.60	128.00	15.52	20.64	Male: 13.5–17.5 Female: 12–15.5
CRP (mg/L)	1.00	3.00	2.32	0.70	<10
AST (mg/dl)	27.00	4680.00	237.10	715.77	8–48
ALT (mg/dl)	21.00	2800.00	146.78	393.07	7–55
ALP (mg/dl)	91.00	453.00	217.21	91.25	40–129
Urea (mg/dl)	31.00	370.00	125.96	84.31	7–20
Creatinine (mg/dl)	0.96	14.80	3.18	2.94	0.84–1.21
LDH (U/L)	2.50	3408.00	1167.65	681.31	140–280
CPK (mcg/L)	33.00	1507.00	459.65	387.01	10–120
SpO_2 (%)	50.00	92.50	78.62	8.59	95–100

BMI: Body mass index, WBC: White blood cell, CRP: C-reaction protein, CPK: Creatine phosphokinase. ALT: Aspartate aminotransferase.

Table 3: The number of organs affected following novel coronavirus infection

Involved organ	Number of patients	Percent
Lung	21	33.9
Lung and kidney	10	16.1
Lung, systematic infection	5	8.1
Lung, kidney, and systematic infection	4	6.5
Lung, systematic infection and heart	11	17.7
Lung, kidney, and heart	5	8.1
Lung, kidney, heart, and systematic infection	4	6.5
Lung and heart	2	3.2
Total	62	100.0

Table 4: The number of comorbidities in patients with COVID-19

Comorbidity	Number of patients	Percent
Hypertension	5	11.1
Heart	4	8.9
Diabetes	3	6.7
Gastrointestinal	2	4.4
Cancer	6	13.3
Heart and diabetes	6	13.3
Heart and gastrointestinal	2	4.4
Hypertension and heart	11	24.4
Hypertension and diabetes	3	6.7
Hypertension and cancer	1	2.2
History of surgery	1	2.2
Cerebrovascular accident	1	2.2

all patients were involved with pulmonary disease (Table 7). Table 8 presents some predictive factors increasing the chance of mortality following COVID-19 including shortness of breath (odds ratio: 1.821, p: 0.011), age more than 60 years (odds ratio: 4.022, p: 0.001), hypertension (odds ratio: 1.944, p: 0.036), diabetes (odds ratio: 2.085, p: 0.002), and cancer (odds ratio: 3.902, p: 0.012). The results of multiple regression showed that age can be one of the main predictive factors. It should be noted that other factors were not significant in univariate regression.

Table 5: The number of symptoms in patients with COVID-19

Symptoms	Number of patients	Percent
Fever	1	1.6
Cough	2	3.3
Shortness of breath	8	13.1
Diarrhea	1	1.6
Fatigue	3	4.9
Lethargy	1	1.6
Fever and shortness of breath	10	16.4
Fever, cough, and shortness of breath	19	31.1
Fever and lethargy	1	1.6
Diarrhea, cough, and shortness of breath	2	3.3
Fever, cough, and lethargy	3	4.9
Fever, shortness of breath, and fatigue	10	16.4

Table 6: Comparison of comorbidities by gender

Comorbidity	Gender (%)		Statistics
	Female	Male	
Hypertension	1 (7.1)	4 (12.9)	X2 Fisher = 10.769 p = 0.444
Heart	2 (14.3)	2 (6.5)	
Diabetes	1 (7.1)	2 (6.5)	
Gastrointestinal	0 (0)	2 (6.5)	
Cancer	0 (0)	6(19.4)	
Heart and diabetes	2 (14.3)	4(12.9)	
Heart and gastrointestinal	0 (0)	2 (6.5)	
Hypertension and heart	6(42.9)	5 (16.1)	
Hypertension and diabetes	2 (14.3)	1 (3.2)	
Hypertension and cancer	0 (0)	1 (3.2)	
History of surgery	0 (0)	1 (3.2)	
Cerebrovascular accident	0 (0)	1 (3.2)	

Discussion

Due to the emergence of COVID and the WHO's announcement of a pandemic in and finally, the need for identifying the clinical and demographic characteristics of COVID-19, we conducted this study. In summary, our study showed that among 62 dead people due to COVID-19, 71% of patients were male and 69.4% had positive PCR test results, indicating low sensitivity of the test; 90.3% of patients had above 60 years old; 56.5 of patients had lymphocytopenia; the mean age was 67.62 years; with symptoms lasting 6.24 days. The mean serum creatinine and blood urea were 3.18 g/dl and 125.9 mg/dl, respectively, indicating renal involvement. All patients had pulmonary involvement accompanied by other organ involvements. Regarding symptoms, 19% of patients had fever, cough, and shortness of breath together. However, 72% of patients showed fever. Some affected patients had diarrhea, lethargy, and fatigue. A comparison of comorbidities by gender showed no significant differences. Regarding age, the frequency of patients died following COVID-19 <60 was low and it makes bias in interpretation. We should know that the majority of our study population consisted of patients who were above 60 years and this finding should not ignore the risk of mortality in younger patients. It is declared that some groups of people are more prone to develop COVID-19, including pregnant women and elderlies, in which older people are predisposed to this disease (age >55 years) [30]. The median age of patients with COVID-19 in a study by Richardson *et al*. was 63 years and 39.7% were female, while these results were consistent with our results [31].

Table 7: The number of organ failures in patients with COVID-19

Organ	Age more than 60 years	Age less than 60 years	p-value	χ^2
Lung	17	4	0.018	16.956
Lung and kidney	10	0		
Lung + systematic infection	4	5		
Lung and kidney + systematic infection	4	0		
Lung + systematic infection + heart	9	2		
Lung and kidney +heart	4	1		
Lung and heart	0	2		

Table 8: Logistic regression to predict the binary outcome (death following COVID-19)

Variable	B	SE	p-value	Odds ratio	95% CI	
					Lower	Upper
Shortness of breath	0.599	0.140	0.011	1.821	1.112	1.928
HB	−0.994	1.011	0.098	0.370	0.211	2.344
LDH	−1.084	1.141	0.599	0.338	0.138	12.112
Neut	0.0009	0.411	0.813	1.001	0.872	4.371
Lymph	0.207	1.057	0.342	1.230	0.239	15.091
Cough	1.099	0.982	0.067	3.003	0.919	43.310
Age more than 60 years	1.391	0.156	0.001	4.022	2.471	4.560
Hypertension	0.664	0.131	0.036	1.944	1.331	2.229
Diabetes	0.734	0.027	0.002	2.085	1.989	2.215
Cancer	1.361	0.141	0.012	3.902	2.656	4.625

Huang *et al*. found that 98% of patients with COVID-19 had a fever. They reported that patients referred with cough (76%), fatigue and muscle pain (44%), dyspnea (55%), sputum expectoration (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). Laboratory tests showed that 25% of infected patients had leukopenia and 64% had lymphocytopenia. Aspartate aminotransferase levels are elevated in 37% of patients. Myocarditis was diagnosed in 12% of patients, and very sensitive troponin I levels were significantly increased in these patients. Abnormalities in chest CT images were observed in 100% of patients [32]. According to Table 7, our study declared that COVID-19 is a multi-organ disease; in such a way that single-organ failure (lung) was shown in just 21 patients. In 10 patients, lung and kidney were involved together. Renal involvement was detected in 18 patients, accompanied by lung and heart involvement.

In a study entitled "Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area" done by Richardson *et al*., the results indicated 3.2% of patients were treated by renal dialysis. Richardson *et al*. reported hypertension as the most common comorbidity consistent with our study because heart disease, especially hypertension, was observed a lot in patients [31].

Zhao *et al*. revealed that Asian men were more likely to develop CoV infection in 2019 [5]. Guan *et al*. reported 1099 cases of the new CoV-2019 infection. They found that fever (78.9%) and cough (67.7%) were the most common symptoms. Diarrhea (3.7%) and vomiting (5%) were rare. Abnormalities in CT images of the chest were observed in 96% of patients infected with COVID-19, and in 82.1% of them, lymphopenia was recorded [22]. These results were consistent with our results. Approximately the reported symptoms and organ failure were recorded for the dead cases. There were no notable differences between the reviewed studies and the results of our study. The display of COVID-19 in Asian people is the same. While in a study by Richardson *et al*., 30.7% was febrile, that's why the display of symptoms can be changed by geographical differences [31]. Our study found more fertile patients compared to the Richarson *et al*. study.

Conclusion

According to our results, the majority of died people affected by COVID-19 were overweight and more than 60 years old. In people who were more than 60 years, multi-organ failure was notable. Fever, cough, and shortness of breath were dominant symptoms like other studies but neurological complications following COVID-19 as meningoencephalitis is possible that can be used as a differential diagnosis. COVID-19 in people more than 60 years rings a dreadful bell to medical staff. Lung is always involved in both genders. We did not found differences between male and female regarding comorbidity, symptoms, and mortality rate.

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COVID-19 Pandemic Impact on Physicians' Decision-making: Digoxin Toxicity in View of Combination of Hydroxychloroquine and Azithromycin: A Case Report

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Abstract

BACKGROUND: Since the WHO declaration of COVID-19 being a global pandemic, the population in general and health-care providers, in particular, became under extraordinary pressure that remarkably impacts their decisions at multiple levels as all of us should make decisions quickly while being uncertain in many times.

CASE REPORT: We are reporting a 64-year-old lady with a medical history of atrial fibrillation and mitral regurgitation that treated with digoxin and warfarin therapy, she was suspected to be a COVID-19 case and prescribed empirical hydroxychloroquine and azithromycin combination without proper adjustment of her baseline therapy, accordingly she developed adverse effect of this combination in the form of digoxin toxicity and long QT, this case highlights how this unprecedented pandemic affects the decision-making of physicians.

CONCLUSION: We should be critical and vigilant in making a decision of prescription or marketing non-evidence-based therapy, and when we are obligated for this decision, we should take all precautions to minimize the adverse effects of these drugs.

Background

Since the WHO declaration of COVID-19 being global pandemic on March 11, 2020 [1], the population in general and health-care providers, in particular, became under extraordinary pressure and in state of panic that remarkably impacts their decisions at multiple levels as all of us should make decisions quickly while being uncertain in many times. Amidst this unprecedented crisis, initial researchers found treating COVID-19 pneumonia with hydroxychloroquine (HCQ) might increase the rate of treatment success, shorten hospitalization, as well as improve outcomes [2]. Others suggested that there was a synergistic effect of the combination of HCQ and azithromycin (AZ) in decreasing viral load and recommended its use to cure COVID-19 patients with subsequent transmission control; however, the study pointed to possible prolongation of QT interval with use of this combination [3]. On March 28, 2020, FDA issued an emergency use authorization that allowed for the use of the drugs to treat patients with COVID-19 [4]. Accordingly, physicians started using this combination therapy worldwide in the hope to decrease this pandemic burden. We are reporting a patient with multiple comorbidities who was suspected to be a COVID-19 case and prescribed empirical HCQ and AZ combination then developed adverse effect of this therapy, this case highlights how COVID-19 pandemic affects the decision-making of physicians.

Case Presentation

A 64-year-old lady had history of hypertension, and moderate mitral regurgitation (MR) due to mitral valve prolapse and paroxysmal atrial fibrillation, for which she was prescribed 1 month before presentation a digoxin tablet 0.25 mg and a warfarin tablet 5 mg; both once daily.

During peak of country lockdown and COVID-19 pandemic panic in Iraq at March 26, 2020, the patient was presented to the ER of a teaching hospital complaining of nausea and vomiting, she denied fever and respiratory symptoms; however, in the era of COVID-19 pandemic the treating physician requested chest CT scan which showed bilateral ground-glass opacity Figure 1, so COVID-19 was his provisional diagnosis. She sought the second opinion by consulting other physician who prescribed HCQ (200 mg twice daily) and AZ (500 mg once daily) without adjusting the baseline therapy, and he recommended her being self-quarantined at home.

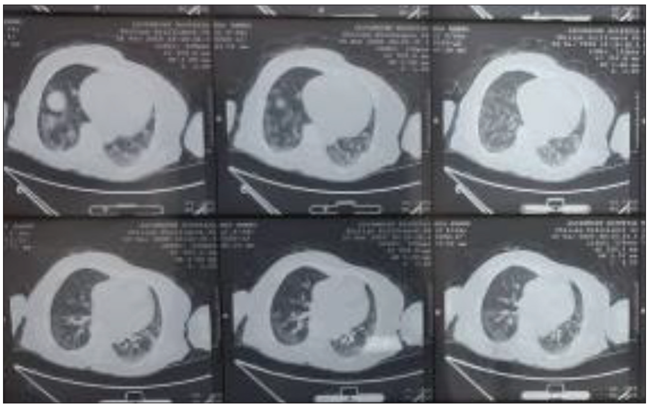

Figure 1: Initial chest computed tomography scan showing bilateral ground-glass infiltrates (in the first hospital)

Two days later, the patient was presented to our facility complaining from abdominal pain, nausea, and vomiting, her examination was remarkable only for heart rate HR of 35 bpm; on further inquiry, she denied syncope or presyncope.

New electrocardiography (ECG) revealed complete heart block (CHB) with escape junctional rhythm, diffuse ST-depression with reverse tick appearance, with long QT interval, these changes were new compared to a previous ECG done 10 days before presentation (on an outpatient clinic follow-up visit for her valve problem), Figure 2a-d. Her biochemical profile revealed elevated renal indices: Blood urea was 115 mg/dL, serum creatinine was 2.3 mg/dL, electrolyte and liver function tests were normal, and her INR was 1.6. The second chest CT scan was done again as she did not inform her treating team about the first chest CT that was done earlier, the second CT scan confirmed the same findings, so the patient was presumed to be a COVID-19 case based on her chest CT findings.

The main provisional diagnosis was digoxin toxicity induced by her impaired renal function and interaction of digoxin with additive potentiation of HCQ, AZ, and warfarin resulting in long QT and CHB. Accordingly, the patient was admitted to a quarantined CCU where she was the only patient there, nasal and throat swabs were taken and sent for polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), she was kept under monitoring, while hydroxychloroquine, azithromycin and digoxin were all withheld. She was treated conservatively with frequent atropine injections; 0.6 mg as needed. At first in-hospital day, the patient heart rate was 30 bpm, so resident on-call gave her frequent atropine injections

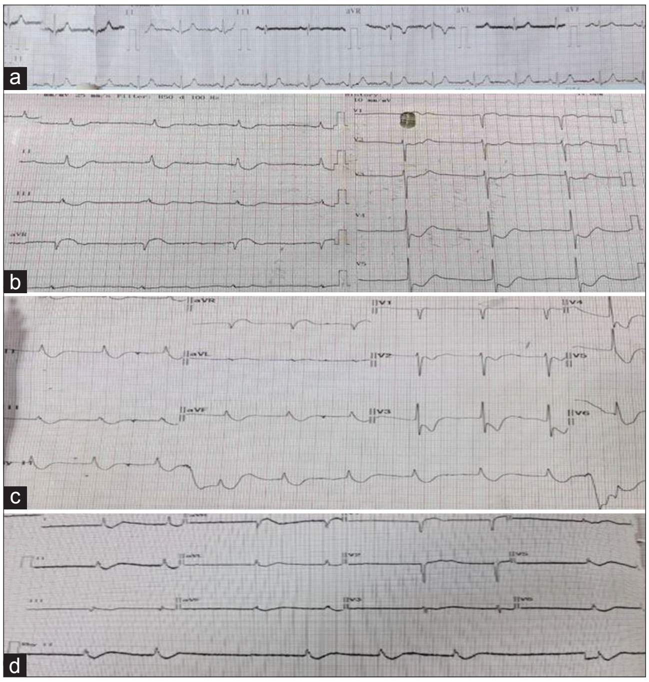

Figure 2: Serial electrocardiography (ECG) of the patient (a) Baseline ECG (before presentation) with normal sinus rhythm. (b) Complete heart block with the regular ventricular response, generalized down sagging ST depression with QTc interval of 411 msec (at presentation). (c) Second in-hospital day ECG with a heart rate of 75 bpm after atropine therapy and QTc of 408 msec. (d) Third in-hospital day ECG showing complete heart block with a junctional escape rhythm

(up to 3 mg), few hours later, the patient developed confusion (at this point heart rate was 60 bpm), brain CT was unremarkable, the treating physician considered this confusion as an adverse effect of atropine. Hence, the patient was kept under observation, and she regained full consciousness 8 h later.

Twenty-four hours later, the result of PCR was negative for SARS-CoV2. An echocardiography was done to assess her valve problem, and it showed moderate eccentric MR with prolapsing anterior mitral valve leaflet, good left ventricular function.

The patient was responding to conservative measures with HR returning to 60 bpm with a junctional rhythm. She was discharged after 5 days on April 2, 2020. Then, she was followed up on an outpatient basis for the next 10 days, she denied any symptoms and returned to sinus rhythm with a rate of (67) bpm, Figure 3.

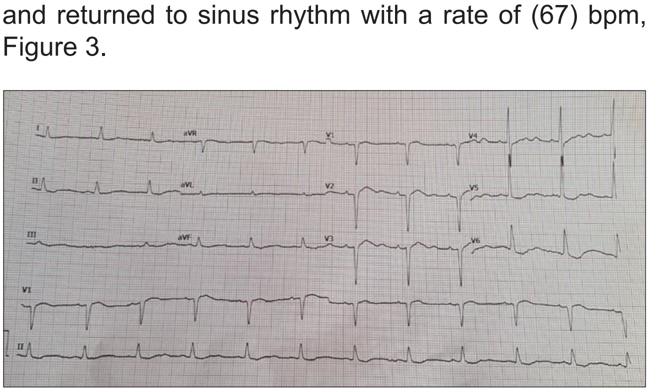

Figure 3: Electrocardiography on follow up visit 10 days after discharge, showing a heart rate of 67 bpm and nonspecific ST-T changes

Discussion

Digoxin is a cardiac glycoside derived from the purple foxglove flower, it is a commonly prescribed drug in practice for heart failure and/or atrial fibrillation [5]. It has very narrow therapeutic index with very wide spectrum of drugs interactions, which made digoxin toxicity once very common; however, it is declining in modern era due to use of alternative drugs in heart failure with greater impact on prognosis and use of more accurate dosing methods [6], among potential causes for digoxin toxicity are coprescription of drugs that increase digoxin absorption or decrease digoxin renal excretion without proper adjustment of digoxin dosage [7]. Macrolide antibiotics are such examples as known to increase digoxin levels by inhibition of P-glycoprotein by reducing energy-dependent digoxin transport from enterocytes into intestinal lumen and limiting transport into the lumen of the nephron [8], [9]. Despite AZ less 4 times than clarithromycin to cause digoxin toxicity, it still can remarkably cause digoxin toxicity [10] as occurred in this patient. HCQ also reported to increase digoxin level mostly due to digoxin displacement from its binding site in tissues or by decreasing renal clearance [11], [12]. Furthermore, this patient was on warfarin therapy which was reported to cause significant interaction with digoxin [13], [14], such polypharmacy was the main driving cause for digoxin toxicity here especially in view of renal impairment. Digoxin toxicity can manifest as gastrointestinal complaints such as nausea, vomiting, and abdominal pain as occurred in this patient or visual disturbance such as yellow vision and neurological manifestations such as headache, lethargy confusion, dizziness, and delirium [15], [16]. Despite this patient had confusion that could be explained by digoxin toxicity or CHB, we think that atropine use can explain this neurological manifestation as atropine was reported to cause such adverse effect especially that the onset of confusion was after atropine administration and her accepted heart rate at time of confusion contradicted CHB as an explanation for this manifestation [17], [18]. Digoxin toxicity can cause many ECG changes, including frequent PVC, junctional tachycardia, junctional rhythm, heart block, atrial fibrillation, atrial flutter, premature atrial contractions, sinus arrest, sinus bradycardia or tachycardia, wandering pacemaker, ventricular tachycardia, or ventricular fibrillation [19]. It is noteworthy to mention that scooping ST-T changes and reverse tick sign in ECG of this patient are considered digitalis effect, that is, they can occur with digoxin in a therapeutic range not necessarily in the toxic range [16]. This patient had CHB with a junctional escape rhythm signifying cardiotoxicity from digoxin. She did not only have digoxin toxicity due to multiple drugs interaction and renal impairment but also prolonged QT interval due to combination of HCQ and AZ which were reported to cause prolonged QT due to blocking of human ether-a-go-go-related gene potassium canal resulting in slow cardiac repolarization [20]. Drug- induced long QT is more to occur in elderly, females, patients with hypoxia, cardiovascular diseases, and metabolic derangement [21], [22]. This patient is a female with structural heart disease and on digoxin and warfarin which can interact remarkably with HCQ-AZ combination, all that resulted in higher risk for developing long QT. Measurement of serum digoxin level and FAB treatment is not available in our facility making the main treatment of digoxin toxicity in this patient by withholding the offending drugs with supportive measures like atropine. Another interesting point, in this case, was the ground-glass opacity finding in chest CT scan, as COVID-19 mainly was excluded by negative PCR, with no clinical evidence of other pulmonary infections in term of fever nor cough, despite acute MR was reported to cause ground-glass opacity [23], no literature reported such finding in chronic MR; however, we think that subclinical pulmonary congestion can be a possibility for such finding as volume overload was reported to cause such radiological manifestation [24].

This patient was not confirmed to be a COVID-19 case nor being critical enough to justify prescribing non-evidence-based drugs such as AZ and HCQ, especially in view of other drugs with potential interactions like digoxin or warfarin without proper dosage adjustment.

During this emergency pandemic, it is well understood that FDA should act quickly and effectively, trying to facilitate all steps toward fulfilling the eager population expectation to find the proper treatment for COVID-19, including experimental therapy based on no proper randomized trials. However, we, as physicians, academics, and researchers, should be critical and vigilant in making a decision of prescription or marketing non-evidence-based therapy and when we are obligated for this decision, we should take all precautions to minimize adverse effects of these drugs.

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Coronavirus Disease-19 and Liver Injury

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Abstract

Coronavirus Disease (COVID)-19 is a pandemic since March 11, 2020. The total case is more than a half million worldwide. Liver injury is quite common in COVID-19 patients. Direct viral infection is possible due to the presence of angiotensin converting enzyme 2 in cholangiocytes and hepatocytes. Other proposed mechanisms are virus-induced cytopathic effects, inflammation process, hypoxia and shock, increased apoptotic activity, increased positive end expiratory effect, and drug-induced. The manifestation of liver injury is mild and transient with elevated liver enzymes, bilirubin, and gamma-glutamyl transferase levels. Deterioration of liver function can occur in subjects with COVID-19 and underlying liver injury. The management is principally supportive. Hepatoprotective drugs may be administered in severe cases.

Introduction

Pneumonia due to unknown etiology was found in Wuhan, Hubei Province, China in December 2019 [1], [2], [3]. Huanan seafood market was suspected as the starting area of the spreading. A virus, namely, 2019 novel coronavirus (CoV) was identified as the etiology of the disease in January 7, 2020. In February 11, 2020, International Committee on Taxonomy of Viruses renamed 2019 nCoV as severe acute respiratory syndrome-CoV-2 (SARS-CoV-2). Later, World Health Association (WHO) announced the disease caused by SARS-CoV-2 infection as CoV disease-(COVID-19) [1], [4]. In March 11, 2020, the WHO announced COVID-19 as a pandemic [3], [5], [6], [7].

CoV is an enveloped, single-stranded positive-sense RNA virus [1], [7], [8]. Its Alpha and Beta generas commonly infect mammals while Gamma and Delta infect birds. SARS-CoV-2 itself is belonged to Beta-CoV genus and Coronaviridae family [1], [5], [7], [9]. Previously, two CoVs had caused epidemics. The first was SARS-CoV in Guangdong, China in November 2002 and the second was Middle East respiratory syndrome CoV (MERS-CoV) in Saudi Arabia in 2012 [1], [3], [10]. The first epidemic caused 774 deaths while the second caused 858 [1]. The mortality rate from SARS-CoV-2 is lower compared to SARS and MERS [9], [10].

Epidemiology

Median age of patients with COVID-19 is between 41 and 57 years. Male is dominant compared to female [1], [11]. Even though, there are several studies reporting comparable proportion of patients based on gender [2], [4]. About 25.2–50.5% patients have comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and malignancy [1]. About 10.8% patients have pre-existing liver disease [12]. The mortality of COVID-19 ranges from 0% to 14.6% [1]. The most common death-leading complication is acute respiratory distress syndrome [10]. Factors contributing to higher risk of mortality are older age, underlying comorbidities, and disease severity based on clinical findings and auxiliary examinations [11], [13]. At the time of writing, there are 5,491,678 cases of COVID-19 with total deaths of 349,190 cases. The most prevalent region is America, followed by Europe [14]. The incidence of liver injury due to COVID-19 was varied between 14.8% and 78% [3], [9]. Other literatures stated that liver injury is observed in 60% patients with COVID-19 [8], [15]. Cai *et al*. found a similar rate of liver injury which was 76.3% of total patients with COVID-19 and 21.5% of all patients on admission [5].

Pathophysiology

Bats are the natural reservoir of SARS-CoV-2 and the virus spreads to human through pangolins as one of the intermediate hosts [1]. The virus may be isolated from pangolins, especially Malayan pangolins. However, genomic sequence of SARS-CoV-2 in human is different from the wild virus, suggesting that mutation may have been occurred which allows human-to-human transmission [13]. Human-to-human transmission occurs through respiratory droplets directly or indirectly [4]. Fecal-oral transmission must also be wary of since viable SARS-CoV-2 can be isolated from patient's fecal sample [16]. SARS-CoV-2 infection is initiated by binding of spike glycoprotein to angiotensin converting enzyme 2 (ACE2). This process is followed by cell membrane fusion [11], [15], [17]. Viral RNA then integrates into host cell DNA. This process initiates viral protein synthesis and assembly of new viruses which readily infect other cells and damaging the cell [15], [18]. The affinity of SARS-CoV-2 to ACE2 is stronger compared to SARS-CoV [12], [13].

Literatures stated that ACE2 is highly expressed in cholangiocytes but only slightly in hepatocytes. As we know that bile duct epithelial cells play an important role in liver regeneration and immune response, it raises possibility that SARS-CoV-2 may directly invade those cells and cause liver function dysregulation [15], [16], [19], [20]. Furthermore, virus-induced cytopathic effects may directly cause liver damage [3]. Inflammation process, which is known as cytokine storm, also played an important role in damaging the liver of patients with critical condition due to COVID-19 [4], [6], [9], [11]. Lymphocytes are important in balancing immune response and preventing cytokine storm. Lymphopenia in COVID-19 patients leads to aggravation of inflammatory response. Lymphopenia and elevated C-reactive protein (CRP) level were associated with the severity of liver injury, confirming cytokine storm as one of the underlying mechanisms of liver injury [3], [11], [15]. Hypoxia and shock from COVID-19 may cause ischemia in body organs including liver. This is another hypothesized mechanism of liver injury in patients with COVID-19 [6], [11].

SARS-CoV-2 infection is also found to increase apoptotic activity of hepatocytes. The process is mediated by SARS-CoV-2-specific protein 7a through caspase-dependent pathway [9]. Increased positive end expiratory pressure may also cause hepatic congestion by increasing right atrial pressure and impending venous return [3], [15]. Drug-induced liver damage should also be put in mind since antiviruses and antibiotics may increase the workload of liver. Hydroxychloroquine is used as one of the treatment choices due to its effect in alleviating disease progression but, in the other hand, it may cause hepatic failure. In patients with underlying liver diseases, such as chronic hepatitis and non-alcoholic fatty liver, the above situation will surely even more impair the liver function [3], [4], [6], [9], [11], [15], [16], [17].

Clinical Manifestations

Clinical symptoms of COVID-19 range from mild to severe. A study reported that moderate clinical severity patients were dominant. Fever is the most common symptom, followed by cough, fatigue, myalgia, sputum production, and headache [1], [2], [3]. Gastrointestinal symptoms are quite common such as diarrheas, loss of appetite, nausea, and vomiting [1], [16]. Gastrointestinal symptoms are more frequent in SARS and MERS compared to COVID-19 [1].

Various degree of liver damage had been reported in COVID-19 patients marked by elevated total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels [19]. A study by Fan *et al*. showed that 37.2% patients with COVID-19 have abnormal liver function on admission and had higher fever compared to those with normal liver function [4]. Autopsy result of deceased patients showed that 58–78% of COVID-19 patients suffer from liver injury [16]. Higher prevalence of liver injury is observed in males, patients with more severe disease course, older age, and patient who received lopinavir/ritonavir [4], [16]. The use of lopinavir/ritonavir increases the risk of liver injury as high as 4 times compared to patients who do not receive those antivirals [5]. The severity of liver injury is associated with the severity of disease course [9], [15], [17]. Table 1 summarizes evidence regarding liver injury in patients with COVID-19.

Table 1: Evidences of liver injury in patients with COVID-19

Authors	Subjects	Findings
Fan *et al*. [4]	148	37.2% subjects had abnormal liver function on admission Patients with liver abnormality had higher fever, higher procalcitonin and CRP levels, and longer hospital stays
Cai *et al*. [5]	417	21.5% subjects had abnormal liver function during hospitalization ALT, AST, total bilirubin, and GGT levels were elevated more than 3 times the upper normal limit within 2 weeks of hospitalization
Huang *et al*. [10]	41	31% subjects had abnormal liver function Subjects admitted to ICU had higher AST level compared to non-ICU
Zhang *et al*. [21]	82	78% non-survivor subjects had hepatic injury
Huang *et al*. [22]	36	13.33% subjects had abnormal ALT, 58.06% had abnormal AST, and 12.9% had abnormal total bilirubin levels
Chen *et al*. [23]	99	28% subjects had elevated ALT, 35% had elevated AST, 18% had elevated total bilirubin, and 98% had low albumin levels

CRP: C-reactive protein. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, ICU: Intensive care unit. COVID: Coronavirus disease.

COVID-19 in Patients with Pre-existing Liver Disease

COVID-19 patients with liver injury tend to develop severe pneumonia and have longer hospital stay [4], [5], [24]. Literature stated that patients with hepatitis B or C viral infection are more prone to suffer from severe hepatitis due to enhanced viral replication during COVID-19 course. On the other hand, patients with pre-existing live diseases such as non-alcoholic fatty liver disease and liver cirrhosis had higher risk to develop severe form of COVID-19. Liver transplantation should be conducted prudently since the virus can be transmitted through transplanted organ [3]. Subjects with chronic liver disease coexisting with COVID-19 tended to suffer from deterioration of liver disease. The deterioration was in line with increasing stage of liver disease, resulting in higher mortality in subjects with liver diseases compared to those without (hazard ratio 19.2) [25]. This finding is confirmed by a study by Iavarone *et al*. They reported that the presence of COVID-19 deteriorates liver function and increases the mortality of subjects with underlying liver injury. The 30-day-mortality rate for subjects with COVID-19 and pre-existing liver cirrhosis was as high as 34%. The mortality was influenced by severity of liver disease [26].

Auxiliary Examinations

The most common laboratory findings are lymphopenia, thrombocytopenia, and leukopenia. Other inflammatory markers such as CRP and interleukin-6 are also elevated [1]. Liver enzymes elevation is also observed [1], [3], [5], [9], [15], [16], [17]. ALT level rose in 16–35% patients while elevated AST was observed in 21% patients [19]. Feng *et al*. reported the elevation of AST level in 6.2–36.6% patients with COVID-19 and elevation of AST level in 21.3–28.1% patients [11]. Ridruejo and Soza found a lower rate of AST and ALT elevation which is between 16% and 35% [6]. Other markers for liver injury are also detected including elevated bilirubin level and decreased albumin level. Gamma-glutamyl transferase (GGT) might also be elevated [3], [5], [9], [15], [16], [17]. In the other hand, alkaline phosphatase did not raise significantly [4], [5], [11], [16], [19]. Chest computed tomography showed ground glass opacity, bilateral patchy shadows, and consolidation in subsegmental areas [1], [10], [27]. Reverse-transcriptase polymerase chain reaction (RT-PCR) from nasopharyngeal swab is considered as gold standard for diagnosing COVID-19 [1]. Other specimens also showed positive result with bronchoalveolar lavage fluid held the highest positive rate (93%), followed by sputum (72%), nasal swabs (63%), fibrobronchoscope brush biopsy (46%), pharyngeal swab (32%), feces (29%), and blood (1%) [28].

From percutaneous liver biopsy specimen of COVID-19 patients with elevated ALT, there was marked apoptosis activity in the liver tissue, ballooning of hepatocytes, and mild-to-moderate lobular infiltration of lymphocytes. RT-PCR showed evidence of SARS-CoV-2 genome in liver tissue but not in serum of patients [8], [9]. Viral particles could not been identified by electron microscopy or histopathology examination [3], [8], [15]. In contract, other literature reported that SARS-CoV-2 particles may be detected in liver tissue from autopsy of patients with COVID-19 [9]. Patients with underlying liver disease have higher risk of COVID-19 infection and poorer outcome [6]. Cirrhosis has higher risk of developing poorer outcome. As liver injury increases the risk of COVID-19 progression, the utilization of liver function tests may be used as predictor of disease outcome [5].

Management

The mainstay of COVID-19 management is supportive therapy. Antivirus (oseltamivir, lopinavir, remdesivir, and ritonavir), antibiotic, and antimalarial (chloroquine) are also administered but need further study regarding their efficacy [1]. Most liver damage in COVID-19 patients is mild and transient and may resolve without specific treatment. Supportive measures must be taken to fulfill pulmonary ventilation and prevent cytokine storm. Hepatoprotective drugs may be utilized in patients with pre-existing liver disease and in case of severely injured liver [11], [16], [17]. The development of vaccine is still under ongoing process and should be able in the next 12–18 months. Implementation of health protocol is important to contain the COVID-19 pandemic [24].

Conclusion

COVID-19 is an emerging pandemic which may cause liver injury. The presence of ACE2 in cholangiocytes and hepatocytes allows direct infection SARS-CoV-2 to liver. Other possible mechanisms are virus-induced cytopathic effects, inflammation process, hypoxia and shock, increased apoptotic activity, increased positive end expiratory effect, and drug-induced. Clinical manifestations are usually mild with elevated liver enzymes, bilirubin, and GGT levels. Albumin level may also decrease. Subjects with COVID-19 pre-existing liver injury tend to have deterioration of liver function and increased mortality. The management of liver injury in COVID-19 is supportive. Hepatoprotective drugs may be administered in severely injured liver.

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Vulnerability and Weaknesses of Eating Habits of Overweight School Children as an Entry Risk for COVID-19

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Abstract

BACKGROUND: In developing countries, overweight among children becomes an alarming problem and a health concern. Obesity is a factor in disease severity of coronavirus disease (COVID-19) having the greatest impact on patients.

AIM: The aim of this study was to determine the prevalence of overweight in some of the Egyptian governmental primary school children, its nutritional and socioeconomic determinants. Special focus was directed to identify the current dietary practices including risky nutritional habits of overweight children as a weak point leading to increasing their vulnerability to catching COVID-19 infection.

METHODS: A cross-sectional observational study was conducted on primary school children aged 6–12 years. General demographic data, socioeconomic data, dietary pattern, intake of a diversity of nutrient-rich food versus calorie-dense food, and anthropometrical data were collected.

RESULTS: Of 1600 child, there were 8% overweight who are considered at risk of COVID-19 infection. Considering the weekly share of the stomach, only one-third of the food consumed by overweight children is nutrient-rich, with high consumption of French fries and Candies (once per day among 95% and 78 % of overweight children, respectively). Moreover, 90% of them consume sugar-sweetened beverages (SSB) more than once per day. The majority of overweight children belonged to small, middle- income families, and had illiterate or read and write mothers.

CONCLUSION: Overweight children eat narrow diversity of nutrient-rich food that includes vegetables, fruits, protein, and dairy products. They eat more calorie-dense foods, every day. The increase of family income increased the likelihood of having overweight children with a high intake of SSB, candies, and chips; consumption of snacks between meals and before sleep. Protective predictors against overweight were highly educated mothers, taking breakfast before school, having dinner, and taking meals on time.

RECOMMENDATION: Nutritional behavioral education aiming at choosing nutritious and varied options of food that is effective for improving children's nutritional status is the key to decreasing vulnerability toward COVID 19.

Introduction

The WHO considers non-communicable diseases such as obesity, a major risk factor for becoming seriously ill with 2019 novel coronavirus disease (COVID-19).

The ongoing coronavirus pandemic 2019 (COVID-19) has millions of confirmed cases all over the world with claimed millions of lives [1]. The WHO considers obesity out of the major risk factors for catching the novel 2019 coronavirus (COVID-19). Good nutrition is considered an essential aspect for defense against COVID-19. Accordingly, one of the key elements for a society's readiness to combat this threat could be achieved through nutritional resilience. Fortunately, focusing on nutritional well-being is among the 2030 Agenda for Sustainable Development, through which the opportunities for establishing synergies between public health and equity could be achieved [2], [3].

A positive energy balance diet leads to overweight and obesity; its prevalence can be estimated using anthropometrics [4]. Overweight is due to excessive fat accumulation; overweight is defined as a body mass index (BMI) at or above the 85th percentile and below the 95th percentile for children and teens of the same age and sex [5].

School-aged children are an important part of the community. The school environment can be an enabling factor for the correction of many nutritional problems [6]. Concerning the fact that nutritional behaviors among children are not so strongly formed and it is easier to modify and develop them in children than in adults, the eating habits acquired or changed during childhood will be likely to track into adulthood [7].

It is important to seize this window of opportunity to get on track toward the sustainable development goals target of ending malnutrition in all its forms by 2030 [8].

There is an alarming increase in overweight in children and adolescents [9]. The consequences of overweight in childhood, including persistence into adulthood and as a risk factor for adverse health consequences (heart disease morbidity and mortality, ovulatory dysfunction, metabolic syndrome, arthritis, gout, and mental health diseases), are of substantial concern given the recent upward trend in prevalence [10], [11]. With the fact that overweight will lead to increased risks of obesity and in this critical period of life, adolescence has major importance not only for their affection but also for their societies. Where obese adolescents, especially with visceral obesity usually will track into obesity in their adulthood, subsequently leads to various medical health complications [12].

The aim of this study was to determine the prevalence of overweight in some of the Egyptian governmental primary school children, its nutritional and socioeconomic determinants. Special focus was directed to identify the weaknesses of the eating habits of overweight children as a weak point leading to malnutrition and increasing their vulnerability to catching COVID-19 infection.

Methodology

Study design

The study was a cross-sectional one that was conducted in three governorates; one representing lower Egypt (Behara governorate), one representing the coastal region (Damietta governorate), and one representing upper Egypt (Fayoum governorate) to represent the different geographical regions in Egypt with different nutritional habits.

Sampling frame and sampling unit

Three sampling frames were chosen: The first sampling frame used was based on stratification of the served rural governorates into three strata representing rural lower Egypt, coastal region, and upper Egypt governorates. The second sampling frame was based on a comprehensive list of the governorates as per regions. The third sampling frame was the stratification of listing the units to be sampled (governmental primary school children). For the third sampling frame, a logical order was used for schools and then a cluster of schools was chosen with probability proportion to size from that listing. This ensured that the units were evenly distributed within the listing and avoided the possibility that, due to chance, one type of school ends up being under-represented.

Sample size

A sample size of 1574 to be rounded to 1600 produces a two-sided 95% confidence interval with a width equal to 0.050 when the sample proportion is 0.500 [13], [14].

Confidence intervals for one proportion – new numeric results for two-sided confidence intervals for one proportion confidence interval formula: Exact (Clopper-Pearson).

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if p = 0.5
0.950	1574	0.050	0.050	0.500	0.475	0.525	0.050

Study participants

The choice of subjects was in the form of clusters (6 clusters/each school); each cluster was formed from 10 students from each grade with a total of 60 children/each primary school children. The actual total number of the randomly surveyed schools was 29 schools distributed along 16 districts within the three governorates with average 1–3 schools/district and 8–10 schools/each of the selected governorates according to the number of schools per district.

Inclusion criteria

Apparently healthy prepubescent boys and girls in the primary schools with six grades were included in the study. The primary school children are aged 6–12 years.

Exclusion criteria

Students proved to have any mental disorder or chronic diseases were excluded from the study.

Methods

Three well-structured questionnaires were administered to each student; questionnaires were designed for assessment of nutritional status, dietary pattern, and socioeconomic factors. A pilot study was done on 10% of the children for testing the questionnaires.

Nutritional status assessment

Nutritional status assessment was carried out through Anthropometric measurements of (weight and height). All measurements were made according to techniques described in the anthropometric standardization reference manual [15]. Anthropometric measurements were taken, height was measured to the nearest 0.1 cm using a Holtain portable anthropometer, and weight was determined to the nearest 0.01 kg using a seca scale balance with the subject dressed in minimal clothes and without shoes. The BMI was calculated as weight (in kilograms) divided by height (in meters) squared, and after the morning exercises of spine stretching. All scores were calculated based on the WHO growth standards with the help of the Anthro-Program of PC [16].

Overweight is defined as a BMI at or above the 85^{th} percentile and below the 95^{th} percentile for children and teens of the same age and sex. Anthropometric indicators provide useful summary measures of nutritional status based on measures of body size and composition, often relative to their distribution in a reference population. Anthropometric indicators measure achieved nutritional status, rather than nutrition inputs, are less subject to measurement error, and are less expensive to collect than dietary intake data.

Dietary pattern assessment

Students provided data on their diet to evaluate dietary habits and behavior of children (skipping breakfast, number of daily meals, eating the served school meal, and source of other meals consumed during the school day). Special emphasis was focused on comparing the intake of different diversity of nutrient-rich foods (this includes: vegetables, fruits, and nutrient-rich sources of protein and dairy) versus calorie dense foods with low levels of nutrients, every day, and every week. Moreover, the intake of SSB per day was also assessed.

The following indicators that are related to the daily share of the plate were measured:

- Number of meals served in proportions as per plate
- Frequency of meals served in proportions as per plate
- Number of nutrient-rich foods eaten per day.

The following indicators that are related to the weekly share of the stomach were measured:

- Diversity of nutrient-rich foods eaten per week
- Number of types of nutrient-rich foods eaten per week
- Frequency of nutrient-rich foods overall and per food groups eaten per week.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0 software. All data were represented by percentages and comparisons between groups were done using odds ratio, to study the association of the studied parameters with overweight and Chi-square to study the pattern of distribution of the studied parameters between normal children and overweight ones. Probability values (p) < 0.05 were regarded as statistically significant. Logistic regression analysis and was done to assess the contribution of each independent variable in explaining the predictors of overweight [17].

Results

Children who did not have breakfast before going school carried more than 4 times the risk to be overweight (OR = 4.031). Children who did not take meals on time carried more than 3 times risk to be overweight (OR = 3.31), while children who did not take breakfast and break snacks, who did not have dinner, and who took snacks before sleep carried more than double risk to be overweight (OR = 2.82, OR = 2.53, OR = 2.2), respectively. Snacks between-meal carried almost 2 times the risk of being obese (OR = 1.89) (Table 1).

Table 1: Comparing dietary behavior in overweight and normal weight children

Parameters	Overweight (n=128) n (%)	Normal (n=1472) n (%)	Test of sig. odds ratio (CI)	p value of Chi-square
Breakfast and break snacks				
No (n=838)	95 (74.2)	743 (50.5)	2.82*(1.88–4.25)	< 0.001*
Yes (n=762)	33 (25.8)	729 (49.5)		
Breakfast before school				
No (n=141)	25 (32.9)	116 (10.8)	4.031*(2.41–6.75)	<0.001*
Yes (n=1005)	51 (67.1)	954 (89.2)		
Source of breakfast and or snacks				
Other (n=1121)	75 (98.7)	1046 (97.8)	1.72 (0.23–12.89)	>0.05
Home (n=25)	1 (1.3)	24 (2.2)		
Number of meals				
<3 (n=191)	18 (14.1)	173 (11.8)	1.23 (0.73-2.07)	>0.05
≥3 (n=1409)	110 (85.9)	1299 (88.2)		
Meals on time				
No (n=662)	87 (68)	575 (39.1)	3.31* (2.25-4.87)	<0.001*
Yes (n=938)	41 (32)	897 (60.9)		
Snacks/anything between meals				
Yes (n=1233)	110 (85.9)	1123 (76.3)	1.89*(1.14–3.17)	<0.001*
No (n=367)	18 (14.1)	349 (23.7)		
Mid-day snack				
Yes (n=1433)	115 (89.8)	1318 (89.5)	1.03 (0.57–1.87)	>0.05
No (n=167)	13 (10.2)	154 (10.5)		
(Snacks before sleep sweets, chips…etc.)				
Yes (n=676)	77 (60.2)	599 (40.7)	2.2*(1.52-3.18)	<0.001*
No (n=924)	51 (39.8)	873 (59.3)		
Dinner				
No (n=248)	38 (29.7)	210 (14.3)	2.53*(1.69-3.81)	<0.001*
Yes (n=1351)	90 (70.3)	1262 (85.7)		

Considering the weekly share of the stomach, almost half (48%) of the food consumed by normal children was nutrient rich, due to the consumption of dairy and beans/meat versus one-third (31%) among overweight children. French fries were consumed less than once per day among 95% of overweight children while candies nearly once per day among 78% of them. On the other hand, chips and SSB were consumed more than once per day among (96% and 90%, respectively) of overweight children (Table 2).

Share of the plate as per meals carried more than the double risk to be overweight when the percentage of energy-dense food is more than nutrient-rich food in breakfast and lunch (OR = 2.38, OR = 2.34), respectively, while in case of dinner and snack between meals it carried almost 2 times risk (OR = 1.89 for each) (Table 2).

Child order did not have an effect on physical growth. The majority of overweight children belonged to small families (68.0 %), middle-income families (60.9%), and had illiterate or read and write mothers (61.7%). Consequently, large family size, low-income family, and highly educated mothers had reduced risk of having overweight children (OR = 0.46, 0.55, and 1.9, respectively) (Table 3).

It was found those positive predictors, increasing the risk of overweight, increased family income; intake of SSB, candies, and chips; consumption of snacks in between meal and before sleep. On the other hand, negative predictors, protecting against overweight, were taking breakfast, taking breakfast before school, having dinner, taking meals on time, an increase of family size, and an increase of maternal education (Table 4).

Discussion

The nutritional status is a well-known risk factor for the development of metabolic and endocrine disorders and recently it was suggested that it can also affect the immune function with a subsequent increase risk for infection [18]. In industrialized countries, the infection rate was found to be increased in obese and adolescent children leading to the subsequent association of childhood obesity with a low-grade

Table 2: Comparison of the weekly and daily dietary intake of nutrient-rich foods versus energy dense food between the overweight and normal weight children

Parameters	Overweight (n=128) n (%)	Normal (n=1472) n (%)	Test of sig. odds ratio (CI)	p value of Chi-square
Diversity of nutrient-rich foods (vegetables, fruits, nutrient-rich sources of protein, and dairy products) eaten per week				
Nutrient-rich foods (overall)	40 (31%)	707 (48 %)	2.03 (1.38–2.99)*	<0.001*
Energy dense food	40 (31%)	339 (23 %)	1.52 (1.03–2.25)*	
Carbohydrates/grains	48 (38 %)	426 (29 %)	1.47 (1.01–2.14)*	
Share of the stomach (frequency of nutrient-rich foods as per food groups eaten per week)				
Dairy	13 (10%)	250 (17%)	1.81 (1.00–3.26)*	> 0.05
Meat/beans/eggs	12 (9%)	236 (16%)	1.85 (1.00–3.39)*	
Fruits	10 (8%)	147 (10%)	1.30 (0.67–2.55)	
Vegetables	5 (4%)	74 (5%)	1.30 (0.52–3.28)	
Proportion and types of the most weekly consumed unhealthy food among children				
Weekly consumption				
French fries	122 (95%)	1222 (83 %)	4.16 (1.8-9.5)*	> 0.05
Chips	123 (96%)	1266 (86 %)	4.00 (1.6–9.9)*	
Sugar sweetened beverages	115 (90%)	986 (67 %)	4.36 (2.4–7.8)*	
Candies	100 (78%)	692 (47%)	4.02 (2.6–6.2)*	
Biscuits	99 (77%)	1001 (68%)	1.61 (1.0–2.5)*	
Chocolate	93 (73%)	1001 (68%)	1.25 (0.83–1.87)	
Pancakes/cakes	78 (61%)	898 (61%)	0.99 (0.69–1.45)	
Ice cream	76 (59%)	765 (52%)	1.35 (0.93–1.95)	
Frequency intake per week				
French fries	5.6	4.4		
Chips	8.2	6.1		
Beverages (SSB)	9.5	4.6		
Candies	6.8	4.1		
Biscuits	4.3	3.9		
Chocolate	3.5	3		
Pastries/pancakes/cakes	4.2	3.9		
Ice cream	3.8	3.4		
Share of the plate as per meals				
Breakfast				
Energy dense food	29 (23%)	162 (11%)	2.38 (1.49–3.82)*	<0.001*
Nutrient-rich foods (overall)	63 (49%)	839 (57%)		
Lunch				
Energy dense food	13 (10%)	74 (5 %)	2.34 (1.23–4.45)*	<0.001*
Nutrient-rich foods (overall)	64 (50%)	854 (58%)		
Dinner				
Energy dense food	15 (12%)	103 (7 %)	1.89	<0.001*
Nutrient-rich foods (overall)	68 (53%)	883 (60%)	(1.04-3.43)*	
Snack/anything between meals				
Energy dense food	87 (68%)	662 (45%)	1.89 (1.28–2.79)*	<0.001*
Nutrient-rich foods (overall)	40 (31%)	574 (39%)		

Table 3: The risky socioeconomic factors associated with overweight

Parameters	Overweight (n=128) n (%)	Normal (n=1472) n (%)	Test of sig. Odds ratio (CI)	p value of Chi-square
Child order				
Child order (≥3) (n=655)	52 (40.6%)	613 (41.6%)	0.959 (0.664–1.385)	>0.05
Child order (1–2) (n=935)	76 (59.4%)	859 (58.4%)		
Family size*				
Large family (n=783)	41 (32.0%)	742 (50.4%)	0.464*(0.316–0.681)	<0.001*
Small family (n=817)	87 (68.0%)	730 (49.6%)		
Family income**				
Low-income family (n=843)	50 (39.1%)	793 (53.9%)	0.549*(0.379–0.794)	<0.001*
Middle-income family (n=757)	78 (60.9%)	679 (46.1%)		
Mother education****				
Illiterate/read and write (n=846)	79 (61.7%)	675 (45.9%)	1.90*(1.31–2.76)	<0.001*
High education (n=754)	49 (38.3%)	797 (54.1%)		
Father education****				
Illiterate/read and write (n=789)	57 (44.5%)	732 (49.7%)	0.812 (0.564–1.167)	>0.05
High education (n=811)	71 (55.5%)	740 (50.3%)		
Father job				
Don't work (n=29)	1 (0.8%)	28 (1.9%)	0.406 (0.054–3.009)	>0.05
Working (n=1571)	127 (99.2%)	1444 (98.1%)		
Mother job				
Don't work (n=1184)	86 (67.2%)	1098 (74.6%)	0.697 (0.474–1.027)	>0.05
Working (n=416)	42 (32.8%)	374 (25.4%)		

*Large family=Family size ≥6, Small family=Family size 1–5, **Low income family: Father and mother are unemployed, day by day worker, farmer, or laborer, Middle income family: Father and mother are employee, professional, employer, or dealer, ***High education=High school and university *=Sig. <0.05

inflammation status [18], [19]. Several studies confirmed the role played by obesity on the immune system leading to impaired immune responses to infection and this proves the close interaction between the metabolic control and immune tolerance [20].

Table 4: Predictors of overweight in primary school children according to logistic regression analysis

Parameters	(B)	Sig.
Taking breakfast (before or inside school)	−0.677	0.007
Increase of family size	−0.590	0.014
Taking breakfast before school	−0.875	0.001
Taking dinner	−0.985	0.000
Consumption of snack before sleep	+1.081	0.000
Taking meals on time	−1.128	0.000
Consumption of snacks between meals	+0.814	0.005
Intake of sugar sweetened beverages	+1.600	0.000
Intake of candies	+1.261	0.000
Intake of chips	+1.362	0.012
Increase of family income	+0.486	0.050
Increase of maternal education	−0.519	0.056

Negative means: For continuous data with the increase, there is decrease in the risk of overweight and for dichotomous data it means that with its absence the risk of overweight increase

Recently, COVID-19 invades the world and scientists are still trying to discover how it affects the body. As obesity may cause the body's immune response to go with unexpected speed leading to cytokines storm, it is now thought to be one of the biggest risk factors in developing severe coronavirus symptoms and even may play a significant role in coronavirus deaths [21].

In obese individuals, the dysfunctional adipose tissue is characterized by altered cytokine secretion patterns leading to severe changes in the serum level of inflammatory and anti-inflammatory cytokines, proteins, in the number, and behavior of immune cells and thus stimulate hyper-inflammation manifestation in severe COVID-19 and may decrease the immune system responsiveness to vaccines and microorganisms [18], [20], [22], [23], [24]. Altogether, obesity per see may be an independent risk factor for SARS-CoV-2 [3].

Preliminary data indicate that the new COVID-19 cases are increasing among younger and obese adults [25]. Deng *et al*., not only confirmed that obesity is a major and independent risk factor for COVID-19 complications in young adults [26] but they also pointed out ectopic and visceral fat depots as potential markers of COVID-19 risk. A high prevalence of obesity in patients with severe COVID-19 requiring invasive mechanical ventilation was recently reported [27]. In developing countries, malnutrition among children is a major public health concern. Young children are the most vulnerable group due to their high nutritional requirements for growth and development. Overweight and obesity result from an imbalance between energy consumed (too much) and energy expended (too little) [28]. Higher prevalence of obesity is linked to poor diet quality, low physical activity, and excessive screen-time, (i.e., television, computers, e-devices such as smartphones, tablets) [29], [30]. In many countries, the school food environment promotes the consumption of unhealthy foods, overweight, and obesity [31].

The current cross-sectional observational study was conducted on primary school children aged 6–12 years. Of 1600 children, there were 8% overweight and this was higher than the global average of 6.2% [32]. Different studies had been conducted in different Egyptian governorates. Among Egypt, for the same comparable age group (6–12 years) much higher results for overweight percentage were reported in Alexandria, Sohag, and Menoufia governorates, (16.8% and 16.5% and 23.7%, respectively) although they worked on nearly the same age group. This so big difference could be attributed to different socioeconomic factors, eating habits, and lifestyle [33], [34]. In the present study, we found that children who carried higher risk to be overweight are those who missed their home breakfast; who did not take meals on time regularly; who did not take breakfast and snacks; did not take dinner; and who took snacks before sleep or between meals, (OR = 4.031, 3.31, 2.82, 2.53, 2.2, and 1.89, respectively). Our results were matching to a great extent to those of Amin *et al*., in a study done in Saudi Arabia on primary school male children, where missing or infrequent intake of breakfast at home was a predictor of overweight among the studied children [35]. Similarly, many Egyptian studies on primary school children found that skipping breakfast was associated with obesity, while its regular consumption or having school meals as breakfast was associated with improved cognitive performance, nutritional adequacy, bone and cardiovascular health as well as healthy body weight [33], [36], [37]. The reason why skipping breakfast is associated with a higher weight is not well understood. According to UNICEF reports (2019), children who miss or skip breakfast have a higher BMI than their peers who do not; this is because they subsequently eat between meals more snacks and sweetened carbonated drinks that are high in calories but low in nutrients [6]. On the other hand, in a study carried in the USA, (2017) on school children they said that this may reflect some degree of reverse causality if overweight and obese students think skipping breakfast will help them lower caloric consumption [38]. In the present study, considering the weekly share of the stomach, one-third of overweight children and nearly half of normal weight children consumed nutrient-rich food in the form of dairy and beans/meat/eggs. It was also found that chips and SSB were consumed more than once per day among 96% and 90% of overweight children (respectively), while French fries were consumed less than once per day and candies nearly once per day in 95% and 78% among overweight children (respectively). Similarly Amin *et al*. mentioned that low consumption of nutrient food (fruits vegetables, milk, and dairy products), as well as frequent consumption of sweets and carbonated drinks, was all predictors of overweight among the studied children [35].

In Tanzania, it was found that random eating of different food categories such as pancakes, crisps, and juice for at least 5 days per week at school was predictor factors for both overweight and obesity. The majority of children missed breakfast and had irregular meals [39]. This was in accordance with our results where children who missed breakfast, who are not eating meals in time and who are eating more snacks carry more risk to be overweight than those who used to eat regularly.

In the current study, the majority of overweight children belonged to small families (68.0%), middle-income families (60.9%) and had illiterate or read and write mothers (61.7%). Furthermore, our analysis shows that reduced risk of having overweight children came with large family size, low-income families, and with highly educated mothers (OR=0.46, 0.55, and 1.9, respectively). Other Egyptian studies, performed on a wider range of school age children (6–17 years), revealed different results compared to the present one. They concluded that the presence of higher percent of obesity was in association with large family size, low SES families in addition to higher percent of illiterate and not working mothers [29] or a lower percent of illiterate mothers [40]. The difference between our results and the previous studies could be attributed to the fact that they represent wider age range group, different geographical regions (urban and rural) with different sociodemographic characteristics and nutritional habits. Previous studies concluded that there is increasing numbers of families with both (or single parent) employed which may impact their abilities to support healthy lifestyles for their children [41], [42], [43] while another study have linked only maternal employment with childhood overweight [44]. In the present study, we found that overweight children belonged to middle-income families (60.9%) where fathers and mothers were working (99.2% and 32.8%, respectively). The lower prevalence of overweight in our study compared to several previous studies done in Egypt, could be attributed to the fact that only one-third of the mothers were working while two-thirds were staying at home. Maternal working had a great impact on the nutritional state of their children due to limited time available for cooking more healthy diets [45], depending more on unhealthy takeout, restaurant meals and/or providing fast and easy prepared food [46], [47]. In addition to lack of maternal-child supervision and that may have adverse implications for their food intake choices and physical activity [45].

Conclusion

The prevalence of overweight among the studied group was much lower than that reported in other previous Egyptian studies. Nutritional behaviors and social factors had a profound effect for the development of overweight in children. Children with overweight should correct their unhealthy habits and take extra measures to avoid COVID-19 contamination by imposing prevention during the current pandemic. Achieved partnership for lasting change that encourages partnerships among parents and carers, governmental (Ministry of Health and Ministry of Education) that share the ambition to improve diets and health is highly required especially through the school feeding support program that proved to have high impact on children [36], [37]. The majority of the Egyptian researches indicated that it is critical to start feeding programs too early with more focus on the promotion of breast breastfeeding due to its marvelous effect on not only the physical growth and health but also on the child cognitive development [48], [49].

Management of the overweight problem necessitates not only the use of medication but to eat healthy to increase immunity. For low socioeconomic communities, this cannot be addressed without designing and implementing community-based programs that are dependent on the cooperation between physicians, parents, and teachers. Similar community-based initiative in Egypt assessed facilitators and barriers of behavioral change as well as addressed the psychosocial problems proved to have a very profound effect on to enhancing well-being. They are considered as compelling and promising solutions to parents and carers through raising their awareness, and improving birth outcome and leading to improve children immunity generally and against COVOID 19 in particular [50], [51], [52].

At the same time, for prevention and/or attenuating the pathological consequences of obesity, dietary intake of natural products together with anti-oxidant and anti-inflammatory is mandatory in addition to preventive measures and caloric restrictions.

Strengths of the study

Our study is characterized by being a facility based one on representing three different geographical areas with very large sample size (1600 children), with a high confidence level of 95% and low two-sided margin of error (0.05). The study targeted all determinants for overweight.

Limitation of the study

This study was limited to assess the weaknesses of the eating habits of overweight children as a weak point leading to increasing their vulnerability to catching COVID-19 infection without assessing the link to coronavirus infection and compare the incidence of its infection among overweight versus normal children. This might be considered as a weakness to our study, yet, because of the lockdown that all government agencies are doing to fight the adverse situation due to the COVID-19 pandemic efficiently, it was difficult to set and achieve this objective.

Declarations

Ethics approval and consent to participate

Ethical issues

The study was approved by the Medical Research Ethics Committee of the National Research Centre with the ethical approval number of 19068. Permission to conduct the research was obtained from the Ministry of Education. Consent from the children's guardians was taken and the information obtained at the individual level was kept strictly confidential. The conduct of the study was complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects [53].

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

The design of the study was done by AMM, EMS. All authors contributed to the implementation of the field visits and data collection. MMS, WS, and FSh assessed all the children to detect any abnormalities and conduct the anthropometric measures. HH did the statistical analyses. All authors shared for the interpretation. WS and MMS took the lead in writing the manuscript. AMM, FSh, and EMS reviewed the manuscript. All authors discussed the results and commented on the manuscript. All authors approved the manuscript.

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Assessment of Knowledge, Attitude, and Practice toward COVID-19 among a Sample of Iranian General Population

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Abstract

BACKGROUND: The new coronavirus (COVID-19) pandemic is rapidly spreading around the world. At present (up to July 11, 2020), 255,117 cases and 12,635 deaths due to this disease have been reported in Iran. Following the guidelines recommended for the prevention and control of the disease is the most important approach to combating this global threat.

AIM: The aim of this study was to assess the knowledge, attitude, practice, and fear of the Iranian people in relation to COVID-19.

METHODS: A cross-sectional study was conducted with the participation of 558 Iranian people who entered the study by convenience sampling method. The knowledge, attitude, practice, and fear of the Iranian general population toward COVID-19 were collected using an online 50-items questionnaire. Descriptive statistics, one-way analysis of variance, independent sample T-test, and bivariate Pearson's correlation were used to analyze the data.

RESULTS: The studied subjects were mostly in urban area (81.0%), female (61.3%), and married (57.9%). The participants' knowledge about personal hygiene (88.9%), using a facemask (82.2%), and the symptoms of the COVID-19 (76.8%) were adequate. However, their knowledge about contaminated surfaces disinfection procedure (41.8%), and the importance of using a facemask for healthy people (43.7%) was lower. The highest level of the subjects' attitude was related to the role of social distancing (94.6%), staying at home (94.5%), and personal hygiene (91.2%). The low levels of attitude were also associated with access to personal protective equipment (84.1%) and the psychological effects of COVID-19 (65.3%). Furthermore, the highest levels of practices were related to avoiding hand shaking with others (91.5%) and washing hands frequently (88.8%). The practices such as following a healthy and nutritious diet (45.1%) and wearing gloves (51.4%) were reported to be less common.

CONCLUSION: The results showed that about half of the subjects did not have enough knowledge about COVID-19. However, the attitude and practice of most of the participants toward COVID-19 were moderate or good. Nevertheless, the extensive health education interventions are needed to promote knowledge about COVID-19 and also to motivate people to do preventive behaviors.

Introduction

The outbreak of the new coronavirus (SARS-CoV-2) was first reported in December 2019 in Wuhan, the capital of Hubei Province, China [1], [2]. In late 2019, the World Health Organization expressed the outbreak of COVID-19 as an international public health emergency [2], [3]. Over time, the disease has spread to all countries and by July 11, 2020 about 12.6 million and 642,000 people around the world have suffered and died from the disease, respectively [4]. At present, the highest cases of COVID-19 are in the United States, Brazil, India, Russia, Peru, Chile, Spain, Mexico, United Kingdom, and Iran, respectively [4], [5]. Furthermore, Iran is the seventh country in terms of the deaths due to disease [5]. The first case of COVID-19 in Iran was reported on February 19, 2020, and at the time of this paper (July 11, 2020), 255,117 cases and 12,635 deaths have been occurred in Iran [5], [6]. The daily increase of morbidity and mortality due to the disease has detrimental effects on the economies especially the health-care systems [7]. Over COVID-19 pandemic, the demand for personal protective equipment (PPE) such as facemasks and disinfectants has been dramatically increased [8], [9]. The lack of PPE has caused great concern and has endangered the public health of human [10]. On the other hand, no specific drug or vaccine has already been made to treat the disease [2], [11]. Therefore, following the protocols and guidelines for the prevention and control of COVID-19 is the most important way to deal with this disease [2].

COVID-19 is highly contagious and can be directly transmitted from person to person through direct contact (less than 1.5 m distance) or indirectly contact with an infected surface [2], [12]. According to the World Health Organization, more than 80% of COVID-19 cases are in mild state and can be cured without medical intervention. About 20% of the individuals also show severe symptoms of the disease [13]. The early symptoms of the disease include fever, dry cough, fatigue and bruising, and in rare cases, headache, and diarrhea [2]. The incubation period of 1–14 days is also reported for the disease [14], [15], [16]. No exposure to SARS-CoV-2 is the most important way to prevent the disease [17]. The main approaches including frequent washing of hands with soap and water, wearing a facemask and quarantine of COVID-19 suspicious people can be applied to prevent the disease [17], [18]. The knowledge and attitude of people toward COVID-19 will play a significant role in preventing and subsequently reducing the morbidity and mortality of the disease [19]. The findings of similar studies during SARS (2003) and MERS (2014) outbreaks showed that people's knowledge and attitudes played a substantial role in their preventive behaviors [19], [20], [21]. The assessment of people's knowledge, attitude, and practice levels toward COVID-19 can be a very important step to assess the health educational needs and planning the effective interventions to fight the disease [22], [23].To the best of our knowledge, the present study is carried out, for the 1st time, to assess the knowledge, attitude, practice, and fear of the general Iranian population regarding COVID-19.

Methods

Study sampling

A total of 558 individuals, from all over Iran, participated in this cross-sectional study. The online convenience sampling was performed from March 27 to April 10, 2020. The questionnaire link was sent to people through WhatsApp and Telegram, the most popular social applications in Iran. The sample size was estimated using online software (Raosoft sample size calculator: http://www.raosoft.com/samplesize.html). The estimated sample size was 383 with a considered margin of error of 5% and a 95% confidence interval. However, to increase the reliability of the results, due to the high volume of the population size, the sample size of 558 was considered. Out of 1131 visitors, 637 individuals answered the questionnaire and due to the incomplete answers of 79 people, the data of 558 respondents were finally analyzed. The explanations related to the questionnaire as well as the conscious participation form were sent to the individuals along with the questionnaire link. The individuals with smartphones with WhatsApp or Telegram apps and internet access could participate in the study. The individuals should also have at least some basic literacy and interest to participate in the study. People under the age of 18 years and those who incomplete the questionnaire were excluded from the study. The average time to answer the questionnaire was about 10 min.

Measurements

A 50-item researcher-made online questionnaire was used to collect data in five sections. The first part evaluated the subjects' demographic information such as age, gender, education level, marital status, job status, family economic status, and place of residence.

The second part assessed the participants' knowledge on COVID-19 with 12 items (e.g., a dry cough is a common symptom of COVID-19). The answers in this section were scored as Yes=2, I don't know=1, and No=0. The total knowledge scores ranged from 0 to 24, which higher scores indicated a higher level of knowledge. According to the median split method [24], the participants with a total score of lower and higher than 18 (median) were considered as inadequate and adequate knowledge, respectively.

The third section determined the individuals' attitude on COVID-19 using 12 items (e.g., If I don't go to the crowded places, I reduce the risk of COVID-19). The answers of this section were scored by a five-point Likert scale from completely disagree=1 to completely agree=5. The total attitude scores ranged from 12 to 60, which higher scores represented a more appropriate attitude.

The fourth section estimated the participants' practice related to COVID-19 with 18 items (e.g., mask wearing in the presence of the suspected persons or attendance at crowded places). The answers in this section were also according to a 5-part Likert scale from never=1 to always=5.

The fifth section was applied to assess people's fear of COVID-19 with one question (how much do you fear of COVID-19?). The answers to this question were based on a 5-part Likert scale from never=1 to so much=5. The total practice scores ranged from 18 to 90, which higher scores showed a more suitable practice.

The subjects' responses of attitude and practice items were divided into three categories as follow. The scores <50%, 50–75%, and over 75% were classified as weak, moderate, and good responses, respectively [25]. The studied parameters of knowledge, attitude, and practice in the questionnaire are shown in Table 1.

The content validity of the questionnaire was qualitatively evaluated using the opinions of six health education and health promotion specialists. The corrective recommendations of the specialists were

Table 1: Relative frequency (%) of participants' answers to questionnaire items (n=558)

Items No	Answers (%)				
Knowledge	Yes*	No		I don't know	
1. The use of facemask is essential for healthy people	43.7	47.1		9.2	
2. It is essential to use a facemask when you are exposed to a sick or symptomatic person	82.2	4.3		13.5	
3. Wearing filtered masks such as the N95 mask is suitable for infected or suspected people	57.9	31.4		10.7	
4. The surgical mask can be used for a maximum time of 2 h	62.2	18.8		19	
5. Industrial alcohol can kill the coronavirus	28.2	55.1		16.7	
6. The minimum distance of 1 m is suitable against infected or suspected people	70.8	25.4		3.8	
7. For disinfection of surfaces such as bathroom and toilet floors, bleach solution with a concentration of a-half percent is suitable	41.8	22.9		35.2	
8. The improvement of personal hygiene is the most important way to prevent COVID-19	88.9	10.9		3.1	
9. Fever is one of the most common symptoms of COVID-19	92	5.6		2.4	
10. Runny nose is a common symptom of COVID-19	24	64.9		11.1	
11. Dry cough is one of the most common symptoms of COVID-19	96.2	1.7		2.1	
12. Fatigue is one of the most common symptoms of COVID-19	69.3	19.2		11.5	
Attitude	Completely agree	Agree	Neutral	Disagree	Completely disagree
1. I am at risk for COVID-19	22.3	38.1	22.2	11.8	5.6
2. My family are at risk for COVID-19	19.5	41.1	20.6	14.4	4.4
3. If I do not observe personal hygiene, I can infect my family with COVID-19	52.3	38.9	3.1	4.3	1.4
4. I'm worried about getting COVID-19	38.7	43.2	12.9	4.3	0.9
5. Because COVID-19 is an unknown and mysterious disease, I am afraid of it	41.1	36.7	14.5	6.6	1.1
6. Hearing the news about COVID-19 mortality scares me	28.7	36.9	18.5	12.5	3.4
7. If I don't attend crowded places, I reduce the risk of COVID-19	66.3	28.3	2.3	3.1	0
8. Staying at home reduces the risk of COVID-19	68.6	26.3	4.7	0	0.4
9. If I don't travel during the COVID-19 outbreak, I will prevent myself and my family from the disease.	65.3	27.2	3.8	2.4	0.2
10. I'm tired to stay at home because of COVID-19	39.1	26.2	17.6	10.4	6.7
11. It is difficult to provide the sanitary items such as facemask and gloves	47	37.1	8.4	5	2.5
12. The information received about COVID-19 is very different and confusing	34.6	23.8	16.7	17.7	7.2
Practice	Always	Often	Some time	Seldom	Never
1. Wear a mask whenever confronting with a person suspected of COVID-19	43.4	28.7	12.4	9.8	5.7
2. Wear gloves whenever contacting with contaminated objects and surfaces	29.4	22	27.4	12.2	9
3. Avoid hand contact with eyes, nose and mouth	35.4	27.9	22.9	8.5	5.3
4. Disinfect the home environment	29.7	21.3	31.2	11.9	5.9
5. Disinfect personal belongings	33.4	23.7	24.4	12.8	5.7
6. Frequent handwashing with soap and water	63.1	25.7	9.8	0.9	0.5
7. Maintain a distance of at least 1 m with suspected people	51	27.2	18	2.9	0.9
8. Cover your mouth and nose when you cough or sneeze	60.6	26	12	0.9	0.5
9. Avoid contact with animals	60.9	24.2	8.1	3.4	3.4
10. Avoid hand shaking with others	79.1	12.4	7.3	0.7	0.5
11. Using healthy and nutritious diet	22.1	23	31.7	17.3	5.9
12. Avoid unnecessary presence in the medical centers	74.7	4.8	7.4	5	8.1
13. Avoid smoking	32.2	18.1	22.2	15.4	12.1
14. Dispose of used handkerchiefs, gloves or masks in a hygienic and safe manner	43.3	23.4	17	9.5	6.8
15. Natural ventilation through windows	36.9	23.7	22.8	10.5	6.1
16. Stay at home	49.2	22	18.5	8	2.3
17. Avoid crowded places	53.1	28.2	11.9	4.3	2.5
18. Avoid unnecessary travel	65	17	10.5	7.1	0.4

*For knowledge items no 3, 5, and 10, the correct answer=No.

carried out on the simplicity, appropriateness, ambiguity, and items necessity and scoring. The reliability of the knowledge, attitude, and practice scales was determined by assessing the internal consistency of the items for each section and the results are presented in Table 2.

Table 2: Means, standard deviations, and internal consistency of knowledge, attitude, and practice toward COVID-19

Variables	Mean number (%)	SD[†]	Items	Score range	Internal consistency*
Knowledge	18.11	2.24	12	0 – 24	0.64
Adequate	320 (56.5)				
Inadequate	243 (43.5)				
Attitude	48.96	5.07	12	12 – 60	0.83
Weak	23 (4.12)				
Moderate	241 (43.18)				
Good	294 (52.68)				
Practice	71.56	8.56	18	18 – 90	0.92
Weak	26 (4.66)				
Moderate	243 (43.54)				
Good	397 (51.80)				

[†]Standard deviation *Cronbach's alpha (α), n=558.

Data analysis

The data were analyzed by SPSS software version 19. Descriptive statistics, one-way analysis of variance, independent sample t-test, and bivariate Pearson's correlation were used to analyze the data. $p < 0.05$ was considered statistically significant in the present study.

Results

The study was carried out on 558 participants with a mean age of 33.3 ± 10.01 years. As listed in Table 3, 61.3%, 57.9%, and 81.0% of the subjects were women, married, and living in urban areas, respectively. Table 3 also shows the comparison of mean and standard deviation of knowledge, attitudes, and practice scores of the subjects related to COVID-19 based on demographic variables. As it can be seen, the knowledge of people living in the city was significantly higher than the rural population ($p = 0.018$). The attitudes of married ($p = 0.001$), employees, and housewives were also significantly higher than other people ($p = 0.006$). The individuals with low-income had a weaker practice than others ($p = 0.001$). The participants' knowledge related to the importance of personal hygiene (88.9%), the necessity of using a facemask in contact with infected or suspicious people (82.2%), and the symptoms of the COVID-19 (76.8%) were at a high level. However, their knowledge about contaminated surfaces disinfection procedure (41.8%), and the importance of using facemasks for healthy people (43.7%) was lower. The highest level of subjects' attitude was

Table 3: Comparison of mean scores and standard deviation of knowledge, attitude, and practices of the participants regarding to COVID-19 based on socio-demographic characteristics

Characteristics	Number (%)	Knowledge Mean ± SD[†]	p-value	Attitude Mean ± SD	p-value	Practice Mean ± SD	p-value
Gender							
Male	216 (38.7)	18.20 (2.07)	0.439	48.52 (5.15)	0.108	71.0 (8.62)	0.223
Female	342 (61.3)	18.16 (2.34)		49.24 (5.01)		71.92 (8.53)	
Marital status							
Single	231 (41.4)	18.26 (2.21)	0.153	47.36 (5.33)	0.001	71.59 (8.71)	0.149
Married	323 (57.9)	17.90 (2.28)		49.72 (4.77)		71.65 (8.44)	
Divorced/widowed	4 (0.7)	18.75 (0.50)		49.54 (2.51)		63.25 (8.51)	
Educational level							
Primary school	13 (2.3)	17.69 (2.95)	0.165	46.92 (3.63)		70.15 (5.24)	0.167
Secondary school	55 (9.9)	18.52 (2.04)		48.87 (4.72)	0.081	69.63 (6.45)	
University graduated/students	490 (78.8)	18.08 (2.24)		49.03 (5.14)		71.82 (7.52)	
Occupational situation							
Householder	112 (20.1)	18.11 (2.59)	0.211	49.93 (4.36)	0.006	72.89 (7.07)	0.093
Employee	190 (34.1)	18.14 (1.97)		51.49 (4.48)		71.72 (9.25)	
Self-employment	72 (12.9)	17.69 (2.28)		49.02 (5.13)		70.41 (8.07)	
Laborer	12 (2.2)	18.25 (2.04)		48.33 (5.29)		69.16 (10.32)	
Retired	154 (27.6)	18.77 (2.71)		48.05 (5.14)		73.16 (7.13)	
Unemployed	18 (3.2)	18.19 (2.22)		48.21 (6.56)		70.96 (7.87)	
Place of residence							
City	491 (81.0)	18.21 (2.16)	0.018	48.84 (5.16)	0.091	71.64 (8.32)	0.215
Village	67 (12.0)	17.36 (2.68)		49.88 (4.28)		71.02 (9.91)	
Socioeconomic status							
High	187 (33.5)	18.13 (2.18)	0.671	48.92 (4.88)	0.124	72.90 (8.59)	0.001
Intermediate	310 (55.6)	18.08 (2.12)		49.06 (4.95)		71.81 (7.87)	
Low	61(10.9)	18.04 (1.27)		48.31 (5.16)		66.43 (8.52)	

[†]Standard deviation, n=558.

related to the role of social distancing (94.6%), staying at home (94.5%), and personal hygiene (91.2%). The low levels of attitude were also associated with the access to PPE (84.1%), the psychological effects of COVID-19 (65.3%), and the information related to COVID-19 (58.4%). Furthermore, the highest levels of preventive behaviors were related to avoiding hand shaking with others (91.5%), washing hands frequently (88.8%), and covering the mouth and nose when sneezing or coughing (86.6%). The behaviors such as following a healthy and nutritious diet (45.1%), wearing gloves when in contact with contaminated surfaces (51.4%), and avoiding smoking (52.3%) were reported to be less common (Table 1). As listed in Table 2, 56.5% of the participants had adequate knowledge, 52.6% had a good attitude, and 51.8% had appropriate practice related to COVID-19. The findings of Pearson's correlation test showed the positive and significant correlation between knowledge and attitude (r = 0.114, p = 0.026), knowledge and practice (r = 0.224, p = 0.011), as well as attitude and practice (r = 0.281, p = 0.005). In addition, the results showed that 28.3%, 22%, and 32.8% of the subjects were so much, much, and somewhat afraid of the COVID-19, respectively (Figure 1).

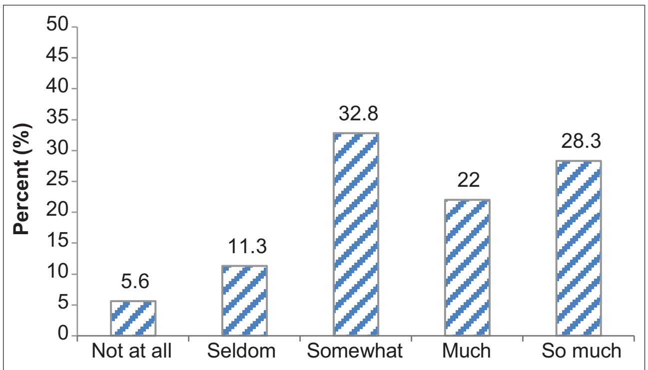

Figure 1: Relative frequency (%) of participants' fear of COVID-19 (n=558)

Discussion

The aim of this study was to investigate the knowledge, attitude, and practice toward COVID-19 among a sample of Iranian people. The findings showed that 56.5% of the Iranians had adequate knowledge related to the COVID-19. The participants had sufficient knowledge about personal hygiene, the symptoms of COVID-19, and social distancing. However, their knowledge on facemask wearing as well as the correct use of disinfectants was not enough. A literature review of similar studies showed that the knowledge, attitudes, and behaviors of the people vary according to the sample type and the time of the study. In a study by Wolf *et al*. (2020), the knowledge of adults with underlying disease in the United States (U.S) on COVID-19 was reported to be insufficient [26]. In a study by Johnson and Hariharan (2017), a significant proportion of Trinidad and Tobago people did not have sufficient knowledge about the H1N1 flu and its prevention strategies [27]. Furthermore, in a study of Srichan *et al*. (2020), the knowledge of Thai people about COVID-19 was poorly reported [28]. In several other studies, the knowledge level of Chinese students [29], Iranian medical students [10], healthcare workers in Vietnam [2], Chinese health workers [30], and Indian dentists [31] about COVID-19 and ways to prevent and control the disease was appropriate. In a study by Roy *et al*. (2020), Indians also had moderate knowledge about the SARS-CoV-2 infection and its symptoms, but their knowledge on ways of preventing the disease was satisfactory [9].

In the present study, the individuals' knowledge on COVID-19 prevention was positively and significantly correlated with their practice. The findings showed that the improvement of people's knowledge on COVID-19 can increase their preventive behaviors for the disease.

However, often high knowledge alone does not lead to optimal practice [32]. The prevention and control of COVID-19 are desirable when in addition to sufficient knowledge; there should be a favorable attitude toward preventive measures against this disease [33].

In the present study, most of the Iranian people had moderate or good attitude toward COVID-19 prevention. Most of the individuals had a good understanding of the COVID-19 risk. They also perceived the importance of personal hygiene to prevent COVID-19 and believed to stay at home and avoid crowded places. However, some individuals believed that access to PPE was difficult. They also expressed that the information received about COVID-19 was confusing and the disease had a negative influence on their mental health. The findings of similar studies showed that there was a good attitude among different types of groups in society in various countries toward COVID-19 [2], [10], [19], [29], [30], [31]. However, study of Taghrir *et al*. (2020) expressed a moderate attitude toward COVID-19 prevention among the Iranian medical students [10]. Furthermore, study of Srichan *et al*. (2020) reported that one third of Thai people had a weak attitude about the disease [28]. In the present study, about 47% of the subjects had a weak or moderate attitude toward COVID-19. Since the announcement of COVID-19 outbreak in Iran, the Ministry of Health and Medical Education (MOHME) has developed extensive instructions to fight the disease. There have also been several national campaigns to combat the disease in Iran, such as “We defeat COVID-19” and “Stay at Home” [34], [35], [36]. The MOHME has also implemented a variety of training programs in cooperation with the Iran Broadcasting to fight COVID-19. The findings of the present study and also similar studies in Iran [10], [30], [31] showed that the Iranian people have successfully followed the MOHME guidelines for prevention and control of COVID-19. However, some Iranians still do not have the acceptable knowledge, attitude, and practice to deal with the disease. The reality is that in addition to scientific and authoritative information and instructions about COVID-19, unfortunately the misinformation, misconceptions, and unscientific procedures have also been spread in the community, especially by virtual social networks [37], [38]. The misconceptions such as rubbing viola and sesame oils on the body, drinking camel urine, gargling with salt water or mouthwash, using a hair dryer, and drinking alcohol may prevent people from following the correct instructions [37], [39]. On the other hand, due to the unknown nature of some behavioral aspects of COVID-19, the authoritative scientific sources may also provide confusing information, such as the necessity or non-necessity of wearing a facemask by healthy people, to the general public [40], [41].

The internet and virtual social networks have been reported as the most important source of information for people about COVID-19 [38], [39]. The virtual social networks, despite their great contribution to the rapid circulation of scientific information, can be a place to spread misinformation and misconceptions [37], [39], [42]. Therefore, it is necessary for people that are aware of the reliable and scientific sources toward COVID-19 and, on the other hand, to avoid spreading misinformation related to the disease [42]. To do this, the MOHME needs to have a scientific channel about the COVID-19 in virtual social networks and provides health education programs, like the World Health Organization that works with social media, including Facebook, Twitter, and WhatsApp, to provide accurate information about COVID-19 [40].

According to the present study, most participants had a good practice about COVID-19. About 48% of the individuals also had moderate or weak practice. The subjects in the study had good behaviors such as frequent hand washing, social distancing, wearing masks, staying at home, and avoiding going to crowded places. However, the behaviors such as wearing gloves, disinfection of home and personal belongings, as well as air conditioning at home were reported at a lower level. The knowledge and attitude of the subjects were directly and significantly related to their practice in relation to COVID-19 prevention and control. Moreover, the weak knowledge and attitude toward some of the facts and strategies about the COVID-19 prevention led to poorer practice. The findings of various studies such as our research reported good practice of the subjects on the protective behavior against COVID-19 [10], [19], [28], [29], [30], [31].

The participants’ knowledge, attitudes, and practice were partly influenced by the demographic factors. The comparison of the knowledge score of the individuals with respect to the demographic variables showed that the knowledge level of people living in urban areas was significantly higher than in rural areas. People in rural areas of Iran have lower education and literacy levels [43], [44]; therefore, they may be more affected by incorrect information related to COVID-19. On the other hand, the quantity and quality of internet access and penetration in the rural areas of Iran are weaker than urban ones [45], [46]. Because of the fundamental role of the internet and virtual social networks to enhance people’s information about COVID-19 [38], [39], the weaker knowledge of the people living in the rural areas was expected. The married subjects had a more suitable attitude toward the COVID-19 than single people. Marital status is known as one of the social determinants on health [47]. The previous studies have shown that married people are more likely to engage in health behaviors and they have a high level of health [48], [49], [50]. The married people have a positive attitude toward health behaviors, due to less stress and more social support, especially from their family. Marital status may provide more opportunities for men to progress their health than women [47], [51]. The employees also had a significantly more positive attitude toward COVID-19 prevention and control. The employees may have more opportunities to learn about the disease than other occupations. One reason for this is that the employees in Iran have often higher level of education and health literacy [52], [53]. The individuals with moderate and good social level and economic well-being had significantly better practice on COVID-19 prevention and control than the low level people. Zhong *et al*. (2020) also reported that people with high socioeconomic status had better knowledge, attitude, and practice toward COVID-19 [19]. Srichan *et al*. (2020) reported that people with higher incomes had a better practice on COVID-19 prevention [28]. The weaker practice of the lower incomes people in the society about COVID-19 prevention can be analyzed from several aspects. First, the high demand of PPE (gloves, facemasks, and disinfectants) during the disease outbreak in Iran led to a shortage of these items and as a result, the prices of them were significantly increased. Therefore, it became more difficult for the lower incomes people to provide these items. Second, most of low-income people in the society are worker or self-employed who do not have a steady income and must work daily. Therefore, follow the instructions of "stay at home" for a long time was the important barrier for these people. Eventually, these people were forced to ignore the social distancing instruction to leave the home.

Study limitations

The present study was first carried out to assess the knowledge, attitude, and practice levels of the general population in Iran toward COVID-19. However, this research had several limitations. First, the subjects often had a university degree, while in Iran about 20% of the population over the age of 18 years is academics [54] Therefore, it is possible that the levels of knowledge, attitude, and practice reported in this study were higher than of their actual values in the general population of Iran. Second, the study was conducted on adults (≥18 years). Third, only literate people were considered in the study. Therefore, it is not possible to generalize the findings to illiterate people. Fourth, because the online study was conducted, people who did not have access to the internet, as well as smartphones, could not participate in the study.

Conclusion

The findings of the study showed that the most of subjects had adequate knowledge and a good attitude and practice toward COVID-19. The participants performed well on COVID-19 protective behaviors including handwashing, wearing facemask, social distancing, and avoiding going to crowded places. However, the behaviors such as wearing gloves, disinfection of home and personal belongings, as well as air conditioning at home were reported at a lower level. The extensive implementation of health education programs to raise knowledge about COVID-19 and also motivate people to do preventive behaviors is critical. In addition, to increase the effectiveness of health education interventions, it is necessary to consider the demographic and socio-economic characteristics of the target groups and their specific educational needs.

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Association of Coronavirus Disease-19 Infected Mothers with Newborn Infants Health – A Review

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Abstract

BACKGROUND: Coronavirus (CoV) is an emerging disease and the World Health Organization declared pandemic in February 2020. Infants were born from CoV disease (COVID)-19-positive mothers who were risk of different diseases.

AIM: The aim of this review is to determine the association of infants health with COVID-19-infected mothers.

METHODS: A review of the literature was done for identifying the association of newborn health risk with COVID-19-infected mothers. Google Scholar, PubMed, Web of Science, and Scopus were used as search engines.

RESULTS: The common finding among newborn infants from COVID-19-infected mothers were rashes, ulceration on the body, tachypnea, fever, and cough and assisted ventilation was needed to support the ventilation of newborn. Most of the COVID-19-infected women were delivered the preterm baby. The most effective way to reducing the health risk is to screening of mothers and appropriate effective surveillance system should be established.

CONCLUSION: The review has found that infants born with COVID-19-infected mothers had various respiratory disorders. There is a need to coordinated efforts for the management of infants.

Introduction

In 2019, the first case of new coronavirus (CoV) disease (COVID)-19 was identified at the city Wuhan in China. In February 2020, COVID-19 infection was declared a pandemic by the World Health Organization and almost all countries were affected [1]. The most affected countries are the United States of America, Italy, Spain, Brazil, and France. The most common age groups affected by COVID-19 were the elderly and children [1]. The main reason for elderly population were affected because they have less immune naturally [2]. The other most common vulnerable group were pregnant mothers. The COVID-19-infected mothers were delivered newborn which had different health risk such as rashes and assisted ventilation after birth. The main caused for this health risk was conventional circulation system in mothers and infants which transferred virus from mothers to infants [2].

COVID-19 virus transferred from mothers to infants in many ways [2]. First through respiratory inhalation in which oxygen carries in the blood and then this blood enter the fetal system [2]. Second ingestion, contaminated hand ingest food and through digestion and blood circulation infants were infected [2]. Sepsis is the another way the infant was affected [3].

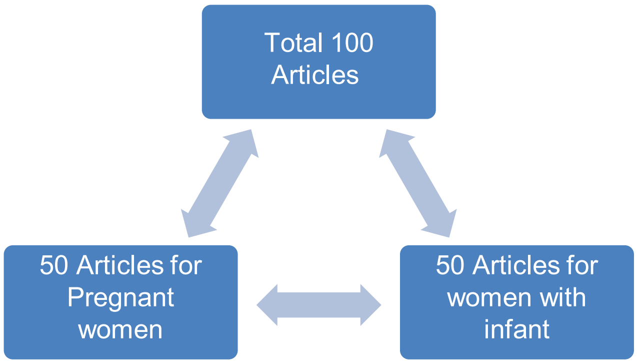
There are different health risks to the fetus from transmission of COVID-19 from mother. There are different studies showed that newborns were developed sepsis in the 1st day of birth and other researches showed that infants developed pneumonia after in neonatal period [4]. This review helps to find the consistency of results of different studies to either there is the association of COVID-19-infected mothers with the health of infants.

Objective

The objective of this review is to identify the association of infants health with COVID-19-infected mothers.

Methodology

A review of the literature was done for identifying various case reports and cases series of COVID-19-infected infants. Google Scholar, Pub Med, Scopus, and Web of Science were used as search engines. Search terms used were "COVID-19," maternal infection, infants, sepsis, and pneumonia. References of the relevant articles were also used for citations.



Results and Discussion

COVID-19 and its effects on pregnant women

This virus belongs to the family of flu virus. The severe acute respiratory syndrome (SARS) virus is also belonging to this family [1]. The previous case series found that case fatality was 25% from SARS infection in 2003 [5]. Laboratory and the clinical finding of SARS were similar in COVID-19-infected mothers [5]. Chest radiograph and computed tomography scan finding showed that pneumonia in the lung of infected patients [5], [6]. Common complications from the COVID-19-infected women were adult respiratory distress syndrome, lung fibrosis, and pulmonary edema [7]. A study done by scientist found that COVID-19 genetically similar to SARS and it comes from bat virus [8].

The virus has 79% nucleotide identity to SARS-CoV and about 50% to Middle East respiratory syndrome (MERS)-CoV [8]. Bats appear to be the natural reservoirs of both SARS-CoV and MERS-CoV [8]. The emergence of these viruses in humans has been attributed to host switching: The virus "jumped" from an intermediary host species (e.g., civet cats for SARS-CoV and dromedary camels for MERS-CoV) to humans [8]. An intermediary host species is thought to be likely for SARS-CoV-2, although it has been yet to be identified. Sequence data show a high degree (>99.98%) of similarity of the virus among different patients, suggesting a recent emergence in humans [8].

They have identical pathogenesis to the SARS virus [8]. A recent study found that preterm deliveries were common among COVID-19-infected women [8]. Another study found that cesarean births were common compared to standard vaginal deliveries among infected women [9]. Another study found that fetal movement was reduced and pregnant women had developed dyspnea and anemia after delivery of baby [9].

COVID-19 and its Effects on Infants

The study was conducted and found that mothers with COVID-19 were delivered preterm and these babies were low birth weight [10]. The result also found that these babies had 1 min Apgar score of 4–6 and 5 min Apgar score of 7–8 [10]. The common practice after delivery, babies were put up on bottle feeding and care of the baby was done in the nursery care center [10]. Another study result found that mother infected with COVID-19 give birth of babies had skin diseases such as itching, rashes, and redness appeared in different parts of the body [11]. Furthermore, babies with macula papules spread on the different region of the body and especially in the forehead with ulceration. The rash on the body of the baby was turned into red papules and it diffuses in nature [11]. Another study found that babies had respiratory distress syndrome which need surfactant and later on developing bronchopulmonary dysplasia [12]. There are various issues during deliveries of babies from COVID-19-infected women. The most common problems were intrauterine growth retardation, miscarriage, and renal failure. After birth, baby needs end tracheal intubation and care in the intensive care unit [13], [14], [15]. Another study found that babies born with COVID-19 mothers had pneumonia [16].

Pregnant Women with COVID-19 Infection

During the pandemic era of this infectious disease, fundamental changes were occurred in public health and society [17], [18]. The distinctive needs are to developed health promotion plan in which emphasis on awareness regarding COVID-19 infection among pregnant women. Lesson learned from common practice during outbreaks, health-care providers were reluctant to intervene in the management of pregnant women because they think that any intervention effect the health of fetus [19]. Pregnant women were the most vulnerable group of any society because it needs special care, especially in that situation where the health risk has high due to pandemic. There is a need for specially designed intervention because there is a risk of side effects on the fetus and always in mind for the rule of risk–benefit ratio. The benefit of surveillance systems in that situation should be recognized, maternal and infant outcomes should be monitored and intervention should be promptly initiated to save the life of mother and infant [20].

Tour Regulation COVID-19-infected Women

It is recommended that COVID-19-infected women were not travel to the epidemic areas. Various countries have made policies for traveler, especially vulnerable group such as elderly and pregnant women. Consultants obstetric advised should be included in the policy-making. These consultants were give recommendations how to save the health of pregnant women. When pregnant women were travel to the epidemic area, a detailed history of women should be taken and advised the women to report frequently to doctors if any symptoms were appeared. Social distancing and contact tracing should be implemented. Health-care providers, including the consultant's obstetricians, should be stay alert and respond quickly if any worse situation appeared.

COVID-19-infected Pregnant Women Management

Universal principle for the management of COVID-19 infection was applied to all pregnant women, such measures were quarantine of the suspected person, isolation of confirmed cases, symptomatic management of affairs, testing of suspect cases, contact tracing, oxygen given to severe cases, and antibiotic treatment of secondary infection. Fetus monitoring and assisted ventilation will be given to the women in a severe case of respiratory problem [20]. A specific group of doctors to be alert and monitor the complicated cases of COVID-19-infected pregnant women. Active surveillance should be established to find out the deterioration maternal path of illness [20].

Management of Infants Born from Infected COVID-19 with Mothers

Coordinated efforts were needed for the management of infants born with COVID-19-infected mother. Appropriate effective surveillance system should be established. Special care unit should be installed at all hospitals, especially primary health-care center.

Conclusion

The finding of the review concludes that there is vertical transmission of infection from mothers to fetus. The cases of COVID-19 disease increasing day by day and pregnant mother were affected most, and there is a need to make specific policies to prevent the infection. There is a need for more studies to explore the factors which affect the health of infants from infected mothers of COVID-19. The affective surveillance system should be active. There is a need to include all areas of expertise of doctors and epidemiologist for monitoring the health of mothers and infants. Health system and health-care provider are the vital stakeholder for reducing the infection during pregnancy; it should be improved to prevent the complication associated with COVID-19 disease.

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Tuberculosis versus COVID-19 Mortality: A New Evidence

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Abstract

BACKGROUND: Coronavirus current pandemic (COVID-19) is the striking subject worldwide hitting countries in an unexplained non-universal pattern. Bacillus Calmette–Guérin (BCG) vaccine was an adopted recent justification depending on its non-specific immune activation properties. Still the problem of post-vaccine short duration of protection needs to be solved. The same protective mechanism was identified in active or latent tuberculosis (TB). For each single patient of active TB, there are about nine cases of asymptomatic latent TB apparently normal individuals living within the community without restrictions carrying benefits of immune activation and involved in re-infection cycles in an excellent example of repeated immunity training sessions of the whole community.

AIM: We aimed to asses the correlation between TB burden and COVID-19 mortality in all affected countries having different BCG vaccination policies.

METHODS: Publicly available data were extracted for 191 countries including population size, TB estimations, national BCG vaccination policy, the World Health Organization regions and economic classification, and COVID-19 mortality and number of cases. The analysis was performed using Spearman's correlation test.

RESULTS: Significant large negative correlation (−0.539, $p < 0.001$) was found between TB prevalence and COVID-19 mortality rate worldwide. Medium negative significant correlations were found between TB cases and COVID-19 mortality in the high and lower middle-income countries, and those having current BCG vaccination programs (−0.395, $p = 0.001$, −0.365, $p = 0.015$, and −0.476, $p < 0.001$, respectively).

CONCLUSION: Countries with high TB prevalence have higher chances of protection against COVID-19 mortality through the theory of widely distributed natural immune activation within community. Confounders should be assessed separately.

Introduction

Less than 3 months were needed for the World Health Organization (WHO) to declare coronavirus disease (COVID-19) pandemic on March 11, 2020, since the first cases appeared in Wuhan, China in December, 2019. At that point of the WHO statement, the disease was found in more than 110 countries all over the world. Up to the time of preparing this article, on July 13, 2020; over 12,685,374 people were infected in 216 countries and territories worldwide, with more than 565,000 patients died [1].

The speed of infection and mortality has shown differential models in various countries, United States has the bigger share globally, while Italy and Spain in Europe and Iran and India in Asia did the same within their continents. The number of confirmed cases in a country depends on many factors such as the availability of the diagnostic tests, efficiency of screening programs, and people's cooperation [1], [2].

Mortality rates differ among countries, although the health infrastructure potency is a vital issue, older patients ≥65 years are the main target. Furthermore, comorbidities such as cardiac, renal, liver, and hematological illnesses, on admission D-dimer elevations, and social habits such as smoking were within reported risks. Immunological defects in cellular immunity of T and B cells along with later escalation of cytokine cells type 2 productions have the major role toward failure of control over viral replication leading to heavier inflammation and damage, especially in ACE 2 receptors rich organs such as kidneys and lungs with net result of poorer fates [3], [4].

Mycobacterium tuberculosis (Mtb) micro-organisms cause tuberculosis (TB) infection which is a common disease worldwide with a clear focus into countries having low and middle-income. One out of four humans on earth is diseased with TB, only 5–15% of them have symptoms and active illness, so that about 90% do not show the disease where the host immune response contained Mtb resulting in a condition called latent tuberculosis (LTB). Most of these LTB individuals are missed and living within the community as normal people having the advantage of lifelong immune system activation which starts with innate response aided by macrophages and dendritic cells, then T-cellular immune activation will come afterward, especially CD4 and eight, in addition to cytokines distinct role [5], [6].

Trying to take control over the widely-distributed TB disease, a vaccine was developed in the form of live attenuated mycobacterium bovis, called Bacillus Calmette–Guérin (BCG) which has a similar approach of immune stimulation caused by LTB infection including cellular and humeral immune response. This training exercise for the natural immunity either caused by the vaccine or the TB disease itself would offer a protection not limited to Mtb, but extended to other viral infections and respiratory illnesses [7], [8].

Herein, this study; influenced by the distinct protective benefits of the non-specific activation of immune system, we evaluated the association between TB prevalence and mortality rates in different countries affected by COVID-19 pandemic, in the presence or absence of BCG vaccination programs.

Methods

Available data on public domains for both COVID19 and TB for 191 countries were collected and analyzed. Population size, number of TB cases, and the WHO regions were obtained from the WHO databases along with the classification of economic classes. Data about BCG vaccination policy were obtained from TB world atlas available at (http://www.bcgatlas.org/index.php. Accessed on July 13, 2020). Data about COVID-19 number of cases and death were obtained from worldometer website available at (https://www.worldometers.info/coronavirus/. Accessed on July 13, 2020). Spearman's correlation test was used for the postulated correlation.

It is noteworthy to mention that we could not control for possible confounding factors including life expectancy, proportion of elderly among population, country preparedness, age, gender, ethnicity, onset of epidemic, migration rate, precision of reporting, and population density.

Results

We tried not to miss any country in the world registered by the WHO in our analysis. Table 1 shows significant large negative correlation between COVID-10 death rate and TB incidence rate per 100 K population.

Table 1: Worldwide TB cases related to current coronavirus prevalence and mortality

Overall	Number of countries	Correlation (R)	p value
COVID-19 versus TB cases	191	0.153	0.035
COVID-19 death versus TB rate	191	−0.539	<0.001

Among high income and lower middle-income countries, there is a significant medium negative correlation between COVID-19 death rate and TB incidence rate per 100 K population, as illustrated in Table 2.

Table 2: Relationship between TB cases and current coronavirus mortality rate according to economic level

Economic class	Number of countries	Correlation (R)	p value
High	66	−0.395	0.001
Low	27	−0.161	0.423
Lower medium	44	−0.365	0.015
Upper medium	52	−0.031	0.826

There is a significant medium negative correlation between coronavirus pandemic death rate and TB incidence rate per 100 K population in countries with current BCG vaccination programs. These findings are clear in Table 3.

Table 3: Correlation between rates of TB incidence and COVID-19 mortality with regard to BCG vaccination status

BCG vaccination status	Number of countries	Correlation (R)	p value
Current	151	−0.476	<0.001
No	19	−0.299	0.213
Previous	21	−0.332	0.141

Discussion

Of interest; COVID-19 spread, morbidity and mortality varied widely within various countries, which may be attributed to differences in background culture, health system programs, and migration movements. Scientists all around the globe are racing against time to understand the pathophysiology and behavior of this viral infection aiming to discover a vaccine or proper treatment plan. Theories were proposed along the way, many of them focused on the immune system as the primary defense mechanism against the virus attack.

Accordingly, BCG vaccination was recently put on the table as an immune stimulant to explain the low incidence rates of COVID-19 in countries with routine BCG vaccination practice [8].

This possibility of BCG vaccine could not stand hard in many countries with BCG immunization and high rates of COVID-19 mortality and morbidity providing that the post-BCG vaccine duration of protection has been thought to last only about 10 years [9], although a single report suggested a substantial protection for a longer time [10].

Moreover; some scientists recommended to repeat BCG at any time after at least 3 months' post-vaccination because peripheral BCG-induced T-cell memory (effector) population could wane between 3 and 12 months in contrast to central T-cell memory which might persist for decades [11], [12].

All these previously-mentioned BCG related parameters would make it difficult to rely only on vaccination data to explain COVID-19 cases as they are usually clustered in older age groups where BCG effects might have been weakened or even disappeared.

Based on the above, we tried something different through focusing on the possible impacts of TB prevalence in affected countries which mirrors the large sector of population carrying latent TB infection when ice burg phenomenon is applied [1], [2].

So that, if one individual has the diagnosis of active TB infection, there has been about nine other people with latent TB diffused within the community and usually unnoticed having the advantage of lifelong immune system stimulation on the contrary of the vaccine where its immune modulation protective effects are vanished with time [9], [10], [11], [12].

We assumed that countries with high TB prevalence have a large population percentage of latent TB individuals whom represent a continuous source of infection and re-infection cycles (mostly asymptomatic) within the community giving it a good chance of ongoing training drills to the immune system making most people resistant to infection complications (including death), a situation which is known as herd immunity [13].

According to our data analysis, we found out a very significant protective (negative) correlation (-0.539, $p < 0.001$) between TB number of cases and COVID-19 mortality rate throughout the world. This crude correlation confirms our above assumption.

Some areas in the world were heavily attacked by COVID-19 leaving more deaths every day. Europe and United States (US) were the major targets of this pandemic regarding deaths per 1 million of population based on worldometer website available at (https://www.worldometers.info/coronavirus/. Accessed on July 13, 2020). This confusing and unexplained matter urged us to look into each country on earth after dividing them according to the WHO income classification, regarding TB prevalence and COVID-19 death rates. A medium statistically significant protective correlation appeared in high income countries including Europe and US, and low middle-income countries (-0.395, $p = 0.001$, -0.365, $p = 0.015$, respectively). A preceding work suggested higher COVID-19 incidence and death rate in high versus medium economic stage countries based on GDP (gross domestic production) per capita. Most high-income countries have higher means of population age, and dramatic decrease in TB cases in the community with more hygienic environment that necessitating non-routine use of BCG vaccination [14] which, in turn, might increase COVID-19 burden following our assumption.

According to the WHO estimations available at (https://www.who.int/health-topics/tuberculosis#tab=tab_1. Accessed on July 13, 2020), half of TB cases in the world were concentrated in eight countries, six of them are low middle-income countries including Bangladesh, India, Pakistan, Indonesia, Nigeria, and the Philippines.

At this point, we tried to investigate the already published hypothesis of non-specific BCG vaccination protection effects through immune stimulation; we divided countries on the basis of vaccination status. Current BCG vaccination seemed to have medium protection significant effects to translate the link between high TB prevalence and low COVID-19 mortality.

Most countries with current BCG according to TB world atlas available at (http://www.bcgatlas.org/index.php. Accessed on July 13, 2020) have high TB burden which might be one of the causes that pushed such countries to keep on the continuity of BCG programs. Based on our presumed opinion, it is easy to judge if that low rates of mortality of current coronavirus infection were due to short-term immune activation resulted from BCG vaccine or the natural asymptomatic infection cycles within the community aided by latent TB.

Some reports suggested that countries with up to date continuous BCG immunization programs did better than countries with interrupted or irregular national vaccination policy. Italy and US were good examples of high COVID-19 mortality while they did not experience universal vaccination programs throughout their history [15]. This could be explained by the above-mentioned observation of low TB cases in countries without universal BCG vaccination as simply they did not need it.

This was also confirmed by another article which claimed that countries with regular present BCG vaccination had better outcomes than countries with the previous or nil vaccination policy [16].

Flattening of incidence and mortality curves of coronavirus pandemic at each country officially ordering BCG vaccination within a month from the beginning of the wide spread, depending on the distinct correlation between universal BCG policy and COVOD-19 prevalence was the findings declared by more researchers [17], [18].

Our data did not show significant effects of the previous BCG vaccination on correlation between TB prevalence and COVID-19 deaths. This is expected according to our hypothesis as it is logical for countries having low TB prevalence to re-evaluate their vaccination strategy and decide to stop BCG, confirming our idea of low TB cases (including latent TB) would leave the community immunity status without activation exercises while early vaccination could not help because of limited protection time. Spain is an example with the previous vaccination policy having one of the highest mortality rates worldwide (deaths per 1 million of population) according to worldometers website available at (https://www.worldometers.info/coronavirus/. Accessed on July 13, 2020).

This was agreed by other scientists who investigated BCG national coverage during 1 year of age from 1980 to 1985 to find out no significant effects on COVID-19 burden [19]. In addition, timing of BCG was not an important risk factor for COVID-19 spread as revealed by some writers [8].

A preceding paper suggested a re-vaccination strategy [20]. Again, this could confirm our idea which says that latent TB could put the community immune system in an alert mode because of high theoretical possibility of continuous infection vicious circles occurred in a natural way in contrast to BCG.

A fresh Japanese paper suggested the protective role of cellular immunity in COVID-19 severity [21]. Although latent TB immune activation is non-specific, cellular immunity is a major participant [7], [8].

It is worthy to say that although concerns were present especially in developed world about latent TB with a potential risk of activation [22], and specific theoretical worries about TB patients when catch COVID-19 infection [23], based on a single retrospective Chinese article that involved only two patients with latent TB but no details of their clinical history [24], there is a clear evidence that latent TB cases represent the immune reactive stage and most of them do not convert into active TB disease even when immune suppressive circumstances have been experienced in line with our alleged consideration [25].

However, many confounding factors could play a role in the mortality or even spread of COVID-19 leading to different trajectories in different countries, such as but not limited to fast and effective general protective measures including social crowdedness prevention, biological and genetic factors, presence of comorbidities and chronic illnesses, and environmental pollution, and prevalence of other respiratory viral infections such as different species of influenza virus, and national vaccination program including other vaccines, preparedness of local health system, and pandemic COVID-19 curve stage in each country. Some of these confounders were studied or suggested to be evaluated by the previous workers [8], [14].

We did not involve number of COVID-19 cases in our data analysis due to two main reasons, first because of differences in accuracy levels of COVID-19 registry systems in different countries depending on available resources, second cause based on our hypothesis of immune protection offered by latent TB which affects the severity of the disease (COVID-19) rather than the incidence, that is, to say if patients have good immunity, the infection is expected to follow a mild course which may be represented by low mortality.

Conclusion

Tuberculosis burden has a distinctive crude effect on COVID-19 mortality through our assumption of immune activation theory which is somewhat close to BCG vaccination mechanism but with longer duration resulting in more effective protection against potential lethal nature of current coronavirus pandemic. Confounding factors should be evaluated through controlled clinical trials [26].

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Potential Antiviral Effect of Chloroquine Therapy against SARS-CoV-2 Infection

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Abstract

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has affected many countries with increasing morbidity and mortality. In the absence of an effective vaccine and medication, chloroquine may be a potential choice.

AIM: This study aims to explore the role of the possible antiviral effects of chloroquine against SARS-CoV-2.

MATERIALS AND METHODS: A systematic search of studies relating to the antiviral effects against coronaviruses was conducted between January 1, 1990, and up to May 26, 2020, for relevant studies using PubMed, Scopus, and Google Scholar.

RESULTS: A total of 174 articles were initially identified. Ninety-seven papers were removed for failing to address the aim of the study. Seventy-seven full-text articles were retrieved for eligibility analysis. Ten studies focused on general inhibition of viral replication, ten evaluated its effects on angiotensin-converting enzyme 2, 19 addressed the effects on alkalizing the cellular pH, 25 concentrated on the immunomodulatory effect, two assessed the potential effects on sialic acid, and 24 explored the therapeutic outcome.

CONCLUSION: Chloroquine has promising antiviral effects on SARS-CoV-2 at different levels.

Introduction

In December 2019, a cluster of reported chest infections among citizens in Wuhan, China, that were caused by a newly isolated β-coronavirus, which was initially named "2019 Novel Coronavirus" (2019-nCoV) on January 12, 2020, by the World Health Organization (WHO). While the WHO officially named the disease coronavirus disease 2019 (COVID-19) on February 11, 2020, the International Committee Coronavirus Study Group suggested naming it "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2) on the same day [1]. Human-to-human transmission of SARS-CoV-2 was observed mainly in close direct contact, a recent history of travel to Wuhan (72.3%) and among healthcare workers (3.8%) [2]. In contrast to COVID-19, SARS infection was relatively high among healthcare workers (33–42%), and almost similar contact rate (62–79%) [3], [4]. On March 12, 2020, the WHO declared COVID-19 to be a global pandemic and Italy was identified as the second most affected country with a higher case fatality rate (CFR) [5]. A week later, over 100 countries reported positive cases of COVID-19 with increased morbidities and mortalities [6]. Surprisingly, a recent time-delay adjusted estimation indicates that the COVID-19 CFR reached 20% in Wuhan compared to the cumulative number of deaths (5.6%) [7]. The rapid spread of the disease to the pandemic level, higher rate of morbidity and mortality, exhaustion of health facilities in the affected countries, non-availability of a vaccine, non-availability of approved medications for COVID-19, and previous reports of antiviral effects of chloroquine suggest chloroquine as a potential treatment option to modify the nature of the disease. The *in vitro* antiviral activity of chloroquine was observed in the late 1960s [8]. Recently, there has been a growing body of evidence during the COVID-19 pandemic that shows the antiviral efficacy of hydroxychloroquine alone or in combination with other medications [1], [9], [10], [11], [12].

The anti-inflammatory and immunomodulatory actions of chloroquine analogs have been reported in the treatment of viral infections and their pathologies [13]. Both chloroquine and hydroxychloroquine can negatively affect the growth of many different members of human coronavirus [14], [15]. Recently, a higher efficacy was reported in an *in vitro* study, favoring the control of SARS-CoV-2 infection [16]. Chloroquine analog in combination with other antiviral drugs is considered an effective option for therapy for viral diseases to avoid the interaction of P-glycoprotein and multidrug-resistance associated proteins in these viruses, which extrude medications from the cells and cellular organelles [17]. The results of chloroquine use in various *in vitro* studies demonstrated its effect on cellular pH [18], and it inhibits replication of several DNA and RNA viruses [19] and interferes with terminal glycosylation of the cellular receptor angiotensin-converting enzyme 2 (ACE2) [20]. Hence, chloroquine was recently used in the management of COVID-19 during the current pandemic outbreak [1], [9], [10], [11], [12]. Chloroquine has long been used as an antimalarial and anti-inflammatory agent. It has a reasonable degree of safety at a low price. For these reasons, we decided to conduct this study to explore the possible antiviral effects of chloroquine and the possible mechanism of action to improve our understanding of this drug and shed light on it for potential future studies.

Materials and Methods

A systematic search of studies relating to chloroquine's antiviral effect against coronavirus was performed between January 01, 1990 and up to May 26, 2020 using PubMed, Scopus, and Google Scholar. We used combinations of the following search terms: "Chloroquine," "hydroxychloroquine," "antiviral action," "mechanism" safety" efficacy" "COVID-19," and "SARS-CoV-2." The preferred reporting items for systematic review and meta-analysis guidelines were adopted, as illustrated in Figure 1 [21]. The electronic database search yielded 174 articles. Ninety-seven studies were removed for not addressing the aim of the study, duplication, lacking a proper citation, and not being within the period decided beforehand. Titles and abstracts were assessed to identify eligibility for full screening. Studies that employed acceptable quantitative and/or qualitative methods, including randomized controlled trials, observational studies (such as cross-sectional, experimental, and interventional studies), review articles, ideas, editorials, letters to the editor, and opinions were included in the study. All articles focusing on the potential possible antiviral effects of chloroquine, the mechanism of action and therapeutic outcomes were eligible for inclusion. Then, all relevant studies were selected and full-text manuscripts retrieved for assessment. The clinical opinions were critically appraised using the recommended checklist by McArthur *et al*. (2015) to focus on relevant articles [22]. The studies were grouped according to the primary aims, focusing on viral replication inhibition, chloroquine's action on ACE2, alkalization at the cellular level, chloroquine immunomodulatory effects, effects on sialic acid, therapeutic trials and studies that addressed more than one item. This enabled grouping of articles that focused specific targets and issues relevant to the study objectives and facilitated the retrieval of information.

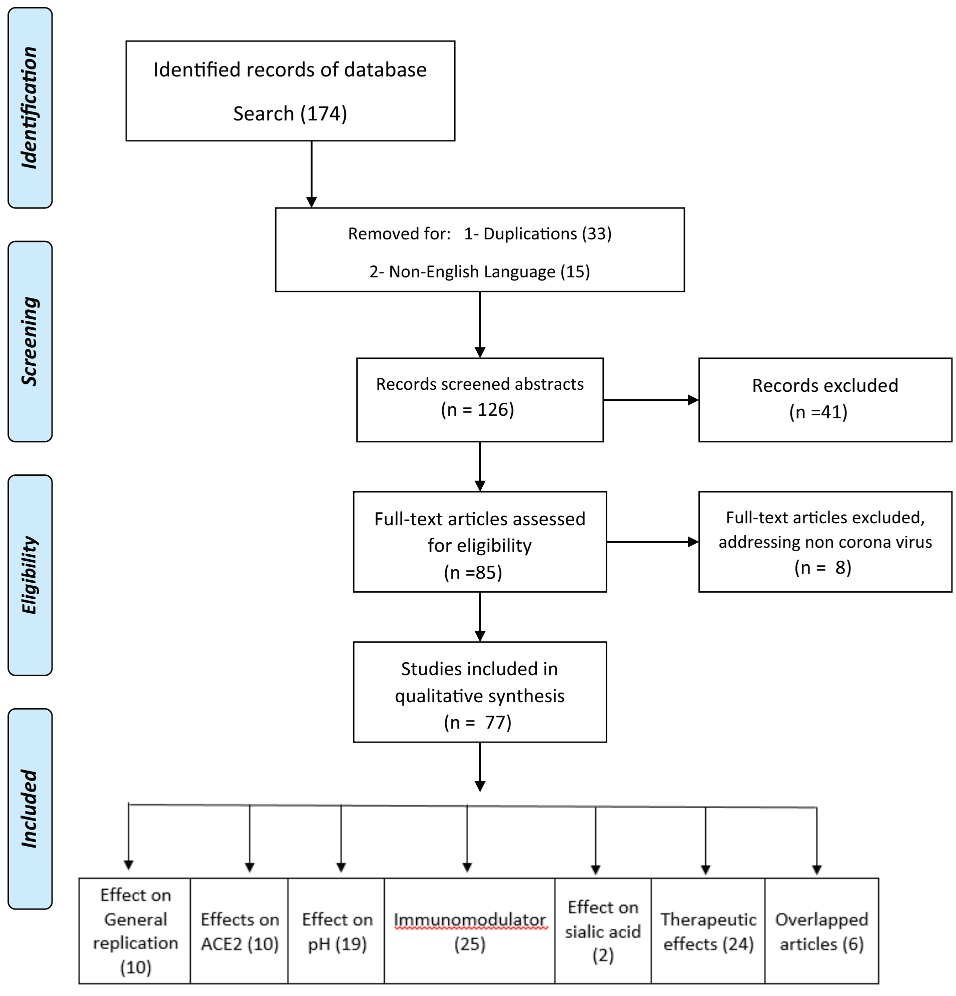

Figure 1: Flow chart of the study selection

Results

A total of 174 articles were initially identified. Ninety-seven studies were removed for not addressing the aim of the study, duplication, lack of proper citations, and poor use of language. After screening titles and abstracts, 77 full-text articles were retrieved for eligibility analysis. Ten studies focused on general viral replication inhibition [14], [19], [20], [21], [22], [23], [24], [25], [26], [27], ten evaluated its effects on ACE2 [13], [15], [28], [29], [30], [31], [32], [33], [34], 19 addressed the effects on alkalizing the cellular pH [13], [15], [31], [32], [33], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], 25 concentrated on chloroquine therapy as an immunomodulator [13], [16], [26], [37], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], two assessed the potential effects on sialic acid [70], [71], 24 articles explored the therapeutic outcome [1], [5], [15], [16], [20], [35], [68], [69], [72], [73], [74], [75], [76], [77], [78], [80], [81], [82], [83], [84], [85], and nine addressed more than one target [13], [15], [16], [26], [31], [32], [35], [33], [37].

Discussion

The review of articles indicates that chloroquine has broad-spectrum antiviral activities at different sites and levels. These properties have caused many researchers to conduct studies and explore their potential effects. Some studies have focused on the general inhibition of viral cycle replication without illustrating details. Chloroquine, widely promoted as an antimalarial and autoimmune disease drug, was recently shown to have a potential broad-spectrum antiviral effect that interferes with the viral replication cycle [23], [24]. This was supported by the outcome of many *in vitro* studies that documented the inhibitory effect on the replication of some coronaviruses in epithelial lung cell cultures [25], [26], a recombinant HCoV-O43 coronavirus [27], and MERS-CoV [86]. A recently published study pointed to the extended inhibitory effect on several DNA and RNA viruses, including most human coronaviruses [19]. In addition, many experimental studies on coronavirus proved that chloroquine had a negative effect at the replication level [14], [19], [20]. However, one study reported ambiguous outcomes [87].

ACE2 is another target for chloroquine's antiviral effect. ACE2 is found in the lower respiratory tract of humans and is a cell receptor for SARS-CoV that is responsible for its replication and pathogenesis [28]. The virion glycoprotein on the surface of coronavirus uses the ACE2 receptor on the surface of human cells as a recognition site to gain access and facilitate both cross-species and human-to-human transmission [29], [35]. Bronchoalveolar lavage fluid is used to diagnose COVID-19 when the presence of ACE2 is indicated in the lower respiratory tract [30]. In *in vitro* studies, chloroquine appears to interfere with terminal glycosylation of the cellular receptor ACE2 to inhibit virus-receptor binding and ultimately abrogate the infection [13], [31]. Chloroquine's potent anti-SARS-CoV effects *in vitro* have been documented in many clinical trials [15], [35], [32], [33]. ACE2 as a site of recognition for coronavirus raises concerns about its interaction with ACE inhibitors and the outcome of coronavirus disease. However, a recently published study confirmed that ACE inhibitors do not inhibit ACE2 because ACE and ACE2 are different enzymes, and no data suggest that ACE inhibitor or Angiotensin II Type 1 receptor blocker therapy facilitates coronavirus entry by increasing ACE2 expression in both animal and human subjects [34].

Chloroquine can negatively affect a pre-entry step of the viral cycle by interfering with viral particles binding to their cellular cell surface receptor by blocking quinone reductase 2, which facilitates the biosynthesis of sialic acids. Sialic acids are present on cell transmembrane proteins as important components of ligand recognition [70], [71]. Interference with sialic acid biosynthesis might represent part of chloroquine's broad antiviral spectrum against coronaviruses that depend on sialic acid moieties as receptors [71].

Changing the intracellular pH is chloroquine's greatest potential antiviral effect because coronavirus replicates in acidic environments. In fact, coronavirus cell entry is achieved through the endolysosomal pathway that depends on a certain internal pH [36]. Increasing endosomal pH promotes chloroquine as a potential powerful antiviral agent. This will affect the transduction of pseudotype viruses decorated with SARS-CoV spike protein and will affect terminal glycosylation of the cellular receptor ACE2 [15], [32], [33], [35]. This may be explained by *chloroquine*'s ability to diffuse spontaneously and rapidly across the membranes of cells and organelles to acidic cytoplasmic vesicles such as endosomes, lysosomes, or Golgi vesicles to alter their pH [13]. This will disturb the activity of several enzymes, including those essential for proteolytic processing and post-translational modification of viral proteins, which will prevent the fusion of the virus to the cell membrane [37], [38], [39]. Its effect may extend to inhibit some vital steps, such as nucleic acid replication, glycosylation of viral proteins, new virus particle transport, virus assembly, virus release to achieve its antiviral effects [39], and other as-yet poorly understood antiviral activity mechanisms [31], [39].

Chloroquine analogs prevent viral entry and replication processes into the cytoplasm of susceptible cells by neutralizing acidic pH in endosomes to abrogate the infections [37], [40], [41], [42], [43], [44] because low pH is essential for fusion of the virus and endosomal membranes to release the viral SARS-CoV genome into the cytosol [45]. In non-human coronaviruses, the intracellular site of coronavirus budding is influenced by the localization of its membrane M proteins that accumulate in the Golgi complex beyond the site of virion budding [46]. This was supported by a recent report that showed that the C-terminal domain of the MERS-CoV M protein contains a trans-Golgi network localization signal [47]. In addition, it affects the virus maturation process by impairing the proper maturation of the viral protein [48].

Chloroquine is an antimalarial and autoimmune disease medication. Its immunomodulatory effects encourage scientists to evaluate its performance on viruses. It enhances the immune response by promoting the export of soluble antigens into the cytosol of dendritic cells and directing human cytotoxic CD8+ T cell responses against viral antigens [49]. Furthermore, it organizes the cross-presentation of non-replicating virus antigens by dendritic cells to CD8+ T-cells migrated to lymph nodes at the site of infection and ultimately establishes a broad protective immune response [50]. Chloroquine inhibits nanoparticle endocytosis by resident macrophages; this effect is dose related [51], [52]. Furthermore, chloroquine prevents the fusion of lysosomes, which is likely to interfere with upstream endocytic trafficking by blocking the effective transport between cellular organelles and the cell membrane [53]. However, one study reported no potential effect *of* chloroquine on primary human monocyte-derived macrophages and dendritic cells in MERS-CoV infection [53]. Chloroquine is a well-known immunomodulatory drug that can mediate an anti-inflammatory response [37]. This effect has been observed in the treatment of viral infections and associated pathologies [13], [16]. Consequently, chloroquine analogs block the release of several cytokines, chemokines, or mediators that are blamed for the severity of viral infections. Therefore, inhibition of endosomal acidification by chloroquine therapy may be promoted as a potential therapeutic target for viral infections and associated pathologies. Cytokines, chemokines, and the activities of several host endosomal proteases depend on endosomal-lysosomal acidification [54], [55].

One of the cytokines strongly implicated in viral pathologies is tumor necrosis factor-a (TNF-α), which activates macrophages to potentiate the production of mediators that facilitate both the permeability and infectivity of endothelial cells [56], [57]. Chloroquine's key effect is its prevention of macrophage activation and inhibition of TNF-a secretion from various cells at clinically relevant concentrations [13], [37], [58] inhibition of TNFα mRNA expression [59], [60], [61] and reduction of interleukin (IL-1 and IL-6) cytokines that are released from monocytes and macrophages [62]. Chloroquine also adopts another pathway to inhibit TNFα production by disrupting cellular iron metabolism [63]. Moreover, it blocks the conversion of pro-TNF into soluble mature TNFα molecules, which modifies the immune response [64]. Chloroquine analogs enhance immune activation in viral infection and reduce systemic T cell activation [65], [66]. Chloroquine inhibits IL-1β mRNA expression in T helper-1 (THP-1) cells and reduces IL-1β production [58]. Likewise, it affects the immune system through cell signaling and regulation of proinflammatory cytokines by inhibiting phosphorylation of p38 mitogen-activated protein kinase in THP-1 cells and caspase-1 [59]. Viruses frequently require the phosphorylation step to replicate [26], [67].

Chloroquine blocks toll-like receptor-mediated activation of plasmacytoid dendritic cells and myeloid differentiation primary response gene 88 signaling through three pathways. First, it decreases the levels of the downstream signaling molecules IL-1 receptor-associated kinase 4 and IFN regulatory factor 7. Second, it inhibits IFN-a synthesis and blocks the negative modulators of T-cells such as indoleamine 2,3-dioxygenase. Third, it promotes downstream signaling of programmed death-ligand 1 [68]. Clinically, both hydroxychloroquine and chloroquine have immunomodulatory effects that impair the increase in immune factors that cause a cytokine storm, which is followed by multiorgan failure and potentially death. Therefore, early treatment with chloroquine can abort or modify these serious complications [41], [69].

Many clinical trials have assessed the therapeutic efficacy of chloroquine against coronavirus. In an *in vitro* study, chloroquine had broad-spectrum antiviral effects in the control arm of SARS-CoV-2 infection [16]. Likewise, in a mouse model, it maintained a higher efficacy against coronavirus [15], [72]. Interestingly, chloroquine showed potent inhibitory effects on the treated primate cells before and after exposure to the virus, which shows both prophylactic and therapeutic advantages [31]. At present, many clinical trials are testing chloroquine as anti-COVID-19 therapy [73]. Chloroquine was recently promoted as a potential possible option for treating patients diagnosed with novel coronavirus pneumonia with a successful treatment rate, shortened hospital stay, and improved patient outcome. The recommended dose of chloroquine phosphate tablets was 500 mg twice per day for 10 days for mild, moderate, and severe cases of novel coronavirus pneumonia, providing that patients had no contraindications [74]. Preliminary reports from China suggest that approximately 100 infected patients treated with chloroquine experienced a more rapid symptomatic and radiological lung computed tomography improvement in addition to a shortened hospital stay and recovery period compared with control groups [1], [74], [75], [76]. This would reflect the first successful story for the use of chloroquine in humans to treat an acute viral disease and supports research into its potential as a therapy option during the current COVI-19 outbreak [77]. Based on this promising result, chloroquine has been included in the list of trial drugs in the guidelines for the diagnosis and treatment of COVID-19 released by the National Health Commission of the People's Republic of China[74], [76]. In addition, the Dutch Centre of Disease Control and the Italian Society of Infectious and Tropical Disease (Lombardy section) recommend chloroquine for patients with COVID-19 [5], [20]. In light of the urgency, the absence of a vaccine and effective medications and the pressure health-care systems face to save lives during the COVID-19 pandemic, many countries, including the United States and France, have suggested using chloroquine to manage patients with COVID-19 under certain circumstances [77], [78], [79], [80]. In a small sample size study that recruited 36 subjects, hydroxychloroquine therapy was significantly associated with a reduction in viral load and viral shedding period and worked synergistically with azithromycin against COVID-19 [81]. Likewise, another study, evaluating 80 cases with a mild presentation, demonstrated rapid clearance of the virus and shortened the mean hospital stay to 5 days with combination therapy of hydroxychloroquine and azithromycin: Progressively negative results of nasopharyngeal PCR assay for the virus were documented at day 7 (83%) and day 8 (93%). In addition, 97.5% of virus cultures from patient respiratory samples were negative on day 5 [77]. Similarly, chloroquine prevented exacerbation of pneumonia with radiological improvement and shortened the course of the disease [1]. Interestingly, in an *in vitro* study on SARS-CoV-2, a similar synergistic effect was obtained in combination therapy of hydroxychloroquine and azithromycin, as both reduce the acidity of the lysosome to impair viral replication [83]. Chloroquine efficacy may support the observational thought that COVID-19 infections are highly pandemic in countries where malaria is the least pandemic and are the least pandemic in nations where malaria is highly pandemic [10]. On the other hand, hydroxychloroquine therapy for patients with COVID-19 infection was associated with a high risk of QT prolongation, and greater changes in QT were observed with concurrent treatment with azithromycin [84], [85] and drug-induced torsades de pointes [85]. Hydroxychloroquine should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency to prevent hemolytic anemia. Both hydroxychloroquine and chloroquine have narrow therapeutic indices for chloroquine and are associated with gastrointestinal symptoms, retinopathy, deafness/tinnitus, and life-threatening toxicity (cardiomyopathy, arrhythmias, and methemoglobinemia) [88]. Recently published data, pointed to increase frequency of ventricular arrhythmias associated with chloroquine therapy for COVID -19infection [89]. Hence, vigilance and cardiac monitoring are recommended to balance the risks and benefits.

Limitations of the study

This study was conducted by one researcher and used only PubMed, Scopus, and Google Scholar databases and timeframes, and some valuable data were not included. Another limitation is related to the article selection criteria that were used.

Conclusion

Chloroquine has a broad-spectrum range of documented antiviral activities and immunomodulators, which is supported by recent limited fruitful clinical trials in humans. In addition, it has a long history of use, anti-inflammatory advantages, safety in reasonable dosages, and low price. Its antiviral effects should be further assessed in large clinical trials in the near future.

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Convalescent Plasma Therapy in Effort of Weaning from Mechanical Ventilation Using Music Stimulation in Severe COVID-19 Patients

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Abstract

Nowadays, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or CoV disease of 2019 (COVID-19) infection is a big threat to global health and becomes a global pandemic. The exact treatment for this disease is still an on-going experiment. Meanwhile, there are more people infected by this disease, leading to severe acute respiratory syndrome (SARS). COVID-19 patients with severe clinical symptoms may need mechanical ventilation. These patients at the same time, struggle with the infection and also the effort to wean from the ventilation. Weaning failure commonly occurred in patients with severe respiratory disease. In this article, we discuss the use of convalescence plasma therapy and the benefit of music stimulation for weaning from mechanical ventilation in COVID-19 patients.

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Introduction

Since December 2019, the epidemic of SARS-CoV-2 has rapidly spread worldwide. Originating in Wuhan, China, this disease has affected hundreds of nations within 4 months. The outbreak of SARS-CoV-2 has become a major concern all over the world [1]. Pneumonia that induced by the SARS-CoV-2 is named CoV disease 2019 (COVID-19). As it has affected thousands of people, the World Health Organization has declared that this disease is a pandemic [2].

Lack of study and knowledge about further treatment has led to many deaths due to the severity of the symptom and comorbid. The efficacy of recent treatment is still on clinical evaluation and investigation, due to there are no approved specific antiviral agents, it is an urgent need to look for an alternative treatment strategy for COVID-19. In order to prevent death among the severe COVID-19 patients [3].

Severe pneumonia caused by human CoV was characterized by rapid viral replication, massive inflammatory cell infiltration, and elevated pro-inflammatory cytokines or even cytokine storm in alveoli of lungs, resulting in acute pulmonary injury and acute respiratory distress syndrome (ARDS). COVID-19 is a type III hypersensitivity reaction due to antigen-antibody immune complex deposition with complement activation [4], [5]. Recent studies on COVID-19 demonstrated that the lymphocyte counts in the peripheral blood were remarkably decreased and the levels of cytokines in the plasma from patients requiring intensive care unit (ICU) support, including interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, and granulocyte-macrophage colony-stimulating factor, were significantly higher than those who did not require ICU conditions [6], [7].

Recently, a Group of study regarding the use of convalescent plasma (CP) therapy as one of COVID-19 treatment. Are still on going research and need to be tested tin severe COVID-19 patients. As we know, CP therapy is classic adaptive immunotherapy and has been applied as a treatment of many infectious diseases. This therapy has been acknowledged more than one century. In 2003, this therapy had been used as a treatment in SARS patients (n = 80) at Prince Wales Hospital, Hong Kong. It had been reported that this therapy demonstrated clinical deterioration despite treatment with methylprednisolone and most of the patients demonstrated good clinical outcome, associated with there was no adverse effect reported during the plasma infusion [8], [9], [10].

In association of the clinical symptom severity and comorbid disease, there were many patients experience the need of mechanical ventilation. As many of the patients experience mechanical ventilation, most of patient having a difficulty in the effort of weaning from mechanical ventilation. This condition was believed related to the dysfunction of the brain during the ventilation. There is a complex interaction between lung and brain in critically ill patients who experienced mechanical ventilation. This review will discuss the effect of music stimulation in weaning from mechanical ventilation among COVID-19 patients.

CP Therapy for COVID 19

As we know, until now, there are still no approved specific antiviral agents for novel CoV disease. Many clinicians and scientists are trying to find an alternative treatment for severe COVID-19 patients, considering the mortality rate still increasing. CP or immunoglobulin is the last resort to improve clinical outcome and survival rate of patients SARS-CoV-2. This therapy known as classic adaptive immunotherapy and had been known for many infectious diseases more than one century. Driven by passive immunity driven bay CP can provide neutralizing antibodies (NAbs) that restrain the infection [11]. SARS-CoV 2 infection induces IgG antibodies production against nucleoprotein that can be detected at day 4 after the onset of disease and with seroconversion at day 14. Shen *et al*. showed that recovered donors from COVID-19 infection had specific antibody titers ranging between 1.800 and 16.200 and NAbs titers were between 80 and 480. The plasma obtained from the donors and transfused in the recipients on the same day leads to viral load decreased. The presence of NAbs in the recipients played a key role in the restriction of viral infections. This study showed that the titers of NAbs in patients infected with SARS-CoV-2 were low before day 10 post-disease onset and then increased, with a peak 10–15 days after disease onset, remaining stable thereafter in all patients [12], [13].

This treatment had been recommended by WHO as an empirical treatment during the outbreak of Ebola virus in 2014. Moreover, it was also successfully used in the treatment of SARS, Middle East respiratory syndrome (MERS), and H1N1 pandemic in 2009 with good and satisfactory clinical outcomes and safety. This treatment associated with the condition of most patients of SARS-CoV-2 whose continue to deteriorate despite treatment with a corticosteroid. Although, according to WHO, the management of COVID-19 mainly focused on infection prevention, case detection and monitoring, and supportive care. Until now, May 2020, no specific treatment is recommended due to the lack of study and clinical evidence [14].

CP therapy was obtained from recovered patients who had established humoral immunity against the virus, contains a large quantity of NAbs of the virus, and eradicates the pathogen from blood circulation and pulmonary tissues. However, the CP therapy was unable to improve the survival in Ebola virus disease due to the absence of data of NAb titration for stratified analysis. Since the virological and clinical characteristics among MERS and SARS were similar to COVID-19, it is suggested that CP therapy might be an option for alternative treatment for COVID-19 patients. Patients who have recovered from COVID-19 with a high NAb titer may be a valuable donor source of CP [15].

This CP therapy had been applied for COVID-19 patients in China on January 2020, with 10 participants of severe COVID-19 patients. This trial using one dose of 200 ml CP transfusion was well tolerated. Among those patients, there are three patients received mechanical ventilation and the others received high flow and low-flow nasal cannula oxygenation. From this trial, after treatment with CP, two patients were weaned from mechanical ventilation to high-flow nasal cannula. Moreover, the clinical symptoms significantly improved within 3 days, followed by the rapid neutralization of viremia [16].

A case series by Shen *et al*., from January 2020 to March 2020, evaluates the benefit of CP therapy in five critically ill patients with laboratory-confirmed COVID-19 and ARDS with severe pneumonia and mechanical ventilation. All five were treated with CP. This study suggested that viral load declined within days of treatment, and the clinical symptoms were improved. Among those patients, four of them who had been receiving mechanical ventilation and ECMO no longer required respiratory support after plasma transfusion [17].

Effort of Weaning from Mechanical Ventilation in COVID-19 Patients

In severe COVID-19 patients, most of the cases required critical care management, including mechanical ventilation. Mechanical ventilation is the most common life-sustaining therapy for COVID-19 patients in ICU. It temporarily replaces spontaneous breathing in COVID-19 patients who suffered from respiratory failure [18].

Many patients who receive ventilator support are "fighting their ventilator" at some point of their therapy. This condition, referred to as "patient-ventilator asynchrony," described the fact that a mechanically ventilated patient keeps a spontaneous respiratory activity and this activity is not in phase with the machine.

This usually happened during awakening from sedation or during ventilator weaning [19].

Weaning defined as the withdrawal of mechanical ventilation to re-establish spontaneous breathing. Weaning covers the entire process of liberating the patient from mechanical support and from the endotracheal tube. Weaning comprises 40–50% of the total duration of mechanical ventilation. Approximately 70% of patients in intensive care successfully weaned without difficulty on the first attempt. While other patients experience more difficulty or prolonged period of weaning, this may lead to a poorer prognosis. Some issue was considered as the caused, but the most possible cause is the weakness or fatigue of the diaphragm and the accessory muscle of inspiration that leads to the failure of weaning from mechanical ventilation. Another cause is considered that mechanical ventilation affects the diaphragmatic structure and functions, known as ventilator-induced diaphragmatic dysfunction, related to the changes in myofiber length and rapid atrophy [20].

Long duration of bed rest and immobility in critical ill patients may result in profound physical deconditioning. These effects may be induced by inflammation, lack of glycemic control, and pharmacological agents. The incidence of skeletal muscle weakness in the ICU is observed in 25% of ventilated patients. Inspiratory muscle training is a technique that loads the diaphragm and accessory inspiratory muscle to improve strength and endurance [20].

During the pandemic of COVID-19, due to the severity of clinical symptoms can lead to respiratory failure, many patients required mechanical ventilation. Weaning from mechanical ventilation is very essential in the care of critically ill intubated patients, especially those who suffered from SARS-CoV-2. This process related to the entire process of liberating the patient from mechanical support and from the endotracheal tube, needs the involvement of the good function of the brain as well. Critically ill patients develop neuropsychological disturbance. Neurocognitive sequelae frequently occurred among critically ill patients [20].

Lung-brain Interactions in Mechanically Ventilated COVID-19 Patients

COVID-19 patients with severe clinical symptoms are associated with high morbidity and mortality rate. Those patients may require mechanical ventilation. Some of them survive the condition while others may not survive from this pandemic. Those patients who survive and still receive mechanical ventilation may suffer neuropsychological alterations such as memory impairment. Although mechanical ventilation is important life support for many critical patients, especially in COVID-19 patients with a severe symptom, it is not without complication. It is intrinsically able to be worsening with possible spread to other organs, including the brain, and ultimately leading to multiorgan failure [21].

Studies described regarding mechanism implicated in lung-brain interaction during mechanical ventilation have been less investigated. It suggested that cognitive impairment seen in patients who received mechanical ventilation [22]. The etiology of these neurocognitive deficits is probably a multifactorial cause such as hypoxemia, the use of sedative and/or analgesics, hypotension, altered regulation of blood glucose levels, the duration of mechanical ventilation usage, the length of stay in the ICU, and the presence of confusional syndrome [23]. Many clinical studies had shown that mechanical ventilation may induce a biological response through infiltration of monocytes and macrophages, the release of mediator inflammation. This mechanism may lead to lung damage. Some studies also suggested that there is a relationship between hypoxia and hippocampal damage since hippocampus is the brain structure related to learning and memory capacity, it is also known to be vulnerable to hypoxia. There is also evidence that ARDS can induce structural alterations in the hippocampus. These studies support the existence of a brain-lung communication axis associated with the release of catecholamines, neurokinins, and neuropeptides [24].

During mechanical ventilation, the lung generates information through the stimulation of the mechanoreceptors or chemoreceptors, which reaches the central nervous system (CNS) through other routes. By this mechanism, the brain responds by altering the

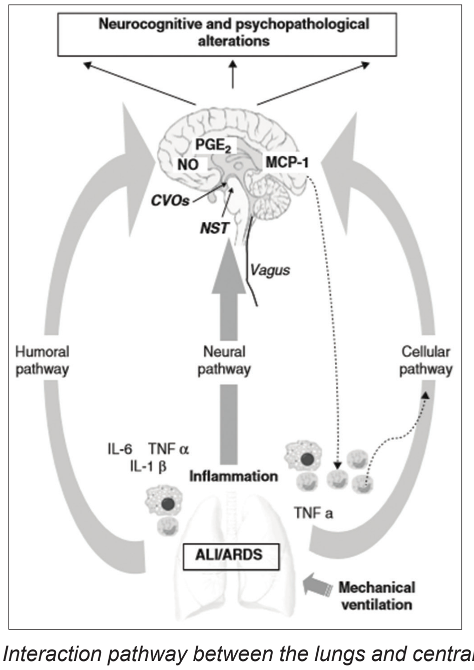

Figure 1. Interaction pathway between the lungs and central nervous system (CNS) during mechanical ventilation. The CNS receives information from the peripheral through three pathways: Humoral, neural, and cellular pathway [26], [27]

permeability of the blood-brain-barrier or by modifying cerebral blood flow. Communication pathways between peripheral and CNS are illustrated in Figure 1. First pathway is the humoral pathway, through inflammatory mediators such as IL-6, TNF-α, and IL-1β, by the recruitment of peripheral monocytes or macrophages, may directly reach the brain [25].

COVID-19 infection, particularly, has a very close relation to respiratory distress since many of the patients suffer from respiratory failure and require mechanical ventilation. In COVID-19, patients who received mechanical ventilation considered to have a similar mechanism between lung and brain communication pathway during mechanical ventilation. An inadequate ventilation strategy may induce the release of certain inflammatory mediators or metabolites into the bloodstream, which can be detected by the CNS. An experimental study by Quilez *et al*. evaluated neuronal activation in a model of mechanical ventilation damage in rats. The lungs and brain share the same inflammatory mediators, and once these are released into the bloodstream, they can also make contact with the brain by interacting with specific CNS receptors. This mechanism involves an active transport mechanism which leads to the release of prostaglandin E2 and nitric oxide [24].

Possibility of Weaning Failure in COVID-19 Patients

Weaning is an essential process, especially in severe COVID-19 patients who receive mechanical ventilation and involve a series of stages in the process of care. The weaning process involves a gradual decrease in ventilator settings as a patient's respiratory status improves, leading to termination of mechanical ventilation support. For some patients, weaning may be difficult due to the patients cannot tolerate independent respirations when the artificial airway is removed [25]. Extubation failure is the inability to sustain spontaneous breathing after removal of the artificial airway with the need for re-intubation within 24–72 h. The incidence rate of extubation failure is reported to be 26–42%. This failure associated with a high mortality rate. From a study by Coplin *et al*., the mortality rate was 12% if there was no delay in extubation and 27% when extubation was delayed [28].

Music Stimulation during Mechanical Ventilation and Weaning in COVID-19 Patients

To do a lifesaving intervention, one of the management is the initiation of mechanical ventilation to treat acute respiratory failure. This involved the administration of numerous sedative and analgesic medication which can prolong ventilation and increase the length of ICU stay [29]. As the patients recover from acute respiratory failure, they can be weaned from ventilator support. There are many factors associated with the success of weaning, such as respiratory muscle strength, adequate respiratory drive, acid-base balance, neurological status, and psychological readiness [20]. Extubation failure can lead to ventilator-associated pneumonia, airway trauma, increased costs, and higher mortality rates [30].

Some studies suggested than a number of non-pharmacological interventions have been shown to be an advantage for anxiety symptoms in ICU patients, this intervention such as music intervention. As we know, in ventilated patients, some of the patients may suffer anxiety during mechanical ventilation. Decreasing anxiety believed to be helpful in promoting ventilator weaning, especially in COVID-19 patients. Music is a non-pharmacological intervention that integrates physiological and psychological components to reduce stress and anxiety and ultimately promotes overall conditions [31], [32], [33].

A study held by Hunter *et al*. and Lee *et al*. had demonstrated that music is an effective complement in a certain condition of weaning difficulty by decreasing anxiety. The duration, frequency, and timing of music intervention approximately at least 30 min music-listening session once per day, from 1 day to up to 30 days. The following music programs were used as a preference: Western classical music, Chinese classical music (e.g., bamboo flute, rain, and tears), and music of natural sounds. All of the music had slow beat (60–80 beats/min) that corresponds to a normal heart rate and thought to be relaxing for the patients [32], [33], [34].

Conclusion

Based on our findings in this article, in severe and critically ill of COVID-19 patients, most patients urgently required mechanical ventilation. One of the problems regarding this management is the weaning failure from mechanical ventilation. Recently, many studies develop other treatment strategies for COVID-19 patients. One of the effective treatments is CP therapy. In order to decrease the weaning failure rate in critically ill of COVID-19 patients, the author suggests the use of CP therapy priory the weaning process.

Regarding the possibility of weaning failure, we suggest to give music stimulation to decrease the psychological symptoms for patients undergoing mechanical ventilation. There are studies suggested that music intervention may lead to improve patients conditions and help to reduce patients' anxiety levels.

These anxiety levels can be measured by indicators of blood pressure, heart rate, and respiration rate. Some study also measures the serum cortisol levels and stated that patients that received music intervention had lower serum cortisol levels. We hypothesize that due to the long duration of mechanical ventilation in COVID-19 patients and the possibility of weaning failure, it may affect the hippocampal function and may lead to cognitive impairment in few years ahead. Further study regarding the effect after the long duration of mechanical ventilation in COVID-19 patients are required to be held, In order to prevent further cognitive deficits by among patients who had experienced mechanical ventilation. Developing an early screening of cognitive functions.

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The Effect of Knowledge and Attitude toward Coronavirus Disease-19 Transmission Prevention Practice in South Sumatera Province, Indonesia

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Abstract

BACKGROUND: Globally, the number of coronavirus disease (COVID)-19 confirmation cases shows an exponential increase. In South Sumatera province, Indonesia, reported positive confirm cases in March 2020 as many as 5 cases, and within 2 months there was an increase to 196 times (982 cases) confirmation cases in May 2020. Transmission prevention practice is essential to inhibit the spread of COVID-19 and reduce the number of cases. Based on past studies, COVID-19 transmission prevention practice is affected by community characteristics, level of knowledge and attitudes, but there is no study conducted in Indonesia.

AIM: The purpose of this study was to determine the effect of knowledge and attitudes toward COVID-19 transmission prevention practice.

METHODS: The study was conducted with cross-sectional study approach. The sample is the people lived in South Sumatra who filled out the questionnaire through the Google form application, total 1187 people. Data were collected by snowball method during the period of April 18–30th 2020. Data were analyzed statistically using multiple logistic regression tests.

RESULTS: The result of this study found that four variables significantly affected COVID-19 transmission prevention practice. They were occupation (odds ratio [OR]: 1.128; $p < 0.01$), gender (OR: 1.309; $p < 0.05$), knowledge (OR: 1.782; $p < 0.01$), and attitude (OR: 2.059; $p < 0.01$).

CONCLUSION: The dominant factor affecting COVID-19 transmission prevention practice is attitude and knowledge. Hence, it is necessary to increase community knowledge about COVID-19 better to change people's attitudes toward COVID-19 transmission prevention so they can implement good COVID-19 transmission prevention practice.

Introduction

Coronavirus (CoV) disease (COVID)-19 is a new infectious disease originating from Wuhan China caused by the CoV. The incubation period for COVID-19 is estimated to be between 2 and 14 days, depending on the age and immunity of the patient. This disease can spread to all age groups, especially in the elderly, and have a history of chronic illness. Common symptoms such as fever ≥38°C, dry cough, and shortness of breath are increasingly dangerous but in some cases there are no symptoms. This disease can spread through small droplets from the nose or mouth patient when coughing or sneezing. The droplet then falls on the surrounding objects. If someone else touches an object that has been contaminated with the droplet, then that person touches the eyes, nose, or mouth (facial triangle), then that person can be infected with COVID-19. The diagnosis of COVID-19 can be determined by examining a blood sample, throat swab test (sputum), or chest content [1], [2].

Globally and nationally, the number of COVID-19 confirmation cases shows an exponential increase. COVID-19 was first reported in Indonesia in early March 2019 in Jakarta, and by the end of April, it had spread to 34 provinces with 72 districts/cities with local transmission. Within 2 months, the number of cases increased to 10,118 cases with a CFR of 7.8%. At the end of May, there was a two-fold increase to 26,473 cases spread across 129 local transmission districts/cities [3], [4].

In South Sumatra, Indonesia, at the end of March 2020, the number of COVID-19 cases was reported as many as 5 cases, which within 2 months increased to 196 time to 982 confirmed cases at the end of May [4].

Transmission and spread of COVID-19 are very fast so prevention efforts need to be done. Referring to the WHO recommendations, the prevention of transmission from the community side is done by (1) implement Clean Healthy Practice especially washing hands using soap with running water, (2) stay at home, (3) social distancing/physical distancing, (4) use a mask when leaving the house, and (5) frequently clean the surface of objects that are frequently touched [5], [6], [7].

The South Sumatera Provincial Government since the beginning has carried out health promotion to increase public knowledge about COVID-19 so that the community is expected to be able to comply with COVID-19 transmission prevention practice. However, the facts show a significant increase in the number of cases in South Sumatera. For this reason, a study is needed to determine the level of knowledge, attitudes, and practice of the public about COVID-19 and its influence on COVID-19 transmission prevention practice.

Approach of knowledge attitude practice model, its used to find out the relationship of knowledge, attitudes, and practice often used in studies of family planning and population has been a long time. Based on the knowledge, attitude, and practice model, it can also be known the effect of knowledge and attitudes toward practices directly and also the relationship of attitudes directly toward practice [8]. The approach knowledge, attitude, and practice model is an appropriate model for obtaining information about the relationship between knowledge, attitudes, and specific practices in specific populations [9].

Knowing the level of knowledge, attitudes, and practice as well as the possible risk factors can help to predict outcomes that will occur in health practice planning [10]. Public practice of the COVID-19 transmission prevention is very influential in decreasing cases that have now become a pandemic in 215 countries in the world [11], [12].

The purpose of this study was to determine the effect of knowledge, attitudes toward COVID-19 transmission prevention practice. By knowing this, appropriate interventions can be carried out to increase the positive practice of the community toward the prevention of COVID-19 transmission in Indonesia, particularly in South Sumatera Province.

Methods

Research design

This research was conducted with a quantitative method through a cross-sectional study approach. The population is all people who live in South Sumatra Province who use social media or WhatsApp and can access the Google form application. The research sample was taken from all respondents who filled out a questionnaire through Google form totaling 1187 people. The sampling technique was carried out through online responses because during the COVID-19 pandemic it was not possible to descend directly into spaciousness.

Research procedure

Data collection techniques are carried out by distributing questionnaires in a snowball through the Google form application that is shared on social media Facebook and WhatsApp during the period from April 18, 2020, to April 30, 2020. Preparation of the questionnaire based on COVID-19 Prevention and Control Guidelines issued by the Ministry of Health Republic of Indonesia [13].

Research variable

The data collected consist of dependent variables and independent variables. The dependent variable is COVID-19 transmission prevention practice. The independent variables are: (1) Respondent characteristics (location of residence, occupation, level of education, gender, and age); (2) knowledge of COVID-19; and (3) attitude toward COVID-19.

All numerical scale variables are grouped into categorical scales. Residential locations are categorized into two categories: District or city. Occupation is categorized into five namely: Civil servants/Army/Police; health workers; private; housewife; and student/student. Education level is categorized into high (high school graduation); middle (high school graduation); and low (not yet graduated from high school). Genders are categorized as male and female. Age is categorized into five groups 13–16 years, 17–25 years, 26–45 years, 46–65 years, and >65 years.

While the variables of knowledge, attitudes, and practices use the median cutoff point by grouping: good (>median); and poor (≤median). Respondent's knowledge of COVID-19 evaluated based on symptoms, transmission, and prevention which were assessed with 14 questions. The attitude of the respondents was assessed with eight questions. The practice of respondents was assessed with eight questions.

Data analysis

Data analysis was performed using parametric statistics, namely, univariate, bivariate, and multivariate. Univariate analysis to describe the frequency distribution and percentage of each variable: Characteristic respondens, knowledge, prevention practice and attitudes. Bivariate analysis to see the relationship of each independent variable with the dependent variable using Chi-squared test. Model candidate selection included in multivariate analysis is a variable that has a $p < 0.25$ bivariate test results. Multivariate analysis was performed with a multiple logistic regression test using SPSS Version 26.

Results

In Table 1, it can be seen that majority of the subject lives in urban areas (58.9%), civil servant/Army/

Table 1: Characteristic of study subject

Characteristic	Frequency (%)
Resident	
City	699 (58.9)
District	488 (41.1)
Occupation	
Civil servants/Army/Police	425 (38.5)
Health workers	84 (7.1)
Private	392 (33.0)
Housewife	70 (5.9)
Student/college student	216 (18.2)
Education	
Low (≤ middle school)	51 (4.3)
Intermediate (finish high school)	181 (15.2)
High (> High school)	955 (80.5)
Gender	
Male	472 (39.8)
Female	715 (60.2)
Age groups (year)	
13–16	60 (7.2)
17–25	246 (20.7)
26–45	659 (55.5)
46–65	217 (18.3)
>65	5 (0.4)

Police occupations (38.5%), high education levels from Diploma to doctoral graduates (80.5%), gender women (60.2%), and age of youth (92.4%).

In Table 2, it can be seen that most subject have a good level of knowledge (55.3%), good attitude (69.6%), and good COVID-19 transmission prevention practice (54.6%).

Table 2: The knowledge, attitudes, and COVID 19 transmission prevention practice of study subject

Variable	Frequency (%)
Knowledge	
Good	656 (55.3)
Poor	531 (44.7)
Attitude	
Good	826 (69.6)
Poor	361 (30.4)
Practice	
Good	648 (54.6)
Poor	539 (45.4)

In Table 3, it can also be seen that most subject get information from print media, electronic media, social media, friends, and family (60.0%).

Table 3: Source information of study subject

Category	Frequency (%)
Print media, electronic media, social media, friend, and family	712 (60.0)
Electronic media, social media, friend, and family	149 (12.6)
Electronic media and social media	70 (5.9)
The other source	256 (21.6)

Based on Chi-square test, in Table 4, it can also be seen that the largest proportion of COVID-19 transmission prevention practices is in all categories for each independent variable, namely, (1) health workers (61.9%), (2) higher education level (56.1%); (3) female (57.8%); (4) age group 46–65 years old (63,6%); (5) good knowledge (62.8%); and (6) good attitude (61.3%). The results of the bivariate analysis showed that there were six independent variables, namely, occupation type, level of education, gender, age groups, level of knowledge about COVID-19, and attitudes toward COVID-19 affected COVID-19 transmission prevention practices ($p < 0.05$).

The final analysis results of the multiple logistic regression test showed that four variables are occupation (OR: 1.128; $p < 0.01$), gender (OR: 1.309; $p < 0.05$), level of knowledge (OR: 1.782; $p < 0.01$),

Table 4: Chi-square test results

Variable	Preventive practice (%), n = 1187		p-value
	Good	Poor	
Resident			
City	392 (56.1)	307(43.9)	0.218
District	256 (52.5)	232(47.5)	
Occupation			
Civil servants/Army/Police	260 (61.2)	165 (38.8)	0.001
Health workers	52 (61.9)	32 (38.1)	
Private	201 (51.3)	191 (48.7)	
Housewife	43 (61.4)	27 (38.6)	
Student/college student	92 (42.6)	124 (57.4)	
Education			
Low (≤ middle school)	536 (56.1)	419 (43.9)	0.038
Intermediate (finish high school)	88 (48.6)	93 (51.4)	
High (> High school)	24 (47.1)	27 (52.9)	
Gender			
Male	413 (57.8)	303 (42.2)	0.007
Female	235 (49.8)	237 (50.2)	
Age groups (year)			
13–16	31 (51.7)	29 (48.3)	0.002
17–25	112 (45.5)	134 (54.5)	
26–45	363 (55.5)	296 (44.9)	
46–65	138 (63.8)	79 (36.4)	
>65	4 (80)	1 (20)	
Knowledge			
Good	412 (62.8)	244 (37.2)	0.001
Less	236 (44.4)	295 (55.6)	
Level of attitude			
Good	506 (61.3)	320 (38.7)	0.001
Poor	142 (39.3)	219 (60.7)	

and attitude (OR: 2.059; $p < 0.01$) significantly affect the COVID-19 transmission prevention practice.

In Table 5, it can be seen that the variable with the strongest effect on COVID-19 transmission prevention practice is attitude (OR: 2.059; $p < 0.01$). Probability of good practice of COVID-19 transmission prevention in subject with good attitudes toward COVID-19 is 2059 times higher than subject poor attitude after being controlled by variables of occupation type, gender, and level of knowledge. Variable level of knowledge is also a relatively strong effect on COVID-19 transmission prevention practice (OR: 1.782; $p < 0.01$). Probability of good practice of COVID-19 transmission prevention in subject with good COVID-19 knowledge is 1782 times higher than subject poor knowledge after being controlled by variables of occupation type, gender, and attitude.

Table 5: Final results of multiple logistic regression analysis

Variable	p-value	OR	95% CI OR
Occupation	0.004	1.128	1.038–1.226
Gender	0.031	1.309	1.025–1.672
Knowledge	0.001	1.782	1.398–2.271
Attitude	0.001	2.059	1.548–2.676

OR: Odds ratio, CI: Confidence interval.

Discussion

The results of this study indicate that the majority of subjects (54.6%) implement good COVID-19 transmission prevention practice. Wango *et al.* stated that all people, both health workers, and non-health workers must follow the same protection standards, namely, wearing masks, regularly washing hands, and using hand sanitizers. Some standards such as wearing a mask are felt to cause social discomfort, which can cause stress but at the same time if they did not wear masks, risk of COVID-19 infection is high [14].

This study found that the variables of knowledge, attitude, type of work, and gender affect COVID-19 transmission prevention practice ($p < 0.05$). Variables that have strong effect are attitude (OR: 2.059; $p < 0.01$) and knowledge (OR: 1.782; $p \leq 0.01$). In line with the results of Zhong *et al*. study which shows that gender, occupation, and knowledge are significantly related ($p < 0.05$) with COVID-19 prevention practice (social distancing). Gender and knowledge are significantly related ($p < 0.05$) with COVID-19 prevention practice (mask use) [15].

To prevent increase COVID-19 positive cases, transmission in the community must be carried out. Prevention of transmission will be achieved if each individual implement good COVID-19 transmission prevention practice. For this reason, efforts should be made to increase knowledge and improve community attitudes continuously through increasing the number and quality of health promotion to the community regarding COVID-19 transmission prevention. In line with the results of Shivalenge's study which states that there is a strong and significant relationship between knowledge and practice of COVID-19 transmission prevention [16]. This is in line with the results of Azlan *et al.* study, which shows that knowledge is significantly ($p < 0.05$) with COVID-19 transmission prevention practice (social distancing and mask use) [17]. Different results were found from the results of Saqlain *et al.* study, which showed that knowledge was not significantly affect to COVID-19 related practice in the health workforce group [18].

Health knowledge can be obtained by the public through the media and advances in information technology such as the internet, with adequate supervision from parents [19]. Clear and precise information and instructions on the prevention practice of severe acute respiratory syndrome-CoV-2 transmission that must be practiced by everyone to reduce exposure to the virus is a very important element in reducing the spread of COVID-19. One of the media used by millions of people to get information about COVID-19 is social media YouTube, with users of more than 2 billion people [20].

Health promotion can be done through print media, electronic media, social media, peer group approaches, and instructions or appeals from the Regional Head, both the Governor and the Regent/Mayor through some communication media. This study found that most subjects obtained information from print media, electronic media, social media, friends, and family. The results of this study are similar to the results of Afzal Basha's study which shows that subject knows things related to COVID-19 through social media (64%), electronic/TV media (27%), and print media (9%) [21].

The study also found that a positive attitude toward COVID-19 transmission prevention significantly affect the good COVID-19 transmission prevention practice after being controlled by other variables. The results of Paul *et al.* study in Bangladesh showed that a positive attitude toward COVID-19 was influenced by a good knowledge of COVID-19. Respondents with better knowledge have a positive attitude toward social distancing (OR: 2.056; $p < 0.01$). This shows the important role of the government to educate the public, bearing in mind that good knowledge will form positive attitude toward COVID-19 transmission prevention [9].

This study shows that women have a greater chance (OR: 1.309; p-value) to behave better in preventing transmission of COVID 19 than men. These findings are in line with the results of Azlan *et al.* study, which shows that gender is significantly related ($p < 0.05$) with COVID-19 transmission prevention practice (use of hand sanitizers and mask use) [17].

The results of this study also showed that occupational groups also affect COVID-19 transmission prevention practice. The proportion of private worker groups who implement good COVID-19 transmission prevention practice (51.3%) was smaller than the civil servants/Army/Police (61.2%). Many of these groups do not do social distancing and find it difficult to do physical distancing because they cannot work from home. They stay out of the house to get income for fear of being laid off and salary cuts. This condition in line with the findings of Shubha study who stated that the impact of the COVID-19 pandemic in the labor sector caused nearly 25 million workers to lose their jobs. Job losses and salary cuts are the most likely to occur in several sectors; airlines, hotels, commerce, malls, restaurants, and more. The company did not reach the income target and was forced to reduce the number of employees [22].

According to Pakpour and Griffiths, the effects of the COVID-19 pandemic were causing Millions of people in the world lockdown at home and many do not allow work to earn money because they cannot carry out their duties from home [23]. The same thing was conveyed by Malagi *et al*. again that many residents will lose their jobs, especially in the fields of retail, hospitality, travel, and construction sector. The government is expected to provide incentives for these companies to keep their workers until the CoV problem ends [24].

Conclusion

This study confirms that factors affecting COVID-19 transmission prevention practice are occupation type, gender, level of knowledge, and attitude. The dominant factor affecting COVID 19 transmission prevention practice is attitude (OR: 2.059; $p < 0.01$) and knowledge (OR: 1.782; $p < 0.01$). Hence, it is necessary to increase community knowledge about COVID-19 better to increase people's attitudes toward COVID 19 transmission prevention so they implement COVID-19 transmission prevention practice.

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Chloroquine and Hydroxychloroquine in Treatment of Coronavirus Disease-19

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Abstract

At present, we are facing coronavirus disease (COVID)-19 pandemic caused by the severe acute respiratory syndrome coronavirus-2 with several treatment choices and reports of different treatment outcomes. Chloroquine and hydroxychloroquine use for the management of severely ill patients started as a quite enthusiastic treatment option, following several small clinical trials, case series reports, public authorities, and media affirmation. However, the evidence we have so far is conflicting and some national societies and professional institutions implicate that we should wait for definite treatment recommendations until there are solid data for or against the use of these drugs. Until we have more powerful evidence in our hands, we should be aware of safety issues of the old drugs for the new application in the emergency state we are facing today with the COVID-19 pandemic. We performed a concise review of strengths, limitations, and awareness for chloroquine and hydroxychloroquine use for COVID-19 infection treatment based on the evidence the science has today.

Introduction

Chloroquine and its analog hydroxychloroquine, drugs that had been used to treat malaria and systemic lupus erythematosus, rheumatoid arthritis, are recently promoted as a potential treatment for the coronavirus disease (COVID)-19. Initial results on the efficacy of chloroquine in severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2) are derived from in vitro studies [1]. The first results from patients with SARS-CoV-2-related pneumonia and chloroquine efficacy come form China [2].

Hydroxychloroquine as an analog of chloroquine with less gastric intolerance and less concerns for drug interactions was found *in vitro* to be more potent than chloroquine in inhibiting SARS-CoV-2 [3].

Food and drug administration (FDA) allowed the use of these drugs since April 2020 to certain hospitalized patients where health-care providers and patients are provided with information about the risks of these drugs [4]. However, after first enthusiasm, FDA has expressed caution against the use of these drugs for COVID-19 outside of the hospital settings or a clinical trial due to the risk of heart rhythm problems and close supervision was strongly recommended. Clinical trials are planned and some have been underway to determine efficacy and safety of these drugs in the treatment of COVID-19 infection. At the beginning of April 2020, World Health Organization has started a multi-arm, multi-country clinical trial for potential coronavirus therapies based on evidence from laboratory, animal, and clinical studies, among which chloroquine and hydroxychloroquine treatment is included in the study.

Rational to use chloroquine analog lays in the fact that this drug is found to be effective against a variety of viral infections by inhibiting acidification of endosomes during the replication of the virus and infection and by their immunomodulatory effects [5]. Therapeutic agents such as chloroquine analogs, acting with the prevention of activation of macrophages, and inhibition of the secretion of tumor necrosis factor α and interleukin 6 from various cells would express benefits in the treatment of viral infections [6], [7].

Materials and Methods

A literature review was performed using PubMed to identify relevant articles published through April 15, 2020. Used search terms were coronavirus, COVID-19, SARS-CoV-2, and chloroquine, hydroxychloroquine. This search resulted in 59 total articles. Additional relevant articles were identified from the review of citations referenced. Case reports were also included.

The search terms COVID-19 or coronavirus or SARS-COV-2 and chloroquine or hydroxychloroquine on clinicaltrials.gov resulted in 14 active trials as of April 15, 2020. Ten of the trials are already recruiting patients, four still not recruiting patients. Seven of them are testing chloroquine or hydroxychloroquine alone, or controlled with placebo, three are testing low versus high dose hydroxychloroquine, and four are testing hydroxychloroquine versus hydroxychloroquine and azithromycin.

Discussion

Chloroquine, as an antimalarial drug, present at the pharmaceutical market more than 70 years has been tested regarding its safety profile multiple times. For many decades, people visiting malaria-endemic geographic areas received chloroquine prophylaxis and continued it for months after return in their homelands. In addition, some local residents in African countries took chloroquine continuously without any remarkable side effects. Hydroxychloroquine, on the other hand, has been used for a long time at much higher doses (up to 600 mg/day) for the treatment of certain autoimmune diseases. Regarding the longevity of clinical use and number of treated patients, nowadays, we can easily talk about good established safety profile of these drugs.

However, in the circumstances of acute viral infection with sometimes severe clinical presentation, attacking multiple systems, producing electrolyte, and metabolic changes, treatment with chloroquine/hydroxychloroquine may lead to dangerous adverse effects.

Results from clinical studies

After the initial modest positive results, the problem had appeared when many hospitals have simply been giving these drugs to all infected patients, without proven efficacy, concerning that treatment is relatively safe. The reports in literature from France, Brazil, China, US are conflicting; some do not include control groups, many have a small number of participants and have no power to draw conclusions, and conclusions are conflicting.

Published studies are summarized in Table 1.

The earliest published studies from China and France have been widely criticized because there was no control group to compare treated versus untreated patients. Some researchers even called this report anecdotal. In the open-label, non-randomized study, Gautret *et al*. reported 100% viral clearance in nasopharyngeal swabs in six patients after 5–6 days of treatment with hydroxychloroquine and azithromycin [8]. Such a rapid and full viral clearance was quite unexpected to other authors. A study from China in patients with COVID-19 infection did not found any difference in virologic clearance with, or without treatment with hydroxychloroquine, and even more no difference in the clinical course of the disease [9].

A small double-blind, randomized study in Brazil (81 patients) was discontinued early for safety reasons after patients on a higher dose of chloroquine showed increased mortality due to QTc interval prolongation on recorded standard 12 lead electrocardiogram and associated proarrhythmias [10].

Despite the again small size of the previous study, infectologists and drug safety experts express their opinion that the study provided further evidence that chloroquine and hydroxychloroquine can pose significant harm to some patients, specifically the risk of a fatal arrhythmia. Patients in Brazilian study were also given azithromycin, which also prolongs QTc interval. It seems that we need more data at every level.

Barbosa *et al*. decided to publish preliminary results, although their dataset is growly rapidly because of concerning safety signals [11]. They showed that hydroxychloroquine did not appear to have a beneficial effect on meaningful clinical outcome measures of mortality, lymphopenia reconstitution,

Table 1: Published studies about treatment with chloroquine or hydroxychloroquine for COVID-19 disease

Title	Drug	Type	Number of participants	Results
Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial [8]	Hydroxychloroquine 200 mg × 3 and azithromycin, versus placebo	Open-label non-randomized	36	Improved virologic clearance in treatment arm addition of azithromycin resulted in superior viral clearance
A pilot study of hydroxychloroquine in treatment of patients with common COVID-19 [9]	Hydroxychloroquine, 400 mg, daily for 5 days plus standard of care or standard care alone in a 1:1 fashion;	Open-label	30	No difference in virologic outcomes
Chloroquine diphosphate for the treatment of severe acute respiratory syndrome secondary to SARS-CoV2 (CloroCOVID19) NCT04323527 [10]	Low dose chloroquine diphosphate (450 mg), 5 days versus high dose (600 mg) 10 days	Double-blind, randomized adaptive clinical trial	440 ongoing data published for 81 pts.	Higher dose of chloroquine for 10 days was associated with more toxic effect and lethality, particularly affecting QTc prolongation
Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: A quasi-Randomized comparative study [11]	Hydroxychloroquine and supportive care versus supportive care alone initial loading dose of 400 mg b.i.d 1–2 days and 3–4 subsequent days 200 mg −400 mg o.d.	Quasi-randomized	63	Hydroxychloroquine was associated with an increased need for escalation of respiratory support. No benefits of hydroxychloroquine on mortality, lymphopenia, or neutrophil-to-lymphocyte ratio improvement
Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial ChiCTR2000029559 [12]	Hydroxychloroquine 400 mg/d (200 mg/bid) between days 1 and 5 versus standard treatment only.	Randomized parallel-group trial	62	Hydroxychloroquine use shortened time to clinical recovery

COVID-19: Coronavirus disease-19.

neutrophil-to-lymphocyte ratio, or risk for intubation. Patients in hydroxychloroquine arm appeared to have a worse clinical outcome in terms of need of respiratory support [11]. These results were in contrast to previously published results from Chen *et al*., showing shortened time to clinical recovery in hydroxychloroquine group in comparison with the control group (body temperature recovery time and cough remission time) [12].

The true answer to whether chloroquine or hydroxychloroquine has a beneficial effect for COVID-19 patients can only be obtained with a prospective randomized clinical study (Table 1).

Recommendations

According to the tendency of doctors and hospitals to give chloroquine or hydroxychloroquine, especially to severe ill patients, some associations, expert groups have published recommendations, and some refrain from making recommendations until the results of relevant clinical studies come out (Table 2).

Table 2: Available guidance about the treatment with chloroquine/hydroxychloroquine up to April 2020

Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. 20 February 2020; 43 (0): E019.	The Panel recommends the use of the chloroquine at a dose of 500 mg BID for 10 days. Alternatively, you can use if it were not available chloroquine, hydroxychloroquine 200 mg BID.
Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7) (Released by National Health Commission and State Administration of Traditional Chinese Medicine on March 3, 2020)	Chloroquine phosphate (500 mg bid for 7 days for adults aged 18–65 with body weight over 50 kg; 500 mg bid for Days 1 and 2 and 500 mg qd for Days 3–7 for adults with body weight <50 kg)
Handbook for the care of people with disease-COVI 19 Edition 2.0, March 13, 2020 SIMIT Italian Society of Infectious and Tropical Diseases SECTION Regione Lombardia	Chloroquine/hydroxychloroquine in prophylaxis for COVID-19 is not recommended. At present, there is no evidence of efficacy of this drug in the prevention of disease COVID-19. Chloroquine 500 mg twice daily for 20 days OR hydroxychloroquine 200 mg BID in patients with COVID-19 irrespective of the severity of symptoms
ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic escardio.org/Education/ COVID-19-and-Cardiology/ ESC-COVID-19-Guidance	Results of ongoing clinical trials of chloroquine/hydroxychloroquine efficacy in the treatment of SARS-CoV2 should be awaited before definite recommendations are provided for or against the use of these drugs
Clinical management of severe acute respiratory infection when COVID-19 is suspected Interim guidance March 13, 2020, | World Health Organization	No recommendation
COVID-19 Interim Clinical Guidance for Management of Patients with confirmed COVID-19 CDC Center for Disease Control and Prevention	No recommendation

COVID-19: Coronavirus disease 2019.

Dose recommendations for chloroquine or hydroxychloroquine

After conducted clinical trials by Chinese teams, recommend a dose of chloroquine phosphate was 500 mg of twice a day in patients with mild, moderate, and severe forms of COVID-19 pneumonia [2].

With huge experience over the past 5 years in patients with long-term treatment (>1 year), for different indications, Lagier *et al*. recommended dosage for hydroxychloroquine of 600 mg/day with which concentration of 1 μg/mL is reached [13]. They also suggest administration of loading dose, followed by a maintenance dose and express their opinion that activity of hydroxychloroquine on viruses is probably the same as that of chloroquine, giving preference to hydroxychloroquine [13].

As a specific treatment for COVID-19 disease, Yao *et al*. recommended that the optimal dosing regimen for hydroxychloroquine should be a loading dose of 400 mg twice daily for 1 day followed by 200 mg twice daily [3]. However, similarly, as for Whipple disease, some authors make alternative recommendations of 600 mg total daily dose [14].

Effects on QT interval and recommendations

Chloroquine and hydroxychloroquine are listed as drugs that have known risk of polymorphic ventricular arrhythmia “Torsades de Pointes” (TdP), due to QT interval prolongation at crediblemeds.org. They have proarrhythmogenic effect through blocking I_{Kr} (rapid delayed rectifier potassium current) channels, causing a significant reduction in the amplitude of potassium tail currents [15] (Figure 1).

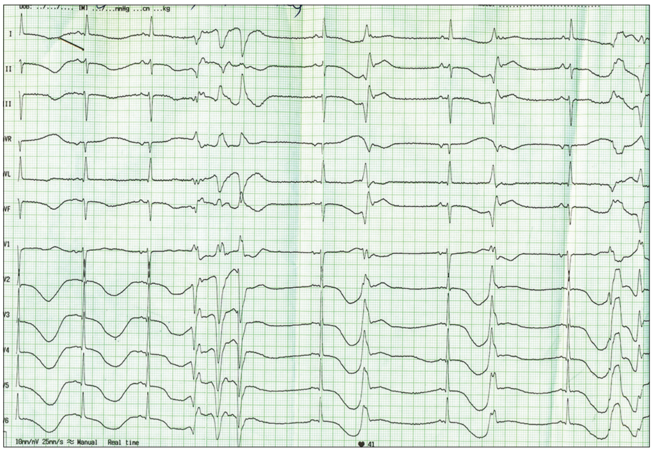

Figure 1: Hydroxychloroquine effect on electrocardiogram

The preliminary findings from the CloroCovid-19 trial suggest that a higher dosage of chloroquine should not be recommended for the treatment of severe COVID-19, especially in combination with azithromycin and/or oseltamivir, because of safety concerns [10]. Increased mortality was observed due to QTc interval prolongation and associated proarrhythmias [10] (Figure 1).

The most used formula for QTc interval calculation is the Bazett formula:

$$QTc=QT/\sqrt[2]{RR}$$

European Society of Cardiology has recently released “Guidance for the Diagnosis and Management of CV disease during the COVID-19 pandemic" last updated on April 21, 2020 [16]. Before administration of chloroquine or hydroxychloroquine therapy, there are some suggestions:

- Drug-drug interactions including antiviral, antiarrhythmic, and anticoagulation drugs should be considered;
- In hemodynamically stable patients with atrial fibrillation or flutter, discontinuation of antiarrhythmic drugs and initiation of rate control therapy to allow safe use of hydroxychloroquine as antiviral medication is a reasonable therapeutic option.

When chloroquine or hydroxychloroquine therapy is started, the following interventions should be considered in order to reduce the risk of malignant arrhythmia and death [16], [17]:

- Withholding the drugs in patients with baseline QT prolongation (especially QTc ≥500 ms) or with known congenital long QT syndrome.
- On-treatment ECGs are recommended to monitor cardiac rhythm and rule out a significant prolongation of QTc (>500 ms, or by >60 ms vs. baseline)
- It is worth exploring alternative ECG monitoring methods (e.g., monitoring leads, smartphone-enabled mobile ECG, and handheld devices);
- Correction of hypokalemia to levels of >4 mEq/L targeting >4.5 mEq/L and hypomagnesemia to levels of >2 mg/dL.

The safety of QT-prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale *et al*., for the prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients [18]. Factors incorporated in this score are: Female gender, age ≥68 years, concomitant use of loop diuretics, antiarrhythmic drugs, and comorbidities such as acute myocardial infarction, heart failure, sepsis, hypokalemia, and admission QTc ≥450 ms. According to present additional factors, Tisdale score predicts low, medium, or high risk of drug-associated QT prolongation. The goal of QTc screening in this setting is not to identify patients whom are not candidates for therapy but to identify those who are at increased risk for TdP so aggressive countermeasures may be implemented [19].

Conclusion

There is a lack of evidence regarding the efficacy and risk of different treatment strategies in patients with COVID-19 disease. In this circumstance, facing deadly disease, many hospitals have simply been giving hydroxychloroquine to patients, reasoning that it might help and probably will not hurt because it is relatively safe.

To stay on a safe side, before we get relevant results from ongoing clinical studies in all patients undergoing antiviral treatment, including chloroquine or hydroxychloroquine, it is necessary to correct modifiable predisposing factors to QTc prolongation: Electrolyte imbalances, concomitant unnecessary drugs, and bradycardia.

Not to forget, while the patient is on chloroquine or hydroxychloroquine treatment ECG should be monitored also for conduction disturbances, despite these are rare and referred only during long-term treatment.

Definite recommendations will emerge once the results of ongoing clinical trials of chloroquine/hydroxychloroquine efficacy in the treatment of SARS-CoV2 will be published.

Until than cautiously use is wise, with an awareness of side effects.

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SARS-CoV-2 Infection: General Characteristics and Specific in Dental Practice

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Abstract

The transmission of the coronavirus and possible routes of infection are still unclear. The most common routes of infection in humans are direct transmission through respiratory droplets and saliva when coughing or sneezing and indirect transmission through contaminated surfaces. Most of the infected people after the incubation period have clinical manifestations with mild or moderate respiratory tract infections (RTIs). Physician of dental medicine performs aerosol procedures which transmit the virus directly from healthy people. Oral fluids, blood, conjunctiva, nasal, and oral mucosa are also a source of infection, so they are highly exposed to the virus, much more than other medical staff and therefore it is crucial to establish appropriate protocols and prevention strategies. Under conditions of a declared global pandemic, dentists are advised to stop their work of all cases that are not urgent. If the dental office is one of those that provide the necessary and urgent medical attention, it is necessary to strictly implement control measures to prevent infection. The basic protocols for the operation of the dental offices have been published by the Dental Chamber of Macedonia and they are recommendations regarding the procedures for the maintenance of the hygiene of the medical staff and the working space. Recent experience has shown that dental health-care services are often neglected and inadequately treated in epidemics. Dental workers are particularly exposed to RTIs due to their specific field and mode of operation, so the current experience will prepare them for future challenges.

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Introduction

SARS-CoV-2 is a zoonosis virus that causes illness named "novel coronavirus-infected pneumonia" (NCIP), COVID-19 which the WHO declared as a global pandemic on March 12, 2020 [1], [2]. The virus belongs to the family *Coronaviridae* of the Nidovirales order and is a non-segmented positive-sense RNA virus [3]. The SARS-CoV-2 (formerly 2019-nCoV) virus, discovered in Wuhan (China), according to phylogenetic analyzes of the viral genome, falls into the genus beta-coronavirus, subgenus Sarbecovirus. 2019-nCoV was more similar to two bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21, than to known human-infecting coronaviruses [4]. Phylogenetic relationship to RaTG13 is very close which provides evidence that it may have originated in bats [5]. The sequence of the genomic nucleotide discovered in the *Rhinolophus affinis* bat (*Bat SARr-CoV RaTG13*) in the Yunnan region of China is 96.2% identical to the SARS-CoV-2, indicated that the natural host of the virus may be the bat [6].

The SARS-CoV-2 which includes coronaviruses is discovered in humans, bats, and other wild animals [7], [8]. It has the typical appearance of "*protein spines*" on the membrane and is composed of polyproteins, nucleoproteins, and membrane proteins such as polymerases, proteases, helixes, and other accessory proteins (Figure 1).

Two types of the SARS-CoV-2 major L (70%) and minor S (30%) were defined, and although the L type was derived from the S type, L is more prevalent, has a higher transmission rate and might be more aggressive than the S type due to the potentially higher transmission and replication rates [9]. The S-protein of the virus introduced into the human body binds to the host receptor, the so-called angiotensin-converting enzyme 2 (ACE-2), enters the target non-immune cells of the respiratory tract, intestinal epithelial, endothelial, kidney cells, cerebral neurons, and immune cells such as alveolar monocytes and macrophages. The pronounced affinity between the virus and the receptors indicates that populations with higher ACE-2 expression are more susceptible to the virus [10]. The symptoms of COVID-19 infection appear after the incubation period as systemic and respiratory disorders dependent on the age and status of the patient's immune system [11]. A recent study showed median incubation period 4 days, median age 47 years and fever and cough presented as most common symptoms [5].

The present study aimed to present a general characteristics and specifics of the novel SARS-CoV-2 infection in the dental practice.

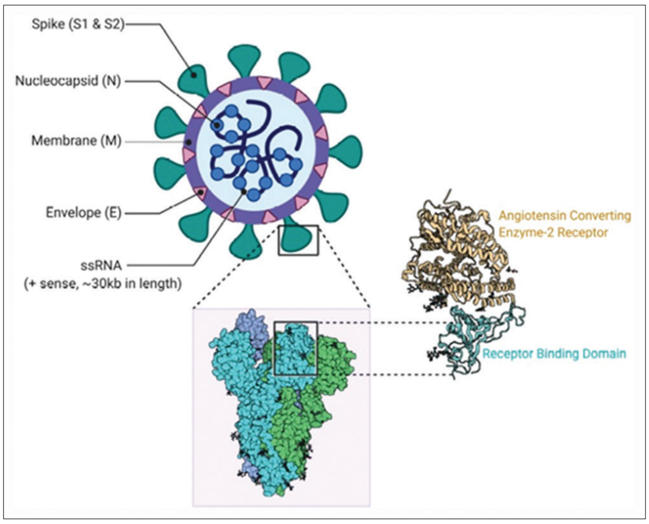

Figure 1: SARS-CoV 2 Structure. (Adapted by: Cascella M, Rajnik M, Cuomo A, et al. Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/.)

Transmission of SARS-CoV-2

Transmission of the SARS-CoV-2 and possible routes of infection are still unclear. The most common routes of infection are a direct transmission from human to human through respiratory droplets and saliva (Figure 2), when coughing or sneezing, transmitting the virus from person to person and contact transmission when in contact with the oral, nasal, and ocular mucous membranes [12], [13]. Indirect contact transmission is made possible through contaminated surfaces (metal, glass, and plastic) on which the virus can remain for several days, and they may be transferred to the hands of the patients and health-care providers. Various environmental factors such as temperature, humidity, ventilation, and virus amount influence this type of transmission [14]. Serological detection of the virus in oral, anal swabs, and blood samples provides cautionary warning that SARS-CoV-2 from the infected patients can potentially shed the pathogen through respiratory, fecal–oral, or body fluid routes [15].

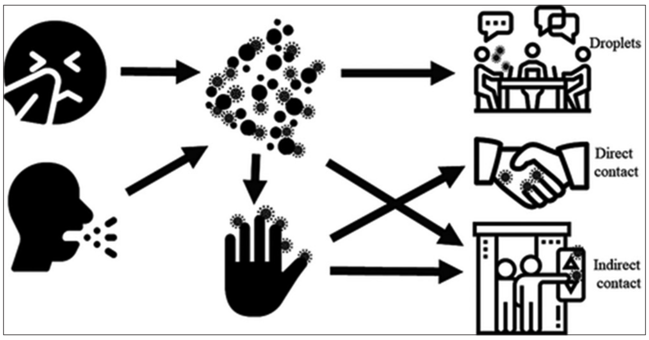

Figure 2: Drivers of transmission of coronavirus (COVID-19) infection consist of short-range, large-droplet transmission (>5 μm in diameter, traveling <1 m); close, unprotected, direct contact; and indirect contact with contaminated surfaces (Adapted by: Cancer cytopathology. 2020;128(5):309-316)

The virus is present in aerosols for up to 3 h after emission and has been identified on surface such as cardboard after 24 h, plastic and steel after 2–3 days [16]. Examination of the stability of the virus on contaminated surfaces in experimental conditions showed a large decrease in titer and viability (from 103.7 to 100.6 TCID50/ml/medium) after 72 h on plastic and 48 h on stainless steel (Table 1). Unlike previous forms of coronavirus, asymptomatic individuals infected with COVID-19 can transmit the infection through aerosols and objects without becoming ill or before developing symptoms of the disease, which may explain the pandemic course of the infection [17].

Several factors affect how long the virus can survive in the air, most notably the size of the droplets as well as some external influences. Large drops quickly fall to the surface, while smaller ones can stay in the air for a while, and air movement and ventilation can reduce their concentration and remove them from the room. To determine the distribution of SARS-CoV-2 in hospital wards in Wuhan, China, a study testing the air and surface samples showed contamination was greater in intensive care units than general wards, and the virus was widely distributed on floors, computer mice, trash cans, and sickbed handrails and was detected in air ≈4 m from patients [18]. The presence of the virus on the protective equipment of the medical staff was lower, but it was also present on the sleeves, gloves, and masks, which indicates the need for proper removal of medical protective equipment from medical facilities and disinfection [19]. Although the exact mode of entry of the virus into the human body is not yet known, the mechanism is thought to be similar to that of SARS-CoV, where the first target cells are the receptors on the epithelial cells of the salivary ducts [20]. The upper respiratory tract is covered by the epithelial cells which possess the receptors in large numbers, and once they enter the human body, the virus binds to them [21].

Clinical manifestations of COVID-19

The mean incubation or the asymptomatic period in infected persons usually lasts 3–9 days after the infection, but in some cases the symptoms appear after 24 days [22]. It is estimated that about 44% of transmission of infection occurred before any

Table 1: Medium survival time of the virus on different surfaces

Surface	Objects	Survival time
Metal	Door handles, cutlery, jewelry	3 days
Plastic	Bottle, buttons, doorknob, seats	2–3 days
Glass	Window, cup, mirror	4–5 days
Paper	Books, newspaper	5 days
Wood	furniture, parquet	4 days
Food	Fruit and vegetables	There is no presence
Water	Bottled, tap	There is no presence

symptom arose [23]. Clinical manifestations are from asymptomatic to fatal pneumonia, and COVID-19 is now classified in four levels based on the severity of symptoms: Mild, moderate, severe, and critical [24]. Most of the infected persons have a mild clinical presentation with moderate respiratory symptoms such as fever, dry cough, and fatigue, while rhinorrhea, nasal congestion, sore throat, or myalgia are less common. Occasionally, non-respiratory symptoms such as palpitation, diarrhea, or headache precede respiratory symptoms [25]. Symptoms of developing a severe clinical picture include shortness of breath, persistent chest pain, or pressure, and livid color of the lips or face, and these individuals need to be treated in a hospital facilities [26]. In some severe cases, the disease rapidly progressed to acute respiratory distress syndrome, septic shock, refractory metabolic acidosis, and coagulation disorder, eventually leading to death [27]. Complications such as pneumonia, hypoxia, secondary infection, multiple organ failure with thromboembolism, gastrointestinal (GI) bleeding, polyneuropathy, and myopathy were the cause of prolonged hospitalization or the fatal outcome of the disease. In these individuals, the laboratory findings showed high erythrocytes count and sedimentation rate, higher D-dimers and prothrombin time, leucopenia, and lymphopenia in the peripheral blood flow [28]. Middle-aged and elderly patients with underlying chronic diseases are susceptible to respiratory failure and may have a poorer prognosis [29]. Hypertension, cardiovascular diseases, diabetes, chronic respiratory diseases, or malignancy are common comorbidities and risk factors for developing a more severe form of COVID-19 [30].

Diagnostics and therapy of COVID-19

Diagnostics of the disease is made by collecting a sample swab from the respiratory tract. A nasopharyngeal swab is best for detecting the virus RNA using a reversible polymer chain reaction (RT-PCR), and an oropharyngeal or nasal sample can also be used. At least 11 nucleic-acid-based methods and eight antibody detection kits have been approved in China by the National Medical Products Administration (NMPA) for detecting SARS-CoV-2 [31]. However, RT-PCR is the most predominantly used method for diagnosing COVID-19 using the upper or lower respiratory samples. The United States Centers for Disease Control and Prevention (CDC) uses a one-step real time RT-PCR (rRT-PCR) assay, which provides quantitative information on viral loads, to detect the presence of SARS-CoV-2 [32]. The ECDC (European Centre for Disease Prevention and Control) and the WHO (World Health Organization) recommend diagnosing the disease with a molecular test that detects the virus, but to expand the testing capacity, the use of rapid antigen tests has been approved [33]. The decision if someone should be tested is based on clinical and epidemiological data, PCR testing of asymptomatic or mildly symptomatic contacts is considered for individuals who have had contact with a COVID-19 [34].

There is still no specific therapy or vaccine to protect against the disease, and people with severe clinical symptoms use many drugs, the effectiveness of which has not yet been clinically proven. The method of physical distancing and isolation to avoid direct interpersonal contacts, the use of protective masks and disposable gloves seems to be the only effective measure to prevent the spread of the disease and the possibility of so-called flattening of the epidemiological curve.

SARS-CoV-2 Infection in the Dental Practice

Infection routes

The presence of the virus in high concentrations in the saliva of infected individuals is the cause of possible direct human-to-human transmission of the infection, but further contact with blood and other body fluids possess an additional risk of transmission. Dentists and other health-care providers who perform aerosol procedures can transmit the virus directly from healthy people or people who have not yet developed symptoms [8]. Dental aerosols are created from dental rotary instruments and ultrasound instruments, so droplets sprayed into the air and can contaminate the clinical environment and this is most important concern in dental clinics [35]. The heavier particles (>50 μm) of the aerosols quickly fall onto the surface, while the lighter ones remain present in the air for a longer time, could be inhaled and cause COVID-19 infection during dental intervention itself (Figure 3). Oral fluids, blood, conjunctiva, nasal, and oral mucosa are also source of infection in both modes of transmission not only through droplets or aerosols that contain the virus when people speak or cough without the masks but also through contaminated instruments and surfaces in the office [21]. In its report, American Dental Organization (ADA) points out that dental workers are highly exposed to the virus, much more than other

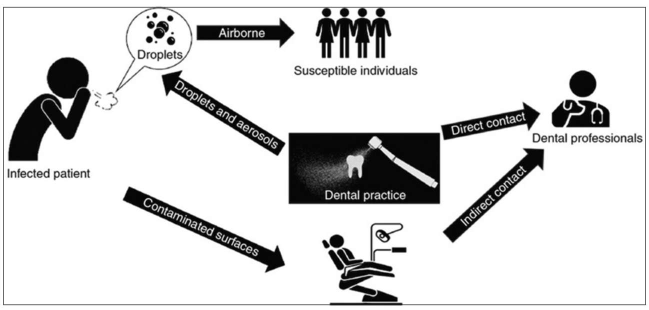

Figure 3: Transmission of the virus in dental practice (Adapted by: Int J Oral Sci 2020;12(1):9. DOI: 10.1038/s41368-020-0075-9)

medical staff and general practitioners, and therefore it is crucial to establish appropriate protocols and prevention strategies. ADA Interim Guidance for Management of Emergency and Urgent Dental Care use algorithms presenting interim guidance for triaging, screening, and minimizing transmission risks during the time of COVID-19 pandemic, by the latest recommendations from health-care agencies [36].

Infection control and prevention in dentistry

Under conditions of a declared global pandemic, dentists around the world were advised to stop their regular work in the practice for all cases that are not urgent (conservative and surgical) for at least few weeks or as long as there is a risk. It was also necessary to stop not only the work of dental laboratories but also the Faculties of Dental Medicine, because students are a population that due to its exposure and wide range of social contacts can be a potential source of infection. The reasons for taking these measures are primarily not only the high exposure of dental workers to the SARS-CoV-2 due to the nature of the work itself but also the possibility of contamination, transfer, and spread of infection in dental offices [37], [38]. According to Occupational Safety and Health Administration methodology, which evaluates data on workers exposure risk levels, dental practitioners routinely perform several aerosol-generating procedures exposing both clinicians and patient to the risk of infection [39]. Producing and inhalation of the saliva aerosols by infected patients can be considered as virus transmission route, which implicate the importance of making dental practice safe from such risks [40].

If the dental office is one of those that provide the necessary and urgent medical attention, it is necessary to strictly implement control measures to prevent infection. The first contact with the patient should be by telephone, video conference, or text message so that the most appropriate screening and triage can be performed. If more patients are admitted to the office during a day, it is necessary to provide sufficient time between each intervention for ventilation and disinfection, and the therapeutic procedures that create aerosols should be scheduled at the end of working hours and performed with the least necessary assistance staff. Health-care providers who have had close and prolonged contact with infected patients at a health facility should undergo testing for even mild symptoms of the disease, along with supporting staff [41].

The first step before admitting patients should always be to measure the body temperature with a non-contact thermometer on the forehead and then conduct an epidemiological screening survey with a questionnaire. The questions refer to the possible presence of fever in the past 14 days, the presence of respiratory symptoms such as coughing and shortness of breath and epidemiological issues for trips to risky areas, contact with sick or suspicious persons, etc. If the patient answers all the questions in the negative and has a body temperature lower than 37.5 degrees, the dentist can treat him by applying all the necessary protection measures. The basic protocols for the operation of the dental offices during the pandemic in Republic of Macedonia have been published by the Dental Chamber of Macedonia (March 14, 2020) and they were recommendations regarding the procedures for the maintenance of the hygiene of the medical staff and the working space [42]. As a result of the exceptional effort and intensive communication between the Dental Chamber of Macedonia, The Ministry of Health of Republic of Macedonia and the Commission for Infectious Diseases, a decision was made to re-adapt the dental health system for its maximum functioning in emergency conditions and epidemics. The Chamber also defines the “List of Emergency Dental Procedures” for all citizens to have had access to the necessary and urgent dental service care.

Working with Suspect Case, Probable Case, and Confirmed Case of COVID-19

All suspected, probable, and confirmed cases of COVID-19 in Republic of Macedonia should be treated in the COVID center at St Panteleymon University Dental Clinic, Republic of Macedonia. No First patients were already treated in the specialized center, they were all without any symptoms of the disease, diagnosed and sent in to the home self-isolation. The therapeutic procedures were according the protocols with taking care of all the preventive and after treatment procedures. COVID-19 positive or suspected patients were treated yet, but working protocols and guidance for working of the dental offices are according recommendations by Dental Chamber of Macedonia, considering the WHO recommendation for personal protective equipment (PPE) when working with aerosol-generating procedures and treatments [43].

Protocols for Patients Requiring Emergency Intervention

Patients in the dental office should be admitted after screening and an epidemiological questionnaire and consent. To reduce the possibility of virus transmission, it is necessary to avoid interventions that create aerosols and use cofferdam whenever necessary, because it allows a significant reduction in aerosol transmission up to 70% [44]. Patients need to perform hand washing with soap and disinfection with an alcohol-based product over 60% or with disinfectant tissues [45]. The presence of high concentrations of the virus in saliva can be reduced, though not eliminated [46]. Preoperational rinse of the oral cavity with antimicrobial solution (1% Hydrogen peroxide or 0.2% Povidone-iodine) is suggested protocol before each dental intervention [47].

PPE

All patients have to be treated with high alert as signs and symptoms may not appear at early infected cases. The operator and other dental staff in the dental office must use additional PPE when working with each patient, and these are usually protective coats or disposable gowns. Particular attention should be paid to the protection of the face and head, disposable hats, goggles, shields for protection of the face, disposable filtering face masks-aspirators FFP3 (or FFP2 and FFP1) masks, N-95 masks and disposable protective gloves are necessary to wear (Figure 4). Research has shown the possibility of infecting health-care personnel due to improper disposal of PPE [48].

Clinical Protocols

Restrictions of all aerosol procedures for pain relieve and infection control are highly recommended. When a patient is diagnosed with caries leading to irreversible pulpitis, a condition accompanied by severe and intense pain, after the application of local anesthesia it is necessary to place a rubber dam and possibly use chemical-mechanical means to evacuate the carious mass and devitalize the pulp [49]. However, if there is a need for use of rotating instruments for trepanation of the tooth, it is advisable to use anti-retraction high-speed dental handpiece to reduce the backflow with an anti-return valve that can prevent aspiration and return of debris and liquids that are created during the procedure [50]. The use of inappropriate techniques and instruments during interventions can lead to additional bacterial and viral contamination of the air and hose of the dental unit and thus the possibility of causing a cross-infection. Standard saliva aspiration systems can be clogged, so it is recommended to use intra/extra-oral suctions evacuators with a larger volume [51].

Figure 4: Personal protective equipment at the St Panteleymon University Dental Clinic, Skopje, Republic of Macedonia

As the most common X-ray technique, small retroalveolar imaging may stimulate increased salivary secretion and cough, and it is therefore recommended that extraoral imaging (panoramic radiography or Cone-Beam Computed Tomography) be performed whenever possible [52]. Special attention should be paid to the auxiliary and waiting rooms where patients can disperse infectious material by coughing or sneezing. It is necessary to remove all newspapers and similar contents and regularly disinfect all surfaces, by placing alcohol-based disinfectants in clearly visible places and the availability of masks to protect patients. Air ventilation systems in the workplace should be disinfected more often than usual [53]. Rooms with natural ventilation should be ventilated frequently and regularly, and a negative air pressure system should be used in operating rooms.

Disinfectants in the Dental Offices

Due to the already proven presence of human coronaviruses on the instruments and objects around the room at room temperature for several days, taking the most appropriate strict disinfection measures is inevitable during and after daily work in the offices. Water and detergents in combination with common disinfectants should be used to clean operationale and areas at high risk for the presence of the virus with 0.05% Sodium Hypochlorite diluted with water (1 g/L) [54]. For disinfection of smaller areas, 70% Ethanol (Ethyl alcohol) can be used, which after 1 min of exposure showed a significant reduction in the vitality of coronaviruses and the effect on SARS-CoV-2 is assumed to be similar [54]. Ethyl alcohol (78–95%), 2-propanol (70–100%), a combination of 45% 2-propanol with 30% 1-propanol, glutaraldehyde

(0.5-2.5%), formaldehyde (0.7–1%), and Povidone-iodine (0.23–7.5%) eliminate virus infectivity by 4 log or more [55]. Hydrogen peroxide (hydrogen) shows effect at a concentration of 0.5% and an exposure period of 1 min [56]. Use of Class B autoclave to sterilize all instrument including high-speed hand pieces with spore tests at least one weekly is highly recommended [54]. Decontamination of the hands of health personnel is of great importance and the recommendation is to perform it with alcoholic wipes (80% Ethanol or 75% 2-propanol) immediately after removing the gloves [57].

Management of Medical Waste and Disposable Protective Equipment

Instruments and disposable items should be recycled, cleaned, sterilized, and properly stored following the disinfection and sterilization procedures of dental instruments [58]. Medical and domestic waste generated by the treatment of patients with suspected or confirmed COVID-19 infection is considered contagious medical waste to which special protocols prescribed by the competent institutions.

Conclusion

Recent experience has shown that dental health-care services are often neglected and inadequately treated in situations when such or similar epidemics occur. State institutions and relevant public health organizations should seriously consider finding ways to respond appropriately and promptly, primarily to the form in which dental health care will have to meet the challenges of these times. There is some uncertainty in all other segments of social action as the world encounters this new pathogen, potentially lethal and with a unique way of inter-personal transmission. We are still faced with unknown regarding immune response, origin, disease dynamics, and therapy. What is undoubtedly of great importance is the protection and strengthening of health systems and health workers at all levels, because they are at the forefront of the fight, and preserving their health is of great importance. Dental workers are particularly exposed to respiratory infections due to their specific field and mode of operation, and understanding routes of transmission of COVID-19 may have positive outcome in prevention of the infection. Current experiences will raise the level of readiness, reduce the risk and enable future challenges to be addressed as quickly as possible with minimal losses in material and human resources.

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Drug-Drug Interaction between Psychiatric Medications and Experimental Treatments for Coronavirus Disease-19: A Mini-Review

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Abstract

The pandemic of coronavirus disease (COVID)-2019 has been affected many people all around the world. Patients with mental disorders are not as safe as others; also, they might be more vulnerable in such situations. These patients take various medications, which can lead to numerous drug-drug interactions with experimental drugs uses against COVID-19. According to the potential critical interactions, we reviewed the reputable databases to find the interactions between main categories of psychiatric medications (e.g., antidepressants, anti-psychotics, sedative/hypnotics, and mood stabilizers) when used in concomitant with COVID-19 experimental agents (e.g., hydroxychloroquine, lopinavir/ritonavir, atazanavir, and chloroquine). We hope the list provided in this review helps the clinical care staff in treating patients with mental illness infected with severe acute respiratory syndrome coronavirus 2 during the COVID-19 pandemic.

Introduction

Coronavirus disease 2019 (COVID-19) was first reported from Wuhan, China, in December 2019 [1] and rapidly spread worldwide to become a pandemic on March 12, 2020 [2]. No specific drug has been approved for the treatment of COVID-19 yet. Infectious Diseases Society of America has suggested a few agents based on limited clinical trials such as hydroxychloroquine (HCQ) and lopinavir/ritonavir (LPV/r) [3]. Atazanavir (ATV) also has been supported by other documents to have a potential benefit for COVID-19 [4], [5].

Mental disorders are listed among the most common causes of chronic diseases. The prevalence was estimated to be 22.1% in 2019 [6]. This group of patients is not as safe as others; also, they might be more vulnerable in such situations [7], [8] due to probable cognitive impairment, lack of awareness regarding transmission risks, and poor personal hygiene [9]. The presence of comorbidities, such as mental disorders in patients with COVID-19, makes the treatment plan more challenging [10]. One of these challenges is drug-drug interaction.

Ritonavir applies a paradoxical inhibitory/induction effect on cytochromes P450 (CYP) family 3, subfamily A (CYP3A) isoenzyme and is a moderate inhibitor against CYP2D6 isoenzyme [11]. ATV is a substrate and inhibitor of CYP isoenzyme 3A and inhibits/induces P-glycoprotein [12]. Therefore, these two medications have many significant drug interactions that may affect the outcome of patients. HCQ and chloroquine (CQ) are highly potential to prolong QT interval and may elevate the adverse effects of drugs in this direction [13].

Thus, we aimed to evaluate the interactions between psychiatric medications (consist of antidepressants, anti-psychotics, sedative/hypnotics, and mood stabilizers) and highly used experimental COVID-19 treatments including HCQ, CQ, LPV/r, and ATV, to help the clinician decisions in choosing appropriate medications with lowest drug-drug interactions according to the underlying disease of patients.

Materials and Methods

We studied four reputable databases of drug interactions including Lexi-Interact [14], Drug Interactions Checker [15], UpToDate [16], HIV drug interactions [17], as well as Stockley's Drug Interactions Pocket Companion and AIDS *info* guidelines for the use of antiretroviral agents in adults and adolescents with HIV [18] to find out the interactions between four categories of psychiatric medications and experimental COVID-19 medications. Additional references (e.g., original articles and FDA drug information) were also included as needed.

Results

Concise and rapid guidance for drug-drug interactions is presented in Table 1. In this table, the green color illustrates no clinically significant interaction, the yellow color mentions the need for monitoring or treatment modification, the red color represents contraindication of combination, and the blue color is used to demonstrate controversy among recommendations of different databases. The detailed information about the mechanism of interaction, consequences, and management were reviewed in this section.

Antidepressants

Citalopram/escitalopram

Citalopram/escitalopram is metabolized through CYP2C19, CYP2D6, and CYP3A4 isoenzymes [16].

Citalopram/escitalopram – HCQ/CQ

Mechanism and consequence

Both selective serotonin reuptake inhibitors (SSRIs) and HCQ/CQ may lead to QT prolongation [14], [15], [19] and hypoglycemia [14]. Concomitant use of these medications enhances such side effects.

Table 1: Rapid drug interactions guidance

Psychiatric medications		Experimental agents for COVID-19			
Drug category	Drugs name	Hydroxychloroquine	Chloroquine	Lopinavir+Ritonavir	Atazanavir
Antidepressants	Citalopram	1.1.1	1.1.1	1.1.2	1.1.2
	Escitalopram	1.1.1	1.1.1	1.1.2	1.1.2
	Fluoxetine	1.2.1	1.2.1	1.2.2	1.2.3
	Fluvoxamine	1.3.1	1.3.1	1.3.2	1.3.3
	Paroxetine	1.4.1	1.4.2	1.4.3	1.4.4
	Sertraline	1.5.1	1.5.1	1.5.2	1.5.3
	Venlafaxine	1.6.1	1.6.1	1.6.2	1.6.2
	Duloxetine	1.7.1	1.7.1	1.7.2	1.7.2
	Amitriptyline	1.8.1	1.8.1	1.8.2	1.8.2
	Maprotiline	1.8.1	1.8.1	1.8.2	1.8.2
	Nortriptyline	1.8.1	1.8.1	1.8.2	1.8.2
	Desipramine	1.8.1	1.8.1	1.8.2	1.8.2
	Doxepin	1.9.1	1.9.1	1.9.2	1.9.2
	Clomipramine	1.10.1	1.10.1	1.10.2	1.10.2
	Imipramine	1.10.1	1.10.1	1.10.2	1.10.2
	Bupropion	1.11.1	1.11.2	1.11.3	1.11.4
	Buspirone	1.12.1	1.12.1	1.12.2	1.12.2
	Mirtazapine	1.13.1	1.13.1	1.13.2	1.13.2
	Trazodone	1.13.1	1.13.1	1.13.2	1.13.2
Anti-psychotics	Aripiprazole	2.1.1	2.1.1	2.1.2	2.1.3
	Clozapine	2.2.1	2.2.1	2.2.2	2.2.2
	Olanzapine	2.3.1	2.3.1	2.3.2	2.3.3
	Quetiapine	2.4.1	2.4.1	2.4.2	2.4.2
	Risperidone	2.5.1	2.5.1	2.5.2	2.5.3
	Chlorpromazine	2.6.1	2.6.1	2.6.2	2.6.3
	Fluphenazine	2.6.1	2.6.1	2.6.2	2.6.3
	Perphenazine	2.6.1	2.6.1	2.6.2	2.6.3
	Thioridazine	2.6.1	2.6.1	2.6.2	2.6.3
	Haloperidol	2.7.1	2.7.1	2.7.2	2.7.2
	Pimozide	2.8.1	2.8.1	2.8.2	2.8.2
Sedative hypnotics	Alprazolam	3.1.1	3.1.1	3.1.2	3.1.3
	Chlordiazepoxide	3.1.1	3.1.1	3.1.2	3.1.3
	Clonazepam	3.1.1	3.1.1	3.1.2	3.1.3
	Diazepam	3.1.1	3.1.1	3.1.2	3.1.3
	Temazepam	3.2	3.2	3.2	3.2
	Lorazepam	3.2	3.2	3.2	3.2
	Oxazepam	3.2	3.2	3.2	3.2
	Triazolam	3.3.1	3.3.1	3.3.2	3.3.2
	Midazolam	3.3.1	3.3.1	3.3.2	3.3.2
	Zolpidem	3.4.1	3.4.1	3.4.2	3.4.2
Mood stabilizers	Carbamazepine	4.1.1	4.1.2	4.1.3	4.1.4
	Valproic acid	4.2.1	4.2.2	4.2.3	4.2.4
	Lithium	4.3.1	4.3.1	4.3.1	4.3.2
	Lamotrigine	4.4.1	4.4.2	4.4.3	4.4.4

Red color: Extremely significant interaction. Contraindicated. Yellow color: Minimally or moderately significant interaction. Monitoring or therapy modification is needed. Blue color: Controversy between different references. Green color: No significant interaction or does not require any action. The paragraph number is cited in the table, Ctrl + Click on paragraph number to refer to the related section of the article for additional information.

Management

It is recommended to use caution in the elderly, females, individuals with a history of cardiovascular disease, hypokalemia, and hypomagnesemia. Close monitoring for QT prolongation and hypoglycemia is required [14], [15].

Citalopram/escitalopram – LPV/r and ATV

Mechanism and consequence

Coadministration of either LPV/r or ATV with citalopram/escitalopram is associated with increased serum concentrations of these medications and QT prolongation effects [17], [18], [19].

Management

It is recommended to initiate SSRIs with the lowest dose and titrate slowly. Regular electrocardiogram (ECG) monitoring and correcting electrolyte abnormalities (hypokalemia or hypomagnesemia) may be required, especially in patients with a previous history of cardiovascular disease or electrolyte abnormalities [15], [17], [18].

Fluoxetine

Fluoxetine is a significant substrate of CYP2C9 and CYP2D6 isoenzymes [16].

Fluoxetine – HCQ/CQ

The interactions are similar to those mentioned for citalopram/escitalopram (Refer to 1.1.1).

Fluoxetine – LPV/r

Mechanism and consequence

Inhibitory effect of LPV/r on the CYP2D6 isoenzyme is predicted to raise the serum concentration of fluoxetine. Furthermore, fluoxetine can increase ritonavir [15], [17], [19], [20]. Serotonin syndrome is reported in a case series of patients that used ritonavir-based HAART with fluoxetine [21]. On the other hand, decreased concentrations of fluoxetine were observed when combined with ritonavir-boosted protease inhibitors (PIs) [22].

Management

Careful monitoring of adverse effects and dose adjustment for fluoxetine may be needed [15], [17], [18], [22].

Fluoxetine – ATV

There are no clinically significant interactions [14], [15], [17], [22].

Fluvoxamine

Fluvoxamine is mainly metabolized through the CYP2D6 isoenzyme [16].

Fluvoxamine – HCQ/CQ

Mechanism and consequence

SSRIs may increase insulin sensitivity and enhance the hypoglycemic effects of HCQ/CQ [14]. Moreover, a study reports an increase in the concentrations of HCQ/CQ [19], while two others do not mention any significant interactions [15], [22].

Management

Monitor for the hypoglycemic effects of medications is required [14].

Fluvoxamine – LPV/r

Mechanism and consequence

Coadministration has not been studied. LPV/r could potentially increase fluvoxamine concentrations by the inhibitory effect of ritonavir on the CYP2D6 isoenzyme [17], [19].

Management

No dosage adjustment is recommended [17]. However, according to another reference, consideration of an alternative antidepressant may be needed [23].

Fluvoxamine – ATV

No clinically significant interactions were found [14], [15], [17], [19], [22].

Paroxetine

Paroxetine is a major substrate for CYP2D6 isoenzyme [16].

Paroxetine – HCQ

Interactions are similar to those of fluvoxamine (Refer to 1.3.1).

Paroxetine – CQ

Mechanism and consequence

Paroxetine concentrations may rise following inhibition of CYP2D6 isoenzyme [14], [19].

Management

Monitor for increased drug effects, and hypoglycemia is recommended [14].

Paroxetine – LPV/r

Mechanism and consequence

LPV/r can increase the serum concentration of paroxetine due to the inhibitory effect of ritonavir on the CYP2D6 isoenzyme [15], [17], [18], [22]. Moreover, decreased paroxetine concentrations are reported with ritonavir-boosted PIs [22].

Management

Monitoring of adverse effects and probably dose adjustment of paroxetine may be required [15], [17], [18], [22].

Paroxetine – ATV

Mechanism and consequence

Interactions are controversial among different studies. Some references mention that there is no significant interaction [14], [15], while some others point to the same interaction that exists for LPV/r (refer to 1.4.3) [17], [18].

Management

As mentioned for LPV/r (refer to 1.4.3) [17], [18].

Sertraline

Sertraline is a minor substrate for CYP2B6, CYP2C9, CP2C19, and CYP3A4 isoenzymes [16].

Sertraline – HCQ/CQ

Refer to citalopram/escitalopram (1.1.1) [14], [15].

Sertraline – LPV/r

Mechanism and consequence

LPV/r may decrease the sertraline concentration through induction of CYP2B6, CYP2C9, and CP2C19 isoenzymes [17], [19], [22].

Management

Monitoring for the efficacy of sertraline and dose titration may be required [17], [22].

Sertraline – ATV

Mechanism and consequence

Sertraline exposure may increase by inhibition of CYP3A4 isoenzyme [17], [19], [24].

Management

Dose adjustment may not be required [17].

Venlafaxine

Venlafaxine – HCQ/CQ

Mechanism and consequence

Although some references did not report any interactions [14], [22], studies reported that both medications could prolong the QT interval [15], [19].

Management

Monitoring QT interval and correction of hypokalemia and hypomagnesemia may be necessary [15], [19].

Venlafaxine – LPV/r and ATV

Mechanism and Consequence

Venlafaxine concentration may be increased if either ATV or LPV/r is simultaneously administered through an inhibitory effect on the CYP3A4 isoenzyme [15], [17], [19], [24].

Management

Dose adjustment is not required, but it is recommended to use it with caution [15], [17], [24].

Duloxetine

Duloxetine is a major substrate of CYP1A2 and a minor substrate of CYP2D6 isoenzymes [16].

Duloxetine – HCQ/CQ

Mechanism and consequence

Plasma concentrations of duloxetine may be elevated through inhibitory effects on CYP2D6 isoenzyme [14], [15], [19].

Management

Monitor for adverse reactions and adjust the dose, if needed [14], [15].

Duloxetine – LPV/r and ATV

Ritonavir induces CYP1A2 and inhibits CYP2D6 isoenzymes; thus, the consequence of interaction is unpredictable, and dose adjustment may not be essential. ATV does not significantly affect duloxetine concentrations [15], [17], [19], [24].

Amitriptyline/nortriptyline/maprotiline/desipramine

These tricyclic antidepressants (TCAs) are major substrates of CYP2D6 isoenzyme [16].

Amitriptyline/Nortriptyline/Maprotiline/Desipramine – HCQ/CQ

Mechanism and consequence

Coadministration of two medications with QT prolongation effects causes additive adverse effects, including torsade de pointes arrhythmias [15].

Management

Correction of risk factors (e.g., hypokalemia and hypomagnesemia) and ECG monitoring may be required [15]. Some references mention that there is no need for taking action [14], [22].

Amitriptyline/Nortriptyline/Maprotiline/Desipramine – LPV/r and ATV

Mechanism and consequence

The serum concentration of the TCAs may be increased with the administration of LPV/r due to inhibitory effects on CYP2D6 isoenzyme [14], [18], [19], [22], [24]. However, it seems that unboosted ATV does not have this inhibitory effect, and enhanced TCA plasma concentrations are not expected [17].

Management

Monitor for adverse effects of TCAs, and dose reduction may be implemented in the case of coadministration with LPV/r. Furthermore, monitor for decreased effects of TCAs if the LPV/r is discontinued. EKG monitoring is also recommended for concomitant administration of LPV/r or ATV with mentioned TCAs, due to QT prolongation [14], [17], [18], [19].

Doxepin

Doxepin – HCQ/CQ

Use with caution is recommended due to QT prolongation, as mentioned in the 1.8.1 section [14], [15].

Doxepin – LPV/r and ATV

The mechanism and consequence of interaction are the same as other TCAs in 1.8.2 section. However, the management, in this case, is controversial; some studies recommended careful monitoring of adverse effects, and a decrease in the dose of doxepin may be required [14], [15], [18], [22], [24]. In contrast, others believe that no dose adjustment is needed [17], [19].

Imipramine/clomipramine

These TCAs are metabolized through CYP2D6, CYP2C19, and CYP1A2 isoenzymes [16].

Imipramine/Clomipramine – HCQ/CQ

Monitor for QT interval prolongation, as mentioned for other TCAs (section 1.8.1).

Imipramine/Clomipramine – LPV/r and ATV

Mechanism and consequence

Both LPV/r and ATV may increase the serum concentration of mentioned TCAs due to inhibitory effects on the CYP450 isoenzymes [14], [15], [17], [18], [19], [22], [24].

Management

Close monitoring of adverse effects, including QT prolongation, is recommended. Furthermore, a decrease in the dose of TCAs may be required [14], [15], [17], [18], [22].

Bupropion

Bupropion is a major substrate of CYP2B6 isoenzyme [16].

Bupropion – HCQ

No clinically significant interaction was reported [14], [15], [22].

Bupropion - CQ

Mechanism and consequence

Bupropion is a potent inhibitor of CYP2D6 isoenzyme and increases CQ exposure [14]. On the other hand, bupropion applies the dose-dependent risk of seizures, mostly when used concomitantly with medications that decrease the threshold of seizures (e.g., CQ) [15].

Management

Both medications should be initiated with lower doses and titrate slowly based on clinical response. If seizures occur during treatment with bupropion, the drug should be discontinued permanently [15].

Bupropion – LPV/r

Mechanism and consequence

LPV/r reduces the area under curve (AUC) of bupropion by 57% [14], [15], [17], [18], [19], [22], [24], [25]. It seems that the induction of CYP2B6 isoenzyme by ritonavir leads to this interaction, contrary to *in vitro* data, which reports inhibition of CYP2B6 by ritonavir [14], [26].

Management

The efficacy of bupropion treatment should be monitored. Initiating therapy with higher doses is not recommended, but titration of bupropion dose is suggested based on clinical response [14], [15], [17], [18], [22].

Bupropion – ATV

There is no clinically significant interaction [14], [15], [17], [18], [19], [22].

Buspirone

Buspirone is metabolized mainly through the CYP3A4 pathway [16].

Buspirone – HCQ/CQ

No significant interactions were found [14], [15], [22].

Buspirone – LPV/r and ATV

Mechanism and consequence

Inhibitors of CYP3A4 isoenzyme increase the plasma concentrations of buspirone and may lead to Parkinson-like symptoms [14], [15], [17], [18], [22].

Management

It is recommended to initiate therapy with the lowest dose of buspirone and titrate based on clinical response followed by monitoring adverse reactions [14], [15], [17], [18], [22].

Mirtazapine/trazodone

Mirtazapine/trazodone – HCQ/CQ

There is no particular recommendation in this regard. Some references did not report a significant interaction [14], [22], but others have focused on the risk of QT prolongation and recommend using caution in susceptible patients [15], [19].

Mirtazapine/Trazodone – LPV/r and ATV

Mechanism and consequence

Either LPV/r or ATV can increase the serum concentrations of mirtazapine/trazodone [14], [15], [17], [19], [22], [24] through inhibition of CYP3A4 isoenzyme [14], [17].

Management

It is recommended to initiate therapy with lower doses and monitor increased central nervous system adverse effects and QT prolongation [14], [15], [17], [22].

Anti-psychotics

Aripiprazole

Aripiprazole is mainly metabolized through CYP2D6 and CYP3A4 isoenzymes [16].

Aripiprazole – HCQ/CQ

Mechanism and consequence

The risk of clinically significant QT prolongation is not definite [15].

Management

No action is needed [14], [22]. According to some references, QT prolongation may occur in patients with underlying cardiovascular disease or concomitant use of medications, which cause QT prolongation [15], [19], and close ECG monitoring may be required [15].

Aripiprazole – LPV/r

Mechanism and consequence

LPV is a potent inhibitor of CYP 3A4, and ritonavir is a strong inhibitor of CYP3A4 and CYP2D6 isoenzymes. Thus, increased plasma concentrations of aripiprazole are anticipated [14], [22], [24]. Besides, QT prolongation may occur, but it is uncertain [15], [19].

Management

Pharmacological responses should be monitored. Up to 75% dose reduction for aripiprazole may be needed [14], [18]. ECG monitoring is recommended based on some references [15], [19].

Aripiprazole – ATV

Mechanism and consequence

ATV inhibits the CYP3A4 pathway and may increase the plasma concentration of aripiprazole [14], [15], [17], [24].

Management

Aripiprazole dose reduction may be required up to 50% [14], [15], [17], [18], [22]. Consider up to 75% dose reduction if concomitant CYP2D6 isoenzyme inhibitors are used [14].

Clozapine

Clozapine is a major substrate of CYP1A2 and a minor substrate of CYP3A4 and CYP2D6 isoenzymes.

Clozapine – HCQ/CQ

Mechanism and consequence

Both clozapine and antimalarial medications have similar adverse effects such as QT interval prolongation and agranulocytosis, which may increase concomitant use of these medications [14], [15].

Management

Use with caution and monitor for adverse reactions. Discontinue treatment if the QT interval increased more than 500 milliseconds (ms). Modifiable risk factors (e.g., hypokalemia and hypomagnesemia) should be corrected [14], [15].

Clozapine – LPV/r and ATV

Mechanism and consequence

Clozapine plasma concentrations may be increased [14], [15], [17], [18], [19], [22] through inhibitory effects of LPV/r and ATV on hepatic isoenzymes [14], [17].

Management

Clozapine should be initiated with lower doses and titrate gradually with monitoring adverse reactions (e.g., QT prolongation) [14], [15], [17], [18], [24]. Some references suggest avoiding concomitant use of LPV/r with clozapine due to severe hematologic side effects [22].

Olanzapine

Olanzapine is a major substrate of CYP1A2 and a minor substrate of CYP2D6 isoenzyme [16].

Olanzapine – HCQ/CQ

Mechanism and consequence

Some references mention that QT prolongation could occur in high-risk patients [14], [15].

Management

Close ECG monitoring and modifying risk factors may be helpful [14], [15]. One reference does not indicate this interaction [19].

Olanzapine – LPV/r

Mechanism and consequence

Ritonavir induces CYP1A2 isoenzyme and leads to decreased (up to 50%) olanzapine concentrations [14], [15], [17], [19], [22], [23], [24], [27].

Management

Close monitoring for the efficacy of olanzapine and dose adjustment may be required [14], [15], [17], [22]. Furthermore, some references advise monitoring QT intervals in high-risk populations [15].

Olanzapine – ATV

There are no clinically significant interactions [14], [15], [17], [19], [22].

Quetiapine

Quetiapine is mainly metabolized through CYP3A4 hepatic isoenzyme [16].

Quetiawpine – HCQ/CQ

As mentioned for olanzapine – HCQ/CQ (Refer to 2.3.1) [14], [15], [19]. Furthermore, due to additive hypoglycemic effects of concomitant QC administration, one reference advices to monitor for hypoglycemia [14].

Quetiapine – LPV/r and ATV

Mechanism and consequence

PIs increase the AUC of quetiapine (up to 6 times) by inhibiting CYP3A4 isoenzyme.

Management

Some references recommend avoiding coadministration [17], [19]; however, some recommend using lower doses of quetiapine. Initiate with the lowest dose of quetiapine and titrate gradually based on the adverse effects and efficacy of the medication. If the patient is stable on a specific dose of quetiapine, it is recommended to reduce the dose by 1/6, if PI is required. Monitor for adverse effects, including QT prolongation [14], [15], [18], [22], [23], [24].

Risperidone

Risperidone is a major substrate of CYP2D6 and CYP3A4 isoenzymes and P-glycoprotein/ABCB1.

Risperidone – HCQ/CQ

The same as olanzapine (Refer to 2.3.1) [14], [15], [19], [22].

Risperidone – LPV/r

Mechanism and consequence

LPV/r increases risperidone exposure through inhibitory effects on CYP2D6 isoenzyme and P-glycoprotein/ABCB1 [14], [15], [17], [19], which may cause risperidone dependent adverse effects including extrapyramidal syndrome and neuroleptic malignant syndrome [17], [22]. Furthermore, dose-dependent QT interval prolongation may occur [14], [15], [17], [22].

Management

Decreased risperidone dose and monitoring for adverse drug reactions are required [14], [15], [17], [18], [22].

Risperidone – ATV

Some references indicate the same interactions that mentioned about LPV/r (refer to 2.5.2) [17], [18], [19], but others declare no interactions between risperidone and ATV [14], [15], [22].

Chlorpromazine/fluphenazine/perphenazine/thioridazine

These medications are metabolized mainly through CYP2D6 isoenzyme [16].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – HCQ/CQ

Mechanism and Consequence

In addition to the QT prolongation effect, which was mentioned for other anti-psychotics, anti-malaria agents could increase the concentrations of phenothiazine-based anti-psychotics by an unknown mechanism [14], [19].

Management

Monitoring for side effects (e.g., QT prolongation) and modifying underlying risk factors should be considered [14], [15], [19].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – LPV/r

Mechanism and consequence

LPV/r could potentially increase plasma concentrations of these anti-psychotics. Additive QT interval prolongation may occur in coadministration [14], [15], [17], [19].

Management

Use with caution as stated for CQ and HCQ (refer to 0) [14], [15], [17], [19].

Chlorpromazine/fluphenazine/perphenazine/thioridazine – ATV

There are inconclusive data. Some references report no interactions [14], [15]; however, one reference remarks QT prolongation in coadministration and recommends close monitoring in this regard [17].

Haloperidol

Haloperidol has a complex pathway of metabolism, including glucuronidation, oxidation, CYP3A4, and CYP2D6 isoenzymes mediated reactions [16], [17].

Haloperidol – HCQ/CQ

Mechanism and Consequence

Concomitant administration of two medications with QT interval prolongation may have additive side effects and lead to serious cardiac arrhythmias. This interaction is more frequent when higher doses or intravenous haloperidol is administered [14], [15], [19].

Management

Close monitoring for adverse reactions and correcting modifiable risk factors such as electrolyte abnormalities are necessary [14], [15].

Haloperidol – LPV/r and ATV

Mechanism and consequence

LPV/r and ATV increase haloperidol exposure by inhibition of CYP2D6 and CYP3A4 isoenzymes, which may lead to increased adverse effects such as QT prolongation [14], [15], [17], [24].

Management

Use caution and monitor as mentioned for HCQ and CQ (Refer to 2.7.1) [14], [15], [17].

Pimozide

Pimozide is metabolized through CYP3A4 isoenzyme.

Pimozide – HCQ/ CQ

Mechanism and Consequence

QT interval prolongation is the main interaction, as mentioned for concomitant use of other anti-psychotics with other medications that have the same effect [14], [15], [19].

Management

Most of the references advise to avoid coadministration of CQ [14], [15], but there are controversial recommendations regarding HCQ. One database recommends avoidance [15]; however, another one suggests not taking any action [14], and the other reference advises monitoring for adverse effects [19].

Pimozide – LPV/r and ATV

Concomitant use of pimozide with PIs is contraindicated due to increased pimozide levels by CYP3A4 isoenzyme inhibitory effects of PIs. Increased exposure to pimozide may lead to lethal cardiac arrhythmias [14], [15], [17], [18], [19], [22], [24].

Sedative/Hypnotics

Alprazolam/chlordiazepoxide/clonazepam/ diazepam

These medications are major substrates of CYP 3A4 isoenzyme [16].

Alprazolam/Chlordiazepoxide/Clonazepam/ Diazepam – HCQ/CQ

There are no clinically significant interactions [14], [15], [19], [22].

lprazolam/Chlordiazepoxide/Clonazepam/ Diazepam – LPV/r

Mechanism and Consequence

LPV/r may increase the plasma concentrations of mentioned benzodiazepines by inhibiting the CYP3A4 pathway [14], [15], [17], [28].

Management

Monitor for increased adverse reactions of benzodiazepines and reduce medication dose if needed, especially in the initiation of therapy. It is recommended to use alternative benzodiazepines with less probable interactions such as lorazepam, oxazepam, and temazepam [14], [15], [17], [18], [23]. There are conflicting data regarding the coadministration of diazepam and ritonavir. Some references recommended avoiding this combination, but most of them recommended monitoring, dose adjustment, or using alternative medications when ritonavir is used as a booster (*e.g.,* LPV/r) [17], [22], [23].

Alprazolam/Chlordiazepoxide/Clonazepam/ Diazepam – ATV

Mechanism and consequence

ATV may increase the serum concentrations of these benzodiazepines, but there is no ample clinical evidence [14], [17], [18], [19].

Management

As stated for LPV/r [14], [17], [18].

Temazepam/lorazepam/oxazepam

These medications are metabolized through non-CYP450 hepatic pathways [16]; thus, there are no clinically significant interactions with HCQ, CQ, LPV/r, and ATV [14], [15], [16], [17], [18], [19].

Triazolam/midazolam

Triazolam/midazolam – HCQ/CQ

No clinically significant interaction was reported [14], [15], [19], [22].

Triazolam/Midazolam – LPV/r and ATV

Mechanism and consequence

LPV/r inhibits CYP3A4 isoenzyme; therefore, the concentrations of mentioned benzodiazepines are increased, which may lead to respiratory failure [14], [15], [17], [18], [19], [23], [29].

Management

The administration of triazolam/oral midazolam should be avoided. The parental form of midazolam could be used with caution and reduced dose [14], [15], [17], [18], [19].

Zolpidem/zopiclone

These medications are mainly metabolized through CYP3A4 isoenzyme [16].

Zolpidem/Zopiclone – HCQ/CQ

No clinically significant interaction was reported [14], [15], [19], [22].

Zolpidem/Zopiclone – LPV/r and ATV

Mechanism and consequence

Increased sedation may occur due to inhibition of CYP3A4 isoenzyme.

Management

Patients should be monitored closely. Reducing the dose of zolpidem/zopiclone may be required [14], [15], [17], [18], [19], [29].

Mood stabilizers

Carbamazepine

Carbamazepine is a strong CYP3A4 isoenzyme inducer [16].C*arbamazepine – HCQ*

No clinically significant interaction was found [14], [15]; however, according to one reference, this combination should be avoided [19].

Carbamazepine – CQ

Mechanism and consequence

Carbamazepine may decrease the plasma concentration of CQ through CYP3A4 pathway induction [14], [15]. CQ-induced seizures have been reported [15], [16].

Management

Monitor for decreased effects of CQ [14] and use with caution in patients with a history of seizure [15], [16]. One reference recommended avoiding combination [19].

Carbamazepine – LPV/r

Mechanism and consequence

Carbamazepine may decrease the LPV/r concentrations, and LPV/r may increase the carbamazepine concentrations in plasma through the CYP3A4 pathway [14], [24], [30], [31].

Management

Consider alternative medications and monitor plasma concentrations of carbamazepine [14], [17]. An increment in LPV/r may be required [17]. Once-daily administration of LPV/r should be avoided [17], [18], [24].

Carbamazepine – ATV

Mechanism and consequence

Decreased plasma concentrations of ATV due to the induction of CYP3A4 isoenzyme, which may lead to viral resistance [14], [15], [17]. Carbamazepine concentrations may be increased through CYP3A4 isoenzyme inhibition [14], [17].

Management

Coadministration should be avoided [15], [17], [18]; if the use of combination is necessary, plasma concentrations of carbamazepine should be monitored [17].

Valproate

Valproate – HCQ

There is no clinically significant interaction [14], [15], [19].

Valproate – CQ

Mechanism and consequence

Seizure threshold may be decreased by CQ [15]. According to some other references, no clinically significant interaction was found [14], [19], [22].

Management

Use CQ with caution in patients with seizures [15].

Valproate – LPV/r

Mechanism and consequence

The combination increases the AUC of LPV by up to 38%. Valproate serum concentrations are decreased through induction of CYP450 enzymes, especially glucuronosyltransferases [15], [17], [18], [22], [24], [32], [33].

Management

Monitor clinical response and serum levels of valproate [14], [17], [18], [22].

Valproate – ATV

Mechanism and consequence

ATV may decrease serum levels of valproate [14], [18]. Some other studies did not report this interaction [17], [19], [22].

Management

Clinical response and serum concentrations of valproate should be monitored [14], [18].

Lithium

Lithium – HCQ/CQ/LPV/r

Mechanism and consequence

Lithium and CQ/HCQ/LPV/r can prolong QT interval, especially in patients with underlying cardiovascular disease or electrolyte abnormalities [15], [19].

Management

Correction of electrolyte abnormalities and monitoring symptoms of QT prolongation is required [15].

Lithium – ATV

No clinically significant interaction was found [14], [15], [19], [22].

Lamotrigine

Lamotrigine – HCQ

There is no clinically significant interaction [14], [15], [19], [22].

Lamotrigine – CQ

Mechanism and consequence

CQ-induced seizure may occur [15], [16]. Other references indicated no significant interaction [14], [19], [22].

Management

Use CQ with caution in patients with a history of seizures [15], [16].

Lamotrigine – LPV/r

Mechanism and consequence

The glucuronidation of lamotrigine enhances by LPV/r [14], [15]; thus, the lamotrigine AUC and half-life reduce by 50% [14], [17], [18], [24], [34].

Management

The lamotrigine dose increment may be needed [17], [18], [22].

Lamotrigine – ATV

Mechanism and consequence

ATV may decrease the lamotrigine AUC up to 12%, but it is not clinically significant [22], [35].

Management

Monitor serum levels of lamotrigine. Approximately all references recommended no need for dose adjustment [14], [15], [17], [18], [19], [22].

Discussion

Physicians, psychologists, pharmacologists, pharmacotherapists, and other drug experts are at the forefront during the COVID-19 pandemic. Pharmacological consultants were always needed hospital care procedures [36]. Furthermore, to provide an up to date information for public and specialists population, application of pharmacokinetic and pharmacodynamic investigations, especially during clinical trials, is essential [37], [38]. In this regard, the study of drug interactions is an important pharmacological preventive procedure to manage multiple drug consumption consequences. Hence, assessing drug-drug interactions with particular focus on psychiatric medications during the COVID-19 pandemic is highly vital, while many patients in different age categories suffer from mental disorders, and their conditions have worsened due to the current situation, especially during quarantine and isolation.

More than 300 clinical trials on various therapeutic approaches are ongoing for COVID-19 [15]. Some of the tested medications, in this case, are highly potential for interacting with individuals' chronic treatments. These interactions mostly appear due to pharmacokinetic features such as induction/ inhibitory effects on cytochrome isoenzymes and renal excretion, or pharmacodynamic properties such as QT prolongation. Furthermore, due to the extensive inflammation in COVID-19 patients, the pharmacokinetic performance of the drugs can be affected through organ dysfunction, CYP isoenzymes downregulation, plasma proteins modification, etc. [39], [40], [41].

Hence, psychiatric drug interactions with experimental agents administered for COVID-19 should be considered carefully. Interactions between psychotropic drugs and drugs used for the treatment of COVID-19 have a wide range of severity from slight changes in the plasma level of the affected drug to life-threatening conditions [42]. Thus, it was essential to prepare a detailed list of all widely used medications in such patients to improve outcomes and prevent adverse drug reactions and drug-drug interactions. We hope the list provided in this review helps the clinical care staff in treating such patients during the COVID-19 pandemic.

Conclusion

Knowledge about SARS-CoV-2 infection is still evolving. There are various projected medications for COVID-19 patients, which might be used in individuals under other chronic treatments, especially patients with mental disorders. Concomitant consumption of these medications may lead to drug interactions and acute adverse effects on the patient's outcome. However, the risk of such interactions can be manageable through an ample knowledge of pharmacokinetic and pharmacodynamic regarding these drugs. Eventually, safe treatment in these patients could be managed by applying measures such as close monitoring, dosage adjustment, and considering relative/absolute contraindications and indications.

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Severe Acute Respiratory Syndrome-coronavirus 2 Interstitial Bilateral Pneumonia: A Case Report and Review of Literature

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Abstract

In December 2019, novel cases of pneumonia were reported for the 1st time in Wuhan, Hubei, China. A novel virus of the big family of coronavirus (COV) was identified as the pathogen, which causes severe acute respiratory syndrome (SARS). The disease is called COV Disease-19 and then SARS-COV 2. The infectious disease has spread worldwide with major number of patients in China, Italy, Spain, France, and the USA. On March 11, 2020, the WHO declared the outbreak of SARS-CoV-2 a pandemic. Morbidity and mortality of the disease cannot yet estimate but have already seen that lethality appears to be particularly higher in older patients. The aim of this article is to present a characteristic clinical picture as case report SARS-COV 2 pneumonia and to provide an overview of the existing literature.

Introduction

In December 2019, many pneumonia cases were reported in China, Wuhan. The source has shown Huanan Seafood Market as the origin discovering an unexplained pneumonia on December 12, 2019 [1]. On January 22, 2020, novel coronavirus (CoV) has been declared to be originated from wild bats as part of beta-COV who cause severe acute respiratory syndrome-associated COV (SARS-CoV). COVs are zoonotic pathogens that are present in humans and various animals with a wide range of clinical features from asymptomatic course to requirement of hospitalization in the intensive care unit, causing infections in respiratory, gastrointestinal, hepatic, and neurologic systems. All CoVs are pleomorphic RNA viruses characteristically crown shape with 80–160 nM in size and 27–32 kb positive polarity [2], [3], [4], [5]. The disease caused by SARS-CoV-2 is called COV disease (COVID)-19 which has since spread worldwide with major number of patients in China, Italy, Spain, France, and the USA. On March 11, 2020, the WHO declared the outbreak of SARS-CoV-2 a pandemic. Morbidity and mortality of the disease cannot yet estimate but have already seen that lethality appears to be particularly higher in older patients. In a cohort study of 41 hospitalized patients, fever, dry cough, myalgia, and fatigue symptoms were reported in most patients, and less often, symptoms of expectoration, headache, hemoptysis, and diarrhea were also observed [6]. Comorbidities such as underlying hypertension, diabetes mellitus, and cardiovascular disease, and autoimmune diseases were found in about half of these patients. Dyspnea, acute respiratory distress syndrome, and cardiovascular complications accompanied by abnormal thorax computed tomography (CT) compatible with pneumonia mean 8 days after the admission. X-rays or thorax CT images of the patients revealed bilateral multilobar ground-glass opacities (GGOs), with peripheral posterior distribution [7], [8].

The aim of this article is to present a characteristic clinical picture as case report as SARS-COV-2 pneumonia and to provide an overview of the existing literature.

Case report

A 60-year-old man with a medical history of prostatectomy for cancer, osseous metastases, and hormone therapy, presented to the emergency department in mid-March after fever, cough, ageusia, and anosmia at home for 20 days. He referred myalgias and cough at the beginning followed by fevers and said that his symptoms persisted despite the medication with paracetamol and antibiotics. The patient stated that he had shortness of breath in the past 3 days. He had had no recent travel outside of the state or internationally. On admission, the patient was afebrile with a mild non-productive cough. He had limitation in exercise tolerance during this acute illness. Admission vital signs were heart rate 80 beats/min, blood pressure 150/90 mmHg, respiratory rate 18, pulse oximetry 99% on air, and temperature 36.5°C. The results of routine laboratory parameters are shown: Leukocytes 10.78 × 10^3/mmc, lymphocytes 17.6%, D-DIMERO 5.246 ng/ml fibrinogen equivalent units, Polymerase Chain Reaction (PCR) 1.10 mg/dl, and pro-calcitonin 0.03 ng/ml. Arterial blood gases (ABGs): pH 7, 450, PCO_2 35.0 mmHg, PO_2 68.0 mmHg, PO_2/FiO_2 (P/F ratio) 324.0 mmHg. PCR testing for other respiratory viruses, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, on the throat swab was negative. Nose and throat samples for SARS-CoV-2 PCR were obtained that returned positive. Examination of the lungs reveals murmur reduced and reduce vesicular murmur and tactile vocal fremitus bilaterally. He had also bilateral scleral injection. After arrival, the patient was placed on maximum isolation precautions (negative pressure room, with anyone entering the room required to wear an N95 respirator, face shield, disposable gown, and gloves). A CT chest showed bilaterally multiple patchy GGOs and crazy paving is seen. Some of the opacities are round and some geographic shaped. Partially, the lesions are sharply demarcated against the surrounding healthy lung. The left lower lobe and the periphery of the lungs are predominantly involved (Figure 1a-i). He subsequently worsened because of his SO_2 became 85% despite 12/l/min of oxygen and his P/F ratio was inferior to 200 in a new ABG. Hence, he was admitted in an intensive care unit for mild respiratory failure. He was treated with oxygen therapy using continuous positive airway pressure, adjusted following continuous ABG. We associated antibiotics such as azithromycin 500 mg a day, hydrossicloroquine 400 mg day for the first 48 h, and then 200 mg for other 10 days and enoxaparin adjusted following patient weight. Darunavir/cobicistat 800/150 mg a day was avoided because 20 days of symptoms onset and tocilizumab was not necessary because the patients improved. He was discharged 15 days after.

Discussion

Novel CoV has been declared to be originated from wild bats as part of beta-COV who cause SARS-associated COV (SARS-CoV). COVs are zoonotic pathogens that are present in humans and various animals with a wide range of clinical features from asymptomatic course to requirement of hospitalization in the intensive care unit, causing infections in respiratory, gastrointestinal, hepatic, and neurologic systems. Coronaviridae was discovered in the 1960s. The name COV originates from the Latin word corona, meaning "crown" or "halo," due to its characteristic appearance under two-dimensional transmission electron microscopy. COVs have club-shaped spike peplomers covering their surfaces [9] (Figure 2a and b). SARS-CoV, Middle East respiratory syndrome (MERS)-CoV, and SARS-CoV-2 belong to the Coronaviridae family. This family of viruses contains a relatively large single-stranded, positive-sense RNA genome of around 27–32 kb. The most important potential therapeutic target is the spike (S) glycoprotein, which is responsible for the binding of the virus to the host cells. It has been reported that the binding of the viral S protein to angiotensin-converting enzyme (ACE)2 receptors. Increased ACE activity consequently results in the elevated levels of angiotensin II. Once angiotensin II binds to its receptor, AGTR1A, pulmonary vascular permeability is increased [10], [11], [12]. As of April 06, 2020, a total of 1,285,257 cases of COVID-19 occurring in at least 170 countries and territories were reported, with approximately 5.4 % of fatality rate

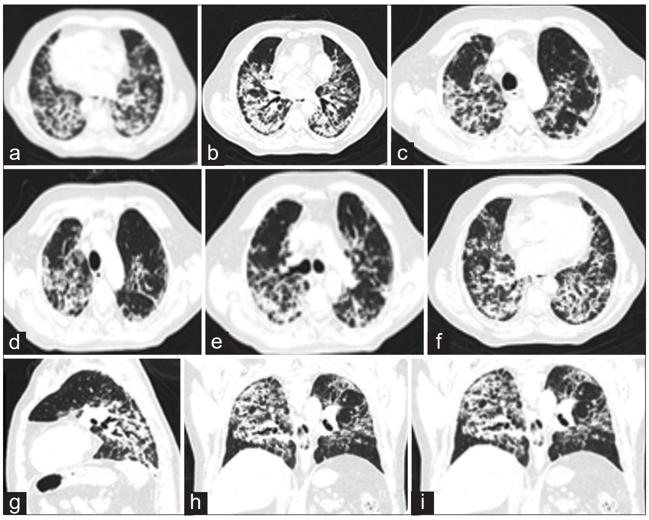

Figure 1: (a-i) Bilaterally multiple patchy ground-glass opacities and crazy paving are seen. Some of the opacities are round and some geographic shaped. Partially, the lesions are sharply demarcated against the surrounding healthy lung. The left lower lobe and the periphery of the lungs are predominantly involved Images

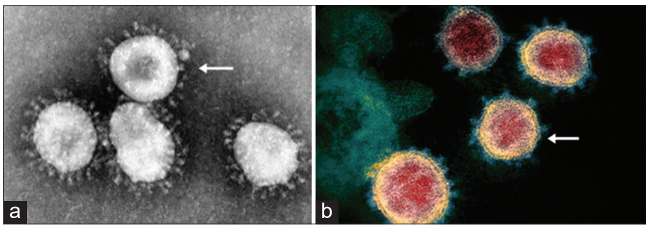

Figure 2: (a and b) Electron microscopy image of SARS-CoV-2

(70,344/1,285,257) [13]. In a study of 1099 patients in China with confirmed COVID-19, the most commonly reported symptom was fever (43.8% on initial admission and 88.7% during hospitalization) followed by cough (67.8%) [14], [15]. Atypical chest and back pain has also been reported as presenting symptoms. Chest CT is more efficient in detecting pneumonia at the early stages of COVID-19. The most common patterns of COVID-19 on chest CT scans include multiple GGO (56.4%), and bilateral patchy shadowing (51.8%), and the other patterns consist of local patchy shadowing (28.1%) and interstitial abnormalities (4.4%) [6], [16], [17]. Today, there is no vaccine or effective treatment to prevent COVID-19 infection. Early diagnosis, reporting, isolation, and basic measures such as hand washing, using disinfectant solutions, avoiding contact with patients, and supportive treatments are the most helpful. There are publications demonstrating that remdesivir has a strong antiviral activity in epithelial cell cultures against SARS-CoV, MERS-CoV, and related zoonotic bat CoV [18], [19]. As part of MERS cure, a randomized control trial (MIRACLE Trial 2016) from South Korea determines that the combination of lopinavir/ritonavir (anti-HIV drugs), pegylated interferon, and ribavirin provided a successful viral clearance [16]. Chloroquine, typically used in the context of malarial or autoimmune disease, has also shown promising results [20], [21]. Tocilizumab is a humanized monoclonal antibody against interleukin-6 receptor (Ab), commonly used as an immunosuppressive in the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis seems to be successful [22], [23]. The duration between onset of symptoms and isolation is about 6 days, and it is expected that each 1 day reduction in this period will decrease the size of peak population by 72–84% and cumulative infected cases and deaths by 68–80%. It is estimated that with the effects of integrated interventions such as promoting the use of face masks and reduced traveling, each 10% reduction in transmission rate, the size of peak population will decrease by 20–47%, and cumulative infected cases and deaths will decrease by 23–49% [24].

Conclusions

SARS-CoV-2 is the COV responsible for the COVID-19 pandemic of 2020. The mean incubation time is 5.1 days (95% confidence interval [CI]: 4.5–5.8 days), with 97.5% of those who develop symptoms doing so within 11.5 days (95% CI: 8.2–15.6 days). Symptoms may vary from mild to severe. Those most affected by COVID-19 are those of advanced age and those with pre-existing chronic medical conditions. Mortality rates are currently unknown: From 0.25% to 10%. Treatment options are limited. Supportive care is the best choice. Ongoing studies are evaluating the efficacy of remdesivir, chloroquine, hydroxychloroquine, tocilizumab, lopinavir, and ritonavir. At present, no vaccine is available but there are progresses to developing a vaccine over the coming year.

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A Review on the Novel Coronavirus and Its Effects on Children

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Abstract

BACKGROUND: The outbreak of the new coronavirus was first reported in China and then spread to other parts of the world. The number of people infected with the virus is significantly increasing, making the disease an international concern.

AIM: The present study aimed to investigate the coronavirus and its effects on children.

MATERIALS AND METHODS: In the present study, search engines, and scientific databases of Google Scholar, Science Direct, PubMed, Medline, and Cochrane were searched to examine the effect of coronavirus on children. To collect information, keywords were also searched in the databases.

RESULTS: In spite of contradictory results, among the children, those under 5 years old are the high-risk group.

CONCLUSION: Some researchers believe that the virus shows fewer symptoms in children. However, the immune system of infants under six months develops pneumonia in rare cases.

Introduction

Coronavirus (CoV) is a severe infectious agent in human and animal, which causes systemic disorder in respiratory and gastrointestinal tracts. CoV can infect certain species of animals, including mammals, bird, and reptiles [1]. On January 3, 2020, a new member of the CoV enveloped RNA was identified in bronchoalveolar lavage fluid samples of a patient in Wuhan and subsequently confirmed as the cause of the disease by the Centers for Disease Control and Prevention (CDC, China) [2]. The pathogenicity of this virus is that after the virus enters the body, it first binds to specific receptors on the cells with proper binding feature. Then, it enters the cell and uses its transcription machinery, multiplying it in large numbers and causing cellular damage [3].

Most of the patients are adults, with a small number of children. Out of 44,672 laboratory-confirmed cases of COVID-19 in China, only 2.1% are under 19 years old.

Studies have shown that COVID-19 has the highest mortality in the elderly. It also causes mild-to-severe respiratory problems in children, with mortality and morbidity lower than other age groups. Most children patients show mild symptoms, with no fever or signs of pneumonia [4], [5], [6], [7].

Given that one of the concerns of the health sector regarding the dangerous consequences of CoV is the dangers of this disease in a vulnerable community of children. There are many questions about the effect of the virus and ways to prevent children from getting the disease. An important issue is recognizing the virus and providing a reliable treatment strategy such as vaccination. Therefore, in the present study, an attempt is made to examine its effect on children and the proposed treatment options by examining the published articles on COVID-19 and the development of new CoV in children.

Materials and Methods

Search strategy

This evaluation was conducted in January and February 2020. Search engines and scientific databases of Google Scholar, Science Direct, PubMed, Medline, and Cochrane were used for obtaining papers on CoV and its effect on children. The keywords were also searched in the databases to collect information on the CoV, including corona, CoV and children, CoV pathogenesis, the virus structure, and COVID-19.

Priority was given to articles from the past year. A reference list of relevant articles was searched to identify additional articles. In addition, search engines such as Google and Google Scholar were used to identify all potential eligible publications. The operators were used to find related articles. The study was conducted from July 5, 2020, to September 5, 2020.

Inclusion and exclusion criteria

Inclusion criteria included articles published after December 1997 to the end of January 2020, qualitative, descriptive, analytical study and articles published in English and Persian. Editorial letters, case studies, and clinical studies were excluded. Furthermore, articles with inadequate reports and a study whose full text was not available were excluded from the study.

Screening and data mining

A trained author performed search strategies. In the first stage, the titles and abstracts were reviewed for the selection of articles, in the next stage, an author independently reviewed the full text of the articles. Differences in findings were resolved through the criterion method of general conclusion of articles and in this study, were organized. Qualitative evaluation of articles was done by preparing a list of titles and summaries of studies in databases and selecting them based on the purpose of the study and content.

CoVs

CoVs are a large family of viruses that cause a flu-like illness in birds and mammals, accounting for 15–30% of common colds. They are spherical or polymorphic viruses containing a positive-sense single-stranded RNA with protein capsid nucleoprotein. There are several CoVs common between human and animal that usually cause mild-to-moderate infections in upper respiratory tract, such as the common cold. The virus rarely evolves and transmits from other animals to human. COVID-19 is a mutant of the CoVs family [2], [8].

The recombination rate of the virus is high because of the RNA-dependent RNA polymerase transcription (RdRPs) and constant transcription errors. However, despite the high mutation, CoVs are a zoonotic pathogens that vary between human and animal with a wide range of clinical manifestation from asymptomatic to requiring hospitalization due to infection in the respiratory, gastrointestinal, liver, and nervous systems [9], [10]. CoV is structurally related to middle East respiratory syndrome and severe acute respiratory syndrome (SARS).

CoV, SARS, and MERS

6LU7 is the COVID-19 main protease (Mpro), which been structured and repositioned in PDB and can be accessed by the public, as of early February 2020. The Mpro of 2019-nCov shares 96% similarity with the Mpro of the SARS-CoV [11]. The Mpro in CoV is essential for the proteolytic maturation of the virus and has been examined as a potential target protein to prevent the spread of infection by inhibiting the cleavage of the viral polyprotein [12]. The discovery of the structure of the Mpro proteinase in COVID-19 provides an excellent opportunity to identify potential drug candidates for treatment.

Proteins represent potential targets for the inhibition of CoV replication, and the protein sequences of the SARS-CoV Mpro and 2019-nCoV Mpro are 96% identical, and the active sites in both proteins remain free from mutation. Thr24, Thr26, and Asn119 amino acids are predicted to be involved in drug interactions [13]. Therefore, usually, host proteases can be used as potential therapeutic targets. In many viruses, proteases play important roles in viral replication; therefore, proteases are commonly used as protein targets during the development of antiviral drug treatment [14].

Nelfinavir and lopinavir are protease inhibitors with high cytotoxic against HIV-infected cells. Lopinavir and ritonavir are protease inhibitors recommended for the treatment of SARS and MERS, which have similar mechanisms of action as HIV. The antiviral effects of nelfinavir on CoV have been studied *in vitro*, in Vero cells infected with SARS-CoV [15], [16]. It is important to pay attention to how infection develops in COVID-19 disease.

Infection

Scientists exploring how CoVs like COVID-19 infect human cells have shown that the SARS-CoV-2 spike (S) glycoprotein binds to the cell membrane protein angiotensin-converting enzyme 2 (ACE2) to enter human cells. COVID-19 has been shown to bind to ACE2 through the S protein on its surface. During infection, the S protein is cleaved into subunits, S1 and S2. S1 contains the receptor binding domain (RBD) which allows CoVs to directly bind to the peptidase domain (PD) of ACE2. S2 then likely plays a role in membrane fusion. Chinese researchers have now used cryogenic electron microscopy to study the structure of the ACE2 when it is bound to one of its typical ligands, the amino acid transporter B0AT1, and also how the COVID-19 RBD may bind to the ACE2-B0AT1 complex. These structures have previously not been identified and could aid in producing antivirals or a vaccine that can block CoV infection by targeting ACE2 (Figure 1) [3].

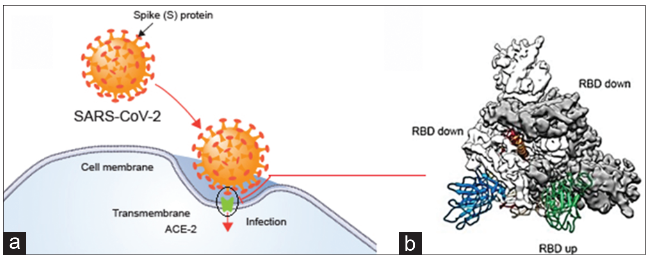

Figure 1: (a) Connection of the S1 receptor to the ACE2 receptor on the pulmonary cells. (b) Three-dimensional structure of the coupled receptor. S1 contains the receptor binding domain which allows coronaviruses to directly bind to the peptidase domain of ACE2

The signs, symptoms, disease progression, and severity

Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. As of February 20, 2020, and based on 55,924 laboratory-confirmed cases, typical signs and symptoms include fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%) (WHO, 2019).

People with COVID-19 generally develop signs and symptoms, including mild respiratory symptoms and fever, on an average of 5–6 days after infection (mean incubation period 5–6 days, range 1–14 days) (WHO, 2019).

Most people infected with COVID-19 virus have mild disease and recover. Approximately 80% of laboratory confirmed patients have had mild–to-moderate disease, including non-pneumonia and pneumonia cases, 13.8% have severe disease. Asymptomatic infection has been reported, but the majority of the relatively rare cases who are asymptomatic on the date of identification/report went on to develop disease. The proportion of truly asymptomatic infections is unclear but appears to be relatively rare and does not appear to be a major driver of transmission. People at high risk for serious illness and death include people over 60 years and those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer. Disease in children appears to be relatively rare and mild, with approximately 2.4% of all reported cases among cases under 19 years old. A very small proportion of those under 19 had severe (2.5%) or critical (0.2%) disease [17], [18], [19].

Mortality increases with age, with the highest mortality among people over 80 years of age (case fatality rate [CFR] 21.9%). The CFR is higher among males compared to females (4.7% vs. 2.8%). By occupation, patients who reported being retirees had the highest CFR at 8.9%. While patients who reported no comorbid conditions had a CFR of 1.4%, patients with comorbid conditions had much higher rates: 13.2% for those with cardiovascular disease, 9.2% for diabetes, 8.4% for hypertension, 8.0% for chronic respiratory disease, and 7.6% for cancer [19].

CoVs in children

According to a new study, CoV disease 2019 (COVID-19) has shown mild symptoms among children in China. However, the young age group is not entirely aware of the virus. Infants had a higher disease rate than older children. It is suggested that further investigation is needed to understand the role of children in the spread of the virus in the community. Approximately 75% of suspected children had COVID-19. Regarding the gender, no significant difference was observed. Approximately 4% of children patients were asymptomatic, 51% had mild and 39% had moderate symptoms. Moreover, compared to 18.5% of adults, approximately 6% of children showed severe or critical condition (with a 14-year-old boy dead). The gap is perceived to be confusing to researchers, suggesting that it may be related to both exposure and host factors. Several reasons were proposed, including (a) children's low exposure to the virus; (b) high levels of antibodies against viruses; and (c) developing different immune responses. The virus may also not bind to children's cells. The present study also found that the illness in infants is more serious than in older children. Compared to 7% of children aged 1–5 years, only 11% of infants had severe or critical condition [20]. A similar study suggested that children are more susceptible to upper respiratory tract involvement rather than lower respiratory tract involvement. There is also evidence of stool shedding for several weeks after diagnosis leading to concerns about oral–fecal transmission of the virus, especially in infants and toddlers who are not toilet trained, and for viral replication in the gastrointestinal tract [6].

Data on individuals aged 18 years old and under suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). Within Wuhan, among testing of ILI samples, no children were positive in November and December of 2019 and in the first 2 weeks of January 2020. From available data, and in the absence of results from serologic studies, it is not possible to determine the extent of infection among children, what role children play in transmission, whether children are less susceptible or if they present differently clinically (i.e., generally milder presentations). The Joint Mission learned that infected children have largely been identified through contact tracing in households of adults. Of note, people interviewed by the Joint Mission Team could not recall episodes in which transmission occurred from a child to an adult [19].

Clinical manifestations

The virus was found in pediatric patients, from 1-month-old infants to 19 years old, and based on the evidences, most have been infected by family members [4]. General symptoms of the early patients included fever 98%, cough 76%, muscle aches or fatigue 44%, shortness of breath (in 2 months old infants, with cough, difficulty breathing, and breathing faster than 60/min; in 1–5 years old infants, with cough, difficulty breathing, and breathing faster than 40 breaths/min) 55%, and acute respiratory distress syndrome (ARDS) 29%. In another study, lymphopenia (a decrease in the number of lymphocytes in the blood) was seen in 80% of adult patients, while <25% of children patients had mild lymphopenia, indicating the severity of infection in these patients. Chest computed tomography (CT) of children showed only one patient with bilateral ground-glass opacity, as in adults [5]. In another report by Xia on 20 children, 70% of cases showed leukopenia, 10% leukocytosis, and 35% lymphopenia. Eight cases were found to be infected with other respiratory pathogens such as mycoplasma and influenza. Lung scan also showed 10 abscesses on both sides of the lung. In 6 cases, only one side of the lung had abscess, and in 12 cases, there observed ground-glass opacities [21].

General symptoms include fever 99%, dry cough 59%, and muscle pain or fatigue 70%. Furthermore, 26% of patients were transferred to ICU and 4% of them died. Interestingly, 41% of patients were infected in hospitals. Severe cases of ARDS and acute kidney failure have also been reported. Symptoms the patients may develop include increased C-reactive protein (CRP) protein, erythrocyte sedimentation rate, lactate dehydrogenase, creatinine, and prothrombin clotting time [17]. Another study by Wei *et al*. indicated that all children were infected by their family members, showing mild symptoms [22].

Inflammatory markers including CRP and procalcitonin showed a 13.6% and 10.6% increase, respectively [10]. After studying four infected children, two showed respiratory disorder and one severe decrease (1 mg/L) in CRP. It is while both proteins in the progressed stages significantly increased in adults [23]. Children CT showed opacity in different regions. The damage was largely similar to that of adults (Figure 2). An important issue was the change in CRP protein and lymphocytes, in which, while the latter had many changes, the former changed a little, indicating a significant difference compared to adults [23], [24].

Important points

There are several salient points from this article. First, although children are less likely than older adults to become severely ill, there are subpopulations of children with an increased risk for more significant illness. These data on disease severity are consistent with data on non-COVID-19 CoVs. The authors of one viral surveillance study in a PICU in China reported that CoV was detected in more children with ARDS than *Human metapneumovirus* [27]. The authors of another study conducted on hospitalized Norwegian children detected CoVs in 10% of hospitalized children with respiratory tract infections [6]. Younger age, underlying pulmonary pathology, and immune compromising conditions have been associated with more severe outcomes with non-COVID-19 CoV infections in children [28].

Second, the attributable risk for severe disease from COVID-19 in children is challenging to discern. The previous studies have revealed that children from whom CoVs are detected from the respiratory tract can have viral coinfections in up to 75% of cases [27]. In the study by Dong *et al*. [4], testing for other viruses was not standardized, and two-thirds of cases were clinically diagnosed, not virologically confirmed. In addition, children without virological confirmation were more likely to have severe disease than children from whom COVID-19 was detected, potentially because their symptoms were caused by other pathogens [29].

Third, children may play an important role in community-based viral transmission.

Fourth, most children are at a high level of immune function. According to studies, while the lymphocytes had many changes, the CRP protein changed a little [24]. Studies showed that an increase in lymphocytes is associated with specific immunity. In people with stronger immune system, lymphocytes, especially T lymphocytes, act more rapidly and specifically eliminate the pathogen. On the other hand, in people with weaker immune system, COVID-19

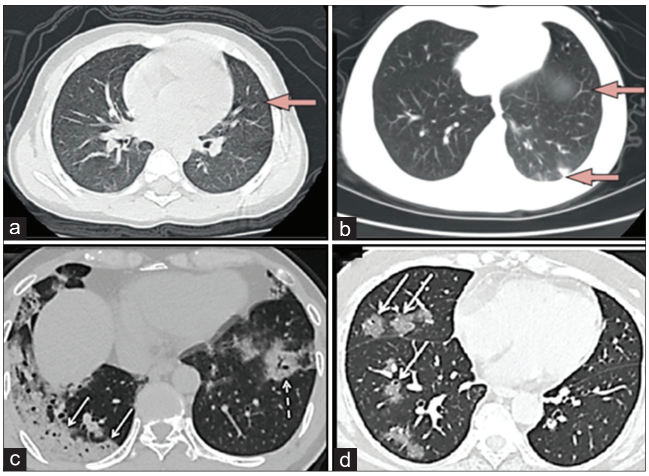

Figure 2: (a) Computed tomography (CT) of a 10-year-old boy showing multiple opacities in lower lobes of both lungs (arrow); (b) CT of a 1.5-year-old girl showing multiple ground-glass opacities with a big patchy opacity in the right lung (arrows); (c) an axial CT image obtained without intravenous contrast in a 42-year-old male in the "late" time group (10 days from symptom onset to this CT) shows bilateral consolidative opacities, with a striking peripheral distribution in the right lower lobe (solid arrows), and with a rounded morphology in the left lower lobe (dashed arrow); (d) an axial CT image obtained without intravenous contrast in a 56-year-old female shows ground-glass opacities with a rounded morphology (arrows) in the right middle and lower lobes. The left lung was normal [25], [26]

exacerbates inflammation by causing pneumonia and increased cytokines. Similarly, the SARS virus is associated with a sharp decrease in the number of T-cells in the blood [30], [31], [32], [33]. The bottom line is that most children produce less inflammatory protein because of their immune system, and instead lymphocytes do their job. However, in people with weaker immune system, especially adults and the elderly, inflammatory proteins are produced, increasing the inflammation and worsening of CoV.

Specific safety in children and COVID-19

The human immune system is a complex network of specialized cells, tissues, and organs that are responsible for identifying and eliminating pathogens. Intrinsic and specific immune systems are the two main parts of the immune system. Intrinsic immunity is a general defense system consisting of inhibitory factors such as mucosa and skin and a specific immune system composed of cells that, with advanced mechanisms, identify only certain pathogens. In viral infection, T lymphocytes play the most important role in specific immunity. In summary, these viruses are specifically identified and killed by lymphocytes in a very complex cellular response [34], [35], [36]. Normally, after detection of viral compounds by cellular receptors, an appropriate and effective antiviral response is initiated by the immune system, which includes the production of a variety of cytokines and immune and inflammatory responses. Interferons I (IFN_β and IFN-α molecules) are key cytokines produced after virus infection that induces the onset of an immune response and subsequent adaptation [37], [38]. The immune response to the CoV is that CoV infects macrophages and then the macrophages deliver CoV antigen to the T cell. This process leads to the activation and detection of T cells and the increase in the production of various cytokines, followed by the widespread release of cytokines to enhance the immune response. Continued production of these mediators has a negative effect on NK function and T cell activation [38].

In people with stronger immune systems, lymphocytes, especially T cells, act more rapidly and specifically kill the pathogen. However, in people with a weaker immune system, COVID-19 causes acute inflammation by causing pneumonia and increasing cytokines and decreasing T cells [30], [39], [40].

This suggests a large role for lymphocytes in specific immunity in relation to their impact on the recovery of corona disease. The important results of the reviewed articles show that there are a large number of T cells in children, which have an impact on the quality of function of the specific immune system in children. In many children, milder symptoms have been observed than in adults due to the specific function of the immune system [24]. The reason for the strength of the immune system of children compared to adults can be summarized in several issues. First, children are exposed to a variety of pathogens for the 1st time in the early years of life, and second, children have the ability to rapidly produce natural antibodies with broad reactivity that has not yet been selected and shaped by the reaction to common environmental pathogens that are more prepared to fight T cells in the body [41], [42], [43].

Treatment

A recent paper reports the inhibitory effect of Ramsdevir (a new antiviral drug) and chloroquine (an old antimicrobial drug) on the growth of SARS-CoV-2 *in vitro* and an initial clinical trial conducted on Chinese patients with COVID-19. It was also shown that chloroquine had a significant effect on the clinical outcome and clearance of the virus compared to the control groups [44].

Chinese experts recommend that patients with mild, moderate, and severe COVID-19 pneumonia without chloroquine contraindication be treated with 500 mg of chloroquine twice daily 10 days. On the other hand, 18,264 (24%) reported cases have improved as of February 20. An encouraging report on February 20 from the Guangdong CDC indicated that out of 125 severe cases, 33 (26.4%) were recovered and discharged and 58 (46.4%) recovered and classified as mild/moderate cases (i.e., + mild pneumonia). Of course, there have also been severe cases, with 13.4% of deaths so far. Early detection and contact with physician may improve treatment [19].

Other adjunctive treatments in China with the help of Chinese medicine have been performed on COVID-19 patients, including use of antioxidants. The current studies in China show that antioxidants are effective in boosting the immune system and reducing inflammation in patients with COVID-19 [45], [46], [47]. Another treatment currently under trial is the production of the vaccine; however, because of the consecutive mutations in the viral antigens, the investigations mostly focused on inhibiting the protease enzymes of the virus [15], [48]. Plasma therapy is another solution that the US Food and Drug Administration and WHO are looking for. It uses blood antibodies from the recovered patients, which is still in the experimental phase [49], [50].

Studies on children recommended the use of therapeutic drugs in reasonable and lowest doses at different ages, and like adults, antioxidants are the priority. In a study conducted in Wuhan, China, the use of antioxidants was recommended as adjunctive therapy for the entire high-sensitivity groups [45], [47], [47], [51].

Conclusion

Children are also diagnosed with COVID-19 like adults. Despite the low prevalence of the disease in children, the issue of prevention and immunosuppression in children is very important. The findings showed that children responded better to CoV than adults because of specific immune function in children.

Many studies have been published focusing on epidemiology, etiology, clinical manifestations, and diagnosis, prevention, and control. However, studies examining prevention and control measures have gradually increased. Government agencies have rapidly incorporated recent scientific findings into public policy at the community, regional, and national levels to slow or prevent further expansion of COVID-19. Our suggestion is to evaluate the difference in children's immune system function in the face of CoV compared to the adults and to provide treatment options for children and those with weaker immune systems. It is also proposed that the scientific community conducts further studies to provide valid and effective ways to manage this type of public health hazard both short and long term.

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First Experience in Management of Coronavirus Disease 2019 (COVID-19) in Kidney Transplant Patient – Case Report

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Abstract

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has recently emerged in the world. There are limited data describing the clinical progression of COVID-19 in transplanted patients. In the general population, clinical presentation ranges from asymptomatic infection to severe pneumonia and may also develop renal failure. In kidney transplant (KT) patients, management of these patients was mainly based on anecdotal experience.

CASE REPORT: We report our first experience of KT patients with COVID-19. A 49-year-old male with KT in 2017 presented on March 20, 2020, with fever, weakness, smell loss, chest pain, and caught. On chest X-ray, he presented ground-glass opacities and bilateral pneumonia. There was a slight progression to acute hypoxic respiratory failure. We reduced immunosuppression therapy and since we suspected seasonal flu, we applied available antiviral oseltamivir till confirmation of RNA sequence of the SARS-CoV-2 virus. Moreover, we applied azithromycin and broad spectrum of antibiotics as well as an anticoagulant therapy. Graft function remained stable during 14 days of hospitalization. The patient clinically improved with decreasing oxygen requirements and manifested clinical recovery. After two negative PCR test, he was discharged and immunosuppression therapy was returned to previous.

CONCLUSION: This case highlights the importance of earlier outpatient hospitalization and testing which may improve COVID-19 outcomes among transplanted patients.

Introduction

In December 2019, in Wuhan, China, a new disease appeared that caused severe pneumonia and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was detected as a causative agent. Disease was called coronavirus disease 2019 (COVID-19). It was spread very fast to all continents, and on March 11, 2020, the World Health Organization (WHO) declared a pandemic [1]. It has been shown that virus was transmitted from person to person during unprotected contact, respiratory droplet, fecal-oral transmission, and vertical transmission from mother to child [2]. Moreover, it was shown that it uses ACE 2 receptors to enter the cell, similar to SARS-CoV. The clinical presentation is very diverse, from asymptomatic, mild, and moderate to severe [3].

Patients with transplanted kidneys are on continuous immunosuppressive therapy. Previous experiences with SARS and MERS have described deteriorating graft function in infections, even with a fatal outcome [4], [5]. At the root of dealing with them, as well as in all infections, is actually timely modifications or discontinuation of immunosuppressive therapy, except for corticosteroids according to the recommendations and appropriate specific therapy [6], [7]. It has been reported that in KT patients with COVID-19, it is necessary to modify the immunosuppressive therapy; unfortunately, there is a lack of reports about appropriate specific therapy for SARS-CoV-2 in KT patients [8], [9], [10].

First imported case of COVID-19 was detected in our country on February 21, 2020, and until May 15, 2020, there were a total number of 1723 patients, 1235 cured, including 1 KT patient and 7 patients on dialysis [11].

Case Report

We present here our first experience with COVID-19 in a 49-year-old male kidney transplant patient. He was transplanted 3 years ago, and the donor was his brother. Treated according to a protocol with four immunosuppressive therapies, Basiliximab as induction therapy and triple immunosuppressive maintenance therapy that included corticosteroids, cyclosporine A (Cy A), and mycophenolic acid (MMF). From comorbidities present arterial hypertension, regulated by the following antihypertensive oral therapy: Calcium antagonist (nifedipine R a 20 mg 3 × 1), angiotensin II receptor blocker (ARB) losartan a 50 mg 2 × 1 and carvedilol a 6.25 mg 2 × 1, and obesity with body mass index (BMI) = 37.7. The patient regularly came for regular follow-up. No signs of transplant rejection were recorded during follow-up. Kidney function was stable, with values for serum creatinine of 110 μmol/L and calculated GFR of 109 ml/min, on the last control on March 3, 2020. The patient was given to sign a written consent.

On March 20, 2020, the patient experienced the first symptoms such as weakness, pain in the knees and hips, temperature up to 38.5°C, loss of taste and smell, and chest pain. According to the protocols of our Ministry of Health, the patient called the epidemiological services. Because the patient had a negative epidemiological history, he was referred to his general doctor with suspicion of seasonal flu. Oral treatment with ciprofloxacin a 500 mg 2 ° 1 and oseltamivir a 75 mg 2 × 1 (Tamiflu) was started immediately. The dose of cyclosporine A (Cy A) and MMF was reduced by 50% of baseline.

The temperature persisted and a persistent dry cough appeared, indicating that the patient needs to be tested. On March 23, 2020, a diagnosis of COVID 19 was made by proving the presence of an RNA sequence of the SARS-CoV-2 virus in the material from the nasal and throat swab. The same day, the patient was hospitalized at the University Clinic for Infectious diseases and febrile conditions.

At the time of admission, the patient was febrile 38°C and the physical status was positive. The auscultatory chest findings were in favor of sharper vesicular breathing.

The initial laboratory test showed an orderly leukocyte count, but a reduced lymphocyte count slightly elevated C reactive protein (CRP) and creatinine kinase (CK). The graft function was normal, but values for serum potassium were close to the lower limit. The hemostasis finding indicated lower platelet counts and a slight increase in d-dimers (Tables 1 and 2). The chest X-ray showed bilateral pneumonia (Figure 1).

The immunosuppressive therapy Cy A and MMF were discontinued and oral decortin a 15 mg were given as maintenance therapy. The ARB was interrupted. The rest of the therapy consisted of intravenous ceftriaxone a 2g 2 × 1, azithromycin a 500 mg 1 × 1, paracetamol when needed, subcutaneous clexane, and other oral supportive therapy such as Vitamin C, probiotics, potassium supplements, and hepatoprotectants (Table 3).

The patient after 9 days was afebrile. Of all the other symptoms, the dry cough lasted longer (Table 4). Regarding the laboratory findings, there has been a continuous improvement in the number of lymphocytes, platelets, as well as serum values for CRP and CC. A moderate increase in d-dimers and moderate transaminase activity also has been observed (Tables 1 and 2). The graft function remained stable with serum creatinine 97 μmoll/L.

Table 1: Biochemical findings during hospitalization

???	March 24	March 28	April 02	April 04
Hb g/L	141	140	136	138
RBC 10ˆ12/L	4.6	4.7	4.6	4.6
WBC 10ˆ9/L	4.4	7.5	7.4	5.8
PLT 10ˆ9/L	123	166	264	259
Htc rv	0.40	0.39	0.38	0.40
Ne 10ˆ9/L	0.84	0.87	0.67	0.63
Ly 10ˆ9/L	0.08	0.07	0.16	0.20
Mo %	0.08	0.06	0.15	0.15
Eo %			0,02	0,02
Glucose mmoll/L	5.3	6.9	5.0	5.2
Urea mmoll/L	7,0	4,0	3,9	4,4
Creatinine/μmoll/L	100	102	104	97
Tot.bil μmoll/L	11			
Dir/ind μmoll/L	3/8			
ALT U/L	41		88	80
AST U/L	36		54	38
LDH U/L	161	334	316	244
CK U/L	239	231	93	
CK-MB U/L	14	17		
GGT U/L				23
Troponin ng/ml	34.6			
K mmoll/L	3.6	3.0	2.9	3.3
Na mmoll/L	138	133	138	138
Ca mmoll/L	2.2	2.2	2.16	2.2
Total proteins g/L	65			
Globulins g/L	29			
Albumins g/L	36			
CRP mg/L	45	87	30	6

Hb: Hemoglobin, RBC: Red blood cell, WBC: White blood cell, PLT: Platelet, Ne: Neutrophils, Ly: Lymphocytes, Mo: Monocytes, Eo: Eosinophils, Tot.bil: Total bilirubin, dir/ind: Direct/indirect, ALT: Alanine Transaminase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, CK: Creatine kinase, CK-MB creatine kinase: MB, GGT: Gamma-glutamyl transferase, K: Kalium, Na: Sodium, Ca: Calcium, CRP: C Reactive protein

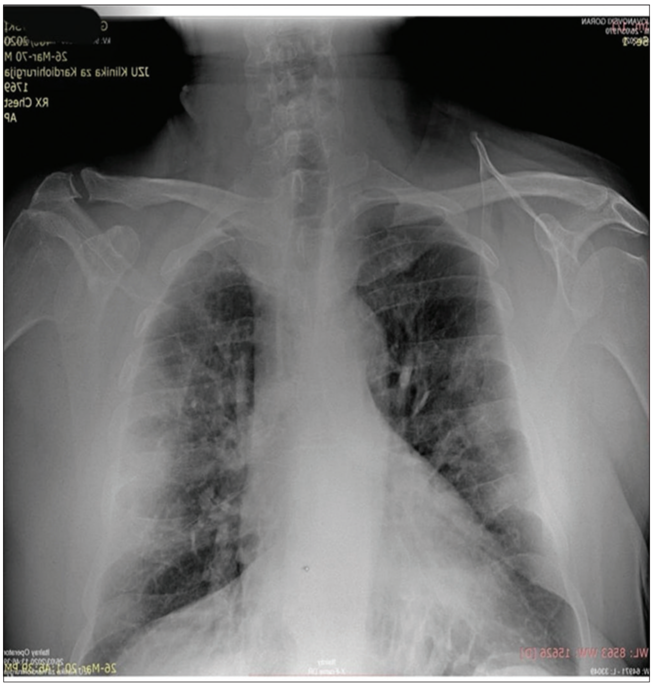

Figure 1: Bilateral pneumonia (chest X-ray on the 3rd day)

After 15 days of hospitalization and two consecutive negative nasal and throat swab tests for SARS-CoV-2, the patient was discharged. After discharge, the Cy A and MMT therapy were restarted, gradually within 7 days to previous maintenance dosage. On the first control 12 days after hospitalization, renal function was unchanged and chest X-ray picture finding showed resolving of pneumonia (Figure 2).

Table 2: Hemostasis findings during hospitalization

Date	PLT 10ˆ9/L	Hematocrit	Prothrombin time (s) (9.8–14.2)	Activated partial (s) (27.9–29.1)	Thrombin time (s) (16.1–19.01)	d-dimers (0–500)
March, 24	111	41.3	10.2	29.1	17.2	581
April, 05	253	39.9	10.36	25.5	19.01	1004

Table 3: Duration of clinical signs and symptoms

	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Temperature	38.0	38.4	38.3	37.4	38.5	36.4	38.3	38.6	38.5	37.3	37.2	37.5	37.5	37.5	37.1	37.1	36.6	36.8	36.6
Fever																			
Dry cough																			
Chest pain																			
Pain in the knees and hips																			
Loss of taste and smell																			
SpO_2 %					92	90	91	86	92		91	95	96	95	97	97	95		

Table 4: Therapeutic approach before and during the hospitalization

Therapy/days	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Decortin mg	5	5	5	5	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
MMF 1 g/day																			
Cy A 50 WWmg/day																			
Caps. Oseltamivir a 75 mg 2 × 1																			
Tab. Ciprofloxacin a 500 mg 2 × 1																			
Amp. Ceftriaxon a 2 g/day																			
Amp. Azitromycin a 500 mg/day																			

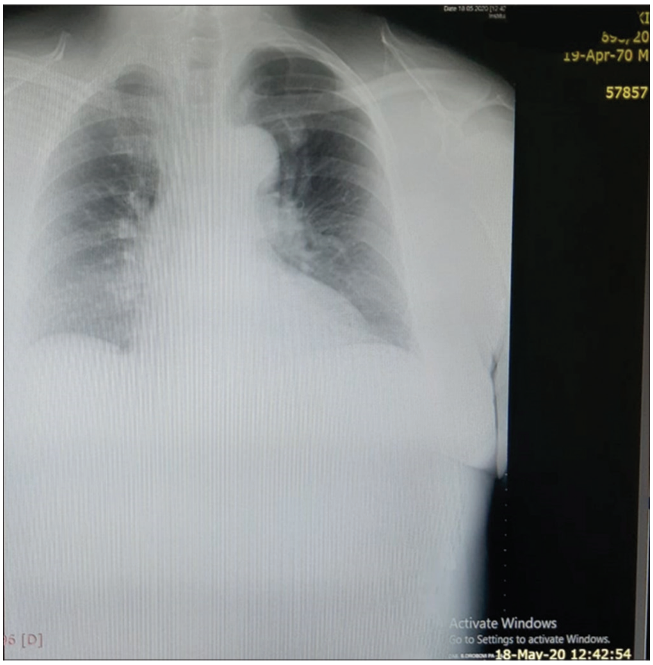

Figure 2: Findings resolved (chest X-ray after 24 days)

Discussion

From the current findings, the biggest risk of becoming infected with COVID-19 disease is through contact with a person with respiratory disease, but the fact that we have a patient with a negative epidemiological survey indicates that the spread of infection by asymptomatic carriers is also important [12]. In terms of gender and age, it has been reported that men and advanced age play a role in the severity of clinical presentation and mortality [13].

Patients with a KT are undergoing permanent immunosuppressive therapy, which causes a state of immunocompromised and often consequently, the infective diseases can have a changed clinical picture. In our first case, the clinical manifestations were fever, high temperature, dry cough, malaise, joint pain, and loss of sense of smell and taste, symptoms identical to those of the general population[2].

Clinical presentation may vary from asymptomatic to severe needing respiratory support. The presence of other comorbidities and conditions, such as high blood pressure, diabetes mellitus, chronic heart disease, chronic respiratory disease, and obesity, has been described as risk factors not only for the onset of COVID-19 but also for the progression and severity of clinical presentation. In our case, the patient was also overweight and had high blood pressure, which was probably the reason for the presentation of moderate to severe clinical picture, but without the need for oxygen support or respirator [14], [15].

Long-term use of immunosuppressive therapy is a reason to reduce T lymphocytes and reduce immunity in patients with transplanted organs. Therefore, modification or total cessation of immunosuppressive therapy, especially of MMF and Cy A, is extremely important in all infections but also in COVID-19 [6], [9]. In our case, the patient was on triple maintenance therapy: Corticosteroids, MMF, and Cy A. During the first three days, the dose of MMF and Cy A was reduced by 50%, and on the day of hospitalization they were discontinued. Table decortin 15 mg/day was established as maintenance therapy. Although experience has suggested that the MMF and calcineurin inhibitor should be discontinued, there are some studies that suggest that Cy A inhibits the replication of the SASR-CoV virus in cell culture [16], [17]. The patient also received ARBs therapy and was discontinued despite insufficient evidence that ACE inhibitors and ARBs may cause a more severe clinical picture [18], [19], [20].

So far, it has been reported that there have been a number of disturbances in the biochemical analyses of patients with COVID-19. Lymphocytopenia is the most common finding. Necrosis or apoptosis of the lymphocytes is a possible mechanism. In non-critical patients infected with SARS CoV-2, up to 37% had mild lymphocytopenia and up to 80% in critically ill patients. In our case, there was no change in the total number of leukocytes, but there was initially a decrease in the number of lymphocytes to 0.07, with a gradual increase to 0.20. An increase in CRP to 87 was registered, followed by its normalization [21], [22].

It is known that SARS-CoV-2 binds to ACE 2 receptors and can enter the cells of the renal tubules and cause acute renal failure [15], [23], [24]. In our patient, graft function remained steady, with serum creatinine values ranged from 104 to 97 μmoll/L. Mild hypokalemia was noted in the absence of diarrhea and forced diuresis with potassium-sparing diuretics, which may be explained by the above.

SARS-CoV-2 can penetrate and replicate in hepatocytes. In 15% of patients who do not have a need for intensive care treatment, an increase in AST and ALT is observed. The same goes for the hepatic lesion in our case, with a gradual spontaneous recovery [25].

The presence of coagulopathy in COVID-19 is usually explained by a secondary bacterial infection and an increase in CRP. It is manifested by a decrease in platelet count and an increase in d-dimers, in our case 111 and 2500, respectively, and in some severe cases with the development of disseminated intravascular coagulopathy [26].

Pneumonia was confirmed by the finding of chest X-ray, as in other cases with COVID-19. Since there was no worsening in the condition, there has not been an indication for computer tomography (CT) of the lungs which is otherwise a method with a very high sensitivity of 98% for diagnosing COVID-19. Despite the extensive findings and the prolonged dry cough, the patient was without oxygen support at all times [27], [28], [29].

The use of a certain group of antibiotics such as the azithromycin has been shown to be effective in treatment. Certain centers have reported the benefits of combining it with chloroquine, but there have been those who have not responded. For severe cases, there are attempts to treat them with antiviral therapy like remdesivir. Special success has been achieved in certain cases with plasma delivery from a convalescent patient rich in antibodies. For cases combined with severe anemia in addition to blood substitution, successful *extracorporeal membrane oxygenation* (ECMO) treatments have been reported. Furthermore, tocilizumab is reported as an effective treatment in severe patients of COVID-19. However, there is still no specific therapy or vaccine for COVID-19 [30], [31], [32], [33], [34].

Conclusion

Our first experience showed that the clinical presentation of COVID-19 in a kidney transplanted recipient is the same as in the general population. Treatment with azithromycin and cephalosporin antibiotics has been shown to be effective in the treatment of bilateral pneumonia, along with the modification of immunosuppressive therapy. Since there is still no specific therapy, the latter seems to be of great importance not only for improving immunity but also for a positive clinical outcome. Experience and analysis of several cases are required to reach a conclusion about the treatment and outcome in kidney transplant recipient and COVID 19, which is the limitation in this presentation.

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Perinatal Mental Health: One of the Biggest Challenges in Coronavirus Disease-19 Crisis

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Abstract

Coronavirus disease (COVID)-19 epidemic is currently conceived as one of the major factors for stress and anxiety for pregnant women around the world. Stress, especially in early pregnancy, is a risk factor for preterm birth. The negative impact of quarantine on mental health in pregnant women should also be taken into account. A large number of benefits of breastfeeding for the mental and physical well-being of both mother and newborn outweigh the potential risks of COVID-19-related transmission and disease. Prenatal and postnatal mental health should be prioritized in facing the current ongoing pandemic.

With the spread of the coronavirus disease (COVID)-19, there has been widespread concern about the possibility of its intrauterine transmission from the mother to the fetus during the pregnancy [1]. As a result, dilemmas for the morbidity and mortality rate in mothers and newborns have arisen together with the complications that would occur during pregnancy or after that. The lack of evidence-based information on these issues among their enormous importance is a source of stress for pregnant women and future mothers [2], [3]. Nowadays, the severe acute respiratory syndrome-CoV-2 epidemic is conceived as one of the major factors for stress and anxiety for pregnant women around the world [4].

One of the biggest problems we want to focus on is the practice of routinely separating the mother from her newborn after birth as a measure against the transmission of the COVID-19 virus. According to research conducted in China, this strategy, apart from stopping breastfeeding, also has huge consequences for the mother's mental health in the form of feelings of shame, self-blame, and the onset of depression [5]. The practice of stopping breastfeeding should be actively avoided. Consequently, proper care and support measures should be taken to reduce or at least mitigate the negative effects. In every socioeconomic position, breastfeeding raises survival and delivers lifelong health and progress advantages to newborns and infants. The transmission of COVID-19 across breast milk and breastfeeding has not been observed. In the group of few cases of confirmed COVID-19 infection in children from other origins, most have confronted only mild or asymptomatic form. During breastfeeding, a mother should carry out proper hygiene measures, involving wearing a medical mask if available, to decrease the possibility of droplets with COVID-19 being expanded to her infant. No active COVID-19 virus has been confirmed in the breast milk of any mother confirmed/suspected to have COVID-19. It is unexpected that the virus can be transferred by a mother with confirmed/suspected COVID-19 virus through breast milk [6]. The message of the authors on this issue is that a large number of benefits of breastfeeding for the mental and physical well-being of both mother and newborn outweigh the potential risks of COVID-19-related transmission and disease.

Within this framework, how to protect the mental health of a pregnant woman from the short- and long-term consequences of this actual pandemic? A lot of pregnant women live in poor households together with other people in a limited space, caring for their other children or for elderly people at the same time. In the current pandemic, this may impact on the mental health of pregnant women. According to two of the Millennium Development Goals (four and five), overall health cannot be ensured without mental health [7]. Stress, especially in early pregnancy, is a risk factor for preterm birth [8]. The development and implementation of dedicated mental health services are urgent for this special category of the population. Anxiety and stress in pregnant women are responsible for consequences such as preeclampsia, depression, increased nausea and vomiting during pregnancy, preterm labor, low birth weight, and low appearance, pulse, grimace, activity, and respiration score [9].

Moreover, many pregnant women currently are not visiting a doctor for fear of contagion with COVID-19. Travel bans and the thought of not having a doctor available every time are especially frightening for a pregnant woman. Both situations pose a huge threat to a pregnant woman's mental health. Providing advice and support through telecommunications is of particular importance. In addition, depression is frequent during pregnancy, affecting up to 28% during late pregnancy [10].

The impact of the quarantine lockdown on the mental health of pregnant women should be not overlooked. In general, quarantine, self-isolation, and loneliness have a negative impact on mental health, resulting in increased levels of stress, anxiety, depression, and self-harm, but not only for pregnant women but also for the entire population [11], [12]. The fear that comes with it may represent an additional source of stress that could negatively affect a mother's pregnancy. The quarantine will be probably responsible for the worsening of pre-existing mental disorders and may also worsen mental stress in future mothers with non-psychiatric disabilities due to the reduced medical care and support during the pregnancy. According to the data received from one Canadian study, pregnant women described significant levels of psychological distress in form of pregnancy-specific anxiety symptoms (68%), general anxiety (57%), and as depression (37%). In comparison with the findings from the previous community pregnancy cohorts, these symptoms are considerably higher [13]. Another study among Turkish pregnant women showed increased scores on screening instruments for depression and anxiety during this pandemic [14]. As stated by an Italian survey, the psychological impact of the COVID-19 is classified as serious by 53% of pregnant women. In addition, two-thirds of the respondents experienced higher levels of anxiety than normal [15]. Clinical care of pregnant women with COVID-19 depends on the severity of the disease. Most (86%) of the pregnant with known or suspected COVID-19 have mild symptoms (no shortness of breath) that now require hospital-level care, while there are no obstetric problems. However, they should be followed and monitored for eventually progression [16].

It is necessary for health professionals to create and disseminate guidelines for mental health for vulnerable categories. What's more significant, measures should be taken by the government, community, and relevant departments to provide timely-specific psychiatric services for pregnant women. Already in February 2020, some reports published in The Lancet indicated that the care of the mental care of mothers is vital [17]. The authors considered that it is crucial for pregnant women and mothers to be in constant contact with reliable and confidential information about the course of the COVID-19-disease, prevention, and its impact on the perinatal and postnatal period [6]. By contrast, receiving inappropriate and unverified information can increase stress and fears [18]. Communication with pregnant women and mothers should be shown empathy, understanding of their needs, feelings, and support for expressing their emotions. Moreover, support from loved ones to identify positive strategies for dealing with their emotions and stress plays an essential role [6]. On the other hand, fathers play an important role in pregnancy. Supporting from the fathers during this crisis is an essential step in preserving the mental health and well-being of pregnant women and mothers. Maintaining contact with the environment through telecommunications and social networks is one of the principal ways to meet the needs that provide welfare. Understanding the needs of mothers and fathers will lead to a faster and better response to future unexpected events. To sum up, prenatal and postnatal mental health should be prioritized in facing the current ongoing pandemic [19].

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Unstable Education System Inducing Mental Stress in COVID-19 Lockdown

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Abstract

Coronavirus disease or COVID-19 caused by SARS-CoV-2 has triggered a respiratory tract infection claiming more than 3 lakh lives worldwide with 4.5 million cases and still counting. This is the worst hit of the 21st century which has made it to be announced as a pandemic by WHO on March 11, 2020. It is not possible at the time to comment if the virus has appeared all of a sudden or its gradual emerging in a short or long time with information passed lately. However, the virus has adjourned the life of humans in almost every aspect with most of the countries, including India announcing nationwide lockdowns. The news of progress over medicine or vaccine over days is no doubt giving hope to the stressed-out humanity which is being striked out again by some higher health officials warning that the coronavirus may never go away. Such news is always creating panic and claiming mental peace, building more stress in individuals. Amidst all these crisis, there is a field which took everyone's attention, that is the education of the students. However, Indians are always known to emerge out stronger in challenges, so did they, when it was the matter of future of the students. Although Indian education system is not much familiar to such measures, it was the call and need of the situation to clasp to a different mode of education effectively and efficiently. Even with this much dedication, there seem to be some points on which the education system is breaking down gradually without the awareness of many. This article has focused on a few of such challenges imposed by the COVID-19 lockdown on the education system in India.

Adapting to a Mode of Delivering Education

The majority of Indian education systems are more focused on the traditional mode of learning, one on one interaction between teacher and students. Physical presence of the teachers and the peer group sets the learning environment of the institutions [1]. Sudden suspension of such classes arose the need of some alternative methods like online classes through video conferencing platforms, delivering PowerPoint presentations, providing e-books, or even using phone calls to solve students' queries related to the subject. Even University Grants Commissions (UGC) has taken many initiatives to promote e-learning through online platforms [2]. However, it is not that easy as it appears to be. Switching to a different learning mode does not go swiftly for the students. It is difficult to accept such changes without preparedness. In many places in India, there is poor internet connectivity which further creates difficulty to cope up with online learning, especially in some rural areas. For the teachers, preparing a single lecture to be delivered online increases the workload even further [3], making them compromise with the study material even if they do not want to. However, they are forced to do it as the call of the situation to save the students' future and even because of mental pressure being built on them.

Distracting Away from the Real Path

Sometimes, "too much" is more precarious than "nothing." The same is going well with the current scenario of education in India. UGC, Indian Government, and respective institutions are taking recognizable steps to hold on to good education. However, this has brought a deluge of learning resources, making it difficult for the learners to choose between them. Without proper guidance and preparedness, everything looks similar and makes it difficult to adhere to some best ones according to their choice. Apart from the flood of learning resources, it has become a trend to conduct webinars on different topics. Every other day, there is a notification of some free webinars claiming to provide certification of attendance. Most of these webinars are unreliable and different from the subjective knowledge of the students which are distracting them from the actual path of learning the respective course.

Conducting Examination

The mid of an year in India is basically the time of conclusion for the students, well known as the time of final examinations for various courses. Coronavirus does not seem to be vanished in the near future, especially in a couple of months or so [4]. This is welcoming a new challenge of conducting examinations and concluding the annual year. Fear of failure is already on a peak for the students and unawareness of the exams may accelerate the underperformance of the students. Teachers are even not spared by this challenge, which is equally a situation of worry for them [5]. Evaluating a large number of students remotely is itself a difficult work and doing it without a well-defined medium is knocking on their mental peace [6].

Financial Uncertainty and Emotional Distress

Indian government has taken a wise step by requesting the private sectors to avoid deducting the salaries of their workers. Even with the hope of a cure to coronavirus in the near future, the reopening of educational institutions seems to be a long way to go. This is what directly or indirectly going to challenge the government's appeal of allowance of monthly income, including that for the teachers. Or it may have already been challenged in some private institutions with no such official reporting till now. This period of uncertainty on being paid for the even harder working and managing resources economically over the long run may raise the emotional distress among teachers [7]. With the threat of the same to happen soon or later, it might get difficult for them to give their best in the work they have been assigned.

With the hard work and dedication of government and private sectors, there is a ray of hope on getting back to normal life soon. However, the present conditions are really depressing. As a nation, there are worldwide signs of united India against this epidemic; still, there might be some sources looking for personal growth more over the basic regular proceedings and needs of their workers' life. Such sectors include the education sector also. Everybody is in a hurry to succeed with the newer methods of teaching and learning, unaware that we are deflecting from the real path of education. Nobody seems to be conscious about the mental stress being faced by students and teachers and nobody has raised a voice for it. Education does not really mean subjective learning only; it actually means mental development also. With the present circumstances, learners and educators are directly or indirectly being pushed toward some serious mental conditions which may build up into a mental illness, that for sure will be responsible for the undergrowth of the education system. This threat is being built up unawarely as a hidden threat after COVID-19 making it a misfortune for India [8].

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The Effects of Personal, Environmental, and Genetic Factors on Epidemic of Coronavirus Disease-19: A Review of the Current Literature

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Abstract

Coronavirus disease (COVID)-19 is a viral disease that broke out in late 2019 in Wuhan, China. The World Health Organization has been forced to declare a public health emergency due to the global outbreak of COVID-19. The concerns about the COVID-19 disease are the rapid increase in the number of patients as well as the number of deaths compared with severe acute respiratory syndrome disease. Given that there is a remarkable variability amongst people for COVID-19 infection, there really is the possibility that there will be genetic and environmental effects, it is a need for their role to be fully clarified as soon as possible. Numerous studies have been performed on the on the stability of COVID-19 virus in different environmental conditions including temperature and humidity. In this study, we aimed to discuss in detail the benefits and effects of these factors on COVID-19. Some studies have confirmed the relationship between environmental conditions and disease transmission and others have rejected. Furthermore, not all COVID-19 exposed people are infected and not all infected patients develop severe respiratory complications. It is quite likely that these disparities are genetically mediated, in part. People who may be occupationally exposed to this virus may be due to different reasons, including lack of health, lack of knowledge and attitude, and working conditions. Reducing human-to-human contact by increasing the level of public health in the community as well as maintaining social distance plays a key role in prevention of COVID-19 disease. However, many aspects of COVID-19 are still unknown and require further and extensive studies.

Introduction

In December 2019, in Wuhan, China, a virus was first identified that was named Coronavirus (CoV) Disease (COVID)-19 because it was caused by the severe acute respiratory syndrome (SARS)-CoV-2 virus. The World Health Organization (WHO) Director-General announced on January 30, 2020, that the outbreak of COVID-19 is a global concern [1], [2], [3]{Sohrabi, 2020 #1}. Evidence recommends that COVID-19 is mainly transmitted through close contact with infected individuals through bodily secretions including nasal fluid, saliva, and respiratory droplets spread by speaking, sneezing or coughing [2], [4], [5]. The most commonly reported symptoms of the disease include fever, dry cough and fatigue, and in fewer frequent cases, headaches, diarrhea, shortness of breath, and sore throat [5], [6], [7], [8], [9].

Study Strategy

The compilation of this review study was carried out in April 2020. To find the related published papers on the effect of personal and environmental conditions and genetics on COVID-19, the recent electronic documents from Google, PubMed, Google scholar, Elsevier, and Scopus were applied. Various key words, including COVID-19, environmental condition (air temperature and humidity), water, wastewater, solid waste, food, genetics, personal health, occupations, and disinfection, were used to investigate the study.

Epidemiologic Characteristics of the COVID-19

The WHO report no108 on COVID-19 global situation on June 14, 2020, was demonstrated that 216 countries had reported confirmed COVID-19 morbidity. At the time of the report, the total number of cases and death were 27,486,960 and 894,983, respectively [10].

CoV is a single-stranded RNA virus resembling a crown under electron microscopy (due to the presence of spike glycoproteins on the envelope), which is divided into four genres including alpha, beta, gamma, and delta CoV. The SARS-CoV and SARS-CoV-2 (COVID-19) genomes have about 80% identity and belong to the beta genre and cause symptoms such as fever, malaise, dry cough, and acute respiratory response [11]. This newly discovered CoV is associated with the recent outbreak of pneumonia in humans and probable bat origin [12].

The diameter of COVID-19 is around 60–140 nm and has a spherical or oval and often pleomorphic form. It is sensitive to heat and ultraviolet rays like other CoVs. In addition, using lipid solvents including ethanol, ether (75%), chlorine-containing disinfectant, chloroform, and peroxyacetic acid, this virus can be effectively eliminated [13].

The median incubation period of COVID-19 from exposure to the first symptoms was reported in Qian *et al*., Xu *et al*., Guan *et al*., and Singhal studies for 3, 4, 4, and 5 days, respectively [6], [7], [8], [14]. Symptoms in most people are mild and, in some cases (often elderly), the symptoms are severe and it is also asymptomatic in most people [8]. The median age of patients was reported in studies of Xu *et al*., Sun *et al*., and Guan *et al*., studies were reported 41, 46, and 47 years, respectively.

The overall case-fatality rate has been reported at between 2% and 3.4% [8], [11], [12], [15]. Mortality is higher in the elderly and in cardiovascular, diabetic, cancerous, or chronic respiratory patients and is very low in children [3], [15]. Although the fatality rate of COVID-19 is lower than its two ancestors the SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV); however, it is much faster to spread [8]. Estimates of contagiousness of COVID-19 (R_0) has been reported in some studies ranging from 1.5 to 5.2 [5], [16], [17]. R_0 is defined as "the average number of people who will contract a disease from one contagious person" [5], [18]. However, within the closed environments as well as in high-density environments such as hospitals, where contact between people is getting closer, the R_0 of COVID-19 has been estimated to be significantly higher (estimates ranging from 5 to 14) [5], [19], [20], [21]. However, with the enhancement of healthcare and increasing public health in the community, the R_0 will decline [17].

Genetic Susceptibility to COVID-19 Infection

In the case of COVID-19, what is controversial for researchers and clinicians is that not all COVID-19 exposed people are infected and not all infected patients develop severe respiratory complications. Although the exact mechanisms behind these dramatically different infection outcomes remain to be elucidated, it is quite likely that these disparities are genetically mediated, in part [22].

For entering into the host cells, many viruses use multiple alternative receptors. The study by Lu *et al*. showed that SARS-CoV and SARS-CoV-2 have similar receptor binding domain structures. Further studies showed that these viruses use the same receptor for entering the cells. This receptor is angiotensin-converting enzyme 2 (ACE2) and is involved in the pathogenicity of SARS-CoV and SARS-CoV-2 [12], [23].

The previous studies have shown that the expression level of ACE2 is influenced by age, sex, and smoking. Thus, the pathogenicity of COVID-19 varies in different populations and races. Zhao *et al*. (preprint) showed the predominant expression of ACE2 in Asian men, which might be one of the possible reasons for the higher prevalence of COVID-19 in this subgroup of patients compared to the women and patients of other populations [24].

In a study of Asian and Caucasian people by Cai (preprint) was shown that there was not any significant difference in ACE2 expression between these groups. Furthermore, ACE2 expression was not affected by sex and age. However, it was significantly higher in smokers than non-smokers of Asian ethnicity [25]. Some studies reported that there was no significant relationship between smoking and the prevalence or severity of COVID-19 [7], [26].

In a study on critically ill patients with COVID-19 by Yang *et al*., it was found that more men were affected (67%) than women [27]. Of the 1099 patients with COVID-19 hospitalized in 30 hospitals in China, 58% were reported to be men [7]. In contrast, one study of 140 patients with COVID-19 reported the equal sex distribution [26].

Different immune responses to pathogens can be due to genetic differences between individuals. When the immune system is compromised, the SARS-CoA-2 can spread in the body and cause extensive damage to tissues that have high expression of the ACE2 gene such as the lung, intestine, and kidney. Innate inflammation that is largely mediated by pro-inflammatory macrophages and granulocytes is induced by the lung damaged cells. Lung inflammation is the main complication of COVID-19 infection at the severe stage [28]. Accordingly, it is very critical to identify human leukocyte antigen (HLA) molecules that have increased binding specificities for peptides of SARS-CoV-2 presented on the antigen-presenting cell surface. Given that there are no related data available so far, we can obtain some information from the work of researchers on SARS-CoV. Several studies have shown the association between HLA polymorphisms and the susceptibility of SARS-CoV, such as HLA-DRB1*1202, HLA-B*0703, HLA-B*4601 [29], and HLA-Cw*0801 [30] and some polymorphisms related to the protection from SARS infection including HLA-A*0201, HLA-Cw1502, and HLA-DR0301 alleles [31]. This information will be very advantageous for the treatment of COVID-19. Together, to identify the mechanism of COVID-19 pathogenicity and the environmental and genetic factors affecting the prevalence and severity of the disease, many studies should be conducted in different populations and races around the world to determine the effects of age, sex, genetic background, and environmental factors on this disease.

The Effect of Environmental Condition (Temperature AND Humidity) on Spread of COVID-19

Several studies have been conducted on the effects of environmental conditions such as ambient temperature and humidity on the stability of the COVID-19 virus. Some of these researches have considered the association between the environmental factors to be effective, and other studies have not found a relationship between these factors and COVID-19 virus transmission and spread. Wang *et al*. (2020) concluded that environmental conditions such as humidity and air temperature play an important role in the spread of disease. Based on this study, the prevalence of the disease was higher in countries with the lower humidity and temperature (Iran and South Korea) than other countries with higher humidity and temperature (Singapore and Thailand) [32]. This finding can due to the high viral stability in the cold weather and the susceptibility of the host immune system to cold air and low humidity [32]. There was also such a trend for the SARS virus [33].

Sajadi *et al*. study (2020) showed that COVID-19 morbidity will decrease in countries above 30°C during the coming months and summer due to rising temperatures. The disease in the tropics may also cause seasonal peaks and in the southern hemisphere may cause outbreaks in the months ahead. In temperate regions, it may lead to outbreaks in late fall and winter. Extensive health care can prevent summer outbreaks in the tropical and southern hemisphere [34].

Wang *et al*. (2020) study on the effect of ambient temperature on the COVID-19 disease transmission in 34 Chinese provinces and 26 countries showed that ambient temperature had significant effects on the disease transmission rate. The study indicated that by reducing the air temperature, the transmission of the disease was increased. According to this study, when the air temperature reaches 30°C, the cumulative number of cases increases by only 3.38, indicating that the COVID-19 virus is sensitive to ambient temperature [35]. There is also a pattern in the spread of other viral diseases, such as the flu. The prevalence of influenza is high from May to September in the Southern Hemisphere and November to March in the Northern Hemisphere where temperatures are low [36]. Other studies have also shown that the prevalence of swine flu is also increased at low air temperature and humidity [37]. Studies on SARS disease also showed that increasing air temperature and humidity from 22 to 25°C and 40–50% to 38°C and 95%, increase the activity of the virus on the surfaces from 5 days to near zero, respectively [33]. In other studies, it was proved that low temperature and humidity had a significant effect on the survival rate of other CoVs, such as MERS [38]. In a study by Bu *et al*. (2020) on the effect of air temperature and humidity on the COVID-19 virus, it was found that temperatures of 13–19°C and humidity of 50–80% were considered as suitable conditions for survival and spread of the disease [39]. Oliveiros *et al*. (2020) on the effect of ambient temperature and humidity on COVID-19 concluded that doubling time was directly and inversely correlated with ambient temperature and humidity, respectively [40]. For this reason, the spread of the disease is expected to slow in the spring and summer of the northern hemisphere. It is also expected that by 20°C increasing the air temperature, the doubling time will be delayed to 1.8 days. These factors account for 18% of the variation in disease doubling time. The other 82% may be connected to personal health measures, population bulk, commuting, and people's customs [40]. Other studies have shown that environmental conditions including temperature and humidity alone do not essentially result in decreasing the number of COVID-19 cases without rigid health interventions [41]. In the study by Cai *et al*. (2020), we reported that there was no relationship between daily ambient temperature and growth rate of COVID-19 epidemic [42]. Poirier *et al*. (2020) stated that high humidity and temperature did not diminish the spread and survival of COVID-19 virus. According to a study conducted in China, Iran, Italy, Japan, and South Korea, the environmental conditions (temperature and humidity) did not appear to affect the number of COVID-19 cases [43]. It seems more extensive studies are needed to prove the effects of environmental conditions (temperature and humidity) on the stability and spread of COVID-19 virus.

The Effect of Water, Wastewater, Solid Waste, and Food on Spread of COVID-19

The risks of COVID-19 transmission through human wastewater (feces) are very low. However, scientific studies have confirmed the presence of viral RNA fragments in human feces [44], [45] and in a study using virus culture from the human stool, viral RNA has also been detected[46]. However, so far, no studies have confirmed the oral-fecal transmission of the virus [47]. In the wastewater containing COVID-19 virus, wastewater treatment plants (especially in the disinfection part) effectively inactivate the virus [48]. Washing hands with soap and water for at least 20 s is a necessity if contact with the stools of suspected or ill persons occurs. Washing hands with soap and water for at least 20 s is sufficient if contact with the stools of suspected or ill persons. Furthermore, given that the feces of COVID-19 persons are considered as biohazard, the people responsible for stool disposal, especially in hospitals, should be provided with masks, gloves, and protective equipment [47]. The COVID-19 virus is a virus with a fragile outer membrane. Membrane viruses are usually low resistant to environmental conditions, especially disinfectants such as chlorine and ozone. The inactivation time of membrane viruses is much lower than of non-membrane viruses [47]. While the presence of virus in drinking water is possible, no studies have been conducted on the presence and transmission of COVID-19 virus in surface and ground waters. As sodium hypochlorite solution can inactivate COVID-19 virus on the surfaces, it seems that in drinking water containing disinfectants, the virus inactivation can rapidly occur. For this reason, the risk of virus transmission through drinking water is very low. Operational measures including water disinfection and proper storage in clean containers can be helpful to prevent virus transmission from contaminated water. For effective disinfection of drinking water containing the virus, it is recommended that the chlorine concentration should be ≥0.5 mg/L with a minimum contact time of 30 min and a pH of <8 [49]. If treated drinking water is unavailable, household water purifiers with nanofilter, ultrafilter and reverse osmosis membranes or ultraviolet radiation can be effective to inactivate the virus. Water boiling and solar radiation can also remove the virus from potable water [47].

Hospital waste management plays a key role in the control of the COVID-19 epidemic and includes separation, collection, and disposal [50]. Hospital waste management should be healthily conducted. The absence of proper management at each stage can result in developing the disease among staff, patients, and also people. The waste generated in the COVID-19 patient's wards should be considered as highly infectious. For this reason, separation is not required for disposing of COVID-19 patient's waste and should be considered as completely infectious. These wastes should be collected in lid standards containers. Hospital waste management workers should be fully equipped with glove, hat, gown, boot, and face shield (mask). The waste collection period at COVID-19 patients' wards was daily (24 h) carried out in China during the disease epidemic time [51]. One of the best ways for the disposal of hospital wastes to prevent the release of COVID-19 virus is incinerators which have a great role in the destruction of biological agents [51]. According to a study by Rafiee *et al*. (2016) on hospital waste management, the use of hydroclave, as well as autoclave, has been suggested as two suitable options for the control of waste infection [52]. So far, no study has been reported on the transmission of COVID-19 virus by hospital wastes [47]. Epidemiological evidence suggests that the zoonotic transmission of the virus occurred in December 2019 at the Wuhan's Huanan Wildlife Market. Molecular researches have also reported that the COVID-19 virus is very similar to the CoV isolated from the horseshoe bat [53]. Therefore, the zoonotic transmission of the virus from animals to humans is possible. Unlike other foodborne viruses such as norovirus and hepatitis A that causes food-borne viral gastroenteritis, COVID-19 virus causes severe respiratory infection. It has been no documents about the food-borne transmission of COVID-19 [54].

COVID-19 and Occupations

In addition to healthcare workers, a large number of people in various professions including industry, agriculture, public services, traffic police, staff public transport, and taxi drivers are at risk for COVD-19 [55], [56], [57], [58]. In 2018, the Bureau of Labor Statistics (BLS) estimated the total number of employees in the United States at 144.7 million. Of these, 18.4% (26.669.810) at least once a month and 10% (14.425.070) at least once a week are exposed to the pathogen [59], [60]. There are 150 million international migrant workers worldwide. About 95% of them are resident in the five WHO regions where COVID-19 has been confirmed [61]. The employment rate for 2018 in the Central and West Asia region was 58.3% [62].

To reduce the prevalence of COVID-19 in businesses, workers, and the general public, it is important that all employers plan to counter COVID-19. The amount of occupational exposure risk depends largely on the type of industry; however, to help employers, Occupational Safety and Health Administration (OSHA) has divided job duties into four levels of risk: Very high-risk, high-risk, medium-risk, and low-risk. Most American workers are likely to be at low or medium exposure levels. In the very high-risk group is occupation such as healthcare workers (e.g., doctors, nurses, paramedics, sampling laboratories, and morgue staff performing autopsies). The high-risk group includes occupations such as healthcare and support staff (people who need to enter the patient room), medical transport staff (ambulance operator), and cold storage staff involved in preparing the bodies of suspected COVID-19. In the middle-risk group is that who need frequent or close contact (e.g., less than 6 feet) with people who may be infected with COVID-19 (Staff with international jobs). Finally, there are low-risk (precautionary) groups in the business that have the least amount of job contact with people and other colleagues [63].

Since the transmission features of COVID-19 have not yet been fully identified, the WHO recommends wearing masks for all occupations in public and crowded environments [64], [65], [66], [67]. Although no study to date has compared the efficacy of N95 masks and surgical masks in preventing influenza or other respiratory infections in healthcare workers, almost all practitioners recommend the use of N95 masks to protect *against droplet* transmission from *coughs and sneezes* of COVID-19 patients [68].

Basic Approaches for the Prevention and Control of COVID-19 Disease

The reviewed studies generally suggest two main approaches for preventing and controlling COVID-19, including promoting public health and maintaining social distance [2], [3], [5], [16], [69]. Preventive measures should be taken by everyone everywhere, including homes, workplaces, hospitals, schools, universities, shopping centers, mosques, churches, and temples. [2], [4], [5], [16], [70].

Quarantine is a very important strategy to prevent infected individuals from contacting healthy people, especially in the early stages of COVID-19 disease. The results of past studies point to the high significance of quarantine in cutting off the COVID-19 disease transmission chain. Accordingly, solutions such as quarantine travelers, who enter the country from high-risk areas, banning intercity travel and restricting intercity movement, closing or postponing school activities, churches, mosques, and workplaces, can be very effective in preventing and controlling of COVID-19 disease [2], [3], [5], [16], [70], [71].

Effect of Disinfectants on COVID-19 Virus

Detailed information about the level of resistance of COVID-19 in the environment is not available, but it seems to behave like other CoVs [72]. Recent studies have shown that the resistance of human CoVs such as SARS-CoV, MERS, and other endemic human CoV, is varied in different surfaces (from 2 h to 9 days) [72], [73]. The survival time of these viruses is affected by many factors such as surface structure, temperature, relative humidity, and type of virus species so that on inanimate surfaces such as metals, glass, and plastics can survive up to 9 days [72], [73].

Unfortunately, there is little information about the suitable disinfectant for confrontation to COVID-19. However, experts believe that effective disinfectants on other CoVs can also be effective to inactivate COVID-19 virus. There is a wide range of disinfectants for surface disinfection. Ethanol 62–71%, hydrogenperoxide 0.5%, and sodium hypochlorite 0.1% can effectively disable the CoVs during 1 min [74]. The WHO believes that a wide range of disinfectants is effective for enveloped viruses such as COVID-19 virus. At present, 70% ethyl alcohol recommends for disinfection of small areas between uses such as reusable equipment (e.g., thermometer). Sodium hypochlorite at 0.5% (equivalent 5000 ppm) is recommended for disinfection of surfaces [72].

The efficiency of other disinfectants such as 0.05–0.2% benzalkoniumchloride or 0.02% chlorhexidinedigluconate was negligible [74]. Ultraviolet (UV)-C has a high ability to deactivate viruses, bacteria, and fungi in an aerosolized form [73]. A study showed that irradiation with UV for 60 min on several CoVs that were cultivated on the medium resulted in a lack of viral growth [74]. Quaternary ammonium compounds are able to remove the odor and have extensive biocidal and sporostatic activities [73]. To wash the clothes, the washing machine contains laundry detergent with a temperature of 60–90°C is recommended. If this is not possible, immerse the clothes in warm soapy water in a large container and use a stick to stir. After the drain of water and soap, it will be submerged in 0.05% chlorine for 30 min then drain, rinse, and dry in sunlight [47]. Ambulances and vehicles for the transport of suspicious cases should be cleaned and disinfected properly. For washing and disinfection, it should be cleaned first by household soap or detergent and then performed by 0.5% sodium hypochlorite as a disinfectant [75].

Conclusion

COVID 2019 is a pandemic with very high transmission power. Several studies have been conducted on the effect of genetic and environmental factors (temperature and humidity) on COVID-19 transmission rate. Some of these studies have confirmed the relationship between environmental conditions and disease transmission and others have rejected. It seems more widespread studies are needed to prove the effects of factors on the stability and spread of COVID-19 virus. Not all COVID-19 exposed people are infected and not all infected patients develop severe respiratory complications.

It is quite likely that these disparities are genetically mediated, in part. Because SARS-CoV-2 enters the cells through ACE2, by examining more cases from different genetic backgrounds and ethnicity and worldwide, ACE2 expression variation can be precisely analyzed and compared to establish whether it contributes to susceptibility to COVID-19 across the different subgroups. The number of people due to the occupation may be exposed to this virus are very high and, in many cases, may be due to different reasons, including lack of health, lack of knowledge and attitude, working conditions, and different safety culture. Reducing human-to-human contact by increasing the level of public health in the community as well as maintaining social distance plays a key role in prevention and control of COVID-19 disease. However, many aspects of Covid-19 are still unknown and require further and extensive studies.

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Pediatric Immunization Practice During Coronavirus Disease-2019 Pandemic

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Abstract

At the end of 2019, coronavirus disease-2019 (COVID-19) started to spread worldwide and caused a pandemic in March 2020. Epidemiologic data of COVID-19 in the pediatric population are not certain. The pandemic also decreases routine immunization coverage in children which lead to increased risk of vaccine-preventable disease outbreak. Routine immunization practice should be continued with due regard to health protocol. Children in contact with COVID-19 patients or children who previously have COVID-19 may be immunized after 14 days of symptom-free or confirmed negative by two polymerase chain reaction tests at a minimum interval of 24 h. Bacillus Calmette–Guerin, influenza, and pneumococcal immunization give a positive effect on COVID-19. Until present, there is no available vaccine for COVID-19.

Introduction

In December 2019, a cluster of patients in contact with a market in Wuhan, Hubei Province, China, was hospitalized due to pneumonia with unknown etiology [1], [2]. Further, investigations confirmed that the disease was caused by a virus named severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and the disease was named as CoV disease-2019 (COVID-19) [3]. In March 2020, the disease had spread to Europe, and on March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic [1], [2]. Children, health-care staffs, and elderly population are at a higher risk for SARS-CoV-2 infection [1]. Unfortunately, screening for COVID-19 is less frequently done in the pediatric population due to asymptomatic disease course in this population, giving uncertain epidemiological data regarding the disease [2], [3]. Children are less affected by COVID-19 compared to adults, with only about 2% of total cases in China and 1.2% in Italy [3], [4]. There was no evidence regarding vertical transmission from mother to child [1], [2], [3]. However, antibody toward SARS-CoV-2 was detected in newborns from mothers with COVID-19 [3].

The most common clinical manifestations of COVID-19 in children are fever (51.6%), cough (47.3%), and sore throat (17.9%) [2], [3]. Extra-respiratory symptoms commonly found are diarrhea (9.7%), vomiting (7.2%), and fatigue (10.6%) [3], [4]. The real-time polymerase chain reaction from the nasopharyngeal swab is considered as the gold standard for diagnosing COVID-19. At present, there is no specific treatment for COVID-19. Broad-spectrum antiviral and antibiotics are utilized. Corticosteroid and intravenous immunoglobulin (Ig) are given for children with severe cases [1], [3]. The estimated mortality for children with COVID-19 from a systematic review was 0.08% [3].

A vaccine against COVID-19 is considered as the most important and powerful weapon to fight the disease. Unfortunately, until the present, there is no effective vaccine which has been discovered [2]. During this pandemic, many countries urge shelter-in-place or stay-at-home policy. This policy, in addition to parental anxiety regarding COVID-19 transmission to their children, extremely decreased routine immunization coverage. This condition increases the risk of vaccine-preventable disease outbreak during or after COVID-19 pandemic [5]. Data from the Ministry of Health Republic of Indonesia showed that 84% of primary health facilities stopped or postponed immunization practice. National immunization coverage was also decreased during COVID-19 pandemic, with a range between 0.5% and 87% [6]. We aimed to describe pediatric immunization during COVID-19 pandemic and to discuss about the effects of routine immunization both in reducing vaccine-preventable diseases and modulate COVID-19.

Pediatric Immunization During COVID-19 Pandemic

Immunization is one of the most important inventions in the medical world. It greatly reduces morbidity and mortality from several diseases, such as smallpox, tuberculosis, and polio [7], [8]. Routine immunization must be conducted to prevent vaccine-preventable diseases outbreak even in COVID-19 pandemic [7], [9], [10]. Prevention of vaccine-preventable diseases outbreak gives huge advantages during this pandemic, such as saving lives and saving resources [7], [10]. Immunization practice may also be used to spread messages regarding COVID-19 prevention and to identify early signs and symptoms of COVID-19 [10]. Parents or proxy should be informed about the importance of completion of routine immunization because if an outbreak occurred, we will face a double burden: COVID-19 pandemic and vaccine-preventable disease outbreak [6].

Immunization practice in children should follow health protocol for decreasing the risk of exposure to subjects with COVID-19 [9], [10]. Before bringing children for immunization, parent and proxy are suggested to make an appointment. This is important to avoid overcrowded rooms [7]. The crowded situation should be minimized by limiting the number of adult who accompanies the child [10]. Children's companions should be screened for fever and other COVID-19 symptoms [7]. The area for immunization practice should be well ventilated and frequently disinfected [7], [10]. The area should be spacious enough with airflow from health personnel to children. Entrance and exit doors should be separated [7]. The separation between well and sick visits, by modifying clinic structure, rescheduling visits, and physical spacing, is important. Younger infants are prioritized to receive immunizations [5], [7], [9], [10]. All health-care personnel should use complete personal protective equipments and practice hand hygiene as often as possible [7], [10]. In a situation of personal protective equipment shortage, health-care personnel should minimally wear the medical mask and fresh gloves for each child. Children should wait for 30 min after immunization in a separated place to monitor vaccine-associated adverse reaction [7].

Children in contact with COVID-19 patients or suspected for COVID-19 may still receive routine immunization since there is no evidence of contraindications reported. However, they should be free from symptoms for 14 days or preferably tested negative for COVID-19 in two consecutive samplings within 24 h interval before immunization [7], [10]. Catch-up immunization should also be continued during this pandemic with similar health protocol with routine immunization [5], [7], [10]. Mobile immunization facility may be optimized to deliver the vaccine to children in remote areas or children who missed their vaccination schedule [7]. School-based immunization is still applicable if conducted with proper health protocol [5], [10].

At present, there is no specific vaccine against COVID-19 [10]. Influenza immunization is suggested during COVID-19 pandemic. The reason is to lower the probability of having influenza which has similar symptoms with COVID-19. By receiving influenza immunization, health-care personnel may at least exclude influenza as the etiology of respiratory symptoms [9]. Passive immunization, using polyclonal and monoclonal antibodies, is being investigated for COVID-19 while waiting for the vaccine. Passive immunization is a process of administering mature antibodies to treat infectious diseases. It can occur naturally or artificially. The antibody may be obtained from the serum of immunized animals or convalescent humans. However, harvesting antibodies require a very high cost. IgY is one of the several candidates for COVID-19 passive immunization. IgY is produced by birds, reptiles, and amphibians, but its function is similar to IgG in mammals. IgY has been used in immunization against several microorganisms such as *Salmonella* sp. and rotavirus. Continuous investigations are being held to obtain SARS-CoV-2 specific IgY [11].

The Role of Immunization in COVID-19

Bacillus Calmette–Guerin (BCG) vaccination is reported to be correlated with the incidence and outcome of COVID-19. BCG vaccination decreases the incidence and alleviates the outcome of COVID-19 in countries which adopt mandatory BCG vaccination program [4], [8], [12], [13]. A study reported that countries which apply universal BCG immunization had a significantly lower incidence and mortality rates compared to those who do not apply universal BCG vaccination program [13]. Furthermore, BCG strain also affects its protective effect against COVID-19. Countries with early strains BCG (Japan and Russia) show a lower incidence of COVID-19 compared to countries with late strains (Denmark). On the other hand, the protective effect of BCG vaccination is affected by other factors, as reported by data from Finland and Australia. Both countries reported low mortality rates from COVID-19 even they had stopped BCG vaccination in their regions [12]. Some factors which affect this result are national disease burden, the difference in testing rate, isolation policy, and demographic parameter [8].

The protective effect of BCG is possible because BCG vaccination is reported to be able to elicit protection against other pathogens through sustained changes in the innate and adaptive immune systems. BCG induces histone modifications and epigenetic reprogramming of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF). This results in known as "trained immunity" [4], [8], [12], [13]. The concept of trained immunity was introduced in 2011. According to the concept, bacterial infection induces cross-protection against other pathogens. Unfortunately, this cross-protection is temporary and quickly disappeared. However, memory lymphocytes triggered by the infection may also provide longer-term cross-protection [4]. *In vivo* studies have confirmed this effect against avian influenza A and yellow fever viruses [8].

Vaccines may also contain immune adjuvant which promotes innate immune function. Influenza vaccination is hypothesized to have a protective effect against SARS-CoV-2 since the S-glycoprotein of SARS-CoV-2 has similarities with the hemagglutinin antigen glycoprotein in the influenza virus. Pneumococcal conjugate and polysaccharide vaccines are also suspected to have an advantage in preventing bacterial coinfection in COVID-19 children. Investigations regarding the effect of available immunization on COVID-19 are being conducted [4]. The WHO has not approved the utilization of any vaccine for COVID-19 management until valid evidence becomes available [8]. The authors did not find any study or report regarding the contribution of other vaccines in the incidence and outcome of patients with COVID-19.

Conclusion

Routine pediatric immunization practice during COVID-19 pandemic must be carried out while still applying standard health protocol. Children in contact with COVID-19 patients or previously have that COVID-19 should be immunized 14 days after the symptom diminished or after COVID-19 showed a negative result. BCG, influenza, and pneumococcal immunization give particular positive effects on COVID-19. Until present, there is no specific vaccine for COVID-19.

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The Emotional State and Physical Condition of Indonesian College Students: An Emerging Situation during the Coronavirus Disease-19 Crisis in Indonesia

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Abstract

BACKGROUND: Since the first cases in Wuhan China have been reported, the Coronavirus disease (COVID)-19 cases increased exponentially over the world. This disease might affect physical and mental well-being.

AIM: This study was aimed to examine the emotional state and physical condition of college students during the COVID-19 pandemic in Indonesia.

METHODS: The study used a cross-sectional survey design in April 2020. The participants of the survey were adult that currently enrolled at one of the universities in Indonesia from diploma-1 to master's degree. Information from a total of 1044 participants could be obtained. We used the developed self-reported questionnaire to collect information regarding socio-demographic, personal hygiene and healthy lifestyle, anthropometric measurement data, and depressive symptoms. Pearson Chi-square and Fisher's exact test were performed using SPSS v.24 with a significant level of $P < 0.05$.

RESULTS: This study found that 31.1% of participants are possible depressed. Of 1044 students, 35.3% were malnourished (16.5% underweight and 18.8% overweight/obese). Factors associated with depressive symptoms are sleep longer than usual, gathering with family members, and working (for income-generating).

CONCLUSION: The COVID-19 probably affected the majority of Indonesian college students, especially for emotional and physical condition. The government should not neglect this group by providing clinical and social supports for their well-being.

Introduction

The coronavirus (CoV) disease 2019 (COVID-19) is a global public health threat, which is rapidly spreading and has become a pandemic. The number of COVID-19 cases has exponentially escalated to more than 2.8 million, with almost 200,000 deaths [1]. Many modeling studies have estimated that COVID-19 will potentially spread across the world until the end of the year. The latest survey predicted that the COVID-19 pandemic is expected to resolve in February next year [2].

In Indonesia, since the first case was identified on March 2, 2020, COVID-19 has been pandemic, infecting more than 15,000 within the past 3 months. The case fatality rate is also steadily high, ranging from 6% to 7% [3]. This massive increase, according to the World Health Organization, implies that community transmission has occurred. A country with a community transmission classification means that the majority of the cases may not be linked to the transmission chain or unrelated clusters cases happened in some areas [1]. To mitigate rapid local transmission in the community, the Indonesian government issued a number of policies. For example, through the presidential decree number 11 of 2020, COVID-19 has been declared a public health emergency threat, requiring all elements of society to be actively involved in resolving this outbreak [4].

The latest policy issued by the government, the Government Decree Number 21 of 2020, regulates large-scale social restrictions in a local region or area. This regulation encourages people to stay at home and do all activities from home, including work, study, and worship [5]. Although this regulation seems to be effective in reducing the intensity of meetings among people, the "lock-down" potentially raises socio-demographic consequences. A recent review reported that actions taken to prevent the spread of the COVID-19 had escalated the incidence of domestic violence, including physical, emotional, and sexual abuse [6]. However, it has remained unknown whether the COVID-19 threat and the related news have affected the physical condition and mental health of people in Indonesia. Furthermore, it is interesting to investigate to what extent a particular age group can modify the effects of COVID-19 and its association on physical and mental health.

Two months after the implementation of COVID-19 as a public health emergency in Indonesia, adolescents and young people may be the group that feels the most profound effects of this extraordinary event. While people from marginal society receive financial and social safety-net support from the government for their basic living needs, there is no program designated for young people, which ensures their aspect of living during the pandemic. Although they would usually be studying at school or college and interacting with each other, they now have to stay at their home or their boarding house with no support from the government. This situation might have implications for their life, including physical and psychological condition. A recent study in China reported that more than half of people experienced psychological impacts of the COVID-19 pandemic [7]. From the survey in the US, the prevalence of depression in adolescents and young adults has increased in recent years [8], indicating that adolescents and young people are vulnerable to mental health problems and that governments should not neglect them.

There is limited information about the extent to which COVID-19 affects adolescents and young people. Furthermore, we do not yet know what the impacts of the implementation of the study-from-home policy will be on the physical and mental health of students. Therefore, this study aims to explore the physical and psychological health status of Indonesian students after 2 months of the COVID-19 outbreak in Indonesia. This study investigates the college students in Indonesia, who still have the burden of studying while being forced to consider going back to their hometown during this pandemic to help prevent virus spread.

Materials and Methods

Design and participant

The study used a cross-sectional survey design conducted over the 2 weeks from April 4, 2020 to April 18, 2020. The survey information was shared online through social media (WhatsApp and Instagram) using an anonymous online questionnaire.

The participants of the survey were adults that were currently enrolled at a university in Indonesia and studying any degree from diploma 1 (D-1) to master's degree. We targeted that the minimum sample size for this survey is 1020 derived from 34 provinces in Indonesia or 30 participants from each province. After the survey completion, we got 1044 participants completed the survey. Distribution of participants is shown in Figure 1. All participants were required to read and sign an informed consent before starting the survey.

Questionnaires and measure

The survey data were collected and managed using the RedCap electronic data capture tool hosted by the University of Sydney digital platform [9], [10]. The developed self-reported questionnaire was used to obtain information about socio-demographic; personal hygiene, health and lifestyle; and anthropometric factors, as well as depression status. The socio-demographic factors asked in this survey included gender, age, region, family members at home, and grade and degree at the college. Information relating to personal hygiene, health, and lifestyle in the past 7 days was also obtained. Personal hygiene, health, and lifestyle included wearing masks, washing hands with soap, using hand sanitizer, and physical activities. For physical activities, the participants were asked: "In the past 7 days, was there any moderate-to-vigorous physical activity (MVPA) that regularly did (at least

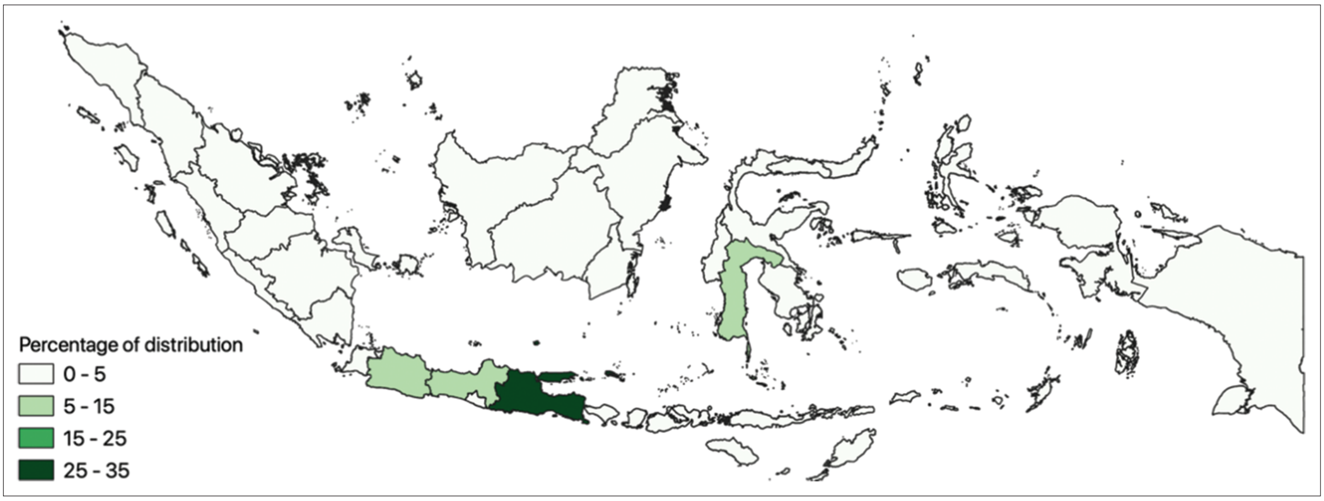

Figure 1: Distribution of participants by regions

10 min)?" If yes, then we asked further questions, "what types?" and "how many days (max 7 days)?" and "how long the duration?."

Depressive symptoms of participants were assessed using the 6-item Kutcher Adolescent Depression Scale (KADS-6). From the score of depressive symptoms, we defined the presence of depression if the total score was at or above six ; the participant was considered probably not depressed if otherwise [11].

Statistical analysis

Socio-demographic factors were provided using descriptive statistics. Pearson Chi-square and Fisher's exact test were used to testing the association between socio-demographic, physical activity, nutritional status, and depression status. All statistical tests were performed using SPSS v.24 (IBM SPSS statistics, the US) with a significant level of P < 0.05.

Results

Data collection took place over 2 weeks, involving a total of 1044 respondents and representing all provinces in Indonesia. Table 1 shows that the majority of participants are 21-year-old female (82.6%); enrolled in bachelor's degree (57.9%), and the grade of the 2nd year (33.4%).

Table 1: Characteristic of the participants

Characteristics	Total (n = 1044)
Age, mean ± SD (min-max)	21.12 ± 2.42 years (16.23–37.53)
Gender (Female), n (%)	862 (82.6)
Degree (Bachelor)‡, n (%)	598 (57.9)
Grade (Second year)‡, n (%)	345 (33.4)
Number of other family member living together at home (3–4 people), n (%)	492 (47.1)
Type of university (State), n (%)	745 (71.4)

‡12 participants did not give their response.

Table 2 describes the behavior of students regarding personal hygiene, health and lifestyle, and other behaviors that may be present due to the implementation of the work-from-home policy. Most students cook their food, and only a few order foods online, or buy food outside (93.2%, 3.2%, and 2.4%, respectively). One-third of the total respondents felt they did not care much about either the consumption of supplements or fruits. Of the 96.7% of students who always wash their hands with soap, more than 80% perceive that their handwashing behavior increased during the COVID-19 pandemic. Regarding the COVID-19 prevention behaviors, a majority of students implemented social distancing (93.8%) and wearing a mask when leaving home (76.3%). While half of the students use hand sanitizer (47.5%), a third of the students have no plan to go back to their hometown (31.2%).

Table 2: Personal hygiene, healthy lifestyle, and WFH-related behaviours

Variables	Total (n = 1044)
Source of getting food (Self-cooking) ‡, n (%)	972 (93.2)
Change of eating behavior in the last 2 weeks (Not changed), n (%)	496 (47.5)
Consumed supplements (No, but consume more fruits), n (%)	450 (43.1)
Washing hand with soap (Yes), n (%)	1,009 (96.7)
Change of washing hand behavior in the past 2 weeks (Increased), n (%)	882 (84.5)
Work-from-home (Yes), n (%)	1,036 (99.2)
Stay at home during WFH policy (Yes, but ever going out 1–3 times), n (%)	630 (60.3)
Activities during WFH and (Answered yes), n (%)	
1. Sleep more than usual	316 (30.3)
2. Doing hobbies	566 (54.2)
3. Studying	849 (81.3)
4. Gathering with other family members	468 (44.8)
5. Doing communication through online apps	319 (30.6)
6. Working (gain-income purposes)	79 (7.6)
7. Tidying the room and house	580 (55.6)
Applying social distancing (Yes), n (%)	977 (93.8)
Wearing the mask every time leaving home (Yes), n (%)	797 (76.3)
Type of masks (Fabric masks)#, n (%)	482 (60.5)
Always using hand sanitizer (Yes), n (%)	496 (47.5)
Type of hand sanitizers (Gel hand sanitizers-commercial products)*, n (%)	209 (40.3)
Plan to go back to hometown (Already went home), n (%)	362 (34.7)

‡One participant did not give response (n = 1043); §n = 1044 for each question; #n = 797; *n = 496.

Nutritional status and physical activities of the participants are demonstrated in Table 3. The percentage of students who were underweight and overweight/obese was 16.5% and 18.8%, respectively. About 31.1% of students perceive that their body weight has increased. Among 1044 students, only 43.9% have performed MVPA during the pandemic.

Table 3: Nutritional status and physical activities of the respondents

Variables	Total (n = 1044)
Weight‡, mean ± SD (min–max)	54.86 ± 12.13 kg (35.0–125.0)
Height‡, mean ± SD (min–max)	157.76 ± 7.42 cm (130.0–185.0)
Body mass index‡, mean ± SD (min–max)	21.94 ± 3.99 kg/m^2 (14.4–41.5)
Nutritional status‡, n (%)	
Underweight	171 (16.5)
Normal	672 (64.7)
Overweight	76 (7.3)
Obese	119 (11.5)
Always check body weight (Yes), n (%)	414 (39.7)
Perception about weight change in the last two weeks (not changed), n (%)	444 (42.5)
Doing moderate to vigorous activities during COVID-19 pandemic (Yes), n (%)	458 (43.9)
Type of activities, n (%) (n = 458)	
Exercise only	100 (21.8)
Cleaning house only	180 (39.3)
Exercise and cleaning house	178 (38.9)
Exercise frequency, mean ± SD (min–max) (n = 435)	4.03 ± 2.12 days (1–7)
Exercise duration, mean ± SD (min–max) (n = 411)	31.39 ± 33.04 min (10–300)

‡Six participants did not report weight and height (n = 1038).

After measuring the depressive symptoms of the students, the results of this study indicate that 31% of students are considered to have a probable depression status (Figure 2). Table 4 shows the factors associated with students' depression status. MVPA and receiving news about COVID-19 were significantly associated with depression among students (P < 0.05).

We also reported the possibility of activities and behaviors during COVID-19 pandemic and implementation of WFH policy affecting depression among students in Figure 3. Excessive sleep habits, gathering with family, and having a job (working for income purposes) were significantly associated with depression. The proportion of depression is higher in students who sleep excessively (41.1% vs. 26.6%), does not gather with other family members (34.4% vs. 26.9%), and does not have a job to gain income (31.9% vs. 20.3%).

Table 4: Factors associated with students' depression

Factors	Depression		*P*
	Possible depressed, n (%) n = 324 (31.0)	Probably not depressed, n (%) n = 720 (69.0)	
Gender			
Female	276 (32.0)	586 (68.0)	0.15
Male	48 (26.4)	134 (73.6)	
Age			
<22 years	255 (32.3)	534 (67.7)	0.12
≥22 years	69 (27.1)	186 (72.9)	
Number of other family member living together			
None	17 (30.4)	39 (69.6)	0.99
1–2 people	39 (31.7)	84 (68.3)	
3–4 people	155 (31.5)	337 (68.5)	
5–6 people	91 (30.1)	211 (69.9)	
>6 people	22 (31.0)	49 (69.0)	
Nutritional status			
Underweight	51 (29.8)	120 (70.2)	0.24
Normal	200 (29.8)	472 (70.2)	
Overweight/obese	70 (35.9)	125 (64.1)	
Doing moderate-to-vigorous physical activity			
No	200 (34.1)	386 (65.9)	0.01
Yes	124 (27.1)	334 (72.9)	
The perception that receiving news about COVID-19 may affect mental health			
Do not affect	167 (25.2)	497 (74.8)	<0.001
Significantly affect	127 (44.7)	157 (55.3)	
Do not know	30 (31.3)	66 (68.8)	
Making efforts to reduce the effect[&]			
Doing nothing	9 (45.0)	11 (55.0)	0.31
Thinking that it is a hoax news	5 (62.5)	3 (37.5)	
Researching to know the truth	61 (39.4)	94 (60.6)	
Finding other entertainment	51 (51.5)	48 (48.5)	
Do not know	1 (50.0)	1 (50.0)	

[&]n = 284.

Discussion

The outbreak of COVID-19 has caused extensive detrimental effects for human beings around the world. A study compiling experiences from many countries and regions highlighted that this disease has the potential to cause widespread socio-economic damage, including affecting physical and emotional health [6]. In this study, we observed the physical condition and depressive symptoms of adolescents and young people during the COVID-19 pandemic in Indonesia. The main finding of the survey reveals that one-third of young people were likely showed depressive symptoms. A survey in 2019 indicated a similar result and found that 24% of young people aged 18–24 years experienced mental health problems. Several depressive symptoms, such as having suicidal thoughts and self-harm, were also reported (33% and 45%, respectively) [12]. In a disaster or an emergency, young people may experience some behavioral, physical, and emotional reactions, such as sadness, hopelessness, exhaustion, withdrawal, anxiety, sleep problems, and crying more frequently. Some of those symptoms are part of major depressive disorder's symptoms. Depression can be a significant mental health problem after a disaster, and the incidence of depression can be very high and common [13].

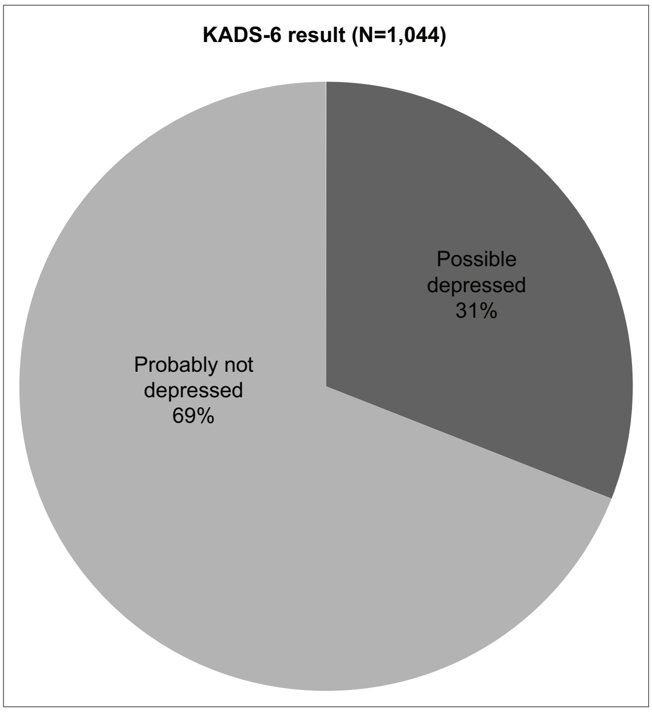

Figure 2: The proportion of possible depressed and probably not depressed participants

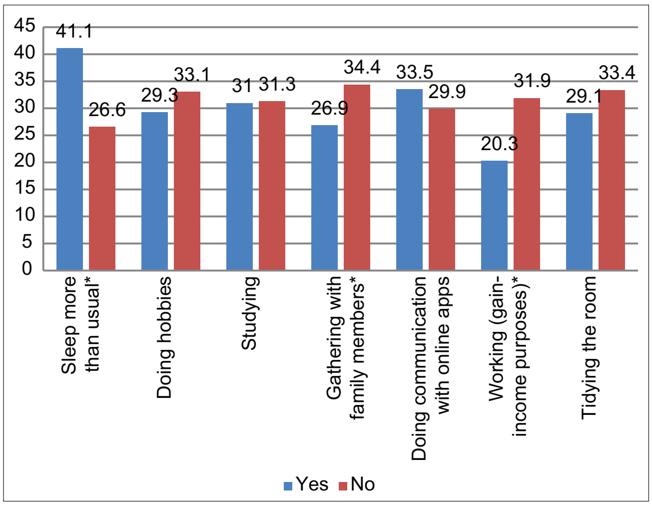

*Figure 3: The percentage of depression based on WFH-related behaviors; [&]n = 1044 for each question; *α < 0.05*

Depression among young people is often related to poor behavior, and it is prudent to mention that this situation often goes undetected. A study pertaining to Brazilian students and factors associated with depressive symptoms reported the effects of gender, family problems, physical activity, financial problems, quitting school or work due to health problems, and insomnia [14]. Surprisingly, we found that sleeping longer than usual was associated with depressive symptoms among the student participants. Sleep disturbance is one of the most notable symptoms of depression. In some cases, people with mild and moderate depression, manifest excessive sleeping tendency and may sleep up to twelve hours a day [15]. People who are depressed or with depressive symptoms are likely to have a lack of power to wake up. Their depressive thoughts (e.g., life is meaningless) and a sense of disinterest in the activity encourage them to choose to sleep, hoping that sleeping longer can solve their problem. Moreover, adequate sleep, not excessive or lacking, may help to perpetuate circadian clock-controlled responses (circadian rhythm), hindering mood disorders [16], [17], [18]. Besides, the quality of sleep, including sleep-onset and bedtime, was also shown to be a significant determinant of depressive symptoms [19].

Gathering with family appeared to have a positive effect on the depressive symptoms of the students. Face-to-face communication and engagement with other family members are often valuable in life, especially for Asian people where culturally all family members being interdependent each other [20], [21]. The family dynamic and functioning play an important role in affecting family members and individual mental health [22]. A study also demonstrated that family could either be involved in a treatment or support the adherence of the treatment for mental illness strengthening [23].

This study also found that the proportion of depression was lower in the students working for income purpose than those who did not work (20.3% vs. 31.9%). Working and earning money might be the reason for this different proportion [24], [25] as economic insecurity (e.g., have debt) is one of the factors that influence mental health. In adolescents, poverty is associated with the development of adverse situations, such as depression, criminal and sexual violence, and drugs abuse [22]. Although the current situation of the COVID-19 may not directly cause chronic poverty, the government supposed to consider the effect of loss jobs on mental disorders. Moreover, by working, people who experienced a difficult situation can get their thoughts distracted from negative things; thus, mental disorders avoided [26].

Another factor that significantly associated with the appearing of depressive symptoms is receiving a large amount of news about COVID-19. Some studies showed significant correlations between media exposure and stress responses, especially during a disaster or emergency. The severity of unfavorable outcomes of mental health may depend on the exposure of the information regarding the disaster situation. The greater the sensory exposure, the more likely mental health problems will manifest [13]. In depressed people, almost any external stimulus is capable of evoking depressive thoughts, such as thoughts about suicide or self-harm, which is showed in this study. For some people, situation, nowadays, is interpreted positively, but for another, they showed dysfunctional thoughts which are leading to a depressive symptom. A cognitive model shows that people's emotions, behaviors, and physiology are associated with how they interpret and think about a situation or events [27].

Existing literature has emphasized that exercise can promote positive mental health by increasing mood and self-esteem and decreasing anxiety [28]. However, the beneficial effect of physical activity on mental health seems to be inconsistent. Bell *et al*. reported that the volume and intensity of physical activity were not associated with mental well-being, although a connection to emotional problems was found [29]. The current study found (data were not shown) that physical activity duration did not affect the depression status of the students. However, the proportion of depression was different between students who did the MVPA and those who did not do MVPA. This study did not obtain data relating to the type and volume of MVPA performed by the students. However, the type of physical activity may be strongly associated with depressive symptoms. The result of some studies indicated that the aerobic exercises were related to a decrease in depression and there was a significant reduction in depressive symptoms in the exercise group compared with the other group two subjects' group. Exercise also can be a distraction from the stressful event, such as staying at home during COVID-19 Pandemic [30]. Inter-Agency Standing Committee suggests exercise as one of the activities that will support the adult's well-being during home isolation [31].

Another interesting finding demonstrated that 18.8% of students were overweight/obese, and 16.5% were underweight, indicating the double burden of malnutrition in this particular group. The trend showed that overweight/obese students with depressive disorders were higher than underweight and healthy weight students, despite not being statistically significant (P = 0.24). A previous study on college students supports this finding and reported that body mass index was not associated with depression but dietary intake. Students' fruit and vegetable intake and food insecurity were the significant predictors of depression, modified by sexes [32]. Although this study, similar to previous studies, reported no association between nutritional status and depression, it was indicated that the students probably had a poor dietary intake, potentially affecting neurotransmitter, and mood-related hormones [33].

Furthermore, information about personal hygiene concerning COVID-19 prevention was gathered in this study. A majority of participants performed COVID-19 preventive behaviors by always wearing a mask when leaving home (76.3%), applying social distancing (93.8%), washing hand with soap (96.7%), and almost half of the participants always used hand sanitizer (47.5%). These behaviors indicated that the students had understood the recommendations from the WHO [34] and the Government of Indonesia [35] concerning following best practice to protect themselves from being infected with CoV.

Strength and limitation

The strength of this study is that the survey, to the best of our knowledge, is the first study that has investigated the impacts of the current situation (the COVID-19 and work-from-home policy) on the emotional state and physical condition of Indonesian young adults. A high response rate relating to depressive symptoms is another strength of this study. However, a limitation of the research has been noted. The study did not report on food intake, which may significantly affect the health condition of the participants, including mental illness and nutritional status. There is a potential bias of anthropometric results due to self-reported weight and height. Finally, although we obtained 1044 participants, it did not reach 30 representatives from each province.

Conclusions

This study found that one-third of college students in Indonesia rated themselves as having symptoms of depression. Factors found to be associated with depressive symptoms among the young adult students in Indonesia include receiving news about COVID-19; performing physical activity; having proportional sleep time; gathering with other family members; and working for income purposes during the period of the work-from-home policy. Therefore, we suggest that the government and policymakers from universities/colleges should pay close attention to students during this COVID-19 pandemic and implement strategies to support their physical and mental health. Physical and psychological health guidelines related to COVID-19 are necessary for this specific group.

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Coronavirus Disease-2019 and Mental Health

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Abstract

BACKGROUND: Coronavirus disease-2019 (COVID-19) emerges in Wuhan, China and becomes a pandemic on March 2020. Its manifestations mainly cover respiratory and gastrointestinal symptoms. In fact, mental health disorders are common in patients with COVID-19 but receive minimum attention.

AIM: We aimed to discuss mental health disturbances in relation to COVID-19 and its management.

MATERIALS AND METHODS: We gathered literature regarding the topic from electronic sources, including PubMed and Google Scholar.

RESULTS: There are several pathogeneses proposed regarding the incidence of mental health problems. The symptoms of mental health problems vary widely and also affect health-care personnel. Diagnosing mental health problem in COVID-19 patients is quite difficult because no examinations are specific enough. The management of mental health problems includes psychological and medical managements.

CONCLUSION: Further study regarding mental health problem and its management in patients with COVID-19 is mandatory.

Introduction

Emerging in Wuhan, China in the end of 2019, coronavirus disease-2019 (COVID-19) has spread throughout the globe and caused significant morbidity and mortality [1], [2]. The World Health Organization had finally declared COVID-19 as a pandemic on March 11, 2020 [3]. There are many manifestations of COVID-19, including respiratory and gastrointestinal symptoms, but only a little attention is paid for mental health problem [1], [3], [4]. Before this COVID-19 pandemic, other coronaviruses had already caused an epidemic which is a severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory syndrome (MERS) in 2012 [4]. Previous coronavirus epidemics also triggered mental health problems. The deficit in neuropsychiatry was reported to be present until 18 months post-discharge [5]. During the previous SARS epidemic, 59% of SARS survivors suffered from psychiatric disorders in the first 3 years [1].

This COVID-19 pandemic is different with other disasters such as earthquake or tsunami. This pandemic showed no sign of ending. Besides, this pandemic affects everyone in every moment and every place. This causes a big uncertainty in one's mind and leads to the mental problem [6]. It is important to note that mental health disturbance can cause more significant effects than the virus itself [7]. Several literatures had described mental health problems in association with COVID-19. A patient with COVID-19 was suffering from meningoencephalitis, marked by neck stiffness and transient generalized seizure [1]. Another study reported that 31% of patients with COVID-19 had altered mental status. Mental health problems seem to occur more often in younger patients [2]. Beach *et al*. reported 4 case series of COVID-19 patients with delirium [8]. There was also a positive association observed between coronavirus seropositivity and mood disorders [1]. A study from Egypt reported a significant psychological impact in the public from COVID-19 pandemic with depression as the most frequent, followed by anxiety [9].

Methods

We gathered literature regarding the topics from electronic sources, including PubMed and Google Scholar. We used "coronavirus," "coronavirus disease 2019," "COVIC-19," "mental," "health," "disorder," and "disturbance" as the keywords in the search engine. We included literature published from December 2019 and on. All literatures were written in English.

Discussion

Pathogenesis of mental health disturbance in COVID-19

Coronavirus is a single-stranded ribonucleic acid virus with four major genera: Alphacoronavirus, betacoronavirus, gammacoronavirus, and deltacoronavirus. Previous epidemics, SARS-CoV, and MERS-CoV, together with SARS-CoV-2, belong to betacoronavirus genera [1], [4], [10]. SARS-CoV-2 particles are detected in patients with multiple sclerosis giving a higher possibility of the virus neurotropism [1]. *In vitro* study had shown that SARS-CoV-2 can replicate in neurons [4], [5].

SARS-CoV-2 is hypothesized to enter the brain through the olfactory bud, resulting in rapid invasion with transneuronal spread and minimal cellular infiltration. This explains the presence of anosmia in patients with COVID-19 [1], [5], [8], [10], [11]. Viral invasion may occur through binding of virus with angiotensin-converting enzyme 2, which expressed in neurons, capillary, and neuronal endothelium. After invasion, the virus will trigger an inflammatory reaction, create cytokine storm [4], [5], [8], [10], [11], and lead to neuropsychiatric symptoms. Invasion into postrema increases the vulnerability of subjects toward depression and delirium [1], [5], [12]. Virus-induced central nervous system demyelination also occurs. Demyelination occurs due to an inflammatory reaction from molecular mimicry between coronavirus envelope S glycoproteins and myelin [1], [5], [12]. Other causes of mental disorders, including secondary to multiorgan failure, hypoxia, and treatment-related [4], [8], [11], [12]. In addition, possible medullary neurons destruction after viral invasion may precipitate respiratory symptoms and cause acute respiratory distress [5], [8], [11]. Stress activates hypothalamus-pituitary-adrenal axis and impairs immune system which further hampers the clinical condition [11].

In this modern era, every subject has the capability to travel and communicate widely. At present, these freedoms are restricted significantly due to COVID-19 [3], [13]. This condition affects both healthy and infected population [4] and leads to frustration and mental problems [3], [4], [5], [11], [13]. Hospitalization and uncertain prognosis of COVID-19 also clearly worsen the mental disorders [1], [5], [13]. Adverse events from medications used in COVID-19 contribute to mental health status such as insomnia from corticosteroid and psychotic disorder from chloroquine [1], [5], [11]. There is a hypothesis that SARS-CoV-2 may induce vasculopathy and coagulopathy. If the conditions occur in the brain, neuropsychiatry syndromes may manifest [2]. Excessive use of the internet during isolation also contributes to impaired mental function, mainly through the spread of unverified information regarding COVID-19 [7], [6], [13]. Risk factors contributing to a mental health problem in COVID-19 patients are female gender, poor-self-related health, and the presence of relatives with COVID-19 [10]. Inadequacy of basic supplies and unclear information regarding the ongoing situation is considered as additional risk factors [13].

The symptoms of mental health disturbance

A wide range of mental health symptoms is observed, including anxiety, fear, loneliness, anger, encephalopathy, delirium, congenital impairment, mood swings, insomnia, suicide, psychosis, and general distress [1], [4], [6], [7], [11], [13]. Loss of significant ones may also result in persistent yearning and symptoms of reactive distress and social/identity disruption causing impairment in daily life. This condition is known as persistent complex bereavement disorder [14]. Mental health symptoms may manifest even in the absence of respiratory symptoms [12]. The impact of COVID-19 to mental health is always neglected in the acute phase of the disease. It is due to the critical course of COVID-19 which needs more attention and prompt management [3], [6]. Around 35% patients with COVID-19 were reported to suffer from psychological distress [6]. Patients with COVID-19 had a higher rate of suffering from post-traumatic stress disorder (96.2%) and depression (29.2%) [10]. Other studies reported that 65% and 69% of COVID-19 patients who admitted to intensive care unit had delirium and agitation, respectively. Altered consciousness was reported in 21% of patients who deceased [4]. Approximately one-third of COVID-19 patients had neuropsychiatric syndromes such as encephalopathy and altered consciousness [8]. Patients with underlying mental problems have a higher risk in developing more severe symptoms; therefore, they should be treated with antipsychotic drugs together with standard COVID-19 treatment [6], [10].

The symptoms are not only present during the disease course but also after the patients recovered. Lower psychological well-being and higher anxiety score are observed in patients survived from COVID-19 [10]. At discharge, 14.8% of patients had anxiety, while 14.9% and 32.2% had depression and post-traumatic stress disorder, respectively [4]. Another study also reported mental health disorders such as post-traumatic stress disorder (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive-compulsive disorder (15.6%). This urges sustained follow-up for the mental health status of post-discharged patients [5].

Mental Health Problem in Health-care Personnel

Mental health problems are also found in health-care personnel in intense contact with COVID-19 patients, particularly general practitioners in emergency and staffs in intensive care units. They usually have fear, psychological distress, burnout, anxiety, depression, insomnia, somatization, post-traumatic stress disorder, and obsessive-compulsive disorders [5], [6], [10], [15]. The identified etiologies for a mental health problem in health-care personnel are lack of personal protective equipment, high working pressure, suboptimal training/confidence when working in extreme circumstances, concerns of being infected or infecting their relatives, and lack of adequate support in the working environment [15].

Diagnosis of mental health problem

Before diagnosing COVID-19 patients with a mental disorder, we must exclude other possibilities such as metabolic disorders, hydration status, and medication effect. Brain magnetic resonance imaging (MRI) of COVID-19 patients with neuropsychiatric syndrome showed leptomeningeal enhancement and bilateral frontotemporal hypoperfusion. EEG finding is not specific, showing diffuse background slowing consistent with encephalopathy [8], [12]. Cerebrospinal fluid examination should be conducted in patients with seizure, encephalitis, and encephalomyelitis as coronaviruses may be detected [4]. After those possibilities have been excluded, we can assess one’s mental health status using several assessment tools. The Mental Health Quotient can be applied. It is safe enough since it is a web-based assessment tool. It is also fast, easy, and comprehensive toll based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 [16]. However, DSM-5 is still being the most common and standard assessment tool for mental disorder used at present [17].

Treatment of mental health problems in COVID-19 patients

Literature regarding mental health problems due to COVID-19 and its management is scarce [3]. Psychological service should be maintained to prevent the effect of COVID-19 to patient’s mental health. Effective education and communication are important along with the management of stigma and discrimination toward patients [3], [13]. Constructive peer support significantly aids the management of mental health problems [7]. Other suggestions regarding calming skills, health and optimism maintenance, and social support system are also important in keeping the wellness of mental health [3], [12]. Cognitive-behavioral therapy (CBT) may be implemented in patients with mental health problems. It is suspected to be able to relieve the symptoms of mental disorder. During the pandemic, online CBT is one of the safest options [14]. Patients should have access to communication devices such as phone and tablet and also early ambulation. If behavioral management does not improve the symptoms, pharmacological management should be started [12]. Medications used to manage mental health problems in COVID-19 patients are antipsychotic agents (olanzapine and chlorpromazine), haloperidol, antidepressants, benzodiazepines, and amantadine [8], [11]. Melatonin, alpha-2 agonist, valproic acid, and dopamine agonists are also administered in patients with delirium. Vitamins are not a standard treatment for delirium. However, they have antioxidant and anti-inflammatory effects, which, more or less, may protect against neuropsychiatric symptoms [12]. Further study regarding the efficacy of each medication is mandatory [8], [11].

Conclusion

Mental health problems are frequently found in patients with COVID-19. The pathogenesis or mental health problems rely on direct invasion of virus, inflammation-induced demyelination, secondary to multiorgan failure, hypoxia, treatment-related, isolation, unconfirmed information, coagulopathy, vasculopathy, and uncertain outcome. Its symptoms vary widely, including delirium and anxiety. The symptoms are reported in both patients and health-care personnel. The auxiliary examinations for its diagnosis are not specific. Its management consists of psychological and medical management.

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OPEN ACCESS

Pulmonary Tuberculosis in Coronavirus Disease-19 Patients: A Report of Two Cases from Nigeria

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Abstract

BACKGROUND: Despite the concern on the impact of coronavirus disease (COVID)-19 on tuberculosis (TB), there is a paucity of information from the developing countries inclusive of Nigeria.

CASE REPORT: Hence, we report two cases of Nigerian' adults with coinfections of severe acute respiratory syndrome coronavirus 2 and *Mycobacterium tuberculosis* (MTB). The two cases were males and aged 30 and 33 years, respectively. They presented with cough, fever, and weight loss with features of acute respiratory symptoms and a history of contact with a confirmed COVID-19. The GeneXpert for MTB detected was high, and chest radiographs showed both features suggestive of TB, and COVID-19. They both received quadruple anti-TB regimen, along with lopinavir/ritonavir. The first case was discharged after 15 days, while the second patient died 6 days into the admission.

CONCLUSION: This case reports showed that COVID-19 superimposed on TB may not be uncommon in our environment and may have a poorer outcome. Hence, there is a need for a high index of suspicion for TB infection in endemic area during the COVID-19 pandemic.

Introduction

The global number of cases of coronavirus disease (COVID)-19 has risen above ten million with more than 500,000 deaths since the outbreak in December 2019 and the subsequent declaration as a global pandemic on the March 11, 2020 by the World Health Organization (WHO) [1], [2]. Nigeria is battling to curtail the disease with more than 25,000 cases and a case fatality rate of about 2.3% [3]. Besides, Nigeria has the seventh-largest tuberculosis (TB) burden in the world and the second highest-burden of TB in Africa [4]. With an estimated 407,000 cases of TB diagnosed annually in Nigeria, the potential impact of COVID-19 may be more devastating [5], [6]. Available literature suggested that elderly and persons with comorbidities inclusive of chronic respiratory diseases such as TB are at higher risk of death than the general population from COVID-19 [7]. Patients with pulmonary TB (PTB) are known to have depressed cellular immunity and are thus susceptible to viral infections [8]. Despite the vulnerability of TB patients to viral infections, there are few reports and data on COVID-19 and TB since the outbreak of the pandemic [9]. Indeed, a recent review of 49 cases of coinfections of COVID-19 and TB had no data representation from Africa [10]. Besides, the common COVID-19 symptoms including cough, fever and shortness of breath overlap with symptoms of pulmonary tuberculosis which may make distinguishing between the two illnesses difficult for health care workers in high burden countries such as Nigeria. Therefore, we provide information on clinical presentation, laboratory findings, treatment, and outcome of two cases of confirmed COVID-19 infection with PTB managed at a treatment facility in Nigeria.

Case Reports

Case one

Patient one was a 33-year-old male adult who presented with a 2 months history of cough, productive scanty whitish sputum, low-grade fever, and weight loss. He had real-time reverse transcription-polymerase chain reaction (RT-PCR) for syndrome coronavirus 2 (SARS-CoV-2) test using oropharyngeal and nasal

Table 1: Demographic and clinical presentation of two adult patients diagnosed with COVID-19 and PTB

Variable	Patient 1	Patient 2
Age	33 years	30 years
Gender	Male	Male
Presenting complaints/ duration	Cough/2 months Fever/2 months Weight loss/2 months Sore throat/2 weeks	Cough/6 months Fever/2 months Weight loss/2 months Shortness of breath/2 weeks
Examination findings	Febrile(37.8°C) Pallor Bilateral coarse crepitations Oxygen saturation – 97% on RA	Febrile(38.2°C) Pallor Ankle edema Tachypnea Right apical flattening and BBS on the right LLZ Oxygen saturation – 89% in RA

RA: Room air, BBS: Bronchial breath sound, LLZ: Lower lung zone. COVID: Coronavirus disease, TB: Tuberculosis, PTB: Pulmonary tuberculosis.

specimens due to a sore throat a week before the presentation and a history of contact with a confirmed case of COVID-19. The examination findings at admission revealed a young man, febrile with an axillary temperature of 37.8°C, mild pallor, and chest findings showed bilateral coarse crepitations with an oxygen saturation of 97% in room air (Table 1). The full blood count showed lymphopenia and anemia (Table 2), Sputum GeneXpert showed MTB detected high, HIV screening was negative, and liver function tests, electrolytes urea, and creatinine were within the normal limit (Table 2). Chest X-ray showed reticulonodular shadowing with peripherally based consolidation worse on the left, loss of volume on the left side with mediastinal shift to the left side, and early tenting of the right hemidiaphragm (Figure 1). He received antiviral (lopinavir/ritonavir), azithromycin, Vitamin C, Zinc sulfate, oral prednisolone, quadruple anti-TB agent, and tabs pyridoxine. We discharged home after 15 days on admission following the resolution of symptoms and two negative RT-PCR test for SARS-CoV-2 done 48 h apart.

Table 2: Laboratory findings of two adult patients diagnosed with COVID-19 and PTB

Variable	Patient 1	Patient 2
FBC ($\times 10^9$/L)	6.2	13.1
Lymphocyte (%)	18.8	23.2
Neutrophils (%)	68.6	66.5
Monocytes (%)	14.9	10.0
Eosinophils (%)	6.3	0.2
Basophils (%)	0.3	0.1
PCV (%)	27.4	32.1
Platelets ($\times 10^9$/L)	236	72
EUCr		
Na^+ (mmol/l)	140	128
K+ (mmol/l)	4.3	4.3
Cl− (mmol/l)	99	99
HCO_3^- (mmol/l)	25	15
Urea (mmol/l)	3.1	2.9
Creatinine (Umol/l)	68	58
LFT		
T/Protein	78	66
Albumin	28	34
ALP	100	100
ALT	21	19
AST	17	25
Total bilirubin	0.45	1.35
Direct bilirubin	0.07	0.1
RVS	Negative	Negative
Sputum GeneXpert	MTB detected high	MTB detected high
Chest radiograph	Reticulonodular shadowing with peripherally based consolidation worse on the left side. Loss of volume on the left side	Extensive in homogenous opacity with some coalescing in both lung fields sparing the left apical and LLZ as well as the lower aspect of the right ULZ. There is air bronchogram seen within these opacities

PCV: Packed cell volume, ULZ: Upper lung zone, LLZ: Lower lung zone, FBC: Full blood count, RVS: Retroviral screening, EUCr: Electrolyte urea and creatinine, LFT: Liver function test, ALP: Alanine phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, MTB: *Mycobacterium tuberculosis*. COVID: Coronavirus disease, TB: Tuberculosis, PTB: Pulmonary tuberculosis.

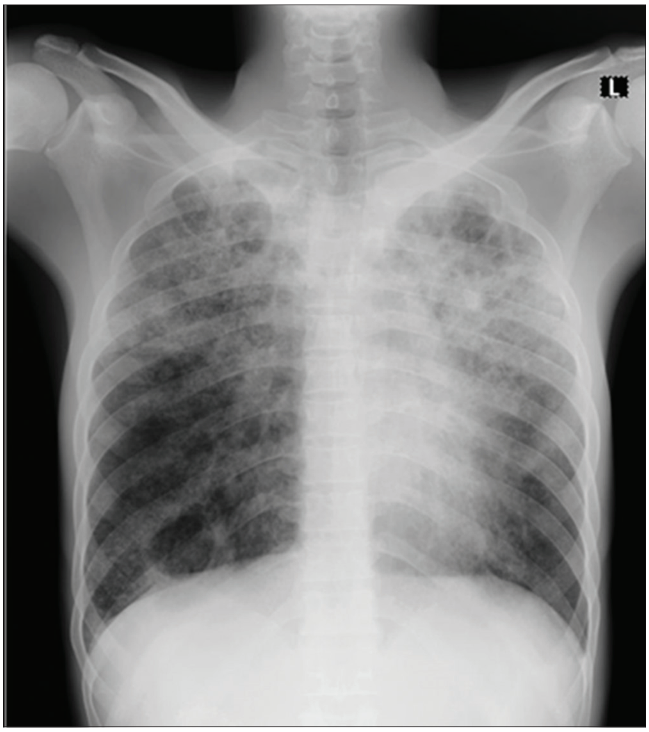

Figure 1: Radiographic changes in patient one

Case two

Patient two was a 30-year-old male who presented with a 6 months history of cough productive of scanty whitish and occasional brownish sputum (non-frothy), no hemoptysis, low-grade fever, and weight loss. He developed difficulty in breathing 2 weeks before his admission, and a history of contact with a confirmed case of COVID-19 prompted the test for SARS-CoV-2 using RT-PCR on oropharyngeal and nasal specimens which turned positive. The examination findings at presentation revealed a chronically ill-looking young man with an axillary temperature of 38.2°C, pallor, and ankle edema. He had a respiratory rate of 36 cpm with the right apical flattening and bronchial breath sound

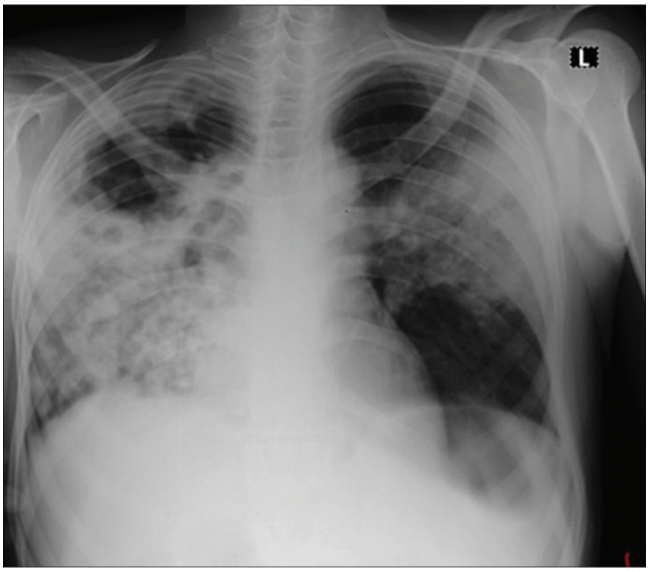

Figure 2: Radiographic changes in patient two

on the right lower lung zone with coarse crepitations on the left hemithorax, and blood pressure of 90/60 mmHg and oxygen saturation of 89% in room air which improved to 96% with administration of oxygen at 4 L/min through nasal prongs (Table 1). Full blood count showed leukocytosis with lymphopenia, anemia, and thrombocytopenia (Table 2), sputum GeneXpert showed MTB detected high, HIV screening was negative, and liver function tests, electrolytes urea, and creatinine were within the normal limit (Table 2). Chest X-ray showed an extensive homogenous opacity with some coalescing in both lung fields, barely sparing the left apical and lower lung zone as well as the lower aspect of the right upper lung zone. There was an air bronchogram seen within these opacities (Figure 2). He received antiviral (lopinavir/ritonavir), azithromycin, Vitamin C, zinc Sulfate, quadruple anti-TB agent and tabs pyridoxine, IV hydrocortisone, and thromboprophylaxis with clexane as well as oxygen therapy. On the 15th day, he developed hypotension (80/50 mmHg) with severe hypoxemia (oxygen saturation of 78%) despite oxygen through facemask with reservoir bag at 8–10 L/min and succumbed to the disease on the 6th day of admission.

Discussion

The two cases in this report had both COVID-19 and TB diagnosed about the same time, with the screening for TB based on the chest radiographic findings and symptoms suggestive of TB. This finding in our report (which the two patients never had treatment for pulmonary tuberculosis) is in contrast to observation from the case series in China where the patients had previous treatment for pulmonary tuberculosis. The detection of the TB for the first time while on admission for COVID-19 is not unexpected due to under-diagnosis and underreporting in most developing countries. Probably, they were cases of active TB moving within the community with the superimposing of COVID-19 that precipitated acute illness prompting the admission. Whereas the patients had typical chronic symptoms (cough, fever, and weight loss) of TB, they both had symptoms of acute respiratory illness before admission. They were also in close contact with confirmed infection of COVID-19. This finding is keeping the case report of COVID-19 and TB from China [8]. Hence, a cautionary reminder to clinicians that mycobacterium infection status should be considered when treating COVID-19 patients (especially in the presence of chronic cough) in TB endemic countries.

The main laboratory findings were lymphopenia and anemia for both patients. Besides, patient two had leukocytosis (who also had severe symptoms), and this is in keeping with the study that examined the laboratory abnormalities in patients with COVID-19 infection [11]. Whereas both patients had chest radiographic changes, they were more extensive in patient two, and he manifested severe symptoms. This observation probably reflected the impact of both COVID-19 and PTB, with more severe damage likely to have a poor outcome. Hence, the poor outcome observed in the patient-two.

Both patients had antiviral, zinc, azithromycin, and anti-TB agent and other treatments in addition to this oxygen therapy and glucocorticoid in the patient with severe disease. The WHO recommends that patient with TB follows all recommended precautions against COVID-19 and continues taking TB treatment throughout the pandemic [12].

Conclusion

This case reports showed that COVID-19 superimposed on TB may not be uncommon in our environment and may have a poor outcome. Hence, there is a need for a high index of suspicion for TB infection in endemic areas during the COVID-19 pandemic. Besides, we recommend screening for TB in patients with chronic cough with superimposed acute respiratory symptoms suggestive of COVID-19.

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Bronchoscopic Intervention May be Associated with Better Outcomes in Mechanically Ventilated Coronavirus Disease-19 Patients: A Case Series

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Abstract

BACKGROUND: The emergence of a new strain of coronavirus infection, the coronavirus infection disease 2019 (COVID-19), has been a pandemic burden across the globe. Severe COVID-19, particularly in patients with acute respiratory distress syndrome (ARDS), is associated with increased risk of admission to intensive care unit (ICU), mechanical ventilation, and mortality. Bronchoscopy has been widely employed as an adjunctive therapy in mechanically ventilated patients. However, the use of bronchoscopy in patients with COVID-19 has been strictly limited due to aerosol transmission.

CASE REPORT: We reported 3 COVID-19 Cases presented to the hospital with ARDS. All of the patients were immediately intubated to improve oxygenation. During admission, the patients produced immense airway secretions that might have resulted in partial airway obstruction. A conventional tracheal suctioning did not help to promote clinical improvement. We decided to perform bronchoscopy with controlled suctioning by following a very tight protocol to prevent aerosol formation. A significant clinical and respiratory improvement was observed in all patients following bronchoscopy. Three of them were transferred to regular ward, however, one patient died during hospitalization.

CONCLUSION: Bronchoscopic procedures may provide significant therapeutic benefits in severe COVID-19 patients. However, it should be kept in mind that this procedure should only be performed with a rigorous protocol to reduce the risk of aerosol generation and subsequent viral transmission.

Introduction

The emergence of a new strain of coronavirus has been a pandemic burden across the globe. Due to the similarity in the genomic sequence and clinical consequence with the previous strains of coronavirus, it has later been named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes a disease called coronavirus infection disease 2019 (COVID-19) [1], [2]. Firstly reported in Wuhan, Hubei Province, China, by the end of December 2019, the number of confirmed SARS-CoV-2 infection cases has been dramatically increasing [3]. As per July 1, 2020, there have been more than 10.6 million cases and over 514,000 COVID-19-related deaths reported by the World Health Organization. A substantial number of new cases has been published in the United States recently, making it the only country that reaches a total of more than 1 million confirmed cases.

On the other hand, although it has been reported to be steadily increasing, the incidence rates in Indonesia are not as overwhelmingly high, as stated in the different parts of the world. This may be attributed to the low rates of screening in our population. However, the case fatality rate of SARS-CoV-2 infection in Indonesia is relatively higher, indicated by the mortality rates of 7.2% [4]. Severe COVID-19, particularly in patients with acute respiratory distress syndrome (ARDS), is associated with an increased risk of admission to the intensive care unit (ICU), mechanical ventilation, and mortality [5], [6]. It has been well documented that patients suffering from ARDS most probably produce thick mucus secretion. This is associated with an increased risk of mucous plug formation and subsequent lung collapse [7]. Similar characteristics of airway secretion have also been reported in COVID-19 infection [8]. Proper and timely secretion management plays essential roles in both the prevention and treatment of respiratory failure. Bronchoscopy has been widely employed for various purposes in severe pulmonary infection, particularly among mechanically ventilated patients. This includes therapeutic suctioning as a part of effective secretion management, both as diagnostic and therapeutic measures [7], [9], [10]. However, the use of bronchoscopy in patients with COVID-19 has been strictly limited as it is associated with the aerosol generation and intensifies viral transmission. It can be performed only in certain situations, such as mucous plug removal as well as to ascertain the presence of any coinfection in patients who do not respond to the standard therapy, by following a very tight protocol as proposed by currently available consensus [3], [11], [12], [13], [14]. However, to the best of our knowledge, there is no presently available data regarding the use of the bronchoscopic intervention in COVID-19 patients with severe clinical presentation. Here, we describe the outcomes of bronchoscopic intervention performed in three cases of mechanically ventilated, COVID-19-confirmed patients.

Case I

A 47-year-old woman was admitted to our facility due to shortness of breath accompanied cough since 1 day before admission. The patient also reported a 1-week course of fever, nausea, and vomitus. She had neither a history of lung nor heart disease. The patient was diagnosed with severe pneumonia. On the 3rd day of hospitalization, the patient experienced clinical deterioration with more intense dyspnea. The initial clinical examination showed decreased oxygen saturation (SpO_2) to 84%, and the patient was immediately given oxygen supplementation. Arterial blood gas (ABG) analysis showed pH 7.480, $PaCO_2$ 34.6 mmHg, PaO_2 159.5 mmHg, and SpO_2 98%. Chest X-ray results were suggestive for bilateral pneumonia (Table 1). The patient was decided to undergo early intubation with subsequent mechanical ventilation. The following ventilator setting was used: Volume-controlled synchronized intermittent mandatory ventilation (VC-SIMV) mode, a fraction of inspired oxygen (FiO_2) 70%, positive end-expiratory pressure (PEEP) 12 cmH_2O, pressure support 12 cmH_2O, tidal volume (VT) 300 ml, and respiratory rate (RR) 20 breaths/min that resulted in oxygen saturation (SpO_2) of 98% immediately. One day following intubation, the patient showed clinical improvement. Subsequent blood gas analysis results showed improved PaO_2 that reached 195.5 mmHg. On the next day, from the physical examination, it was found that there was an excessive mucus production that might have partially obstructed the patient's airway. We performed tracheal suctioning as the primary measure to evacuate the obstructing mucus; however, no clinical improvement was observed. Subsequently, we decided to perform controlled suction through bronchoscopy. Pre-bronchoscopy ABG showed pH 7.492, PaO_2 150 mmHg, $PaCO_2$ 34 mmHg, and SpO_2 99%. Even when there was no vivid hypoxemia, we considered that early bronchoscopic suction would be a favorable measure to improve the patient's clinical status. The ventilator parameters before bronchoscopy were set as pressure support ventilation (PSV), PEEP +5 cmH_2O, RR 19 breaths/min, VT 400 ml, FiO_2 40%, and PS 6 cmH_2O. Bronchoscopy was performed on day 24 of hospitalization in a negative-pressured room. We use fentanyl, atracurium, and midazolam as sedation before bronchoscopy. Bronchoscopy was performed with Olympus TF180, and we found a large amount of thick reddish black-colored secretions were evacuated from the lower airway. Ventilator settings were adjusted to SIMV, PEEP +6 cmH2O, RR 15 breaths/mnt, VT 360 ml, FiO_2 70%, and PS 5 cmH_2O. Immediate post-bronchoscopy ABG evaluations showed the following results: pH 7.5230, pO_2 242.9 mmHg, pCO_2 29 mmHg (Figure 1). On the following days, the patient showed significant clinical and respiratory improvement. Weaning of the respiratory support was started on day 3 and was discharged from the ICU on 28 days of hospitalization.

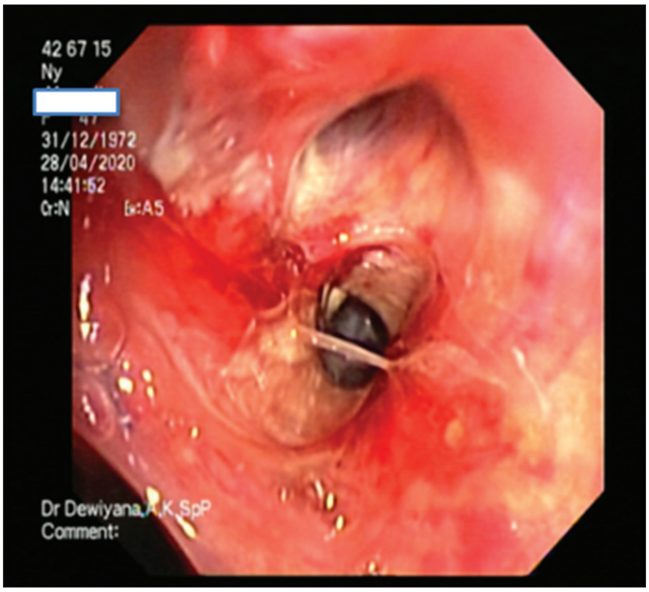

Figure 1: Bronchsocopy showed thick reddish black colored secretions

Case II

A 70-year-old man was admitted to our facility due to cough and fatigue. After a series of examination, the patient was confirmed to have suffered from COVID-19 pneumonia. On day 16 post-hospital admission, the patient experienced worsening shortness of breath. Immediate ABG evaluation showed pH 7.48, PCO_2 31.5 mmHg, PO_2 121.3 mmHg, and SpO_2 84.3%. Accordingly, he was decided to undergo endotracheal intubation with subsequent mechanical ventilation support with the following ventilator settings: VC-SiMV, VT 400 ml, PEEP 10, PSV 10, RR 12 breaths/minute, and FiO_2 80%. A significant hemodynamic improvement was observed following mechanical ventilation. Around 6 days following intubation, it was noted that the patient produced enormous airway secretions, as evidenced by pulmonary auscultation showing significant pulmonary rales. Further, ABG showed pH 7.57, PCO_2 26.6 mmHg, and PO_2 145.3 mmHg. Similarly, tracheal suction was performed initially as an effort to evacuate the obstructing mucus. However, the attempt was not successful. Therefore, a controlled suction was also performed through bronchoscopy. We were able to evacuate the thick obstructing secretion from the lower respiratory tract. The bronchoscopy showed the presence of thick secretion obstructing the distal trachea, which was removed (Figure 2). Subsequently, the ventilatory settings were adjusted to SIMV, PEEP +6 cmH_2O, RR 12 breaths/mnt, VT 360 ml, FiO_2 60%, and PS 6 cmH_2O after the procedure. The patient demonstrated clinical improvement. Subsequent ABG evaluation showed pH 7.52, PCO_2 35.1 mmHg, and PO_2 171.7 mmHg. Ventilator weaning was successfully attempted on day 16, and the patient was discharged from the ICU on 26 days of hospitalization.

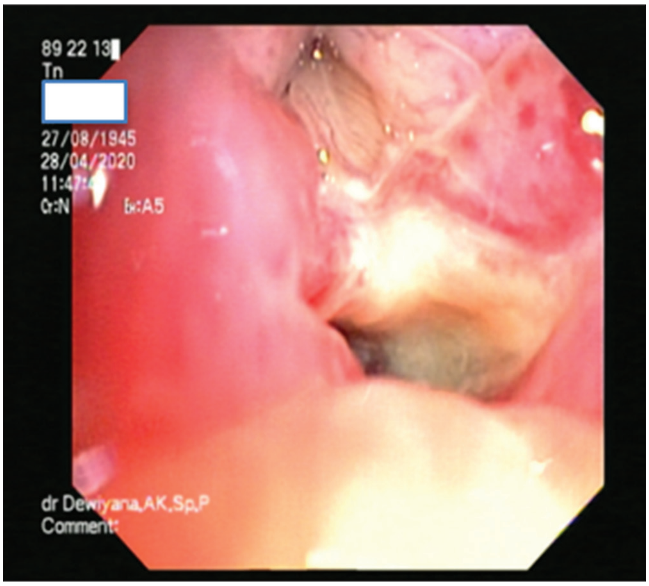

Figure 2: Bronchoscopy showed thick secretion obstrutcting the ditstal trachea

Case III

A 75-year-old man was confirmed to have suffered from COVID-19 pneumonia. The patient had a history of diabetes mellitus, hypertension, and cardiac disease. On day 3 post-hospital admission, the patient experienced worsening shortness of breath and decreasing of saturation. Immediate ABG evaluation showed pH 7.5, PCO_2 22.6 mmHg, PO_2 60.3 mmHg, and SpO_2 86%. Accordingly, he was decided to undergo endotracheal intubation with subsequent mechanical ventilation support with the following ventilator settings: VC-SiMV, VT 600 ml, PEEP 10, PSV 10, RR 12 breaths/min, and FiO_2 60%. A significant hemodynamic improvement was observed following mechanical ventilation. Around 7 days following intubation, tracheal suction was performed initially as an effort to evacuate thick and green mucoid obstructing mucus. However, the attempt was not successful. Therefore, a controlled suction was also performed through bronchoscopy. The bronchoscopy showed thick yellow mucoid secretion, hyperemic in entire bronchus lumen, and prone to bleed (Figure 3). There are no adjusting ventilatory settings. The patient demonstrated clinical improvement. Subsequent ABG evaluation showed pH 7.466, PCO_2 34.8 mmHg, and PO_2 173.2 mmHg. Ventilator weaning was successfully attempted on day three, and the patient was discharged from the ICU on 15 days of hospitalization. Unfortunately, the patient had a cardiac arrest and died in the hospital ward.

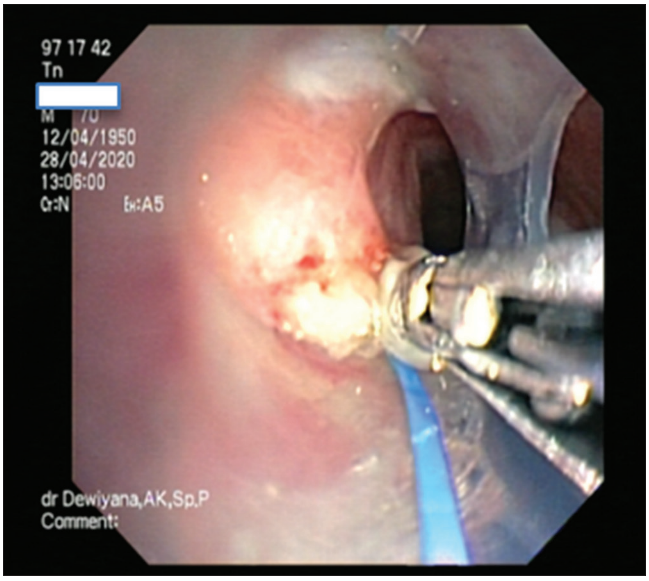

Figure 3: Bronchoscopy showed thick yellow mucoid secretion and hyperemic bronchus lumen

Discussion

COVID-19 is an extremely infectious disease caused by a newly identified SARS-CoV-2 virus. It has affected more than 3.5 million individuals in almost every country within the past 4 months [4]. SARS-CoV-2 is an enveloped, non-segmented, positive-sense, and single-stranded RNA virus that is considered a member of beta-coronavirus [15], [16]. The clinical presentations of COVID-19 vary among individuals. Some people may not have any signs and symptoms of infection and become carriers. Some others may develop symptoms within 14 days following the initial exposure to the viral particles [17], [18]. The majority of patients (81%) demonstrated mild symptoms; only 14% and 5% of patients presented with a severe and critical disease, respectively [19]. The most common symptoms reported include fever (83–98%), cough (50–80%), fatigue (34–69%), and dyspnea (20–40%) [5], [20], [21], [22]. Patients with severe manifestations may present with signs and symptoms of pneumonia, ARDS, sepsis, and septic shock [23]. Patients who initially present with mild

Table 1: Characteristics of the presented patients

Parameters	Patient 1	Patient 2	Patient 3
Age (years)	47	70	74
Sex	Female	Male	Male
Symptoms			
Fever	Yes	No	Yes
Cough	Yes	Yes	Yes
Myalgia or fatigue	Yes	Yes	Yes
Headache	No	No	No
Hemoptysis	No	No	No
Diarrhea	No	No	No
Dyspnea	Yes	No	Yes
Comorbidities			
Diabetes	No	No	Yes
Hypertension	No	No	Yes
Cardiovascular disease	No	No	Yes
Chronic obstructive pulmonary disease	No	No	No
Malignancy	No	No	No
Chronic liver disease	No	No	No
Immunosuppresion	No	No	No
Vital signs at admission			
Blood pressure (mmHg)	136/80	124/73	167/81
Heart rate (bpm)	103	68	98
RR (×/min)	30	20	28
Temperature (°C)	38	36	36.8
Oxygen saturation (%)	84%	88%	98%
Laboratory parameters*			
Hemoglobin (g/dL)	11.3	11.2	16.4
White blood cell count (×10)	5820	7490	14690
Neutrophil count (×10)	80	56	91
Lymphocyte count (×10)	14	37	6
Platelet count (×10)	231	227	296
PT (s)	13.1	11.8	10.9
APTT (s)	37.4	40	25.9
D-dimer (mg/dL)	380	3480	2130
Albumin (g/L)	3.9	3.2	2.9
ALT (U/L)	39	19	40
AST (U/L)	52	21	25
Sodium	145	130	137
Potassium	3.6	4.1	3.9
Creatinine (mg/dl)	0.79	1.01	2.27
Ureum (mg/dl)	19	42	70
Swab results	Yes	Yes	Yes
CRP	7.84	14.14	24.47
Radiographic signs of pneumonia	Yes	Yes	Yes
Treatment			
Antiviral	Yes	Yes	Yes
Antifungal	No	No	No
Antibiotic	Yes	Yes	Yes
Antiparasitic	Yes	Yes	Yes
High-dose Vitamin C	Yes	Yes	Yes
Ventilator-related parameters			
Onset to mechanical ventilation (days)	3	16	2
Modea	VC-SIMV	VC-SiMV	VC-SiMV
Peak pressure (cmH_2O)a	12	10	10
PEEP (cmH_2O)a	12	10	10
FiO_2 (%)	70%	80%	50%
Bronchoscopy-related parameters			
Day of bronchoscopy	24	28	10
Onset to bronchoscopy (days)	31	31	13
Positioning	Prone	Prone	Prone
Bronchoscope diameter (mm)	2.1	2.1	2.1
ETT diameter (mm)	7.5	7.5	7.5
BAL	No	No	No
Monitoring			
MAP (mmHg)			
Baseline	83	86	93
During bronchoscopy	93	86	93
Oxygen saturation (%)			
Baseline	99	99	99
During bronchoscopy	99	99	98
Outcomes			
Discharged from hospital	Yes	Yes	No
Discharged from ICU	Yes	Yes	Yes
Dead	No	No	Yes

ALT: Alanine aminotransferase, APTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, BAL: Bronchoalveolar lavage, CRP: C-reactive protein; PCO_2: Carbon dioxide, ETT: Endotracheal tube, FiO_2: Fractional concentration of inspired oxygen, ICU: Intensive care unit, LDH: Lactate dehydrogenase, LOS: Length of stay, MAP: Mean arterial pressure, PCT: Procalcitonin, PEEP: Positive end-expiratory pressure, PT: Prothrombin time, VC-SIMV: Volume-controlled synchronized intermittent mandatory ventilation, RR: Respiratory rate.

symptoms could also experience clinical progression toward more severe illness. Rapid progression can also be encountered in an otherwise healthy patient without any significant medical history.

Goh *et al*. reported a case with a similar pattern of progression affecting a 64-year-old Singaporean man. The patient presented to the hospital with mild symptoms since around 1 week before admission and rapidly deteriorated with severe hypoxemic respiratory failure within only 48 h following admission [24]. Other evidence also suggested that the median time of ARDS development was 2 days from the admission day [6]. All of our cases presented with relatively mild disease complaining of having some respiratory and constitutional symptoms, including fever, cough, fatigue, and dyspnea. Following the previous evidence, the first patient demonstrated rapid progression, of which she demonstrated worsening of her clinical status within 3 days of admission. The second case, on the other hand, demonstrated a relatively slower clinical course, where the patient experienced an intense worsening of his complaints after 2 weeks of hospitalization.

One of the biggest concerns in COVID-19 is a further compromise in respiratory function. It has been noted that COVID-19 patients, particularly those who develop ARDS, produce thick mucus secretion. This puts the patients at a substantial risk of developing airway obstruction due to plug formation and subsequent lung collapse [7], [8]. Hence, airway management and optimal oxygenation serve as the constructing pillars in the management of severe COVID-19 infection. The concept of early intubation in COVID-19 patients has been a matter of debate. It is noteworthy that mechanical ventilation itself can exacerbate functional and structural alterations in the lung and is related to the morbidity and mortality in ARDS [25]. Therefore, timely, but not premature, endotracheal intubation is always preferred [26]. In our cases, all of the patients experienced clinical deterioration. Both of the patients experienced respiratory alkalosis, as indicated by their ABG results. Hence, endotracheal intubation was performed, followed by mechanical ventilation which resulted in clinical improvement. During observation in the ICU, both patients showed clinically significant production of airway secretions, as evidenced by abnormal lung sound on physical examination. Conventional tracheal suction has failed to evacuate the airway secretion, and hence, bronchoscopy was scheduled to vacate the secretion and prevent further airway compromise. Conventionally, bronchoscopy has been widely used as a standard procedure in the setting of severe respiratory problems for both diagnostic and therapeutic purposes in patients with a critical illness [10]. Unfortunately, the practice of performing bronchoscopy during the COVID-19 pandemic has been very restricted. Bronchoscopy is considered an aerosol-generating procedure, and hence, it possesses a substantial risk of viral transmission to the surrounding and puts both medical professionals and unconfirmed patients at risk of getting the infection. Therefore, it is always recommended to consider the risks and benefits of performing bronchoscopy, particularly among patients with confirmed COVID-19 disease. The decision should be individualized based on the patient's clinical condition. Once decided to perform a bronchoscopic intervention, it has to be done only in a negative-pressure room and by a highly experienced clinician to minimize the amount of time needed to complete the response. It is recommended to perform bronchoscopy with general anesthesia as well as with muscle relaxant administration while avoiding emergent intubation to reduce the risk of aerosol generation. Standard personal protective equipment and disinfection protocol are highly warranted [14]. Indications for performing bronchoscopy during COVID-19 pandemic have been categorized into emergent, semi-urgent, and elective indications. Patients with symptomatic central airway obstruction related to either neoplasm, foreign body aspiration, or mucous plug; massive hemoptysis, tracheal stenosis, and stent migration should be referred for further bronchoscopic evaluation. As for the evaluation of lung nodules, mediastinal lymph node enlargement, whole pulmonary lavage, suspected lung infection in patients with impaired immune function, assessment of obliterative bronchiolitis in transplant recipients, as well as evaluation of lobar atelectasis, bronchoscopy is advised to be performed in a semi-urgent manner. Among patients in an otherwise stable condition, elective bronchoscopy can be performed for tracheobronchomalacia evaluation, bronchial thermoplastic, cryobiopsy, as well as bronchoscopic lung volume reduction surgery [11], [14].

The role of bronchoscopy in the management of patients with a severe phenotype of COVID-19 infection is minimal. Bronchial or pulmonary toileting is not recommended as a routine therapeutic intervention in these subsets of patients. However, therapeutic aspiration is advisable in patients with airway obstruction due to mucous impaction that impairs gas exchange function. In our cases, the main reasons for performing bronchoscopy were the evidence of enormous airway secretions, as evidenced by clinical examination. We decided to perform bronchoscopy-directed bronchial toilet as an effort to help to evacuate the abundant mucoid secretion in the patients lower respiratory tract and to prevent the formation of mucus plug. We performed this bronchoscopic intervention under a very secure protocol as proposed by various consensus. Following the response, the patients showed favorable clinical and hemodynamic outcomes. Weaning of the mechanical ventilation could be performed earlier with desirable results. One of the primary concerns in performing bronchoscopy is which technique would result in a limitation of infection spread while maintaining the safety of the procedure. Some data suggested that prone positioning is associated with a reduction in mortality in mechanically ventilated patients with severe ARDS and that bronchoscopy performed in a prone position is safe without significantly aggravating the risk of clinical deterioration [9], [27]. In addition, fiberoptic bronchoscopy performed in a prone position helps to avoid undesirable premature interruption of mechanical ventilation and consequent loss of physiological gains, an increase in intrapulmonary shunt, a fall in the oxygen saturation as well as elevated pulmonary artery resistance [9].

At present, there is no standardized recommendation on a ventilator setting during bronchoscopy. Guarracino *et al*. (2012) successfully and safely performed bronchoscopy by increasing FiO_2 to 1, reducing PEEP level and respiratory frequency to avoid an increase in PEEP while increasing inspiratory pressure to maintain minute volume and prevent an increase in carbon dioxide [9]. Some data suggested that bronchoscopic tube internal diameter of 4 mm is optimal and safer in patients with ARDS [7]. In a case series of patients with severe ARDS who were mechanically ventilated, Kalchiem-Dekel *et al*. (2018) showed that no significant hemodynamic compromise was observed during bronchoscopic aspiration and BAL procedures using a maximum internal diameter of 4 mm and without changing the mode of mechanical ventilation except for 100% FiO_2. However, significant oxygen desaturation and rising in COs_2 pressure were observed in one patient. At last, 4 out of 7 patients survived 30 days following discharge from ICU [28].

Conclusion

Bronchoscopic procedures may provide significant therapeutic benefits in severe COVID-19 patients. However, it should be kept in mind that this procedure should only be performed with a rigorous protocol to reduce the risk of aerosol generation and subsequent viral transmission. More well-designed studies are needed to elucidate further the role of bronchoscopic intervention among severely ill COVID-19 patients as well as addressing the most optimal and the safest ventilator setting during the procedure.

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Liver Transaminase Levels and Neutrophil to Lymphocyte Ratio as Prognostic and Predictor in Coronavirus Disease 2019

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Abstract

BACKGROUND: Coronavirus disease 2019 (COVID-19) was a disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus with severe respiratory distress syndrome. SARS-CoV-2 can attack the gastrointestinal and liver system. In several studies, elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported, ranging from 14% to 53%. The increase of neutrophil to lymphocyte ratio (NLR) also increases the risk of mortality in COVID-19.

AIM: This research wants to study ALT, AST, and NLR as prognostic and predictor in COVID-19.

METHODS: A cross-sectional retrospective study was conducted on COVID-19 patients. The diagnostic criteria are based on the recommendations of the Indonesian Ministry of Health. The patient's blood was examined in a central laboratory at the hospital. Data analysis was done using SPSS version 22.

RESULTS: A total of 126 patients with COVID-19 were included in this study. There are 57 (45.2%) patients having abnormal liver test. There was a significant difference in the mean AST and NLR between non-survival and survival outcome in COVID-19 patients (82.91 ± 103.82 vs. 40.54 ± 33.59 U/L; p = 0.0001 and 7.42 ± 3.65 vs. 3.47 ± 2.41; p = 0.0001). High AST (≥34.5 U/L) and NLR (≥4.7) independently associated with non-survival outcome in COVID-19 patient with odds ratio 5.31 and 9.49 (1.89–14.95, 95% confidence interval [CI]; p = 0.002 and 3.57–25.22, 95% CI; p = 0.0001).

CONCLUSION: This study revealed that high AST and NLR at hospital admission were associated with high mortality risk in COVID-19 patients. Therefore, AST and NLR can be a significant prognostic of outcome in COVID-19 patients.

Introduction

At the end of 2019, it was discovered pneumonia caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus in Wuhan, China, which was named coronavirus disease 2019 (COVID-19). COVID-19 was declared a pandemic in the world by the World Health Organization (WHO) at the end of March 2020. SARS-CoV-2 has an almost identical genome sequence with SARS-CoV. SARS-CoV-2 can be transmitted between humans through close contact and air droplets inhalation. So far, COVID-19 has spread in 215 countries around the world [1], [2].

Viral pneumonia is the primary manifestation of COVID-19, which has symptoms such as fever, fatigue, dry cough, anosmia, and headache. Lately, several studies show that COVID-19 can also attack other organs besides the respiratory system, such as the gastrointestinal and liver system. This is due to the spread of main viral entry, angiotensin-converting enzyme 2 (ACE2), which is abundant in other organs such as the upper esophagus, enterocytes of the ileum and colon, liver, and bile duct cells [3], [4].

The neutrophil to lymphocyte ratio (NLR) is an easy test to do, by dividing the absolute count of neutrophils by the absolute count of lymphocytes. NLR was reported to indicate the inflammatory status of patients. Increased NLR was a factor in the risk of mortality from various diseases such as cancer, acute coronary syndrome, and cerebral hemorrhage. Recent research has also revealed that increasing the NLR value also increases the risk of mortality in COVID-19 [5], [6], [7].

Liver impairment has also been reported as a common manifestation, although it is not a prominent feature of the illness. Several studies have shown different degrees of elevated serum liver biochemistries in COVID-19 patients, mainly indicated by abnormal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Recent studies have found that SARS-CoV-2 can bind to ACE2 in cholangiocytes, which triggers cholangiocyte dysfunction and triggers a systemic inflammatory response that ends with liver injury. In several studies, elevated levels of ALT and AST were reported, ranging from 14% to 53% [8], [9]. It remains unclear whether these laboratory test alterations are associated with a worse prognosis. This research wants to study ALT, AST, and NLR's comparison of patient outcome and their best cut point for outcome prediction in COVID-19 patients.

Methods

Patient selection

This study was a cross-sectional retrospective study conducted on COVID-19 patients who had been confirmed at Prof. Dr. R.D. Kandou hospital. Inclusion criteria are stated as follows: Male or female aged ≥18 years old, patients were diagnosed with COVID-19. From March 1, to June 30, 2020, 145 patients were diagnosed with COVID-19 based on the guideline for diagnosis and prevention coronavirus 2019 in Indonesia. This study was approved by the Local Ethics Committee.

Confirmation of COVID-19

The presence of SARS-CoV-2 was detected by real-time reverse transcription PCR. Two pairs of primers targeting the open reading frame 1ab (ORF1ab) and the nucleocapsid protein (N) were amplified and examined. The corresponding sequences for ORF1ab were 5'-CCCTGTGGGTTTTACACTTAA-3' (F), 5'-ACGATTGTGCATCAGCTGA-3' (R), and 5'-CY3-CCGTCTGCGGTATGTGGAAAGGTTATGG-BHQ1-3' (probe), and those for N were 5'-GGGGAACTTCTCCTGCTAGAAT-3'(F), 5'-CAGACATTTTGCTCTCAAGCTG-3'(R), and 5'-FAM-TTGCTGCTGCTTGACAGATT-TAMRA-3'(probe). These diagnostic criteria are based on the recommendations of the Indonesian Ministry of Health.

Data collection

Medical records from 145 patients were collected and examined by researchers. Identity, laboratory, and outcome data from patients were obtained from the hospital information system. Patient outcomes are categorized as survival and non-survival.

NLR, ALT, and AST

The patient serum and peripheral venous blood were taken from all COVID-19 patients who were confirmed when the patient entered the hospital. The patient's blood was examined in the central laboratory at Prof Dr. R.D. Kandou Hospital following the hospital's standard operative procedures. Liver test abnormalities were defined as the elevation of AST >40 U/L and ALT >40 U/L [9].

Statistical analysis

Data analysis was performed through univariate and bivariate analyses using the SPSS 22^{nd} version (SPSS Inc., Chicago) with a 95% confidence interval (CI). Bivariate analysis was performed using Mann–Whitney. Multivariate analysis was performed using logistic regression. Data were also analyzed using receiver operating characteristic (ROC) curve and Youden's index, $p < 0.05$ was considered statistically significant.

Results

In this study, 145 confirmed COVID-19 patients were found, but only 126 patients had complete data. Of the total, 126 patients consisted of 60 men (47.6%) and 66 women (52.4%). A total of 32 (25.4%) patients died during hospitalization. The mean age of the patients was 48.81 ± 15.70 years. There are 57 (45.2%) patients with an abnormal liver test consisted of increasing AST (38.1%) and ALT (31%). The baseline characteristics of the patients are shown in Table 1. NLR, AST, and ALT were higher in non-survival than survival outcomes in COVID-19 patients (Table 1).

There was a significant difference in the mean AST levels between non-survival and survival outcomes in COVID-19 patients. Patients in the non-survival group had higher AST levels than the survival group (82.91 ± 103.82 vs. 40.54 ± 33.59 U/L; p = 0.0001) (Table 1).

There was no significant difference in the mean ALT levels between non-survival and survival outcomes in COVID-19 patients (56.72 ± 71.71 vs. 34.57 ± 32.28 U/L; p = 0.136) (Table 1).

There was a significant difference in the mean NLR between non-survival and survival outcomes

Table 1: Basic characteristics of the study population

Characteristics	Outcome												p
	Non-survival						Survival						
	n	Min	Max	Median	Mean	SD	n	Min	Max	Median	Mean	SD	
Age (years)	32	32.00	80.00	58.50	57.31	12.14	94	19.00	82.00	44.00	45.91	15.78	0.0001
NLR	32	1.71	15.17	7.04	7.42	3.65	94	0.70	13.00	2.58	3.47	2.41	0.0001
AST (U/L)	32	21.00	544.00	50.00	82.91	103.82	94	15.00	207.00	30.00	40.54	33.59	0.0001
ALT (U/L)	32	10.00	358.00	30.00	56.72	71.71	94	3.00	198.00	25.00	34.57	32.28	0.136

Min: Minimal; Max: Maximal; SD: Standard deviation; n: Count. NLR: Neutrophil to lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

in COVID-19 patients. Patients in the non-survival had NLR significantly higher than the survival group (7.42 ± 3.65 vs. 3.47 ± 2.41; p = 0.0001) (Table 1).

Analysis using the ROC test showed that AST had an area under the ROC of 0.739 (p = 0.0001), and NLR had an area under the ROC of 0.830 (p = 0.0001) (Figure 1).

Youden's index was calculated to determine the best AST and NLR cut off point to give better sensitivity dan specificity to predict COVID-19 patients' outcome. For AST, the best cutoff point was 34.5 U/L to get 78.12% sensitivity and 61.70% specificity, and for NLR, the best cutoff point was 4.7 to get 75% sensitivity and 79.78% specificity.

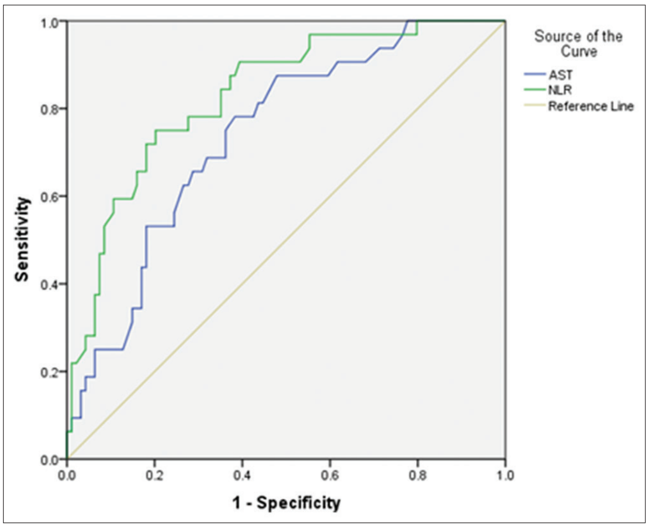

Figure 1: ROC curve of AST and NLR

After logistic regression analysis was performed, high AST (≥34.5 U/L) and NLR (≥4.7) remained independently associated with non-survival outcome in COVID-19 patient with odds ratio 5.31 (1.89–14.95, 95% CI; p = 0.002) and 9.49 (3.57-25.22, 95% CI; p = 0.0001), respectively (Table 2).

Table 2. Logistic regression analysis of predictors of COVID-19 patients' mortality

Variable[a]	OR (95% CI)	p
AST (≥34.5 U/L)	5.31 (1.89–14.95)	0.002
NLR (≥4.7)	9.45 (3.57–25.22)	0.0001

CI: Confidence interval; OR: Odds ratio; [a]adjusted for gender. NLR: Neutrophil to lymphocyte ratio, AST: Aspartate aminotransferase

Discussion

In this study, 45.2% of COVID-19 patients had abnormal liver tests, where there was an increase in AST by 38.1% and ALT by 31%. Fan *et al*. also found that there were abnormal liver tests in 37.1% of patients with COVID-19 [10]. This result is almost the same as the study conducted by Chen *et al*., where the increase in AST was 35%, and ALT was 28% [11].

Liver impairment is closely related to mortality in COVID-19 patients. In this study, it was found that AST and ALT values were higher in COVID-19 patients with the non-survival group, where statistically, AST levels had a significant difference between COVID-19 patients with non-survival and survival outcome (p < 0.05). Several studies also found that AST increases more frequently than ALT in severe COVID-19 patients [12], [13]. A study conducted by Lei *et al*. gave similar results, in which patients with elevated AST had a high risk of mortality [14].

Several studies have shown that SARS-CoV-2 requires ACE2 as a receptor to enter cells, where ACE2 is mainly expressed in the heart, lungs, and kidneys. In addition, ACE2 is also slightly expressed in the colon and liver. The previous studies have shown that ACE2 expression is present in cholangiocytes, suggesting that cholangiocyte is the direct target of SARS-CoV-2 to attack the liver. The increase in AST and ALT is an indicator of liver cell damage. However, pathological analysis of the liver tissue of COVID-19 patients failed to prove that cholangiocyte damage and viral infiltration in liver tissue occurred. The specific cause of liver damage and elevated liver transaminase enzymes is not clear and needs further study [8], [9], [14], [15], [16], [17], [18], [19].

In this study, it was found that there was an increase in NLR in COVID-19 patients with the non-survival outcome, which was statistically significant when compared with COVID-19 patients with survival outcome (p < 0.05). Liu *et al*. also obtained the same results, where a higher increase in NLR was associated with an increased risk of mortality in COVID-19 patients [7] Research conducted by Yan *et al*. also found the same thing [20].

NLR is an easy method to evaluate the systemic inflammatory response, where the NLR is calculated by taking the neutrophil and lymphocyte values into account. Neutrophils play an important role in the innate immune response, while lymphocytes play an important role in the inflammatory response. The increase in NLR results from an inflammatory response that stimulates neutrophil production and accelerates the apoptosis of inflammatory lymphocytes. Increased neutrophils result in increased systemic arginase activity, which depletes systemic arginase reserves. Where arginine is a single subtract for the formation of nitric oxide (NO), which has antiviral activity against RNA viruses such as SARS-CoV-2. Therefore, an increase in NLR indicates an imbalance of the inflammatory response that can result in death [7], [20], [21].

Based on the ROC curve analysis, the AST and NLR showed the significant performance to predict COVID-19 patient's mortality. The best cut-off point for AST and NLR was 34.5 U/L and 4.7. This study supports that a high AST (≥34.5 U/L) and NLR (≥4.7) are a strong predictor for mortality in patients with COVID-19. COVID-19 patients with high AST and NLR were 5.31 and 9.49 times more likely to have a non-survival outcome. However, a scoring system is needed to assess the prognosis of COVID-19. It is hoped that the prognosis will be more accurate with scoring system so that early treatment can be given.

There are some limitations to this study. First, this study was retrospective, and there some cases did not have enough data. Second, we did not do multiple testing of liver transaminase enzymes and NLR during hospitalization. Third, all subjects in this study were Manado patients with COVID-19, so this study's results might not directly be applied to other races.

Conclusion

This study revealed that high AST and NLR at hospital admission were associated with high mortality risk in COVID-19 patients. Therefore, AST and NLR can be a significant prognostic of outcome in COVID-19 patients. However, a scoring system is needed to have a more accurate prediction of prognosis.

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Oral Manifestations of Coronavirus Disease-19: A Mini-review

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Abstract

BACKGROUND: Recently, outbreak of novel coronavirus (CoV) (severe acute respiratory syndrome-CoV-2 [SARS-CoV-2]) has been emerged as a serious public health concern. On February 11, 2020, the WHO announced an official name for this disease, CoV disease-(COVID)-19. The virus can cause systemic complications such as lung involvement, skin, and oral complications.

AIM: The aim of this study was to review of the oral manifestations of COVID-19.

METHODS: In this narrative review study, we searched all articles between 2010 and 2020 in PubMed, Scopus, Science Direct related to COVID-19, and its oral manifestations, using the following terms: "Coronavirus," "COVID-19," and "SARS-CoV-2" in combination with "Stomatognathic diseases," "Oral manifestation," and "Mouth diseases."

RESULTS: The most common oral manifestations in people with COVID-19 that we get after searching are: salivary gland disease, xerostomia, taste and smell alterations, and oral mucosal lesions.

CONCLUSIONS: Since almost all of the oral findings appear at the asymptomatic phase of disease, identification of these symptoms can help to timely diagnosis of the main disease.

Introduction

The novel coronavirus (CoV) disease 2019 (COVID) (severe acute respiratory syndrome-CoV-2 [SARS-CoV-2] or COVID-19) presents as a serious public health concern and urgent threat to global health [1].

In December 2019, COVID-19 was detected in Wuhan, China. It has a very high transmission capacity and is known as SARS-CoV-2 [2].

COVID-19 is highly contagious and it has the ability to get transmitted even during asymptomatic phase. The infectivity of COVID-19 is greater than that of influenza; it is necessary to identify infected people as soon as possible, even during the asymptomatic period [3].

The current CoV outbreak is the third epidemic viral infection in the 21st century [3]. The lungs are the primary site of infection for COVID-19, with patients presenting symptoms ranging from mild flu-like symptoms to fulminant pneumonia and potentially lethal respiratory distress [1].

All age groups are susceptible to the virus and some people are more susceptible to the virus such as older people (≥ aged 65), patients with immunodeficiency or liver and kidney failure, healthcare staff caring for COVID-19 patients, and other individuals who closely are in contact with these patients in clinical settings [3].

Although the complete clinical representation regarding COVID-19 is not fully understood, here are some common clinical manifestations. This virus can cause disease ranging from mild to severe, the clinical characteristics of mild COVID-19 include symptoms common to other viral infections (i.e., fever, cough, dyspnea, myalgia, fatigue, and diarrhea) [3], [4].

In severe cases, COVID-19 may present as acute respiratory distress syndrome, with or without both distributive and cardiogenic shock [4].

The oral manifestations of COVID-19 are varied and there is insufficient evidence to establish an efficient and safe pharmacological agent against COVID-19 yet, and the potential ones are related to several adverse reactions, including oral lesions [1].

The mouth is one of the sites that can be infected by the virus and show manifestations of the disease. Therefore, dentists can be one of the first people to diagnose the disease based on oral manifestations, even in the asymptomatic stages, and prevent the spread of the disease. Our purpose in this study is to identify and summarize oral manifestations related to COVID-19.

Search Strategy

This article is a narrative review study and according to its nature as "narrative," we chose the most relevant contributions to oral manifestations of COVID-19.

The search was conducted using six MeSH keywords including, "Coronavirus," "COVID-19," "SARS-CoV-2," "Stomatognathic diseases," "Oral manifestation," and "Mouth disease" in PubMed, Scopus, and Science Direct databases among articles between 2010 and 2020. Of 80 related articles, 42 were excluded due to lack of full text, being written in a language other than English or containing repetitive material and 38 were closely relevant to the title. Finding 24 well documented English articles were chosen, including clinical trial (5 articles), review (6 articles), cohort (2 articles), case report (3 articles), cross-sectional studies (1 article), and letter to editor (7 articles) were reviewed.

Results

Finally, we found four different types of oral manifestations of COVID-19 which are included as salivary gland disease, xerostomia, taste/smell alterations, and oral mucosal lesions (Table 1).

Discussion

There have been limited studies about oral manifestations of COVID-19, review of literature showed that most researchers paying more attention to systemic manifestations, and therefore we focused on oral-related symptoms, which may provide new clinical information for COVID-19.

In the following, we will refer to oral finding and its relation to clinical findings. Some of the side effects that we get after searching are:

Salivary Gland Disease

Salivary gland can be involved in patients with CoV infection [5]. Angiotensin-converting enzyme II (ACE2) has been reported as an important receptor for COVID-19 [6], [7]. Xu *et al*. demonstrated that the expression of ACE2 in minor salivary glands was higher than in lungs, which suggests salivary glands could be a potential target for COVID-19 [8]. In accordance to these findings, Chen *et al*. evaluated the expression of ACE2 receptor of 2019-nCoV in salivary gland epithelial cells and demonstrated the possibility of 2019-nCoV infection of the salivary glands. They also mentioned the reason that the positive saliva detection rate was as high as 75% in critically ill patients may be related to virus invasion caused by high viral loads or destroyed salivary glands at the late stage of the disease [9]. The same results have been also reported by To *et al*. and Kotfis and Skonieczna-Żydecka [10], [11]. It is important to know, COVID-19 was only detected in saliva, with no evidence for its presence in the nasopharynx [12].

Xerostomia

In a study by Chen *et al*., among the oral-related symptoms in COVID-19 patients, amblygeustia (47.2%) overall, male (36.5%), female (57.1%) and xerostomia (46.3%) overall, male (46.2%), female (46.4%) had the most frequencies of occurrence. In addition, 11.1% male (13.5%) and female (8.90%) of the patients exhibited dryness and inflammation of the mouth. One female patient (0.9%) had enlargement of lymph nodes in the submandibular regions [8]. In a study by Yifan *et al*., the ten most frequent symptoms in the studied patients were chest discomfort (31.4%), dyspnea (30.7%), nausea (21.4%), headache (19.3%), dizziness (17.9%), xerostomia (15.7%), fatigue (15%), sleepiness (9.3%), sweating (8.6%), and waist pain (7.1%) [13]. Besides viral invasion to the salivary glands and its negative effect on peripheral and central nervous systems, dry mouth may also be due to the patient's

Table 1: Oral manifestations of COVID-19 in some published articles

Author	Year of publication	Oral manifestations			
		Salivary gland involvement	Xerostomia	Taste and Smell alterations	Oral mucosal lesion
Xu *et al.* [7]	2020	*			
Chen *et al.* [9]	2020	*	*	*	
To *et al.* [10]	2020	*			
Kotfis and Skonieczna-Żydecka [11]	2020	*			
Keyhan *et al.* [12]	2020		*		
Yifan *et al.* [13]	2020		*		
Amorim Dos Santos *et al.* [1]	2020		*		*
Odeh *et al.* [14]	2020			*	
Giacomelli *et al.* [15]	2020			*	
Lechien *et al.* [16]	2020			*	
Vaira *et al.* [17]	2020			*	
Hopkins *et al.* [18]	2020			*	
Chaux-Bodard *et al.* [20]	2020				*
Martín Carreras-Presas *et al.* [22]	2020				*
Dziedzic and Wojtyczka [23]	2020				*
Vieira [24]					*

change in psychological status, poor oral hygiene, or adverse drug effects [9], [12]. According to Amorim Dos Santos *et al*., the occurrence of xerostomia in COVID-19 patients linked to decreased salivary flow [1].

Taste and Smell Alterations

Taste and smell abnormalities have been recognized as symptoms of 2019-nCoV [14]. According to Giacomelli *et al*., about 34% of COVID-19 patients had at least one taste or olfactory disorders and 18.6% had both of them [15]. More than 20% of patients presented the symptoms before the hospital admission, whereas 13.5% experienced the symptoms during the hospitalization. Taste alterations were more common (91%) before hospitalization, whereas after hospitalization, taste and olfactory alteration appeared with an equal percentage. Women reported olfactory and taste disorders more frequently than men (52.6% vs. 25%). Moreover, patients with at least 1 olfactory and taste disorder were younger than those without [15]. In a multicenter European study by Lechien *et al*., 79.7% of patients with mild-to-moderate forms of the coronavirus disease were hyposmic or anosmic [16]. In addition, according to Vaira *et al*., in 15.3% of patients, temporary taste and smell abnormalities were only manifestations of COVID-19 and there is a statistically significant relationship between the duration of the chemosensitive disorder and the severity of the disease [17]. For example, patients who had a history of taste and smell alteration for more than 10 days, the risk of developing a severe pulmonary clinical picture was 2.4 times greater [17]. In another study by Hopkins *et al*., 86.4% of patients reported complete anosmia and 11.5% reported a very severe loss of smell at the time of the first survey. At follow-up 1 week later, lower severity, unchanged severity, and higher severity scores have been reported in 80.1%, 17.6%, and 1.9% of cases, respectively [18]. These abnormalities could be explained by the interaction between virus and ACE2 receptors. In fact, the expression of ACE2 was found to be higher in the tongue, where the taste buds are most frequent than other sites such as gingival or buccal mucosa [9]. On the other hand, Keyhan *et al*. described that the presence of dysosmia and dysgeusia can be related to olfactory nerve and trigeminal nerve damage caused by virus invasion or excessive exposure to chemicals and disinfectant agents that are used by people due to the viral epidemic [12].

Oral Mucosal Lesions

Cutaneous lesions related to 2019-nCoV infection have been described by dermatologists [19], but to our knowledge, there is limited information about oral mucosal lesions with a proven COVID-19 infection. In this regard, Chaux-Bodard *et al*. reported a COVID-19 related oral ulcer in a 45-year-old female. History of the lesion revealed painful inflammation on the dorsal side of the tongue, followed by 24 h of the erythematous macula, which changed into an asymptomatic and irregular ulcer. Three days after the occurrence of the oral lesion, asymptomatic erythematous area was appeared on the big toe; however, general symptoms were mild asthenia. The oral ulcer completely healed after 10 days without a scar. The tongue ulcer occurred after a short time of erythematous macular lesion, which could be explained by vasculitis [20]. COVID is in association with variable inflammatory reactions that can lead to vasculitis [21]. Thus, an irregular, acute, and solitary oral ulcer could be an inaugural symptom of 2019-nCoV infection which needs to be proven in large cohorts of patients [20]. In another case report by Martín Carreras-Presas *et al*., they showed oral vesiculobullous lesions associated with SARS-CoV-2 infection in three cases. The first case was a 56-year-old healthy male with the lesions resembled a herpetic recurrent stomatitis on the hard palate. The second case was a diabetic 58-year-old male with multiple small ulcers on his palate with unilateral affection and the last case was a 65-year-old female with blisters in her internal lip mucosa as well as desquamative gingivitis. It is important to know that all reported cases had pain, oral ulcers, and blisters before seeking medical advice [22].

On the other hand, stomatitis, oral ulcers, and dry mouth may be related to the side effects of anti-viral drugs such as interferon-alpha and beta in <2% of cases [23].

Amorim Dos Santos *et al*., in a case report study, showed that COVID-19 could potentially contribute to adverse outcomes concerning oral health, likely leading to various opportunistic fungal infections, recurrent oral herpes simplex virus-1 infection, and gingivitis as a result of the impaired immune system and/or due to treatments for COVID-19 [1]. Vieira showed that in severe cases of COVID-19, prior underlying untreated moderate or severe periodontitis may worsen COVID-19. Hence, periodontal therapy in patient with initial symptoms of COVID-19 may reduce the risk of the condition to become severe [24].

Conclusion

Salivary gland disease, xerostomia, taste and smell alternation and oral mucosal lesions are the most common oral changes reported about COVID-19. Since almost all of the oral findings appear at asymptomatic phase of disease, identification of these symptoms can help to timely diagnosis of the main disease. Furthermore, it is unclear that these oral manifestations are coexisting or the result of a cause and effect that the virus reality has the ability to cause these manifestations. Due to the fact that the virus has not been around for a long time and many of the long-term effects of the virus have not been known yet, more extensive studies are needed.

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Coronavirus Disease-19 Pandemic and Dermatology. What to Expect?

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Abstract

The novel coronavirus (CoV), CoV disease (COVID)-19, and the ongoing pandemic, is changing every aspect of the human life. Furthermore, the COVID-19 pandemic has a profound impact on health-care worldwide, with no exception in dermatology care units. At the time of pandemic, constant fear and stress are present on the surface. Skin diseases are the most common somatic causes of psychological disorders and, conversely. During a stressful situation, the body has power to adjust and to maintain its well-being, but with prolonged exposure to stress, the first negative changes such as fear, anxiety, and depression will eventually lead to chronic fatigue and an increased risk of disease. The proportion of patients reporting emotional triggers varies with the disease, ranging from approximately 50% in acne to 90% in rosacea, alopecia areata, psoriasis, neurotic excoriations, and lichen simplex and may be 100% for patients with hyperhidrosis. In this paper, we will look at the most common psychodermatological disorders and its implication in the era of COVID-19 pandemic. According to all the pathophysiological conditions that indicate the association of skin diseases with stress, it is normal to expect their deterioration and occurrence in this pandemic period. We will be witnessing a growing number in patients' consultations with chronic urticaria, dermographism, worsening rosacea, generalization, and relapses of psoriasis. It is needed to be prepared for as many cases as possible, because the psychological consequences will still be felt. We encourage more comprehensive studies of the implications of the COVID-19 pandemic in these patients.

Introduction

The coronavirus (CoV) disease (COVID)-19 pandemic, or COVID-2019, is caused by several acute respiratory syndrome CoV-2. On January 12, 2020, the World Health Organization (WHO) confirmed that a novel CoV was the cause of a respiratory illness in a cluster of people in Wuhan City, Hubei Province China. The WHO declared the outbreak a public health emergency of international concern on January 30, and a pandemic on March 11. On the end of May almost 6 million cases of COVID-19 have been reported in more than 230 countries, resulting in more than 370,000 deaths.

The novel CoV, COVID-19, and ongoing pandemic, is changing every aspect of human life. Furthermore, COVID-19 pandemic has a profound impact on health-care worldwide, with no exception in dermatology care units. The dermatological practices are affected, although with much OR less extensity than the emergency and intensive care departments which are working with the suspected and confirmed COVID-19 patients. Chen *et al*. reported the impact on dermatology outpatient care at the outbreak epicenter in Wuhan, China [1]. To meet the medical requirements and reduce the flow of patients to the dermatology departments, the measures which were taken by the public hospitals and private practices are dramatically reduction in outpatient consultations. In order to care for the patients safely and effectively, dermatological practices converted the face-to-face examination to telephone and online consultations. Esthetic dermatological procedures, laser sessions, have been stopped, almost completely. Only patients with dermatologic emergencies and acute skin failures are admitted in hospitals. In an era of quarantine and isolation, dermatologists utilize teledermatology better than other specialties. Communication modes can be video, audio, and text based – Viber, WhatsApp, and Facebook messenger, are the virtual tools being used for teledermatology practices. The advantages using teledermatology are: Permits consultation without increased risk of infection, very important is cost-effective, and provides accurate diagnostic information [2]. The key aspect of risk management in the dermatology practices is prevention of COVID-19 in population at risk, and that is the patient with chronic inflammatory skin disease, patients on immunosuppressive, and biologics therapy. British Association of Dermatologists (BAD) provided guidelines for high risk patients on immunosuppressive medications or biologics/

Monoclonal (anti-tumor necrosis factor drugs, Interleukin (IL) 17 agents, anti-B cell, IL-6 agents, and IL-1) or novel molecule immunosuppressant (apremilast, JAK inhibitors) and patients on corticosteroid dose of ≥20 mg of prednisolone/daily for more than 4 weeks; to undergo with self-isolation up to 12 weeks. Patients treated with single immunosuppressant or biologics and no comorbidities, stressed the need to maintain social distancing [3]. BAD advises using teledermatology and avoiding hospital visits as much as possible [4]. American Academy of Dermatology and international Psoriasis council also suggest recommendations on using the biologics and immunosuppressant in COVID-19 positive patients [5], [6]. Guidelines for dermatoscopy during COVID-19 pandemic have been also suggested [7].

COVID-19 Pandemic and Psychodermatological Disorders. What to Expect?

At the time of COVID-19 pandemic, constant fear and stress are present on the surface. During a pandemic and restricted movement, the constant need to wear face masks, adhere to the rules of keeping a social distance of 2 m, constantly washing hands, and continuously media accentuating about the danger of the virus and infection led to milder or more severe mental problems. Skin diseases are the most common somatic causes of psychological disorders and, conversely. During a stressful situation, the body has the power to adjust to maintain its well-being, but with prolonged exposure to stress, the first negative changes such as fear, anxiety, and depression will eventually lead to chronic fatigue and an increased risk of disease. In this paper, we will look at the most common psychodermatological disorders and its implication in the era of COVID-19 pandemic.

Dermatological conditions are closely related to stress. Stress is a trigger factor for a lot of cutaneous diseases: Alopecia areata, psoriasis, vitiligo, lichen planus, acne, atopic dermatitis, and urticaria. What matter is the “perceived stress,” or patient’s perception of the stressful situation, which sometimes its greater than the stress itself. This perception is usually influenced by the psychological state of the patient. Anxiety, depression could change the perception of the event [8].

The exact prevalence of psychological factors that affect skin disease is not known; however, it has been estimated to be 25–33% in various studies [8]. Brain, nerves, and skin are embryologically derived from the neural plate in the ectoderm. The neuro-immuno-cutaneous-endocrine model was proposed by O’Sullivan *et al*., to explain the relationship of the body and mind [9].

The role of the neuropeptides, hormones, and neurotransmitters in the pathogenesis of psychotic diseases is subject of research by a number of scientists. Stress is known to activate the two major neural pathways, the first is the hypothalamic-pituitary-adrenal axis and the second is the sympathetic nervous system. Stress triggers the secretion of adrenal glucocorticosteroids and catecholamines, the secreted amount of which, will act as a negative feedback on the secretion of corticotropin-releasing hormone, which stimulates the sympathetic nervous system and the secretion of epinephrine and norepinephrine [8].

Catecholamines and corticosteroids have an inhibitory effect on the immune system, reduce the secretion of IL-2 and IL-8, affect the differentiation of T cells, and activate cellular immunity. From the terminal nerve endings in the skin begin to release neuropeptides such as calcitonin gene released peptide and substance P, which are the main culprits for the existence of psychosomatic skin diseases. As a result of these reactions, the body’s allergic and inflammatory responses increase [8]. Psychological stress has a negative influence on barrier function of the skin and its antimicrobial defense, both by glucocorticoid-dependent mechanism [10].

Although there is no single universally accepted classification system of psychocutaneous disorders and many of the conditions are overlapped into different categories, the most widely accepted system is that devised by Koo and Lee [11]. In psychophysiological psychocutaneous disorders, the skin disease is not caused by stress but appears to be precipitated or exacerbated by the stress [11]. The proportion of patients reporting emotional triggers varies with the disease, ranging from approximately 50% in acne to 90% in rosacea, alopecia areata, neurotic excoriations, and lichen simplex and may be 100% for patients with hyperhidrosis [11]. Onset or exacerbation of psoriasis can be triggers by a number of common stressors. Stress has been reported in 44% of patients before the initial flare of psoriasis, and recurrent flares have been attributed to stress in up to 80% of individuals [12]. In a study analyzing, the stressful situations described in psoriatic patients the most common were death of a family member, own disease or serious disease of a family member [13]. Stressful life events precede the onset of disease in more than 70% of atopic dermatitis patients [14]. A case–control study of Willemsen *et al*. reported higher score and impact of lifetime and childhood traumatic events, in alopecia areata adults [15]. There are reports that alopecia areata pediatric patients experienced more stressful events [16]. Stressful events precede the onset of lesions in vitiligo patients, compared to controls [17]. Severe emotional stress may exacerbate pre-existing urticaria. Increased emotional tension, fatigue, and stressful life situations may be primary factors in more than 20% of cases and are contributory in 68% of these patients [11]. There is increasing evidence that stress has a role in recurrent herpetic infection [18]. Several psychological stress of any sort, may depress cell-mediated immune response, predisposing children to the Herpes zoster virus [19].

Such evidence raises the possibility that the psychosocial stress induced by the COVID-19 pandemic can potentially lead to exacerbations or onset of common inflammatory skin conditions (e.g., psoriasis, atopic eczema, urticaria, and pruritic conditions), both in the short term and after the resolution of the pandemic [20]. Soon, we will have to deal with short- and long-term psychosocial effects related to the COVID-19 pandemic on patients with dermatological disorders, and we encourage comprehensive studies of the implications of the COVID-19 pandemic in these patients.

Conclusion

As COVID-19 pandemic rapidly spreads across the world, it is inducing a considerable degree of fear, worry and stress, for many individuals, arising from the disease itself, and from measures such as social and physical distancing. In public mental health terms, the main psychological impact to date is elevated rates of stress or anxiety. However, as new measures and impacts are introduced, especially quarantine and its effects on many people's usual activities, routines or livelihoods – levels of loneliness, depression, using drugs, alcohol, and self-harm or suicidal behavior are also expected to rise.

Stressful events could induce a psychosomatic disease, especially in some patients with high reactivity to stress. We will be witnessing a growing number in patient consultations with chronic urticaria, dermographism, worsening rosacea, seborrheic dermatitis, generalization, and relapses of psoriasis and alopecia. Mental stress can influence the disease, causing flare-ups and being the main triggering factor. Stress suggests a poor prognosis. In general, there is a need for improved coordination of primary healthcare, dermatovenereologists and psychiatric, and psychological services in the health system. It is needed to be prepared for as many cases as possible, because the psychological consequences will still be felt.

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The Dermatological Spectrum of Coronavirus Disease-19 Disease: Cutaneous Signs for Diagnostics and Prognosis and an Expanded Classification

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Abstract

During severe acute respiratory syndrome coronavirus (CoV)-2- induced CoV disease (COVID)-19 pandemic cutaneous signs of the disease gained increasing interest for early diagnosis, to establish a prognosis and for differential diagnoses. The present review aims to summarize current knowledge on cutaneous findings in COVID-19. The findings are classified and described clinically. The spectrum of cutaneous signs include acro-ischemic lesions, rash, chilblain-like eruptions, and androgenetic alopecia. Their significance is given, and treatment options are presented. This may allow the clinicians to support triage and optimal treatment for COVID-19 patients.

Key Bullets

- The COVID-19 pandemic has affected patients world-wide. Despite the leading symptoms are in the respiratory, cardiovascular, hematologic, and neurologic systems, cutaneous manifestations are increasingly be observed.
- Cutaneous findings in COVID-19 patients may have prognostic and therapeutic consequences. This review attempts to classify cutaneous symptoms, document the observed frequency of their occurrence, the significance for triage of COVID-19-patients, and the treatment of cutaneous manifestations.

Introduction

The coronavirus (CoV) disease (COVID)-19 pandemic originated in Wuhan, China, and is caused by a new beta-CoV, named severe acute respiratory syndrome-CoV (SARS-CoV)-2 [1]. The virus enters host cells with the support of its surface spike proteins. Angiotensin-converting enzyme 2 (ACE2) has been identified as the entry receptor and employs the cellular serine protease TMPRSS2 for S protein priming [2]. Since ACE2 is regulated by androgens, this may contribute to the higher rate of males affected [3].

Infection can be from animals to humans and human-to-human. Among humans, the most common transmission is by respiratory droplets. The primary entry point is the respiratory system, although the virus can also infect the digestive, urinary, neurologic, and hematologic system. Other possible ways of transmission are fecal-oral and mother-to-child. Incubation time varies between 5 and 14 days, seldom longer [4].

Typical symptoms of infection by SARS-CoV-2 are fever, fatigue, dry cough, dyspnea, with or without nasal congestion, runny nose or other upper respiratory symptoms, lymphopenia, thrombocytopenia, and leukopenia. Patients may present with atypical symptoms such as headache, vomiting, diarrhea, and hemoptysis or stay asymptomatic [5], [6].

Complications include the acute respiratory distress syndrome, acute heart injury, stroke, encephalopathy, and secondary infections [5], [7], [8]. Patients older than 60 years and/or comorbidities are at higher risk for complications, hospitalization, and mortality. The rate of patients to be treated at the intensive care unit (ICU) varies from nearly 30% in the initial Wuhan epidemic to around 12% on northern Italy and 7% in Germany [9], [10], [11].

Distribution of SARS-CoV-2 in Human Tissues

Three autopsy cases from Chongqing, China, demonstrated by immunohistochemistry that alveolar epithelia and macrophages were partially positive for the 2019-nCoV antigen. Real-time -polymerase chain reaction (rT-PCR) analyses identified positive signals for 2019-nCoV nucleic acid [12]. In two autopsies from Cleveland/OH, USA, viral RNA was detected in lungs, bronchi, lymph nodes, and spleen using quantitative rT-PCR method on formalin-fixed paraffin-embedded tissue specimen [13]. Among 26 autopsy cases from Wuhan, China, immunostaining with SARS-CoV nucleoprotein antibody was positive in renal tubules [14]. In 12 patients who died from COVID-19 in Hamburg/ Germany, SARS-CoV-2 RNA was detected in the lung at high concentrations. Viremia in 6 of 10 and 5 of 12 patients demonstrated high viral RNA titers in the liver, kidney, or heart during autopsy [15]. In three autopsy cases from Zürich, Switzerland, presence of viral elements within endothelial cells and the induction of endotheliitis in several organs as a direct consequence of viral involvement have been documented [16].

The expression of ACE2 was demonstrated in human skin samples using single-cell RNA sequencing. It was significantly higher in keratinocytes than other cell types in skin, such as fibroblasts and melanocytes. Immunostainings for ACE2 were positive in epidermal basal layer, stratum spinosum and stratum granulosum [17]. SARS-CoV-2, on the contrary, has not been detected in skin [12].

By the support of neuronal network possible conceptual associations from unstructured text and triangulation with insights from single cell RNA-sequencing (seq), bulk RNAseq and proteomics from diverse tissue types have been analyzed. It could be demonstrated that tongue keratinocytes, olfactory epithelial cells, airway club cells, and respiratory ciliated cells are potential reservoirs of the SARS-CoV-2 receptor. The gut was identified as the putative hotspot of COVID-19, where a maturation correlated transcriptional signature is shared in small intestine enterocytes among CoV receptors (ACE2 and others) [18].

Epidemiology of Cutaneous Manifestation of COVID-19

The initial trials from Wuhan suggested a low prevalence of 0.2% of any cutaneous findings among symptomatic patients [19]. The prevalence of cutaneous manifestations in uncontrolled trials and reports varies extremely from zero (Tibetan highland) to almost 100% (Thailand) [20].

There is a need for better epidemiological data on the subject. One initiative to improve data collection and analysis comes from the American Academy of Dermatology [21].

Classification of COVID-19-related Cutaneous Manifestations

A nationwide Spanish study among dermatologists included 375 COVID-19 cases with cutaneous manifestations. Based on this large data set, the authors tried to classify the cutaneous findings into five categories [22]:

- Asymmetrical distributed chilblain-like acral areas of erythema and/or edema with some vesicles or pustules (pseudo-chilblain) on digits hand and feet and heels
- Vesicular monomorphic eruptions (varicella-like)
- Urticarial lesions
- Maculopapular rash
- Acro-ischemic lesions (Livedo or necrosis).

We had like to add some more possible cutaneous findings:

1. Symmetrical flexural and intertriginous exanthema
2. Purpuric rash
3. Erythema multiforme-like rash and Kawasaki-like disease/multisystemic inflammatory syndrome in children (MIS-C)
4. Others (Mottling, Sweet syndrome-like, pustular eruptions, and androgenetic alopecia [AGA]) (Table 1).

Table 1: Cutaneous signs of COVID-19, their frequency and significance

Cutaneous signs	Frequency	Remarks	Significance
CE	up to 19%	Mostly children	Mild or silent disease
Vesicular eruptions	9–15%	Symptomatic adults	Could be a sign of a viral coinfection
Urticarial lesions	1.4–19%	Often with pyrexia	In case of eosinophilia, the prognosis might be better
Maculopapular rash	up to 47%	Mostly adults	Nonspecific, drug hypersensitivity should be excluded
Acro-ischemic lesions	2.8–6%	Thromboembolic, DIC	Red flag for severe course, mortality is high
SDRIFE-like	Rare		Exclude a drug reaction
Purpuric rash	Unknown	Underestimated in developing countries	Exclude other viral diseases, coinfections with dengue possible
EM	Rare		Unknown
KD	Unknown	Children	Severe course, but often good prognosis
MIS-C	Unknown	Children	Severe disease, ICU support
Mottling	Rare	Newborn	Unknown
SS-like		Rare	Adults
Pustular eruptions	Rare	Adults	Probably hydroxychloroquine-induced
AGA	≤75% (males)	Adults, More severe course	Mediterranean Sea

AGA: Androgenetic alopecia, CE: Chilblain-like eruptions, EM: Erythema multiforme, DIC: Diffuse intravascular coagulation, KD: Kawasaki disease, MIS-C: Multisystemic Inflammatory Syndrome in Children, SS-like: Sweet syndrome-like eruptions, SDRIFE-like: Symmetrical flexural and intertriginous exanthema.

Chilblain-like Acral Lesions

Clinics

Mostly asymmetrical distributed chilblain-like violaceous, infiltrated acral areas of erythema, and/or edema with some vesicles or pustules ("pseudo-chilblain") can be observed on hand and feet (Figure 1) [22]. Proximal nail fold capillaroscopy/ dermoscopy remains normal [23].

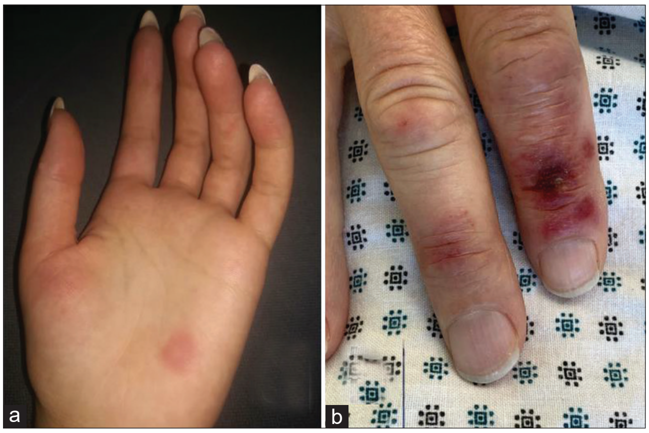

Figure 1: Asymmetric chilblain-like lesions. (a) Erythematous plaque on the antithenar. (b) Ill-defined infiltrations on two fingers. Nail fold capillaries are without abnormalities

There is a number of case reports on chilblain-like lesions mainly in children and adolescents. Pruritus and (mild) burning pain are two equally distributed major symptoms [24], [25], [26]. In a series of 63 patients, there was no significant gender difference. The median age was 14 years and feet alone were mostly affected (85.7%), followed by feet/hands together (7%) and hands alone (6%). Asymptomatic lesions were present in 25.4% of cases [27].

Frequency

The nationwide Spanish study reported chilblain-like lesions in 19% of cases [22]. In a retrospective observational nationwide study among French private practices, 277 patients were enrolled with a median age of 27 years. Chilblain-like lesions were the most frequent acral lesions (n=106/142, 75%) [28].

In the rare cases with a lesional skin biopsy, vasculitis signs were noted in small to medium sized vessels with endothelial cell swelling and red blood cell extravasation. Fibrin thrombi was evident in superficial capillary vessels [29]. In an adult case, absence of significant papillary dermal edema was associated with a superficial and deep lymphoplasmacytic infiltrate, vacuolar interface dermatitis with some apoptotic keratinocytes and smudging of the basement membrane zone. The venules surrounded by the lymphoplasmacytic infiltrate had plump endothelial cells. Neither intraluminal fibrin thrombi nor venule wall fibrin deposits were detected. Direct immunofluorescence result was negative. Altogether these findings suggest a type I interferon response [30].

Significance

The percentage of patients with this type of cutaneous lesions tested positive for SARS-CoV-2 is between 15% (prospective study) and 25% (retrospective study). This raises questions, if the chilblain-like lesions are markers of COVID-19 [31]. Some authors recommend SARS-CoV-2 testing in children and adolescents with chilblain-like lesions to support early detection of silent carriers [32].

Treatment

In uncomplicated cases topical mometasone furoate and heparin gel for a few days is recommended [33].

Vesicular Monomorphic Eruptions

Clinics

Vesicular monomorphic eruptions on the trunk or the extremities, with possible hemorrhagic content have been observed mostly in symptomatic COVID-19 cases [22].

These lesions present initially as erythematous papules with a tendency to superficial vesiculation that eventually leads to crust formation. The presentation is varicella-like although most patients may be in good general health condition [34]. In a series of 22 patients from Northern Italy tested positive for SARS-Cov2, the median age was 60 years, and 72.7% of patients were male. The trunk as involved in all cases and the median time to remission was 8 days. Facial skin and mucosa were spared. Itch was noted in about 40% of patients [35].

Frequency

Vesicular monomorphic eruptions on the trunk or the extremities, with possible hemorrhagic content accounted for 9% of cases in the Spanish nationwide study [22]. In France, vesicular eruptions were observed in 41 outpatient cases (15%) [28].

Significance

The vesicular eruptions are considered probably COVID-19 specific, but vesicular drug-reactions and other viral (co-)infections might contribute [36], [37]. Further studies are needed.

Treatment

These eruptions do not need any treatment, they can pass by itself. Wet dressing can be done to relieve the patient from itch. Topical antibacterial cream can be added if secondary impetiginization occurs.

Urticarial Rash

Clinics

Urticaria with wheals and flares is a non-specific cutaneous symptom in COVID-19 patients (Figure 2). Here, urticarial lesions occur mostly on the trunk, rarely palmar. Pyrexia with urticaria may be more characteristic than urticaria alone [22].

Figure 2: Urticaria

Frequency

Urticaria was observed in 19% of Spanish COVID-19 patients and in in 1/14 in a French study [22], [26]. Among 140 hospitalized Chinese patients in Wuhan 1.4% self-reported urticarial [38]. A recent literature review reported urticaria in 9.7% of cases (7/72) [39].

Significance

In case of urticaria with eosinophils, theoretically a better outcome is possible [40]. Differential diagnoses include idiopathic urticaria, drug eruptions, and other viral infections with urticarial rash. If the patient is not taking medication and does not have idiopathic urticaria diagnosis, it is more likely to think of COVID-19 specific urticaria.

Treatment

Symptomatic treatment with oral antihistamines and topical corticosteroids is an option.

Maculopapular Rash

Clinics

Maculopapular rash is a non-specific cutaneous finding in COVID-19 patients (Figure 3). Lesions may show a possible perifollicular distribution. Variants were described as pityriasis rosea-like with a variable degree of purpuric areas or erythema elevatum diutinum-like. The rash lasts on average 9 days. It is uncommon among children affected by COVID-19 [20].

Figure 3: Maculopapular rash. (a) Follicular type, (b) confluent lesions, (c) lichenoid follicular type

Erythema multiforme-like eruptions have rarely been reported. They can spread to facial and palmoplantar skin and the average duration is double as long as the usual maculopapular rash with nearly 20 days. In a series of four adult patients, histologic examination revealed a normal basket-weave stratum corneum, and mild-to-moderate epidermal spongiosis. Dermal vessels were dilated and filled with neutrophils with some extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate. These patients needed systemic corticosteroids [41].

Pityriasis rosea-like eruptions are a rare pruritic cutaneous manifestation of COVID-19 [42].

Frequency

In the Spanish trial maculopapular rash was a common cutaneous finding observed in 47% of cases [22]. Face and palmoplantar skin is usually spared. Histologic and clinical presentation is not uniform. If needed, symptomatic topical treatment with corticosteroids and oral antihistamines can be used [20].

Significance

Maculopapular rash is a non-specific cutaneous finding in COVID-19. The most important differential diagnosis is drug-induced exanthema.

Treatment

Symptomatic treatment with oral antihistamines and topical corticosteroids is an option.

Acro-ischemic Lesion (Livedo or Necrosis)

Clinics

Transient livedo reticularis-like lesions have occasionally been observed in symptomatic COVID-19 patients. The livedoid changes may be unilateral in nature. They can eventually result in skin necrosis. The lesions are thought to be secondary to SARS-CoV-2-induced thrombotic vasculopathy [22], [26]. Acro-ischemia presenting with finger and toe cyanosis, skin bullae, and dry gangrene are a red-flag sign for severe illness (Figure 4).

Figure 4: Acro-ischemic ulcerations. (a) Transitory livedoid erythema. (b) Ulcerated papule. Disseminated ulcerated papules may be a sign of DIC. (c) Two neighboring ulcerations on the foot. (d) Ulcerated lesion on the heel

Frequency

The frequency of livedo and necrosis was 6% in Spain and 2.8% in a recent literature review [22], [39].

Significance

If livedoid and necrotic eruptions occur in COVID-19 patients, this could be a clue for systemic thrombotic vasculopathy. It will be particularly important to recognize the eruptions clinically, since they may have (strong negative) prognostic value in these patients.

It is important to separate acral lesions in the elderly from chilblain-like eruptions in youngsters since these could have a necrotic outcome [43]. Acro-ischemia presentations are associated with severe COVID-19 disease and high mortality [44].

Treatment

Treatment is dependent on underlying pathology (acral ischemia, and disseminated intravascular coagulopathy [DIC]). In the initial phase of the SARS-CoV-2 infection, D-dimer and fibrinogen levels are increased, while prothrombin time, activated partial prothrombin time, and platelet counts are often normal. Diagnosis of DIC needs laboratory evaluation of soluble fibrin, protein C, and plasminogen activator inhibitor 1.

For hospitalized COVID-19 patients, thromboprophylaxis using low-molecular-weight heparin is recommended [45]. Recombinant human soluble thrombomodulin has proven clinically useful for treating DIC leading to a higher resolution rate after 7 days of application [46]. Adjuvant plasmapheresis has been used occasionally in DIC [47].

Symmetrical Flexural and Intertriginous Exanthema

Clinics

Symmetrical flexural and intertriginous exanthema are a rare manifestation of COVID-19. It resembles clinically Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDRIFE).

Frequency

This symptom has been seen in single cases several days after the COVID-19 fever developed [48].

Significance

Drug-induced SDRIFE needs to be excluded before the diagnosis of COVID-19 SDRIFE can be made.

Treatment

Symmetrical flexural and intertriginous exanthema is temporary. In one case, it disappeared after 18 days without any specific treatment [48].

Purpuric Rash

Clinics

Acute undifferentiated febrile illness is one of the initial presentations of COVID-19. Purpuric rash in COVID-19 may resemble other viral rashes like dengue fever [49], [50]. Very rare is Schamberg's-like purpura in mild COVID-19 [51].

Frequency

The frequency is obviously dramatically underestimated in tropical countries [52].

Significance

In hotspots of arboviral diseases, these disorders need to be excluded [53]. On the other hand, SARS-CoV-2 and dengue fever have been reported as coinfections from various developing countries [54], [55], [41].

Treatment

Antipyretics and topical corticosteroids can be combined.

Erythema Multiforme-like Rash and Kawasaki-like Disease/MIS-C

Clinics

Four female hospitalized COVID-19 patients in Madrid, Spain, presented an erythema multiforme-like rash. The mean age was 66.8 years. The mean time between onset of COVID-19 to the appearance of erythematous lesions was 19.5 days. Three patients developed the rash 4–7 days after clinical improvement with negative COVID-19 PCR test. These lesions developed from erythematous papules on the upper trunk that progressively turned into targetoid erythematous or violaceous patches with a dusky center, and a pseudo-vesicle in the middle. They spread to the face and limbs within 1 week, but spared palms and soles. Oral mucosa was also involved with palatal macules and petechiae. Histological examination showed dilated dermal vessels filled with neutrophils, extravasation of red blood cells, and lymphocytic perivascular and interstitial infiltrate [41]. One case report from France described a 6-year-old boy with erythema multiforme-like mucocutaneous lesions [56].

A prospective observational study from Paris, France, reported on 14 children with COVID-19 and Kawasaki-like disease. Almost 60% originated from sub-Saharan Africa or Caribbean islands. All children had marked gastrointestinal symptoms and high levels of inflammatory markers. Eleven patients presented with Kawasaki disease (KD) shock syndrome requiring ICU support, and 12 suffered from myocarditis [57]. Kawasaki-like eruptions including generalized exanthema, cheilitis, stomatitis, and bilateral conjunctivitis, bilateral palmar edema, glossitis, and cervical lymphadenopathy had been reported in a 3-year-old boy. Cutaneous desquamation of the extremities was noted later on [56]. A 6-year-old girl with rT-PCR confirmed COVID-19 met criteria for incomplete KD, including fever for more than 7 days with conjunctivitis, rash, edema of the hands and feet, elevated CRP and erythrocyte sedimentation rate, hypoalbuminemia, anemia, and 2-D echocardiogram findings suggestive of myocarditis [58].

An important differential diagnosis of Kawasaki-like disease is MIS-C. MIS-C is characterized by (1) prominent cardiac dysfunction with troponin leak and extremely elevated brain natriuretic peptide, (2) frequent and often severe enteropathy, and (3) relative thrombocytopenia. In some patients, fever and gastrointestinal symptoms precede the classical KD features such as cutaneous rash, conjunctivitis, mucous membrane changes, and extremity edema [59].

Frequency

One series of 17 children and several case reports have been published so far [41], [56], [57], [60], [61].

Significance

Other viral (co-) infections such as parvovirus B19 and herpes simplex have to be excluded. Kawasaki-like disease often needs ICU support for affected children.

Treatment

If necessary, oral corticosteroids may be given temporary for erythema multiforme-like eruptions. In case of Kawasaki-like disease, intravenous immunoglobulins at 2 g/kg, systemic corticosteroids, and aspirin have been recommended [57], [61].

Other Cutaneous Findings

Mottling

A 15-day-old neonate of a SARS-CoV-2 positive mother developed COVID-19 without cough.

The cutaneous findings were described as mottling. The newborn was isolated and subjected to supportive care. Antibiotic and antiviral treatment was initiated. The outcome was complete remission after 6 days [58].

Sweet syndrome-like eruptions

A 61-year-old woman without respiratory symptoms but fever, fatigue, arthralgia, and myalgia, was admitted to a hospital in Istanbul, Turkey. On examination, she presented numerous erythematous nodules on the cheeks, scalp, extremities, and the trunk. Minor aphthous ulcers were observed on the hard palate and buccal mucosa. Thoracic computerized tomography presented multifocal ground-glass opacities. The laboratory was remarkable for leukocytosis, neutrophilia, and mild lymphopenia, C-reactive protein was elevated with 78.2 (<5.0 mg/L). Although an initial SARS-CoV-2 rT-PCR was negative, a repeated test became positive. A skin biopsy from the elbow revealed a diffuse neutrophilic infiltration in the upper dermis and vascular proliferations with swollen endothelial cells and extravasated erythrocytes. In the lower dermis and at the periphery of the lobules of subcutaneous fat tissue, there were granulomas, composed of epithelioid histiocytes and multinuclear giant cells and other inflammatory cells. Clinical and histopathological features were considered as erythema nodosum-like Sweet syndrome [62]. Another case is shown in Figure 5.

Figure 5: Sweet-like plaques and pustules on the arms

Pustular rash

A 69-year-old woman from Madrid, Spain, with confirmed COVID-19 disease developed a pustular rash resembling acute exanthematous pustulosis 33 days after onset of COVID-19 symptoms. Histology revealed subcorneal pustulosis, spongiosis, papillary edema, and discrete neutrophilic inflammatory infiltrate [63]. Several other cases have been reported in adult COVID-19 patients [64], [65]. Since these patients were treated with hydroxychloroquine, a delayed drug-reaction is possible [66]. A direct effect of SARS-CoV-2 remains unproven (Figure 6).

Figure 6: Acute exanthematic pustulosis due to hydroxychloroquine treatment of COVID-19

AGA; Gabrin sign

AGA severity reflects the androgen activity over age. Among 175 confirmed and hospitalized COVID-19 patients in Spain, 122 were males and 53 were females. AGA was present in 67% of the patients, 70 patients presented with clinically relevant AGA. The frequency of AGA was 79% in males and 42% in females. The prevalence of age matched males in a similar Caucasian population was estimated to be 31–53%, in females >70 years and the prevalence reported was 38% [67]. This argues for a significant higher rate of AGA at least in COVID-19 positive males. Furthermore, it seems to be a marker for a more severe course of COVID-19 [68].

Dr. Gabrin was the first physician to die from COVID-19 in the US and suffering from AGA. Therefore, the eponym "Gabrin sign" has been proposed for AGA in COVID-19 patients [67].

Conclusions

During the COVID-19 pandemic dermatologists play an active role in patients' triage, in early diagnosis of cutaneous signs, in the recognition of cutaneous red-flags for an unfortunate course of the disease. Their active participation is necessary to record cutaneous findings, to confirm diagnoses and make the necessary differential diagnostic procedures [69]. The most important diseases to be considered are tropical and other viral disorders and drug hypersensitivities. However, we are still at the beginning and should be aware of unexpected findings.

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Management of Chronic Myeloid Leukemia with Sever COVID 19: A Case Report

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Abstract

Coronavirus disease-19 (COVID-19) is a pandemic viral disease that can cause devastating complications such as acute respiratory disease, especially in patients with comorbidities. We do not know yet full pictures of this disease, especially in hematological malignancies. Here, we present management of a 57-year-old male with chronic phase chronic myeloid leukemia, tested positive for COVID-19, then complicated with acute respiratory distress syndrome.

Introduction

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate. The peripheral blood shows an increased number of granulocytes and their immature precursors, including occasional blast cells.

CML is caused by a single, specific genetic mutation, known as the Philadelphia chromosome. CML progresses through three phases: Chronic, accelerated, and blast. CML accounts for 20% of all leukemia affecting adults. Historically, the median survival of patients with CML was 3–5 years from the time of diagnosis. At present, patients with CML have a median survival of 5 or more years. In fact, CML patients are currently approaching normal life expectancyas a result of the improvement of earlier diagnosis, improved therapy with target therapy, tyrosine kinase inhibitors (TKI).

The coronavirus pandemic, is an ongoing pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak was first identified in Wuhan, China, in December 2019. Cases presentation ranged from mild asymptomatic cases up to sever pneumonia, cytokine storm syndrome, and ARDS.

There are no available specific data on the COVID-19 in CML patients treated with (TKI).

At present, we have no evidence to suggest that chronic phase CML patients on TKI are at higher risk of contracting SARS-CoV-2 or having a more severe form of the viral infection compared to the general population.

In this case report, we will present how we managed a case of CML that presented with sever COVID 19 infection.

Case Presentation

A 57-year-old male patient with history of diabetes mellitus (DM) on metformin 850 mg twice daily, diagnosed as chronic phase CML 10 years ago and he was started and maintained on imatinib 400 mg OD and achieved major molecular response (MMR). Last PCR for BCR-ABL 3 months ago 0.0001%.

He presented to Emergency Department (ED) May 19, 2020, in King Salman Specialist Hospital, Hail, Kingdom of Saudi Arabia, complaining of cough for 2 days, with fever, nausea no shortness of breath, no abdominal pain no vomiting, no diarrhea, no history of contact with positive case of COVID 19. On examination: He looks well, conscious, temperature was 38.4°C, other vital data within normal, chest examination was normal, abdomen: Soft and lax. White blood cell 5.75 × $10^6/\mu L$ absolute neutrophil count (ANC) 4.37 × $10^6/\mu L$ lymphocytes 1.1 × $10^6/\mu L$ hemoglobin 14.6 g/dL platelet 220 × $10^9/L$, normal kidney and liver function tests, blood sugar 12 mmol, and normal chest X-ray (CXR).

COVID 19 swab taken and patient received paracetamol and antitussive, his medications of DM are modified, and advised for home isolation and to continue on imatinib 400 mg.

Two days later he returned to ED with complain of epigastric burning sensation, associated with loss of appetite, diarrhea for 1 day and productive cough.

Temperature was 37.5°C, heart rate was 103/min, oxygen saturation (O_2 Sat) 89% on room air, BP 160/90, chest examination: Equal bilateral air entry, and no adventitious sounds (Table 1).

He was admitted in isolation ward and he was started on hydroxyclorouquine, azithromycin, ceftriaxone, and prophylactic enoxaparin as per protocol. With ECG monitor of QT interval, and he continued on imatinib 400 mg OD.

On 2nd day of admission patient developed dyspnea his temperature increased to 39°C, O_2 sat 88% on 5 L/min nasal cannula. Chest exam showed bilateral crepitations, CXR: Bilateral infiltrations.

Patient shifted to ICU for close monitoring and we continued on imatinib 400 mg daily as no drug interaction with his medications and normal ANC, platelet, and liver function tests (Table 2, Figure 1).

Patient stayed in ICU for 2 days with stable condition, but with fluctuation of temperature, and O_2 Sat.

On 3rd day of ICU admission, his O_2 Sat markedly deteriorated.

Patient was sedated, intubated and kept on mechanical ventilation AC (MODE) VT, 440. RR, 20. PEEP, 10. FIO_2, 50%.

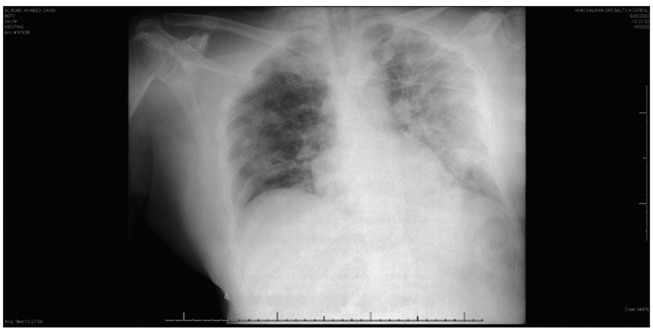

Figure 1: Chest X-ray of patient on day of admission to ICU

We started patient on following medications based on local COVID-19 management protocol: Therapeutic dose of anticoagulation of enoxaparin 1 mg /kg/BID SC, as D-DIMER more than 1 and he has severe COVID 19 pneumonia.

Methylprednisolone 40 mg IV q12h, lopinavir/ritonavir 400/100 mg q12h oral for 14 days, ribavirin 400 mg q12 h oral for 14 days, interferon Beta 1-b 8MIU SC every other day for 3 doses.

4 h later he developed metabolic acidosis as he developed DKA that was appropriately managed.

We kept him on mechanical ventilation for 5 days, he was stable, afebrile, maintained normal O_2 Sat, and normal vital data. With regular laboratory follow-up, especially D-dimer and lymphocytes count (Figures 2 and 3) We kept imatinib on hold during days of intubation and mechanical ventilation.

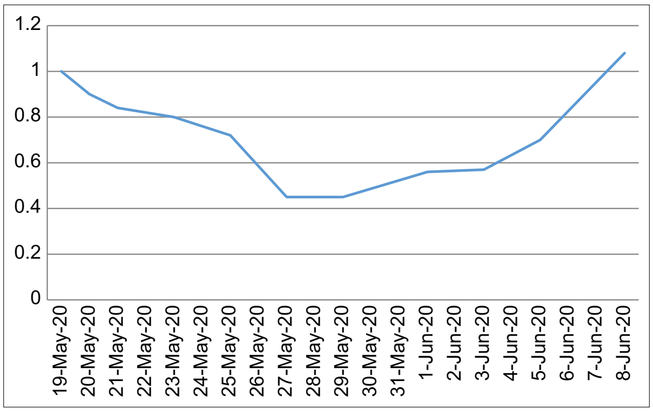

Figure 2: Lymphocytes count during course of the disease

After extubating him, as patient is clinically stable, we resumed imatinib. However, as patient is receiving ritonavir which has interaction with imatinib leading to increasing effect of imatinib, we reduced dose of imatinib by 50%, 200 mg OD till he finished antiviral therapy.

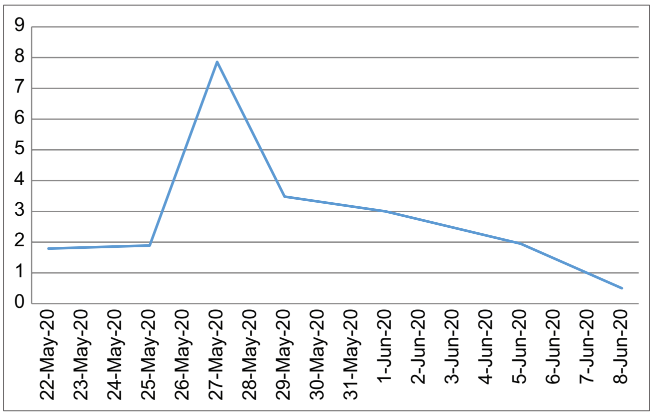

Figure 3: D-dimer level during course of the disease

Patient finished 14 days of antiviral, his PCR for COVID 19 come negative twice, we resumed imatinib 400 mg daily and discharged patient on prophylactic dose of enoxaparin 6000 IU for 45 days, we could not start direct oral anticoagulant due to its interaction with imatinib as both potentiate toxicity of each other. Twenty days later Q-PCR for BCR-ABL is repeated and confirm patient still in MMR.

Discussion

SARS-CoV-2 is a zoonotic beta-coronavirus, similar to Middle East respiratory syndrome (MERS) and SARS-CoV-1, which causes a respiratory illness known as COVID-19. Most cases have mild symptoms, for example, fever, exhaustion, and dry cough [1]. Notwithstanding, a few cases are serious and may be confounded by ARDS prompting mechanical ventilation. The infection could be serious and complications are frequently found among patients with comorbidities, such as hypertension and respiratory and cardiovascular system diseases [2].

Some studies have suggested that cancer patients are more vulnerable to infection with SARS-CoV-2 than healthy people and have a worse prognosis because their immune systems are suppressed by the effects of the tumors and anti-cancer treatment [3]. However, this view is controversial [4].

CML is a neoplastic disease of hematopoietic stem cells that have an annual incidence of 0.4–1.75/100,000 11–15, the therapeutic landscape of chronic myeloid leukemia (CML) has significantly changed over the previous year. Most patients with chronic phase (CP) now have a normal life expectancy. Our goal is achieving a stable deep molecular response (DMR) and discontinuing medication for treatment-free remission (TFR). TKIs have improved patient outcomes to near-normal, and thereby survival. Imatinib was the first generation TKI that showed higher rates of cytogenetic and molecular responses [5].

There is no proof that hematological neoplasms, for example, CML, regardless of whether they are on TKIs, may put the patient at high hazard for COVID-19 and its complications [6].

In one study done in Wuhan, they studied SARS-CoV-2 infections in CML patients according to their response to anti-CML therapy, and found that just 1 of 299 (0.3%) patients with an optimal response was diagnosed with COVID-19. Of the 50 patients who failed to respond to CML treatment or had a poor response, 1 patient (2%) had a clinical diagnosis of COVID-19. Thus, patients who failed to achieved an optimal response to CML therapy appear more likely to have a symptomatic infection with SARS-CoV-2 [7]. This may be explained by; an optimal response to TKI treatment may be associated with immune recovery. CML patients exhibit selective depletion of effector T-reg cells [8], [9], while TKIs increase the number of natural killer cells (NK), NK-LGL, and T-LGLs cells [10], which play a role in regulating immunity. Moreover, the previous studies have reported that imatinib and other TKI drugs have antiviral activity *in vitro* against MERS-COV and SARS-COV [11], although the risk of infection in patients with CML on dasatinib is debatable [6].

Table 1: Laboratory test results on the day of admission

Laboratory test	Value	Normal range
White blood cell	$8.18\times10^6/\mu L$	4–10
Absolute neutrophil count	$6.34\times10^6/\mu L$	2–7
Lymphocytes count	$1\times10^6/\mu L$	1.5–3
Hemoglobin	13.9 g/dL	13–17
Platelet	$240\times10^9/L$	150–400
Ferritin	1594 ng/mL	22–322
LDH	419 U/L	125–135
D-dimer	1.79 mg/L	0.00–0.49

LDH: Lactate dehydrogenase.

In case presented here, our patient had optimal response to imatinib, so we did not stop imatinib during course of the disease based on the previous data but after intubation and mechanical ventilation, his prognosis was dismal, and we do not have enough data about continuation of CML therapy at that time, so we hold it.

Table 2: Laboratory tests on date of ICU admission

Laboratory test	Value	Normal range
WBC	$6\times10^6/\mu L$	4–10
Absolute neutrophil count	$4.57\times10^6/\mu L$	2–7
Lymphocytes count	$0.45\times10^6/\mu L$	1.5–3
Hemoglobin	12.5 g/dL	13–17
Platelet	$454\times10^9/L$	150–400
Ferritin	1650 ng/mL	22–322
LDH	600 U/L	125–135
D-dimer	7.9 mg/L	0.00–0.49

LDH: Lactate dehydrogenase.

There is a variable risk of infectious complications with targeted therapy. According to Reinwald *et al.*, kinase inhibitors that target the mTOR, Janus kinase and BCR pathways exhibit an increased risk of infection, sometimes fatal complications; while this risk is minor with kinase inhibitors of the angiogenesis-related growth factors [12].

Interestingly, analysis of virus-host interaction retrieved available anti-cancer target therapy that can potentially act against the SARS-CoV-2, among these drugs, a TKI (afatinib) and a proteasome inhibitor (ixazomib) [13]. Furthermore, the previous studies have highlighted the use of kinase inhibitors in the reduction of virus infectivity and this led some researchers to investigate the role of anti-tyrosine kinase such as sunitinib and erlotinib in the treatment of COVID-19 [14].

Our patient responded as all other patient with profound lymphopenia and high D-dimer when he developed sever COVID 19 pneumonia and ARDS.

Lymphopenia is the most common laboratory finding. However, leukocytosis and leukopenia have been reported [15]. Lymphocyte count and lymphopenia may serve as a rapid tool that can quickly identify COVID-19 patients with more severe clinical presentation, viral infection may either directly suppress bone marrow or induce an immune-mediated destruction of lymphocytes resulting in lymphopenia [16], [17]. Thrombocytopenia is more common in patients with critical diseases, and it could also distinguish between mild and severe cases [18]. Some patients might develop cytokine storm or secondary hemophagocytic lymphohistiocytosis, which is characterized mainly by cytopenias and hyperferritinemia plus the other features [19].

Infection with the novel coronavirus SARS-CoV-2 has been associated with inflammation and a hypercoagulable state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers and it associated worse clinical outcomes [20]. There is a potential role for coagulopathy in COVID-19. Although the exact mechanism may remain controversial, it is not typical of disseminated intravascular coagulopathy of the kind seen in septicemia [21].

Heparin has been implicated in binding to COVID-19 spike proteins as well as down-regulating interleukin-6 (IL-6) [22], which has been shown to be elevated in COVID-19 patients, and thus unfractioned heparin or LMWH remains as the best choice of anticoagulant for those patients. It is possible that these patients may even require continued anticoagulation for a certain period of time following hospital discharge [21] and we followed this statement in our patient.

Finally, good responders to TKIs in CML are less likely to develop symptoms of SARS-CoV-2 than non-responders [7]. Hence, clinicians are encouraged not to withhold targeted therapy for good responders rather than pursuing it where not indicated; and this principle is also true irrespective of the pandemic.

Conclusion

In the presence of non-severe confirmed SARS-CoV-2, interruption of TKI treatment is not necessary. In case of severe SARS-CoV-2, TKI interruption should be discussed on a case-to case basis.

Statement of Ethics

The case was approved by the ethical committee of our center and the patient signed a written informed consent to publish the case (including publication of images).

Availability of Data and Materials

The datasets during and/or analyzed during the current case available from the corresponding author on reasonable request.

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Author Contributions

All authors equally contributed in witting and editing.

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Factors Associated with Psychological Distress among Filipinos during Coronavirus Disease-19 Pandemic Crisis

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Abstract

BACKGROUND: During the coronavirus disease 2019 (COVID-19) pandemic, psychological reactions of the population play a critical role in both the spread of the disease and the occurrence of emotional distress and social disorder.

AIM: This study aimed to measure the prevalence and severity of psychological distress to evaluate the current mental health burden on society that leads to the provision of a concrete basis for tailoring and implementing relevant mental health intervention policies to efficiently and effectively respond to the challenges brought by the pandemic.

METHODS: An anonymous, internet-based, cross-sectional survey was conducted from March to April 2020. In this regard, a structured online questionnaire was utilized to collect sociodemographic data and the COVID-19 Peritraumatic Distress Index (CPDI). Descriptive statistics were used to summarize the sociodemographic and prevalence of CPDI among respondents. Logistic regression analysis was performed to identify significant predictors of distress.

RESULTS: Most of the respondents did not feel distressed about COVID-19 (52.1%), whereas 39.5% and 8.4% had mild-to-moderate and severe distress. The regression analysis demonstrated that higher religion and faithfulness levels, lower levels of education, and living in Mindanao (unlike those living in the Visayas) were associated with lower levels of psychological distress among the Filipino respondents during the COVID-19 pandemic.

CONCLUSIONS: Policy-makers and practitioners in the in Filipino society need to consider key factors such as religion, education, and the region where they live in to reduce psychological distress among Filipinos.

Introduction

Coronavirus (CoV) disease 2019 (COVID-19), referred to as severe acute respiratory syndrome CoV 2 (SARS-CoV-2), started in Wuhan, China, and has spread rapidly across the world [1], [2]. The disease was declared a Public Health Emergency of International Concern by the WHO on January 30, 2020. As of May 27, 2020, the global statistics of SARS-CoV-2 infections have included five million positive cases and 300,000 deaths; Southeast Asian Region with 218,523 positive cases reported with 6359 deaths. In the Philippines, there have been 15,049 positive cases and 904 reported deaths since May 28, 2020 [2].

The emergence of COVID-19 in Wuhan has created a confused and rapidly evolving situation. As expected, the UK media has reported a substantial psychological impact of both the outbreak and the response. Residents have been comparing the situation to the "end of the world." Hospitals have been "overwhelmed," and there have been concerns about food shortage. "Panic in Wuhan" is a common refrain [3].

The COVID-19 pandemic represents complex events, that is, complexities in its origin, spread, effects, and consequences at multiple levels and fields, including tourism [4], medical, social, political, economic, religious, cultural, and civilizational [5]. Unfortunately, the effects of CoV on mental health have not been extensively and systematically studied; nevertheless, the COVID-19 may have a rippling effect, particularly based on current public and political reactions [6].

Fear caused by COVID-19, severe clinic picture and deadliness, a strict quarantine, curfew and legal punishment, mistrust of officials who mismanaged the outbreak, and overflowing social media with misinterpretation and theories of conspiracy all have taken their toll on mental health [5], [7].

During an outbreak of an infectious disease, the psychological reactions of a population play a critical role in shaping both the spread of the disease and the occurrence of emotional distress and social disorder (even after the outbreak). However, sufficient resources are typically not provided to manage or attenuate the effects of a pandemic on mental health and well-being [8]. This might be understandable in the acute phase of an outbreak. When healthy systems prioritize testing, reducing transmission, and critical patient care, psychological and psychiatric needs should not be overlooked during any phase of pandemic management [8].

It is known that psychological factors play an important role in adherence to public health measures and how people cope with the threat of infection and consequent losses. Psychological reactions to pandemics include maladaptive behaviors, emotional distress, and defensive responses [8]. People at risk of psychological problems are vulnerable and may be affected by their mental health condition [8], [9], [10].

This study aims to identify the factors associated with psychological distress among Filipinos during the COVID-19 pandemic crisis. Furthermore, the prevalence and severity of psychological distress are measured and the current mental health burden is evaluated on society, which leads to the provision of a concrete basis for tailoring and implementing mental health intervention policies to cope with challenges efficiently and effectively.

Materials and Methods

Study setting and population

An anonymous, internet-based, cross-sectional survey was conducted from March to April 2020 at the time of movement restriction. The study population was Filipinos. Inclusion criteria were as follows: At least 18 years of age and naturally born Filipino. The only exclusion criterion was residence in the Philippines of less than 1 week when the COVID-19 pandemic announcement was issued by the WHO. The structured online questionnaires were conveniently distributed through email and some social media platforms throughout the Philippines. The respondents' social media accounts were identified and linked with all coresearchers and colleagues.

Instruments

Data were collected through a structured online questionnaire. The questionnaire has two parts: Sociodemographic data (stage, gender, age, education, marital status, and comorbidities); COVID-19 Peritraumatic Distress Index (CPDI), which was developed by Qiu *et al*. [9]. COVID-19 CPDI is a self-reported questionnaire with 24 questions based on a Likert scale (never, occasionally, sometimes, often, and always) for anxiety, depression, specific phobias, cognitive change, avoidance, compulsive behavior, physical symptoms, and loss of social functioning in the past week. The questionnaire incorporated relevant diagnostic guidelines for specific phobias and stress disorders specified in the International Classification of Diseases (11^{th} Ed.) and expert opinions from psychiatrists and psychologists. The total score ranges from 0 to 100; a score between 28 and 51 indicates mild-to-moderate distress; A score of ≥52 stands for severe distress [9]. After translating CPDI into Filipino, linguistic and content validation was conducted by the group of expert panel members, that is, psychiatrists, clinical psychologists, and public health professionals. A pilot study of 50 participants was used to assess the validity and internal consistency of the instrument. The Cronbach's alpha of 0.92 indicated that the questionnaire was an excellent internal consistency.

Data collection

Our study was an online survey with completely voluntary and anonymous participation. After obtaining the participants' consent, they could respond to the questions only once through a single account by setting the feature to prevent more than 1 response from the same history. The participants were asked to give a response based on their previous 1-week experience.

Statistical analysis

Data were analyzed using Stata 15.1. Descriptive statistics (using count and proportion) were employed to summarize the sociodemographic profile of survey respondents. Besides, the prevalence of the three-level CPDI was described for all respondents by sociodemographic profile. Logistic regression analysis was performed to identify significant predictors of

Table 1: Sociodemographic profile of the Filipino respondents (n = 407)

Variables	n	%
Age		
<30 years	200	49.1
30–45 years	152	37.3
>45 years	55	13.5
Gender		
Male	176	43.2
Female	231	56.8
Religion		
Non-Christian	33	8.1
Christianity	374	91.9
Education		
Primary	15	3.7
Secondary	43	10.6
Tertiary	349	85.7
Employment status		
Students	79	19.4
Unemployed	54	13.3
Employed	274	67.3
Monthly family income		
<Php 19,040	151	37.1
Php 19,041–66,640	211	88.9
>Php 66,641	45	11.1
Region		
Luzon	130	31.9
Visayas	120	29.5
Mindanao	157	38.6
Occupation		
Non-health care	358	88.0
Health care	49	12.0

distress on a two-level scale with model building through backward elimination. This downgrade from a three-level to two-level scale was due to the violation of the proportional odds assumption when ordinal logistic regression was used to identify significant predictors of distress on a three-level scale. Binomial logistic regression was preferred to multinomial logistic regression for the ease of interpretation.

Results

There were 407 Filipino survey participants with an average age of 32.0 years; almost half of them aged below 30 years (49.1%). Most respondents were female (56.8%), Christian (91.9%), degree holders (85.7%), non-health care workers (88.0%), and employed (67.3%) with monthly incomes within Php 19,041–Php 66,640 (88.9%). The majority of the respondents were living in Mindanao (38.6%), the South Philippines (Table 1).

Most of the respondents did not feel distressed about COVID-19 (52.1%), whereas 39.5% and 8.4% experienced mild-to-moderate and severe distress, respectively (Figure 1). Table 2 summarizes the prevalence of distress severity based on socioeconomic and demographic characteristics among Filipino respondents.

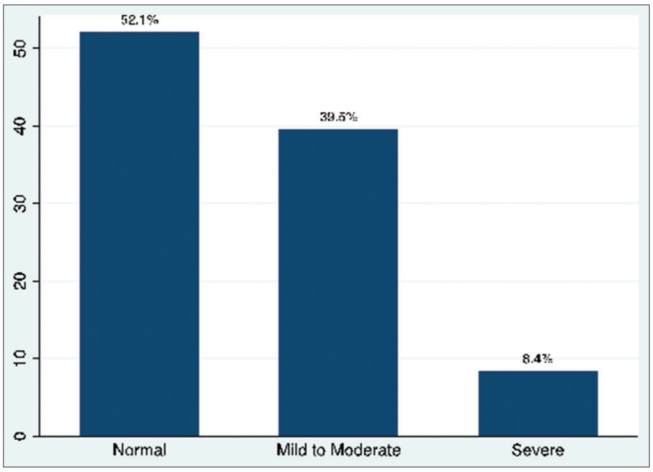

Figure 1: Prevalence of psychological distress due to COVID-19 among Filipino respondents (n = 407)

The key factors involved in distress among Filipino respondents due to COVID-19 included religion, education, and the region of residence (Table 3). Higher religion and faithfulness levels led to a decrease in the odds of being distressed by 50%. On the other hand, the status of completed secondary and tertiary education increased the odds of being distressed by 21% and 27%, respectively, compared to those who only finished primary education. Finally, respondents living in the Visayas showed greater odds of being distressed by 48% compared to those living in Luzon. Participants living in Mindanao indicated lower odds of being distressed by 14% compared to those living in Luzon.

Table 2: Prevalence of CPDI by socioeconomic and demographic characteristics among Filipino respondents (n = 407)

Variables	Normal or no distress n (%)	Mild-to-moderate distress n (%)	Severe distress n (%)
Age			
<30 years	104 (52.0)	83 (41.5)	13 (6.5)
30–45 years	80 (52.6)	65 (42.8)	7 (4.6)
>45 years	28 (50.9)	13 (23.6)	14 (25.5)
Sex			
Male	80 (45.5)	84 (47.7)	12 (6.8)
Female	132 (57.2)	77 (33.3)	22 (9.5)
Religion			
Non-Christian	12 (36.4)	16 (48.5)	5 (15.1)
Christianity	200 (53.4)	145 (38.8)	29 (7.8)
Education			
Primary	5 (60.0)	5 (13.3)	5 (26.7)
Secondary	14 (32.6)	21 (48.8)	8 (18.6)
Tertiary	189 (54.2)	138 (39.5)	22 (6.3)
Employment status			
Students	43 (54.4)	28 (35.4)	8 (10.2)
Unemployed	29 (53.7)	15 (27.8)	10 (18.5)
Employed	140 (51.1)	118 (43.1)	16 (5.8)
Monthly family income			
<PHP 19,040	82 (55.0)	47 (31.6)	20 (13.4)
Php 19,041–66,640	110 (51.7)	94 (44.1)	9 (4.2)
>Php 66,640	20 (44.4)	20 (44.4)	5 (11.2)
Region			
Luzon	84 (64.6)	38 (29.2)	8 (6.2)
Visayas	28 (23.3)	77(64.2)	15 (12.5)
Mindanao	100 (63.7)	46 (29.3)	11 (7.0)
Occupation			
Non-health care	184 (51.4)	144 (40.2)	30 (8.4)
Health care	28 (57.1)	17 (34.7)	4 (8.2)

CPDI: Coronavirus disease-19 Peritraumatic Distress Index.

Discussion

Although the majority of Filipino respondents did not experience distress induced by the current situation of the COVID-19 pandemic, several participants showed mild-to-moderate and severe distress, which may be due to a lot of factors. Among the different socioeconomic and demographic factors investigated in this study, religion, education, and region of residence were recognized as the significant predictors of distress due to COVID-19.

Religious participants were less likely to be distressed due to their strong faith in God. Most researches have indicated that a strong faith correlates with diminished depression [11], [12], [13], anxiety [14], and suicidal ideation [15], [16] as well as elevated self-esteem and overall well-being. Research has indicated that during a health crisis, many individuals turn to their religion for emotional comfort, strength, and hope. Spiritual beliefs and practices can provide a sense of meaning and purpose when facing negative health circumstances largely beyond one's control [17], [18]. The majority of the Philippines' population is Christian (90%), with 80% Roman Catholic and approximately 5% are Muslims [19].

The participants with at least the secondary level of education showed increased odds of distress compared to those with a lower educational level. This might be because people with higher educational

Table 3: Predictors of psychological distress for COVID-19 among Filipino respondents (n = 407)

Factors	Univariable analysis				Multivariable analysis			p-value
	OR	95% CI		p-value	Adj. OR	95% CI		
		Lower	Upper			Lower	Upper	
Age								
<30 years	reference							
30–45 years	0.98	0.64	1.49	0.906				
>45 years	1.04	0.58	1.9	0.886				
Sex								
Male	Reference							
Female	0.63	0.42	0.93	0.020				
Religion								
Non-Christian	Reference							
Christian	0.5	0.24	1.04	0.063	0.38	0.17	0.83	0.016
Education								
Primary	Reference							
Secondary	3.11	0.92	10.46	0.067	3.17	0.85	11.78	0.085
Tertiary	1.27	0.44	3.64	0.657	1.21	0.38	3.82	0.742
Employment status								
Students	Reference							
Unemployed	1.03	0.51	2.06	0.934				
Employed	1.14	0.69	1.89	0.601				
Monthly family income								
<Php 19,040	Reference							
Php 19,041–66,640	1.15	0.75	1.74	0.525				
>Php 66,640	1.53	0.78	2.99	0.214				
Region								
Luzon	Reference							
Visayas	6	3.44	10.45	<0.001	5.48	3.12	9.62	<0.001
Mindanao	1.04	0.64	1.69	0.871	0.86	0.52	1.43	0.559
Occupation								
Non-health care	Reference							
Health care	0.79	0.43	1.45	0.451				

attainment might be capable of comprehending the situation that they were experiencing in the pandemic. Furthermore, higher educational attainment is strongly associated with better mental health [20]. As further, higher levels of education are thought to generate additional economic resources, fewer chronic stressors, healthier lifestyles, more social support, and, ultimately, better mental health [21].

The Philippines is an archipelago of 7641 islands with three major islands: Luzon, Visayas, and Mindanao. Those living in the Visayas have shown greater odds of distress compared to those living in Luzon, which may be explained by relatively high fatality rate of COVID-19 (2.2%) in Central Visayas [22]. A paper in Iran [23] highlighted the role of unpredictability, uncertainty, seriousness of the disease, misinformation, and social isolation in stress and mental morbidity. Moreover, the welfare provision role of local to national government necessarily contributes to overcoming the COVID-19 pandemic [24]. Besides, Shigemura *et al*. [25] emphasized the economic impact of COVID-19 and its effects on well-being, as well as the possible high levels of fear and panic-related defensive behaviors such as hoarding and stockpiling of resources in the general population. It also identified populations at higher risk of adverse mental health outcomes, that is, patients with COVID-19 and their families, individuals with existing physical or psychiatric morbidity, and health care workers.

Limitations of the study

Although the participants were recruited from different regions of the Philippines, the respondents in this quantitative sample did not represent their regions of residence. Therefore, readers should be mindful that the findings of this study cannot be generalized to the entire archipelagic regions in the Philippines. Indicators used in the study are limited only to the factors associated with psychological distress during the COVID-19 pandemic crisis through the CPDI questionnaire. Future studies can employ qualitative methods to extend the current study.

Conclusions

This study aimed to examine factors associated with psychological distress among Filipinos during COVID-19 pandemic. The results revealed that demonstrated that more than half (52.1%) of Filipino respondents did not suffer psychological distress due to the COVID-19 pandemic. Among affected participants, 39.5% had moderate distress, and only 8.4% experienced severe distress. Having a strong faith and living in Mindanao led to lower odds of being distressed. Filipinos with higher education levels and those living in the Visayas showed higher odds of being distressed. Relevant mental health intervention policies must be directed to these groups to decrease the current mental health burden in Filipino society.

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Authors' Contributions

RRM conceived and designed the study. RRM and EMF performed validation and reliability of the questionnaire. RRM, EQV, EMF, and AMB collected the data. EQV conducted the statistical analysis and interpretation of the findings. RRM, EQV, EMF, and AMB wrote the final manuscript. All authors read and approved the final version of this manuscript.

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A Review on Novel Coronavirus Outbreak: Current Scenario of Bangladesh

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Abstract

Coronavirus disease (COVID)-19 outbreak was the first time experienced in Wuhan City, China, at the end of December 2019 which spreads rapidly in China and then worldwide approximately all countries of America, Europe, Australia, and Asia including Bangladesh. There are more than 1,039,135 mortalities and 35,207,771 people have been affected globally until October 4, 2020, and the figure is still increasing. The global information on the COVID-19 case was collected from a reliable database (worldometers.info) and domestic information was taken from the government circulating websites and analyzed. Different steps have been taken to control the COVID-19 worldwide. Even with few resources, Bangladesh also has taken rigorous measures such as designed special hospitals, laboratories, quarantine facilities, social distance awareness campaigns, and lockdown to control the spreading of the virus. As Bangladesh is an overpopulated country and vast population lives under the poverty line, it was difficult to maintain a strict lockdown to curb the COVID-19. In this study, we have focused the government efforts to combat this deadly pneumonia and presented recent situations and challenges of Bangladesh. We compiled general treatments, COVID-19 specific treatments, and antiviral treatments should be prescribed in fighting COVID-19. We suggest certain nutritional elements and natural products which can boost up the immunity of individuals and protect from the infection of this virus. The review was undertaken to synopsis the recent conditions, challenges of Bangladesh arise after the COVID-19 pandemic and summarize certain possible intervention options for management of COVID-19.

Introduction

Coronaviruses (CoVs) fits the subfamily Orthocoronavirinae, in the family of *Coronaviridae*, and the order of Nidovirales. There are four categories of CoV; alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV [1]. Mainly, CoVs cause enzootic infections in mammals and birds. In the past periods, they have shown their competence in infecting humans [2]. At present, a novel flu-like CoV (severe acute respiratory syndrome [SARS] -CoV-2) is related to the Middle East respiratory syndrome (MERS) and SARS that outbursts in 2002 and 2012, respectively, was found at the end of 2019 in Wuhan, Hubei Province of China [3], [4]. This CoV had >95% homology with bat CoV and >70% similarity with SARS-CoV [3]. Compared with SARS and MERS, this virus is highly infective and transmissible despite a low mortality rate [5]. Human-to-human transmission of this virus is confirmed [6]. It is important that though the number of new cases was comparatively condensing in China, exponentially increased in other countries such as Italy, Spain, America, South Korea, and Iran. Bangladesh had reported only 368,690 cases until October 4, 2020. Among them, 5348 patients have already died. Until October 4, 2020, around 35,207,771 cases of CoV and 1,039,135 deaths have been reported in all over the world. Providentially, children have been intermittently pretentious with no deaths. The upcoming course of this virus is still unknown. In this review, we have tried to figure out a clear observation of Bangladesh's cause of the CoV Disease (COVID)-19 pandemic. This includes monthly cases of COVID-19 infections around the county, mortalities, health service facilities, and lacking. We discuss the burdens which Bangladesh faces now such as economical and educational pressures. Finally, certain potential intervention options are discussed in Bangladesh perspective which might be beneficial for the world against COVID-19. The objectives of this review are to summarize the present condition, challenges, and focus on potential medication, including both modern treatments and traditional home therapies to control CoV.

Genetic Structure of SARS-COV-2

CoV encircled single-stranded positive-sense RNA viruses with a diameter of 60 nm–140 nm, which containing spike-like projections on its surface that giving it a crown-like presence under the electron microscope. For this reason, its name is CoV [7]. They have a typical genome structure that belongs to the cluster of beta-CoVs. It is more than 82% identical to SARS-CoV [4], [8]. The SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) of the host cell, as a receptor-like SARS-CoV [9]. In general, this type of CoV recognizes the target cell's equivalent receptor through the S-protein on its surface and enters into the cell for instigating the infection [8]. Wrapp *et al*. also showed by a structural model analysis that SARS-CoV-2 binds with ACE2 with the affinity above 10 folds higher than SARS-CoV [10]. COVID-19 is high in occurrence, and the population is generally susceptible to SARS-Cov-2, which spread rapidly from a single Wuhan city to the entire country within 3 days [8]. Infection of this virus occurs not only through large droplets formed from coughing and sneezing by symptomatic patients but also from asymptomatic people [11]. These droplets spread 1–2 m easily and can remain attached on surfaces. In advantageous conditions, the virus can remain live on surfaces for days but can be destroyed in less than one minute using disinfectants such as hydrogen peroxide, sodium hypochlorite, and so on [12]. Other human infection is assimilated either by inhalation of these droplets or touching the surfaces contaminated by them. The virus is also present in the patient's stool and can pollute the water supply through aerosolization [3].

COVID-19 Pathophysiology

The genome of SARS-COV-2 is similar to a previously identified CoV strain that caused the SARS outbreak in 2003 [13]. Structurally, the SARS CoV has a well-defined composition comprising of 14 binding residues that directly interact with the human ACE2 receptor. Among these amino acids, 8 are conserved in SARS-CoV-2 [14]. Although the precision pathophysiological mechanisms of SARS-CoV-2 are unknown, genomic similarities to SARS-CoV may assist to elucidate the resulting inflammatory response that could lead to the onset of severe pneumonia [14]. Until the laboratory trials initiated, the precise mechanism of SARS-CoV-2 remains hypothetical. All types of CoVs contain specific genes in ORF1 downstream regions that are responsible for encoding proteins for viral replication, nucleocapsid, and formation of spikes [15]. The glycoprotein spikes situated on the outer surface of CoVs are responsible for the attachment and entry of the virus to host cells (Figure 1). The receptor-binding domain (RBD) remain attached loosely among virus, so that, the virus may infect many hosts [16]. SARS-CoV-2 possesses the typical CoV structure with spike protein and also expressed other membrane proteins, polyproteins, and nucleoproteins [17]. The spike protein of SARS-CoV-2 comprises a 3-D structure in the RBD region for maintaining the Van der Waals forces [18]. The 394 glutamine residue in the RBD region of SARS-CoV-2 can recognize by the critical lysine 31 residue on the ACE2 receptor [19]. The description of the entire pathogenicity mechanism of SARS-CoV-2 from attachment to replication is in Figure 1. ACE2 is a membrane-bound aminopeptidase that has an important contribution to the immune system and cardiovascular. ACE2, a receptor, engages in heart function and the development of diabetes mellitus and hypertension. ACE2 can be a functional receptor not only for SARS-CoV but also for SARS-CoV-2 [20]. SARS-CoV-2 infection is activated by binding the virus's spike protein to ACE2, which is highly articulated in the lungs and heart [20]. SARS-CoV-2 mainly attacks alveolar epithelial cells, which outcomes in respiratory symptoms. Weather, ACE2 is an efficient receptor for SARS-CoV-2, the well-being and potential effects of anti-hypertension therapy with ACE inhibitors or angiotensin-receptor blockers in patients with COVID-19 should deliberate prudently. If patients with COVID-19 and hypertension are taking an ACE2 inhibitor or angiotensin-receptor blocker can be an antihypertensive drug. Patients with COVID-19 are showing high cardiovascular symptoms. ACE2 is extensively expressed not only in the lungs but also in the cardiovascular system. Therefore, ACE2-related signaling pathways might also have a role in heart injury.

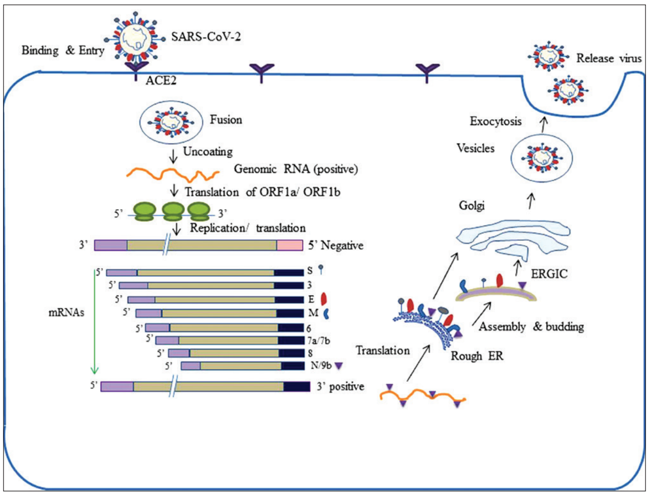

Figure 1: An outline of the life cycle of SARS-CoV-2 in the host cell; the life cycle of the virus starts when S protein attaches with cellular angiotensin-converting enzyme 2 (ACE2). After the ACE2 receptor binding, there happens a structural modification in the S protein which enables the viral envelope fusion with the cell membrane through a route called the endosomal pathway. Then, SARS-CoV-2 releases RNA into the host cell. Genomic RNA is translated into viral replicase polyproteins pp1a and 1ab, which are then cleaved into small products. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Viral proteins and RNA are subsequently accumulated into virions in the Endoplasmic Reticulum and Golgi and then transported through vesicles and released out of the cell (ACE2: Angiotensin-converting enzyme 2; ER: Endoplasmic reticulum; ERGIC: ER-Golgi intermediate compartment)

Current Situation in Bangladesh

The first patient of COVID-19 identified in the country on 8th March. According to the Health Ministry of Bangladesh, there are almost 368,690 positive cases in the country and 5348 people have died until October 4, 2020. The highest cases appeared in the Dhaka Division (142,741) followed by Chattogram (47,473), Khulna (21,936), Rajshahi (20,158), Sylhet (12,685), Rangpur (12,083), Barishal (8399), and Mymensingh (6471) have been confirmed (Figure 2). A total of 281,656 infected people have been recovered in Bangladesh to date. The mortality rate in Bangladesh is 1.45% and the recovery rate is 76.39% [21]. After identifying the first patient of COVID-19 in Bangladesh on 8th March, it is being dangerous day by day. Not only total cases but also total death number is increasing every day. Every month, the total cases and death rates became more than double until June and then slightly declined (Figure 3) [22].

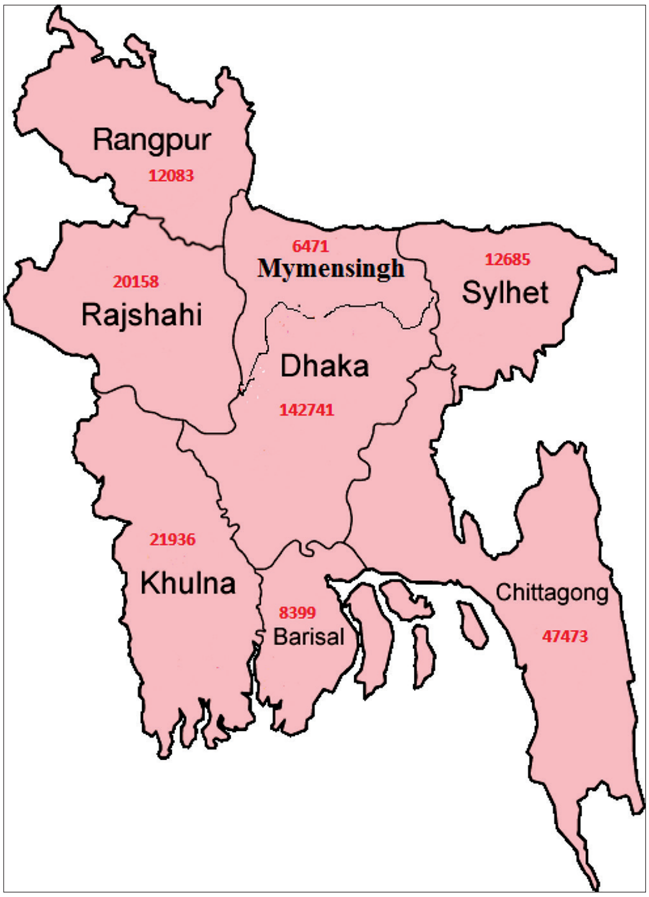

Figure 2: Division-wise COVID-19 cases in Bangladesh

Bangladesh is a dense population country with inadequate resources. The testing or diagnostic facility is limited in Bangladesh. The pandemic has proven to be a big challenge in Bangladesh, as the infectious nature of the virus can rapidly infect a large number of people in any given time or place. Many poor people in Bangladesh are living in different slams; they use a single toilet and bathroom for a large number of people. As CoV is so contagious, so if any person from a slum will be corona

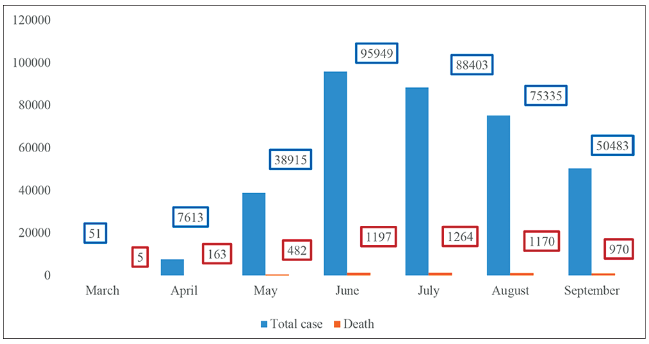

Figure 3: Monthly-wise COVID-19 outbreak in Bangladesh

positive, it will be so dangerous for that slum [23]. There has a large number (836,000) of Rohingya population residing in different camps [24]. Because of the fast infectious nature of the virus, the infection in one of the camps can be disastrous. Bangladesh is currently suffering from the availability of not only the testing kits but also testing labs that are essential for the detection of the virus. It is difficult to have social isolation in the densely packed camps, where several people are residing in a small space and have to rely on the collective effort for their collective survival. Any form of mass infection can be alarming for the rest of the countries.

In Bangladesh, millions of dollars' worth of readymade garments products of many international apparel brands had withdrawn their buying orders from a huge number of companies. It has created a knock-on effect on the Bangladeshi economy. For this reason, many small companies are already closed, and many people became unemployed and their livelihood condition is becoming worsen. The top companies are not recruiting now and reducing their employees. If this situation would run for more time, those people may involve in various crimes and it will be another challenge for the whole country.

Like most of the countries, Bangladesh also closed their educational institutes for more than 7 months to control the COVID-19. This is why nearly 40 million students are now out of institutions. This condition will continue until the epidemic returns to a normal stage [25]. The government is trying to use online or satellite television platforms to deliver education during the pandemic, but it is not enough to meet the complementary levels. Since the price of internet packages is higher, and almost 90% of students do not have any large-screen devices which can help them more in online education. Approximately 75% of people were affected by the decrement of family earnings during the lockdown and also worried about the job of their family members [25]. Many peoples are becoming jobless; most of their monthly payments are decreasing. During the COVID-19, many private companies are giving <50% payment [26]. As a result, the ability to buy nutritious food for their family is declining day by day, which affects their children in various malnutrition diseases. As family income has been decreased, some of the students are forcing to join multiple risky jobs such as construction, garment-sector, driving bus, auto-rickshaw, and many more. Parents are forcing their girls to marry at an early age [25]. However, there are several non-government organizations that provide free food and necessary things to street children for education. Due to the COVID-19 outbreak, their educational activities have been postponed that may affect their mental development and future growth. Dropped-out students can be involved in any illegal and criminal activities [27].

Facilitation by the Government of Bangladesh against COVID-19

The Government of Bangladesh has taken all necessary measures against the virus, to provide and ensure the responsibilities of the country. Since the 1st day when the first case was confirmed by IEDCR, Dhaka, all the services and measures were used with the extreme capabilities to ensure the safety of life in the region. The government affords COVID-19 extenuation strategies with their measures such as early case detection, tracing and tracking of contacts, social distancing, risk communication, quarantine, and isolation to avoid the spreading of COVID-19 [28]. The Government of Bangladesh has announced several packages to address the impact of CoV. Our prime minister announced several packages for supporting not only the various private export-oriented companies but also for the agricultural sectors so that after this outbreak, the country can overcome the situation as soon as possible. She declared a BDT 5000 crore (emergency) incentive package for paying the salaries and allowances of export-oriented industries' workers and employees [28]. Relief is also ongoing for poor and middle-income people. The test center is also increased with time. Now testing is done in every division of the country. Even though our government is trying so hard to control the outbreak, general people are unwilling to follow the lockdown. Law enforcer agencies are working on maintaining the lockdown properly.

Hospitals for COVID-19 in Bangladesh

Being a populated country, Bangladesh is doing arrangements to fight against the COVID-19. Lots of measures have been taken by the government of Bangladesh to control the outbreak. Many hospitals are working in this scenario, to bring back life and fight against the deadly outbreak of COVID-19 in the country. In the capital territory of Dhaka, there were 12 functional hospitals. In every division, at least one hospital is reserved for COVID-19 patients.

Isolation Beds Facilities for COVID-19 in Bangladesh

Isolation centers are the separation of ill or infected persons from others for preventing the spread of infection. The hospitals use isolation centers for COVID-19 people to keep them safely care and provide a healthy environment to stay mentally and physically strong. According to the Directorate General of Health Services (DGHS), there are 7693 isolation beds in Bangladesh. Among them, 29% is in the Dhaka division, 11% Chattogram, 9% in Khulna, 4% in Sylhet, 15% Rajshahi, 7% in Barishal, and 13% Mymensingh [29]. ICU is not so available in a developing country like Bangladesh. Although there are 190 ICU beds in Bangladesh, and this is not sufficient for a huge country's people (Figure 4) [21].

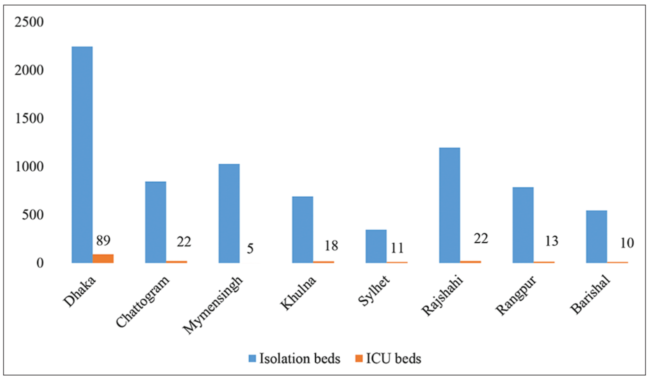

Figure 4: Division-wise isolation facilities in Bangladesh

Division-wise Quarantine Facilities for COVID-19 in Bangladesh

The quarantines, being considered to restrain people's activities who are not sick now but might have been contacted to an infectious agent, such as, COVID-19 with the purpose of monitoring symptoms. The spaces use for quarantine of COVID-19 suspected people was widely distributed in divisions. Until September 2020, 344,660 individuals were kept in home quarantine all over the country; out of them 48% (47,812) have been already safe and released [21]. At present, the number of people in home quarantine has been decreasing and the decrease rate of almost 60%.

Testing and Diagnostic Facilities in Bangladesh

Globally, PCR is used for the COVID-19 test, which is the gold standard method. Bangladesh's government also recommends the PCR test for COVID-19 diagnosis. At present, a total of 109 labs are conducting CoV tests, 63 are located in the capital Dhaka city, and other 46 labs are situated in the different district outside Dhaka [28]. Samples are collected from the test seekers of these districts are being sent and tested at the facilities lab in nearby districts or in Dhaka [30]. People also can give samples by contacting the lab authorities. In Bangladesh, currently, no rapid testing method is government approved, for example, antigen-antibody testing method. The maximum testing number was around 20,000 samples each day in June month and this is inadequate for an overpopulated (160 million) country. Clinicians and experts suggest vigorous testing for mass-people. Since the outbreak, the country has tested nearly 1,989,664 CoV samples [31]. Government assures that new testing labs will be set up soon across the country with expert opinion.

Social Distancing Maintaining is Tough in Many Areas of Bangladesh

In starting, Bangladesh could not execute any strict restriction, and thousands of people were out on the roads, particularly in Dhaka, which is a megacity having 46 thousand people per square kilometer [32]. It seems that social distancing is really tough while taking public travel and living in the purlieus. In the context of enormously populated and lower-middle-income countries like Bangladesh, the implementation of social distancing which is recommended by the WHO seems to sound fancy but unreasonable. Over 1.1 million purlieu dwellers are living in the capital of Bangladesh, Dhaka [33]. Most children and parents have never gone to school and are living in an extremely close environment, scarcely aware of the threat from CoV. The household income of slum dwellers in Dhaka is around $100 per month and they use more than 70% of their incomes on food and housing [34]. Even a small pack (400-mL) hand soap, which costs around BDT 80 Taka, is hard for them to buy. Besides, every 10–16 families have access to only a single bathroom and toilet, where there is lacking water supply and poor hygienic conditions [34], [35]. Along with slum dwellers, there are over one million Rohingya refugees are living in Bangladesh, most of them are living in close quarters in refugee camps where the sanitization facilities are not so good [36]. Fear of COVID-19 is already gearing up among those people in these camps. Instantaneous implementation of social distancing is practically impossible in a populated country like Bangladesh.

Clinical Characteristics of Sars-Cov-2 Infection

COVID-19 makes an acute viral infection in humans within 3 days incubation period [37]. The presenting features of COVID-19 prominent in adults. The clinical features of infection are varied, ranging from an asymptomatic to acute respiratory distress syndrome (ARDS). Sometimes it also shows multi-organ dysfunction [3]. Fever (87.9%), cough (67.7%), and fatigue (38.1%), whereas diarrhea (3.7%) and rarely vomiting (5.0%) are the most common indication of this virus infection [38]. Sometimes patients also experience headaches, myalgia, sore throat, and breathlessness [3]. Most patients had some degree of dyspnea because the onset time of symptoms to the development of ARDS was only 29% [39]. Hence, severe heart damage and secondary infection might happen for patients [40]. There are already some pieces of indication that COVID-19 also can cause damage to other tissues and organs instead of the lung. In a study, researchers reported that 36.4% of COVID-19 patients had neurological manifestations [41]. Furthermore, there are already some indications of ocular surface infection in patients with COVID-19 and SARS-CoV-2 [42]. Some COVID-19 patients have arrhythmia, acute heart injury, impaired renal function, and abnormal liver function (50.7%). A case report of the pathological manifestations of a patient with pneumonia showed modest microvesicular steatosis in liver tissue [43]. Normally the radiographical features of COVID-19 were similar to community-acquired pneumonia caused by other organisms [44]. A recent study stated that most of the patients (90%) had bilateral chest computed tomography (CT) findings. The compassion of chest CT suggests that COVID-19 was 97% combining clinical symptoms and laboratory tests with chest CT imaging features could expedite the early diagnosis of COVID-19 pneumonia. Laboratory examination revealed that 82.1% of patients were lymphopenia and 36.2% of patients were thrombocytopenia. Most of the patients had normal leukocytes, but leukopenia observed in 33.7% of patients [8]. Most of the COVID-19 patients confirmed dominant levels of C-reactive protein, creatinine kinase, and lactate dehydrogenase. The minority of patients showed abnormal myocardial enzyme spectrum, higher transaminase, or elevated serum creatinine [8]. In addition, lower levels of CD4+T and CD8+T, higher levels of interleukin (IL)-6 and IL-10, were present in COVID-19 patients [45].

Potential Treatment of SARS-COV-2

Antiviral Western medicine treatment

At present, COVID-19 patient's treatments are mainly symptomatic. It has been reported that *Remdesivi*r, an antiviral drug, can be used as a potential agent against a wide array of RNA viruses. Holshue *et al*. got decent results for the first time using *Remdesivir* against COVID-19 [46]. Meanwhile, analysts likewise found that *Chloroquine* contains a safe regulating action on COVID-19 patients, which can viably hinder this infection [8]. Clinical preliminaries likewise demonstrated that *Chloroquine* ends up being working for COVID-19 patients [47]. A small indole derivative molecule (Arbidol) found to block viral fusion against influenza A, B, and hepatitis C viruses [48] and also *inveterate* having an antiviral effect on SARS-CoV in cell experiment [49], so it might be a choice for COVID-19 treatment. Apart from the above, neuraminidase inhibitors, *remdesivir, lopinavir/ritonavir,* nucleoside analogs, and peptide EK1 could also be the choices of antiviral drugs against COVID-19 [50]. *Baricitinib* might decrease the process of both virus invasion and inflammation. It can be a potential treatment against COVID-19 [7].

Chinese medicine treatment

Chinese medicines are also being used for the treatment of SARS-CoV-2 infection. Numerous traditional Chinese medicine prescriptions are also published by local governments and medicinal institutions. Novel CoV, pneumonia, diagnosis, and treatment plan encouraged clearing lung and detoxification decoction in the clinical treatment [8]. CAS found that Shuanghuanglian oral liquid can inhibit SARS-CoV-2. Previous studies have proved that chlorogenic acid, baicalin, and forsythin in Shuanghuanglian oral liquid have definite inhibitory effects on a variety of viruses and bacteria [51]. These components played a therapeutic role by reducing the inflammatory response of the body. Lianhuaqingwen capsule has been proven to have a wide-spectrum effect on a series of influenza viruses, including H7N9, and could regulate the immune response of the virus [52].

Immunoenhancement therapy

Synthetic recombinant interferon α has proven to be an active treatment in clinical trials for the SARS virus [53]. Interferon is an effective inhibitor of the replication of MERS-CoV [54]. These findings suggested that we can use interferon for treating COVID-19 patients. Moreover, Thymosin alpha-1 (Ta1) can be a promoter for an immune system of SARS patients, meritoriously controlling the spread of COVID-19 disease [55]. Immunoglobulin, intravenous, and Ta1 may also be considered as therapeutics for COVID-19 disease.

Convalescent plasma therapy

Convalescent plasma therapy is a promising treatment that could be an effective way to assuage the course of disease for severely infected patients when no specific drugs and vaccines are sufficient [56]. It is more effective than severe doses of hormonal shock in patients with severe SARS, reducing mortality, and shortening days to stay hospital [57]. From the immunology perspective, most of the patients who recovered from COVID-19 would produce specific antibodies against the SARS-CoV-2 in their blood and serum. Those antibodies can be used to prevent reinfection. At the same time, those types of antibodies can limit the reproduction of the virus in the acute phase of infection and help to clear the virus, which is satisfactory to the rapid recovery of the disease.

Auxiliary blood purification treatment

According to the latest study, the main target to attack for novel CoV could be the kidney [58]. Most of the severe patients who are positive with novel CoV might agonize from a cytokine storm. Damage of the immune system can occur not only by the imbalance of pro-inflammatory but also by anti-inflammatory factors. Therefore, blood purification technology can be used for eliminating inflammatory factors, removing cytokine storm, adjusting electrolyte imbalance, and maintaining acid-base balance [59]. In summary, the drug treatment for COVID-19, mainly founded on four types of antiviral Western medicine, Chinese medicine, immunoenhancement therapy, and viral-specific plasma globulin.

Nutritional interventions

As no exact treatment is available for this virus, there needs an urgent alternative method to improve our immune system. Some vitamins can protect us from this virus by improving body immunity. Vitamin A could be a promising option not only for the treatment of CoV but also for the prevention of lung infection. Vitamin A and retinoid can block measles duplication, which is an up-regulating element of the innate immune response, making them rebellious to fruitful infection during subsequent rounds of viral replication [60]. Vitamin B plays an indispensable role in the body's immune function. Hence, it should be complemented to the virus-infected patients for improving their immune system [4]. Vitamin C also augments immune functions and guards against CoV [61]. A few analysts suggested that Vitamin C may hold the weakness of the infection of the lower respiratory tract under specific circumstances [62]. The COVID-19 essentially causes contamination in the lower respiratory tract, so we can say Vitamin C could be one of the effective treatments for COVID-19. Vitamin D likewise invigorates the advancement of insusceptible cells [4]. Vitamin D could fill in as another helpful open door for treating the novel virus. Studies found that long-chain PUFAs are significant intermediaries of adaptive immune responses and inflammation [63]. Therefore, Omega-3, including protectin D1, served as a novel antiviral drug that could be painstaking for one of the probable interventions of this virus. In addition, the combination of zinc at low concentrations and pyrithione can inhibit the replication of SARS-CoV [64].

Antiviral role of natural products and their compounds

Right now, exact treatments are accessible for COVID-19 yet, explicit immunizations or medications are not in the markets, and even though trials are ongoing 65]. There is developing proof of the antiviral capability of herbal compounds and medicinal plant extracts [66]. These compounds are bioactive elements and show antiviral properties, efficacy standards, and safety in various reports. Modern pharmacologists already revealed different pharmacological bioactive compounds. Curcumin is the bioactive ingredient of turmeric, which is the best example of phytochemicals with a multi-functional mode of action [67], [68], [69]. In trials, curcumin shows a positive effect, and it can change the structure of the surface protein in viruses, hindering the entry of virus and their replication. Besides, curcumin affects membrane proteins by modulating the characteristics of the host lipid bilayer [70]. In molecular docking, it was proved that curcumin can bind to the target receptors, including SARS-CoV-2 protease, spike glycoprotein-RBD, and PD-ACE2 [71]. Onion and garlic are common sources that are known to have antiviral properties [72]. Notably, onion and garlic are rich homes of organosulfur compounds. Organosulfur compounds such as quercetin and allicin are associated with shame of viral disease [73]. Phytochemicals present in these plants have been functional to obstruct the development of protein and hereditary material in the infection [74], [75], [76]. Onion contains quercetin and kaempferol as main flavanols. These compounds have been found to affect the growth of many viruses [77]. Experiments have proved that garlic extract can minimize influenza A and B viral infections and strong inhibitory effects against the multiplication of the Infectious Bronchitis Virus (IBV), which affect the poultry industry [78], [79]. Similarly, ginger is a common spice and a widely used medicinal plant.

Ginger contains an important antiviral source of compound [80]. Neem (*Azadirachta indica*) is a medicinal plant and its parts such as leaves, seeds, flowers, barks, and routes are widely using in various diseases. Methanolic extract of neem leaves exhibited antiviral activity against herpes simplex virus (HSV) type 1 infections by inhibiting HSV-1 glycoprotein mediated viral fusion [81]. Nimbolide is an active constituent of the Neem tree explored as a pharmacological modulator in treating various diseases. Tumor necrosis factor (TNF)-α is a pleiotropic cytokine involved in the activation of different signaling cascades and this cytokine might be playing a role in respiratory failure associated with COVID-19 mediated pneumonia. Nimbolide is found to be a TNF-α inhibitor and also suppresses the nuclear translocation of p65 NF-κB and HDAC-3 and inhibited the cytokine storm observed in ARDS experimental model [82]. Thus, it might show beneficial effects in SARS-CoV-2 infections by direct antiviral activity or indirect supportive therapy by controlling the inflammatory cytokine storm. This natural product may have clinical significance in inflammation associated with viral diseases. The other natural product Withaferin A is isolated from Ashwagandha (*Withania somnifera*) and widely used to treat various diseases like COVID 19. It has shown the antiviral activity against HSV-1 and 2, which may show plausible effects against COVID-19 [83].

CRISPR-Cas technique

Genome editing (CRISPR) could use for the treatment of this CoV, but this technique can only edit or target DNA [84]. Whether a new RNA-targeting CRISPR systems design is possible, it will be conceivable to treat this virus. In an outstanding new resource for the scientific community published in Nature Biotechnology, researchers in the lab at the New York Genome Center and New York University have developed a new kind of CRISPR screen technology to target RNA. They categorized the CRISPR enzyme named Cas13 that can targets RNA instead of DNA [85].

Potential Treatment in Bangladesh

Although the vaccine is the ultimate solution for COVID-19 management, it is not possible to get on time. Drug repurposing has become a promising approach for reducing the timelines of new drug development, cost, and making the treatment strategy easy [86]. At the initial stage of covid-19 infection and before starting community transmission in the country, Bangladesh government has given the approval to use certain potential antiviral drugs in fighting the CoV. These drugs are remdesivir [46], [87] and favipiravir [88] which have efficacy against viruses. Anti-parasitic medicine named ivermectin was also trialed on COVID-19 patients between 40 and 65 years olds. Bangladesh-based International Centre for Diarrhoeal Disease Research (ICCDR’B) has conducted the safety and efficacy of anti-parasitic medicine ivermectin in combination with antibiotic doxycycline or ivermectin alone. They found that initially the combination showed efficacy and cured all the COVID-19 patients who were administered with the drugs [89]. Hydroxychloroquine is a debatable drug for CoV and was trialed on COVID-19 patients. An observational study that was trialed in Bangladesh showed a combination of hydroxychloroquine and antibiotic azithromycin can reduce the mortality rate. The patients were given standard of care and administration of hydroxychloroquine and azithromycin. According to this finding, out of a total of 33 patients, 1 patient died at days 4 after admission, and the rest patients recovered [90].

Conventional or traditional home remedies are also playing a vital role alongside modern treatment to combat this virus and boosting the immunity of patients. Natural products such as spices in Bangladesh such as ginger, garlic, onion, clove contain phytochemicals, and bioactive compounds have antiviral activity against many viruses. Garlic, turmeric, ginger, cinnamon, black pepper, and honey were reported to be used in Pakistan as home remedies against COVID-19 [91]. Leaf extract of holy basil, black cumin seeds, juice of lemon, and sliced rhizomes of ginger was supplemented with slightly hot water to COVID-19 patients and found a positive effect [92] in Bangladesh. Holy basil is very popular as a medicinal plant and the antiviral activity of this plant has been reviewed [93]. Lemon contains Vitamin-C and enhances body immunity. Although *Citrus limon* was reportedly showed antiviral activity against different viruses, this food item should be taken to boost up immune system [94]. Tea is a popular hot drink in Bangladesh and East Asia. About 65 biomolecules of tea plants have been evaluated by bioinformatics tools (molecular docking) for their binding affinities to the main protease (Mpro) of the SARS-CoV-2 virus, which is considered the main target for the development of antiviral drugs [95]. Drinking tea alone or together with spices may protect from COVID-19 by improving defense mechanism. In this case, natural products and their home remedies could be an alternative option indirectly to improve immunity and protection from CoV in Bangladesh and worldwide.

Conclusion and Future Prospects

The current scenario of Bangladesh is not satisfactory because daily cases are more than a thousand still now. Bangladesh is a much-populated country that requires more facilitation. Bangladesh is a lower-middle-income country where the financial position is not better as compared to China, the USA, UK, and Russia to combat with COVID-19 outbreak. The number of quarantine and hospital facilities is not fulfilling as required. If these medical facilities can be improved, it would not be difficult to control the transmission of CoVs and the treatment of patients. At present, the testing facilities are much lower than the required target. The testing facilities could augment by 5-10 folds. Bangladesh needs more screening facilities for the arrivals as well as for the departures.

We should take the right steps to control the situation worst such as staying at homes as much as possible, maintain lockdown and social distancing, use sanitizers, facemask, and PPE when necessary. Moreover, people should uptake Vitamin-C and dietary supplements to increase immunity boosting. We hope that Bangladesh will overtake the COVID-19.

Authors' Contributions

Both authors equally contributed to this work.

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Community Preventive Measures Related to Coronavirus Disease-19 among Iraqi Population

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Abstract

BACKGROUND: Coronavirus (CoV) disease (COVID)-19 outbreak is considering as a health disaster which threatens the world right now because of its higher infectivity and unavailability of definite vaccine or treatment. The only effective strategies are a commitment to prevention and quarantine of the diseased people to decrease the transmission and spreading.

AIM: The objective of the study was to assess the preventive measures adopted by the Iraqi population to protect themselves from acquiring severe acute respiratory syndrome-CoV-2 infection in correlation with their age, sex, educational level, and occupation.

METHODS: A total of 619 volunteers were involved in this online cross-sectional study, all of them answered a semi-structured questionnaire including 14 questions regarding the preventive practices. The questionnaire was distributed into three general and mixed Facebook groups during the period from April 18 to 28. Data analyzed by SPSS version 23 using frequency tables and descriptive statistics for numerical continuous age variable, t-test, and ANOVA were used for mean differences in the preventive scores.

RESULTS: The sociodemographic features of participants were showed that 81.3% were women and 91.9% had college or higher education. The majority (75.6%) were <30 years old and 42.5% governmentally employed.

The mean preventive practice score mentioned by them was 2.60 ± 0.28 with the highest three scores was for stay away from infected and sick people, avoid crowded places, and avoid travel and commuting. A significant difference was found in the practice score according to age, gender, and occupation ($p < 0.001$).

CONCLUSIONS: Iraqi people mentioned that they always adhere to the health instructions related to COVID-19 prevention as suggested by the government, health workers, and organizations. Male, students, and people younger than 30 years are less frequently followed the main preventive measures.

Introduction

Coronavirus (CoV) disease (COVID-19) is a new highly contagious disease distinct from other diseases caused by CoVs, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome. The virus is characterized by a rapid spread rate and outbreaks can grow at an exponential rate. Till now, there are no drugs or vaccines established to cure or prevent COVID-19. According to data collected from the early affected countries in the pandemic, about 40% of cases had mild disease, 40% experienced moderate disease including pneumonia, 15% of cases experienced severe disease, and only 5% of cases had a critical disease [1].

At the end of 2019, the COVID-19 first discovered in Wuhan, China, then it had spread to 200 countries so the World Health Organization (WHO) announced it as a global pandemic [2].

This virus is transmitted through saliva or nasal secretions when an infected person sneezes or coughs [3]. Most patients have symptoms such as fever with mild-to-moderate respiratory illness as sore throat, cough, and dyspnea [4]. Serious illness is more likely to develop in an older age group and those with underlying comorbidities [5].

All suspected cases should be tested and the confirmed cases must promptly and effectively have isolated with receiving appropriate management. The close contacts are rapidly identified so can be quarantined and medically monitored for the 14 days' viral incubation period, this will lead to stopping and reduce the rate of infection spread [1].

The best available way to limit the spread of the virus is the limitation of community activities among people through the application of governmental instructions [6] and the two most important nationwide social measures are social distancing and self-isolation with the lockdown [7].

Hence, the prevention of the disease is only the grand solution until discovering an effective treatment or vaccine against COVID-19 [8]. The WHO submits the most efficient preventive measures such as maintaining physical distance (minimum 3 ft or 1 m) from other persons; cleaning of the hands immediately after contact with the respiratory tract; averting frequently touching face; regular cleaning and disinfection of environmental and other frequently touched surfaces; improve living room airflow by opening as possible as many windows and doors; and if a person develops fever, cough, and dyspnea so then must seek immediate treatment [9], [10], [11].

People's commitment to control measures is very important and necessary which is affected predominantly by their knowledge, attitude, and practice (KAP) to COVID-19 in association with KAP theory [12], [13].

In this study, we focused on investigating the extent to which Iraqi people implement and adhere to the preventive measures in correlation with their age, sex, educational level, and occupation.

Methods

This is an online cross-sectional study conducted on a convenient sample of the Iraqi population. A semi-structured questionnaire was prepared by the authors using information regarding the preventive precautions that must be done by individuals in the community announced by the WHO and mentioned by the government. Using the equation [$n = Z^2P(1–P)/d^2$] for calculation of sample size and considering 50% of the population practicing the preventive measures against COVID-19 (as to the best of our knowledge, there is no previous study that demonstrates the practices toward COVID-19 among the Iraqi population), 95% confidence interval, 5% marginal error (d), and 15% non-response rate. The minimum number for the sample required is 443.

After the questionnaire was pretested on five people, it was spread to the population by the internet, mainly Facebook groups to be answered by them. This questionnaire consisted of introductory information about the aim of the study, sociodemographic data, and questions related to their practice in the past 2 weeks regarding COVID-19 infection. All these questions have to be answered according to the Likert scale (always, sometimes, and never/rarely).

The questionnaire was disseminated electronically for 10 days (from April 18 to 28) for three general mixed Facebook groups. The questionnaire consisted of two parts: The first part includes demographic data such as age, gender, educational level, and occupation while the second part consisted of measures taken by peoples to prevent infection with CoV.

Data were analyzed by SPSS version 23 using a frequency table for categorical variables and descriptive statistics for numerical continuous age variable. The three levels of the Likert scale were considered as ordinal numeric data and coded by 3, 2, and 1 for always, sometimes, and never, respectively, and the mean score was calculated for each item (mean score 1–1.66 explained as never or rarely, 1.67–2.33 for sometimes, and 2.34–3 for always) [14]. Both frequencies and descriptive statistics were used to explain the community responses regarding COVID-19 prevention. Differences between the mean scores of practices with sociodemographic features were performed by independent t-test and one-way ANOVA test where requested.

Ethical approval was obtained from the ethical committee of the College of Medicine at Wasit University. All participants were formally consented to voluntarily participate in the study at the beginning of the questionnaire then clicked for "continue" to complete answering questions related to the study. They also informed about keeping their data confidential.

Results

The results of this study were based on the response of 619 participants who agreed to be involved in the study. The sample mean age was 27.34 ± 6.9 years old, the younger participants were 15 years while 57 years old was considered the maximum age.

Table 1 shows the frequency distribution of the sociodemographic features of the respondents. Females represented 81.3% of the whole sample, the majority of participants (91.9%) were had college educational level or higher education with more than one-third of them (38.8%) were still students. The highest percentage of participants was from Baghdad (24%), Waist (20%), and Babylon (10%).

Table 2 shows the best five preventive measures followed by the respondent were stay away from infected and sick people, avoid crowded places, avoid travel and commuting, cover your nose and mouth when sneezing or coughing, and avoid leave home unless necessary. The lowest rank was for keep a distance of more than 6 ft from others.

The first preventive measure was stay away from infected and sick people with a mean practice score of 2.89 and SD (0.39) and about 91.9% of the sample doing this always while the last preventive measure is keep a distance of more than 6 ft from others with mean score 2.43 and SD (0.67), near half 52.8% of people in this study always keep a safe distance from others. Furthermore, the results of this study found that the mean (standard deviation) of general precautions score among all participants was equal to 2.60 (0.28).

Table 3 shows that there was a significant mean difference in the practice score according to gender, age, and occupation ($p > 0.001$), whereas there was no significant mean difference according to educational attainment (p = 0.119). The highest scores of practicing preventive measures were recorded from females, participants above 30 years old, and retired people.

Table 1: Frequency distribution of sociodemographic features of the respondents

Variables	Frequency	Percentage
Gender		
Female	503	81.3
Male	116	18.7
Educational level		
Illiterate, read and write, primary	8	1.3
Intermediate and secondary	42	6.8
College or higher education	569	91.9
Occupation		
Self-employer	29	4.7
Student	240	38.8
Unemployed	83	13.4
Retired	4	0.6
Governmental employee	263	42.5
Age groups		
≤30	468	75.6
More than 30	151	24.4
Participated Iraqi provinces		
Erbil	8	1.3
Al Anbar	8	1.3
Al-Qadisiyah	15	2.4
AL-Muthana	11	1.7
Najaf	32	5.2
Babylon	62	10.0
Basra	17	2.7
Baghdad	194	24
Duhok	10	1.6
Diyala	23	3.7
Saladin	4	.6
Karbala	20	3.2
Kirkuk	15	2.4
Nineveh	28	4.5
Maysan	10	1.6
Dhi Qar	36	5.8
Wasit	126	20.3

Discussion

As COVID-19 has no approved treatment or vaccine yet [15], thus prevention is the current strategy to battle against it. This study aimed to assess the preventive measures adopted by the Iraqi population to protect themselves from acquiring SARS-CoV-2 infection.

To the best of our knowledge, this study is the first descriptive study that investigates the preventive measures toward COVID-19 among Iraqi residents. In this well-educated and predominantly females sample, it was found that the mean ± standard deviation of general precautions score was 2.60 ± 0.28, indicating that responders always followed the main precautions of health authorities. Most responders (91.9%) staying away from infected and sick people, 88% of them avoiding crowded places, and 88.4% of them avoiding travel and commuting. However, other important measures had been reported in lower frequency such as cleaning and disinfecting of frequently exposed surfaces (57.5%), get a healthy diet (55.7%), avoiding touch the eyes, nose, and mouth with unwashed hands (54.9%), keeping a distance of more than 6 feet from others (52.8%), get enough sleeping time, rest (53.8%), and a suitable amount of fluid (50.6%).

Compared with measures taken to prevent SARS-CoV-2 infection by Chinese residents [16], we found a lower frequency of wearing a mask in public (63.7% vs. 99.4%), washing hands frequently with soap and water (62.7% vs. 86.7%), and staying at home (80.9% vs. 95.7%).

The current result of lower frequency of wearing a mask in a public could be explained by different factors including norms of Iraqi society about wearing of face mask, scarcity of face masks, and other personal protective equipment in Iraq and all over the world due to increase request with the emergence of COVID-19 [17], [18]. Another online survey conducted to determine perceptions among residents in the United Kingdom (UK) and United State (US) [19] found that a total of 86.0% of the UK participants and 92.6% of

Table 2: Community preventive measures regarding COVID-19 in a sample of Iraqi populations

Variables	n (%)	Always	Some times	Never or rarely	Mean	Std. deviation	Ranks
Get a healthy diet	n	345	244	30	2.51	0.58	8
	%	55.7	39.4	4.8			
Get enough sleeping time and rest	n	333	226	60	2.44	0.66	12
	%	53.8	36.5	9.7			
Get a suitable amount of fluids	n	313	267	39	2.44	0.61	12
	%	50.6	34.1	6.3			
Avoid crowded places	n	545	51	23	2.84	0.45	2
	%	88	8.2	3.7			
Avoid travel and commuting	n	547	39	33	2.83	0.49	3
	%	88.4	6.3	5.3			
Avoid leaving home unless necessary	n	501	94	24	2.77	0.50	5
	%	80.9	15.2	3.9			
Keep a distance of more than six feet from others	n	327	229	63	2.43	0.67	13
	%	52.8	37	10.2			
Stay away from infected and sick people	n	569	32	18	2.89	0.39	1
	%	91.9	5.2	2.9			
Repeat hand washing with soap and water for 20 s	n	388	192	39	2.56	0.61	6
	%	62.7	31	6.3			
Use sterilizers containing alcohol to sterilize hands and materials	n	359	191	69	2.47	0.68	10
	%	58	30.9	11.1			
Cleaning and disinfection of frequently exposed surfaces	n	356	204	59	2.48	0.66	9
	%	57.5	33	9.5			
Avoid touching the eyes, nose, and mouth with unwashed hands	n	340	220	59	2.45	0.66	11
	%	54.9	35.5	9.5			
Wearing a mask when present with others	n	394	152	73	2.52	0.69	7
	%	63.7	24.6	11.8			
Cover your nose and mouth when sneezing or coughing	n	506	100	13	2.80	0.45	4
	%	81.7	16.2	2.1			

COVID: Coronavirus disease.

Table 3: Association between people’s sociodemographic features and the practice score mean

Variables	n	Mean	Standard deviation	p-value
Gender				
Male	116	2.48	0.32	>0.001*
Female	503	2.62	0.26	
Age category				
≤30	468	2.57	0.27	>0.001*
More than 30	151	2.68	0.29	
Occupation				
Student	240	2.54	0.29	>0.001**
Self-employer	29	2.59	0.21	
Governmental employee	263	2.66	0.25	
Retired	4	2.75	0.04	
Unemployed	83	2.56	0.33	
Educational levels				
Read and write, primary	8	2.65	0.38	0.119**
Intermediate and secondary	42	2.51	0.32	
College and higher education	569	2.60	0.27	

*Independent sample t-test. **One-way ANOVA test.

the US participants adhere to three effective measures for preventing infection with SARS-CoV-2 including avoiding close contact with sick people; washing hands; and avoiding touching eyes, nose, and mouth with unwashed hands, our participants less frequently adhere to these measures although they were avoiding contact with sick people in a higher percentage (91.9%).

In this study, nearly 22% of participants did not avoid crowded places, whereas in China, only 3.6% of participants went to crowded places [20], this discrepancy in findings could be attributed to poor knowledge about the SAR-CoV-2 virus and its high infectivity, which can be easily transmitted through by respiratory droplets. This is also could be due to the difference in the control measures implemented by local governments such as public gatherings and banning. Although banning was applied in different Iraqi governorates for weeks before the time of this study, most of the people did not obey these mandates and still gathering in different places such as in markets and weddings. This indicates the need for proper knowledge about COVID-19, regarding its risk, mode of transmission, and prevention, thereby personal conviction would be responsible for adherence with main preventive measures.

Regarding age, gender, and occupation differences in the practicing of main preventive measures toward COVID-19, this study found that males, younger participants (<than 30 years), and students had a significantly a lower mean of preventive score than females, older participants (>30 years), and other occupations, respectively ($p < 0.001$), which is in congruence with the previous studies [16], [20]. These findings could be ascribed by younger age, and males are more likely to engage in risky behaviors as suggested by previous researchers [21], [22]. Meanwhile, the significantly lower mean score of preventive practices among students could be attributed to their younger age.

Higher educational attainment was found to be significantly associated with higher knowledge and improved practice toward COVID-19 [20]. In contrast, the present findings demonstrated a non-significant association between level of education and adherence to the preventive measures against novel CoV ($p > 0.05$), current result could be justified by characteristics of the studied sample where the vast majority (91.9%) of the participants were well educated, and hence, a significant association was not determined.

The current study had some limitations. First, the sample was convenient, which is unrepresentative to the general population. Besides, the sample of this research is over a representative of higher educated, younger than 30 years’ people, and females, which does not represent the demographic of the Iraqi population [23]. This limits the generalization of the results. Second, this study was not investigated the public knowledge about COVID-19 and its associated commitment with principles of prevention. This is to avoid lengthening the questionnaire which leads to boredom and reluctance to the response [24]. The strategies are investigated in this study represent the main preventive measures as recommended by health authorities, health workers, and government. Third, the participants are possibly reporting a socially suitable response, they may have answered questions with always undertaking preventive strategies as they recognize to be expected from them. However, this study questionnaire was distributed throughout different groups on Facebook, it included large sample size, from different Iraqi cities, during the early stage of the COVID-19 epidemic in Iraq. Furthermore, internet-based surveys are regarded as the most suitable method for data collection during communicable diseases like COVID-19 as it prevents disease transmission during direct surveys.

Conclusions

The results of this study demonstrated that the participants always followed the main preventive strategies toward COVID-19 as suggested by the government, health workers, and organizations. Males, students, and people younger than 30 years are less frequently followed the main preventive measures. Health education programs are recommended to improve COVID-19 knowledge and maintain a safe practice of targeted population specifically males, young, and students. As the sample is unrepresentative to the population, more studies are required to investigate the practice related to novel CoV among Iraqi residents of low educational attainment.

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Coronavirus Disease-19 Quarantine Experience in the Middle East Region: Emotional Status, Health Patterns, and Self-efficacy Survey

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Abstract

BACKGROUND: The coronavirus disease (COVID)-19 pandemic can provoke anxiety, stress, sadness, and fear; therefore, the timely assessment of individual psychological health status is urgently necessary for society.

AIM: The aim of the study was to assess the emotional states (depression, anxiety, and stress), functional health patterns, and self-efficacy among individuals from Egypt, Jordan, and Saudi Arabia during the home quarantine experience associated with COVID-19.

METHODS: A descriptive and cross-sectional research design was applied to a convenience sample that included 704 participants from Egypt, Jordan, and Saudi Arabia. Data collection was performed in April 2020, using a self-administered questionnaire that consisted of a sociodemographic data sheet, the Depression, Anxiety, Stress Scale (DASS), a functional health pattern survey, and the General Self-Efficacy Scale (GSES).

RESULTS: Overall, the sample was found to have mild-level DASS scores, with significantly higher scores identified for Egyptian participants compared with those from other countries. In contrast, participants from Egypt presented significantly reduced GSES scores than those from other countries. Higher mean DASS scores were identified among females, participants who reported inappropriate housing conditions and participants who were unemployed, young, widowed, and school-educated. A high mean DASS score was significantly associated with reported disturbances in sleep, sexuality, and social communication, work schedule changes, the inability to concentrate on positive thoughts, the inability to empty their brains of daily thoughts, and not caring about regular interactions with family. Increased mean GSES scores were significantly associated with males, participants who reported appropriate housing conditions, participants who live alone, are older, married, hold higher education degrees, and who are employed with sufficient incomes, whereas lower mean GSES scores were significantly associated with participants who reported engaging in regular exercise, experiencing disturbances in sexuality and social communications, and reduced appetites. However, a significant inverse correlation was detected between the mean DASS and GSES scores, with significant positive correlations among the DASS.

CONCLUSION: The COVID-19 quarantine was associated with a mild level of depression stress and normal anxiety levels, with higher psychological distress and lower self-efficacy identified among participants from Egypt. The emotional status of individuals during the COVID-19 pandemic should be explored further, and awareness programs, designed to address the psychological effects of quarantine, should be promoted, through mass media and other means, with consideration of the effects on the general population, COVID-19 cases, individuals with close contacts with COVID-19 cases, and health-care professionals.

Introduction

Quarantine refers to the separation and restriction of movement of individuals who have been exposed to a contagious disease, to confirm whether they have been infected and reduce the chance that they will infect others [1]. Quarantine differs from isolation, which is the separation of individuals who have been diagnosed with contagious and infectious diseases from individuals who are not sick; however, the two phrases are frequently used interchangeably, particularly in the public discourse. In just a few months, the upward trajectory of coronavirus infections has closed schools, offices, stores, and factories. Airplanes have been grounded and borders have been closed to travelers. Modern quarantine consists of a variety of disease prevention strategies that can be used individually or in combination, including a temporary, voluntary home curfew, the minimization and prevention of group meetings, the cancellation of public events, the closure of mass transit systems, and the implementation of other restrictions on international and cross-country travel [2].

Functional health patterns can be described as the ability to perform daily living activities. Gordon's functional health patterns supply a holistic model for the evaluation of families, with functional assessments classified under the following eleven headings: Health perception, nutrition, elimination, exercise, perceptual pattern, sleep, self-concept pattern, relationship pattern, sexuality, coping, and health belief pattern [3].

Various research has shown that human behavioral changes, such as reducing social contacts during outbreaks, can have considerable effects on disease spread [4]. This social distancing response can be especially beneficial during the early stages of an epidemic, when pharmaceutical interventions, such as antiviral medications and vaccinations, may not yet be conveniently available. Social distancing can also be enforced centrally, through the closure of faculties and offices and the cancellation of events, or emerge naturally, due to individual actions [5].

Recently, quarantine was instituted during the coronavirus disease 2019 (COVID-19) pandemic outbreak. During this outbreak, entire cities in China were effectively placed under mass quarantine restrictions and thousands of expatriated nationals who have returned home from China have been requested to self-isolate, either at home or in government-run facilities [6], [7], [8]. Many precedents exist for such measures, including the citywide quarantines that were imposed in areas of China and Canada during the 2003 outbreak of severe acute respiratory syndrome (SARS), and whole villages in many West African nations were quarantined during the 2014 Ebola outbreak, as reported by the Public Health England organization [6], [8].

The COVID-19 pandemic is both an epidemiological and psychological crisis. The current state of affairs can provoke anxiety, stress, sadness, and fear; therefore, the timely assessment of individual psychological health status is urgently necessary for society [9]. Previous studies have revealed profound and various psychosocial impacts on people, at the individual, community, and worldwide levels during infection outbreaks. On the individual level, people are likely to experience worry regarding sickness and death, experience internal feelings of helplessness, and stigma. During one influenza outbreak, approximately 10–30% of the general public were very or fairly concerned about the possibility of contracting the viral disease [10]. With the closure of faculties and business, the negative thoughts experienced by most individuals can be compounded [11].

Widespread outbreaks of infectious diseases, such as COVID-19, are generally associated with increased psychological stress. In addition to feelings of unpredictability and uncertainty, the seriousness of the disease, misinformation, and social isolation can contribute to stress and psychological sickness [12]. Another study revealed substantial concerns regarding the impacts of social isolation and social distancing on general well-being, and social isolation has been associated with increased anxiety, depression, stress, loneliness, self-harm, suicide attempts, and many other negative emotions. In addition, pandemic responses are also associated with financial difficulties, which can increase stress responses [13].

According to Bandura [14], self-efficacy plays a key role in the regulation of emotional states. Self-efficacy beliefs facilitate the interpretation of potentially threatening expectations as manageable but considerable challenges, which allows individuals to experience reduced feelings of burden and stress during difficult situations. By decreasing the negative thoughts and worries associated with potential threats, individuals with self-efficacy can regulate and control their emotional states more effectively. In addition, various studies have identified a relationship between poor mental and psychiatric well-being and general self-efficacy, as individuals' beliefs in their own capabilities can affect their experiences of stress and despair [15], [16].

Many studies have validated the finding that self-efficacy is an independent predictor of mental health. Inverse relationships exist between self-efficacy and depression, stress, and emotional coping strategies [17], [18]. Other studies have shown that low self-efficacy expectations are correlated with the increased use of emotion-focused coping strategies, such as denial and self-criticism, which are associated with the signs and symptoms of despair, stress, psychosomatic disorders, and poor well-being. Moreover, self-efficacy has considerable consequences for essential aspects of personality and situation-specific behaviors that are associated with wellness (e.g., coping with stress and conflict resolution) and is regarded as an element that can protect an individual's health, lowering their risks of biological and psychological diseases [19], [20].

Significance of the study

Local and international health emergencies associated with the COVID-19 pandemic are likely to have negative impacts on the physical and psychological health of the population, increasing the incidence of psychological crises [9]. Crisis managers rely on public compliance during self-quarantine efforts. Officials often have limited abilities to implement and monitor these measures; hence, the public health benefits of household quarantine can only be achieved if the public cooperates.

Current research priorities include the monitoring and reporting of emotional status issues, such as depression, anxiety, and stress, both to recognize the mechanisms that drive these negative emotions and to identify necessary corrective interventions. Identifying functional health pattern changes that occur among the public during home quarantine is an important task that can reflect the general public health status and uncover susceptibility to some chronic diseases, such as diabetes, hypertension, and coronary heart disease. Functional health pattern assessments should be adopted throughout the general population, especially among vulnerable groups, including front-line healthcare workers. The assessment of emotional status, functional health pattern issues, and self-efficacy during the home quarantine experience associated with COVID-19 is, therefore, necessary. We will perform such an assessment on a large sample of the population, utilizing a comparative study design, to examine accessible countries in the Middle East region, including Egypt, Jordan, and Saudi Arabia. Saudi Arabia is a country in Western Asia that constitutes the bulk of the Arabian Peninsula, with a population of 34 million, as reported in 2019 [21]. Jordan is an Arab country in Western Asia, on the East Bank of the Jordan River, with a population of more than 10 million, as reported in 2020 [22]. However, Egypt is a transcontinental country that spans the northeast corner of Africa and the southwest corner of Asia, through a land bridge formed by the Sinai Peninsula, with over 100 million inhabitants, as reported in 2020 [23]. All three countries are located in the Middle East region.

Methods

Design and setting

A descriptive, cross-sectional, and comparative research design study was conducted, simultaneously, in Egypt, Jordan, and Saudi Arabia, during the COVID-19 pandemic outbreak. These three countries were selected due to the convenience, accessibility, and availability of researchers in these countries.

Study sample

A convenience sample of the general populations of Egypt (198 participants), Jordan (148 participants), and Saudi Arabia (358 participants) were recruited. The sample size was calculated according to the proportionate populations of the three countries, at a 99% level of confidence, with 5% confidence limits, 50% anticipated frequency, and a design effect value of 1.0. Using the Open-Epi, V3 software package, the required sample size was determined to be 664 subjects, which was increased to 704 subjects to assure the achievement of the targeted confidence level.

Data collection tools

The researcher used a self-administered questionnaire form, which included scales to assess the emotional status and general self-efficacy, in addition to the personal characteristics of the study participants, including age, gender, marital status, work, monthly income, current living status, housing conditions, number of people living in the same dwelling, level of education, chronic illnesses, and the recurrence of infection. The questionnaire also included questions regarding changes in functional health patterns associated with home quarantine, such as smoking, exercise, appetite, body weight, sleep and sexuality, communication, job schedule, family meetings, and thinking and belief patterns, which were derived from the 11 functional health pattern categories [3].

The Depression Anxiety Stress Scales 21 (DASS-21) was utilized to assess the emotional status of individuals [24]. The whole questionnaire consisted of three reliable, 7-item scales, which utilized 4-point Likert scales to measure the extent to which each state has been experienced over the past week (0 = did not apply to me at all; 3 = applied to me very much or most of the time). Scores were calculated as described by a previous study, with questions 3, 5, 10, 13, 16, 17, and 21 forming the depression subscale, questions 2, 4, 7, 9, 15, 19, and 20 forming the anxiety subscale, and questions 1, 6, 8, 11, 12, 14, and 18 forming the stress subscale [25]. The mean score for each subscale was calculated (0-3), and the levels of depression, anxiety, and stress were determined based on the mean (normal: <0.6; mild: 0.6 ≤ 1.2; moderate: 1.2 ≤ 1.8; severe: 1.8 ≤ 2.4; and extremely severe: 2.4–3). The DASS-21 subscale reliability was tested repeatedly, using Cronbach's alpha, which revealed acceptable levels of subscale reliability (depression =0.83, anxiety =0.78, and stress =0.87) [26], [27]. The DASS-21 form and permission for use are available online [28]; however, we adopted the Arabic version of the DASS-21, with no modifications [29].

The General Self-Efficacy Scale (GSES), established by Schwarzer and Jerusalem [30], was adopted to assess the self-efficacy of participants with regards to COVID-19, in the current study. The GSES was adapted to investigate perceptions of personal competence, based on ten items that participants respond to using a four-point Likert format, ranging from "1 = Not true about me" to "4 = Totally true about me" [31]. The Cronbach's alpha value for GSES was 0.87 when including responses for all 10 items from the pilot study. The self-efficacy levels of participants were defined according to the total GSES score (low = 10–19, moderate = 20–30, and high = 31–40). The Arabic version of the GSES and permission for use is publicly available online, as provided by the original authors [32].

Pilot study

A pilot study was performed prior to the main study, to determine the clarity of the scales and the feasibility of the study. The pilot study was conducted on 10% of the calculated study sample to test the applicability of the data collection tool and the feasibility of the study. Based on the pilot study results, the average time necessary to respond to the tool, including all three scales, ranged from 15 to 20 min, depending on the respondent's level of understanding and cooperation. Based on the pilot study results, the questionnaire was finalized. Since some modifications were made to the phrasing of some items included in the sociodemographic and functional health pattern assessments, the pilot subjects were not included in the main study sample. The pilot study was also used to assess the reliability of the scales used.

Study procedure

Similar to other countries around the world, the governments of Egypt, Jordan, and Saudi Arabia recommended the minimization of face-to-face interactions and asked the public to isolate themselves at home. Potential respondents for piloting and study were, therefore, electronically invited, through the researchers' social networks, friends, and colleagues. Data were collected using an electronic survey that took approximately 15–20 min to complete. The online questionnaire was designed using Google Forms and was sent to participants through various social media platforms (WhatsApp, Messenger, Facebook, and Imo application). The data handling procedures followed all required national data protection standards. The study did not include any deception, and participants were debriefed at the end of the survey. The study only collected non-personally identifiable data. Data collection occurred over 10 days (11 April–20 April 2020), after the World Health Organization (WHO) declared the COVID-19 outbreak to be a public health emergency of international concern. The duration of data collection was determined based on the time required to gather a sufficient number of responses to meet the predetermined sample size.

Statistical analysis

Data retrieved from Google Forms were collected, revised, and coded using a personal computer. Statistical analysis was performed using the Statistical Package for Social Sciences, version 26. Data are presented using descriptive statistics, as the mean and standard deviation or number and percentage. The mean and standard deviation were used for continuous variables, whereas number and percentages were used for categorical variables. The Shapiro–Wilk test indicated that the data were not normally distributed; therefore, the Kruskal–Wallis test was used to compare the mean DASS and GSES scores across all three countries. The Mann–Whitney U test was used to identify significant differences in the mean DASS and GSES scores between two countries and to compare dichotomous sociodemographic and functional health pattern variables, such as gender, employment, smoking, sexual pattern changes, and others. The Mann–Whitney U test and the Kruskal–Wallis test are nonparametric tests that can be used to compare mean ranks values but cannot be used to compare medians or distributions. A Pearson's correlation coefficient test was used to examine correlations among the DASS subscales and between the DASS and GSES scores. Multiple linear regression analysis was used to determine whether the DASS subscales were independent predictors of GSES scores and to formulate a predictive linear equation.

Ethical considerations

The research proposal was submitted to the ethical committee at Al-Ghad International Colleges for Applied Medical Sciences in Saudi Arabia and was approved before commencing data collection. Participation in this study was completely voluntary, and participants did not receive any form of coercion or financial compensation. Participants were asked to read and approve the included informed consent form before answering the questionnaire. Before participating in this study, subjects were informed regarding the purpose and type of study, the researchers' contact information and affiliations, and their rights to refuse or withdraw at any time. Potential breaches of confidentiality were minimized by the use of survey identification numbers; however, no identifying information, including names, email addresses, or mobile numbers were requested from the participants, and their responses were completely anonymous. No harm or risk, except for discomfort or inconvenience, was expected as a result of completing the questionnaire, and participants were given the option of choosing "I'd prefer not to answer this question" when they decide to avoid responding to some embarrassing or inconvenient questions in the sociodemographic part of the survey. All ethical principles regarding medical research involving human subjects, in accordance with the Declaration of Helsinki, were followed [33]. In addition, official permission for the use of the DASS and GSES scales was granted by the original authors [24], [30].

Results

The results of the current study are summarized in twelve tables (Tables 1–12), which describe the main findings. Table 1, for example, describes the sociodemographic information for the sample, which revealed that slightly more than one-third of the study sample across all three countries (Jordan, Egypt, and Saudi Arabia) were aged between 30 and 39 years, with a mean age of 35.32 ± 9.8 years (n = 704). Approximately two-thirds of all participants were male, married, and employed (60%, 70%, and 73%, respectively). In contrast, approximately half of the sample holds a bachelor's degree and has a medium family size, ranging from 4 to 6 members (50% and 53%, respectively). Most participants lived with their families and earn a sufficient monthly family income (86% and 82%, respectively) and reported living in appropriate housing conditions, with sufficient ventilation and lighting (94%). Finally, 16.8% of the sample indicated that they have chronic diseases, with a higher percentage of participants from Saudi Arabia reporting the occurrence of hypertension, diabetes, and psychiatric illnesses (7.8%, 5.6%, and 3.4%, respectively), compared to those in Jordan and Egypt,

Table 1: Sociodemographic characteristics (n = 704)

Sociodemographics	Place of residence							
	Jordan (n = 148)		Egypt (n = 198)		Saudi Arabia (n = 358)		Total (n = 704)	
	n	%	n	%	n	%	n	%
Age categories								
24 years or younger	6	4	36	18	58	16	100	14
25–29 years	20	14	20	10	62	17	102	14
30–34 years	32	22	38	19	60	17	130	18
35–39 years	24	16	42	21	68	19	134	19
40–44 years	22	14	32	16	54	15	108	15
45–49 years	24	16	16	9	28	8	68	11
50 and older	20	14	14	7	28	8	62	9
Mean ± SD (years)	38.45 ± 9.09		34.4 ± 10.0		34.54 ± 9.83		35.32 ± 9.85	
Gender								
Female	54	36	80	40	150	42	284	40
Male	94	64	118	60	208	58	420	60
Marital status								
Divorced	4	3	8	4	10	3	22	3
Married	112	76	148	75	236	66	496	70
Single	30	20	38	19	110	30	178	26
Widow	2	1	4	2	2	1	8	1
Current living status								
Living alone	14	9	16	8	68	19	98	14
Living within a family	134	91	182	92	290	81	606	86
Housing conditions, in terms of sufficient ventilation and lighting								
Appropriate	142	96	186	94	332	93	660	94
Inappropriate	6	4	12	6	26	7	44	6
Household size (number of people)								
Small (3 or less)	40	27	30	15	118	33	188	27
Medium (4–6)	86	58	140	71	148	42	374	53
Large (7–9)	22	15	20	10	62	17	104	15
Too large (10 or more)	0	0	8	4	30	8	38	5
Employment								
Employed	116	78	120	61	280	78	516	73
Unemployed	32	22	78	39	78	22	188	27
Monthly family income								
Sufficient	118	80	142	72	320	89	580	82
Insufficient	30	20	56	28	38	11	124	18
Educational level								
Bachelor's degree	54	36	92	46	208	58	354	50
Diploma	32	22	60	30	16	4	108	15
Postgraduate studies	42	28	28	14	106	30	176	25
School	20	14	18	10	28	8	66	10
Has chronic diseases	24	16.2	28	14.1	66	18.4	118	16.8
Has diabetes mellitus	8	5.4	10	5.1	20	5.6	38	5.4
Has hypertension	10	6.8	14	7.1	28	7.8	52	7.4
Has coronary artery disease or atherosclerosis	6	4.10	8	4.00	12	3.30	26	3.70
Has psychiatric illness	2	1.4	6	3.0	12	3.4	20	2.8
Has Recurrent infections	12	8.1	6	3.0	18	5.0	36	5.1

N = Sample size; n = frequency; % = percent; SD = Standard deviation

Table 2: Functional health patterns (n = 704)

Functional health patterns	Place of residence							
	Jordan (n = 148)		Egypt (n = 198)		Saudi Arabia (n = 358)		Total (n = 704)	
	n	%	n	%	n	%	n	%
Regular exercise								
No	112	75.7	164	82.8	232	64.8	508	72.2
Yes	36	24.3	34	17.2	126	35.2	196	27.8
Smoke tobacco regularly								
No	92	62.2	162	81.8	292	81.6	546	77.6
Yes	56	37.8	36	18.2	66	18.4	158	22.4
Appetite pattern								
High	36	24.3	34	17.2	64	17.9	134	19.0
Low	6	4.1	24	12.1	34	9.5	64	9.1
Usual	106	71.6	140	70.7	260	72.6	506	71.9
Body weight								
Normal	80	54.1	92	46.5	184	51.4	356	50.5
Overweight	60	40.5	92	46.5	156	43.6	308	43.8
Underweight	8	5.4	14	7	18	5.0	40	5.7
Suffer from sleeping disturbance due to quarantine?	72	48.6	126	63.6	180	50.3	378	53.7
Suffer from sexuality disturbance due to quarantine?	36	24.3	56	28.3	64	17.9	156	22.2
Suffer from social communication disturbances due to quarantine?	80	54.1	140	70.7	184	51.4	404	57.4
Experienced changes in the nature or time schedule of your current job due to quarantine?	102	68.9	174	87.9	294	82.1	570	81.0
Concentrate on positive thoughts during difficulties?	116	78.4	108	54.5	282	78.8	506	71.9
Empty the brain of thoughts regarding tomorrow's schedule at bedtime?	94	63.5	64	32.3	196	54.7	354	50.3
Care about meeting and communicating with your family on a daily basis?	110	74.3	140	70.7	276	77.1	526	74.7

N = Sample size; n = frequency; % = percentage.

whereas any infection recurrence was reported more frequently in Jordan (8.1%) and Saudi Arabia (5%) than in Egypt (3%).

Table 2 shows the functional health patterns, demonstrating that the majority of the study sample does not engage in regular exercise, does not smoke, and has a normal appetite pattern (72.2%, 77.6%, and 71.9%, respectively). Half of the participants have normal body weights (50.6%), whereas slightly more than two-fifths (43.8%) reported being overweight. Slightly more than half of the sample reported sleep and social communication disturbances associated with quarantine (53.7% and 57.4%, respectively). Approximately 49.7% of participants reported difficulty emptying their brains of thoughts at bedtime. In addition, 81% of the study sample reported recent changes in the nature or time

Table 3: Difference in the mean depression, anxiety, stress, and DASS scores among the three countries (n = 704)

DASS & Subscales	Jordan (n = 148)	Egypt (n = 198)	Saudi Arabia (n = 358)	Total (n = 704)	Total level	Mean rank			Kruskal–Wallis test	Sig. (2-tailed)
	M ± SD	M ± SD	M ± SD	M ± SD		Jordan	Egypt	KSA	Chi-Square	
Depression	0.57 ± 0.47	0.84 ± 0.65	0.63 ± 0.60	0.68 ± 0.60	Mild	325.45	405.21	334.53	18.9	0.000**
Anxiety	0.32 ± 0.40	0.56 ± 0.58	0.42 ± 0.55	0.43 ± 0.54	Normal	319.23	399.31	340.37	16.410	0.000**
Stress	0.67 ± 0.58	1.06 ± 0.77	0.74 ± 0.67	0.82 ± 0.70	Mild	317.49	420.12	329.58	31.036	0.000**
DASS	0.52 ± 0.43	0.82 ± 0.61	0.60 ± 0.55	0.64 ± 0.56	Mild	318.55	413.53	332.78	25.365	0.000**

**Significant at the 0.01 level (2-tailed). N = Sample size; n = frequency; M = Mean; SD = Standard deviation. Scoring: Normal: M < 0.6, Mild: M = 0.6 ≤ 1.2; Moderate: M = 1.2 ≤ 1.8; Severe: M = 1.8 ≤ 2.4; Extremely severe = 2.4– 3. DASS: Depression, Anxiety, Stress Scale.

Table 4: Differences in the mean GSES scores across countries (n = 704)

GSES	Jordan (n = 148)	Egypt (n = 198)	KSA (n = 358)	Total (N = 704)	Total level	Mean rank			Kruskal–Wallis test	Sig. (2-tailed)
	M ± SD	M ± SD	M ± SD	M ± SD		Jordan	Egypt	KSA	Chi-square	
Total of general self-efficacy scale	32.16 ± 5.18	29.22 ± 6.03	32.38 ± 5.57	31.45 ± 5.79	High	376.65	274.69	385.55	40.688	0.000**

**Significant at the 0.01 level (2-tailed). N = Sample size; n = Frequency; M = Mean; SD = Standard deviation. Scoring: Low: M = 10–19; Moderate: M = 20–30; High: M = 31–40. GSES: General Self-Efficacy Scale

schedule of their current jobs due to quarantine. Most of the participants reported that they do care about meeting and communicating with their families on a daily basis and that they concentrate on positive thoughts during difficulties (74.7% and 71.9%, respectively). Almost one-fifth of participants reported sexual pattern disturbances, due to home quarantine (22.2%).

Table 3 revealed mild levels of depression and stress and low total DASS scores, for the entire sample, with normal anxiety levels, and significant differences were found when comparing the DASS scores among the three countries ($p < 0.01$). Participants from Egypt demonstrated significantly higher mean scores for depression, anxiety, stress, and total DASS compared with those from Saudi Arabia and Jordan.

A significant difference in the mean GSES scores was found among the participants of the three countries, as shown in Table 4. At the time of the survey, participants from Egypt displayed a moderate level of self-efficacy during home quarantine, whereas participants from Jordan and Saudi Arabia showed high self-efficacy levels ($p < 0.01$).

The Mann–Whitney U test was used to identify significant differences between the mean scores of the DASS total score, the DASS depression, anxiety, and stress subscale scores, and the GSES scores when two countries were compared directly. Table 5 shows that highly significant differences were observed for the mean depression, anxiety, and stress subscale scores, the mean total DASS scores, and the mean GSES scores between Egyptian and Jordanian participants and between Saudi Arabian and Egyptian participants ($p < 0.01$). Nonetheless, no significant difference was observed between the Jordanian and Saudi participants in that regard.

Table 5: Matrix of differences between the mean scale and subscale scores between countries

Mann–Whitney U test Asymp. Sig. (2-tailed)	Scale	Egypt	Saudi Arabia
Jordan	Depression	0.000**	0.708
	Anxiety	0.000**	0.292
	Stress	0.000**	0.581
	DASS	0.000**	0.564
	GSES	0.000**	0.557
Egypt	Depression	-	0.000**
	Anxiety	-	0.001**
	Stress	-	0.000**
	DASS	-	0.000**
	GSES	-	0.000**

**Significant at the 0.01 level (2-tailed). DASS: Depression, Anxiety, Stress Scale. GSES: General Self-Efficacy Scale.

A high DASS mean score was significantly associated with the female gender, participants who reported inappropriate housing conditions, and unemployed participants ($p < 0.05$), as shown in Table 6. Significant differences were found in DASS mean scores according to age, marital status, the number of household members, and the educational level of participants. Using the Mann–Whitney U test, DASS mean scores were found to be significantly higher for participants younger than 24 years compared with those who were older than 45 years. Widowed participants had higher DASS mean scores compared with both married and single participants. Participants from medium family sizes (4–6 members) had higher DASS mean scores compared with those from large and too large family sizes (7 members or more). Finally, participants who had a basic school education had higher DASS mean scores than participants with all other levels of education (Diploma, Bachelor's degree, and Postgraduate).

Similarly, a high GSES mean score was significantly associated with the male gender, participants who reported appropriate housing conditions, participants who lived alone, employed participants, and participants with sufficient monthly incomes ($p < 0.05$), as shown in Table 7. Significant differences were found in the GSES mean scores according to age category, marital status, and educational level. Using the Mann–Whitney U test, GSES mean scores were found to be significantly higher for older participants (50 years and older) compared with participants younger than 24 years. GSES scores were also higher for married participants compared with single and divorced participants. GSES scores increased with education, as participants with postgraduate educations presented higher GSES scores than those with bachelor's degrees, diplomas, and basic school educations, bachelor's degree holders presented high scores than participants with diplomas and basic school educations, and diploma holders presented higher scores than basic school-educated participants.

A high DASS mean score was significantly associated with reporting disturbances in sleep, sexuality, social communication, and job schedules, due to quarantine, among participants (Table 8). Higher DASS mean scores were reported for participants who reported

Table 6: Differences in DASS mean scores according to sociodemographic categories

Sociodemographics	M ± SD	Mean rank	Test	p-value
Age categories				
24 years or less	0.84 ± 0.69	408.80	Kruskal–Wallis test Chi-square = 24.17	0.000**
25–29 years	0.64 ± 0.51	357.74		
30–34 years	0.66 ± 0.47	379.02		
35–39 years	0.62 ± 0.53	341.63		
40–44 years	0.63 ± 0.58	348.30		
45–49 years	0.44 ± 0.48	265.15		
50 and more	0.56 ± 0.52	324.08		
Gender				
Female	0.71 ± 0.60	371.08	Mann–Whitney U = 54364	0.046*
Male	0.59 ± 0.51	339.94		
Marital status				
Single	0.70 ± 0.58	376.71	Kruskal–Wallis test Chi-square = 9.44	0.024*
Married	0.60 ± 0.54	339.52		
Divorced	0.71 ± 0.47	398.77		
Widow	1.08 ± 0.68	491.50		
Current living status				
Living alone	0.68 ± 0.57	367.09	Mann–Whitney U = 28264	0.44
Living within a family	0.63 ± 0.55	350.14		
Housing conditions, in terms of sufficient ventilation and lighting				
Appropriate	0.63 ± 0.55	348.34	Mann–Whitney U = 11776	0.035*
Inappropriate	0.78 ± 0.53	414.86		
Household size (Number of people)				
Small (3 or less)	0.66 ± 0.54	364.05	Kruskal–Wallis test Chi-square = 12.52	0.006**
Medium (4–6)	0.68 ± 0.58	366.20		
Large (7–9)	0.52 ± 0.48	312.12		
Too large (10 or more)	0.43 ± 0.45	271.08		
Employment				
Unemployed	0.82 ± 0.61	418.37	Mann–Whitney U = 36120	0.000**
Employed	0.57 ± 0.52	328.50		
Monthly family income				
Insufficient	0.68 ± 0.56	369.81	Mann–Whitney U = 33814	0.296
Sufficient	0.63 ± 0.55	348.80		
Educational level				
School	0.81 ± 0.59	423.53	Kruskal–Wallis test Chi-square = 9.43	0.024*
Diploma	0.62 ± 0.58	344.64		
Bachelor's degree	0.63 ± 0.55	349.77		
Postgraduate studies	0.59 ± 0.48	336.17		
Has chronic diseases				
No	0.62 ± 0.53	346.44	Mann–Whitney U = 31024	0.078
Yes	0.75 ± 0.64	382.58		

**Significant at the 0.01 level (2-tailed). M = Mean; SD = Standard deviation. *Significant at the 0.05 level (2-tailed). DASS: Depression, Anxiety, Stress Scale.

Table 7: Difference in GSES mean scores according to the sociodemographic characteristics

Sociodemographics	M ± SD	Mean rank	Test	p-value
Age categories				
24 years or less	29.80 ± 5.4	282.00	Kruskal–Wallis test Chi-square = 33.72	0.000**
25-29 years	30.73 ± 5.43	329.48		
30-34 years	30.56 ± 6.5	321.07		
35-39 years	32.41 ± 5.96	388.31		
40-44 years	31.85 ± 5.53	370.11		
45-49 years	31.94 ± 5.46	372.21		
50 and more	33.71 ± 5.33	440.31		
Gender				
Female	30.71 ± 6.23	332.38	Mann–Whitney U = 53926	0.031*
Male	31.94 ± 5.41	366.10		
Marital status				
Single	30.38 ± 6.32	315.92	Kruskal–Wallis test Chi-square = 10.75	0.013*
Married	31.92 ± 5.43	368.38		
Divorced	29.54 ± 7.18	292.41		
Widow	30.75 ± 7.3	347.50		
Current living status				
Living alone	32.65 ± 5.42	390.62	Mann–Whitney U = 25958	0.045*
Living within a family	31.25 ± 5.82	346.33		
Housing condition, in term of ventilation and lighting				
Appropriate	31.68 ± 5.61	359.30	Mann–Whitney U = 10032	0.000**
Inappropriate	27.81 ± 7.08	250.50		
Number of people living				
Small (3 or less)	32.17 ± 5.45	373.72	Kruskal–Wallis test Chi-square = 6.38	0.095
Medium (4-6)	30.89 ± 5.98	334.91		
Large (7-9)	31.67 ± 5.83	364.50		
Too large (10 or more)	32.63 ± 4.76	387.82		
Employment				
Unemployed	29.60 ± 5.99	288.80	Mann–Whitney U = 36528	0.000**
Employed	32.11 ± 5.56	375.71		
Monthly family income				
Insufficient	30.38 ± 5.90	317.50	Mann–Whitney U = 31620	0.034*
Sufficient	31.67 ± 5.74	359.98		
Educational level				
School	28.3 ± 6.02	247.02	Kruskal–Wallis test Chi-square = 39.96	0.000**
Diploma	29.94 ± 5.86	302.09		
Bachelor	31.66 ± 5.53	357.87		
Postgraduate studies	33.11 ± 5.49	412.19		
Has chronic diseases				
No	31.41 ± 5.76	350.78	Mann–Whitney U = 33564	0.616
Yes	31.61 ± 5.92	361.06		

**Significant at the 0.01 level (2-tailed). M = Mean; SD = Standard deviation. *Significant at the 0.05 level (2-tailed). GSES: General Self-Efficacy Scale.

Table 8: DASS mean score difference according to participants' health patterns

Health pattern	M ± SD	Mean rank	Test	p-value
Regular exercise				
No	0.65 ± 0.55	182282.00	Mann–Whitney U = 46572	0.184
Yes	0.60 ± 0.57	65878.00		
Smoke tobacco regularly				
No	0.72 ± 0.58	187893.00	Mann–Whitney U = 38562	0.192
Yes	0.61 ± 0.54	60267.00		
Appetite				
Low	1.02 ± 0.60	483.63	Kruskal–Wallis test Chi-square = 29.47	0.000**
Usual	0.61 ± 0.54	341.03		
High	0.58 ± 0.52	333.19		
Body weight				
Underweight	0.78 ± 0.47	432.95	Kruskal–Wallis test Chi-square = 7.150	0.028*
Normal	0.61 ± 0.54	342.46		
Overweight	0.65 ± 0.57	353.66		
Disturbance in sleep due to quarantine?				
No	0.47 ± 0.48	283.41	Mann–Whitney U = 39090	0.000 **
Yes	0.78 ± 0.57	412.09		
Disturbance in sexuality due to quarantine?				
No	0.58 ± 0.54	327.62	Mann–Whitney U = 29110	0.000**
Yes	0.85 ± 0.56	439.90		
Disturbance in social communications due to quarantine?				
No	0.41 ± 0.43	261.97	Mann–Whitney U = 33440	0.000**
Yes	0.81 ± 0.58	419.73		
Experienced changes in the nature or time schedule of your current job due to quarantine?				
No	0.48 ± 0.49	288.38	Mann–Whitney U = 29598	0.000**
Yes	0.68 ± 0.56	367.57		
Concentrate on positive thoughts during difficulties?				
No	1.04 ± 0.61	491.35	Mann–Whitney U = 22602	0.000**
Yes	0.48 ± 0.44	298.17		
Empty your brain of thoughts regarding tomorrow's schedule at bedtime?				
I cannot	0.85 ± 0.58	434.48	Mann–Whitney U = 33258	0.000**
I can	0.43 ± 0.43	271.45		
Care about meeting and communicating with your family on a daily basis?				
No	0.87 ± 0.59	437.92	Mann–Whitney U = 31610	0.000**
Yes	0.56 ± 0.52	323.60		

**Significant at the 0.01 level (2-tailed). M = Mean; SD = Standard deviation. *Significant at the 0.05 level (2-tailed). DASS: Depression, Anxiety, Stress Scale.

Table 9: Difference in GSES mean-scores based on participants health patterns

Functional health patterns	M ± SD	Mean rank	Test	p-value
Regular exercise				
No	32.42 ± 5.65	172124.00	Mann–Whitney U = 42838	0.004**
Yes	31.06 ± 5.80	76036.00		
Smoke tobacco regularly				
No	31.60 ± 5.75	195621.00	Mann–Whitney U = 39978	0.16
Yes	30.91 ± 5.90	52539.00		
Appetite				
Low	28.87 ± 6.89	280.81	Kruskal–Wallis test Chi-square = 9.313	0.011*
Usual	31.83 ± 5.38	362.67		
High	31.22 ± 6.39	348.32		
Body weight				
Underweight	29.70 ± 7.43	317.90	Kruskal–Wallis test Chi-square = 1.262	0.532
Normal	31.52 ± 5.57	353.33		
Overweight	31.58 ± 5.77	356.04		
Disturbance in sleep due to quarantine?				
No	31.76 ± 5.86	363.60	Mann–Whitney U=57996	0.178
Yes	31.17 ± 5.71	342.93		
Disturbance in sexuality due to quarantine?				
No	31.65 ± 5.83	361.08	Mann–Whitney U = 38040	0.035*
Yes	30.71 ± 5.57	322.35		
Disturbance in social communication due to quarantine?				
No	33.06 ± 5.14	408.45	Mann–Whitney U = 43814	0.000**
Yes	30.24 ± 5.94	310.95		
Experienced changes in the nature or time schedule of your current job due to quarantine?				
No	31.86 ± 5.75	365.32	Mann–Whitney U = 36472	0.416
Yes	31.34 ± 5.79	349.49		
Concentrate on positive thoughts during difficulties?				
No	28.46 ± 5.48	243.77	Mann–Whitney U = 28566	0.000**
Yes	32.61 ± 5.48	395.05		
Empty your brain of thoughts regarding tomorrow's schedule at bedtime?				
I cannot	29.96 ± 6.13	301.05	Mann–Whitney U = 43942	0.000**
I can	32.90 ± 5.02	403.37		
Care about meeting and communicating with your family on a daily basis?				
No	28.56 ± 5.93	253.54	Mann–Whitney U = 29200	0.000**
Yes	32.42 ± 5.40	385.99		

**Significant at the 0.01 level (2-tailed). M = Mean; SD = Standard deviation. *Significant at the 0.05 level (2-tailed). GSES: General Self-Efficacy Scale

the inability to concentrate on positive thoughts during difficulties, participants who reported the inability to empty their brains of thoughts at bedtime, and participants who reported no interest in meeting or communicating with their families on a daily basis ($p < 0.05$). The Mann–Whitney U test revealed that participants who suffered from low appetite had significantly higher DASS mean scores compared with those for participants with usual or increased appetites. Underweight participants had significantly increased DASS mean scores compared with both normal-weight and overweight participants.

A lower GSES mean score was significantly associated with participants who reported engaging in regular exercise and experiencing disturbances in sexuality and social communication due to quarantine (Table 9). However, a higher GSES mean score was found among participants who reported concentrating on positive thoughts during difficulties, who were able to empty their brains of thoughts at bedtime, and who cared about meeting and communicating with their families on a daily basis ($p < 0.01$). Using the Mann–Whitney U test, participants who had low appetite were found to have significantly lower GSES mean scores compared with participants with usual and increased appetites.

Table 10: Correlations among the depression, anxiety, and stress subscale scores

	Mean depression	Mean anxiety	Mean stress
Mean depression			
Pearson correlation	1	0.721**	0.773**
Sig. (2-tailed)		0.000	0.000
n	704	704	704
Mean anxiety			
Pearson correlation	0.721**	1	0.734**
Sig. (2-tailed)	0.000		0.000
n	704	704	704
Mean stress			
Pearson correlation	0.773**	0.734**	1
Sig. (2-tailed)	0.000	0.000	
n	704	704	704

**Correlation is significant at the 0.01 level (2-tailed).

Pearson's correlation coefficient indicated significant correlations among the mean depression, anxiety, and stress subscale scores ($p < 0.01$). As shown in Table 10, a strong positive correlation was identified among the three variables, in which an increase in the mean score of any one subscale was significantly associated with an increase in the mean scores of the two other subscales.

Table 11: Correlation between DASS and GSES scores

	Mean DASS	Mean GSES
Mean DASS		
Pearson correlation	1	−0.526**
Sig. (2-tailed)		0.000
n	704	704
Mean GSES		
Pearson correlation	−0.526**	1
Sig. (2-tailed)	0.000	
n	704	704

**Correlation is significant at the 0.01 level (2-tailed). DASS: Depression, Anxiety, Stress Scale, GSES: General Self-Efficacy Scale.

Table 11 illustrates a significant inverse correlation between the mean DASS and GSES scores ($p < 0.01$), indicating that increases in the mean DASS scores were associated with decreases in the mean GSES scores.

Table 12: Regression analysis of DASS subscale and GSES scores

Model	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. error	Beta		
(Constant)	35.028	0.296		118.321	0.000**
Mean depression scale	–1.675	0.522	–0.174	–3.210	0.001**
Mean anxiety scale	–1.396	0.544	–0.130	–2.565	0.011*
Mean stress scale	–2.249	0.457	–0.272	–4.916	0.000**

Dependent variable: Mean GSES scores. *Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). DASS: Depression, Anxiety, Stress Scale, GSES: General Self-Efficacy Scale.

Table 12 shows that the depression, anxiety, and stress subscale scores were significant independent predictors of the mean GSES score ($p < 0.01$). Based on the significance of the regression coefficient, the following linear regression equation was formulated, to predict the GSES mean-score from the depression, anxiety, and stress subscale mean scores, as follows: $y = 35.028–1.675x^1–1.396x^2–2.249x^3$, where 35.028 is a constant, y is the mean GSES score, x^1 is the mean depression scale score, x^2 is the mean anxiety scale score, and x^3 is the mean stress scale score.

Discussion

Unfortunately, we are all currently going through a crisis. The global outbreak of COVID-19 has impacted every-day life in a remarkable way. The daily number of victims continues to rise and many of us remain quarantined at home. COVID-19 does not solely affect individuals who test positive for the virus; the pandemic effect is extremely massive and affects every person, worldwide, as most people are experiencing increased levels of anxiety, stress, and depression, reduced exercise and physical activity, and reduced social interactions due to the compelled lockdown.

The findings of this study revealed normal anxiety levels, and mild depression and stress scores, and mild total DASS scores, with significant differences among the three studied countries, with Egyptian participants demonstrating higher mean scores for depression, anxiety, stress, and total DASS. This study was performed during a period when COVID-19 reporting in Egypt was minimal, with a small number of cases reported daily, and the population may not have had sufficient information regarding this recently developed pandemic. People appear to be more inclined to experience anxiety, depression, and worry when dealing with unknown issues, challenges, or diseases. When humans become more worried, they become more anxious and, thus, more careful. Anxiety reflects worry regarding anticipated danger, and panic is the dissemination of anxiousness among a group. In this context, the anxiety of individuals continuously disseminates, through the speedy transmission of information, advancing into group anxiety and panic. As the reported number of confirmed cases and death associated with COVID-19 increases, the public's psychological status is likely to worsen. However, a mild to moderate level of anxiety is likely to improve people's attention to disease prevention, decreasing the incidence of disease.

These results were congruent with those reported by Leung *et al*., [34] in a study from Hong Kong, who stated that a positive level of anxiety could encourage the population to take extra preventive measures, decreasing the velocity of SARS transmission. Similarly, a recent study performed in India by Varshney *et al*. [35] concluded that most of the respondents (66.8%) experienced minimal psychological distress in response to the COVID-19 outbreak, whereas a small proportion (15%) experienced mild psychological impacts. In contrast, the findings of this study differed from the findings of a study performed in China, by Wang *et al*., [36] which stated that 53.8% of respondents suffered from psychological manifestations due to the outbreak, ranging from moderate to severe, in a sample of 1210 respondents.

Several studies have identified relationships between the prevalence of infectious disease outbreaks and a variety of psychological and behavioral consequences. Among the most common negative psychological complications include the increased incidence of depression and psychological misery [37], worry [38], and anxiousness about becoming infected [39]. Furthermore, Kelvin and Rubino [40] in their study, which was performed in China, mentioned that intellectual health problems can manifest, worsen, or trigger psychological and emotional distress in self-isolated and quarantined individuals.

The results of the current study demonstrated that the DASS scores were significantly higher among participants younger than 24 years compared with those older than 45 years. In addition, DASS scores were higher for women, which may be because women are more prone to anxiety than men, due to increased psychological stress regarding both herself and her children, and women tend to be responsible for the social productivity of their families, which may result in the endurance of increased psychological tension. Young individuals were more likely to suffer from symptoms of anxiety, depression, and stress when confronted with epidemics, possibly because young people obtaining massive amounts of information from social and mass media, which could easily trigger and increase psychological distress.

A similar result was reported by Qiu *et al*., [13] in their survey study of more than 50,000 Chinese respondents, in which nearly 35% of contributors reported trauma-related distress symptoms, with women and younger adults displaying notably higher levels of psychological distress. Similarly, Cheng *et al*. [41] and Liu *et al*. [42] reported higher stress scores among the young adult group (18–30 years), which was consistently associated with a higher risk of different mental health outcomes.

Some evidence has suggested that fluctuations in ovarian hormone levels may be responsible for altered sensitivity to emotional stimuli during specific phases of the menstrual cycle, during which intrusive flashbacks are enhanced and form a foundation that makes women particularly vulnerable to psychological disorders [43].

The results of this study showed that DASS mean scores were higher among participants with family sizes of 4–6 members, and small family sizes were associated with increased risk for the development of depression, stress, and anxiety. This association may represent the increased concern and worry that younger adult with children experiences regarding the potential effects of the COVID-19 outbreak on the health of their children. However, this finding was contradicted by Naushad *et al*., [44] who concluded that no link exists between having children and psychological consequences, in their review of previous studies.

The WHO speculates that new measures such as self-isolation and quarantine that affect the daily activities, routines, and livelihoods of humans that may result in increased feelings of loneliness, anxiety, and depression, insomnia, dangerous alcohol and drug use, and in some rare cases, deliberate self-harm or suicidal behavior [45].

The results of the present study confirmed a significant association between high DASS mean scores and widowed participants compared with the DASS scores of both married and single participants, which may be due to household financial losses, the lack of psychological support against fear and anxiety emotions or depression symptoms, and a lack of opportunities to communicate with other individuals, which can result in psychological problems, such as despair and anxiety, further highlighting the significance of household support during the course of this emergency. Participants with basic school educations had significantly higher mean DASS scores compared with participants with all other education levels. An individual with a higher educational level may better able to understand the problems associated with post-traumatic stress disorder (PTSD) and psychological distress, allowing these individuals to take positive measures to avoid the development of psychological symptoms, increasing the individual's confidence in mental health recovery. A similar result was reported by Liang *et al*., [46] who concluded, in their study in China, that younger participants with lower education levels and divorced/widowed individuals were more likely to exhibit PTSD symptoms and psychological distress.

The current study revealed that mean DASS scores were higher among individuals who reported unemployment and insufficient income, which may due to the precautionary measures associated with COVID-19 that has limited working conditions and significantly impacted families' financial situations. This result was consistent with the result of a previous study by Brooks *et al*., [6] who analyzed the role played by financial income and how income changes following labor measures taken for the duration of an epidemic. Thus, decreased or low financial earnings were persistently associated with elevated risks of psychological impacts. Gómez-Salgado *et al*. [47] reported that general indicators of mental health in Spain suggested that low levels or the lack of financial income and the lack of employment were linked with diminished psychological wellness. Brown and Arnholz [48] reported that, in the United States, businesses and people were required to follow social distancing protocols, maintaining at least 6 feet away from other people, limiting most face-to-face interactions, and the unemployment rate due to the COVID-19 outbreak could increase the despair and depression levels.

The results of this study demonstrated that DASS mean scores during the course of home quarantine were significantly higher among participants who reported a low appetite, being underweight, and disturbances in sleep, sexuality, and social communication due to quarantine, and among those who were not able to concentrate on positive thoughts during difficulties and did not care about meeting and communicating with family on a daily basis. As the outbreak progressed, with the increasing implementation of restrictive measures, the number of people who became isolated at home, due to lockdown and obligatory domestic quarantine, increased significantly, worldwide, resulting in unexpected, sudden, and radical changes in the habits and lifestyles of the population, including the drastic deterioration of any form of socialization. Physical distancing and self-isolation strongly impacted citizens' lives, affecting food consumption habits and day-to-day behaviors, which subsequently resulted in a variety of negative emotional outcomes.

This result agreed with the results of Lippi *et al*., [49] in their study showing that the dramatic reduction in physical exercise due to obligatory homestay was one of the most obvious consequences of the general lockdown, not only among those active and energetic individuals who habitually participate in leisure sports but for those who commute to work by walking or cycling and those whose work involves physical activity. Furthermore, Harris and Bargh [50] mentioned that extended shelter-in-place ordinances and sedentary lifestyles will predispose people to weight gain, an issue magnified by the unhealthy dietary habits that very often accompany home setting and extended TV viewing. This result was supported by recent evidence that demonstrated that the sedentary behaviors of younger individuals may also be an essential cause of despair and nervousness [51].

These outcomes were similar to those reported by Huang and Zhao [52], who performed a web-based study that revealed a high risk of generalized anxiety disorder and interrupted sleeping patterns among the Chinese public during the COVID-19 outbreak. In addition, almost one-fifth of participants reported depressive symptoms and sleep problems, indicating that the uncertainty of the epidemic outbreak development may have increased the psychological stress experienced by the public. In contrast, Gleeson *et al*. [53] revealed that the state of self-isolation, lockdown, and social distancing is essential measures necessary to reduce the curve of the disease, despite the severe consequences that these measures may have on an individual's life. The act of being restricted to one's home has substantial effects on one's health, including modifications to eating and food consumption patterns, sleeping habits, and physical activity. Home quarantine, therefore, promotes sedentary behaviors, which affects both psychological and physical wellness and, subsequently, may lead to greater obesity risk. Fear and anxiety may also induce adjustments in dietary habits, leading to unhealthy dietary patterns, less desire to consume food or less enjoyment during eating [54].

The results of the current study revealed that participants from Egypt displayed a moderate level of self-efficacy during home quarantine, whereas those from Saudi Arabia and Jordan displayed high self-efficacy. Self-efficacy is a reflection of an individual's perception of their capability to engage in protective actions, such as the ability to implement proposed hygienic and protection measures, to stay at home with their household, to reduce leisure and recreational activities, and to protect themselves and prevent illness. High self-efficacy is also an indication people have begun to pay attention to their health and were more likely to seek and find social assistance from their households, as an alternative to meeting with friends, which suggested that the interests and concerns of individuals have been influenced by restricted transport and travel policies and the self-isolation rules established by the health authorities and central governments.

These results were congruent with a previous study, reported by Schwarzer and Hallum [55], who found that self-efficacy distinguishes how people think, feel, and act. According to social cognition theory, human motivation and actions are regulated by forethought. This theory implies that self-efficacy is an independent predictor of behavior, affecting intentions, goals, and outcome expectations, which, in turn, are additional predictors of behavior. Similarly, Barofsky *et al*., [56] who studied the consequences of fear, the perception of threats, and worry regarding health behaviors, found that higher threat perception will only predict precautionary behaviors when human beings realize and believe that high-quality defensive responses are readily available (known as adequate response efficacy) and when they believe in their own abilities and competencies to engage in such defensive and protective activities (sufficient self-efficacy).

The perceived efficacy of behavior has been assessed and the degree to which respondents felt that their behaviors would effectively protect and guard them against the COVID was evaluated in the current study. In a UK study, an association was identified between perceived efficacy and the performance of preventive behaviors (hand hygiene, adopting flu friend plans, sterilizing, and cleaning surfaces) that protected against swine flu, as reflected by the reports of that robust study [57]. In a Saudi Arabian study, evidence suggested that performing some interventions, such as continuing education, awareness-raising, continuous monitoring processes, and use of reminders and warning signs, can increase the commitment of individuals and health professionals to continued infection control and prevention measures, including hand hygiene and the use of alcohol hand rubs [58], which will likely have a positive impact on increasing self-confidence and self-efficacy for dealing with such infectious diseases.

In agreement with other recent studies, Chen *et al*., [59] stated that few established, medically confirmed measures have been presented that people can implement for the duration of a pandemic to mitigate their risks of contracting the disease. These measures include, but are not limited to, washing hands, minimizing social contacts, the use of protective masks, wearing protective gloves, and cleaning and disinfecting surfaces. These measures have been communicated to people internationally, through news, social media, posters, lectures, and other formal reports, starting in early 2020, when the COVID-19 disease emerged as a worldwide issue. In addition to individual-level health protection measures, governments issued some instructions and orders to prevent large gatherings, in addition to placing many cities and areas with pandemic outbreaks in quarantine [60].

The present study identified a highly significant association between increased self-efficacy level and postgraduate education, employment, and appropriate housing conditions. During the current coronavirus pandemic, most educated individuals, experts, and professionals were aware of this infection, the use of accessible preventive measures, the necessity for social distancing, and the need to comply with authorities' initiatives to restrict the dissemination of infection. This result was supported by Bish and Michie [61], in their study examining the demographic and attitudinal determinants of protective behaviors during pandemics, in which they suggested that highly educated and older individuals were more likely to undertake, implement, and abide by disease prevention and avoidant behaviors.

An Australian cross-sectional study that addressed the public intention to comply with quarantine restrictions in the event of pandemic influenza found that distinctly educated citizens and residents reported greater intentions to comply with influenza disease prevention measures [62]. Australia individuals who were employed but unable to work from home were much less likely to report their intent to comply with quarantine restrictions [63]. Another study, performed in Hong Kong, revealed that married individuals reported that they were more likely to comply with quarantine regulations and policies during the catastrophe of an avian influenza outbreak [64].

The results of the current study illustrated a highly significant relationship between increased self-efficacy and the lack of regular exercise, the maintenance of social communications, the ability to concentrate on positive thoughts, the ability to empty one's brain of thoughts at bedtime, and prioritizing meeting and communicating with family on a daily basis. Individuals who participate in regular exercise are likely to suffer during this curfew period, due to restrictions that prevent them from practicing their regular daily exercise; however, individuals who experienced no interruptions in their social communications due to COVID-19 reported better self-efficacy than others, which reflected the importance of social communications for providing psychological support and improving self-efficacy. People who usually concentrate on positive thoughts, who are able to ignore bad thoughts at bedtime, and who regularly discuss their issues with family members are likely to present an improved psychological status, less stress, and higher self-efficacy level than individuals who are unable to perform these acts. In addition, the COVID 19 pandemic may result in negative emotional impacts for the population, increasing depression, anxiety, and distress within the population, which may make some individuals feel safer when at home, as quarantine provides these individuals the perception that they are capable of managing and coping with the current pandemic situation. This result was consistent with the report by Zhang and Ma [65], who found that after the onset of the pandemic, the majority of participants reported paying more attention to their psychiatric and mental health and spent extra time relaxing, praying, resting, and exercising. These advantageous influences on mental and spiritual wellness may have helped individuals cope with the various negative impacts on psychiatric and mental health that can be attributed to the pandemic outbreak and the precautionary measures taken.

Similarly, Thomasson and Psouni [66] reported that a sense of high self-efficacy can be understood as the experience of believing in one's capability to cope with the issues and challenges that arise, which is likely to encourage the active participation and engagement in attempts to manage various problems; therefore, self-efficacy increases the likelihood of engaging in problem-focused coping, rather than becoming dysfunctional.

Individuals who reported a low appetite and sleep and sexual disturbances were also associated with lower self-efficacy levels, which was reflected in the results of the current study. Significantly reduced GSES scores can be attributed to a disturbed psychological and physical status, as those participants reported poor appetite, interrupted sleep, and sexual disturbances associated with the COVID-19 quarantine.

The current study showed a strong negative correlation between DASS and GSES scores, indicating that when the DASS increased, self-efficacy decreased. The mean scores of the depression, anxiety, and stress subscales were identified as independent predictors of GSES scores. A similar result was reported by a study, conducted among a large sample of normal adolescents from the Netherlands, which found that low levels of self-efficacy were highly associated with and accompanied by high levels of trait anxiety, neuroticism, despair, and depressive symptoms in this cohort [67].

Singh *et al*., [68] recruited 160 elderly Indian respondents and discovered that perceived self-efficacy emerged as an essential predictor of psychiatric and mental health among elderly participants of both genders. The older participants who perceived themselves to be self-efficacious and to have control over their surroundings reported better mental health and psychological stability. In another study of adolescents, the self-perception that one has the poor ability to cope with unusual situations and dramatic changes and to lose control during unusual social situations was associated with higher levels of social anxiousness and the increased feeling that anxiety limits one's abilities and has a handicapping effect [69].

Conclusion

The COVID-19 quarantine has been associated with mild levels of depression stress and normal anxiety levels, with moderate to high self-efficacy levels. Participants from Egypt suffered from greater levels of stress, anxiety, and depression and lower self-efficacy compared with those among individuals from Jordan and Saudi Arabia.

Gender, housing conditions, employment, age, appetite, weight, education, sleeping patterns, sexuality, social communications, work schedules, the ability to concentrate on positive thoughts, the ability to empty thoughts at bedtime, and conversing with family members were associated with depression, anxiety, and stress. Females, poor housing conditions, unemployment, young age, low appetite, being underweight, having a basic school educated, suffering from sleep and sexuality disturbances, having poor social communications, changes in work schedules, the inability to concentrate on positive thoughts, the inability to empty thoughts at bedtime, and not caring about meeting and communicating with family on a daily basis during the COVID-19 quarantine were significantly associated with increased DASS scores.

Gender, housing conditions, loneliness, employment, monthly income, age, marital status, education, exercise, sexuality, social communication, concentrating on positive thoughts, emptying thoughts at bedtime, and conversing with family members were associated with self-efficacy. Males, appropriate housing conditions, living alone, being employed with a sufficient monthly income, older age, being married, higher educational levels, no regular exercise, no sexual or social communication disturbances, the ability to concentrate on positive thoughts, the ability to empty thoughts at bedtime, and caring about meeting and communicating with household members on a daily basis during the COVID-19 quarantine were significantly associated with higher GSES scores.

A significant positive correlation was identified among depression, anxiety, and stress subscales, whereas a significant negative correlation was confirmed between psychological distress and self-efficacy in individuals.

Recommendations

Additional exploration and focus on the emotional status of individuals during the COVID-19 pandemic is recommended, and awareness programs designed to address the psychological effects of quarantine should be implemented, using mass media and other means. Effectively addressing emotional needs during and after COVID-19, as well as preparing for potential future outbreaks, will require an understanding of the nature and extent of the emotional impacts and the factors linked to negative emotional outcomes during disease outbreaks; thus, the evidence regarding the effectiveness of interventions can be rapidly implemented to prevent and overcome emotional problems that may arise.

The effects of the COVID-19-associated quarantine on emotional status in various populations (general population, COVID-19 cases, close contacts of COVID-19 cases, and healthcare workers) should be carefully examined to design effective intervention strategies that are tailored for each population. However, focusing on improving self-efficacy among the public, in terms of protecting themselves and preventing disease contraction, is likely to play a vital role in improving their emotional status and reducing psychological distress during the pandemic outbreak. Finally, a similar study, conducted using random, larger sample size, should be performed that includes more countries in the region and utilizes a longitudinal research design.

Acknowledgment

We would like to dedicate this research work to those who have suffered from the COVID-19 virus infection and to the deceased. Furthermore, we would like to dedicate the results of this research study to the health-care providers around the world, who are on the front lines, defending societies against this deadly virus.

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COVID-19 and Face Mask Use: A St. Kitts Case Study

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Abstract

BACKGROUND: Mask wearing in the COVID-19 pandemic was previously hypothesized as a protective symbol that decreases compliance with other measures such as face touching and social distancing. However, the face mask is now central to the prevention of viral spread.

AIM: In this paper, we looked at the shift of guidelines regarding mask use and the mask-wearing adherence habits of the Kittitian population at the onset of the pandemic.

METHODS: In this study, we observed 468 individuals, each for 5 min, for the different types of face masks used and their adherence to the Center for Disease Control guidelines for the use of this personal protective equipment. We did the observation at three different locations at Basseterre, St. Kitts, from the 21st to April 30, 2020.

RESULTS: We noted that 49.31% had medical-grade masks (N95 and surgical), 36.11% had improvised masks, and 14.74% had no facial covering. About 34% of persons with masks were not correctly covering their nose or mouth and 16.45% were touching their face with their hands. Wearing any face-covering appears to lead to more face touching than no covering at 18.25% versus 5.8%. The highest proportion of errors was seen in wearers of surgical masks, leaving the mouth/ nose uncovered at 12.08% of all errors.

CONCLUSION: We recommend for public education and political efforts to increase adherence to mask use in conjunction with other protective measures such as social distancing and hand washing for curbing the COVID-19 transmission in St. Kitts and Nevis.

Introduction

Masks have been flying off store shelves virtually and physically leading to worldwide shortages, leaving front line workers and the general population vulnerable and unprotected because of the ever-changing landscape of the COVID-19 pandemic. The first reports of the virus were in December of 2019, but it was not until late January that person to person transmission was reported [1]. Unfortunately, the Center for Disease Control (C.D.C.), the World Health Organization (WHO)/Pan American Health Organization (PAHO), and the St. Christopher and Nevis government have differing opinions on the use of masks amid this pandemic. As of April 3, 2020, the C.D.C. released a recommendation for the full use of face masks, specifically recommending them in areas with significant community-based transmission [2]. Due to the shortage of surgical and N95 masks, the C.D.C. has been firmly steering the general population toward handmade cloth masks. This C.D.C. recommendation reverses their previous advice that only healthcare workers or those dealing directly with the infection should be wearing masks [3].

Similarly, St. Christopher and Nevis, through their Ministry of Health, issued protocols in their daily COVID briefing on April 3, 2020, encouraging citizens to wear masks when in public, in contrast to their previous statements that restricted the use of masks to medical professionals [4]. Universal community masking was integrated into the Statutory Rules and Orders for the Federation shortly thereafter, explicitly stating: "A person shall wear a face mask, covering their nose and mouth, when in a public place once a period of emergency is declared concerning COVID-19" [5]. Conversely, the WHO/PAHO has not veered from their original advice and does not endorse mask-wearing by the general population. Instead, they firmly suggest that masks, especially N95 and surgical masks, be for medical personnel only, which would, therefore, curve worldwide shortages. The WHO/PAHO believes that masks may provide a false sense of security for community members because it may lead to the neglect of personal hand hygiene practices, reduce physical distancing and even lead to excessive touching of the face and eyes [6]. They further suggested that there is limited evidence that wearing a medical mask by healthy individuals while interacting with sick contacts or those in large gatherings is significantly beneficial in prevention; as well as the lack of evidence supporting universal community masking and the reduction in respiratory infection such as COVID-19 [6].

As the C.D.C. and WHO/PAHO are attempting to flatten the curve and reduce community-based transmissions, the twin-island Federation of St. Christopher and Nevis has equally made great strides in the war against COVID-19 allowing for a perfect opportunity to create mask guidelines for this pandemic and future one.

Background into the Widespread mask use in St. Kitts

The use of masks during flu season and other pandemics is nothing new. It has always been recommended that individuals who are sick or show potential symptoms should wear proper personal protective equipment (P.P.E.) to protect the general public. The concern with the COVID-19 is that it has become increasingly understood that many people can carry the virus and spread it while being asymptomatic. In Monterey County, California, it was found that 29% of their current COVID-19 patients acquired the virus from being in the general public, and not due to direct contact with a positive patient [7]. It has additionally been shown that with each individual positive for COVID-19, there has been statistical spread to up to four other individuals during this pandemic [8].

Mask use in the public can be correlated with the effectiveness of masks in hospital settings as it has been shown to reduce the spread of infection in aerosol-based viruses dramatically. A 2014 Saudi Arabian study investigated medical staff in contact with Middle East respiratory syndrome coronavirus, another type of coronavirus. It showed that the group that used N95 masks had a 56% decrease in transmission compared to those that did not [9]. The use of surgical masks in a surgical setting has recently come under scrutiny after a 2016 Cochrane review concluded that wearing a mask during surgery has no effect on the number of wound infections [10]. Another literature review of surgical mask use highlighted the possibility of "venting," where air leaks at the interface between the mask and skin through the path of least resistance, as well as facilitation of contaminant movement through capillary action with moisture accumulation [11]. Finally, a review of the evidence for surgical mask use showed studies to be out of date, and largely of poor methodology – but concludes that absence of evidence of effectiveness is not to be equated with evidence of ineffectiveness; and without evidence that masks cause harm, acknowledge that proponents of mask use in the surgical setting prefer to stay on the side of caution and continue the practice of mask-use [12].

There are three ways of transmission for respiratory viruses – airborne (with droplet particles 5–10 um), droplet (<5 um), and direct contact (of fomites directly touched by infected persons) [13]. According to the WHO guidelines, COVID-19 is transmitted in the community by droplets and fomites that can carry the virus from the hands to the mouth or nose and is only airborne when intensive intervention measures such as endotracheal intubation, bronchoscopy, and positive pressure intubation which indicates a higher risk environment for healthcare workers and necessitates the use of N95 masks [13]. COVID-containing droplets have been shown to remain suspended in air for up to 3 h with the infectious titer reducing from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ per liter of air or land on surfaces and remain there for up to 72 h on steel and plastic, with infectious titers decreasing from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ in 48 h on steel and in 72 h on plastic [14]. A 2009 study of influenza patients showed 7/9 collected cough droplets had detectable virus compared to none of those who coughed through an N-95 mask – however, it is not a study of transmission directly [15]. Further evidence for the possibility of aerosol transmission comes from the severe acute respiratory syndrome (SARS) outbreak in 2003, where it was found that recycled air in a housing building in China spread the SARS virus by transporting aerosols to other units several floors higher [16]. Due to these findings, more and more governments around the world have started implementing policies requiring general public use of masks.

Education of the general public, government officials, and their media on the proper use of P.P.E. and viral transmission in China and Taiwan has actively increased compliance [17]. The aim is to prevent the spread of COVID-19 from infected individuals through the use of masks, as well as reducing the risk of uninfected individuals becoming infected through improper mask use. The most significant task of educating the general public on mask use is to give them guidelines on the effective use of masks, mask disposal, and the mode of contracting COVID-19. Of importance is the mask disposal, as the virus can be resuspended as an aerosol [18]. While individuals may be able to avoid catching the virus in the general public, there remains a risk of bringing it home and contracting it from improper techniques of mask removal and disposal.

In this study, we aim to look at the types of face masks worn in St. Kitts, and the errors associated with the use of these types of masks. We also aim to relate our findings to the psychological relevance of the use of face mask, possible preemptive fear of the virus, and whether the threat is being taken seriously by the citizens of St. Kitts.

St. Kitts demographics

According to C.D.C., several groups are at a higher risk for severe disease presentation for

COVID-19: Those over 65 years, residents of nursing homes, persons of all ages with poorly controlled lung disease, serious heart conditions, immunocompromised, severe obesity, diabetes, chronic kidney, and liver disease [19]. In the epidemiological review of the 2009 H1N1 outbreak in the Caribbean, it was shown that a significant proportion of hospitalized persons (24%) had underlying medical conditions, compared to 1% who was previously healthy. With a case mortality rate of 1.8%, with the highest among the 65–69 and 60–64 groups (33% and 13%, respectively), and more than half had underlying health conditions (diabetes, asthma, and congestive heart failure) [20].

Limited data on non-communicable chronic disease in St. Kitts exists. Still, the 2008 STEPs survey shows a high prevalence of the non-communicable disease in the population – 45% are obese, 26.5% have Stage I hypertension (vs. 19.5% diagnosed), 7.6% have been diagnosed with diabetes, and 8.8% have been told they have high cholesterol [21]. With a significant proportion of the population at a higher level of risk of developing complications, the local transmission policies such as public mask use and mandatory social distancing measures seem prudent.

Testing for respiratory viruses in the Caribbean

Before the H1N1 epidemic spread to the Caribbean in May 2009, testing for influenza and other respiratory viruses were very limited. The only published report of respiratory virus trends in the Caribbean identified difficulty in analyzing seasonal trends before November 2010 due to the lack of data; and expressed concern that 78% of samples submitted to the Caribbean Epidemiology Center came from only 3 of the 26 Caribbean countries [20]. The recommendation was to drastically increase testing to establish reliable patterns. However, no known published data exist till date. Hence, there are no publicly available statistics on whether St. Kitts has had a higher incidence of influenza-negative pneumonia this winter before the implementation of testing mid-March 2020, as this trend has been suggested in other sources previously [22].

A further complication with COVID-19 is that asymptomatic carriers contribute to rapid viral spread – a California study with antibody testing of 3300 individuals suggests that the actual number of those who have been exposed to COVID-19 is 50–80 times greater than the number of confirmed positive cases [23]. The premise is that masks are worn by the general public to prevent droplet transmission when an infected person sneezes or coughs, as well as droplets released when speaking by asymptomatic carriers. Hence, in the absence of adequate universal testing, all should be presumed carriers until proven otherwise.

Methodology for this Case Study

Asides limiting viral transmissions, masks have also been claimed to increase the level of self-awareness, that is, to reduce face touching and practice social distancing. WHO has stated that incorrect use of masks can increase transmission instead of curbing it [24].

The method of observation was structured as follows: in downtown Basseterre, St. Kitts from the 21st to April 30, 2020, we surveyed three environments – street, public transportation, and grocery store line. We observed each person for 5 min, and for every person, we noted the type of mask worn, as well as whether errors in wearing them were made – not covering the nose, not covering the mouth, and touching the face.

Results

Of the 468 persons observed altogether, 74 had N95 masks (16.01%), 156 had surgical masks (33.3%), 102 had handmade masks (21.79%), 67 had a bandana (14.32%), and 69 had no mask (14.74%) (Table 1).

Table 1: % errors by mask type

Condition	N95 (%)	Surgical mask (%)	Handmade mask (%)	Bandana/ scarf (%)	No mask (%)	Total
Not covering nose/ mouth by mask type	39.19	41.67	33.33	41.79	100	48.08
Touching their face by mask type	18.92	15.38	25.49	13.43	5.8	16.45

These data suggests that at the moment of observation, 48.08% of persons were not covering their nose/mouth correctly and 16.45% were touching their face with their hands. Handmade mask users were more likely to have the mask properly covering their mouth and nose – possibly because they were more comfortable to wear. The same group, however, appeared to touch their face more often while wearing the mask. Wearing any face-covering seemed to lead to more face touching than no covering at 18.25% versus 5.8%.

Comparing medical masks (N95 and surgical) to nonmedical masks (bandanas and handmade) suggested that nonmedical masks had a higher face touching probability at 20.71% versus 16.45% for medical. Table 2 indicates that of all errors observed, leaving the mouth/nose uncovered while wearing a surgical mask comprised the highest portion of total mistakes observed at 12.08%. It also suggests that wearing any mask led to more face touching than not wearing a mask at all.

Table 2: % errors of total errors

Setting	N95 (%)	Surgical mask (%)	Handmade mask (%)	Bandana/ scarf (%)	No mask (%)
Touching face of total errors	2.6	4.46	4.83	1.67	0.74
Uncovered nose/mouth of the total # errors?	5.39	12.08	6.32	5.2	15.75

Discussion

While policy implementations such as public mask-wearing are perceived to be beneficial for reducing viral spread, data suggest that there is also a positive psychological impact. In a recent study, it was found that early implementation of preventive measures, such as mask use, lowered levels of depression, anxiety, stress, and many other psychological symptoms that can arise from a pandemic [8]. It is thought that this is because early planning and implementation of protective measures by the government gave reassurance and control to the general public. There is evidence that this belief is applicable in the Caribbean as a Jamaican news agency conducted a poll on mask use and found 48% of respondents believe a nation-wide mandate is only effective in curtailing COVID-19 spread if everyone uses them correctly, compared to 12% who do not believe masks are effective at all, and 8% that believe quarantine measures are sufficient [25]. Our study also corroborated the positive psychology behind mask use as about 85% of the population observed had a form of face covering.

An important distinction should be made between members of the public that use medical-grade masks and homemade replacements. For one, public perception of the validity of threat has implications on the protective choices being made by individuals. A study of people's attitudes during the SARS epidemic in 2004 showed that 21/103 people concerned about SARS bought a mask ahead of time, while 10/146 not concerned bought one in Toronto which was the North American Epicenter, while in the USA 4/121 concerned and 3/387 not concerned bought one out of those surveyed [26]. It is plausible to suggest that individuals who were concerned about COVID had procured a medical-grade mask when they were available on the market. Our study revealed 16.01% and 33.3% of our observed population had N95 and surgical masks, respectively, accounting for about 50% with a medical-grade mask. This finding suggests a likely correlation with an increased level of preemptive fear locally. Although local Caribbean analyses of attitudes are not available, evidence can be found elsewhere [27].

While there are claims in the American media that blacks have been disproportionately affected by COVID-19 due to them not taking the threat seriously and neglecting the advice of public health officials, a national survey by Pew Research Center between March 10 and 16 showed that 46% black respondents viewed the COVID-19 as a major threat to their health, compared to 21% of white respondents; and 23% of white respondents did not believe this to be a threat at all compared to 21% black respondents [27]. Our findings suggest that the residents of St. Kitts, who are predominantly black, are taking this threat seriously as 85% of the observed population had a face covering as advised by the Government of St. Kitts and Nevis.

According to C.D.C. guidelines, a face mask should be taken off by the ear bands and avoiding touching the front of the mask, which has a high likelihood of being contaminated. One study done on adherence to proper techniques of P.P.E. removal of healthcare practitioners studied 162 instances in the care for 52 patients with respiratory symptoms, of whom 30 were in droplet and contact isolation, 21 in droplet, and 1 in contact [28]. It was found that of these interactions, 26% of healthcare workers removed the mask from the front and not by the loops, and 49% touched the potentially contaminated front with their bare hands during disgowning. Overall, accounting for the gowns, gloves, face shields, and mask procedures and sequence of doffing, the study showed a 90% error rate [28]. While healthcare workers in this study had many more steps of P.P.E. donning/removal than the average mask wearer in public, this study suggests that even individuals who have been trained in proper P.P.E. procedures make a significant number of errors. Although our study only considered the face mask, we observed that 16.45% of those who had a face covering touched the front of their mask and this percentage might have been higher had we observed the sample population for a longer period of time.

There has been limited data on adherence to mask use in the general population. A randomized control study of limitation of the familial spread of influenza had family members of confirmed cases wear surgical masks any time the index case or other symptomatic person was in the same room. Information was also provided for proper use of masks through a phone-call explanation and followed up with an in-home visit by study personnel to demonstrate the correct use of the intervention. Adherence to mask-wearing was around 50% for days 3–6 and then decreased afterward [29]. Our study revealed a non-adherence to proper use of the P.P.E. as 48.08% did not cover their nose and mouth correctly. The main issues cited by participants were heat/humidity (53% children, 35% adults) and pain/discomfort [29]. The concerns cited by these participants were reflected in our study as our data revealed that the use of medical-grade masks showed a greater percentage of non-adherence compared to the handmade mask, which seemed more comfortable with less heat and humidity. However, nonmedical masks had a higher face touching probability at 20.71% versus 16.45% for medical.

The public views the surgical mask as a method of prevention of the virus. The German sociologist Ulrich Beck formulated that "risk occurs not only in the form of threat and possible loss but also in society's organized management and response to these risks, which create a forwarding of present risk into the future." Thus, a mask becomes the cosmetic symbol for eliminating risk, while effective measures such as social distancing, proper mask wear, and hand hygiene are downplayed [30]. Our study showed that wearing any face-covering appeared to lead to more face touching than no covering at 18.25% versus 5.8%. The question then is; could non-adherence to proper face mask use be more of a risk to contracting the virus than no covering at all, while ensuring social distancing as the pivot?

Recommendation

After the 1996 plague outbreak in India, Dr. Alladi Mohan expressed concerns toward proper mask use and its efficacy [25]. He recommended proper education for masks to cover nose and mouth, investigating materials to decrease pore size to under 5 um, and changing masks every 30–40 min in non-infectious areas, and more frequently in high-exposure areas [31].

Today, in a different pandemic, we are recommending much of the same – public health education in conjunction with prudent national policies. There is much to be learned from patient adherence literature, which cites 40% of patients to not comply with physician recommendations, and which recommends participatory decision making and reciprocal information sharing to increase compliance [32]. In the future, more efforts should be expended at schools and workplaces to educate on basic disease processes. In addition to implementing regulation, there is a need to use public messaging that considers barriers to change. One way is to highlight the gap between thoughts and action, as studies have shown that cognitive dissonance is a powerful impetus for changing behavior [33]. For example, as many persons seen not wearing masks were the young individuals, public health officials should highlight that masks are used for protecting others in case one is an asymptomatic carrier. The use of questions instead of direct messaging shifts the role of the listener from mentally organizing counterarguments to formulating an opinion which requires weighing of personal beliefs and feelings and increases buy-in into the call of action [34].

Finally, much of the messaging associated with the pandemic has asked the public to make drastic broad changes such as banning all public gatherings and cutting off all nonessential social interactions. However, studies show that having large scale demand is more likely to be rejected than using a "foot-in-the-door" technique and gradually increasing the demand in manageable portions [35].

Looking inward, the government and the Ministry of Health of St. Kitts and Nevis should be given a lot of credit for their conscientiousness. The government instituted a full lockdown and a week after the first two cases on March 24, 2020, a complete lockdown on March 31, 2020, and politically ensured mandatory face mask use and other preventive measures [36]. Despite the errors observed in the face mask use, the result of this intervention is undeniable as the number of cases has stayed stable at 15 since April 20, 2020 [36]. At the time of submission of this manuscript, all the infected patients have recovered with no new cases. The government of St. Kitts and Nevis has proven that these measures have been effective, and if had been implemented earlier in some regions, might have helped to reduce the spread and save lives.

Overall, the recommendation for the future is that public education campaigns on potential pandemic management, viral transmission, and risk reduction should begin in times of stability so that the population is prepared to accept the necessary measures when the time comes.

Limitation

The observation was 5 min per person, and there was no basis for the choice of observational time. Hence, there is every possibility that the statistics might be altered by increased time. However, as a justification, our literature search did not show any study of this nature that we could have used as a possible basis for comparison of observational time.

Conclusion

In this COVID-19 pandemic, the Caribbean, specifically St Christopher and Nevis, must examine public adherence to universal community masking holistically; by not only combining the positive psychological effects but also the correct technique of mask usage.

Public health education must be the catalyst that ushers innovative and comprehensive legislation and policy into the Federation. Education encompassing hygiene, social distancing, and adequate use of respiratory protectors can potentially eliminate community-acquired transmission and aid to flatten the disease curve drastically.

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The Effects of COVID-19 Lockdown on Air Quality in Macedonia

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Abstract

BACKGROUND: Faced with the novel coronavirus outbreak (2019-nCoV), various urgent and coordinated actions have been taken worldwide to reduce spread of the disease. Slowing down economic activities, transportation, restrictions of the human public gatherings, and interaction resulted with a tremendous decline in air pollutant concentration especially in nitrogen dioxide, registered by National Aeronautics and Space Administration and European Space Agency satellites.

AIM: The aim of the study was to assess the impact of COVID-19 lockdown conditions on the air quality in selected cities in Macedonia.

METHODS: Daily mean concentration of the particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide, ozone, and carbon monoxide measured in the national air quality monitoring network, was analyzed separately comparing following periods: past week of February 2020 to the end of May 2020 with the same period in 2017–2019. Depending on the data distribution, parametric independent-samples t-test or nonparametric Mann–Whitney U-test was run to determine if there were differences in the pollutants concentration during the COVID-19 and non-COVID-19 period.

RESULTS: Implementation of strict restrictions of the movement along with reduced economic activities and vehicular transport, led to notable decrement of air pollutant concentrations. We have found an evident decrease in the concentration levels of all pollutants measured during COVID-19 period in 2020, compared to those from 2017 to 2019 with exceptions for $PM_{2.5}$ in Kumanovo and carbon monoxide in Skopje (7% and 3% higher concentration). The most notable decrement was for NO_2, with a concentration 5–31% lower during COVID-19 period.

CONCLUSIONS: Although beneficial to human health, there is a need to assess economic implications of the lockdown that could have a negative impact on the health as well.

Introduction

Starting from December 31, 2019, when the first cluster of cases of pneumonia in Wuhan, Hubei Province (China) has been reported, a novel coronavirus was eventually identified. Setting the Incident Management Support Team, reporting on social media and publishing the first disease outbreak news, World Health Organization (WHO) took a comprehensive package of measures providing to all countries a guide how to detect, test, and manage potential cases with knowledge regarding the virus present at that time. One month later, after the first reports of limited human-to-human transmission were reported outside China, WHO Director-General accepted recommendation of emergency committee and declared a novel coronavirus outbreak (2019-nCoV) as a Public Health Emergency of International Concern (PHEIC). This is the 6th time, the WHO has declared a PHEIC since the International Health Regulations (IHR) came into force in 2005 [1]. The response worldwide varied from restrictions of the human public gatherings and interaction to various types of restricted economic activities. As of May 7, 3,672,238 confirmed cases have been reported in 215 countries and territories worldwide, with 254,045 confirmed death cases [1], [2].

Republic of Macedonia has confirmed its first case of SARS-CoV-2 on February 26, 2020, with a positive epidemiological anamnesis that has been traveling in Northern Italy. Initial national measures against a potential outbreak and treat have been implemented in late of January starting with installing thermal camera at the national airport and providing personal protective equipment and reagents for virus detection. Series of public health measures and recommendations followed.

Increasing number of new cases, led to a need for implementation of more reliable measures to prevent further spreading of the virus. On March 10, closure of all education institutions (from kindergartens to universities) has been introduced. A state of emergency was declared on March 18 and first movement restrictions were introduced on March 23 on the national level. However, restriction of the movement from 9 pm to 5 am next day in working days and special regime for elderly and younger than 18, has not been sufficient to control spreading of the virus. Thus, stricter movement restrictions were introduced on April 8 (ban for movement from 4 pm to 5 am next day and complete ban during the weekends, starting from 4 pm on Friday to 5 am on Monday). Complete lockdown was introduced during religious holidays in the country, Orthodox Easter (17–21 April) and during Eid al-Fitr (24–26 May) to prevent further spreading of the virus caused by traditional family reunions, as well for the International Labor Day (from 1 May to 4 May) [3].

On May 7, 1 572 confirmed cases have been reported in Macedonia, and 89 death cases.

The scale, suddenness, and global scope of the pandemic have raised urgent and coordinated actions to identify the key factors including ambient air pollution as a modifiable environmental factor that could increase the severity of the health outcomes and other social and economic consequences of the pandemic [4]. In reality, the world was facing a tremendous decline in air pollutant concentration especially in nitrogen dioxide (NO_2). National Aeronautics and Space Administration (NASA) [5] and European Space Agency[1] satellite [6] images visualized that significant reduction in NO_2 in China from January to February. According to the evidence, this change is at least partly related to the economic slowdown following the outbreak of coronavirus, namely, shutting down the transportation into and out of Wuhan, local business as well to reduce spread of the disease have resulted with decrement of nitrogen dioxide.

NASA scientist has previously seen such a decline during other events: economic recession in 2008, Beijing Olympic games in 2008, but those were gradual, or around the city, different than this dramatic drop-of on a wide area due to pandemic [5].

And while the pandemic continues to reap human lives, many countries have reported an improvement in the quality of environmental media and a return of biodiversity even in urban areas. Due to restricted movement and gathering of the people, non-functioning industries, almost empty streets and roads, ecosystems started to recover [7], [8], [9]. That was an ideal moment to analyze the effect of this unexpected situation on the air quality in some cities and to look for any possible decline of the pollutant concentration related to the decreased or stopped economic activities due to pandemic.

This study aims to assess the impact of COVID-19 lockdown[2] conditions (especially reduction of the traffic among other sources of pollution) on the air quality of the four selected cities in Republic of Macedonia.

1 NASA collect the data using Ozone Monitoring Instruments (OMI) on its AURA satellite. While, ESA collect the data through Sentinel-5P satellite using TROPOMI (TROPOsphericMonitoring Instrument).

2 Lockdown in general means that people need to stay indoors but can go out to buy essential commodities. In the Macedonia case means all commercial establishments to be shut down, except for those providing essential services. Places of mass gatherings such as malls, theatres, stadiums, etc. have been shut completely, curfew has been introduced and special permits for movement have been issued.

Materials and Methods

To compare current air quality and air pollutant levels to years past, we have analyzed the daily mean concentration of the particulate matter (PM_{10} and $PM_{2.5}$), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO), measured in the national air quality monitoring network in the selected cities: The City of Skopje, Bitola, Tetovo, and Kumanovo.

The pollutant concentration was analyzed separately comparing following periods: Last week of February 2020 to the end of May 2020 (named COVID-19 period) with the same period in 2017–2019 (non-COVID-19 period).

Statistical analysis

Statistical analysis of the data is performed using the IBM Statistical Package for the Social Sciences (IBM SPSS Statistic for Windows, Version 19.0. Amonk, NY: IBM Corp.). The following methods have been applied: Descriptive statistics is done in series with numerical marks (pollutants concentration), means and standard deviation; ±95%CI, minimum, and maximum. Correlation matrix between air pollutants has been made and Spearman correlation coefficient calculated.

Assumptions checking are performed to run appropriate test (significant outliers, data distribution – tests of normality (skewness and kurtosis, Shapiro-Wilk and Kolmogorov–Smirnov test, and homogeneity of variances – Levene's test). Depending on the data distribution, parametric independent-samples t-test or nonparametric Mann–Whitney U-test were run to determine if there were differences in the pollutants concentration during the COVID-19 and non-COVID-19 period.

Study area

Based on the latest State Statistical Office estimates, in 2019, Republic of Macedonia has 2.076,255 inhabitants, the City of Skopje 554,972 residents (26.7% of the total population), Bitola 90,895 and Tetovo 92,946 and Kumanovo 109,521 that present about 14.1% of the total population [10]. We analyze the City of Skopje only as a separate unit of the local self-government consisting ten urban municipalities. The broader area (Skopje Region) comprised seven more rural municipalities and it is not covered by this study. In Bitola, one urban and 64 rural settlements are present while municipality of Tetovo, comprises one urban and 19 rural settlements and municipality of Kumanovo with 37 rural settlements [11], [12].

The City of Skopje as a capital city of the Republic of Macedonia is the main educational, political economic and cultural center in the country. The last decade it is one of the most polluted cities in the world. With an average annual concentration of PM_{10} ranging from 49.6

to 124.3 μg/m^3 in the period 2010–2019 for the City of Skopje; 49.6–147.2 μg/m^3 in Tetovo; and 44.2–89.6 μg/m^3 in Bitola, particulate air pollution is top priority public health and environmental problem in entire country. The mountainous terrain and meteorological conditions cause extra challenges for the national air quality management. Many sources of air pollution have been identified: Traffic (poorly maintained vehicle fleet), domestic heating, and energy production which rely mostly on poor-quality lignite in old thermal power plants, the absence of proper waste management, etc. [11].

Environmental data

Daily mean concentration of selected pollutants (PM_{10}, $PM_{2.5}$, 8-h ozone, NO_2, and CO) from five monitoring stations in the City of Skopje, one located in Tetovo and Kumanovo, and two in Bitola was analyzed. Data have been obtained from the Macedonian Environmental Information Centre (MEIC) in the Ministry of Environment and Physical Planning (MEPP).

Meteorological data

Due to poor maintenance of the monitoring stations within national air quality monitoring network, very often meteorological data are absent (not measured) or there is not continuity in the measurements. Thus, we present only daily mean temperature of the ambient air, wind speed, and relative humidity for Skopje and Bitola, measured in monitoring station Centar for the City of Skopje and average temperature of both monitoring station in Bitola (Tables 1 and A1). There are no continuous measurements of meteorological data from other monitoring stations (Kumanovo and Tetovo).

Table 1: Meteorological conditions for non-COVID-19 and COVID-19 period

Meteorological factor	2017–2020			COVID-19, 2020		
	Avg. ± Std.	Min	Max	Avg. ± Std.	Min	Max
Temperature (°C)						
Skopje	14.2 ± 5.4	−4.2	23.9	12.4 ± 5.4	0.8	24.9
Bitola	10.9 ± 5.2	−6.1	21.1	10.4 ± 5.6	−0.6	24.4
Wind speed (m/s)						
Skopje	0.6 ± 0.4	0.0	2.5	0.6 ± 0.4	0.0	1.5
Bitola	0.3 ± 0.2	0.0	1.1	0.3 ± 0.2	0.0	1.0
Humidity (%)						
Skopje	61.1 ± 12.3	31	92	61.8 ± 13.8	37	94
Bitola	63.2 ± 12.6	36	95	63.4 ± 16.2	33	97

Source: MEIC, MEPP, 2020

Results

Aiming to understand the impact of implementation of the collective measures of restrictions as a response of the COVID-19 outbreak on the air quality, we have analyzed particulate matter (both, PM_{10} and $PM_{2.5}$), NO_2, ozone, and carbon monoxide obtained from the national air quality monitoring network of MEPP in the selected cities. Then, we compared the pollutants concentrations week by week during COVID-19 period with the average levels for the same time period from 2017, 2018, and 2019 (or, in some cases for 2018 and 2019), and % of change compared with previous week of the COVID-19 period only.

For that purpose, several tables (Appendix, Tables A1-A6) were prepared.

We have found an evident decrease in the concentration levels of all pollutants measured during COVID-19 period in 2020 compared to those from 2017 to 2019 (or 2018–2019), with some exceptions for $PM_{2.5}$ in Kumanovo (7% higher concentration) and carbon monoxide in Skopje (3% higher concentration). The most notable and sharp decrement were for NO_2, with a concentration 5–31% lower during COVID-19 period (Table 2).

Table 2: Average concentration of the air pollutants during non-COVID-19 and COVID-19 period

City	Period	PM_{10}	$PM_{2.5}$	NO_2	Ozone	CO
Skopje	2017–2019	41.8	26.6	26.1	39.6	0.44
	COVID-19, 2020	34.1	22.3	18.1	37.4	0.46
	% change	−18	−16	−31	−6	3
Bitola	2017–2019	37.4	22.6*	14.6	59.6	0.36
	COVID-19, 2020	35.8	22.1	11.1	49.0	0.32
	% change	−4	−2	−24	−18	−10
Tetovo	2017–2019	40.8	29.2*	24.8*	41.5	0.37
	COVID-19, 2020	39.0	27.0	18.2	24.9	0.36
	% change	−5	−7	−27	−40	−4
Kumanovo	2017–2019	45.7	26.2*	20.2*	38.1*	0.50
	COVID-19, 2020	41.9	28.2	19.2	20.4	0.34
	% change	−8	7.0	−5	−47	−31

*Two years' average, 2018 to 2019; Source: MEIC, MEPP, 2020

On Figures 1-5 are presented the effect of some major implemented measures of restrictions on the air quality during the COVID-19 pandemic.

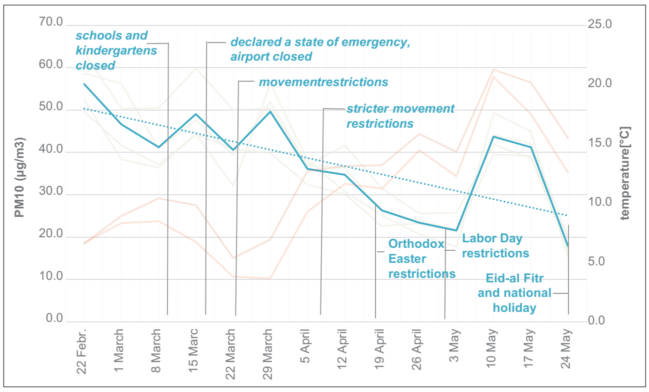

Figure 1: Effects of the implemented measures on the week average concentration of PM_{10}. Dark blue line: Average concentration of the four cities; light gray lines: Measured weekly concentration of PM_{10}; light red lines: Ambient air temperature, weekly average measured in Skopje and Bitola

Detailed analysis of the data shows that the fourth observed week (15–21 March 2020) had high percentage change of particles concentration compared to the previous week (16%-22% increment of PM10 concentration and 19% to 27% of PM2.5 concentration); the highest percentage change of particles concentartion was reported in the twelve week (10-16 May) were the increment of PM10 concentration from 63% to 189% have been reported and 8% to 61% for PM2.5; in the sixth week (29 March to 4 April) was reported high percentage change of PM concentration in Bitola and Tetovo (76% and 32% for PM10 and 67 % and 23% for PM2.5 respectively) (Tables A2 and A3, Figures 1 and 2).

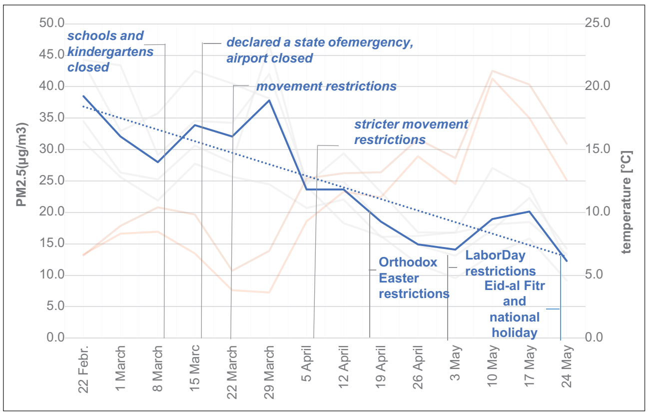

Figure 2: Effects of the implemented measures on the week average concentration of $PM_{2.5}$. Dark blue line: Average concentration of the four cities; light gray lines: Measured weekly concentrations of $PM_{2.5}$; light red lines: Ambient air temperature, weekly average measured in Skopje and Bitola

In terms of NO_2 concentration, such an increment is notable in the 12 observed week and for ozone, in the 4th, 6th, and 7th week of the analyzed period in 2020 (Figure 3, Tables A4 and A5).

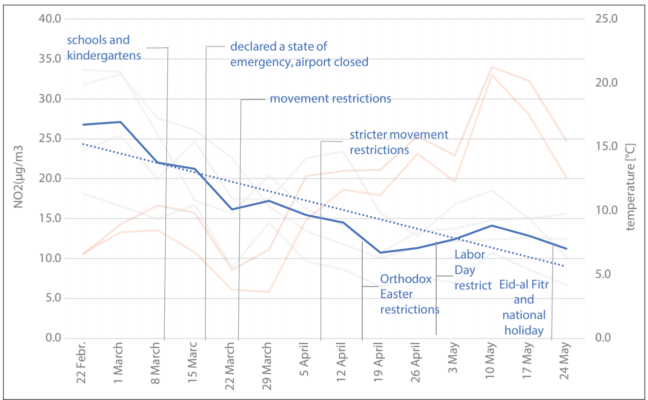

Figure 3: Effects of the implemented measures on the week average concentration of NO_2. Dark blue line: Average concentration of the four cities; light gray lines: Measured weekly concentrations of NO_2; light red lines: Ambient air temperature, weekly average measured in Skopje and Bitola

Regarding the temperature, there is no obvious change during two periods in Bitola (10.9 ± 5.2°C vs. 10.4 ± 5.6°C in 2020), while in Skopje, the temperature

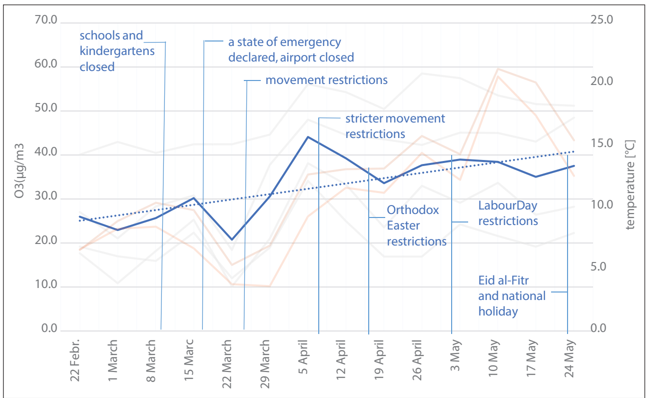

Figure 4: Effects of the implemented measures on the week average concentration of ozone. Dark blue line: Average concentration of the four cities; light gray lines: Measured weekly concentrations of ozone; light red lines: Ambient air temperature, weekly average measured in Skopje and Bitola

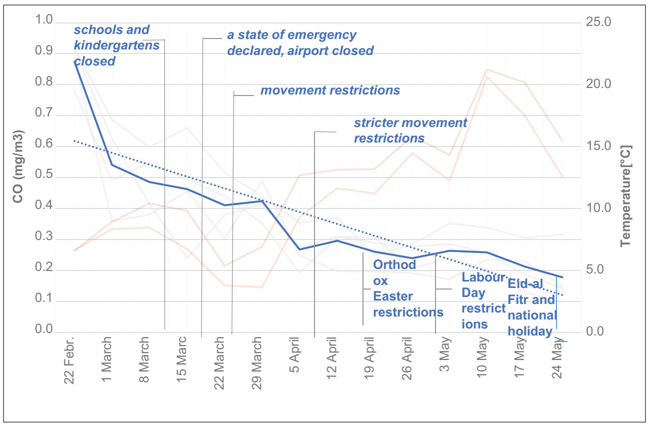

Figure 5: Effects of the implemented measures on the week average concentration of carbon monoxide. Dark blue line: Average concentration of the four cities; light gray lines: Measured weekly concentrations of carbon monoxide; light red lines: Ambient air temperature, weekly average measured in Skopje and Bitola

is lower in 2020 (12.4 ± 5.4°C) compared to 2017–2019 period 14.2 ± 5.4°C (Table 1). The period from 22 February to the end of May 2020 in the City of Skopje was characterized with minimum daily temperature (0.8°C) and maximum daily temperature (24.9°C) that presents (24.2°C) difference. The difference in Bitola was 24.9°C (minimum daily temperature −0.6–24.4°C maximum daily temperature). Both differences are significant, but absence of meteorological data for other two cities prevents a final conclusion to be reached.

In terms of the wind speed and humidity, there are no any significant differences in the two analyzed periods (Table 1).

Due to violation of the assumptions for normality of the data distribution, significant statistical difference has been found between the concentrations of PM_{10} in COVID-19 period, 2020 compared to the same period in 2017–2019 in Skopje using Mann–Whitney U-test. COVID-19 period were associated with statistically significantly lower concentration of PM_{10}, 34.1 µg/m^3 (*Mdn* = 29.9), compared to the 3-years period, 40.6 µg/m^3, (*Mdn* = 37.8). Mann–Whitney U-test indicated that the difference was statistically significant, $U(N_{COVID\text{-}19\ period} = 100, N_{non\text{-}COVID\text{-}19\ period} = 297) = 10670.00$, $z = -4.21$, p = 0.000.

Same apply for the concentration of $PM_{2.5}$ in Skopje, where the mean concentration of particles during COVID-19 period was 22.0 µg/m^3, (*Mdn* = 20.9), while for the previous 3-years period was higher, 26.1 µg/m^3, (*Mdn* = 24.7). Mann–Whitney U-test indicated that the difference was statistically significant, $U(N_{COVID\text{-}19\ period} = 100, N_{non\text{-}COVID\text{-}19\ period} = 297) = 11810.00$, $z = -3.06$, p = 0.002.

The most notable decrement of the pollutant concentration obviously due to the decreased human activity during COVID-19 pandemic in Republic of Macedonia was found for NO_2 concentrations. Data distributions for NO_2 in Skopje and Bitola were sufficiently normal for the purposes of conducting a t-test (i.e., skew <|2.0| and kurtosis <|7.0|, z-score was calculated [13],

[14], Shapiro-Wilk test and Kolmogorov–Smirnov test >0.05. Homogeneity of variances was tested through Levene's F test.

The City of Skopje, with an average concentration of NO_2 of 18.1 μg/m^3 in 2020 compared to 26.1 μg/m^3 during 2017–2019, was the most notable prove of effectiveness of the reduced human activities in the country due to COVID-19 pandemic. An independent samples t-test confirmed the statistically significant difference between two analyzed periods (M = 18.1, SD = 9.04 for the COVID-19 period) and M = 26.1 SD = 8.29 for 3-years period; M = 7.93, 95% CI [6.01, 9.86], t(395) = 8.09, p = 0.000. In Bitola, the difference in the concentrations was smaller but still, statistically significant M = 15.8, SD = 6.81 for the COVID-19 period, and M = 17.5, SD = 7.60 for non-COVID 2 years period M = 1.64, 95% CI [0.08, 3.21], t(383) 2.06, p = 0.040.

In Tetovo, statistically significant difference in terms of NO_2 concentration has been found as well, 18.8 μg/m^3, (*Mdn* = 16.1), and 25.1 μg/m^3, (*Mdn* = 23.4) during 2017–2018 (Mann–Whitney test, $U(N_{COVID\text{-}19\ period}$ = 100, $N_{non\text{-}COVID\text{-}19\ period}$ = 192) = 5147.00, z = -6.50, p = 0.000).

In terms of ozone, statistically significant lower concentrations were found in all cities with exemption of the City of Skopje. The higher drop of the ozone concentrations was found in Kumanovo (−47%) and Tetovo (−40%) (Table 1). Lower average ozone concentration was reported in 2020 in Kumanovo (M = 20.5, SD = 7.95), while in non-COVID-19 period M = 39.0, SD = 12.41; M = 18.49, 95% CI [16.11, 20.88], *t*(275) 15.27, p = 0.000; Tetovo (M = 25.0, SD = 11.39 for COVID-19 period, and M = 41.5, SD = 13.21 for non-COVID-19 period, and M = 16.45, 95% CI [13.53, 19.37], *t*(381) 11.08, p = 0.000; and Bitola (M = 49.2, SD = 9.41 for 2020 and M = 59.1, SD = 11.91 for non-COVID-19 period, and M = 9.87, 95% CI [7.57, 12.17], *t*(214) 8.452, p = 0.000.

Unexpectedly, in our study, we found statistically significant higher concentration of carbon monoxide in Skopje, 0.532 mg/m^3 (*Mdn* = 0.39) in 2020, and 0.440 mg/m^3 (*Mdn* = 0.37) during 3 years period ($U(N_{COVID\text{-}19\ period}$ = 69, $N_{non\text{-}COVID\text{-}19\ period}$ = 296) = 8049.00, z = −2.74, p = 0.006). The same situation was confirmed in Tetovo where the concentration of carbon monoxide during the pandemic in 2020 was higher, 0.459 mg/m^3 (*Mdn* = 0.30) and 0.357 mg/m^3 (*Mdn* = 0.27) in 2017–2019 ($U(N_{COVID\text{-}19\ period}$ = 69, $N_{non\text{-}COVID\text{-}19\ period}$ = 296) = 6954.00, z = −4.13, p = 0.000).

Discussion

Impact of the lockdown on the particulate matter

The observed period (last week of February to the end of May) is somehow a transitional period in terms of ambient temperature characterized with gradual increment of the temperature and consequently subsequent lesser use of the wood (or coal) for household heating. In the source apportionment study for the City of Skopje (2015–2016), biomass combustion from household heating has been identified as a major source of pollution, contributing with 36% of the total share of emissions of particulate matter [11]. The trend of the PM_{10} and $PM_{2.5}$ concentrations is declining in the same period of preceding 3-years (the end of February to May). However, in 2020 the concentrations are 18% and 16% lower, indicating that these changes in air pollution caused by city lockdown are unlikely to be correlated with other factors like weather conditions or to be coincidental (Table 2, Tables A2 and A3).

On March 10, closure of all education institutes (from kindergartens to universities) has been introduced. The slight reduction of the PM concentrations (15–18% lower concentration of $PM_{2.5}$ compared to the previous week), probably could not be attributed to this decision due to same trend of decrement in the pre-COVID 3-years period. Instead to have same decreasing trend further on, concentration of PM particles during the 4th week of the analyzed period started to increase in all cities (16–22% higher than previous week). The unfavorable meteorological conditions small decrement of the ambient temperature (6% in Skopje and 21% in Bitola), as well as drop of the wind speed (36% decline in Bitola), could be a possible explanation (Table A1).

The first movement restrictions in the country were introduced on March 23, followed by stricter movement restrictions on April 8 (Figures 1 and 2). As a result, substantial decrement of PM concentrations has been reported in all cities observed in the study (19–32% for PM_{10}, and 15–48% for $PM_{2.5}$ in the 7th week during COVID-19 period) (Tables A2 and A3). That was likely attributable to the significant reduction of vehicular traffic and transport, and to the reduction or complete stop of industrial activities given by the restrictions imposed by the authorities. As reported in Source Apportionment Study of the City of Skopje, city traffic counts for a 19–20% of the total PM emissions [11], thus even a slight reduction of work related traveling or commuting might have influenced the overall concentrations. Similar trend of reduction of PM_{10} by 33–41% was reported in Milan, (Italy) study during the partial lockdown and additional 13–19% during total lockdown; and for $PM_{2.5}$, reduction from 37–44%. As concluded in Milan study, small difference of PM concentrations between partial and total lockdown can be attributable due to low contribution of the industrial sector [15].

The concentration difference of PM between two periods was statistically significant for PM_{10} and $PM_{2.5}$ in the City of Skopje (41.8 μg/m^3 in non-COVID period and 34.1 μg/m^3 in 2020 for PM_{10}; and 26.6 μg/m^3 and 22.3 μg/m^3 for $PM_{2.5}$). It is unexpected finding for the capital city, bearing in mind the smaller difference in the other cities, or even increment in the $PM_{2.5}$ concentrations in Kumanovo. We found that $PM_{2.5}$ concentrations in Skopje are moderately correlated with carbon monoxide in all four cities (r = 0.51–R^2 = 0.27) and with NO_2 in Skopje and Bitola (r = 0.61; R^2 = 0.37) (Table A7).

Concentration of $PM_{2.5}$ and PM_{10} decreased by 32% and 34%, respectively, have been reported in the study of Yangtze Delta River, (China) after implementations of Level I and Level II response that means particularly serious and serious level of measures according to their National Emergency Response Plan [16], and 24% reduction of $PM_{2.5}$ in cities in China that have been locked down [17]. In its recent report, World Bank reported no change of $PM_{2.5}$ concentrations in France, Beijing and other bigger cities in China after the lockdown, while in India and Hubei, China levels of $PM_{2.5}$ were lower after the lockdown but similar trend is reported in that part of the year prior COVID-19 outbreak. The effects in Delhi, India, were visible after 10 days after the lockdown, while in Kolkata, the decline came over 3 weeks after [18].

The smaller, or lack of reductions in $PM_{2.5}$ concentrations reflect the fact that "$PM_{2.5}$ has a complex source structure and not all sources of $PM_{2.5}$ were affected by the economic lockdown" such as natural sources, windblown dust, and dust. Secondary formed $PM_{2.5}$ from precursors such as ammonia mixed with sulfur dioxide (SO_2), nitrogen dioxides (NO_2), or low range transportation are significant source of particulate matter apart from direct emissions [19]. Many reports summarized that "air quality has many components and improvements were not consistent as a result of the economic lockdown, particularly when it comes to the pollutant that is the most harmful to human health – $PM_{2.5}$" [16], [18], [19].

Impact of the lockdown on the NO_2, ozone and carbon monoxide

The most significant reduction of the concentration in the study was found in terms of NO_2 concentration (by 5% in Kumanovo; 24% in Bitola; 27% in Tetovo and 31% in Skopje). The NO_2 and $PM_{2.5}$ concentrations correlated well (r = 0.61 in Skopje; r = 0.78 Tetovo; r = 0.73 Kumanovo) (Table A7) which could indicate that two pollutants originate from common source. NO_2, a noxious gas emitted by motor vehicles, power plants, and industrial facilities had a constant decrement of the concentrations during the analyzed period except in the 12 weeks, after the Labor Day restrictions, when the temperature increment has been reported in Skopje and Bitola (by 48–68% respectively). The slight relaxation of the implementation of the measures and their control, as an introduction to the overall re-opening of the country to the upcoming parliamentary elections, might be the possible explanation.

In the study of Almaty, Kazakhstan, correlation was found between NO_2 and carbon monoxide during COVID-19 period, but decrement of NO_2 concentration was partly related to higher precipitations in the analyzed period [19]. The most prominent drop of NO_2 concentration has been reported in the Yangtze River Delta Region, China as well (by 30–52%) as a result of the stoppage of industrial activities in various enterprises. World Bank reported sharp decrement in Hubei (China), France, and India through satellite that was as nearly as those measured by ground level monitoring stations [18]. Our study findings are similar to the studies conducted in Milan, Italy [15]. Measures and lockdown implemented in Barcelona led to NO_2 reduction from 47.0% to 51.4% [20], [21], similarly to other major cities such as Madrid and Seville in Spain (by 20 to 30% after the lockdown). Furthermore, same reduction through NASA satellite has been reported in northeastern part of USA [5], [22] and Bay Area, San Francisco USA [23].

Surprisingly, in our study, we found a significant drop of the concentration of ground level ozone compared to the pre COVID-19 3-years period by 6–47% (see section Results, Table A5). Having in mind the missing meteorological data in the other cities (Tetovo and Kumanovo where the highest drop of the concentration was reported), we were not able to define the role of those factors on this decline. However, a moderate inverse correlation between ozone and NO_2 levels is evident in this study and expected, due to complex photochemical reactions between nitrogen oxides and volatile organic compounds in the presence of sunlight that results with formation of ozone. Many studies have found that reduction in the level of nitrogen dioxide (NO_2) is invariably accompanied by an increase in the atmospheric concentration of O_3 [17], [24], [25], [26], [27], [28]. Still, the absence of data on VOCs and benzene emissions has stopped us to make final conclusion on this. The rising of O_3 is usual during spring and summer due to higher solar radiation, which promotes the photolysis of NO_2 [15], [29], [30]. In our study, increment of the ozone concentration followed after the increment of the ambient temperature is evident in the 6th and the 7th week of the analyzed COVID-19 period (Figure 4 and Table A5).

The effect of implemented measures in Republic of Macedonia was not so homogeneous in terms of carbon monoxide concentrations. The highest drop we found was in Kumanovo (31%), 10% in Bitola and 4% in Tetovo, while in Skopje, the concentrations were even higher by 3% compared to the 2017–2019. Having in mind that main sources of CO emissions are incomplete combustion processes (household heating, traffic etc.), in the absence of new source apportionment study and meteorological data for other two cities, it is very hard to make a final conclusion for all analyzed air pollutants including CO.

Monitoring of air quality and pollutant concentrations along with population and health data such as fraction of population that live in areas at high levels of pollutants, incidence, hospital admission, and mortality due to respiratory and cardiovascular diseases and number of people infected by COVID-19, is very important to analyze the effects of long-term and short-term effects of air pollution on the spread and outcomes of COVID-19 infections. Many studies already found conclusive data that indicate correlation between long-term and short-term pollution with the cases of COVID-19 and those factors may represent a favorable context for the spread of the virus [31], [32], [33], [34], [35].

This study has some limitations. Missing continuous measurements of meteorological data in the city of Tetovo and Kumanovo could be considered as one of them. Second, "comparison between air pollution levels before and after the outbreak can be problematic because it lacks a proper counterfactual analysis" [17]. In the setting of Macedonia, this could be also a problem due to slightly decreasing trend of air pollutants over the last years caused by implementations of some measures and enforcement of environmental regulations (stricter measures for emissions from industries for example), or might be due to increased environmental public awareness. During the COVID-19 period, a complete (total) lockdown or better to say quarantine has been implemented only in one city (Debar), but absence of monitoring station nearby, small population size and density of the city, stopped us to use Debar as a control city (counterfactual).

Conclusions

Its well-known that air pollution has a various adverse health effects. It affects our mental health, cognition, productivity, has effects on morbidity and mortality and quality of our lives in general.

In our study, we have found substantial decrement of the air pollutants concentration due to reduced human activities caused by COVID-19 pandemic. Still, concentrations of particulate matter especially, remained high during lockdown, 2–3 times higher than levels considered safe by the WHO (10 $\mu g/m^3$ for the annual mean) [36]. That indicates there are other pollution sources devastating the air that we breathe. Our findings could have an important implication on future policy making processes. Still, there is a need of cost-benefit study to assess economic cost due to lockdown in Republic of Macedonia. According to the experiences from China, similar levels of air quality improvement can be achieved at a much lower cost, for example, restrictions on gasoline fuel standards (more stringent standards), introducing control zones in cities, implementation of stringent short-term environmental regulations during some bigger events or gathering of people, stringent control of emissions from coal-fired power plants, etc. As is concluded in China studies, "is highly inefficient to use city lockdowns to reduce pollution, and many other, cheaper, ways to achieve the same environmental target exist" [17]. Although beneficial to human health, economic implications of the lockdown could have a negative impact on the health as well.

Aggregating and analyzing morbidity and mortality data timely will enable to assess the overall health burden of lockdown. Further studies regarding chemical composition of particulate matter in terms of polycyclic aromatic hydrocarbons (single molecules and their ratios), nitro-compounds, metals, and semimetals might lead to a more accurate description of this or similar phenomena.

Finally, from this unexpected situation, we should learn how to reduce pollution on long-term basis implementing more sustainable practices and behaviors in our daily routine.

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Appendix

Table A1: Average temperature of ambient air and % change compared with previous week of the COVID-19 period

Meteorological factor	Period	22 February	1 March	8 March	15 March	22 March	29 March	5 April	12 April	19 April	26 April	3 May	10 May	17 May	24 May
Temperature (°C)															
Skopje	2017–2019	5.2	9.0	10.2	11.7	10.4	14.2	14.3	15.3	14.7	18.6	17.6	18.1	18.9	20.2
	Covid-19, 2020	6.6	8.9	10.4	9.8	5.4	6.9	12.7	13.1	13.2	15.8	14.3	21.3	20.2	15.5
			36%	17%	−6%	−45%	29%	83%	3%	0%	20%	−9%	48%	−5%	−23%
Bitola	2017–2019	2.7	6.9	7.4	9.3	7.2	10.2	10.8	13.4	11.2	16.1	13.9	14.5	15.1	16.1
	Covid-19, 2020	6.64	8.32	8.47	6.72	3.80	3.64	9.29	11.64	11.21	14.46	12.27	20.64	17.51	12.59
			25%	2%	−21%	−43%	−4%	155%	25%	−4%	29%	−15%	68%	−15%	−28%
Humidity (%)															
Skopje	2017–2019		64.8	64.7	63.6	59.3	58.3	49.3	61.9	60.9	51.8	58.9	64.4	66.5	65.1
	Covid-19, 2020		51.9	53.8	64.7	55.6	83.4	72.1	46.9	52.9	67.2	60.0	57.9	54.7	61.6
				4%	20%	−14%	50%	−14%	−35%	13%	27%	−11%	−4%	−5%	13%
Bitola	2017–2019		71.2	60.2	60.9	55.1	63.8	55.4	67.0	63.7	60.5	56.6	63.7	69.3	67.5
	Covid-19, 2020		64.0	68.6	71.9	59.4	85.0	83.0	52.9	50.7	65.9	56.6	57.7	43.1	60.4
				7%	5%	−17%	43%	−2%	−36%	−4%	30%	−14%	2%	−25%	40%
Wind speed (m/s)															
Skopje	2017–2019	0.8	0.4	0.8	0.6	0.8	0.7	0.7	0.6	0.9	0.5	0.6	0.5	0.5	0.5
	Covid-19, 2020	0.5	0.4	0.6	0.6	0.6	0.9	no data							
Bitola	2017–2019	0.4	0.3	0.4	0.4	0.4	0.4	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2
	Covid-19, 2020	0.2	0.3	0.4	0.2	0.3	0.2	0.4	0.2	0.3	0.4	0.3	0.1	0.1	0.1
			12%	32%	−36%	25%	−30%	80%	−32%	30%	14%	−28%	−56%	0%	25%

Table A2: Average concentration of PM_{10} ($\mu g/m^3$) and % change compared with previous week of the COVID-19 period

City	Period	22 February	1 March	8 March	15 March	22 March	29 March	5 April	12 April	19 April	26 April	3 May	10 May	17 May	24 May	Average of the two periods
Skopje	2017–2019	66.3	62.6	44.7	48.4	47.1	41.4	32.4	37.9	35.0	43.2	34.9	29.2	31.1	30.6	41.8
	COVID-19, 2020	49.6	41.6	37.1	44.2	40.8	39.8	32.4	30.2	22.6	23.2	21.2	39.5	39.2	16.3	34.1
			−16%	−11%	19%	−8%	−2%	−19%	−7%	−25%	3%	−9%	87%	−1%	−58%	−18%
Bitola	2017–2019	55.5	46.3	31.8	46.4	38.4	37.1	36.6	39.3	36.9	49.7	29.3	28.3	25.5	22.1	37.4
	COVID-19, 2020	52.6	38.4	36.3	44.4	32.1	56.3	38.1	30.7	25.1	20.7	17.7	49.3	44.9	15.2	35.8
			−27%	−5%	22%	−28%	76%	−32%	−19%	−18%	−18%	−15%	189%	−9%	−66%	−4%
Tetovo	2017–2019	52.7	57.5	42.3	47.0	46.8	41.2	41.2	38.6	33.3	45.5	37.7	34.2	24.9	29.0	40.8
	COVID-19, 2020	58.7	56.3	40.9	47.6	39.4	51.9	36.9	36.4	26.0	23.9	21.6	44.1	42.1	20.1	39.0
			−4%	−27%	16%	−17%	32%	−29%	−1%	−29%	−8%	−10%	104%	−5%	−52%	−5%
Kumanovo	2017–2019	76.6	75.9	57.3	57.6	50.3	52.5	33.8	36.9	38.7	45.9	33.3	28.8	27.6	25.0	45.7
	COVID-19, 2020	63.6	50.3	50.4	59.9	50.1	50.4	36.9	41.6	31.5	25.6	25.7	41.9	38.6	19.7	41.9
			−21%	0%	19%	−16%	1%	−27%	13%	−24%	−19%	0%	63%	−8%	−49%	−8%

Table A3: Average concentration of $PM_{2.5}$ ($\mu g/m^3$) and % change compared with previous week of the COVID-19 period

City	Period	February 22	March 1	March 8	March 15	March 22	March 29	April 5	April 12	April 19	April 26	May 3	May 10	May 17	May 24	Average of the two periods
Skopje	2017–2019	41.3	42.0	29.2	31.5	32.8	28.3	21.5	23.5	23.9	23.8	21.1	18.1	18.7	16.3	26.6
	COVID-19, 2020	31.3	25.6	21.9	27.8	25.7	24.5	20.7	22.0	16.1	16.2	16.8	27.1	23.9	12.5	22.3
			−18%	−15%	27%	−8%	−5%	−15%	6%	−27%	1%	4%	61%	−12%	−48%	−16%
Bitola	2018–2019	41.9	41.0	21.0	25.3	35.4	16.9	19.4	23.8	14.3	18.6	18.9	13.4	14.1	13.2	22.6
	COVID-19, 2020	34.5	26.4	25.2	30.6	27.9	46.7	24.2	18.3	16.2	11.8	9.5	13.3	15.8	9.2	22.1
			−24%	−4%	21%	−9%	67%	−48%	−24%	−11%	−27%	−19%	40%	19%	−42%	−2%
Tetovo	2018–2019	44.5	57.6	31.3	37.1	41.3	28.7	24.2	25.3	20.3	25.2	24.1	16.1	14.8	18.0	29.2
	COVID-19, 2020	44.3	43.4	29.1	34.6	34.3	42.0	25.2	24.9	18.6	14.8	13.1	17.3	22.3	14.2	27.0
			−2%	−33%	19%	−1%	23%	−40%	−1%	−25%	−21%	−11%	32%	29%	−36%	−7%
Kumanovo	2018–2019	35.8	56.5	40.7	33.6	32.8	33.1	20.5	21.9	20.3	18.1	17.0	12.6	11.6	12.4	26.2
	COVID-19, 2020	43.8	32.9	35.7	42.5	40.5	38.1	24.5	29.4	23.3	16.8	16.8	18.0	18.5	13.3	28.2
			−25%	8%	19%	−5%	−6%	−36%	20%	−21%	−28%	0%	8%	2%	−28%	7%

Table A4: Average concentration of NO_2 ($\mu g/m^3$) and % change compared with previous week of the COVID-19 period

City	Period	22 February	1 March	8 March	15 March	22 March	29 March	5 April	12 April	19 April	26 April	3 May	10 May	17 May	24 May	Average of the two periods
Skopje	2017–2019	29.7	33.7	31.4	32.9	31.4	28.0	21.7	23.2	22.9	21.1	21.8	20.8	23.2	23.5	26.1
	COVID-19, 2020	31.8	33.1	27.6	26.1	22.6	16.5	13.4	11.8	10.1	11.4	12.1	12.4	12.6	12.4	18.1
			4%	−17%	−5%	−13%	−27%	−19%	−12%	−15%	13%	7%	2%	2%	−1%	−31%
Bitola	2017–2019	16.6	25.0	12.7	15.8	15.3	15.2	14.8	13.2	13.2	13.9	11.6	13.1	13.0	11.4	14.6
	COVID-19, 2020	18.1	16.6	14.9	16.7	8.8	14.5	9.7	8.6	6.5	7.7	7.0	10.8	8.6	6.7	11.1
			−9%	−10%	12%	−47%	64%	−33%	−11%	−25%	20%	−10%	54%	−20%	−22%	−24%
Tetovo	2018–2019	23.9	39.4	29.6	29.2	29.5	28.7	23.7	24.7	23.6	20.7	20.8	19.5	17.5	16.2	24.8
	COVID-19, 2020	33.7	33.4	25.6	17.3	15.7	20.5	16.2	14.1	10.7	13.4	13.8	14.8	15.1	10.2	18.2
			−1%	−23%	−33%	−9%	31%	−21%	−13%	−24%	25%	3%	8%	2%	−32%	−27%
Kumanovo	2018–2019	19.4	32.2	29.8	22.6	19.9	25.4	24.1	18.3	20.5	16.9	15.4	13.8	13.5	11.5	20.2
	COVID-19, 2020	23.6	25.4	20.0	24.8	17.5	17.3	22.6	23.4	15.7	12.8	16.8	18.5	15.0	15.6	19.2
			8%	−22%	24%	−29%	−1%	30%	4%	−33%	−18%	32%	10%	−19%	4%	−5%

Table A5: Average concentration of O_3 (μg/m^3) and % change compared with previous week of the COVID-19 period

City	Period	22 February	1 March	8 March	15 March	22 March	29 March	5 April	12 April	19 April	26 April	3 May	10 May	17 May	24 May	Average of the two periods
Skopje	2017–2019	32.4	32.8	33.4	31.7	40.4	47.4	40.6	39.9	45.9	40.0	42.2	40.7	43.1	43.3	39.6
	COVID-19, 2020	27.0	21.1	28.3	30.8	18.4	37.7	48.1	44.6	43.5	42.3	45.0	45.0	43.0	48.5	37.4
			−22%	34%	9%	−40%	105%	27%	−7%	−2%	−3%	6%	0%	−4%	13%	−6%
Bitola	2017–2019	46.1	54.6	58.2	55.3	56.1	63.6	53.4	65.7	66.0	63.4	70.5	61.9	61.0	58.7	59.6
	COVID-19, 2020	40.1	42.9	40.4	42.4	42.4	44.6	56.1	54.3	50.4	58.5	57.4	53.5	51.6	51.2	49.0
			7%	−6%	5%	0%	5%	26%	−3%	−7%	16%	−2%	−7%	−4%	−1%	−18%
Tetovo	2017–2019	33.8	33.1	36.2	35.4	39.9	45.3	35.3	38.7	44.3	45.3	45.5	42.5	51.8	53.7	41.5
	COVID-19, 2020	17.7	10.9	18.2	25.3	10.2	21.0	38.2	33.3	23.5	33.0	29.2	33.7	26.4	28.2	24.9
			−39%	68%	40%	−60%	107%	82%	−13%	−29%	40%	-12%	15%	−22%	7%	−40%
Kumanovo	2018–2019	37.2	24.4	31.2	37.0	47.5	55.0	31.9	30.3	46.0	38.2	38.3	35.6	41.2	40.0	38.1
	COVID-19, 2020	19.2	17.0	15.9	22.3	12.0	19.0	34.1	25.0	16.9	16.9	24.2	21.6	19.2	22.3	20.4
			−12%	−6%	40%	−46%	58%	80%	−27%	−32%	0%	43%	−11%	−11%	16%	−47%

Table A6: Average concentration of CO (mg/m^3) and % change compared with previous week of the COVID-19 period

City	Period	22 February	1 March	8 March	15 March	22 March	29 March	5 April	12 April	19 April	26 April	3 May	10 May	17 May	24 May	Average of the two periods
Skopje	2017–2019	0.85	0.69	0.52	0.58	0.50	0.43	0.39	0.40	0.34	0.32	0.29	0.28	0.31	0.31	0.44
	COVID-19, 2020	0.92	0.69	0.60	0.66	0.52	0.44	0.35	0.37	0.25	0.28	0.35	0.34	0.30	0.32	0.46
			−25%	−13%	10%	−22%	−15%	−19%	4%	−33%	14%	24%	−4%	−10%	4%	3%
Bitola	2017–2019	0.67	0.58	0.43	0.47	0.41	0.32	0.36	0.28	0.28	0.23	0.26	0.26	0.22	0.26	0.36
	COVID-19, 2020	0.88	0.36	0.38	0.46	0.30	0.49	0.25	0.20	0.20	0.19	0.17	0.24	0.23	0.15	0.32
			−59%	6%	20%	−33%	61%	−49%	−20%	−1%	−2%	−10%	38%	−3%	−34%	−10%
Tetovo	2017–2019	0.69	0.78	0.46	0.55	0.48	0.36	0.29	0.29	0.26	0.23	0.26	0.21	0.19	0.19	0.37
	COVID-19, 2020	0.91	0.63	0.42	0.24	0.38	0.42	0.27	0.31	0.29	0.28	0.29	0.26	0.19	0.14	0.36
			−31%	−34%	−42%	58%	9%	−34%	13%	−7%	−4%	3%	−10%	−28%	−23%	−4%
Kumanovo	2017–2019	0.96	1.15	0.77	0.69	0.55	0.48	0.64	0.26	0.25	0.27	0.34	0.23	0.20	0.17	0.50
	COVID-19, 2020	0.78	0.49	0.55	0.49	0.44	0.35	0.19	0.31	0.31	0.21	0.24	0.20	0.13	0.10	0.34
			−37%	12%	−10%	−11%	−20%	−45%	58%	0%	−33%	18%	−18%	−36%	−22%	−31%

Table A7: Spearman correlation coefficients between air pollutants measured in selected cities

	$PM_{2.5}$ Skopje	$PM_{2.5}$ Bitola	$PM_{2.5}$ Tetovo	$PM_{2.5}$ Kumanovo	NO_2 Skopje	NO_2 Bitola	NO_2 Tetovo	NO_2 Kumanovo	O_3 Skopje	O_3 Bitola	O_3 Tetovo	O_3 Kumanovo	CO Skopje	CO Bitola	CO Tetovo	CO Kumanovo
$PM_{2.5}$ Skopje	1															
$PM_{2.5}$ Bitola	0.473**	1														
$PM_{2.5}$ Tetovo	0.455**	0.753**	1													
$PM_{2.5}$ Kumanovo	0.422**	0.681**	0.774**	1												
NO_2 Skopje	0.612**	0.280**	0.274**	0.253**	1											
NO_2 Bitola	0.598**	0.317**	0.182**	0.132*	0.667**	1										
NO_2 Tetovo	0.463**	0.575**	0.775**	0.664**	0.320**	0.198**	1									
NO_2 Kumanovo	0.280**	0.380**	0.500**	0.734**	0.185**	0.118*	0.647**	1								
O_3 Skopje	−S.300**	−0.158*	−0.136*	−0.071	−0.449**	−0.276**	−0.295**	−0.114*	1							
O_3 Bitola	−0.185**	−0.274**	−0.124*	−0.134*	−0.178**	−0.334**	−0.036	−0.087	0.372**	1						
O_3 Tetovo	−0.126*	−0.125	−0.041	−0.205**	0.031	0.063	−0.146*	−0.184**	0.469**	0.560**	1					
O_3 Kumanovo	−0.146*	−0.019	−0.082	−0.240**	0.006	0.051	0.070	−0.119*	−0.221**	0.102	.0220**	1				
CO Skopje	0.658**	.345**	0.290**	0.305**	0.612**	0.418**	0.295**	0.202**	−0.444**	−0.464**	−0.397**	−0.205**	1			
CO Bitola	0.534**	0.413**	0.367**	0.411**	0.416**	0.537**	0.448**	0.357**	−0.318**	−0.461**	−0.290**	−0.080	0.661**	1		
CO Tetovo	0.510**	0.309**	0.251**	0.405**	0.379**	0.357**	0.313**	0.381**	−0.313**	−0.393**	−0.430**	−0.175**	0.627**	0.613**	1	
CO Kumanovo	0.654**	0.281**	0.213**	0.304**	0.556**	0.433**	0.298**	0.249**	−0.355**	−0.328**	−0.299**	−0.199**	0.776**	0.618**	0.657**	1

Sig. (2-tailed)**

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Susceptibility of Coronavirus Disease-19 in Pediatric Population

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Abstract

Since the end of 2019 until present, coronavirus (CoV) disease (COVID)-2019 has spread globally and caused a pandemic. The disease is caused by severe acute respiratory syndrome-2 (SARS-CoV-2). The disease is showed to be less affecting pediatric population. The proportion children suffering from COVID-19 is only around 2% of total cases with only 0.08% mortality rate. Several hypotheses have been proposed regarding this condition. Children are supposed to be less exposed to patients with COVID-19, have lesser amount of angiotensin converting enzyme 2, have different immune response compared to adults, and have faster tissue recovery ability. All of them decrease the possibility of SARS-CoV-2 infection in pediatric population.

Introduction

In December 2019, new cases of pneumonia were reported in China. The epicenter of the disease was suspected in Huanan seafood market in Wuhan, Hubei Province [1], [2], [3]. The disease was caused by severe acute respiratory syndrome-2 (SARS-CoV-2) and was later named as coronavirus (CoV) disease-2019 (COVID-19) [4]. COVID-19 spread rapidly around the globe and was declared as a pandemic by World Health Organization in March 11, 2020 [5]. The most common mode of transmission is through respiratory droplet. There was no evidence regarding vertical transmission from mother to child [6], [7], [8]. However, antibody toward SARS-CoV-2 was detected in newborns from mothers with COVID-19. Therefore, separation of newborns from their COVID-19 infected mothers is advised [7].

The epidemiological data regarding COVID-19 in children is not certain. It is due to lack of COVID-19 screening in pediatric population from asymptomatic disease course in most of this population [7], [8]. Children are also less affected by COVID-19 compared to adults. The prevalence rates of pediatric COVID-19 in China and Italy are 2% and 1.2%, respectively [7], [9]. Even more, neonatal case is very rare. Male children are affected more than female ones [7]. Most pediatric cases of COVID-19 are asymptomatic to mild with reported mortality of 0.08% [7], [8], [9]. Several hypotheses are raised regarding the low susceptibility and mortality of COVID-19 in children. We will discuss about the hypotheses in this review.

Pathogenesis of COVID-19

CoV is an enveloped single-stranded positive-sense ribonucleic acid (RNA) virus. It consists of alpha and beta genera where SARS-CoV-2 belongs to beta genera [6], [10]. At first, COVID-19 is thought to be transmitted from snakes. Latterly, studies showed that mammals are the possible carriers for the disease [6]. After entering human's body mainly through respiratory tract, virus' spike glycoprotein (a surface glycoprotein) binds angiotensin converting enzyme (ACE) 2. This process is followed by fusion of virus with cell membrane. Virus' RNA will integrate into host deoxyribonucleic acid. Host cell will then synthesize virus' proteins. New viruses are assembled and ready to infect other cells, causing death in previous host cell [6], [11], [12]. The symptoms of COVID-19 are fever, cough, fatigue, dyspnea, and diarrhea. Some upper respiratory tract symptoms may present in COVID-19 patients such as rhinorrhea, sneezing, and sore throat [6], [8], [9]. Real-time polymerase chain reaction from nasopharyngeal swab is considered as the gold standard for diagnosing COVID-19 [6], [7].

"Lack of Exposure" Hypothesis

Human to human transmission occurs due to mutation of SARS-CoV-2 genome from its wild ancestor [13]. Compared to adults, children tend to have fewer outdoor activities. This gives this population a forced social and physical distancing even before the COVID-19 pandemic [14]. A study stated that the probability of children in contact with infected patients is 1.3% compared to 3.5% in adults [15]. This clearly lower the susceptibility of COVID-19 compared to adult population.

"Lack of Receptor" Hypothesis

Children have less mature and functional ACE2. As ACE2 is important viral receptor, this condition is suggested to be protective factor for COVID-19 in children [7], [9], [14]. This is supported by a fact that viral load in pediatric population is not different from that in adult ones. However, a study in rats showed that the quantity of ACE2 is decreased in older rats compared to younger ones [7].

"Different Immune Response" Hypothesis

Children have more active innate immune system which allows a more rapid clearance of the virus [14], [15], healthier respiratory tract due to less exposure of cigarette smoke and air pollutant, and less comorbidity [14]. Innate immune system consists of neutrophils, monocytes, macrophages, and dendritic cells. In newborns, both innate and adaptive immune system functions are not perfect. As time goes by, innate immune system getting more active before decreasing into adult state while adaptive immune system gradually active. As age advances, the immune system becomes impaired due to remodeling and declining processes [16]. The amount of antigen presenting cells in respiratory tract of children is similar with those in adults. In contrast, the amount of macrophages and monocytes is higher in children [17]. The presence of thymus in children causes an increase in lymphocyte maturation and number. Even though the lymphocyte function is impaired, its amount may improve host immunity toward viral infections [16].

Innate immune system eliminates viruses through production of interferons by dendritic cells and monocytes [15]. Those cells recognize viral nucleic acids through toll-like receptors. Interferons will activate natural killer cells and adaptive immune response to further helping in viral elimination. Natural killer cells lyse virus-infected cells and prevent viral replication and spreading [16], [18]. Innate immune system combined with T and B cell responses are important for viral clearance [15].

In the other hand, recurrent infection of the upper respiratory tract in children is postulated to induce a condition called trained immunity [15]. The concept of trained immunity was introduced in 2011. According to the concept, bacterial infection induces cross-protection against other pathogens [9]. In this condition, monocytes and other myeloid cells undergo epigenetic changes which increase their capability to eliminate antigens including SARS-CoV-2 [15].

Less comorbidity in children prevents immune over reactivity and further cytokine storm [15]. Adaptive immune system in children is also not well-developed, giving less cytokine production, and lower probability of cytokine storm [17]. That's why children usually only show asymptomatic to mild COVID-19 manifestations. Similar reason underlies the low mortality rate of children with COVID-19 [15].

"Faster Recovery" Hypothesis

In children, tissue repair process is better compared to adults. Tissue repair is influenced by efferocytosis (non-inflammatory cell death) and M2 repair program which is related with monocytes/ macrophages. These processes are mediated by resolvins. Resolvins are expressed more during childhood. However, infants aged <1 year are at higher risk of COVID-19. It is hypothesized that this population has immature immune response and absence trained immunity [15].

Conclusion

Several hypotheses have been proposed regarding the low susceptibility of COVID-19 in pediatric population. Children are less exposed to patients with COVID-19. They also have lower expression of ACE2 and the SARS-CoV-2 receptor. Immune response in pediatric population is also different from adult, giving protective effect toward COVID-19. Lastly, pediatric population possesses an ability of faster tissue recovery.

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When Will Coronavirus Disease-19 Patients be allowed to Work at the Office Again?: A Literature Study

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Abstract

As numbers of coronavirus disease (COVID)-19 cases in the world rises gradually, both from unending first waves and resurging waves following successful reduction of cases on first waves, both the world and healthcare workers face an impending situation in the near future. For the world, the question may be, "When will we be allowed to work at our office again?" For caregivers, the question will be, "What may happen if over capacitance of healthcare facilities resumes until indeterminate time?" New published guidelines by WHO on clinical management of COVID-19 provided most recent recommendations on criteria for stopping isolation of COVID-19 patients based on new findings that patients positive of severe acute respiratory syndrome coronavirus 2 is not always transmitting virus to surroundings. Furthermore, criteria for terminating isolation are suitable for all COVID-19 cases regardless of the location of isolation or the severity of the disease without the requirement of repeated swab examinations. This further gives an advantage by lowering healthcare costs and effective allocation of health resources. Even if a negative swab result is still a condition to be deemed not to be able to transmit the virus, this should not be a barrier for someone to return to their normal activity and lifestyle while waiting for the test swab results. In the end, the choice whether to pursue a result that has no clear benefits by allocating funds for repeated swab tests at expensive costs and ignoring the productivity of professionals by carrying out prolonged isolation or to optimize the resources at our disposal.

Introduction

An important question often asked by a confirmed coronavirus disease (COVID)-19 patient is: "Doc, when will I be allowed to work at my office again?" followed by "Can I still transmit this virus to other people or my family?"

During these times – at least until this paper is written – patients recovered from COVID-19 may not simply be happy after getting past the acute phase of the disease. This is because at the next phase they will still need to wait for the next re-swab schedule, with the goal to find whether the person is still positive or is already negative of COVID-19, in other words, is the person still able to transmit the virus or not. During these waiting moments, they need to be isolated, unable to go to the office because of the stigma that the patient may still transmit the virus to other people, both at home and at the working environment, therefore, unable to contact closely and need to be physically distanced/stayed away from. Therefore, these long and rigorous processes may inflict a heavy psychological burden for a person recovered from COVID-19; and for patients without any symptoms, it may be something heavier than the disease itself. On the other side, there is no certainty in the matter of time that the following swab test will be negative. No matter how many times the test is conducted, there is no guarantee that the next one will be negative. WHO stated that the test may result in reactivity even though it was conducted weeks after the first infection, while CDC in August 2020 showed that a patient recovered from COVID-19 tested 3 months after first infection may still be reactive to COVID-19 swab test [1].

The question is: If that is the reality and that a reactive swab test is identical to virus transmission, is a negative swab test result an absolute term for someone to live and move normally? Is there prove that someone with a reactive swab test result is still able to transmit severe acute respiratory syndrome coronavirus (SARS-CoV)-2? [2].

What is the Risk of Transmitting SARS-CoV-2?

COVID-19 is caused by an easily transmitted virus called SARS-CoV-2. After someone was exposed to this virus, the RNA virus will be able to be detected at the patient 1–3 days before the occurrence of any symptom. On the upper respiratory tract, viral load will reach its peak in the 1st week following exposure (highest on the 4th day after the symptoms occurred), followed by a progressive decrease over time. On feces and lower respiratory tract, viral load will reach its peak 2 weeks after first exposure. There is a tendency that the RNA virus will be detected longer on people with severe symptoms and immunodeficiency and that there is a connection between transmissibility and onset of symptoms. The highest risk for transmission occurs during symptoms onset and 5 days following the first infection. Usually, 5–10 days after SARS-CoV-2 infection, patients infected will be producing neutralizing antibody progressively. The production of this antibody will lower the risk of infection. Based on these data, 10 days following infection, the risk of patient transmitting COVID-19 is relatively low [3], [4].

Is SARS-CoV-2 Transmissible in a Reverse Transcriptase-polymerase Chain Reaction (RT-PCR) Positive Patients?

COVID-19 (SARS-CoV-2) is confirmed by the presence of the RNA virus detected through molecular tests, usually RT-PCR. The presence of RNA viruses in a person does not always mean that the person is infectious and can transmit the virus to other people [5], [6]. There are factors that determine the risk of transmission, namely the ability of the virus to replicate, symptoms such as coughing, infectious droplets, and environmental conditions and factors associated with the infected individual [4], [5].

In many viral diseases (e.g., SARS-CoV, MERS, influenza virus, Ebola virus, and Zika virus), it is well known that viral RNA can be detected for a long time after the infectious virus has ceased to exist. For example, measles virus, its viral RNA can still be detected 6–8 weeks after the infectious virus itself has disappeared. The immune system can neutralize the virus that prevents subsequent infections but does not eliminate nucleic acids, which remain detectable by RT-PCR, which will gradually decrease over time [5], [7], [8].

In COVID-19, the duration of infectious viral transmission period varies widely and may depend on the severity of the disease and the patient's immune condition. A study obtained repeated viral RNA tests with negative results in 90% of cases with mild disease, while severe disease had positive results with a longer period of time [6], [9]. Zhou *et al*. reported that the median duration of the viral transmission period in COVID-19 patients who were in severe or critical condition was 31 days (range of 18–48 days) [7], [9], [10]. Wolfel *et al*. reported that COVID-19 patients with mild to moderate symptoms did not find the SARS-CoV-2 virus cultured from airway samples 8 days after of onset of symptoms. Other studies with varying degrees of disease have shown an inability to multiply the virus after days 7–9 of symptom onset [4], [8], [11]. In a study of 129 critically ill COVID-19 patients, of whom 30 were immunocompromised, the mean duration of viral transmission as measured by culture was 8 days after onset, with the interquartile range of 5–11 days [9], [12], [13]. The likelihood of detection of the virus on culture is <5% after 15.2 days of symptoms. This study as well as several other studies have reported a correlation between decreased infectivity with decreased viral load and increased neutralizing antibodies. Although viral RNA can be detected by RT-PCR even after symptoms have disappeared, the amount of viral RNA detected is substantially reduced over time and is generally below the threshold for the virus' ability to replicate. Therefore, it is a safe approach to combine the time between the onset of symptoms and the disappearance of symptoms based on current data [4], [14].

When Can Patients Return to Work After Confirmed of COVID-19?

On 27 May 2020, WHO published guidelines on clinical management of COVID-19 and provided most recent recommendations on the criteria for stopping isolation of COVID-19 patients. The updates are based on new findings that asymptomatic patients still tested positive for the COVID-19 virus (SARS-CoV-2) with RT-PCR even for the following weeks. Even though the test result is still positive, it turns out that it cannot infect other people. The criteria for terminating isolation are suitable for all COVID-19 cases, regardless of the location of isolation or the severity of the disease and without requiring a repeat swab examination, namely: [4], [15], [16], [17]

1. For symptomatic patients: 10 days after symptom onset, plus at least 3 additional days without symptoms (including no fever and no respiratory symptoms)
2. For asymptomatic cases: 10 days after testing positive for SARS-CoV-2.

This latest WHO recommendation (27 May) differs from and also revises the previous recommendation (12 January) that patient isolation is terminated upon clinical recovery and two negative RT-PCR results are obtained in sequential samples taken at least 24 h apart [10].

Based on the CDC, there are three principles to stop isolation of COVID-19 patients, namely “symptom-based strategies,” “time-based strategies,” and “test-based strategies.” The “symptom-based strategy” is the CDC’s latest revised release for isolation for symptomatic COVID-19 patients. Patients may move out from isolation and return to work if the following three conditions are met [10], [17], [18]:

1. At least 10 days from when symptoms first appeared; and
2. At least 24 h since the last fever without using fever-reducing drugs; and
3. All COVID-related symptoms (e.g., cough and shortness of breath) have improved.

The “time-based strategy” remains valid for patients with a positive but asymptomatic swab test (i.e., 10 days of isolation from the date of positive test), as well as for patients (including healthcare professionals) with severe to critical illness or who are severely immunocompromised. Adults, the duration is at least 10 days–20 days after symptom onset, while the “test-based strategy” is no longer resisted by the CDC (except in severely immunocompromised patients). The reason it is no longer considering a test-based strategy is that it will result in prolonged isolation because the SARS-CoV-2 RNA virus is still detected, but the patient is not able to transmit the virus anymore (CDC, update August 10) [11], [19].

In our hospital (a University Hospital in Bali, Indonesia), when our government adopts the old criteria from WHO, we used 2 times negative results of PCR for stopping isolation, many problems happen. In many cases, sometimes patients already did not have any symptoms again, but the PCR result is still positive. In our hospital from April until June 2020, 42 (16.5%) patients have hospitalized for more than 14 days, even though they do not have any symptom, but the PCR results were positive. One of the patient, already hospitalized 58 days, but she did not have any symptom since day 6 after admission. Since July 2020, our government adopts the newest WHO guidelines. From that time, the length of patient care can be shorter. The average patient was treated for 13–14 days.

Public Health Impact

This study focuses on the exploration of COVID-19 patients isolation time and factors in relation to isolation time. We also did a literature-based critical analysis on the exact necessity of prolonged isolation time as well as repeated swab test in deciding whether a COVID-19 patient is to be released from hospitalization or not. Based on the finding of this study, we could conclude that approximately 2-weeks isolation time starting from symptoms onset is safe and reliable enough as a standard for COVID-19 patient release, especially those with mild symptoms. Thus, the result of this study poses as scientific-based supporting data to aid effective decision making for stakeholders in the management of health resources regarding COVID-19 inpatients and hospitalization, namely, a faster release of COVID-19 patients after 14 days of hospitalization means there will be more space of new patients, specifically those critically ill and in need of active supervision. Other than hospital bed and facilities, fewer patients to tend also means healthcare team could also put more focus on urgent and severe patients, increasing productivity and lessening burden, which might lead to medical errors. The results from this study could also be considered by the government and local ministry of health to reconsider and perhaps change their old way of managing COVID-19 funds. The previous statement refers to the fact that “unnecessary” fund spent on hospital fee for mild or recovered patients with no symptoms who are fully capable of home-care and self-quarantine is a waste of resources, which could be allocated more effectively for other aspects of COVID-19 management [19], [20].

Perspective

Based on research evidence and recommendations from WHO and CDC above, of course, it will raise a belief that the negative swab criteria as a reference for someone to be able to stop their isolation and be allowed to return to work are no longer relevant to be applied because there is no rational basis for using the negative swab reference to be considered cured of COVID-19.

Sometimes professionals who are accustomed to critical thinking who always put forward evidence (evidenced based) forget about this. It may be that this is based on excessive worry and fear of contracting so that in the end, they put forward baseless opinions and no longer consider the aftereffects as a result of improper application of guidelines.

In this world, no one is the same, everyone has their own uniqueness. Likewise, there is no diagnosis of the same disease, which will give the same outcome. It is commonly known in medical circles that the management of disease must apply the principles of personalized medicine and an individualized treatment approach. Implementing an action must be personal or individual and in accordance with the conditions at that time. This also applies for patients with confirmed

COVID-19. Before deciding on the next step (e.g., the length of time for isolation and the need for a re-swab for evaluation), an evaluation of each condition must be carried out individually, especially the presence or absence of symptoms (mild, moderate, severe, or critical), the presence or absence of sequelae that may describe the severity of the complications that occur, the presence or absence of comorbid conditions, and so on. This is so that the available resources, which are generally limited, will actually be used effectively and efficiently and can be allocated to other needs that are more appropriate. From patient's perspective, there is a sense of satisfaction after having received proper care, which has been adjusted to their personal conditions.

Even if a negative swab is still a condition need to be met to be deemed not to transmit the virus, then this should not be a barrier for someone to be able to return to their normal activity and lifestyle while waiting for the test swab results. The person (the "patient") is clear, has been confirmed with COVID-19, so with this clear status, it is easier to be able to implement stricter transmission prevention patterns, for example, using N95 masks or the equivalent, especially when treating patients for health workers. The application of a more stringent pattern of prevention of transmission over a certain period of time in patients with confirmed COVID-19 feels more human while waiting for a laboratory examination schedule (if necessary) rather than isolation.

Another thing that needs to be paid attention to regarding the mere provision of the negative swab is the risk of a shortage of staff/professionals to care for patients, especially if there is a significant spike in confirmed positive COVID-19 cases affecting medical professionals. At the same time, to anticipate this, health facilities must be prepared to face potential staff shortages and have a plan and process to address them, including by implementing the latest WHO and CDC recommendations.

WHO does not prohibit a country from continuing to use the recommendation issued at the beginning of the pandemic, namely 2 negative swabs with a distance of at least 24 h as a criterion for stopping isolation. On the other hand, we all certainly agree that the facilities and infrastructure that we have related to COVID-19 are still very limited, still far from the minimum required. Therefore, the use of sophisticated and expensive laboratories such as the RT-PCR examination for SAR-CoV-2 virus must be right on target, allocated appropriately, so that it can reach more target patients. How much money can be saved if the RT-PCR examination is only done once for each patient for diagnostic purposes only, without re-examinations that may need to be repeated many times with a target of only negative swab results? A laboratory-based approach may still have a place for COVID-19 patients, but of course, it is selective, only in patients with certain conditions based on the evaluation of a competent doctor.

In the end, the choice is ours, whether to pursue something that has no clear benefits (keep allocating funds for swab tests at this inexpensive cost and ignore the productivity of professionals by carrying out prolonged isolation), or whether we will optimize the resources we have at our disposal. Our country, Indonesia, is a country that belongs to the developing country category with limited resources, so if there is a good choice and at a much cheaper cost, of course, we will choose it.

Conclusion

Based on the evidence that shows that the virus can no longer be cultured (no ability to replicate) after 9 days from the onset of symptoms (especially in patients with mild disease), it is safe to stop isolating COVID-19 patients based on clinical criteria with a minimum isolation time of 13 days since symptom onset, and not strictly based on repeated PCR results. Whereas in patients with severe or critical symptoms, as well as those with severe immune disorders, a laboratory-based approach (measurement of viral load and neutralizing antibodies) may be helpful in making decisions about whether or not a person should undergo prolonged isolation [12].

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Overview of Pathology and Laboratory Features of COVID-19

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Abstract

BACKGROUND: The third identified severe respiratory disease in the past two decades and the first to result in a pandemic is the coronavirus disease 2019 (COVID-19) specifically caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

AIM: The aim of this study was to provide an overview of the basic pathology and diagnostic laboratory features of COVID-19.

METHODS: This review involved search of literatures on PubMed, Science alert, Medline, and Advanced Google search using the keywords "SARS-CoV2," "Coronavirus" along with "pathology of COVID-19" and "diagnosis of COVID-19" with related articles pooled, relevant information extracted, and properly referenced.

RESULTS: The recommended method of diagnosis is by nucleic acid testing of the viral ribonucleic acid in which real-time reverse-transcription polymerase chain reaction followed by nucleic acid sequencing when required is performed while some serologic techniques developed include enzyme-linked immunosorbent assay, immunochromatographic lateral flow assay, neutralization bioassay, and specific chemosensors to detect the immunoglobulin M and immunoglobulin G antibodies produced, although sole use of serologic tests is highly discouraged by monitoring agencies. The hematological features display leukocytosis with lymphocytopenia, eosinopenia, reduced procalcitonin along with increased D-dimer, C-reactive protein, serum amyloid A, fibrin, fibrin degradation products, and some inflammatory markers such as interleukin (IL)-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, MCP10, interferon gamma-induced protein 10, and tumor necrosis factor-α. The pathologic presentations include pleurisy, lung consolidation, pulmonary edema and pericarditis along with other features of acute respiratory syndrome, myocardial injury, and acute kidney injury.

CONCLUSION: There are highly efficacious and reliable methods of diagnosis of COVID-19 which also determine the stage and severity of the condition, and these methods are performed in line with specific clinical presentations. However, more studies are required to identify the capabilities, characteristics, and tendencies of this novel virus.

Introduction

Coronavirus disease 2019 (COVID-19), a latest outbreak proclaimed as a pandemic by the World Health Organization (WHO), is a diseased condition resulting from infection of the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) [1]. The disease was named on February 11, 2020, by the WHO and subsequently declared a pandemic, on March 11, 2020 [2], [3], when it was recorded that there were more than 118,000 cases in 114 countries and 4291 deaths as a result of its rapid spread through human to human transmission by aerosol droplets to all continents of human existence with 13-fold increase [4]. COVID-19 is the third identified severe respiratory illness caused by the coronavirus in the past two decades and the first to cause a pandemic [4]. Others such as SARS and Middle East respiratory syndrome (MERS) have been earlier identified possessing similar susceptibility [5].

SARS-CoV-2 was classified by the International Committee on Taxonomy of Viruses (ICTV) as a newly identified strain of ribonucleic acid (RNA) viruses which had not been previously isolated in humans until recently when it was discovered to be transmitted from human to human resulting in series of respiratory tract disorders, ranging from various levels of severity which commenced in Wuhan, China [6], [7], [8], [9]. The complete genome sequencing information from two assemblage revealed that the SARS-CoV-2 comprises six major open reading frames and shares approximately 80% of similarity with SARS-CoV, but 98.65% nucleotide identity to partial RNA-dependent RNA polymerase (RdRp) gene and 96.2% identity to RaTG13 of SARS-related CoronaVirus family found in bats, respectively [6], [10], [11], [12].

Globally, as at July 17, 2020, there have been 13,616,593 confirmed cases of COVID-19, including 585,727 deaths with 7,154,840; 3,008,972; 1,346,792; 1, 308,441; 543,122; and 253,495 confirmed cases in America, Europe, Eastern Mediterranean, South-East Asia, Africa, and Western pacific continents, respectively [13], [14]. Despite the documented comparatively low mortality, the transmissibility of COVID-19 is observably elevated [15], [16]. This transmissibility potential is the R_0 value which is a pointer of the viral ability to transmit, thereby representing the average figure of new infections produced by an infectious person in a an uninfected populace. When $R_0 > 1$, this indicates that there is the possibility of increased infection while $R_0 < 1$ indicates the fading off of transmission. An essential concept of infectious disease epidemiology is the reproduction number which indicates the menace associated with the endemic spread of an infectious agent [17]. The basic reproduction number (R_0) of COVID-19 has been estimated to range from 1.4 to 6.47, while some studies have shown the R_0 value to be >3 [16], [17], [18].

The COVID-19 is characterized by various degenerative symptoms such as pyrexia, dry or hoarse cough, sputum, gasping or cessation of breath, loss of taste sensation and/or smell, exhaustion, and lymphopenia in infected persons with the infections causing viral pneumonia which may lead to SARS and mortality in more severe cases or persons with underlining conditions such as diabetes and hypertension [6], [7], [8], [9], [19].

With the current trend in the management, epidemiology and occurrences in this pandemic, this review attempts to appraise the pathology, diagnosis, and laboratory features of COVID-19.

Methodology

This review involved search of the literatures on PubMed, Medline , Science alert, and Advanced Google search using the keywords "SARS-CoV2," "Coronavirus" along with "pathology of COVID-19" and "diagnosis of COVID-19"in this text with related articles pooled and relevant information extracted, and properly referenced. From the search, we obtained 205 (220) articles out of which relevant information for this study were specifically extracted from 96 of the publications for this article.

Pathogenesis of COVID-19 infection

Coronaviruses are a family of enveloped single-stranded RNA viruses with zoonotic features, and clinical signs analogous to the regular flu, neurological, severe respiratory, hepatic, and gastrointestinal symptoms [4], [20]. The six other identified coronaviruses which can infect humans aside the SARS-CoV-2 [21], are HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-CoV [6], [21], [22], [23]. They have created two major pandemics in the past 20 years which are the SARS [24] and MERS [11], [21], [25]. In detection of the major source of COVID-19, China Centre for Disease Control (CDC) analysts pointed that it originated from wild animals that are sold in the Wuhan local market (Chinese CDC, 2020). The researchers obtained and analyzed throat swab, lung fluid, and blood samples of 15 patients infected with the virus. The analyses discovered that the virus-specific nucleic acid sequences in the sample differ from those of previously known human coronavirus (hCoV) species displaying that SARS-CoV-2 has similar properties to some of the beta (β) coronaviruses genera identified in bats [8], [11], [26], [27], among the SARS/SARS-like CoV group [11], [21].

The outcome of the next-generation sequencing performed by these researchers indicated that the features of SARS-CoV-2 differ from SARS-CoV (with about 79% sequence identity) and MERS-CoV (with about 50% sequence identity) than from the group of two bat-derived SARS-such as coronaviruses – bat-SL-CoVZC45 (with 87.9% sequence identity) and bat-SL-CoVZXC21 (with 87.2% sequence identity) [28]. Studies also reported that COVID-19 S-protein supported strong relationship with human angiotensin converting enzyme 2 (ACE2) molecules in spite of the variation in its sequence with that of SARS-CoV [11], [21], [29]. Although detailed pathogenesis of this novel infection is emerging day by day, the mechanism of infection has been described to entail the adhesion of the viral spike protein to the ACE2 molecule of the type II pneumocyte receptor (a precursor of type I pneumocyte) and the virion is endocytosed by the help of a serine protease TMPRSS2. On entering the cell, the virion RNA is released and translated by the cells machinery into non-structural polyproteins that are cleaved into proteases, which are RNA-dependent, RNA polymerases, and structural proteins. Then replication complex forms to produce more RNA with viral proteins and RNA assembling into a newly manufactured virion in the Golgi consequently releasing the virion to infect new Type II pneumocytes [30]. This, in turn, result in aggressive inflammatory response leading to vascular endothelial dysfunction and subsequently endotheliopathy, with sepsis-induced coagulopathy (SIC) as described by the international society for thrombosis (ISTH) [31], [32]. The SIC in COVID-19 could occur by activation of coagulation through several procoagulant pathways such as viral adhesion on an ACE2 receptor present on endothelial cells, inflammatory cell infiltration coupled with apoptosis of endothelial cells, and microvascular prothrombotic effects [33] which explains the myocardial ischemia and increasing reports of macro- and micro-thromboembolic complication in some patients [33], [34], [35].

Furthermore, the pathobiology of this process has been further classified into three stages [36] which are: The asymptomatic state occurring within 1–2 days of infection whereby the inhaled virus will bind the epithelial cells of the nasal cavity through the assistance of the ACE2 receptors with the consequent initiation of a limited innate immune response [37], [38]; the next stage is symptomatic phase characterized by the upper and conducting airway response occurring within few days of infection triggering a more robust innate immune response evidenced with the presence of beta and lambda interferons, especially C-X-C motif chemokine ligand 10, an excellent interferon responsive gene to the alveolar type 2 cell in SARS and influenza infection. Finally, the third stage is associated with hypoxia, ground-glass infiltrate with progression to acute respiratory distress syndrome (ARDS) which occurs as the virus reaches the gas exchange units of the lung infecting the peripheral and subpleural alveolar type II cells leading to apoptosis and cell death. This, in turn, will trigger a secondary pulmonary epithelial regeneration as was seen in influenza pneumonia [36], [39], [40]. The recovery will, however, require an energetic innate and acquired immune response coupled with aggressive pulmonary epithelia regeneration which is quite slow in the elderly due to their diminished immune response and reduce ability to regenerate or repair damaged epithelial cells [36].

Laboratory diagnosis of COVID-19

The diagnosis of the infection is majorly by molecular methods whereby reverse-transcriptase polymerase chain reaction (RT-PCR) is the choice technique [41], [42], [43], [44], [45]; serological tests have been developed by CDC (2020) for optimization and validation of other serologic reagents manufactured for diagnostic purposes. The severity of the condition can also be evaluated by the various laboratory analyses, across the hematology, chemical pathology, histopathology, microbiology and immunology field, so as to correlate their results with the clinical manifestation in the management of the patients.

Specimens for diagnosis

To ensure accurate diagnosis of the viral pneumonia infection (COVID 19), collecting good quality and the correct specimen from the patient promptly are important. According to the CDC guidelines, upper and lower respiratory specimens such as throat swab, nasal nasopharyngeal (NP) swab, sputum, and bronchial fluid are recommended [46]. In patients with more severe respiratory disease, upper respiratory specimens such as NP and oropharyngeal (OP) swab including lower respiratory specimens such as sputum (SP) and endotracheal aspirate or Broncho-alveolar lavage can be used. Previously, Wang *et al*. reported that OP swabs were used more often than NP specimen in China during the COVID-19 outbreak and that SARS-CoV-2 RNA was significantly detected in NP swabs [47]. The CDC also recommended the collection of the upper respiratory swab. Collection of an OP specimen was considered of a lower priority and when collected may be combined in a single tube as the NP swab [46]. Swab specimens are recommended to be placed and transported in a universal or viral transport medium or stored 2–8°C for up to 72 h after collection. Specimens can be stored at −70°C or below when a delay in testing or shipping is anticipated [46]. In addition, Cheng *et al*. have recommended the collection of both upper and lower respiratory samples such as Sputum and Broncho alveolar lavage fluid [48]. SARS-CoV-2 has also been detected from urine, stool, and blood specimens, although less frequently than from respiratory specimens. Cheng *et al*. publish that 70% (n = 38) of the fecal specimen at the peak of viral (9–11 days) shedding was positive following testing. Furthermore, a case report by Tang *et al*. have recorded a positive test in an asymptomatic child who was positive for the 2019 novel coronavirus by rRT-PCR from stool specimen even 9 days after respiratory tract specimens were negative [49]. The use of nucleic acid detection of COVID-19 in fecal specimens has been appraised to be equally accurate in diagnosis [7]. Likewise, the use of serum for the detection of SARS-CoV-2 has been previously reported. Zhang *et al*. showed that serological tests can improve detection rate and recommended its usage in future epidemiological studies [50]. Rectal sourced specimens have likewise been reported positive in patients infected with SARS-CoV-2 [51].

Molecular diagnosis

SARS-CoV-2 is a single-stranded positive-sense RNA virus and its entire genetic sequence was uploaded to the Global Initiative on Sharing All Influenza Data platform on January 10, 2020. The sequence data have since been helpful in designing primers and probes useful for the molecular diagnosis of SARS-CoV-2 [49], [52]. According to the WHO's guidelines, nucleic acid amplification tests (NAAT) for COVID-19 SARS-CoV-2 have been recommended. Routinely, confirmation of COVID-19 casesis based on detection and analysis of the sequences of virus RNA by NAAT such as real-time rRT-PCR, followed up by nucleic acid sequencing when required. The viral genes usually targeted include the N, E, S, and RdRP genes [53]. It is recommended that RNA extraction is done avoiding contamination in a biosafety cabinet in a BioSafetyLevel-2. Heat treatment of samples before RNA extraction is not recommended [54], [55]. A major advantage in the use of molecular diagnostic strategy is its ability to detect a positive case in an asymptomatic population thus preventing the spread of the virus to close contact. A study by Mizumoto *et al*., on the passengers (n = 3,711) on a diamond princess cruise ship tested for SARS-CoV-2 revealed an estimated asymptomatic proportion (among all infected cases) at 17.9% (95% CrI: 15.5–20.2%) [56].

RT-PCR

RT-PCR is recommended as the gold standard detection method for the identification of SARS-CoV-2 virus and relies on the principle of amplifying a small amount of viral genetic components in a sample. At present, RT-PCR test for SARS-CoV-2 has been used to test samples collected from the upper respiratory system using swabs. There are studies which have employed the use of this method in identification of SARS-CoV-2 in serum, stool, and other specimens [57], [58]. Although RT-PCR is the most widely used method for detecting SARS-CoV-2 infections, its major limitation is that it requires expensive laboratory instrumentation and reagents as well as highly skilled laboratory personnel to man such laboratories. Thus, a number of companies and laboratories around the globe are working on means of improving the efficiency and timeliness of the RT-PCR technologies and developing various other diagnostic methods [52].

Other molecular techniques in use include: Isothermal nucleic acid amplification which allows gene amplification at a constant temperature and eliminates the need for a thermal cycler [59]. This principle is used in reverse-transcription loop-mediated isothermal amplification (RT-LAMP). RT-LAMP provides an alternative and a more rapid and cost-effective testing method for SARS-CoV-2 but requires a set of four primers to target the genes and enhances the sensitivity of the test with a reverse-transcription step to allow for the detection of RNA. The amplified product can be detected using a photometric apparatus to measure the turbidity caused by magnesium pyrophosphate precipitated in the solution as a byproduct of amplification [52]. The reaction can be monitored in real time by measuring the turbidity or fluorescence using intercalating dyes since RT-LAMP diagnostic testing requires heating and visual inspection. The simplicity and sensitivity of this technique make it a promising candidate for virus detection [52], [60].

Microarrays have equally provided a rapid and high-throughput detection for SARS-CoV-2 nucleic acids. This technology relies on the use of reverse transcription to generate complementary DNA (cDNA) from viral RNA and subsequently labeling the cDNA with specific probes. In principle, the arrays are prepared either by an *in situ* synthesis of biomacromolecules on solid substrates or by spotting *ex situ* synthesized biomacromolecules on a substrate surface [61]. This is followed by loading the labeled cDNAs into the wells of microarray trays containing solid-phase oligonucleotides attached onto their surfaces. If hybridized and after washing away the unbound DNA, they remain bound, signifies the presence of virus-specific nucleic acid [41]. The use of microarray assay has been previously reported and identified as a useful tool in detecting mutations associated with SARS-CoV-2 [53], [54]. Guo *et al*. detected and characterized viral strains with 100% accuracy and thus recommended this method for the detection and epidemiological surveillance for SARS-CoV-2 [62], [63]. At present, more studies are needed to further substantiate and to evaluate the sensitivity of this method in SARS-CoV-2 diagnosis especially in Africa.

Serological and Immunological assays

Serologic assays have important public health applications in the current COVID-19 response. RT-PCR-based viral RNA identification has been used globally and appraised as the gold standard in diagnosis of COVID-19 but has inability to monitor the progress of the disease stages and cannot be applied to the identification of past infection and immunity [52]. It is believed that serologic testing can aid the understanding of disease patterns and transmission as well as improve data collection from serologic surveys among different ethnic groups and populations [64].

Serologic testing involves analysis of blood serum or plasma and other biological fluids. In principle, it involves recognition of antibodies, which are specific proteins produced in response to infections. This screening method plays an important role in epidemiology and vaccine development. It also provides an assessment of both short-term (days to weeks) and long-term (years) trails of antibody response in the tested population. Immunoglobulin M (IgM) first becomes detectable in serum after few days and lasts for some weeks on infection. This is usually followed by a switch to immunoglobulin G (IgG). Thus, IgM may be used as an indicator for early stage of infection and IgG is indicating a current or prior infection. IgG may also be used to suggest the presence of post-infection immunity. In the recent COVID-19 pandemic, serologic tests have been identified to have huge potential for the epidemiology of COVID-19 [64].

However, the United States' CDC has cautioned on the direct adoption of serologic testing for SARS-CoV-2 as more studies are needed to comprehend if the antibodies produced from SARS-CoV-2 infection will confer immunity from a future infection. CDC scientists are conducting studies to better understand the level of antibodies needed for protection, the duration of such protection, and the factors associated with whether a person develops a protective antibody response [64]. The U.S. Food and Drug Administration (FDA) recommended (revised policy) that the use of serologic tests and reagents intended for antibody detection to SARS-CoV-2 to identify people who may have been exposed to the SARS-CoV-2 virus or who have recovered from the COVID-19 infection be subjected to validation and approval, it was also emphasized that serological (antibody) tests should not be used as the sole basis to diagnose COVID-19 [65].

The serologic techniques in use include the enzyme-linked immunosorbent assay (ELISA), immunochromatographic (ICG) lateral flow assay, neutralization bioassay, and specific chemosensors. They vary in speed, multiplexing, automation, as well as limitations such as requirements for trained personnel and availability of dedicated laboratories. The FDA had earlier granted emergency use authorization status to the first serology test, qSARS-CoV-2 IgG/IgM Rapid Test, manufactured by Cellex Inc., on April 1, 2020 [65].

A study by Pan *et al*. demonstrated the serologic ability of ICG strips in identifying SARS-CoV-2 infection to be sensitive and consistent and thus considered it as an excellent complementary approach in clinical application [66]. In another study, Haveri *et al*. assessed the presence of neutralizing antibody response along with specific IgM and IgG targeting nucleocapsid and spike proteins and recommended this technique has a candidate test which can enhance better understanding of SARS-CoV-2 infection. However, monitoring of the binding antibodies is suggested to be a more sensitive method than measuring functional neutralizing antibodies for serological detection of hCoV infections [67].

Hematological features and other laboratory findings

The hematological analysis reported by various researchers include the total leukocyte count, lymphocyte, eosinophils, monocyte, platelet counts, D-dimer, procalcitonin (PCT), serum amyloid A (SAA), erythrocyte sedimentation rate (ESR) and they are categorized based on the concentration of parameters, severity of disease (severe and non-severe conditions), 5 and 4-days post-hospital presentation, and complication conditions as represented in Table 1 obtained from the studies by Zhang *et al.* and Bingwen *et al.* [1], [68]. Zhang *et al.* reported that the total leukocyte count, D-dimer, C-reactive protein (CRP) ($p < 0.001$), and SAA were increased in patients with severe condition than those whose conditions were not severe while decreased value was observed in lymphocyte , eosinophils, and PCT in severe conditions with observable lymphopenia and eosinopenia at 5 days post-clinical presentation. The population distribution demonstrated 12.3%, 43.2%, 34.7%, and 90.2 % of the COVID-19 positive population had increased leukocyte, D-dimer, PCT, and SAA, respectively, while 19.6 %, 75.4%, and 52.96 % had decreased leukocyte, lymphocyte, and eosinophil counts, respectively [1]. In addition, corroborating work by Bingwey *et al*. reported similar white cell results along with moderate platelet count and hemoglobin concentration [68]. Some other studies that relate COVID-19 infection with thrombosis also observed increased level of D-dimer along with increase in some other coagulation markers such as fibrin, fibrin degradation products (FDP) with minimal change in prothrombin time, activated partial thromboplastin time, and platelet count which are pointers of thrombosis as reviewed by Connors *et al.* and Robbin *et al.* [32], [69]. In addition, the assessment of 11 patients in the intensive care unit in Italy display reduced mean antithrombin concentrations with slightly low protein S free antigen along with an increased mean vWF and vWF-ristocetin cofactor activity [70]. These observations coupled with other severe thrombotic developments led the ISTH developing an interim guidance on recognition and management of coagulopathy in COVID-19 whereby D-dimer, prothrombin time, platelet count, and fibrinogen (if fibrinogen measurement is feasible) are to be measured

Table 1: Distribution of hematological parameters across various serenity conditions and post-presentation days as described by Zhang *et al.* (2020) [1] and Bingwen *et al.* (2020)

Parameters	Condition/n-138 (Zhang *et al*., 2020) [1]		p-value	Condition at 5 days post-presentation/n-138 (Zhan *et al*., 2020) at 5 days post-presentation		p-value	Condition/n-67 (Bingwen *et al*., 2020)		p-value	Condition at 4 days post presentation/n-67 (Bingwen *et al*., 2020)		p-value
	Non-Severe	Severe		Non-severe	Severe		Non-severe	Severe		Non-severe	Severe	
Hb (g/dl)	-	-		-	-		14.2 (12.9–15.2)	13.2 (12.5–14)	0.70	13.6 (12.7–15.1)	11.1 (10.2–11.9)	<0.001
Total leukocyte (×10^9/L)	4.5 (3.5–5.9)	5.3 (4.0–9.0)	0.014	-	-	-	4.7 (4.0–5.8)	5.1 (3.5–8.2)	0.87	-	-	
Lymphocte (×10^9/L)	0.8 (0.6–1.2)	0.7 (0.5–1.0)	0.048	1.1 (0.7–1.6)	0.7 (0.4–1.1)	<0.001	1.3 (0.9–1.7)	0.5 (0.48–0.8)	<0.001	1.2 (0.8–1.6)	0.4 (0.3–0.5)	<0.001
Monocyte (×10^9/L)	-	-		-	-		0.5 (0.4–0.6)	0.3 (0.2–0.5)	0.12	0.4 (0.3–0.5)	0.2 (0.19–0.23)	<0.001
Eosinophil (×10^9/L)	0.02 (0.008–0.05)	0.01 (0.0–0.06)	0.451	0.04 (0.01–0.08)	0.01 (0.0–0.09)	0.157	-	-	-	-	-	-
Neutrophils (×10^9/L)	-	-	-	-	-	-	2.6 (2.1–3.8)	4.2 (2.1–6.9)	0.17	3.5 (2.6–4.4)	11.6 (9.3–13.8)	<0.001
Platelets (×10^9/L)	-	-	-	-	-	-	201 (157–263)	217 (154–301)	0.81	192 (150–261)	154 (131–216)	<0.001
D-dimer (µg/ml)	0.2 (0.1–0.3)	0.4 (0.2–2.4)	<0.001	-	-	-	-	-	-	-	-	-
CRP (mg/l)	28.7 (9.5–52.1)	47.6 (20.6–87.1)	<0.001	-	-	-	-	-	-	-	-	-
PCT (ng/ml)	0.05 (0.03–0.1)	0.1 (0.06–0.3)	<0.001	-	-	-	-	-	-	-	-	-
SAA (mg/L)	91.5 (24.9–163.2)	108.4 (54.1–161.6)	0.600	-	-	-	-	-	-	-	-	-

p-value denotes comparison between the severe and non-severe groups across each study [1], [59].

in patients presenting with COVID-19. The patients with abnormal results are to be admitted and subsequent treatment (heparin or blood product transfusion) based on the severity of results obtained [71].

Furthermore, another study by Shuchang *et al*. on the CT features of COVID-19 infected persons with pneumonia in some 62 patients in Wuhan, China, observed that the routine blood analyses conducted on 30 of the patients displayed 6 (20.0%), 24 (80.0%), and 15 (50.0%) with leucopenia, lymphocytopenia, and decreased percentage of lymphocytes, respectively [72]. The ESR and high-sensitivity CRP level assessed yielded 66.7% and 100% elevated values for both parameters, respectively, thus are corroborating the report of the study by Zhang *et al*. [1]. A usual or diminished total white blood cell count along with reduced lymphocyte count can be demonstrated in the early phase of the infection as researched by Cascella *et al*. [73]. Furthermore, their article reported that lymphopenia is visibly negative prognostic factor for COVID-19 infection with amplified values of CRP and standard procalcitonin value. In severe condition, it was reported that D-dimer value is augmented, blood lymphocytes declined persistently, and analytical variations of multiple organ imbalance evident by high amylase as well as disordered coagulation activities [73].

In addition, leukopenia, lymphocytopenia, and eosinophil cytopenia were observed to be recurrent in COVID-19 induced pneumonia more than those in non-COVID-19 induced pneumonia [74]. Furthermore, a marked reduction in CD4 and CD8 lymphocytes series was noted at the onset phase of the disease by Wang *et al.* [8] with patients in the critical care facility displaying higher levels of interleukin (IL) 2, IL-10, IL-7, monocyte chemotactic protein 1 (MCP1), granulocyte colony-stimulating factor (GCSF), interferon gamma-induced protein 10 (IP10), tumor necrosis factor-α (TNF-α) and macrophage inflammatory protein alpha along with other abnormal coagulation, and cell count parameters described by some other researchers [7], [75]. The lung injury presentation in this infection has been strongly analyzed by emerging evidences to result from the excessive release of pro-inflammatory markers such as IL-1, IL-6, and TNF-α and interferon, a situation called cytokine storm [76]. This is because their secretion results in influx of immune cells into the site of infection producing destructive effects on tissues damaging cell interaction, multi-organ failure, and eventual death [77]. This is ascertained by the further analysis of cytokines in infected patients with the observation that they are increased in patients and even more elevated in severe cases [7], [78], [79], [80], [81], [82] as well as in children from ages 2 months to 15 years [83].

In addition, infected individuals with blood Group A were studied to be significantly most-at-risk for contracting COVID-19 compared with non-A blood groups while blood Group O has a appreciably lower risk for the infection compared with non-O blood groups as reported by some researchers in Wuhan, China [19]. Although, there are still some categorical questions concerning the study with regard to the distribution of blood groups in China populace, ethnicity, and statistical inferences.

Histopathological features of COVID-19

The macroscopic view of COVID-19 is observed more to be in the chest and can also include pleurisy, lung consolidation, pulmonary edema, and pericarditis. The weight of the lung may increase above normal. It can also be noted that a secondary infection can be super imposed on the viral infection which can lead to purulent inflammation that is more of a typical bacterial infection [84]. A recent article explained the early pathological features in COVID-19 in two patients who had gone through surgical resections for lung adenocarcinoma, but it was later discovered during the procedure of the operation that the two patients had COVID-19 [11]. The findings obtained were not specific and these include edema, pneumocyte hyperplasia, focal inflammation, and multinucleated giant cell formation, while hyaline membranes were not observed. These patients did not show any symptoms of COVID-19 as at the time of the operation; these are likely to reflect only in the early changes of acute lung injury in the infection [11].

Furthermore, a reported case of biopsy samples from 50 years deceased of COVID-19 in Wuhan city, China, was harvested from the liver, lungs, and heart organs of the patient. Histomorphological examination revealed bilateral diffuse alveolar damage with cellular fibromyxoid exudates [85]. The right lung revealed evident of desquamation of pneumocytes and hyaline membrane formation, which indicates an ARDS. The left lung showed pulmonary edema with hyaline membrane formation, which suggests of early-phase ARDS [85]. Both the right and left lungs also revealed interstitial mononuclear inflammatory infiltrates, which are dominated by lymphocytes. Multinucleated syncytial cells with atypical enlarged pneumocytes, characterized by large nuclei, amphophilic granular cytoplasm, and prominent nucleoli were observed in the intra-alveolar spaces, which showed viral cytopathic like changes [85]. There were no obvious intracytoplasmic or intranuclear viral inclusions were seen. In addition, the liver biopsy specimen of the same patient with COVID-19 revealed moderate microvesicular steatosis, mild lobular, and portal activity which indicates that the injury might have been caused by either SARS-CoV-2 infection or drug induced liver injury. There was no other substantial damage observed in the heart tissue except a few interstitial mononuclear inflammatory infiltrates [85]. According to Sufang *et al*., 2020, who also carried out postmortem fine-needle core biopsies on some selected organs (liver, heart, and lungs) on four patients who also died of COVID-19 pneumonia, each of these patients had one or two underlying diseases, which include immunocompromised status (chronic lymphocytic leukemia and renal transplantation) or some other conditions, which are liver cirrhosis, diabetes, and high blood pressure [86]. The time frame from the onset of the disease to death for the patients ranged from 15 to 52 days. The main features observed in their histology were in the epithelial tissues, formation of hyaline membrane, and hyperplasia of type II pneumocytes, all the components of diffuse alveolar damage. Fibroblast proliferation with extracellular matrix and fibrin forming clusters in airspaces is evident with an abundant intra-alveolar neutrophilic infiltration, consistent with super imposed bacterial bronchopneumonia in one of the patients. The liver showed a mild lobular infiltration with small lymphocytes and centrilobular sinusoidal dilation and a patchy necrosis was also observed [86].

The heart showed only focal mild fibrosis and mild myocardial hypertrophy. The postmortem examination showed an advanced diffused alveolar damage as well as superimposed bacterial pneumonia in some of the patients. The histomorphological changes observed in the heart and liver were most likely to be secondary or caused as a result of the effects of the underlying disease [86].

Complications of COVID-19 Infection

Acute respiratory syndrome

The presence of ACE2 on the cells of the heart, kidney, and lungs encourages the SARS viruses infection [87] and about 42% of COVID-19 patients do develop ARDS [88]. Diabetes mellitus is also a factor associated with the development of ARDS [78]. Other diseases that can cause complications in COVID-19 patients include hypertension, cardiovascular disease, and chronic kidney disease [88], [89]. Medical laboratory findings associated with the development of ARDS include lymphopenia, neutrophilia, elevated CRP, elevated blood urea nitrogen, prolonged prothrombin time, elevated d-dimer, and elevated lactate dehydrogenase (LDH) [88], [89].

About 36% of ARDS cases are mild, 45% cases are moderate while 18.9% cases are severe [17]. Mortality increases with the severity of the disease. Patients above 65 years of age do have worse degree of ARDS and they also have higher mortality likelihood [89]. Medical laboratory markers that can predict the mortality of COVID-19 ARDS patients include low albumin, elevated blood urea nitrogen, and elevated LDH [88], [89].

Myocardial injury

Most commonly causes of COVID-19 related deaths are usually associated with the hearts and lungs [90]. There are two main theories explaining the mechanism by which myocardial injury occurs with COVID-19. The first theory explains that the heart has similar ACE2 levels as that of the lungs [77], which allows viral entry into the myocardial cells [91]. The second theory involves a cytokine storm causing myocardial injury [91]. Myocardial injury includes heart failure, myocarditis, acute coronary syndrome, hypotension, or shock and sepsis [92]. To have a definitive characterization of the injury, endocardial biopsy is possibly required and magnetic resonance is required [92].

Arrhythmias have been observed to arise with severe COVID-19 cases [93], [94]. Malignant arrhythmias, including ventricular tachycardia and fibrillation, always occur at a rate of 6% and can be elevated more frequently in patients with elevated troponin levels (17.3% of patients with elevated troponin) [85]. Heart failure is commonly observed in severe cases of COVID-19, irrespective of previous cardiac history [85]. This presents with elevated levels of N-terminal pro B-type natriuretic peptide (NT pro-BNP) and troponin levels, mostly in severe cases [49]. Some studies have also revealed that pulmonary hypertension which causes right heart failure can also contribute to these cases.

Elevated high sensitivity troponin (HS-troponin) and creatinine kinase-myocardial brand (CK-MB) levels can also self-sufficiently predict severe COVID-19 cases [88], [92], [93], [94], [95]. A recent meta-analysis revealed that troponin is more elevated in severe cases [96]. Cytokines do not predict severity [88]. It has been revealed that patients with elevated HS-troponin (□28 ng/L) and CK-MB are suspected to have myocarditis or heart failure [7], [88].

Acute kidney injury

Acute kidney injury presents with elevated urea and cystatin-C levels in severe COVID-19 infection [89]. Concerning the cause of acute kidney injury, there are two hypotheses to it. One of the hypotheses is from kidney able to harbor more ACE-2 levels than the lung or heart, most especially in the proximal convoluted tubules. However, COVID-19 RNA is not encountered in the urine. The second theory has to do with the injury incurred through a cytokine storm [96]. Patients may need to do continuous renal replacement therapy (CRRT) due to the severity of kidney injury. Speculation exists concerning CRRT potentially serving as a way of removing large cytokine levels from the system, regardless of kidney injury [96].

The prognosis predictors of COVID-19 infection include cardiovascular disease, hypertension, cerebrovascular disease, and chronic kidney disease [48] which can all result in severe conditions. In patients with cardiovascular disease, they present with a 10.5% coronary flow reserve (CFR); other diseases that can also present with a high CFR include chronic lung diseases (6.3%); cancer (5.6%); hypertension (6.0%); and diabetes.

Conclusion

The diagnostic analysis of this new infection is majorly by NAAT such as real time RT-PCR followed by nucleic acid sequencing. Although some serologic and immunologic assays such as ELISA and ICG lateral flow assay have been developed which detects the IgM and IgG antibodies, there are still lots of cautious remarks on the direct adoption of these tests due to the need for more studies to determine the immunologic capabilities and strength of the antibodies in prevention of future infection. Based on severity, the laboratory features of COVID-19 infection include lymphopenia, eosinopenia, reduced procalcitonin along with leucocytosis, increased D-dimer, CRP, SAA, fibrin, FDP with mild to moderate increase in PT, and APTT while the major pathologic presentations present with features of acute respiratory syndrome, myocardial injury, and acute kidney injury. Furthermore, some inflammatory markers such as IL-2,IL-6, IL-7, IL-10, GCSF, MCP10, IP10, and TNF-α are apparently increased in COVID-19 infection signaling cytokine storm in the course of the infection and associated SIC. Therefore, as much as there are some established pathologies, diagnosis, and laboratory features of COVID-19 by clinical presentation and hospitalization, more studies are required to identify the capabilities, characteristics and tendencies of this novel virus as well as the most efficient prevention and treatment.

Author's Contributions

All authors contributed responsibly to this manuscript, have accepted accountability for the entire content, and approved its submission.

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Analysis of Community Behavior in Coronavirus Disease-19 Prevention in Medan

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Abstract

BACKGROUND: Coronavirus (CoV) is a type of virus that can cause interference with the respiratory tract. The development of CoV disease (COVID)-19 is happening fast in the world, especially in Indonesia. In Medan, the highest number of COVID-19 cases was spread in the Medan Selayang sub-district. One of the steps taken by the government to reduce transmission of COVID-19 is by implementing prevention and social distancing behavior. Community behavior is influenced by various factors such as age, sex, physical nature, level of education, and socioeconomic to culture.

AIM: The aim of this study was to find out the factors that influence the community behavior of Medan Selayang people in the effort to prevent COVID-19.

METHODS: This cross-sectional study was conducted on 102 respondents. Data collection methods, in the form of primary data, are carried out by distributing and filling out questionnaires through the Google form media.

RESULTS: One hundred two respondents were found that 90.2% of respondents had good behavior in COVID-19 prevention efforts. The multinomial logistic regression found sig. (P) on the variables of gender, age, education level, and employment status, respectively, 0.360, 0.772, 0.860, and 0.878 (p > 0.05).

CONCLUSIONS: In this study, no significant relationship was found between sex, age, education level, and employment status on COVID-19 preventive behavior.

Introduction

Coronavirus (CoV) is a type of virus that can cause interference with the respiratory tract. CoV consists of several types, such as severe acute respiratory syndrome CoV (SARS-CoV) and Middle East Respiratory Syndrome-related CoV (MERS-CoV). The most recent CoV found in China is the 2019 CoV Novel (2019-nCoV) [1]. On December 31, 2019, the World Health Organization (WHO) China Country Office reported a case of pneumonia of unknown etiology in Wuhan City, Hubei Province, China. On January 7, 2020, China identified pneumonia of unknown etiology as a new type of CoV (nCoV). Then, on January 30, 2020, the WHO established the disease by this virus as a Public Health Emergency of International Concern/World-Anxious Public Health Emergency (KKMMD). On February 12, 2020, the WHO officially determined that this novel human CoV would be called the CoV disease 2019 (COVID-19). COVID-19 is caused by SARS-CoV-2 which belongs to the same large family of CoV as the cause of SARS in 2003, only with different types of viruses [2].

The development of the COVID-19 case was rapid. The COVID-19 case in Indonesia was initially found in Depok, West Java, but has now spread to 34 other provinces.1. In North Sumatra, COVID-19 cases also continue to increase, especially in the city of Medan. As of May 16, 2020, the number of people under monitoring (PUM) was 1171 people, asymptomatic cases (ASC) were 1125 people, patients under surveillance (PDP) was 526 people, and COVID-19 positive patients were 147 people. This amount is spread, especially in the district of Medan Selayang which is one of the red zones in Medan [3].

In dealing with the COVID-19 pandemic, a number of strategies and steps have been taken by the government to be able to suppress transmission of COVID-19, one of which is by applying prevention and social distancing behavior. Social distancing to be able to reduce or even break the chain of COVID-19 infection is done by maintaining a safe distance between individuals/other human beings that are at least as far as 2 m, not in direct contact with others, and avoiding mass gatherings as for a number of Indonesian people not responding to this well. School entertainment or the application of work at home, which were implemented by the government some time ago with the aim of reducing transmission, were used by the community for vacation. In addition, there are also Indonesian people who underestimate the pandemic of this virus and do not heed the government's appeals; as a result, the addition of cases of COVID-19 continues to occur [4].

Balkhi *et al*., in his study, found that during the COVID-19 pandemic, some concerned populations in Karachi, Pakistan, made behavioral changes [5]. Behavior is a form of response or reaction to stimuli or stimuli from outside organisms (people), but in providing this response very dependent on the characteristics or other factors of the person concerned [6]. The factors that play a role include such as age, sex, physical nature, level of education, socioeconomic to culture.

The attitude or behavior showed by the phenomenon above, as well as remembering quite a number of cases of COVID-19 in the Medan Selayang sub-district, encouraging the writer to analyze further regarding the behavior of the people of Medan Glance in the face of a pandemic COVID-19, especially in efforts to prevent COVID-19.

Methods

This research is analytic research with a cross-sectional research method conducted in Medan Selayang district, Medan, during the period from May–June 2020.

Study population and sampling

The population of this study is all people who live in Medan Selayang District. The sample is done by consecutive sampling, that is, all samples that come and meet the inclusion criteria are included in the study until the minimum number of subjects is met. The inclusion criteria consisted of (1) people who live in the Medan Selayang sub-district, (2) people aged ≥17 years, and (3) people who are willing to take part in the research. The minimum sample size needed in this study is 102 respondents, which are determined through three steps, namely, (1) determining the sample size of each independent variable studied, (2) rules of thumb, and (3) rules of thumb with correction.

Study tool

Data collection, in the form of primary data, is obtained through filling out questionnaires through Google form. A questionnaire is a data collection technique that is done by giving a set of questions or written statements to respondents to be answered. The questionnaire used by researchers is to refer to the Likert scale, and validity and reliability tests have been performed.

Statistical analysis

The data collected will then be carried out a series of processes ranging from editing, coding, entry, cleaning, and saving. Then, the data will be processed and analyzed using the SPSS (Statistical Package for the Social Sciences) computer program. Data analysis begins descriptively to see the characteristics of the data. To see the effect of gender, age, level of education, and employment status on behavior, a logistic regression test was performed. Data are presented in the form of a frequency distribution table.

Ethical consideration

All the participants agreed to the study procedures and expressed their willingness to all in the Google Form, which was sent through WhatsApp.

Results

Based on research conducted in the Medan Selayang sub-district during the period of May to June, 2020, 102 respondents who met the inclusion and exclusion criteria were met.

Characteristics of research respondents. The total respondents obtained in the study were 102 respondents. The characteristics of respondents are shown in Table 1:

Table 1: Characteristics of research respondents in Medan Selayang

Characteristic	Frequency (person) n=102	Percentage
Gender		37.5
Male	38	62.7
Female	64	
Age (years)		
17–25	71	69.6
26–35	16	15.7
36–45	11	10.8
46–55	4	3.9
55–65	0	0
>65	0	0
Level of education		
Primary school	0	
Junior high school	3	2.9
Senior high school	35	34.3
Bachelor	64	62.7
Employment status		
Still working	29	28.4
Not working	73	71.6

The table above described the characteristics of respondents consisting of 38 male respondents (37.3%) and 64 respondents' women (62.7%). Based on age, the highest number of respondents was those with age range 17–25 years with 71 respondents (69.6%), and the least respondents were with the age range 46–55 years with four respondents (3.9%). In this study, there were no respondents in the age range above 55 years. The table also describes other characteristics, namely, the level of education and employment status at the time of the pandemic. Based on the level of education, it was found that the highest number of respondents with a bachelor's level of education (64 people; 62.7%) and the least was respondents with a junior high school/ equivalent level of 3 people (2.9%). Based on the current employment status of the pandemic, 29 respondents were still working (28.4%), and 73 respondents were not working (71.6%).

The factors studied were gender, age, level of education, and employment status. Each factor is assessed and divided into three categories of behavior, namely, poor, neutral, and good.

In Table 2, it is showed that 90.2% of respondents have good behavior in the prevention of COVID-19, only 9.8% of respondents behaved neutral, and no respondents were found to behave poorly.

Table 2: Distribution of COVID-19 prevention behaviors in Medan Selayang

Behavior	Frequency (person) n=102	Percentage
Neutral	10	9.8
Good	92	90.2

COVID: Coronavirus disease.

Table 3 shows that good prevention behavior is more prevalent among respondents in the 17–25 years age group (91.5%). While based on gender, good prevention behavior was found more in women (92.2%) compared to men (86.8%). The majority of respondents have education levels up to the bachelor level, with good preventive behavior shown by 89.1% of graduates. Respondents with good preventative behavior were also found in the group of high school/ vocational/equivalent graduates which are around 91.4%. The majority of respondents who do not work have good preventive behavior (91.7%). In contrast to respondents who were still working, good preventive behavior was shown by 25 of the total 29 respondents working (86.2%).

Table 3: Distribution of behavioral factors in an effort to prevent COVID-19

Characteristic	Behavior		Jumlah	p
	Good	Neutral		
Gender				
Male	33 (86.8)	5 (13.2)	38 (100)	0.360
Female	59 (92.2)	5 (7.8)	64 (100)	
Age (years)				
17–25	65 (91.5)	6 (8.5)	71 (100)	0.772
26–35	14 (87.5)	2 (12.5)	16 (100)	
36–45	9 (81.8)	2 (18.2)	11 (100)	
46–55	4 (100)	0	4 (100)	
Level of education				
Junior high school	3 (100)	0	3 (100)	0.860
Senior high school	32 (91.4)	3 (8.6)	35 (100)	
Bachelor	57 (89.1)	7 (10.9)	64 (100)	
Employment status				
Still working	25 (86.2)	4 (13.8)	29 (100)	0.878
Not working	67 (91.8)	6 (8.2)	73 (100)	

COVID: Coronavirus disease.

Apart from the results of the above research, a multinomial logistic regression test was also carried out to find out the factors that influence the behavior of the people of Medan Selayang in their efforts to prevent COVID-19. The analysis shows the value of sig. (P) in each independent variable (p>0.05) – this value indicates that in this study, there were no independent variables (factors of gender, age, level of education, and employment status) which statistically significantly influences the dependent variable (behavior).

Discussion

This study aims to look at the effect of several demographic variables, namely, age, sex, education level, and employment status, on prevention behavior toward COVID-19 disease. From the research data collected, 90.2% of respondents have good preventive behavior toward COVID-19. After analysis, the four factors studied (independent variables of the study) did not have a statistically significant effect on COVID-19 disease prevention behavior.

In the previous studies, gender was considered to have an influence on preventive behavior [7], [8]. In a study by Yildirim *et al*., women had better preventive behavior and statistically had significant differences with men. In addition to having better preventive behavior, women are also considered to have a better risk perception and have a higher fear [8]. This was also shown by Shahnaz *et al*., which found significant differences between men and women [7]. Clinically, men tend to have worse cases when compared to women. This is also in line with the higher mortality in men compared to women [9]. Clinically, age has an influence on the severity and mortality of COVID-19 disease. In a meta-analysis study, an exponential increase in mortality risk was found in the age group above 50 years in patients with COVID-9 [10]. This is also consistent with findings of higher infection susceptibility, as well as worse clinical manifestations found in patients with older age [10], [11]. In a study conducted by Atchison *et al*., age was assessed as having an influence significant toward preventive behavior, especially the adoption of social distancing actions. Research data show that people aged >70 years have a positive association with social distancing when compared with young adults aged 18–34 years [12]. While in a study in Hong Kong that assessed the adoption of social distancing has not shown statistically significant differences, however, based on the regression analysis conducted on the study data, it shows that the odds ratio of OR decreases with age, although not significantly [13].

In the education level variable, several studies have shown a significant effect of education level on preventive behavior in COVID-19. Research by Atchison *et al*. assesses the influence of education level on work from home behavior that is associated with total income. It was shown that respondents with better levels of education had higher incomes and savings compared to respondents with lower levels of education, making it difficult to do work from home. Meanwhile, the differences in prevention based on education level did not differ too much. Prevention measures differed more based on the socio-economic status of the respondents. Respondents with lower levels of education were judged to have a lower ability and desire to isolate themselves compared to higher levels of education [12]. Other studies have shown that education levels have an influence on preventive actions, but do not specifically explain preventive actions that are judged differently [8].

In addition to the education level variable, the researcher also assessed the employment status. In the previous studies, employment status was grouped into more specific subcategories such as working full time (30 hours or more), working part-time, full-time students, retiring, not working, or unemployed. One study showed employment status as demographic data; in the research data, the researcher more closely related the amount of income and socioeconomic status with preventive measures [12]. In another study by Kwok *et al*., no significant differences were found between subcategories of employment status but found odds the highest ratio that is for pensioners and workers [13].

In contrast to some previous studies which showed a significant relationship on several factors that influence preventive behavior toward COVID-19, based on data collected in this study, no significant relationship was found between the variables studied (gender, age, education level, and employment status) toward preventive behavior toward COVID-19. The difference in the results of this study can be caused by the presence of other factors that are more instrumental in the formation of COVID-19 prevention behavior in the Medan Selayang community. Some other factors that can influence the behavior of the people of Medan Selayang, especially in efforts to prevent COVID-19, include public trust (fear of infection), the presence or absence of chronic diseases (diabetes mellitus, hypertension, heart disease, or lung disease), and the level of socioeconomic.

At present, there are many and adequate sources of information about COVID-19 so that public knowledge of COVID-19 should be good enough. People's fears of a pandemic are one of the factors that result in better preventive behavior. Besides the things mentioned above, the differences in the results of this study can also be caused by the limitations of researchers, especially in sampling in the pandemic era, where the distribution of questionnaires is done through online media which are difficult to monitor and are less effective to reach affordable populations [14]. This limitation, coupled with the narrow duration of sampling, causes the number of research samples collected to be small so that the samples obtained are also less variable. Apart from the above circumstances, this research has been carried out for a long time since the first case was announced so that the behavior of the community is likely not the same as when the pandemic began. Therefore, the researcher recommends further research, both by involving the variables above and by including other variables such as community trust, comorbid disease, and socioeconomics. In addition, researchers also suggest taking more samples with an adequate time span.

Conclusions

In this study, no significant relationship was found between sex, age, education level, and employment status on COVID-19 preventive behavior. As in the previous studies, a significant relationship can be found in some of these variables. This may be influenced by other factors, such as the availability of adequate sources of information and public fear of this pandemic. The difference in the results of this study can also be caused by the minimal number of samples involved in this study due to the short duration of the study. For this reason, we recommend further research by taking more samples with an adequate time span, and by involving other variables such as community trust, comorbid disease, and socioeconomics.

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Emerging Neuropathological and Acid-base Disorders in Coronavirus Disease-19: A Close Look at Diagnostic Prospect in Containment Operations

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Abstract

The two major barriers militating against rapid containment of the spread of coronavirus (CoV) disease (COVID)-19 include lack of effective contact tracing and the failure to detect and diagnose the infection early. Lack of diagnostic tools for early diagnosis has contributed to the bane of the current wild spread of COVID-19 and its containment. The current chest computed tomography (CT) for COVID-19 screening, an evolving technique, is arguably reported to have 97% diagnostic sensitivity over the viral polymerase chain reaction (PCR) that has detection of 70%. However, CT has largely been criticized as speculative and thus generates disagreement among various international radiology societies and organizations. Until now, nucleic acid detection by real-time PCR (advanced with next-generation sequencing) remains the gold standard test and clinical diagnosis technique for COVID-19. The use of this method in diagnoses, while it is more precise, is also time-consuming and may not meet the goal of rapid detection of early infection with severe acute respiratory syndrome CoV-2. Although many available tests, such as other PCR-based, serology, isothermal nucleic amplification, and among others, are coming up, the testing accuracy and/or timeliness have hampered their expected performance level. As a result, there is still a need to develop more methods to detect the current spread of COVID-19 rapidly. COVID-19 is now associated with olfactory dysfunctions in several reports. Recently, the Centers for Disease Control (CDC) established that anosmia is a notable symptom of COVID-19. Furthermore, acute systemic acidosis has been associated with COVID-19. This report critically discusses the potential pathophysiologies of COVID-19 in association with neuropathological and acid-base disorders and their prospect for diagnostics.

Highlights of the Study

- Detection of early cases of COVID-19 remains a big concern against the containment operation
- This report discusses the pathophysiology of a neuropathological disorder, anosmia, as a possible diagnostic tool
- It also discusses the pathophysiology and potential diagnostic use of an associated acid-base disorder in COVID-19 patients
- The report concludes that putting apparatus, such as respiratory or smelling testing panels, into use could add to the benefit of early detection operation.

Introduction

The two major barriers militating against rapid containment of the spread of coronavirus (CoV) disease 2019 (COVID-19) include lack of effective contact tracing and the failure to detect and diagnose the infection early. Lack of adequate diagnostic tools for early diagnosis has impacted the current wild spread of COVID-19 and its containment. Extensive studies are ongoing to address these problems, especially for asymptomatic and presymptomatic patients. Majority of COVID-19 cases (81%) show mild or no symptoms [1]. Unfortunately, these individuals may shed the virus and fuel the contagion. It becomes a matter of urgency to develop and improve on rapid diagnostic tools to aid early detection of severe acute respiratory syndrome CoV 2 (SARS-CoV-2) infected individuals, who are oftentimes asymptomatic before they can spread the disease. It is believed that asymptomatic spread has been aggravating the pandemic control of COVID-19.

In search of rapid techniques for detection of early infection with SARS-CoV-2, the chest computed tomography (CT) for COVID-19 screening has been found to detect 97% of COVID-19 cases and rapidly within 10 mins, while viral polymerase chain reaction only detects 70% sensitivity [2]. However, 97% sensitivity report with CT screening has been largely criticized as speculative and shows a lack of consensus among various reputable societies such as the American College of Radiology, Royal College of Radiologists, Royal Australian and New Zealand College of Radiology, and Canadian Association of Radiologists [2]. Recently, millions of antibody test kits ordered by UK governments in the wake of an urgent call to detect asymptomatic and presymptomatic patients and to prevent the rapid transmission of COVID-19 were not consistent and, thus, unreliable. Likewise, millions of test kits purchased by Slovakia, Czech Republic, and Spain from China were largely inaccurate [3].

Meanwhile, COVID-19 draws myriads of signs and symptoms with related pathogeneses. Of recent, the CDC established six more symptoms to the list of COVID-19 symptoms, including anosmia [4]. Up till date, the report has been associating anosmia/hyposmia, a neuropathological disorder with COVID-19 [5], the pathogenesis of which has not been clearly identified. Although an earlier study conducted retrospectively in Italy through a self-report identification method shows a low incidence rate of 19.4% [6]. In general, incidence rates of olfactory dysfunction (OD) in COVID-19 patients ranging between 33.9% and 68% [7] from further studies showed increased discovery rates. In other words, as time evolved with more research studies intensified toward containment of COVID-19, various investigations involving larger sample sizes, and/or more robust techniques show continued to show higher prevalence rates with the cases of OD becoming more evident and gradually taken into clinical considerations [8-11]. Of note is a multicenter-study that later reported an 85.6% prevalence rate with larger coverage, including many European countries such as Belgium, France, Spain, and Italy using questionnaire method [8]. Remarkably, a study conducted in Iran with the aid of a validated method using a 40-odorant test (University of Pennsylvania Smell Identification Test, method) reported about 98% smell dysfunctions proposing that ODs would serve as a key indicator to identify SARS-CoV-2-infected patients [10]. In addition, apart from OD, the respiratory disorder is generally associated with ventilation problems and a possible etiology of acute and chronic systemic acidosis in some pulmonary affected diseases. This report discusses the pathophysiologies of neuropathological and acid-base disorders in relation to olfactory dysfunction and systemic acidosis and their prospect in the diagnoses of COVID-19 and population surveillance.

Emerging Neuropathological Disorder in COVID-19 and its Diagnostic Prospect

Report from the experts in rhinology shows that, currently, there are large numbers of patients who tested for COVID-19 infection and developed anosmia/hyposmia in South Korea, China, Germany, Iran, US, France, and Italy [5]. The report further explains that majority of these patients present with anosmia even without other symptoms [5]. Recently, the CDC enlisted six more to the tally of COVID-19 symptoms [4]. It is believed that certain forms of OD may be impacted in anosmia/hyposmia. Post-viral olfactory disorder has been described as one of the possibilities in developing anosmia [12]. The exact mechanism of olfactory neurobiology behind the development of post-viral anosmia in COVID-19 has not been reported. Nonetheless, two possible etiologies may be associated with the apparent loss of smell. The first probable etiology could be related to loss of maintenance or replacement of olfactory neuron as a result of post-viral damage in relation to the reduction of basal stem cell in the olfactory neuroepithelium. Another but different mechanistic plausibility is immunobiological which may be related to constant inflammatory post-viral damage that may have impaired either or both olfactory neuron and basal cell function. In a related study, early data show that provoked inflammatory reactions (implicating some inflammatory cytokines, such as interleukins-6 and 1β) occur in both upper and lower respiratory tracts following infection with SARS-CoV-2 with consequent respiratory problems ranging from mild to extensive life-threatening lung injury [13].

While in search of simple and sensitive detection diagnostic or screening tools, the development of smell testing kits and/or symptom diagnostic criteria may offer significant testing opportunities in this area of COVID-19 pathology. In clear terms, the development of symptom diagnostics may involve identifying vital differentials that will clearly indicate loss of smell, specifically in relation to post-viral infection with SARS-CoV-2, following the exclusion of unrelated pathological disorders that may range from chronic rhinitis to neurodegenerative processes. In addition to testing diagnostic kits, the development of OD symptom diagnostic criteria may add values to early detection of COVID-19 in combination with the existing diagnostic techniques for various OD manifestations. It is believed that the use of simple odorant testing kits and symptom diagnostic criteria could reduce the time spent on laboratory diagnoses and possibly aid in early detection or screening process during containment operations.

COVID-19 with an Associated Acid-base Disorder and the Diagnostic Utility

Apart from asymptomatic cases, several individuals with mild symptoms or presymptomatic may also escape quarantine control measure and continue to spread the virus through several contacts. It may be essential to develop screening panels or diagnostics in relation to change in body physiology. The successful development of screening panel and rapid diagnostic tools required for the detection of COVID-19 suspected cases have been hampered due to complex mechanisms of pathogenesis of the disease that underlie the development of signs and symptoms. Besides, signs and symptoms in patients suffering from COVID-19 are diverse in range and this also contributes against the development of effective rapid diagnostics. Pathophysiologically, the development of signs and symptoms is generally a result of alteration in body physiology. In other words, the development of signs and symptoms has clinical correlations with changes in body function. Alteration in body chemistry could also serve an advantage to develop screening or detection panel to support early diagnosis.

Cases of COVID-19 have been reported with the involvement of multiple organs. Likewise, SARS-CoV-2 has been detected in blood, feces, and urine samples [14]. It is not certain whether SARS-CoV-2 is transported through a lymphohematogenous route to other organs similar to other agents of pulmonary infection that has been reported elsewhere in distal body tissues [15]. However, the common signs and symptoms in COVID-19 are particularly related to respiratory problems. Clinical manifestations relating to respiratory symptoms such as cough, dyspnea (shortness of breath), runny nose, and other secondary effects of a respiratory problem involving tachycardia, hypoxia, acidosis, and among other findings have been reported [14], [16]. Respiratory acidosis is a complication of breathing problem. In the buildup of body acidosis, there is a reduction in arterial body pH and stimulation of peripheral chemoreceptors that result in increased ventilatory drive under body regulation through a compensatory mechanism. As described in Figure 1, the presence of an obstructive gas exchange body tends to increase more CO_2 in the body in consequence of alveolar hypoventilation that drives respiratory acidosis due to the creation of an acidic environment. Alveolar hypoventilation leads to an increased $PaCO_2$. Ventilatory defect that leads to the acid-base disorder may offer useful diagnostic information in identifying suspected cases of COVID-19. Estimation of changes in arterial pCo_2/pO_2 can be done through a breathing record of inspired and expired gasses using various respiratory gas measurements and thus stands a rapid advantage to pave new screening or diagnostic opportunities.

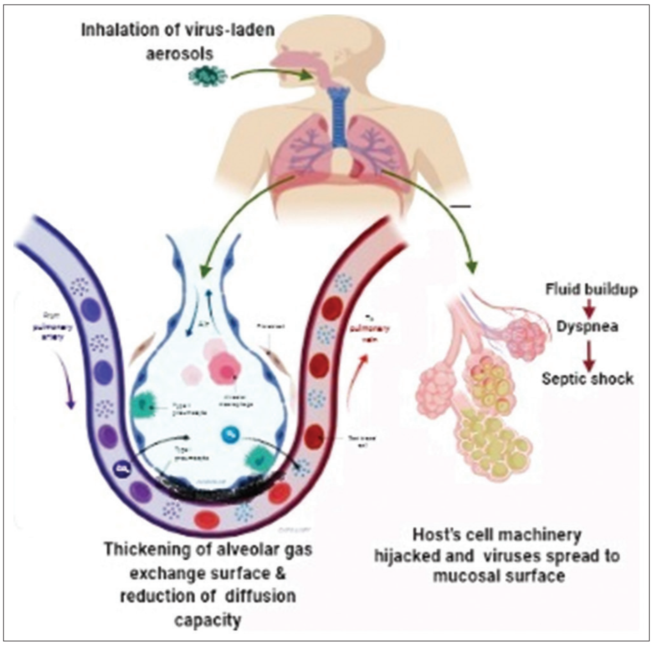

Figure 1: Development of acute respiratory distress in critical cases associated with COVID-19

Conclusion

Knowledge of the changes in body physiology and/or chemistry from the available clinical information in relation to the pathophysiologies of associated neuropathological and acid-base disorders in COVID-19 may help in better understanding the disease and also aid the development of screening or diagnostic tests. Perhaps, this may circumvent waiting long for laboratory analyses or development of biomarkers or add to the diagnostic efficiency of COVID-19. Thus, the development of respiratory virus testing panels that are highly sensitive and specific for SARS-CoV-2 target may help in containment operation through the detection of the hidden carriers who are asymptomatic or presymptomatic.

Declarations

Ethical approval

Ethical approval and written informed consent not required for this study.

Consent for publication

No data in this study required written informed consent before publication.

Availability of data and material

Data sharing is not applicable; no dataset was generated or analyzed during the present study.

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Dengue Lurks During Coronavirus Disease-19 Pandemic in Indonesia: A Narrative Review

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Abstract

BACKGROUND: Most attention and healthcare resources in Indonesia have been geared toward battling the coronavirus (CoV) disease (COVID)-19 pandemic, and less overture has been given to the looming risks of dengue that has been endemic in many areas of Indonesia. Despite related constraints, the Primary Health Cares (PHC) in Indonesia plays an important role in the face of emergency situations.

AIM: This study aimed to review the dengue and COVID-19 infection, clinical manifestations in children and adults, clinical pathology findings, as well as the prevention strategies that could be applied in PHC.

METHODS: This study is a narrative review based on the research articles and reports that were published between 2010 and 2020. A total of 70 articles and reports were obtained and after careful consideration, 58 articles and reports were used as references of this study.

RESULTS: Both dengue virus (DENV) and severe acute respiratory syndrome-CoV (SARS-CoV-2) share the similarity of antigenic structure, common symptoms, and laboratory findings. The immune response in SARS-CoV-2 may cause a cytokine storm, which can increase vascular permeability and organ damage. Secondary infection of DENV with different strains may allow the occurrence of antibody-dependent enhancement. The cross-reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positive on rapid dengue infection serological tests.

CONCLUSION: PHC as the front line of health services has a fundamental role in the crisis situation. The prevention and control of DENV and SARS-CoV-2 infections are based on the mode of transmission and need compliance to the related health protocols.

Introduction

The Indonesia's healthcare system has been overwhelmed by the sudden struck of coronavirus (CoV) disease (COVID)-19 pandemic. After the first two confirmed cases of COVID-19 in Indonesia were reported in March 2, 2020 [1], the disease has spread rapidly to almost all parts of Indonesia that were totally unprepared for the crisis. Being the world's fourth most populous nation [2], Indonesia might suffer immensely compared to less-populous countries [3]. Based on the rising cases, fatalities, and a large-scale socioeconomic impact, on April 13, 2020, the President declared COVID-19 as a national disaster in Indonesia [4].

Most attention and healthcare resources in Indonesia have been geared toward battling the COVID-19 pandemic, and less overture has been given to the looming risks of dengue, despite the fact that dengue has been endemic in many areas of Indonesia and around the period of 1968-2009, Indonesia had a history of the highest cases of dengue hemorrhagic fever (DHF) in South East Asian region [5]. As of 9 July 2020, the Ministry of Health of the Republic of Indonesia revealed that five provinces with high cases of DHF also reported a high case fatality rate (CFR) of COVID-19, namely East Java (5948 DHF cases and COVID-19 CFR 7.3%), Special Capital Region of Jakarta (4227 DHF cases and COVID-19 CFR 5.0%), Central Java (2846 DHF cases and COVID-19 CFR 4.3%), West Java (10,772 DHF cases and COVID-19 CFR 3.8%), and Bali (8930 DHF cases and COVID-19 CFR 1.3%) [6], [7].

Both DHF and COVID-19 battle on two fronts of healthcare need. The heterogeneity of 514 districts in Indonesia by geographical features, demographical characteristics, cultures, local living styles, health-seeking behaviors, and community participations [8] creates challenges in the prevention and control strategies to combat the double burden of diseases. The introduction of universal health coverage with a single-payer system in 2014 that currently covers around 203 million people makes the Primary Health Care (PHC) Centres play a significant role in the face of emergency situations. Accordingly, this study aimed to review the dengue and COVID-19 infection, clinical manifestations in children and adults, clinical pathology findings, as well as the prevention strategies that could be applied in PHC.

Search Strategy

This study is a review based on the research articles and reports related to dengue virus (DENV), pathogenesis of dengue, epidemiology of dengue in Indonesia, dengue prevention, COVID-19 virology and pathogenesis, COVID-19 and DHF clinical findings, COVID-19 and DHF clinical pathology findings, epidemiology of COVID-19 in Indonesia, and COVID-19 prevention that were published between 2010 and 2020. References from published articles were also included in the review, as long as they were published between 2010 and 2020. We excluded expert's point of views. A total of 70 articles and reports were obtained and after careful consideration, 58 articles and reports were used as references of this study.

Epidemiology of DHF and COVID-19 in Indonesia

In Indonesia, DHF was first reported in Surabaya in 1968, with a high CFR of 41.38%. Dengue has spread to many areas in Indonesia and has become a public health concern since then [5]. DHF usually reaches its peak around March and diminish in the following months, which are the transition months between rainy and dry season. Nonetheless, during the COVID-19 pandemic, DHF cases in Indonesia have still been escalating with reports of more than 71,663 cases and 459 deaths from January to July 2020, even though the recorded cases and deaths were lower compared to reports from January to July 2019 with 112,954 cases and 751 deaths [6].

The incidence rate of DHF in Indonesia (red curve in Figure 1) seemed to increase in a span of half a century, from around 0.05 cases per 100,000 person-years in 1968 to around 77.96 cases per 100,000 person-years in 2016; with a peak of cyclic pattern occurring nearly 6–8 years. In contrast, the annual CFR of DHF has decreased afterward (green curve in Figure 1), from more than 20% in 1968 to 0.79% in 2016 [9].

Figure 1: Incidence rate (per 100,000 person-years) and case fatality rate (%) of dengue hemorrhagic fever in Indonesia from 1968 to 2017 [9]

In the meantime, the Ministry of Health of the Republic of Indonesia recorded the increase number of COVID-19 confirmed cases from the first two cases reported in March 2, 2020, to 365,240 confirmed cases reported on October 19, 2020 (Figure 2). There was a sharp increase in attack rate (AR = percentage of confirmed cases by population size per 100,000 people) from 0.7% in March 2, 2020, to 136.4% in October 19, 2020. The calculation was based on the estimated current population of Indonesia in 2020 (267,700,000 people). There was a decrease of case positivity rate (CPR = percentage of confirmed cases by number of specimens tested) from 24.1% in April 2, 2020 to 14.3% in October 19, 2020; an increase of case recovery rate (CRR = percentage of recover cases by confirmed cases) from 6.3% in April 2, 2020 to 79.2% in October 19, 2020; and a decrease of (CFR = percentage of death cases by confirmed cases) from 9.5% in April 2, 2020 to 3.5% in October 19, 2020 [10]. Yet, the recorded COVID-19 data might not represent the number of actual infections, which could be undetected due to several factors, including lack of proper tracing and diagnoses [3].

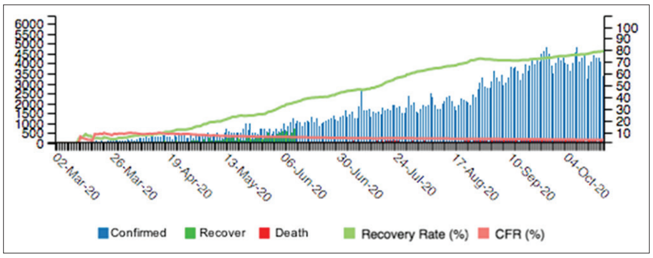

Figure 2: Number of coronavirus disease-19 confirmed cases, recover, death, RR, and CFR as of October 19, 2020 [10]

Epidemiological studies of COVID-19 may provide an insufficient representation of pediatric population. A study involving 582 children conducted in 25 European countries reported a CFR of 0.69%. Conversely, CFR in infants less than a month old to adolescents with COVID-19 reach 1.1% in Indonesia [11].

Dengue and severe acute respiratory syndrome-CoV (SARS-CoV-2) viruses

DENV belongs to the *Flaviviridae*, a family of positive, single-stranded, enveloped RNA viruses [12]. The transmission of DENV is mediated by mosquito vectors, *Aedes* spp. DENV consists of four serotypes, namely, DEN-1, DEN-2, DEN-3, and DEN-4 [13].

Dengue viral genome component (Figure 3) comprises genes that encode structural proteins and non-structural proteins. The structural protein genes contain codes to form protein M (membrane), C (capsid), and E (envelope), and these outer proteins

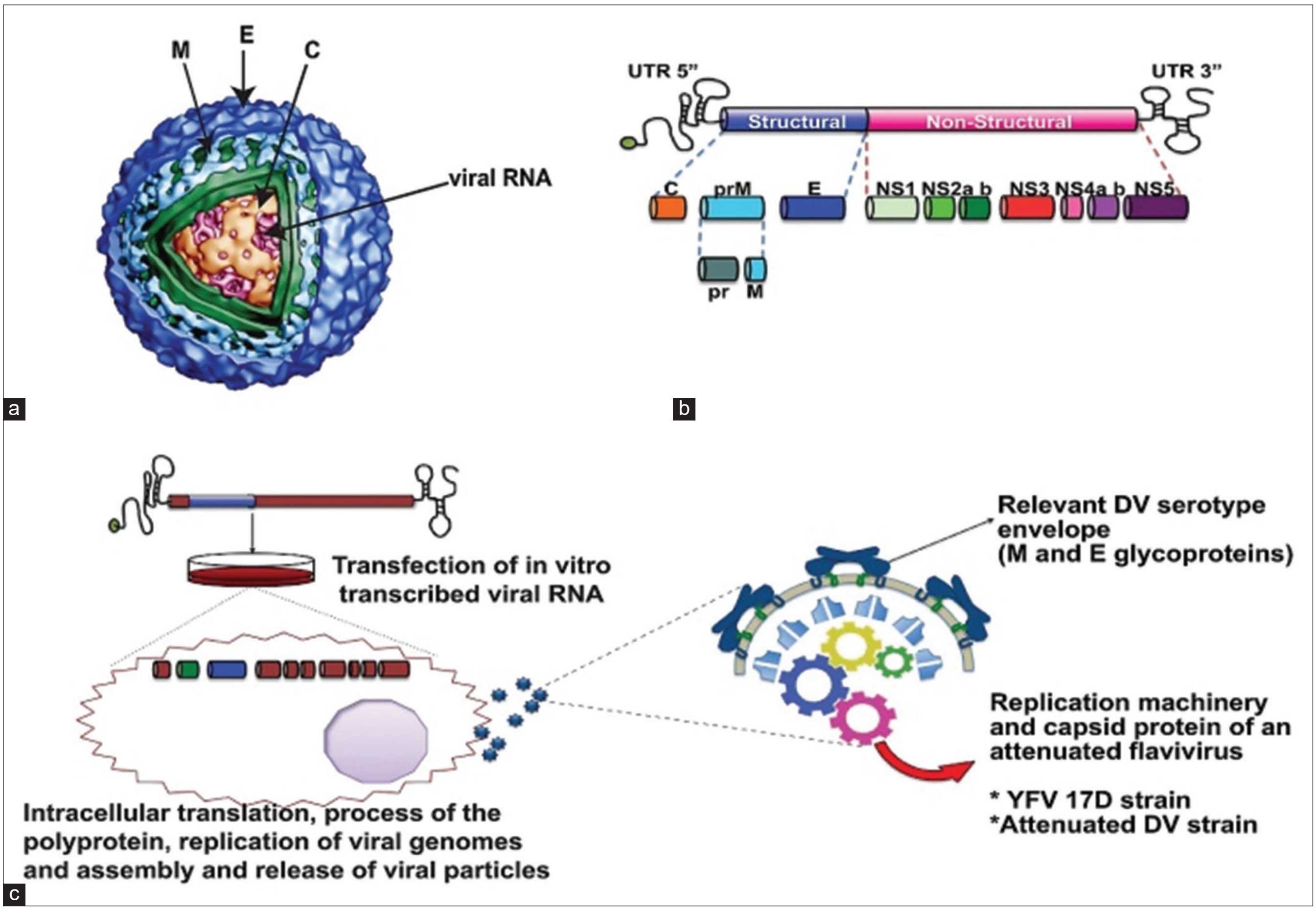

Figure 3: (a-c) Dengue viral genome component [14]

will bind to human antibodies. In contrast, the non-structural protein genes contain codes to form enzymes that are needed for virus replication [14].

Virus that causes COVID-19 (SARS-CoV-2) is one of the *Corona* strains that infect humans (Figure 4). The CoV genome encodes four main proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). S protein is responsible for the entry of viruses into cells that express angiotensin-converting enzyme 2 (ACE2) receptors. Approximately 75% of the SARS-CoV-2 genome is identical to the SARS-CoV genome, in which both viruses use ACE2 receptors to infect epithelial and endothelial barrier cells of the airway mucosa [17].

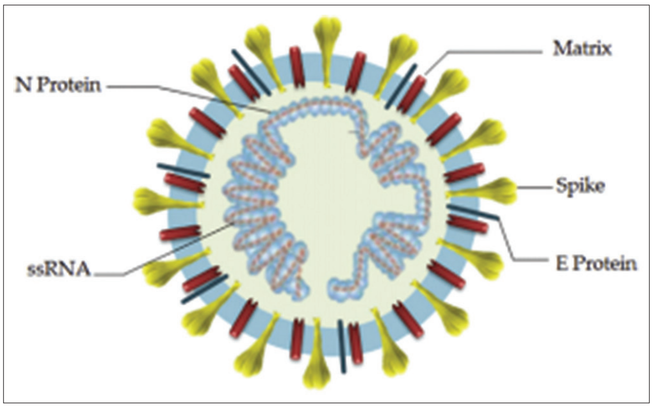

Figure 4: SARS-CoV-2 structure [15], [16]

DENV Infection

Following infection, DENV replicates in the skin cells, including keratinocytes and Langerhans cells [18], which then trigger various host innate immune responses, including macrophage [19], [20], [21]. The bonding complex between receptors on the surface of cytotoxic T cells, major histocompatibility complex I (MHC I) molecules, virus peptides, and macrophage cells will act as antigen-presenting cells. After the bonding complex occurs, CD8 cells will produce cytokines, which will cause macrophage to undergo apoptosis [22], [23], [24]. Dengue may also infect mast cells, causing degranulation and release of several inflammatory mediators, which can increase vascular permeability and vascular leakage [25], [26].

The innate and adaptive immune response phases will determine the clinical symptoms that appear in infected patients. If both systems successfully kill the DENV, then there will be a low viremia or no virus so that the patient does not show clinical symptoms (subclinical). However, if the virus remains in moderate amounts (moderate viremia), then the clinical symptoms appear as dengue fever. If the virus escapes from the immune system and lead to severe viremia, then the clinical symptoms appear as dengue hemorrhagic fever, with life-threatening emergency symptoms, such as bleeding, shock, and death [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27].

DENV is also able to infect endothelial cells (Figure 5). The demise of endothelial cells by apoptosis will increase blood vessel permeability and cause plasma and red blood cell leakage, which is clinically seen as bleeding [28].

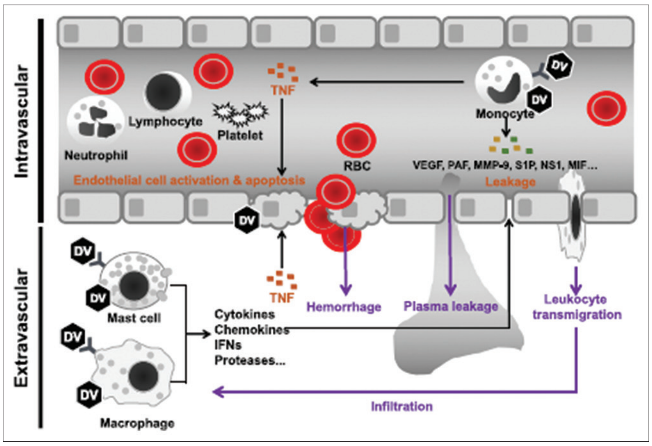

Figure 5: Pathogenesis of extra and intravascular bleeding [28]

Antibodies in dengue infection are produced by plasma cells derived from differentiation of B lymphocytes, by activation of CD4 cells through the intermediary molecule MHC II. Anti-dengue antibodies, part of host humoral pathways, are specific to DENV and will bind as lock and key to neutralize the virus [13]. The mechanism occurs in the first infection by DENV and secondary infection from the same serotype. However, if a secondary infection is caused by a different serotype of DENV (Figure 6), the antibodies assembled from the previous infection are not able to neutralize the virus from the second infection but will cause the fragment crystallizable region (Fc) antibody fragment to attach to antibody receptors on the macrophage cell surface. This attachment causes the entry of DENV into these cells and causes massive viral replication, increase in viral load, and release of several inflammatory mediators, which is referred to as antibody-dependent enhancement (ADE). Clinical manifestations that occur are dengue hemorrhagic fever, dengue shock syndrome, or death [29], [30].

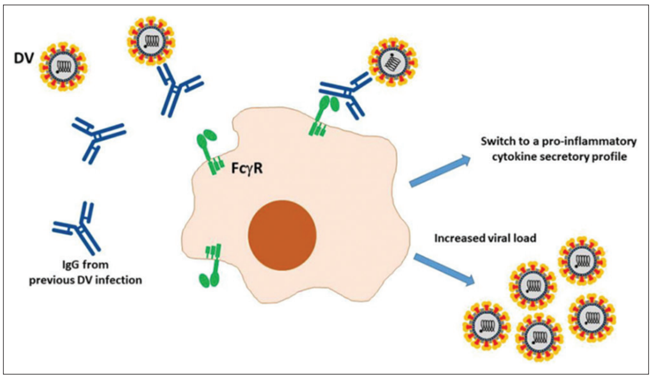

Figure 6: Pathogenesis of ADE in secondary dengue infection with different serotype [29]

SARS-CoV-2 Infection

When a CoV infects macrophage cells (Figure 7), NK cells as part of the innate immune system lyse both the infected macrophage cells and the viruses inside them. If macrophages fail to lyse the virus, they will activate CD4 cells. CD4 cells will differentiate into Th2 and Th1. Th1 cells will release inflammatory mediators to strengthen the role of macrophage cells. Whereas Th2 cells will help differentiate B lymphocyte cells into plasma cells and produce specific antibodies for this virus and then act as neutralizing antibodies [31], [32].

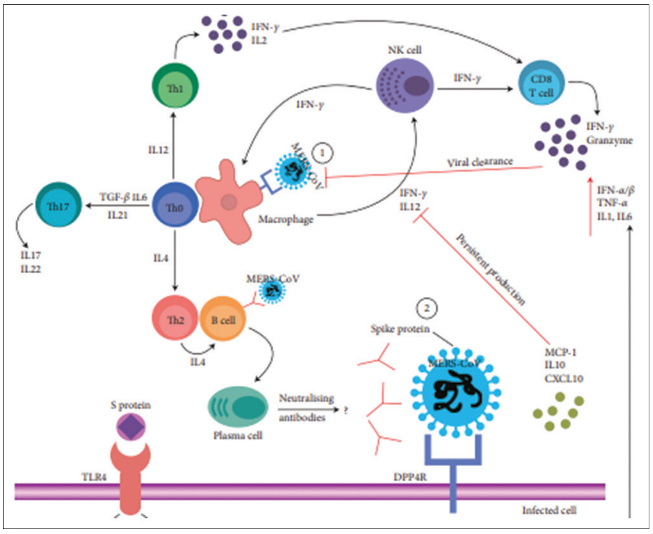

Figure 7: Immune response to coronavirus infection [32]

One of the main features of SARS-CoV-2 infection is the emergence of cytokine storms that produce an uncontrolled systemic inflammatory response from the release of pro-inflammatory cytokines and chemokines by immune cells. Cytokine storms trigger severe inflammatory responses that cause acute respiratory distress syndrome, multiple organ failure, and death [17].

Dengue Fever and COVID-19 Infection

Previous research [33] proposed a possibility of viral interference mechanism [34] of SARS-CoV-2 over DENV. SARS-CoV-2 has a high virulence and pathogenicity, and both SARS-CoV-2 and COVID-19 have a tropism toward endothelial cells [35], [36], which could lead to competitive inhibition. Dengue fever and COVID-19 may have similar clinical symptoms in the early stages and similar laboratory features [37], [38]. COVID-19 cases may be misdiagnosed as dengue, especially when relying on DENV IgM, which can remain positive months after infection [39]. Some common symptoms observed in COVID-19 and dengue patients may include fever, malaise, myalgia, headaches, and weakness [40]. COVID-19 may also produce symptoms such as cough, dyspnea and dysgeusia, sore throat, anosmia, and diarrhea, whereas adult patients with dengue may also suffer from retro-orbital pain, nausea/vomiting, rashes, and arthralgia [39].

It is still puzzling why children with COVID-19 suffer less severe symptoms than adults. A previous study suggested that children might be less sensitive to SARS-CoV-2 due to the maturity and function (e.g., binding ability) of ACE2 in children may be lower than that in adults. Further, the developing immune system in children may respond differently to pathogens [41].

Some common hematological findings in COVID-19 are lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia, and rarely thrombocytosis [42]. Neutrophil-lymphocyte ratio (NLR) in dengue fever is inversely correlated with the degree of severity, whereas NLR in COVID-19 is in line with the severity of the disease [43]. The increase in the inflammatory factor that occurs in COVID-19 may cause a decrease in erythrogenesis and cause erythrocyte destruction, which results in anemia [44]. In addition, coagulation abnormalities often occur in COVID-19, namely an increase in prothrombin time and d-dimer [45].

In dengue-endemic areas, there is also a possibility of false-positive results in serological tests for dengue fever. Due to the similarity of antigenic structure, SARS-CoV-2 can trigger the production of anti-DENV antibodies from immunological memory of T and B cells derived from previous exposure to the DENV virus. The anti-DENV antibodies against dengue may cause a false positive result of rapid dengue test and fail to consider COVID-19 infection, which leads to serious implications for both patients and public health [37]. Moreover, in patients with chronic co-morbidities, overlapping infections may increase the number of the patient requiring intensive care unit and mechanical ventilation [33].

Preventing DENV and SARS-CoV-2 Transmission

A vaccine to prevent dengue is available in some countries for people ages 9–45 years old with confirmed prior DENV infection [46]. DHF prevention and control focus on breaking the life cycle of *Aedes* spp. mosquito vectors with biological, physical, and chemical approaches that have been part of national health programs and have been introduced to the community since 1968 [47]. The popular physical approach of DHF prevention in the community is to eradicate mosquito's breeding place by draining water reservoirs once a week, covering water reservoir, and recycling used containers [48]. The application of biological agents, which are directed against the larval stages of dengue vectors, include fish (e.g., *Gambusia affinis*), bacteria (e.g., *Bacillus thuringiensis*), Cyclopods, and autocidal ovitraps. The chemical control may include chemical larviciding, insect growth regulators, and space sprays with organophosphate insecticides [49].

In contrast, SARS-CoV-2 may be transmitted primarily through contact, respiratory droplet (>5–10 μm in diameter), and droplet nuclei (aerosol, ≤5 μm in diameter) [50] when an infected person talks, coughs, sings, or sneezes [51]. However, it may also be possible to be transmitted through airborne [52], fomite (contaminated services) [53], fecal-oral [54], bloodborne, mother-to-child, and animal-to-human [55].

Many countries apply lockdown strategies to reduce the impact of COVID-19 pandemic [56]. PHC as the front line of health services has a fundamental role in the crisis situation, related to its knowledge of the catchment areas, accessibility, following up on suspected and mild cases that are directed toward restraining the pandemic and preventing the spread of the disease, as well as preventing the disease progression [56].

The prevention of COVID-19 may include washing hands with soap and water or an alcohol-based hand sanitizer; maintaining physical distance between persons; avoid going to crowded places; and avoid touching eyes, nose, and mouth [57], [58]. The health protocols to prevent the transmission of SARS-CoV-2 have been applied in workplaces, schools, health-care facilities, homes, and other public places in Indonesia [58], and compliance to the health protocols is needed.

Conclusion

Both DENV and SARS-CoV-2 share similarity of antigenic structure, common symptoms, and laboratory findings. The immune response in SARS-CoV-2 may cause cytokine storm, which can increase vascular permeability and organ damage. Secondary infection of DENV with different strains may allow the occurrence of ADE. The cross-reactions between SARS-CoV-2 antibodies and DENV antigens may cause false positive on rapid dengue infection serological tests. DENV is transmitted by *Aedes* spp., whereas SARS-CoV-2 may be transmitted through contact, respiratory droplet, aerosol, and other modes.

The sudden struck of COVID-19 pandemic and the surge of dengue causes a huge impact on health-care system in Indonesia. PHC as the front line of health services has a fundamental role in the crisis situation in restraining the pandemic and preventing the spread of the disease, as well as preventing the disease progression. The prevention and control of DENV and SARS-CoV-2 infections are based on the mode of transmission and need compliance to the related health protocols.

Authors’ Contributions

Study design: WD and RB. Data acquisition: WD, RB, PAN, MFI, and VB. Drafting of manuscript: WD and RB. Critical revision of the manuscript: WD, RB, PAN, MFI, and VB.

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The Use of Dupilumab in Atopic Dermatitis During Coronavirus Disease-19 Era – A Review

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Abstract

The global pandemic of coronavirus (CoV) d0isease 2019 (COVID-19), caused by severe acute respiratory syndrome CoV (SARS-CoV 2), has been a challenging event for every individual. It is known that COVID-19 may exhibit a vast range of symptoms ranging from mild to severe. Acute respiratory distress syndrome (ARDS) and multiple organ failure are the most common causes of death in COVID-19 cases [3]. Accumulating evidence shows that T-helper type (Th-1) inflammation cascade plays a major role in COVID-19 pathogenesis. It is proposed that aberrant immune reaction, or known as cytokine storm, is one of the main causals of ARDS in COVID-19 case, while dupilumab, the first Food and Drug Administration-approved immunomodulatory treatment for atopic dermatitis, is known for its effectiveness in suppressing the Th-2 inflammation pathway. It is postulated that both types of inflammation can cross-regulate each other. Therefore, some may believe that the regression of Th-2 cascade may upregulate the Th-1 cascade, leading to an exaggerated cytokine storm. This hypothesis leads to the uncertainty of the safety of continuing this modality during the pandemic.

Introduction

Atopic dermatitis (AD) can be deemed as one of the most common non-communicable dermatological ailments. It affects approximately 20% of children and 2–8% adults in most nations of the world [1], [2], [3], [4], [5], [6], [7], [8]. An international study shows that the figure has increased two-or three-fold within three decades in the developed countries. Therefore, it is predicted that the number will always accumulate, and this also shows that AD is a global health problem both in developing and developed nations [9].

Both personal and social aspects are greatly influenced by uncontrollable AD. For instance, the social stigma of visible skin efflorescence may affect individual's self-confidence, and debilitating itch might lower one's quality of life [10], [11]. Dupilumab, as the first Food and Drug Administration-approved biologic treatment, has been proven effective and has significantly improved quality of life. Some concerns about the safety of the utilization of dupilumab have been raised during coronavirus (CoV) disease (COVID)-19 pandemic. Some may fear that dupilumab may increase the susceptibility of acquiring COVID-19 or worsen the condition. However, it is also not recommended to discontinue dupilumab because of the chronic nature of AD and the unknown period of this pandemic [12].

In this article, the literature reviews of both clinical and immunology aspects of dupilumab in AD and COVID-19 have been explored. The aim is to provide the latest reference about dupilumab in AD patients and COVID-19. Thus, it can assist physicians in generating the best clinical judgment in a practice setting.

A Glance of AD

What is AD?

AD is defined as a chronic inflammatory skin disorder, with one of the major hallmarks of extremely pruritic, and it is very common to be found during infancy and childhood period [13]. It is crucial to bear in mind that the diagnosis of AD includes an array of major and minor features. There is no single feature that can represent AD itself nor a diagnostic assessment [14], [15] (Table 1). Many guidelines and suggestions have been published to aid clinicians in establishing the diagnosis. However, it is implied by Tada [16] that mostly adopted guideline for diagnosing both in practice settings and clinical trials is the revised Hanifin and Rajla criteria. The diagnostic can be established when at least three major features and three minor features are noted [17].

AD is a very complicated and debilitating condition, and individuals may suffer from both physical and mental issues due to uncontrollable AD. Literature shows that AD is significantly affecting all aspects of the quality of life of patients and their families [11], [18], [19] (Figures 1 and 2).

Pathogenesis

The pathogenesis of AD is subsequently complex and is not fully elucidated until now. Many theories are proposed and postulated; however, it is widely agreed that AD is orchestrated from defective skin integrity, particular genes, and dramatic response of the immune system against exacerbating factors [14], [21], [22].

In general, it is found that AD individuals' skin lacks essential genes that are needed to form a perfect skin barrier. For instance, some individuals may have filaggrin mutation; filaggrin is a gene that encodes essential proteins in building the epithelial barrier and ceramide, a lipid substance that plays an important role in retaining water permeability barrier function [22], [23] The lack of these two major materials leads to excessive trans-epidermal water loss, resulting in pH alteration and skin dryness. In addition, an antimicrobial peptide called cathelicidin, which is one of the very first layers of immune barrier, is also found to be depleted in most AD patients. [10]. Thus, exacerbating environmental stimuli such as aeroallergens, irritating chemicals, and pathogens are easier to penetrate the skin, initiating inflammation [14], [22], [24].

Th-2 type cells are widely accepted to be associated with both acute and chronic AD course [10], [14], [15]. However, Fujii [25] believes that either in acute and chronic lesion, there might be a switch from Th2 to Th1 activity.

In the acute event, interleukin (IL)-4, IL-5, IL-13, IL-25, and IL-33 levels increase [15]. Especially, in the early lesion of AD, it is shown that IL-4 and IL-13 dominate the inflammatory cascade [14], [15]. Meanwhile, in chronic AD, IL-31 has recently been discovered to be overly expressed and linked to the severity of the course.

On the other hand, it is also found that IL-4, IL-13, and IL-33 might downregulate the filaggrin, and thus, it is like a loophole of the immune system and defective skin barrier cascades [26].

Management

Overview

In general, many findings agree that the aim of the treatment of AD must be focused on inflammation cessation by repairing the skin barrier and reducing the itch. The importance of education about the nature of the ailment, skin hydration, pharmacological regime, identification, and elimination of flare causal factors is often highlighted in virtually all guidelines [10], [14], [27]. Therefore, holistic and multi-faceted approaches are needed to manage this ailment. [8], [10], [28]. The Japanese guideline for AD believes that the management of AD must be based on three fundamental aspects. First is the investigation and countermeasures of the causal and exacerbating elements. Second is the repairment if the skin defect (skincare). Last is pharmacotherapy [28]. Similarly, the European Consensus Guidelines' treatment option is quite similar to most guidelines and literature, aside from its agreement to divide the management into four phases: Baseline, mild, moderate, and severe [8]. The phases depend on the SCORing AD (SCORAD) (Appendix 1). SCORAD is one of the tools that can be used in assessing the extent and severity of AD. Less than SCORAD 25 is defined as mild, 25–50 as moderate, and more than 50 as severe. It is also suggested that in each phase, adding additional medication and antiseptic or antibiotic may be beneficial in treating superinfection.

A Brief Review of Dupilumab

Dupilumab is a human analogue monoclonal antibody that blocks IL-4 and IL-13 pathways by binding a shared α-subunit of IL-4 and IL-13, both of which are the major cytokines for Th-2 inflammation in AD [4], [29], [30].

Some experimental research demonstrated that early treatment with IL-4 and IL-3 blocking agents will dampen the responses to IFN and IL -17. In brief, when the early lesion of AD is exposed to IL-4 and IL-13, long-lasting persistent effects are doable [31]. Therefore, not only will dupilumab decrease the flare but it may also prevent the course of recalcitrant AD in the future. Dupilumab can be used either as monotherapy or combination therapy. Studies of dupilumab in 4 weeks and 12 weeks as monotherapy and as a combination with topical glucocorticoid in moderate-severe AD show significant improvement [5]. Not only were skin lesions improved but the severity of itch also rapidly decreased, allowing individuals to have a better quality of life. These results were also supported by a separate study, where Eczema Area and Severity Index score and peak pruritus Numerical Rating Score were reported to be significantly improved by the end of week 16th [32]. In terms of adverse effects, both placebo and intervention groups were almost equal [5], [32]. However, in a two phase 3 trial, it is also observed that nasopharyngitis was the second most common adverse effect after infection and infestation in the dupilumab groups [32]. A similar result is also discovered in a study of dupilumab and asthmatic patients [33].

COVID-19

What is COVID-19?

History

In December 2019, several pneumonia-like cases with unknown etiology were reported in Wuhan, China. This disease has started with suggestive symptoms of progressive respiratory infection, with some patients developing acute respiratory distress syndrome (ARDS), acute respiratory failure, and other life-threatening complications [34]. A novel beta-CoV was discovered later in January 2020 to be the culprit. International Virus Classification Commission named the virus as Severe Acute Respiratory Syndrome-CoV 2 (SARS-CoV 2), while the World Health Organization (WHO) officially named the disease as COVID-19 in the next month [1], [35]. In March 2020, the WHO asserted that this disease is a global emergency, affecting every aspect of life, and thus, declared COVID-19 as a pandemic [36] (Figure 3).

Incubation and Clinical Characteristic

Data show that symptoms of COVID-19 usually appear after an incubation period of 5.1–12 days [37]. Fever, dry cough, and fatigue are the most common symptoms. However, other symptoms such as headache, hemoptysis, and gastrointestinal symptoms such as diarrhea and vomiting are likely to be exhibited as well. In addition, dyspnea is found to be developed in more than half of the patients [1], [38], [39]. A recent study also discovered that olfactory dysfunction such as anosmia and hyposmia was found prominently in COVID-19 patients [40]. However, COVID-19 can still yield in a person without showing any symptom, which makes this ailment easily transmitted.

Route of Transmission

Human-to-human transmission is feasible due to respiratory fomites or droplets. It is also suggested that direct and non-direct contacts through mucous membrane of eyes, nose, mouth, and skin are another potential routes of transmission [39], [41]. However, a recent study discovered that aerosol transmission is highly plausible through smaller droplets or droplet nuclei. Therefore, proper inter-personal distancing and usage of mask are very essential to control the spread of infection [42], [43]. Due to a recent study that shows COVID-19 cases with enteric symptoms, it is also suggested that the digestive tract might be another possible route of transmission [44].

An article also suggests that percutaneous transmission is possible due to the high expression of Angiotensin-Converting Enzyme-2 (ACE2) in the skin tissue cells [45]. ACE-2 is known to facilitate the entry of the virus (further explanation will be explained in the next chapter). However, a thorough study is still needed to elucidate this hypothesis.

Pathogenesis

Virus structure

CoVs are enveloped with single-stranded, positive-strand RNA genome (26-32kb in weight) which comes from Coronaviridae family. There are four genera of CoVs; α, β, γ, δ, and COVID-19 belongs to the beta-CoV genus. Within beta genus itself, there are four lineages (A, B, C, and D) [3], [46].

The appearance of the virus is a rough, spherical and has prominent club-shaped elongations which contain its spike protein. This novel CoV has shown 88% similarity to bat-related SARS-like CoVs' sequence (bat-SL-CoVZC45 and bat-SL-CoVZXC21), and approximately 50% identical to Middle East Respiratory Syndrome CoVs' sequence. Due to its similar structure, the pathogenesis of SARS-CoV 2 can be postulated. However, the complete pathogenesis of COVID-19 has not been fully elucidated [47].

Table 1: Major and minor features. Adapted from Goldsmith *et al*. and Correale *et al*. [14], [20]

Major features
1. Pruritus
2. Recurrent or relapse course of dermatitis
3. Typical lesion (Facial and/or extensor rashes in infants and young children, and flexural lichenification in older children and adults)
4. Family history of atopic diatheses (asthma, allergic rhinitis, and atopic dermatitis)
Minor Features
1. Xerosis
2. Ichthyosis/palmar hyperlinearity, and keratosis pilaris
3. Immediate (type I) skin test reaction
4. Elevated IgE level
5. Early age of onset
6. Tendency toward cutaneous infections (especially staph. aureus and herpes simplex), impaired cell- mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor, and facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Relaps influenced by environmental and emotional factor
23. White dermographism, delayed blanch

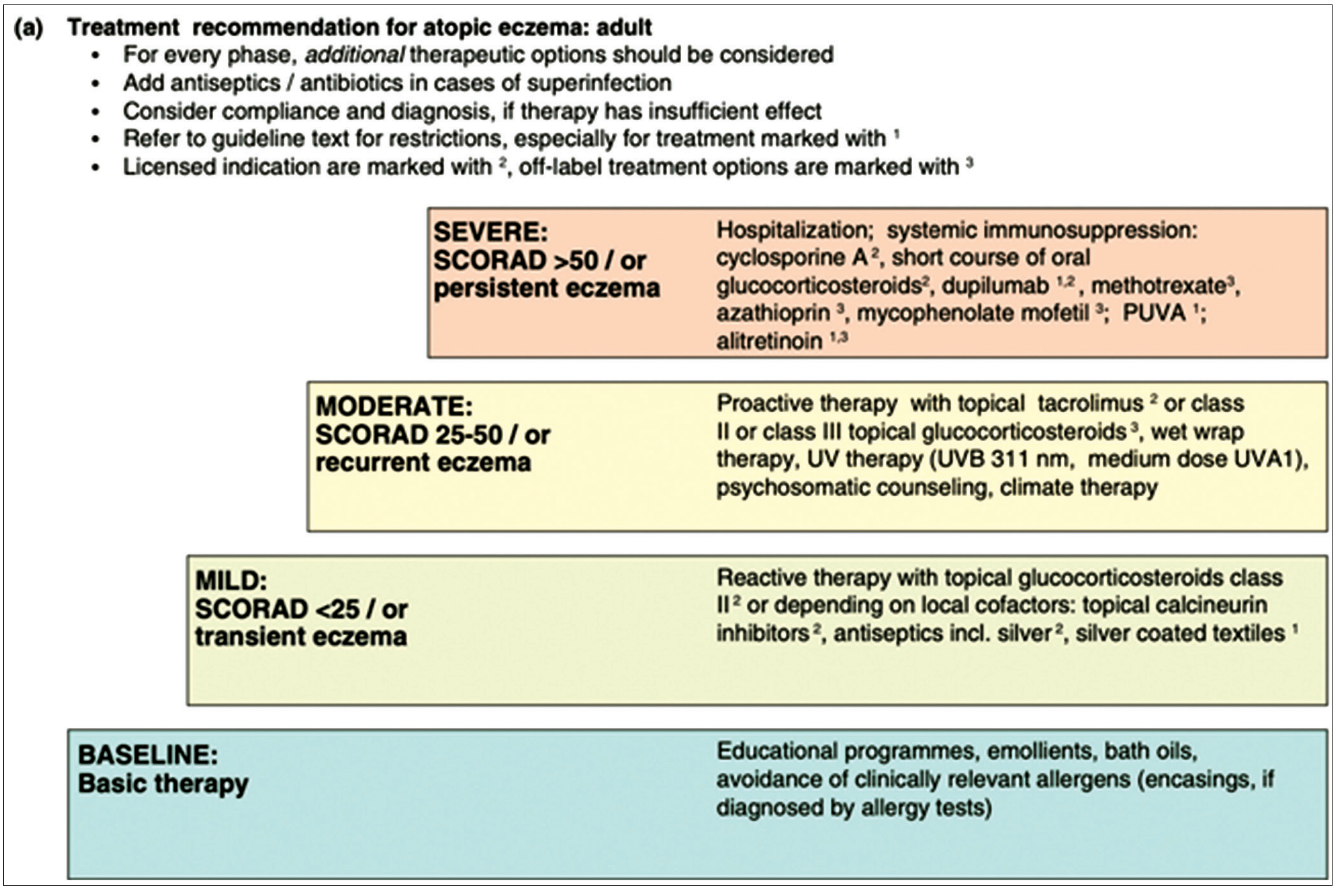

Figure 1: Management scheme of AD in adults. Adapted from Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018 May;32(5):657–82

Host Entrance and Immune Response

SARS-CoV 2 can enter the host cells by direct membrane fusion. First, the envelope spike glycoprotein will bind to the host cellular receptor, facilitated by ACE2 [48]. After entering the cell, the virus RNA genome will be released to the cytoplasm and then commenced to the replication phase [49].

Subsequently, after the virus has successfully hijacked the cells, its antigen will be presented to the antigen presentation cells. Antigen presentation will evoke host immune response which is both humoral and cellular immunity. T cells and B cells play a major role as the immune mediators in this event [35].

Since COVID-19 is caused by a virus, similar to any viral infection, the innate immune pathway is the first line of defense. However, a further aberrant and disarrayed immune response might damage the immune systems, leading to fatality [3], [50]. This event is often known as a cytokine storm. Several studies report that ARDS is the main cause of mortality of COVID-19 patients, and ARDS is one of the results of the cytokine storm [3], [51], [52]. This dramatic cytokines response makes COVID-19 difficult to manage and threaten lives.

T-helper type 1 (Th-1) cascade plays an essential role in COVID-19 infection. It is observed that cytokines that generate Th-1 pathway such as IL-1B, IFN-γ, IP-10, and monocyte chemoattractant protein 1 rise [51]. This hypothesis is also supported by several studies and reports discovering highly expressed Th-1 related cytokines in many COVID-19 patients. For instance, a study by Huang *et al*. revealed that levels of IL-7, IL-8, IL-9, IL-10, fibroblast growth factor, granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, MIP-1A,MIP1-B, platelet-derived growth factor, tumor necrosis factor (TNF)α, and VEGF surge in both ICU and non-ICU required COVID-19 patients compared to healthy individuals [51].

An analyzing case study in China also saw a high expression of IL-10, IL-6, and TNF-α in severe cases compared to moderate cases [53]. An identical result is also found in a study of assessment of laboratory data reporting that IL-6 level significantly rises in severe cases compared to mild cases [54]. A multicenter study also supports previous data, in which it is observed that IL-6 was found higher in mortality cases than successful cases [55].

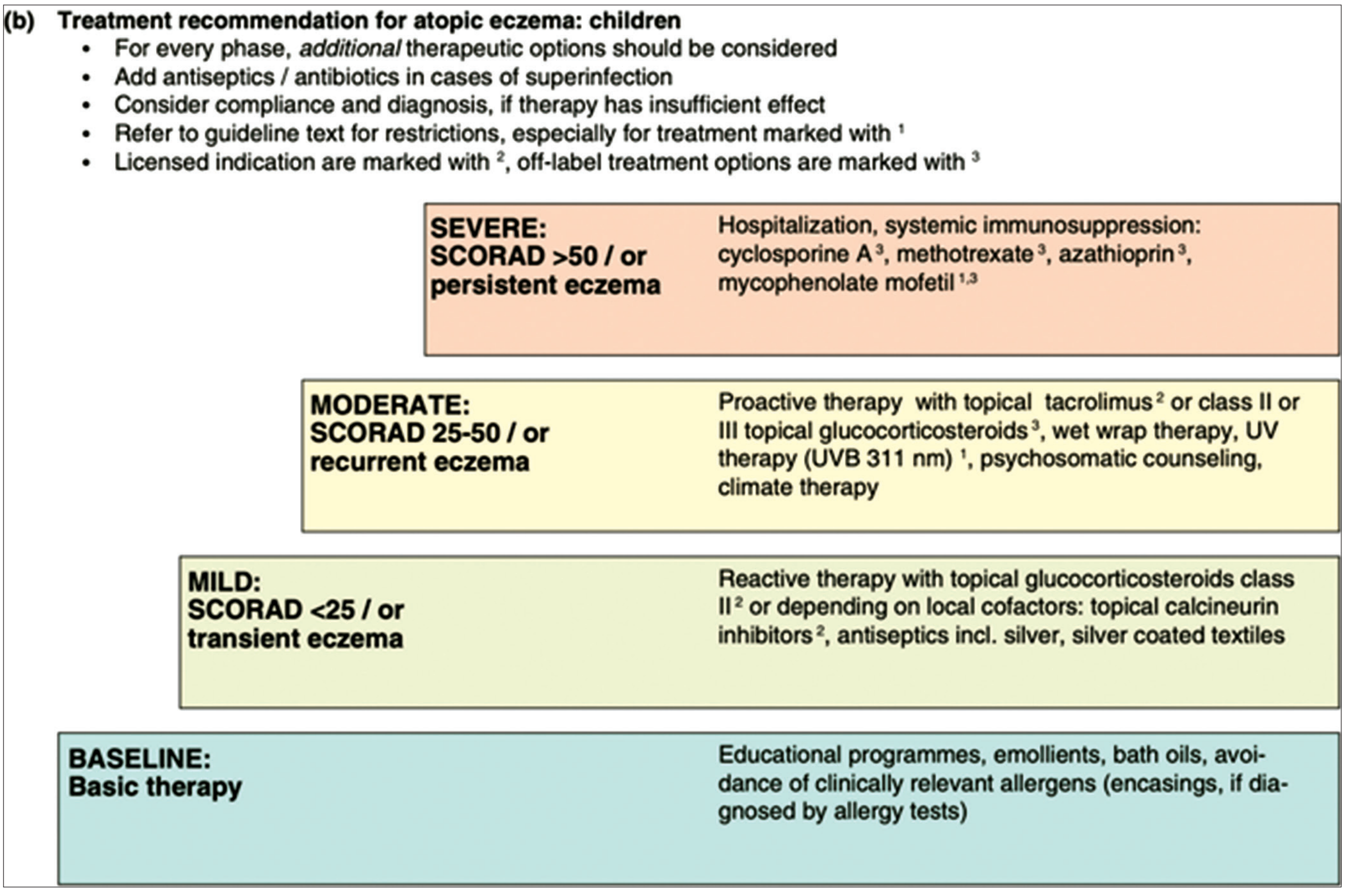

Figure 2: Management scheme of AD in children. Adapted from Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. J Eur Acad Dermatol Venereol. 2018 May;32(5):657–82

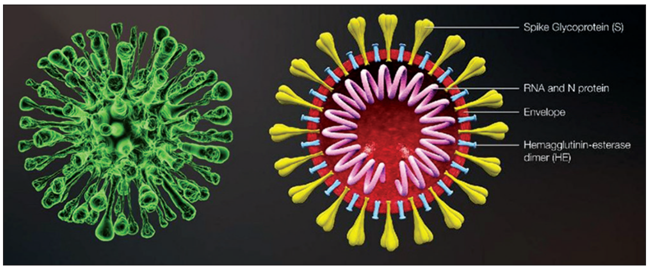

Figure 3: Structure of SARS-CoV 2. Adapted from https://microbeonline.com/sars-cov-2-properties-transmission

Discussion

Dupilumab during COVID-19 era

It is understandable that COVID-19 alters the nature of AD management with dupilumab. Some AD patients may abruptly cease the treatment or refuse to take it routinely. Some cases may be caused due to the difficulty for accessing dermatology practices that are closed during lockdown or the fear of contracting COVID-19 from clinic visit [56]. Others may have concerns about the effect of dupilumab therapy and susceptibility of acquiring COVID-19.

Even though there are some letters of statement about the usage of immunomodulators usage in dermatology cases during COVID-19 [57], [58], more sources that provide information about the safety of biologic treatment during the COVID-19 outbreak are needed [59]. Even though dupilumab is not an immunosuppressant nor steroid that might reduce the immune systems, it is postulated that immunomodulators may affect the balance of the immune system [6]. The Th1/Th2 immune balance has been studied for decades. However, it is ultimately complex and has not been fully elucidated until now. It is believed that the integration of the immune system is achieved by cell-to-cell communication, facilitated by cytokines. Therefore, it can modulate those cells to become more active (upregulate) or less active (downregulate) [7]. It is hypothesized that suppression of Th-2 polarized cytokines may upregulate the Th-1 cascade activity. For instance, IL-10 is known to release from the Th-2 pathway, and it can downregulate Th-1 production [6]. This hypothesis is also supported by a study in autoimmune disease, stating that Th-1 and Th-2 inflammations work to antagonize each other. This may be achieved either by inhibiting the production of the other cell type or by hindering each other effector function. For instance, abundant expression of IL-3 or IL-6 may block the generation of Th-1 cells from naive T cells [60].

In other words, it is plausible that the production of Th-1 polarized cytokines is upregulated due to the decreased Th-2 activity, resulting from the lower expression of IL-4 and IL-13, blocked by dupilumab. This may worsen or increase the risk of aberrant cytokine storm in COVID-19 patients. However, a study disputes that dupilumab affects Th-1 activity. It is shown that no elevation of Th-1/IFN-g-related gene expression was observed in AD patients with dupilumab [61]. Moreover, a hypothesis is also proposed that dupilumab might give AD patients more protection from COVID-19 infection. It is known that expression of IL-6, one of the infamous cytokines that play role in cytokine storm, is depended on endogenous production of IL-4, which obviously decreases in patient on dupilumab. This mechanism gives the possibility of protective effect of dupilumab in the nature of COVID-19 [62].

Many have proposed that the concept of Th-1/Th-2 immune balance is very complex and not only influenced by the cytokines profile but also by antigen presentation, immunogenic and non-immunogenic cells, genetic, hormones, oxidative stress, and environment [6], [60], [63], [64]. Thus, further research is needed to elucidate this matter.

Limitations and Recommendation

One of the limitations of this article is the sparse data of COVID-19 due to its novelty. Another limitation includes the strength of the data of dupilumab, since the most common available sources are randomized-controlled trials. In addition, most of the sources of the immunology cascades are theoretical data, and there is still little clinical evidence that can support the theory. It is recommended that physicians strictly follow-up patients with dupilumab and record their development during this pandemic.

The use of biologic modality in dermatological conditions during the pandemic may be challenging. Any decision either discontinuation or continuation of the modality may be obtained based on the evaluation of patient's profile and the risk of contracting COVID-19, particularly in high caseload zone. The continuation of biologic treatment is highly suggested with careful monitoring of any undesirable or uncommon side effects. Finally, further studies are required urgently to elucidate this matter.

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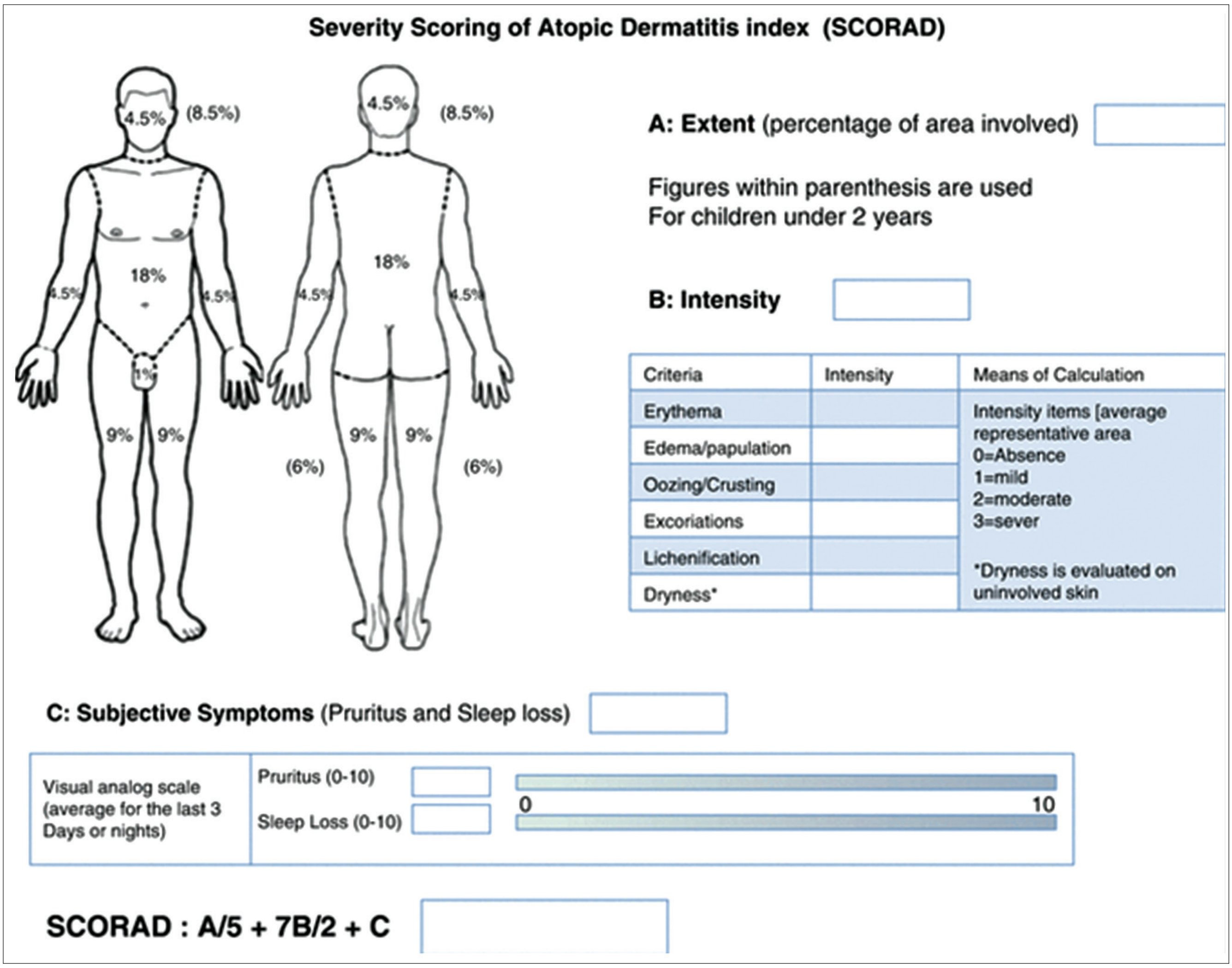
Appendix



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Utility of Combined Echocardiography and Lung Ultrasound for Coronavirus Disease-19 Intensive Care Unit Patients: Case Series

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Abstract

BACKGROUND: A little evidence existed for ultrasound evaluation of coronavirus disease (COVID)-19 patients.

AIM: We aimed to present combined transthoracic echocardiography and lung ultrasound in 17 COVID-19 patients in the intensive care unit (ICU).

METHODS: Patients were on age 57 + 14 years, 9 on mechanical ventilation and 8 on oxygen support, with average 1.2 comorbidities per patient. Ultrasound was performed by a single experienced sonographer and an assistant.

RESULTS: Impaired left ventricular ejection fraction (EF) was found in 2 patients (pts) of them (11.8%) and diastolic dysfunction in 7 (41.2%), which was significantly higher in those ones with comorbidities. In 2 pts (11.8%), the presence of pulmonary hypertension with enlarged right ventricle was found. Later one pulmonary thromboembolism was confirmed in them with computed tomography angio. B-lines were found in 8 pts (47.1%), finding that was significantly higher in pts on mechanical ventilation, but not in relation with decreased EF. In one pt (0.6%), pleural effusion was found, but in none of them lung consolidation.

CONCLUSIONS: Our findings revealed that combined echocardiography and lung ultrasound in COVID-19 ICU pts have been an accurate method for diagnosing right and left ventricular function and should be a useful one for guiding of their treatment and prognosis.

Introduction

Nowadays, cardiopulmonary injury has been recognized in patients with coronavirus (CoV) disease (COVID)-19, the clinical disease state caused by infection with the novel CoV, severe acute respiratory syndrome (SARS)-CoV-2. While originally believed to be a primary lower respiratory infection, as more cases are identified, treated, and examined, thrombotic complications are being identified as a significant driver in morbidity and mortality associated with the disease. Elevated D-dimer levels and troponin values have been identified as being associated with increased mortality [1]. Yet, D-dimer and troponin could not prove a valuable tool to identify patients who are likely to have poorer outcomes and allow for prophylactic treatment and monitoring of secondary complications [2].

The first case that was confirmed in Republic of Macedonia by polymerase chain reaction (PCR) for SARS-CoV-2 virus in Institute for Public Health was on 26th of February 2020, and the first death was reported in Clinic of Infective Diseases on 25th of March same year. The case fatality rate for COVID-19 pts for Republic of Macedonia is 4.1.

Transthoracic echocardiography (TTE) is a basis for heart imaging, diagnosis of left and right ventricle overload, heart failure, but also for hemodynamic monitoring of these pts. European Association for Cardiovascular Imaging postulated consensus document for using a TTE in patients with COVID-19 [3].

However, a little evidence existed for echocardiographic evaluation of COVID-19 patients, combining it with a lung ultrasound in the intensive care unit (ICU) [4].

In this paper, we present a case series of 17 patients COVID-19, evaluated with combined echocardiography and lung ultrasound.

Methods

The group consisted of COVID-19 patients (n = 17), hospitalized in the ICU of Clinic for Infective Disease in Skopje, with moderate and severe clinical symptoms. All tested positive for SARS-CoV-2 RNA through PCR in the Institute for Public Health.

Ultrasound was performed by a single experienced physician and an assistant. Standard transthoracic echocardiographic evaluation was performed in all of pts. Bilateral lung ultrasound was done at all. GE Vivid T8 device was used.

Results

Patients were aged 57 + 14 years. Nine of them were on mechanical ventilation and 8 on oxygen support. Three of them died during hospitalization.

There were average 1.2 comorbidities per patient. Most frequent comorbidities were arterial hypertension (64.7%) and diabetes (58.9%). There were histories of cerebrovascular diseases in 1 pt, chronic pulmonary disease (chronic obstructive pulmonary disease and asthma) in 3 pts, and chronic kidney diseases in 2 pts. Malignant diseases, immunodeficiency disorders, were not noticed in the study population. At the admittance, most of the pts presented clinical symptoms of cough (9 pts), dyspnea (13 pts), and fever (7 pts).

In a study population mean value of D-dimmer (1300 ng/ml + 900), CRP (49 mg/L + 13), and white blood cell ($19 \times 10^9 + 5$) was found. Antiviral therapy was administered in 13 pts and antibiotic in 15 of them.

Impaired left ventricular ejection fraction (EF) was found in 2 pts of them (11.8%), and diastolic dysfunction in 7 (41.2%), which was significantly higher in those ones with comorbidities ($p < 0.05$).

In 2 pts (11.8%), the presence of pulmonary hypertension with enlarged right ventricle was found (Figure 1). Later one pulmonary thromboembolism was confirmed in them with computed tomography (CT) angiography.

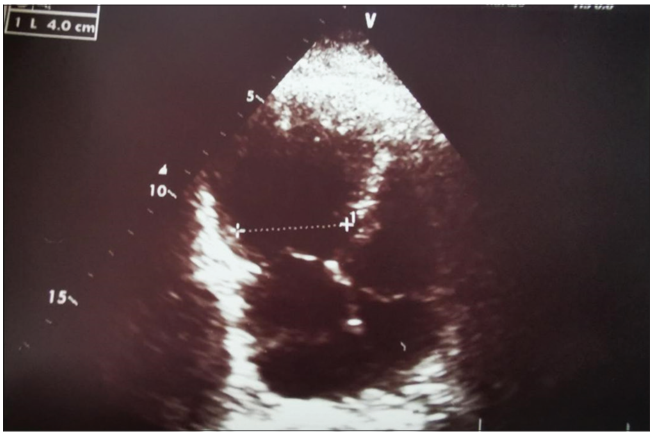

Figure 1: Increased diameter of the right ventricle

B-lines were found in 8 pts (47.1%), finding that was significantly higher in pts on mechanical ventilation, but not in relation with decreased EF. That was shown in Figure 2.

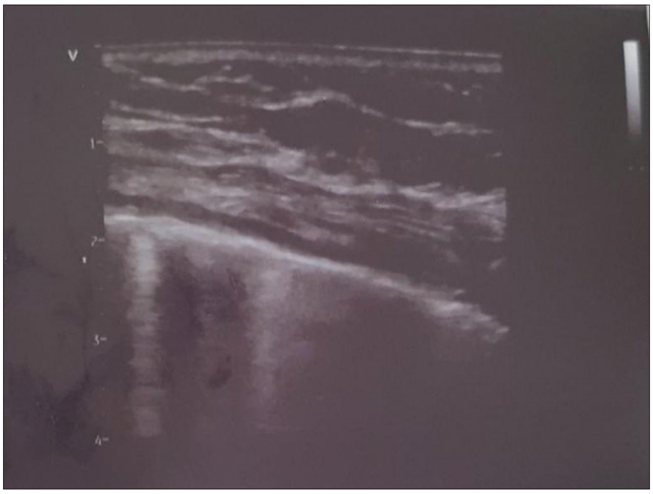

Figure 2: B-lines in lung parenchyma

In one pt (0.6%), pleural effusion was found. In 9 pts (52.9%), irregular thickened pleural line was found (Figure 3). In none of them was found a lung consolidation.

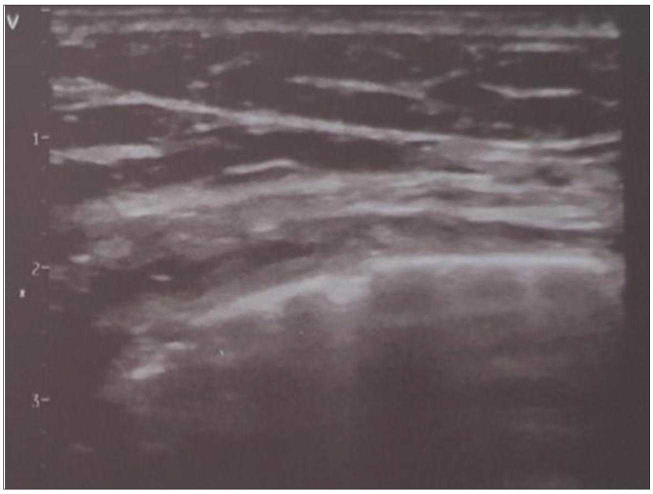

Figure 3: Irregular thickened pleural line

Discussion

We found LV dysfunction in 11.8% of pts. It is not a very common condition in COVID-19 pts [5]. However, diastolic dysfunction is found in 42.3% of pts. Similar results were found in a study by Yishay Szekely [3]. Analysis of COVID-19 pts by Edler in International data found heart failure as a reason for death in one-third of them [6].

RV dysfunction is common findings in these pts. We found it in only 2 of pts. This is due to pulmonary thromboembolism (found in 11.8% of our pts), pneumonia, increase pulmonary vascular resistance [7]. Finding the reason for RV overloads sometimes in impossible if CT angio is not done. However is it very useful for administration for therapy.

Definition of pulmonary edema and interstitial lung disease is very controversial. One of the conditions that confirm interstitiopathy in the presence of B lines is normal LVEF. Distribution of B lines (no homogeneous) and fragmentation or irregularity of pleural line confirms lung disease. Lung ultrasound could potentially distinguish two types of disturbances. It has high sensitivity and low specificity to diagnose lung disease and pulmonary edema. It is more specific if the probe is used in lateral and posterior parts of the lungs. These could be increased by clinical settings of pts [8]. We found B lines in almost in half of the pts.

Focused echocardiography and lung ultrasound were also used for guiding treatment of pts with heart failure when administered serial [9].

There was a lack of ECG trace for echo images. X-ray was used in 3 pts and CT only in one pt. Non-randomization and non-homogeneity was also a study limitation.

This small case study group that we described allows identification and possible prognostication of CIVID-19 pts. Future larger studies are needed [10].

Conclusion

Our findings reveal that combined echocardiography and lung ultrasound in COVID-19 ICU pts has been an accurate method for diagnosing right and left ventricular function and can be a useful one for guiding of their treatment and prognosis.

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MASKNE: Mask-Induced Acne Flare During Coronavirus Disease-19. What is it and How to Manage it?

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Abstract

The coronavirus disease (COVID)-19 is a global pandemic caused by severe acute respiratory syndrome (SARS)-CoV-2. Due to the rapid spread of the disease, several measures have been proposed to mitigate its transmission, including wearing a mask in certain circumstances. This new proposition leads to some novel skin adverse effects; one of them is acne flare. This particular outbreak has significantly affected people's quality of life. In this minireview, a brief current knowledge of SARS-CoV-2 and its related-acne-flare, or popularly called as mask-acne (MASKNE), are discussed. This review aims to provide some information that may be helpful in opting for the most suitable management and treatment for each individual.

Introduction

Coronavirus disease (COVID)-19 is a disease caused by SARS-CoV-2. It was first discovered in late December 2019, in Wuhan, China [1]. The World Health Organization (WHO) later declared in as a pandemic due to its rapid spreading [2]. The outbreak of COVID-19 has affected many facets of life globally, including personal habits and lifestyle. It is implored by the Center for Disease Control and Prevention and WHO for people to take preventive measures in mitigating the spread, including covering mouth and nose with a mask when around others [3], [4]. This new arrangement has a distinct impact on daily life. Individuals are wearing masks more often and longer than before, especially health workers who are working at a higher risk of transmission environment. Thus, it leads to a local acne outbreak in the area covered by the mask, which is popularly called as "maskne or mask acne." This phenomenon is supported by accumulating data about adverse effects on the skin against personal protective equipment (PPE), including mask. A study discovered that 59.6% of individuals wearing mask regularly have experienced acne outbreak [5]. This finding is supported by several literature resources highlighting this phenomenon [6], [7], [8].

Many have agreed that acne may affect many aspects of an individual's life. A study asserts that acne impacts greatly in one's psychological state; persons with acne are often at greater risk of lowered quality of life [9]. A cohort study also shows that adolescents and adults suffering from acne have higher rates of anxiety, low self-esteem, and depression compared to individuals without acne [10]. Therefore, this rising undesirable phenomenon should be addressed and mitigated properly since the pandemic is still continuing to allow individuals to have a decent quality of life.

COVID-19

A brief review

SARS-CoV-2 is a β-coronavirus (CoV), which primarily targets the respiratory tract [11]. It is an enveloped virus with a single positive-sense stranded RNA genome [12]. The CoV has 4 genera (α, β, δ, and γ). However, it is identified that only α and β can infect mammals, while δ and γ can infect birds [13]. The origin of SARS-CoV-2 has remained elusive, but it is found that its genome sequence is identical to a bat CoV RaTG13 (96.2%), while it is also shared 79.5% similarity to SARS-CoV-2. Thus, it is postulated that the natural host of the originate virus is bat, with an unknown intermediate host [13].

Route of Transmission

Due to its nature, it is believed that person-to-person transmission is plausible through inhaled respiratory microdroplets spread by coughing or sneezing from an infected person or carrier [14]. However, the exact route of transmission is still elusive. Several findings show that it may also be transmitted through the mucous membrane of the eyes, and it is also proposed that transmission through gastrointestinal tract is plausible [14], [15], [16].

The understanding of the basic reproduction number is imperative in managing the transmissibility. The R nought (R0) can be defined as the ability of the pathogen to produce a secondary infection through an infected person. The R0 of SARS-CoV 2 is estimated in a range of 1.46–6.49, with a mean of 3.28 [17], which means that COVID-19 is considered contagious.

Pathogenesis

It is discovered that angiotensin-converting enzyme 2, which can be found in the lower respiratory tract, acts as a receptor for SARS-CoV-2. The envelope spike S glycoprotein will bind and initiates membrane fusion into the host cell [12], [13]. After successfully fused, the viral genome RNA is then released into the cytoplasm, and the uncoated RNA encodes non-structural protein to form a replication-transcription complex (RCT). The RCT then synthesis a new set of subgenomic RNA which plays a major role in encoding the necessary accessory and structural proteins to form a new virus [12]. When the virus enters the cells, its antigen will be presented to the antigen presentation cell of the host. This event will induce the immune response of the body.

Clinical Manifestation

The clinical characteristic of COVID-19 varies from mild-to-severe. The main symptoms are usually fever (98%), dry cough (76%), myalgia, or fatigue (44%) [18]. Other less common manifestations include nasal congestion, headache, runny, nose, sore throat, vomiting, and diarrhea. In severe condition, hypoxemia and dyspnea are often found, leading to acute respiratory distress, difficult-to-manage metabolic acidosis, and coagulation, which may lead to fatality [14], [18], [19]. It is noteworthy that some individuals may spread the virus while being asymptomatic. Therefore, it is essential to follow the recommended preventive measures such as practicing hand hygiene, wearing a mask, and limiting social gatherings [3].

Acne

Pathogenesis

Acne is a multifactorial pilosebaceous inflammatory disease. It is very common and most often seen in adolescents [20], [21]. Even though the exact pathogenesis of acne has not been fully elucidated, there are four essential facets that have been widely adopted in its pathogenesis. First is the hyperproliferation of follicular epithelial cells, leading to follicular plugging, excess sebum, inflammation, and the role of Propionibacterium acne or recently is called as *Cutibacterium acnes* (*C. acnes*) [20], [22], [23], [24].

Hormones and immune responses are believed to have a distinct role in each phase.

Initially, the infundibulum part of a hair follicle is packed with an abundant number of keratinous cells and highly cohesive keratinocytes resulting in microcomedone. It is believed that the formation of microcomedone is also influenced by the decreased level of linoleic acid and increased *C. acnes* metabolism [23], [24]. It is also proposed that an elevated level of androgen and increased activity of interleukin 1 plays a role in the overproduction of the sebum [22], [23]. When the excess sebum is trapped in the follicle with the keratinous squamae, a thin wall cystic lesion (comedone) is formed. The overgrowth of *C. acnes* and excess sebum as its nutrient emulates a bigger formation of the previous lesion (papule or nodule). Finally, the mixture of keratin, hair, and sebum provokes a non-immune foreign body inflammation process [23], [24].

Acne and Mask

During this pandemic, one of many means of mitigating the spread of the virus is wearing a mask. In June 2020, the WHO also updated its guidance, stating that individuals and healthcare workers should wear a mask in appropriate settings and environments [2]. This guidance leads to a fact that many people wearing mask in a longer period. Acne flare due to prolonged mask-wearing has been reported lately in both general and healthcare populations. Several case reports and literature have been addressed to discuss and manage the undesirable effects of the prolong-use of PPE, including mask-related acne outbreak [5], [7], [8], [25].

The lesions are mostly found in the local area covered by the mask, and the severity varies from mild-to-severe in each literature [6], [7], [8]. It is proposed that the possible factor of this particular localized outbreak is the increased humidity and temperature in the covered area. It is known that high temperature can affect the rate of sebum secretion. It is also postulated that increased humidity might increase the amount of squalene in the skin [26]. In addition, studies have discovered that increased humidity and excess sweating lead to swelling of the epidermal keratinocytes [27]. All these alterations lead to acute obstruction and acne aggravation [26] (Figure 1).

Figure 1: MASKNE. Adapted from https://www.marketwatch.com/story/maskne-yes-mask-acne-is-now-a-thing-2020-06-26

These hypotheses are also supported by a case study of tropical acne. It is known that hot and humid environment has a significant correlation with acne flares [28]. However, it is concluded that the exact pathogenesis of acne flare due to mask-wearing remains a puzzle.

It is noteworthy that not only may prolonged mask-wearing affect acne outbreak but it also might increase the temptation of touching the face due to annoying acne or itch, which may increase the risk of COVID-19 transmission through the respiratory tract [29].

Recommendation and Prevention

The duration of this pandemic is still uncertain, with a probability of an upcoming of second wave in most continents. Thus, suggestions and recommendations in enduring the effects of long-term mask-wearing are crucial for the sake of the health and comfort of each individual, especially for healthcare workers, who need to wear both regular and medical masks most of the time.

There are several preventive measures that might be implemented. Frequent break time of wearing mask is highly recommended to shorten the duration and exposure of the mask [30]. It is also recommended to replace the surgical mask and N95 mask routinely. Han *et al*. [7] suggest that mask should be replaced after 4 h for surgical mask and 3 days for N95 mask, while Desai *et al*. [31] recommend to take a 15-min break after 2 h of wearing mask. Preventative measures such as applying oil-controlling moisturizer (i.e., with licochalcone A as one of the ingredients) or dressing application before wearing a mask is also suggested to decrease sebum secretion [7], [32], [33]. However, it is also implored to always reassure that those vehicles do not interfere with the mask seal, allowing less protection against the virus. A literature source also asserts the importance of an improved mask design focused on safety, comfort, and tolerability [34]. American Academy of Dermatology Association also suggests avoiding new skincare that might irritate skin or increase the use of strong products such as retinoid, chemical peeling agents, and exfoliant [35].

Another literature source also suggests a general approach to control the acne outbreak. First is to wash the face twice daily with warm water and opt for an appropriate cleanser; a strong alkaline soap is not recommended. A study also stresses the importance to do this routine before wearing the mask [31]. Second, it is advisable to wear no cosmetic or light cosmetic only. Finally, mild lesions can be treated with topical antibiotic or retinoid, while severe condition might be treated with systemic minocycline or isotretinoin [36].

Although there are some inevitable adverse effects in the prolonged use of mask, wearing mask properly is one of many essential approaches in protecting ourselves and others. The abovementioned suggestions aim to hinder and alleviate the undesirable effects and maintain compliance.

Limitation and Conclusion

There are some limitations of this review, including the lack of robust data and variation of the duration of wearing the mask. Due to the complexity of acne pathogenesis, there are some gaps in the literature sources that have been reviewed since most of the sources do not consider other risk factors, such as body mass index, skin type, and hormonal imbalance. In addition, further information about the material of the mask has not been included yet in most literature, this may contribute to a mistaken diagnosis of contact dermatitis eruption. Most of the literature reviews published are either case reports or clinical reviews. Thus, a thorough study is needed to elucidate and manage this issue. To conclude, in this era of the pandemic, assuring the safety of ourselves and others by wearing proper PPE is of paramount importance. However, occupationally induced skin condition (in this case, due to PPE) cannot be neglected and must be minimalized.

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Two Serial Case of Coronavirus Disease-19 Patients Coinfected with HIV: Comparison of Pre-anti-Retroviral (art) and on Art Patient

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Abstract

BACKGROUND: Today, coronavirus disease (COVID)-19 has become a worldwide pandemic. People living with HIV are one of the special populations who are susceptible to COVID-19 infection and suspected of having a poor prognosis.

CASE REPORT: We reported two serial cases of COVID-19 with HIV coinfection. First case was a COVID-19 patient coinfected with HIV who had received anti-retroviral therapy (ARV) and had an absolute CD4 cell count of 781 cells/uL. Patient was found with mild symptoms of COVID-19 and had normal laboratory results and chest X-ray. Patient was declared cured after 26 days of treatment in isolation room with complete clinical improvement since day 5 of isolation. Second case was a COVID-19 with HIV coinfection that had not yet received ARV therapy and had absolute CD4 cell count of 155 Cell/uL. Patient came with moderate clinical symptom of COVID-19 and experienced secondary bacterial and tuberculosis infection. Patient was declared cured of COVID-19 on the 8th day of treatment with clinical improvement but still needed further treatment in a non-isolation room.

CONCLUSION: Clinical characteristics of COVID-19 in HIV and non-HIV patients are the same. A history of ARV therapy and CD4 count did not affect the length of isolation until a negative result on two reverse-transcription-polymerase chain reactions, but could affect prognosis and clinical severity due to the high risk of secondary infection in HIV-positive patients without ARV or HIV/AIDS who had a CD4 count ≤200 cell/uL.

Introduction

Coronavirus (CoV) disease (COVID)-19 infections that are caused by the severe acute respiratory syndrome (SARS)-COV-2 virus today become a worldwide pandemic [1]. Patients who had underlying diseases such as diabetes mellitus (DM), chronic kidney disease, hypertension, heart disease, and chronic lung disease based on epidemiological data more susceptible to get COVID-19 infection with more severe prognosis than the general population due to chronic systemic immunodeficiency and inflammatory conditions in patients [2]. Other immunodeficiency conditions such as people living with HIV/AIDS (PLWHA) are also thought to have a higher risk of becoming infected with COVID-19 with a worse prognosis.

Epidemiological facts regarding this matter are still inconclusive [3]. Articles about COVID-19 infection in HIV/AIDS patients still provide various results in terms of susceptibility to COVID-19 infection, clinical characteristics, symptom severity, and prognosis. In the COVID-19 with HIV coinfection case series written by Cooper *et al*. in 2020 said that viral load and CD4 count were factors that influenced the severity of symptoms, but not the individual's susceptibility to COVID-19 infection. There was also another hypothesis which states that HIV is a protective factor for organ damage due to cytokine storms in COVID-19 patients with HIV/AIDS [4]. Research by Karmen-Tuohy *et al*. in 2020 with a number of subjects dominated by COVID-19 patients with controlled HIV infection showed no significant difference in mortality rates in HIV patients compared to controls (population without HIV) [5]. Another study article by Harter *et al*. in 2020 found significantly higher mortality, hospitalization, and critical infection rates in patients with COVID-19 coinfected with HIV than in the general population [6].

We reported two serial cases of COVID-19 with HIV coinfection. First case was a COVID-19 patient with HIV who was already undergoing anti-retroviral therapy (ARV) therapy and the second case was a COVID-19 patient with HIV who had not received ARV treatment.

Case

First case was a 67-year-old woman who came to the COVID-19 polyclinic with chief complaints sore throat and cough without sputum for last 3 days.

Patient said that she had a history of close contact with a confirmed case of COVID-19. She is a PLWHA who regularly takes ARVs, rilpivirine 25 mg every 24 h, and tenofovir/emtricitabine 300 mg/200 mg every 24 h and has hypertension as other comorbidity and has been controlled with Amlodipine 10 mg every day. Physical examination was in normal limits. Twice reverse-transcription-polymerase chain reaction (RT-PCR) nasopharyngeal swab diagnostic were performed and both tests were positive. Patient was hospitalized after being confirmed positive for COVID-19 through a nasopharyngeal RT-PCR swab examination. Both nasopharyngeal swab RT-PCR examined by kit that used Nucleocapsid 1, Nucleocapsid 2, and RNA-dependent RNA polymerase (RdRp) viral component as protein target. First RT-PCR swab obtained Cycle Treshold (C_T) value for each target gene ware, respectively, 20.19; 20.84; and 27.82. Second RT-PCR swab obtained C_T values for each target gene were, respectively, 18.55; 20.30; and 27.12. Complete blood count performed on the 1st day of hospitalization was within normal limits, there was an increase in the Ferritin value of 480.30 and C-Reactive Protein of 5.87. Liver function tests showed a slight increase in aspartate aminotransferase (AST), which was 41.4, while the alanine aminotransferase (ALT) value was within normal limits. Renal function tests were also found within normal limits. Patient's absolute CD4 count was 781 cells/uL. Patient also performed a chest X-ray at the time of admission to the hospital, with the result was no lung abnormality (Figure 1a).

During hospitalization, ARV therapy was continued. Patients received hydroxychloroquin at a dose of 400 mg every 12 h orally on the 1st day and continued with 200 mg every 12 h until the 10th day. Patients continue consume Amlodipine 10 mg every 24 h regularly and other symptomatic therapy. Evaluation of the RT-PCR swab examination was carried out every 5–7 days. The evaluation of the X-ray examination was carried out on the 16th day of hospitalization with an normal lung configuration result (Figure 1b). The patient gets full recovery in the 5th day of hospitalization and was declared cured after 26 days of treatment.

Second case was a woman, 43 years old, who came to the Emergency Unit with an acute complaint of fever since 6 days, cough with phlegm, and chest hard to breath since 1 day before admission accompanied by decreased appetite. Chronic symptom in the form of weight loss of 10 kg within 1 month was also found. Patient was currently undergoing intensive phase of anti-tuberculosis treatment for lymphadenitis tuberculosis and had been diagnosed with HIV, but has not received ARV treatment. The history of contact with a confirmed COVID-19 person was unknown, but the patient lives in a local transmission area of COVID-19. On physical examination, there was an increase in body temperature (38.6°C), increase in the respiratory rate of 22 times/min, SpO_2 93% room air, and raunchy on lung auscultation in basal of the right lung. Laboratory examination was found normal leukocyte value with an increase in neutrophils percentage (81%), lymphopenia (0.42 10^3/μL), moderate anemia (7.58 g/dl), and thrombocytopenia (92.95 10^3/μL). There was also an increase in the AST and ALT values, respectively, 386.8 and 52.60. Patient's absolute CD4 count at admission was 155 cells / uL. A chest X-ray on the 1st day of hospitalization showed a reticular pattern in both lung fields (Figure 2a). Patient was diagnosed with a suspected COVID-19 accompanied by community pneumonia and was treated in an isolation room. Furthermore, a diagnostic RT-PCR nasopharyngeal swab examination was carried out. First RT-PCR was positive for COVID-19 and second RT-PCR was found negative for COVID-19. RT-PCR examination used kit with the non-sturctural protein 1 (NSP-1) gene as a positive control. First RT-PCR swab obtained CT values for positive control and internal control were 37.98 and 33.56, respectively. The patient was diagnosed with confirmed COVID-19 and treatment was continued in an isolation room. RT-PCR swab evaluations were carried out every 5–7 days and chest X-ray evaluations were carried out when the patient was declared cured of COVID-19.

During hospitalization, patients received empiric antibiotic therapy in the form of Cefoperason-sulbactam 1 g every 12 h intravenously and Levofloxacin 750 mg every 24 h intravenously for 7 days, symptomatic therapy, and continued anti-tuberculosis treatment. Patient did not receive antiviral treatment. Patient was declared cured of COVID-19 on the 8th day of treatment after two negative RT-PCR results. Patient left the isolation room with partial clinical improvement and further treatment was carried out in the non-isolation

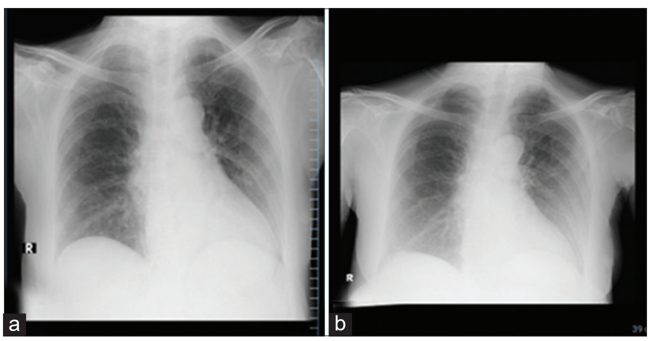

Figure 1: Chest X-ray of the first patient, (a) 1st day of admission; (b) 6th day after hospitalization

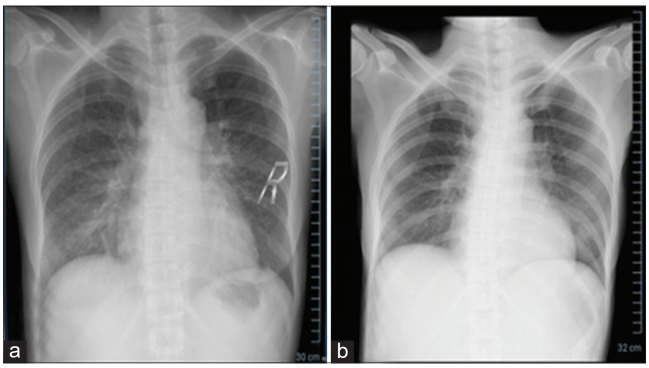

Figure 2: Chest X-ray of second patient, (a) 1st day of admission; (b) the last day of hospitalization

room. The evaluation of the chest X-ray when the patient was declared cured showed a reduction of lung infiltrate (Figure 2b).

Discussion

Today, there have been various articles that discuss about characteristics of COVID-19 infection in HIV patients [4]. Immunodeficiency in HIV is thought to be a factor that increases the risk of COVID-19 infection. CD4 count and viral load are also thought to be factors that influence the poor prognosis in patients, but several articles have shown various results [7]. In this article, two case series of COVID-19 with HIV coinfection were reported comparing HIV cases with ARVs and HIV without ARVs.

In a study conducted by Huang *et al*. in 2019 regarding the clinical characteristics of COVID-19 patients in Wuhan, the median age of COVID-19 patients was found to be 49 years. That study used 41 subjects with 32% of them having underlying diseases such as DM, hypertension, and cardiovascular disease, but none of the subjects had HIV infection. It was found median time of hospital stay was 7 days after symptom onset and experienced dyspnea 8 days after symptom onset. It also mentioned some of the major symptoms experienced by the patients, including fever (98% subjects), cough (76% subjects), and myalgia or fatigue in 44% of subjects [2]. Another study conducted by Harter *et al*. in 2020 regarding the characteristics of COVID-19 cases with HIV coinfection obtained similar median age with the previous studies; it was 48 years with range of 26–82 years. In our study, all subjects had received ARV therapy and had a median $CD4^+$ count 670/mm^3. It also mentioned some of the major symptoms experienced by the patient; they were cough (78%), fever (69%), atralgia or myalgia (22%), and sore throat (22%) [6]. A case report by Patel *et al*. in 2020 regarding a COVID-19 patient with HIV coinfection aged 37 years who had an absolute CD4 cell count 34 cells/uL had experiencing symptoms such as fever, dry cough, and chest pain since 1 month before being admitted to the hospital. Physical examination found that high body temperature of 38.8°C, oxygen saturation (SpO_2) of 85–90% on ambient air, with high respiratory rate (40 beats/min), and pulse rate were 119 beats/min [8].

Demographic and clinical characteristics of two patients in this case report were similar to those of the patients in other case reports. COVID-19 patients with HIV and without HIV have similar demographic and clinical characteristics. Patients who have received ARV and have CD4 + count ≥200 cells /uL showed mild COVID-19 clinical symptom with cough without phlegm and sore throat. Patients who have not received ARVs with CD4 + counts <200/uL showed moderate clinical symptom of COVID-19 with cough, fever, accompanied by hard to breath sensation and increase in respiratory rate. Based on the case report by Patel *et al*. in 2020, clinical severity of the second patient could be affected by the possibility of secondary infection. Viremia was also cannot rule out as a caused of more severe clinical symptom in the second patient [8].

First patient had normal laboratory results and chest X-rays. Second patient's laboratory examination showed an increase in neutrophils percentage, lymphopenia, and thrombocytopenia accompanied by a reticular pattern on chest X-rays. Second patient also had chronic symptoms such as weight loss associated with lymphadenitis tuberculosis beside signs of acute infection caused by bacteria or other opportunistic infections.

In a study conducted by Huang *et al*. in 2019 on the COVID-19 population without coinfection, only four patients (10%) had secondary infections and required intensive care. Laboratory results showed normal leukocyte values (in 45% of patients), with an average absolute neutrophil count was 5 × 10^3/L, leukopenia occurred in 63% of patients, normal platelet values were found in 95% of patients, and dominantly liver and kidney function were found. Within normal limits with a mean procalcitonin value was 0.1. A case series in Barcelona, Spain regarding COVID-19 with HIV coinfection by Blanco *et al*. in 2020 comparing four patients who were taking ARVs routinely and had an absolute CD4 + count> 200/uL and one patient who had not taken ARVs and had a CD4 + count <200/uL. Two patients who had received ARV therapy had mild clinical symptom without laboratory and chest X-ray abnormalities, two patients who received ARV had moderate symptoms, and one patient who had no ARV and had a $CD4^+$ 13 Cell/uL count had severe COVID-19 symptoms with secondary bacterial infection signs such as increase in leukocyte to 14,670 cells per 10^3/L. Lymphopenia occurred in two cases with ARV and one case without ARV with the lowest lymphocyte count value were 900 cells per 10^3/L [9]. Case reports by Wang *et al*. in 2020 have different characteristics. They reported COVID-19 patients with HIV coinfection and a $CD4^+$ 34 Cell/uL count had a severe clinical presentation but no leukocytosis or signs of secondary infection, especially bacterial infection [10]. Other secondary infections that can occur in HIV patients are Pneumocystis carinii (Pneumocystis pneumonia [PCP]), tuberculosis, Hepatitis B, Hepatitis C, Cryptococcal Meningitis, and Toxoplasmosis [11]. It can be considered to conduct a clinical evaluation of the infection if you get a COVID-19 patient with HIV coinfection to improve the prognostic outcome of the patient, especially HIV/AIDS patients who have a CD4 + count <200 Cells/uL.

In this case report, first case had normal laboratory and chest X-ray result, while second case showed normal leukocyte values accompanied by increased in neutrophil, lymphopenia, moderate anemia, and thrombocytopenia. A normal leukocyte value in HIV patients does not absolutely rule out the possibility of secondary infection, especially bacterial infection. Based on a study conducted by Huson *et al*. in 2016 in patients with bacteremia, it was found that increasing of leukocyte average in HIV patients was lower than non-HIV patients. That study was conducted on patients with a mean $CD4^+$ count 150 cells/uL [12]. In case series reported by Blanco *et al*. in 2020, HIV patients who had a CD4 + count >200 cell/uL and were already taking ARVs routinely showed a higher increase in leukocytes than HIV patients with $CD4^+$ counts <200 cells/uL and had not received ARVs [9]. Lymphopenia and thrombocytopenia were accompanied by a reticular pattern in chest X-ray consistent with viral infection sign. Mild anemia can be caused by chronic inflammation due to tuberculosis and HIV. Nutritional intake from food can also affect the occurrence of anemia in patients. Various articles have reported no significant association between HIV conditions and the risk of SARS-COV-2 infection; however, severe lymphopenia in HIV/AIDS patients with COVID-19 can affect the severity of symptoms. Based on research conducted by Qin *et al*., it was found that the number of B cells, T cells, and NK cells significantly decreased in COVID-19 patients. If coupled with HIV/AIDS can cause severe lymphopenia, thereby increasing the risk of severe pneumonia and secondary infection in HIV patients which affect the severity of symptoms and poor prognosis [13].

The SARS-COV2 viral nucleic acid RT-PCR test from nasopharyngeal swab is currently the standard method to diagnosed COVID-19 [14]. First patient had twice positive diagnostic swab PCR results, while the second patient had only one positive PCR diagnosis. SARS-COV-2 RT-PCR examination result can be influenced by various factors, such as the type of specimen, specimen collection time, number of viruses, and examination tool or kit [15].

Specimen type can determine the rate of positivity for RT-PCR examinations in COVID-19. There are several types of specimens that can be used; they are Bronchoalveolar lavage (BAL), Fibro bronchocope biopsy, sputum, nasopharyngeal swab, oropharyngeal swab, feces, and urine. Nasopharyngeal swab and oropharyngeal swab are two types of specimens that are commonly used as samples for COVID-19 testing in the world, especially in Indonesia. This is due to easy sampling process with a high positive rate [15]. Based on the article written by Wang *et al*. in 2020, the nasopharyngeal and oropharyngeal swab positivity rates were 63% and 32%, respectively, where nasopharyngeal swab was superior to oropharyngeal. Specimens derived from BAL and sputum are two types of specimens that have the highest rate of positivity compared to other specimen types with the percentage of positivity, respectively, 93% and 72% [15]. Systematic review article with meta-analysis method also shows the same thing, specimens derived from nasopharyngeal swabs have a lower sensitivity than sputum, where sputum has a sensitivity of 97.2% with a 95% confidence interval of 90.3–99.7% [16]. In this case, a negative result on one of the diagnostic swab examinations of the second patient could be due to the rate of positivity of the specimen used.

Specimen collection time and number of viruses can also affect the SARS-COV-2 RT-PCR results. Timing of specimen collection is related to the presence of the SARS-COV2 virus in the examination specimen [16]. Research conducted by Wang *et al*. in 2020 regarding differences in shedding duration for sputum and nasopharyngeal swabs specimens found a correlation between viral shedding time and the positivity of each specimen. In this study, it was found that median duration of viral shedding from sputum was 34 days, while viral shedding from nasopharyngeal swab specimens was 19 days. Nine patients found positive sputum specimens after negative nasopharyngeal swab examination. Chronic lung disease and systemic steroid use was also found to be associated with viral detection in sputum specimens; however, HIV/AIDS was not mentioned as a factor affecting the location of viral shedding [17]. Specimen collection time is also related to the amount of virus in the nasopharyngeal specimen. In a study by Lirong *et al*. in 2020, the highest number of viruses in nasopharyngeal swab specimens was found on days 3–6 after the onset of symptoms and began to decline on the 7^{th} day after symptoms [18]. The incubation period must also be taken into account as a factor for bias in the results of nasopharyngeal swabs [19]. Hence, a negative result on nasopharyngeal RT-PCR swab can also be caused by the location of the viral shedding which is not suitable for the specimen and the time of specimen collection.

There are various kits that are used in Indonesia with different gene targets or primers [20]. Two patients on the diagnostic swab used a different kit, where first patient used a kit that detected N1, N2, and RdRp as gene target while the second patient used a kit targeting the NSP-1 gene as gene target. Target gene largely determines the sensitivity and specificity of an assay. Multitarget RT-PCR can improve the accuracy of the RT-PCR results, because negative results can be found in one of the target genes if there is a mutation in that section [21]. Second patient had one negative RT-PCR diagnostic nasopharyngeal swab. This can be affected by the RT-PCR kit used. Based on research conducted by Chan *et al*. in 2020 regarding the detection accuracy of the NSP-1 gene for COVID-19 diagnostics in 101 clinical specimens, the test sensitivity and specificity were 93.1% (95% confidence interval 86.2–97.2%) and 100% (95% confidence interval 92.9–100%), so there is still a possibility of false negatives in approximately 6.9% of the specimens [22]. The C_T value of the second patient was higher than first patient, but could not be compared because of differences in target genes in the two RT-PCRs kit. These results can be used to illustrate the relationship between baseline C_T values and the length of time to achieve negative RT-PCR nasopharyngeal swab evaluation results.

Recommendation therapy for COVID-19 patients with HIV coinfection is similar to COVID-19 without HIV coinfection [14]. The high risk of secondary infection in HIV/AIDS patient's makes the optimization of secondary infection therapy was very important [4]. Giving systemic steroids to COVID-19 patients with HIV coinfection are still recommended, especially in patients with severe clinical COVID-19 or with secondary infection in the form of severe PCP, although systemic steroid administration in a study conducted by Huang *et al*. in 2020 and Wang *et al*. in 2020 said could be slowering viral clearance and prolong viral shedding period [2], [17]. The recommendations issued by British and American health institutions for people with HIV during the pandemic are to ensure that they have a supply of ARVs and that they are vaccinated against Influenza and Pneumococci regularly. Until now, there have been no specific reports regarding the relationship between the types of ARVs used and the severity of COVID-19 symptoms in patients with HIV, but there is a case series that show clinical differences in patients with different history of ARVs [9]. A case series report by Blanco *et al*. in 2020 showed two patients taking the combination of the ARVs tenofovir alafenamide, emtricitabine, and darunavir-boosted Cobicistat had mild symptoms of COVID-19 and two patients taking the combination of the ARV abacavir, lamivudine, and dolutegravir had a moderate to severe COVID-19 presentation and require intensive care [9]. Combination of Lopinavir and Ritonavir in *in vitro* studies can shorten viral shedding period, but its effectiveness in clinical studies of COVID-19 has not been shown to significantly increase patient outcomes compared to standard therapy [23].

The outcome of COVID-19 patients can be assessed based on the length of time to achieve negative result in nasopharyngeal RT-PCR swab and morbidity and mortality risk. First patient had a negative RT-PCR nasopharyngeal swab on the 26th day of treatment and the second patient had a negative result on the 8th day of treatment. A case report by Wang *et al*. in 2020 regarding a COVID-19 patient with HIV coinfection who had a CD4 + count <200 Cells/uL reported something similar to the second case, it was only getting positive results on the first RT-PCR and negative on 3 RT-PCR nasopharyngeal swab evaluation. It is due to the baseline value of each C_T, but cannot be compared because of using a kit with different target genes. Another possibility is second patient's viral shedding on the day of evaluation was found in the sputum, so it was not detected in the nasopharyngeal swab specimen. Two cases reported by Menghua *et al*. in 2020 showed long cases of COVID 19 and it took 28 days to get a negative RT-PCR swab, but, in this case, RT-PCR was carried out on a sputum specimen. This can be due to prolonged viral shedding in patients associated with damage to cellular function of CD4 + cells even though the CD4 + cell count is within normal limits [24]. The outcome of mortality risk in several articles is still inconclusive. Systematic review article on COVID-19 in HIV patients by Cooper *et al*. 2020 said that patients with HIV with an undetectable viral load and an adequate CD4 cell count had no worse outcome than the general population. Uncontrolled HIV infection and AIDS are one of the factors in the poor prognosis of patients with COVID-19. This is associated with the occurrence of bacterial superinfection in patients [4]. Another study by Karmen-Tuohy *et al*. in 2020 with the number of subjects dominated by COVID-19 patients with controlled HIV showed no significant difference in mortality rates between HIV patients and control (population without HIV) [5]. Another study article by Harter *et al*. in 2020 found significant higher mortality, hospitalization, and critical infection rates in patients with COVID-19 with HIV than general population. In those studies, mortality rate in COVID-19 patients with HIV was 9% [6].

Conclusion

The clinical and demographic characteristics of COVID-19 in HIV and non-HIV patients are the same. A history of antiretroviral therapy and CD4 count did not affect the outcome of the length of care until a negative result on two RT-PCRs, but could affect prognosis and clinical severity due to the high risk of secondary infection in HIV-free or HIV/AIDS patients who had a CD4 count ≤200 Cell/uL.

Future Research

Further research is needed regarding: (1) The accuracy of RT-PCR swab examinations in various specimens, especially in HIV/AIDS patients who have a CD4 + count <200/uL; (2) the effect of various combination ARV therapy in COVID-19 patients with HIV coinfection on the severity of clinical symptoms and the prognosis of COVID-19 patients; (3) antiviral and supportive therapy options in COVID-19 patients with HIV coinfection; (4) patient prognosis COVID-19 with HIV coinfection and factors affecting the prognosis.

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Coronavirus Disease-19: Public Health Nurses' Knowledge, Attitude, Practices, and Perceived Barriers in Indonesia

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Abstract

BACKGROUND: The coronavirus disease (COVID)-19 outbreaks and its rapid rise in prevalence has been a major concern internationally. We conducted a short survey to understand the knowledge, attitude, and practices regarding COVID-19 and estimated barriers to disease transmission perceived by public health nurses (PHN) in Indonesia.

AIM: The study aimed to identify the association of sociodemographic characteristic with knowledge, attitude, and practices regarding COVID-19 among PHNs in Indonesia and highlight barriers to the control of infection perceived by PHNs.

METHODS: A national, online, and cross-sectional survey was conducted from May 28 to June 9, 2020, with a total of 368 participants. A questionnaire was used to assess knowledge, attitude, and practice. An independent t-test was used to compare attitude differences of PHNs in gender and place of work. One-way analysis of variance was used to compare differences in attitude of PHNs by age, work experience, educational level, and source of information. The Pearson's correlation test was used to measure the correlation between knowledge, attitude, and practices.

RESULTS: The majority of participants had good knowledge of COVID-19 (77.4%), had mean scores of attitude toward COVID-19 of 33.0 ± 2.7, and had good practices regarding COVID-19 (84.2%). Factors associated with knowledge were sources of information ($p = 0.013$). Factors associated with attitude were gender ($p = 0.003$), work experience ($p = 0.010$), and sources of information ($p = 0.035$). Factors associated with practices were gender ($p = 0.011$) and sources of information ($p = 0.029$). There were significant, positive linear correlations between knowledge and attitude ($r = 0.435$, $p = 0.000$), knowledge and practices ($r = 0.314$, $p = 0.000$), and attitude and practices ($r = 0.362$, $p = 0.000$). Most participants strongly agreed that limitations on infection control materials (50.8%) and patients hiding their travel history, resulting in screening inaccuracies (59.8%), were barriers.

CONCLUSIONS: A significant association between sources of information and knowledge, attitude, and practices, with the addition of other related factors. There were also significant positive linear correlations between knowledge, attitude, and practices. Nevertheless, the majority of the PHN perceived that limitations on infection control materials and patients hiding their travel history, resulting in screening inaccuracy, were major barriers.

Introduction

Since the first reported case in Wuhan, China, in December 2019, the novel coronavirus of 2019 coronavirus disease (COVID-19) has spread quickly around the world [1]. COVID-19 has infected 216 countries to date. As of August 7, 2020, there had been 18,854,287 confirmed cases of COVID-19, including 708,639 deaths [2]. In Indonesia, as of August 7, 2020, there had been 121,226 confirmed COVID-19 cases and 5593 deaths related to the disease [3], including 49 Indonesian nurses [4].

Nurses, including public health nurses (PHNs), are on the front line of this crisis [5]. PHNs who work in public health centers have a vital role in the epidemic chain for controlling COVID-19. PHNs provide care for COVID-19 patients, families, and the community [6]. They provide safe, effective, and nondiscriminatory care to the communities in which they serve [5]. They must have contact with patients, are exposed to pathogens and are at high risk of infection [7]. PHNs who care for patients in their homes are among those at the highest risk in pandemics [8]. Nurses play additional roles in screening potential cases, recognizing patients' need for isolation or quarantine, and monitoring cases [9].

In public health centers, PHNs are responsible for care of asymptomatic patients and exposure to infected individuals. Lack of personal protective equipment and poor infection controls are risk factors for COVID-19 [10], [11]. Disease knowledge may affect attitude and practices [12]. Poor knowledge may lead to delayed diagnosis, disease transmission, and lack of infection control practices [13].

As healthcare workers (HCWs) in primary health centers, PHNs play an important role for preventing and controlling the spreading of COVID-19. In the health care system in Indonesia, public health centers, as primary health care, treat and care for patients before transferring them to secondary or tertiary health care. Thus, it is important for PHNs to have adequate knowledge, attitude, and practices in considering and controlling infections.

The study aimed to identify the association of sociodemographic characteristic with knowledge, attitude, and practices regarding COVID-19 among PHNs in Indonesia and highlight barriers to the control of infection perceived by PHNs.

Materials and Methods

Design and subjects

This was a national, online, cross-sectional survey. It was conducted from May 28 to June 9, 2020, during the lockdown period in Indonesia. The investigators collected the data by an online method because of the current lockdown situation.

The sample size, calculated using a sample size calculator [14], was 368, assuming 95% confidence level, a Z of 1.96, and a margin of error of 5%. The population used in this study comprised Indonesian PHNs working in public health centers (Puskesmas) in Indonesia. Participants from all 34 provinces in Indonesia were eligible to participate.

Data collection

A questionnaire was designed using Google Forms. The questionnaire's link was shared to Indonesian PHNs' WhatsApp group and, alternatively, personally to PHNs in the contact lists of the investigators. The questionnaire included an introduction to the study containing the title, aims, procedures, voluntary participation, declarations of anonymity and confidentiality, and notes for filling in the questionnaire. Reliability was calculated using Cronbach's alpha was 0.813. The data from the pilot study were not used in the final analysis.

Measurements

The questionnaire was adapted from Saqlain *et al*. [15]. Permission to use and modify the questionnaire was obtained, and required modifications were done. The questionnaire consisted of three parts: Sociodemographic characteristics; knowledge, attitude, and practices; and perceived barriers to disease transmission. The sociodemographic characteristics included age, gender, work experience, living area, educational level, place of work, and sources of information. Responses are presented as frequencies and percentages. The knowledge variable consisted of 12 items and each question was answered "yes," "no," or "don't know." The scoring of the knowledge questions was determined by giving 1 point for each correct answer and 0 for an incorrect answer or unknown answer. The total knowledge score ranged from 0 to 12, with a higher score denoting a better knowledge of COVID-19. The attitude variable included seven items, and responses were recorded on a five-point Likert scale (1, strongly agree; 2, agree; 3, undecided; 4, disagree; 5, strongly disagree). The total attitude score ranged from 7 to 35, with a higher score denoting a positive attitude toward COVID-19. The practices variable contained seven items and each item was answered "yes" (1 point), "no" (0 points) or "sometimes" (0 points). The total practices score ranged from 0 to 7, with a higher score denoting better practices regarding COVID-19. Seven items assessed the perception of PHNs regarding barriers to controlling infection. Responses were recorded on a five-point Likert scale (strongly agree, agree, undecided, disagree, strongly disagree). Responses are presented as frequencies and percentages.

Ethics approval

This study was approved by the Ethics Committee of National Health Research and Development, Ministry of Health, Republic of Indonesia, with approval number LB.02.03/1/0033/2020. The participants had to answer a yes-no question to confirm their willingness to participate voluntarily. After a yes confirmation, the participant was directed to complete a self-report instrument.

Data analysis

The data were analyzed with SPSS software version 21. A Chi-square test was used to understand how sociodemographic characteristics related to knowledge and practices of PHNs. An independent t-test was used to compare attitude differences of PHNs in gender and place of work. One-way analysis of variance was used to compare differences in attitude of PHNs by age, work experience, educational level, and source of information. The Pearson's correlation test was used to measure the correlation between knowledge, attitude, and practices.

Results

A total of 368 PHNs participated in this study. Table 1 shows the demographic characteristics of the participants.

The largest percentage of participants were women (70.1%) and 31-39 years old (43.2%), had more than 10 years of work experience (44.8%), lived in central Indonesia (49.2%), held a diploma (61.4%), had a rural workplace (54.9%), and got information about COVID-19 from social media (40.2%). The majority had good knowledge of COVID-19 (77.4%), with mean scores of attitude toward COVID-19 of 33.0 ± 2.7, and good practices regarding COVID-19 (84.2%).

Table 1: Sociodemographic characteristics of participants (n = 368)

Characteristics	n (%)
Age	
≤30 years	100 (27.2)
31–39 years	159 (43.2)
40–49 years	85 (23.1)
≥50 years	24 (6.5)
Gender	
Female	258 (70.1)
Male	110 (29.9)
Work experience	
≤5 years	94 (25.5)
6–10 years	109 (29.6)
>10 years	165 (44.8)
Living area	
Eastern Indonesia	45 (12.2)
Central Indonesia	181 (49.2)
Western Indonesia	142 (38.6)
Educational level	
Diploma	226 (61.4)
Bachelor's degree	126 (34.2)
Master's degree	16 (4.3)
Place of work	
Rural	202 (54.9)
Urban	166 (45.1)
Source of information	
Social media	148 (40.2)
Television and radio	37 (10.1)
Newspapers, magazines, posters, and pamphlets	7 (1.9)
Nurses and other healthcare workers	57 (15.5)
Seminars and Workshops	17 (4.6)
WHO and ministry of health websites	102 (27.7)
Knowledge	
Poor	83 (22.6)
Good	285 (77.4)
Attitude: Mean ± SD	33.0 ± 2.7
Practices	
Poor	58 (15.8)
Good	310 (84.2)

The results of the study demonstrate that age, gender, work experience, living area, educational level, and place of work were not significantly associated with knowledge. The factor associated with knowledge was the source of information (p = 0.013; Table 2). The findings demonstrate that age, work experience, living area, educational level, and place of work were not significantly associated with practices. Factors associated with practices were gender (p = 0.011) and source of information (p = 0.029; Table 2).

The findings demonstrate that there were no significant differences of attitude in age, living area, educational level, and place of work. However, there were significant differences in gender (p = 0.003), work experience (p = 0.010), and source of information (p = 0.035; Table 3).

There were significant, positive linear correlations between knowledge and attitude (r = 0.435, p = 0.000), knowledge and practices (r = 0.314, p = 0.000), and attitude and practices (r = 0.362, p = 0.000; Table 4).

The largest percentage of participants agreed that a lack of knowledge about the mode of transmission of COVID-19 (39.9%), a lack of policies and procedures regarding infection control (37.8%), insufficient training on infection control measurement (39.4%), less commitment of PHNs to the policies and procedures (33.4%), no technical or management instructions for handling COVID-19 patients (26.4%), and no psychological counseling (38.6%) were barriers. Most participants strongly agreed that limitations on infection control materials (50.8%) and patients hiding their travel history, resulting in screening inaccuracies (59.8%), were barriers. The largest percentage of participants disagreed that not wearing a mask while examining or being in contact with patients (25.5%) and not handwashing after examining or being in contact with patients (32.1%) were barriers (Figure 1).

Table 2: Comparison of sociodemographic characteristics between public health nurses with different knowledge and practices (n = 368)

Variables	Knowledge		p-value	Practices		p-value
	Poor	Good		Poor	Good	
Age						
≤30 years	22 (6.0)	78 (21.2)	0.871	20 (5.4)	80 (21.7)	0.221
31–39 years	36 (9.8)	123 (33.4)		25 (6.8)	134 (36.4)	
40–49 years	18 (4.9)	67 (18.2)		8 (2.2)	77 (20.9)	
≥50 years	7 (1.9)	17 (4.6)		5 (1.4)	19 (5.2)	
Gender						
Female	55 (14.9)	203 (55.2)	0.464	32 (8.7)	226 (61.4)	0.011
Male	28 (7.6)	82 (22.3)		26 (7.1)	84 (22.8)	
Work experience						
≤5 years	19 (5.2)	75 (20.4)	0.740	15 (4.1)	79 (21.5)	0.136
6–10 years	27 (7.3)	82 (22.3)		23 (6.3)	86 (23.4)	
>10 years	37 (10.1)	128 (34.8)		20 (5.4)	145 (39.4)	
Living area						
Eastern Indonesia	10 (2.7)	35 (9.5)	0.969	7 (1.9)	38 (10.3)	0.545
Central Indonesia	40 (10.9)	141 (38.3)		25 (6.8)	156 (42.4)	
Western Indonesia	33 (9.0)	109 (29.6)		26 (7.1)	116 (31.5)	
Educational level						
Diploma	48 (13.0)	178 (48.4)	0.349	37 (10.1)	189 (51.4)	0.889
Bachelor's degree	33 (9.0)	93 (25.3)		19 (5.2)	107 (29.1)	
Master's degree	2 (0.5)	14 (3.8)		2 (0.5)	14 (3.8)	
Place of work						
Rural	47 (12.8)	155 (42.1)	0.814	35 (9.5)	167 (45.4)	0.444
Urban	36 (9.8)	130 (35.3)		23 (6.3)	143 (38.9)	
Source of information						
Social media	46 (12.5)	102 (27.7)	0.013	32 (8.7)	116 (31.5)	0.029
Television and radio	7 (1.9)	30 (8.2)		4 (1.1)	33 (9.0)	
Newspapers, magazines, posters, and pamphlets	3 (0.8)	4 (1.1)		3 (0.8)	4 (1.1)	
Nurses and other healthcare workers	10 (2.7)	47 (12.8)		5 (1.4)	52 (14.1)	
Seminars and workshops	1 (0.3)	16 (4.3)		1 (0.3)	16 (4.3)	
WHO and ministry of health websites	16 (4.3)	86 (23.4)		13 (3.5)	89 (24.2)	

Table 3: Comparison of sociodemographic characteristics between public health nurses with mean scores of attitude (n = 368)

Variables	Attitude		t/F	p-value
	Mean	SD		
Age				
≤30 years	33.28	2.95	1.154	0.327
31–39 years	33.00	2.47		
40–49 years	32.97	2.81		
≥50 years	32.12	3.28		
Gender				
Female	33.19	2.63	−2.99	0.003
Male	32.79	2.87		
Work experience				
≤5 years	33.69	2.53	4.655	0.010
6–10 years	32.53	3.00		
>10 years	32.95	2.63		
Living area				
Eastern Indonesia	32.48	3.64	2.138	0.119
Central Indonesia	33.29	2.11		
Western Indonesia	32.82	3.10		
Educational level				
Diploma	32.83	3.01	1.338	0.264
Bachelor's degree	33.29	2.23		
Master's degree	33.43	2.47		
Place of work				
Rural	33.19	2.63	1.40	0.163
Urban	32.79	2.87		
Source of information				
Social media	32.75	3.17	2.428	0.035
Television and radio	33.94	1.74		
Newspapers, magazines, posters, and pamphlets	32.85	2.34		
Nurses and other healthcare workers	33.36	2.41		
Seminars and workshops	34.29	1.10		
WHO and ministry of health websites	32.65	2.66		

Discussion

To the best of our knowledge, there is no other study exploring the knowledge, attitude, and practices of PHNs and possible barriers perceived by PHNs to infection control practices in Indonesia. However, several studies have shown high levels of COVID-19 knowledge among the general population [16], [17]. This means that the transmission of disease will be very high if these barriers are not addressed.

Table 4: Correlation between knowledge, attitude, and practices among public health nurses (n = 368)

Variable	Correlation coefficient	p-value
Knowledge-attitude	0.435*	0.000
Attitude-practices	0.314*	0.000
Knowledge-practices	0.362*	0.000

*Correlation significant at 0.01 level (2-tailed).

The results of this study show that the majority of participants had good knowledge of COVID-19. This study is in line with previous studies in other countries that found that the majority of nurses and other HCWs had good knowledge about COVID-19. Saqlain *et al*. demonstrated that the majority of nurses (90.5%) had good knowledge regarding COVID-19 in Pakistan [15]. Similarly, Giao *et al*.'s study showed that 88.4% of HCWs had sufficient knowledge regarding COVID-19 [18] and Shi *et al*. showed that 89.51% of HCWs had a good knowledge of the COVID-19 epidemic. Their study results are slightly higher than the results of our study [19]. Olum *et al*. demonstrated that 69% of HCWs indicated good knowledge of COVID-19 at MaKCHS Teaching Hospitals in Uganda [20]. Nemati *et al*.'s study showed that 56.5% of nurses had good knowledge regarding COVID-19 infections in Iran [21]. Their study results are slightly lower than the results of this study. This small difference could be explained by the cultural background of where the research was conducted.

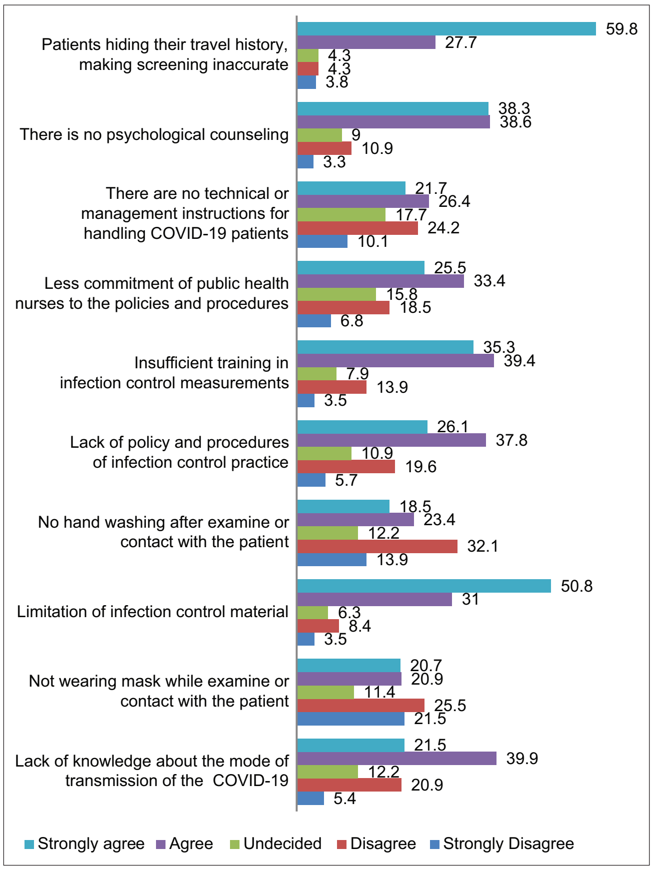

Figure 1: Perceived barriers to infection control practice among public health nurses in Indonesia (n = 368)

The results of this study demonstrate that demographic characteristics such as age, gender, work experience, living area, educational level, and place of work were not significantly associated with knowledge. However, this study is slightly different from the studies conducted by Nemati *et al*. and Al-Hanawi *et al*. [21], [22]. Their studies demonstrated that knowledge was affected by age and educational level. The factor associated with knowledge in this study was the source of information. We report that social media was the first and main source for COVID-19 information for PHNs while the second source of COVID-19 information was the WHO and Ministry of Health websites. This result is in line with previous studies by Karasneh *et al*. [23] and Saqlain *et al*. [15] in which social media was the main source of HCWs' information about COVID-19. Media can improve the knowledge of HCWs by providing up-to-date information [23]. It can also bridge effective information and rapid global response for researchers, scientists, and public health experts [23], but some sources of information are unreliable, which has resulted in disinformation [24], [25]. Thus, PHNs must get information from the WHO and Ministry of Health of Indonesia's websites as reliable and trustworthy sources of information for COVID-19. This finding reinforces the result of a previous study that showed how good knowledge was supported by various news reports and media portals [26]. During the pandemic period in Indonesia, there have been many seminars and trainings held by the Indonesian National Nurses Association and Nursing Education Institution in Indonesia. These unyielding efforts by the nurse's association and education institution can be accessed easily to improve PHNs' knowledge.

The results of this study demonstrate that the majority of participants had a positive attitude toward COVID-19. This result is supported by Saqlain *et al*. [15] and Bhagavatula *et al*. [27], but differs with Olum *et al*., in which the majority of respondents had a poor attitude and only 21% had a good attitude. This study showed a positive correlation between knowledge and attitude. A similar result was also found by Zhang *et al*. [12]. Further analysis demonstrated that attitudes did not significantly different with age, living area, educational level, or place of work but were significantly different with gender, work experience, and source of information. Our study also reports that gender, work experience, and source of information affected PHNs' attitude regarding COVID-19. The result of our study does not agree with Saqlain *et al*. [15] or Giao *et al*. [18], in which attitude did not differ significantly based on work experience or gender, but does agree in that attitude had no significant difference based on age.

The results of this study show that the majority of participants had good practices. This is in line with previous studies in other countries in which the majority of nurses and other HCWs had good practices to prevent and control COVID-19. Saqlain *et al*. [15] demonstrated that 91.4% of nurses had good practices; Zhang *et al*. [12] showed that 89.7% of HCWs had good practices, and Olum *et al*. [20] showed 74% of HCWs had good practices regarding COVID-19. The findings of the present study demonstrate that age, work experience, living area, educational level, and place of work were not significantly associated with good practices. Factors associated with practices that we found were gender and source of information. Gender became one predictor of less optimistic attitudes toward COVID-19 [28]. This study is in contrast with a previous study by Olum *et al*. [20], which demonstrated that age and educational levels were significantly associated with good practices. Saqlain *et al*. also demonstrated that work experience was significantly associated with good practices but that age and gender were not significantly associated with them. Interestingly, 77.4% of our study participants believed that every piece of relevant COVID-19 information should be relayed to their fellow nurses. This indicates that information plays a large role in shaping knowledge, attitudes, and general practices during the COVID-19 pandemic.

Our findings show that there were significant, positive linear correlations between knowledge and attitude, knowledge, and practices, attitude, and practices. These results complement conclusions from previous studies associating higher levels of knowledge with higher confidence and positive attitudes during the COVID-19 outbreak [16], [19]. Knowledge is essential for establishing prevention beliefs, fostering positive attitudes, and promoting good practices [12]. According to reasoned action theory, the motive of a behavior is related to an attitude [15]. These findings clearly indicate the importance of knowledge and how good sources of information are needed during the rapid rise of COVID-19 cases through health education. However, a specific design to deliver this health education should be tailored to address how male participants had worse health practices compared to female participants.

The results of our study demonstrate that the majority of PHNs perceived that limitations to infection control materials and patients hiding their travel history, making screening more inaccurate, were the major barriers. The government should provide more infection control materials to prevent and control infections in a primary health care setting. All residents should be honest in conveying their travel history to help break the chain of transmission and to help with early detection.

Study limitation

This online survey had a few limitations. The oversampling of specific sociodemographic characteristics such as gender (70.1%) and a high proportion of diploma graduates (61.4%) might have led to a selection bias. However, this study may serve as an important source of knowledge and awareness for PHNs living in Indonesia. Furthermore, this study was based on a self-reported questionnaire with a limited number of items that might not be representative of actual practice. Consequently, further study with focus-group discussions and interviews might be needed to resolve this issue.

Conclusions

There was a significant association between the source of information and knowledge. There were significant differences of attitudes based on gender, work experience, and source of information. Factors associated with practices were gender and source of information. There were significant, positive linear correlations between knowledge, attitude, and practices. The majority of PHNs' perceived that limitations to infection control materials and patients hiding their travel history, making screening inaccurate, were the major barriers.

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Hospital Preparedness for Critical Care during COVID-19 Pandemic: Exploratory Cross-sectional Study

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Abstract

AIM: The researchers conducted the study to assess intensive care units (ICUs) preparedness in Cairo University Hospitals to deal efficiently and effectively with COVID-19 upcoming waves.

METHODS: An exploratory cross-sectional study was conducted at Cairo University Intensive Care Units 6 pediatric ICUs, and 2 adult ICUs in the period from the end of February to the first week of March, 2020; almost 2 weeks after the appearance of the first case of COVID-19 in Egypt by hand-delivered questionnaire method with one of the ICU staff members who were available and have time to take part in the study. WHO checklist for hospital readiness was used; this checklist based on current knowledge and available evidence on the COVID-19 pandemic for WHO's Regional Office for the Eastern Mediterranean Region. The WHO has developed the checklist to help hospital managers prepare for COVID-19 patient management by optimizing each hospital's capacities. The list composed of 10 key components: (1) Leadership and coordination; (2) operational support, logistics and supply management; (3) information; (4) communication; (5) human resources; (6) continuity of essential services and surge capacity; (7) rapid identification; (8) diagnosis; (9) isolation and case management; and (10) infection prevention and control.

RESULTS: The overall preparedness in both pediatric and adult ICUs was 54%. Overall, adult ICUs were more prepared than pediatric ICUs, especially in communication; continuity of essential services and surge capacity; rapid identification; diagnosis; isolation; and case management. Both of them were comparable regarding operational support, logistics and supply management; human resources; and infection prevention and control, while information component was lower in both types but reached critical values 10% in adult ones.

CONCLUSION: The current study demonstrated the intermediate readiness of ICUs at initial outbreak; further assessment during different phases of pandemic is required. Continues education of HCWs and active communication should be established.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has promptly turned to a universal pandemic [1]. A high incidence of acute respiratory distress syndrome (ARDS) [2] and critical illness (23–32%) among hospitalized patients was reported worldwide [3]. In Egypt, similar rates of critical illness (84%) were also reported [4]. The reported Intensive care units (ICU) mortality rates are alarmingly high [5]; deaths from COVID-19 has already far exceeded the combined deaths from MERS and SARS [6]. During a pandemic, challenging situation is experienced mandating of increasing the capacity of ICU and the fact that critically ill patients might need to get care outside the traditional ICU [5]. The progressive spread of disease during an outbreak can overwhelm hospitals' ability to respond, as there are too many patients needing medical care at the same time. Intensive care units were concurrently challenged on numerous aspects. These include resource limitations, infection control, protection of healthcare workers (HCWs), and adaptation of services to a rapidly evolving pandemic situation. During the early phase of the outbreak in Wuhan, China, shortages in equipment meant that 75% of the deceased did not receive mechanical ventilation [7]. ICU resources in Egypt are also reported to be overwhelmed [4]. Intensive care units should prioritize and implement actions specified in their emergency preparedness plans for COVID-19 to identify suspected cases, limit transmission within the facility, and provide specialized medical care. This includes activating protocols and procedures in safe physical spaces, emphasizing isolation measures, education, and training of personnel in the use of personal protective equipment (PPE), patient management, sample collection and handling, and handling and disposal of hazardous biological waste. Consequently, the researchers conduct the current exploratory cross-sectional study to assess ICUs preparedness in Cairo

University Hospitals to deal efficiently and effectively with COVID-19 upcoming waves.

Methods

Study type and study setting

An exploratory cross-sectional study was conducted at Cairo University Intensive Care Units(6 pediatrics ICUs and 2 adult ICUs) in the period from end of February to the 1st week of March, 2020; almost 2 weeks after the appearance of the first case of COVID-19 in Egypt by hand-delivered questionnaire methodology with one of the staff members who were available and have time to take part in the study.

Data collection tool

WHO checklist for hospital readiness was used; this checklist based on current knowledge and available evidence on the COVID-19 pandemic for WHO's Regional Office for the Eastern Mediterranean Region. This checklist has been developed to help hospital managers prepare for COVID-19 patient management by optimizing each hospital's capacities [8]. The list composed of 10 key components: (1) Leadership and coordination; (2) operational support, logistics and supply management; (3) information; (4) communication; (5) human resources; (6) continuity of essential services and surge capacity; (7) rapid identification; (8) diagnosis; (9) isolation and case management; and (10) infection prevention and control (Figure 1).

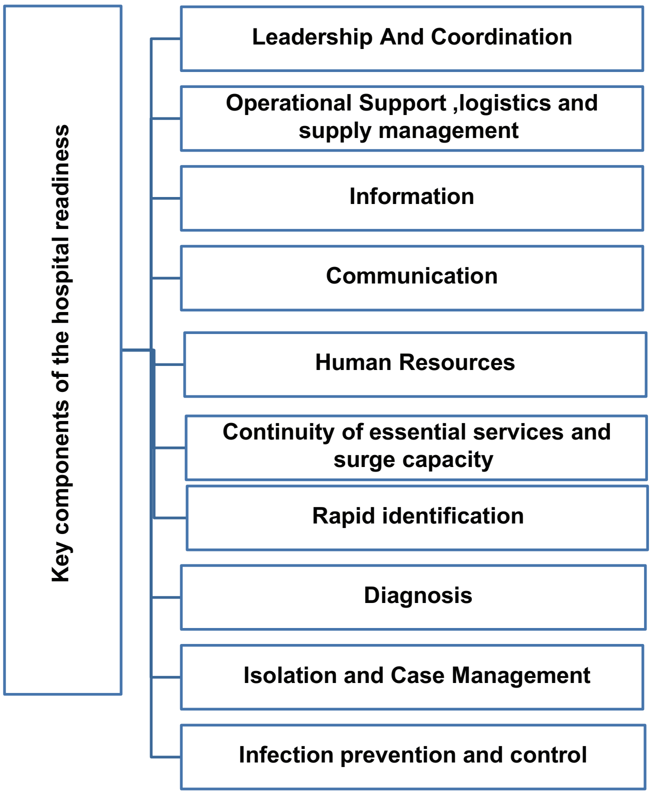

Figure 1: Key components of the hospital readiness checklist for COVID-19

Statistical analysis

The researchers did the statistical analysis using the EXCEL program version 10. Each component consisted of several response readiness activities with answers: Yes, in progress and no; this transformed to 1, 0.5, and 0 points, respectively. All points (scores) in each component were summed up to total score per component, then overall percent readiness was calculated as; Component readiness percentage = (summation of achieved scores/total maximum possible score)*100. The higher the percentage was the better readiness. They calculated average ICU readiness and overall average for each component on the summed score and percentage also calculated for pediatrics and adults.

Ethical considerations

Approval of the study protocol was obtained from the Ethical Committee of the Faculty of Medicine, Cairo University. Confidentiality of data, safe data storage, and privacy rights had been respected. Only those who agreed were included, and those who refused were excluded from the study. All procedures for data collection were treated with confidentiality according to the Helsinki declarations of biomedical ethics [9]. Results of the survey for every ICU were sent to the participant staff member to evaluate the current status of ICU readiness.

Results

The facilities screened were all related to Cairo University, which is public hospitals linked to the Ministry of Higher Education. All hospitals had diagnostic facilities such as the laboratory, X-ray, CT, and MRI. The overall preparedness in both pediatric and adult ICUs was 54% (Table 1, Figure 2).

Table 1: Overall pediatric and adult Cairo university ICU readiness for COVID-19

Component	Overall (%)	Pediatric	Adult
1. Leadership and coordination	71	68	82
2. Operational support, logistics, and supply management	75	76	75
3. Information	28	33	10
4. Communication	43	38	60
5. Human resources	28	28	29
6. Continuity of essential services and surge capacity	60	55	75
7. Rapid identification	61	57	72
8. Diagnosis	61	54	83
9. Isolation and case management	47	35	86
10. Infection prevention and control	68	65	75
Overall	54	51	65

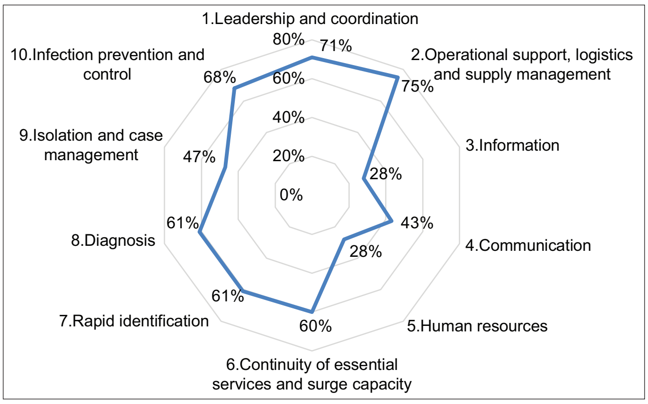

Figure 2: Overview of hospital readiness: Key components

Overall, adult ICUs were more prepared than pediatric ICUs, especially in communication; continuity of essential services and surge capacity; rapid identification; diagnosis; isolation; and case management. Both of them were comparable regarding operational support, logistics, and supply management; human resources; and infection prevention and control, while information component was lower in both types but reached critical values 10% in adult ones as displayed in Table 1.

DISCUSSION

Researchers conducted the current exploratory study to explore the readiness of Cairo University ICUs to deal with the current COVID-19 pandemic and the upcoming waves, the study revealed that the overall preparedness in both pediatric and adult ICUs was 54%. This was an alarming figure because of the high ICU bed occupancy rates as reported by the Minister of Health and Population in Egypt (84%) by COVID-19 patients according to the latest figures released from the Ministry of Health and Population in Egypt [4].

The study showed that adult ICUs were more prepared than pediatric ones; this might be due to the current belief of COVID-19 is mainly affect adults more than pediatrics.

The overall prevention and control component achieved 65% only. For the safety of hospital personnel and the prevention of nosocomial infections of COVID-19, training and strict adherence to infection control measures recommended by national and international bodies are of great importance. Training on-site and periodic refresher re-training are required to guarantee staff readiness and proficiency with a particular emphasis on personal protective equipment (PPE) [10], [11]. In Italy, up to 20% HCWs have also been confirmed to be infected doing their work at COVID hospitals[12], unsurprising that concern regarding human resources where it is fulfilled by 28% only. Particularly outside of the pandemic, there is an insufficient supply of qualified nursing staff and intensive care physicians. A short-term increase in skilled personnel, which would be appropriate to intensely increase intensive care capability, even outside of the pandemic, the availability of trained nursing staff and doctors in ICUs is limited worldwide [4], [5]. Therefore, a short-term increase in qualified staff, which would be essential to significantly increase intensive care capacities, is unrealistic. Unconventional ideas for recruitment must be considered early, like to draw manpower from different departments and divisions in the hospital with the application of the needed training.

The study detected a defect in communications; this reflects the need for the presence of open communication channels and rapid distribution of information to keep staff informed of new developments.

We should view the current study finding in accordance with the following limitation that this study was limited to one hospital, so its findings may not be generalizable to other hospitals; however, the researchers conducted the current study to explore the situation in this new area of inquiry; COVID-19 pandemic.

Conclusion

The current study demonstrated the intermediate readiness of ICUs at initial outbreak; further assessment during different phases of pandemic is required. Continues education of HCWs on infection control measures is required until the pandemic fenced. Active communication is vital in pandemic response. Information should be circulated to all HCWs in a timely fashion, and two-way communication should be established online disaster management plans, protocols for identification and isolation had to be placed in place to sustain medical treatment or at least maintain emergency care. Increasing in ICU bed capacity is mandatory.

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Social Mobilization in the Wake of Coronavirus Disease-19: A Brief Report of a Planned Approach to Community Health in Iran

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Abstract

BACKGROUND: Several plans have been taken by health system to deal with COVID-19. The rapid spread of the virus and the special care that critical patients need put a major pressure on the healthcare system, which may not be able to compensate for its dimensions in various aspects. Therefore, the participation and cooperation of the society in the form of mobilizing the society with the health system will be effective in controlling and preventing this disease.

AIM: The overall purpose of this study is to design a community mobilization framework based on the PATCH Model to prevent the spread and control of coronavirus disease.

METHODS: This community-based research is a type of health system research (HSR) which designs the community mobilization framework based on the PATCH Model

RESULTS: In this project, the community mobilization framework is in the form of the PATCH Model. In this study, interventions and activities will be performed based on the PATCH Model in the neighborhood. Health volunteers consist of popular volunteers, Basij, clerics, neighborhood trustees, donors. After training and issuing the identification card, Corona Anti-Corruption Assistant will start operating. Activities will be purposeful in three areas: education and information, neighborhood surveillance, and disinfection.

CONCLUSION: Community mobilization for disease prevention and control in the neighborhood using the PATCH model as presented will be effective.

The coronavirus disease-19 (COVID-19) pandemic started in late 2019 and swiftly disseminated in Asian countries, such as Iran. In many countries, the pandemic has been controlled using widespread lockdowns, quarantines, and direct involvement of the government [1]. These series of involvements are of greater importance in underdeveloped, overpopulated areas. Unfortunately, not all governments have the needed infrastructure to make these interventions, with these governments mostly being located in poor countries with densely populated cities [2].

To increase health-related behaviors among a population, two distinct areas should be addressed. One being the role of the government and the other the role of the community as a whole. To insure promotion of health in a society, each member of a society must be able to identify the correct actions to preserve a healthy lifestyle, and until all members are able to understand the factors affecting their health, no wide scale governmental intervention can be made [3]. Importantly public interest in health promotion is dependent on active persuasion by the government. As mentioned by the world health organization, participation of the public in health promotion is done through investment of time, resources in a voluntarily manner so that each member of the society can achieve the benefits of health promotion. This benefit is also passed down to each other member of the community and the society as a whole, as responsible and capable individuals are able to act as both enablers, policy makers, and promotors of those policies. This involvement of the public also enables them to participate in agenda setting and determining key priorities in their communities [4].

Planned approach to community health (PATCH) is a systemic stepwise method of health promotion initially presented by the center of disease control and then implemented in numerous settings. This method consists of five phases, including mobilization of communities, collection, and organization of data, choosing health priorities, developing an intervention plan, and finally evaluation of the program [5], [6] (Figure 1).

PATCH was implemented in an underdeveloped suburban neighborhood of a major metropolitan area within Iran and was implemented on a population of 80,000. In the first phase of community mobilization,

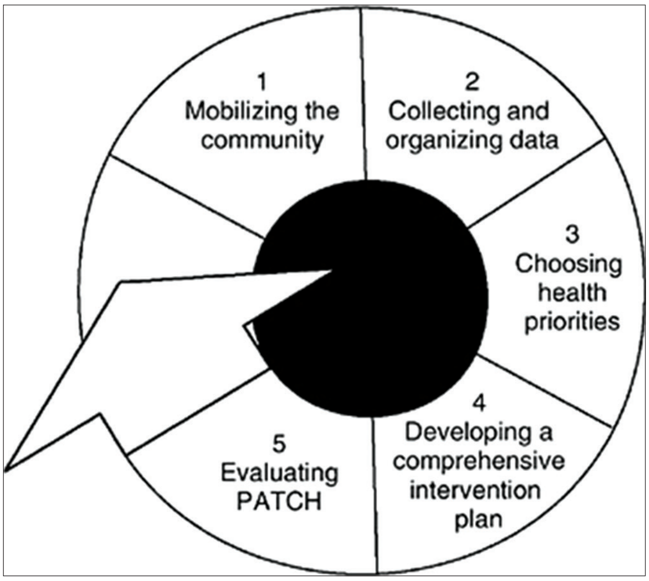

Figure 1: Five-phase PATCH model

various social groups and representatives were educated and involved in the process of policymaking for COVID-19. Multiple committees were formed and different representatives of social groups were included in each of them. These committees acted as mid-level policy developers, and all acted under the umbrella of the ministry of health. Data gathering and management were done by a task force composed of the media, medical specialists, and social workers, who were responsible for gathering data and disseminating it in other committees and the general public. Health priorities were done after an extensive stakeholder analysis and were broken into smaller attainable objectives in different fields.

During this step, groups and organizations such as military, religious scholars, business owners, law enforcement, social workers, and charities were included and were further divided between the most suitable committees.

The execution was done after a primary goal list was constructed, and after each committee had consolidated. This committee was composed of volunteers, public health workers, religious preachers, social workers, doctors (both general practitioners and specialists), law enforcement and the military, and the media. During this phase, many activities with the potential for disease spread were limited or controlled by introducing specific measures. For instance, Friday prayers were canceled, restaurants were closed, small businesses had limitations on the number of customers, and on services, they could deliver. Social groups made sure that unnecessary commute had stopped and that those with pre-existing conditions were isolated. Doctors and healthcare workers were instructed to stratify subjects based on guidelines made available by the ministry of health and revised by the scientific committee and to rule out potential infection if necessary. They were also in charge of referring patients to tertiary care centers and post-discharge care of those infected with the virus.

A financial committee was composed of the chamber of commerce, business owners and governmental institutions to financially support those families with hardship and to support businesses which are temporarily closed. This committee was also responsible for providing the basic protective wearables and disinfectants for wide scale use.

The law enforcement and the military were responsible for holding up the lock down. Volunteers were responsible for implementing the measures in their own communities.

The final phase of PATCH is evaluation of the method adapted. At present, the program has been able to reduce contamination in the aforementioned neighborhood. At present, initial attempts are being made to formulate evaluation methods to quantify the results.

This system was interconnected with the Behvarz program which is the back bone of public healthcare in Iran, especially in sub-urban areas. The volunteers were instructed by Behvarzes and general practitioners and used the already existing infrastructure of the Behvarz program. The central executive functions were coordinated in urban health houses, which were previously used for public health delivery, basic child and neonatal care, and routine pregnancy checkups.

Two dimensions can be considered to promote community health. Activities that involve direct government intervention and strategies; and public action activities that involve community participation. To promote the health of the individual and the society, we need to create the power of proper management and decision-making in all members of society. In other words, as long as people cannot identify and control the factors that affect health, ensuring, and promoting health in the general sense will be unattainable. People’s participation in their health is one of the important issues that should be strengthened and encouraged in line with government measures and development sectors. The World Health Organization believes that participation in health is a form of cooperation in which people accept voluntarily or for encouragement and justification, which interacts with health-related interventions and benefits by providing labor or other resources. To acquire, participation is also an empowerment tool through which the local community learns responsibility, diagnosis, and work to solve their health problems and strives to develop their community.

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OPEN ACCESS

Analysis of the Factors Associated with Negative Conversion of Severe Acute Respiratory Syndrome Coronavirus 2 RNA of Coronavirus Disease 2019

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Abstract

AIM: To understand the factors associated with negative conversion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA, targeted surveillance and control measures can be taken to provide scientific basis for the treatment of the disease and to improve the prognosis of the disease.

METHODS: Using the method of retrospective cohort study, we collected the data of Coronavirus Disease 2019 (COVID-19) patients in Tongji Hospital of Wuhan, China from 10 January to 25 March, 2020. Among the data of 282 cases, 271 patients, according to whether the negative conversion happened, were divided into negative conversion group and control group. We made the quantitative variables into classification; Chi-square test single-factor and Cox regression were used in univariate analysis and extracted 30 meaningful variables, then through the collinearity diagnosis, excluded the existence of collinear variables. Finally, 22 variables were included in Cox regression analysis.

RESULTS: The gender distribution was statistically significant between two groups ($p < 0.05$). While in the negative conversion group, the patients of non-severe group occupied a large proportion ($p < 0.001$). The median time for the negative conversion group was 17 days, and at the end of the observation period, the virus duration in control group was 24 days ($p < 0.05$). A total of 55 variables were included in univariate analysis, among which 30 variables were statistically different between the two groups. After screening variables through collinearity diagnosis, 22 variables were included in the Cox regression analysis. Last, lactate dehydrogenase (LDH), age, fibrinogen (FIB), and disease severity were associated with negative conversion of SARS-CoV-2 RNA.

CONCLUSION: Our results suggest that in the treatment of COVID-19, focus on the age of more than 65 years old, severe, high level of LDH, FIB patients, and take some targeted treatment, such as controlling of inflammation, reducing organ damage, so as to provide good conditions for virus clearance in the body.

Introduction

At present, the coronavirus disease (COVID)-19 has been a global outbreak, which was first reported in Wuhan, the capital of Hubei, China. A novel CoV, named severe acute respiratory syndrome CoV 2 (SARS-CoV-2) was isolated and it is the seventh member of the family of CoVs that infect humans [1]. It is so highly contagious that most individuals are susceptible to infection. As for main sources, the wild animals and infected patients are of infectiousness [2]. COVID-19 has been spread to 216 countries, areas or territories [3]. According to the latest statistics of the World Health Organization, as of July 26, 2020, more than 15,785,641 cases of the disease have been confirmed with over 640,016 deaths, making COVID-19 a major health concern [4]. Current research on COVID-19 focuses on the epidemics, its clinical features, and treatment [5]. In this case, study the factors associated with negative conversion of viral RNA is of necessary to guide the isolation precautions and antiviral treatment.

This study aims to assess the risk factors associated with prolonged viral shedding to improve treatment and prognosis of COVID-19 by considering or adjusting relative factors.

Materials and Methods

Study design and data collection

This retrospective cohort study contains a total of 282 laboratory-confirmed COVID-19 patients who were admitted to Tongji Hospital of Wuhan, China from 10 January to 25 March, 2020. All patients were collected throat swab samples and SARS-CoV-2 RNA was detected using real-time reverse transcription polymerase chain reaction. Data of demographic characteristics, comorbidities, symptoms, and laboratory values were collected using electronic medical records. A total of 271 patients were included in the study, excluding 11 cases whose results changed repeatedly and cannot judge the time of negative conversion. Ethical Committee of Tongji Hospital of Huazhong University of Science and Technology (No. TJ-IRB20200364) and China-Japan Union Hospital of Jilin University (No.2020032607) approved the study and waived the written informed consent for rapid emerging infectious.

Definitions of basic concepts

To minimize the uncertainty of nucleic acid test, the time when a viral nucleic acid test was negative was defined as the time from the first onset of related symptoms to the time when two consecutive nucleic acid tests results were negative before discharge from the hospital, while for cases with the absence of the time of first symptom, the time of admission was replaced. If both were missing, the first sampling time was used instead. In the case of death, the time interval between the onset of symptoms and discharge was calculated without nucleic acid test data and was classified as non-negative group. Patients who returned to positive nucleic acid test after discharge and patients who were impossible to judge the time of negative conversion were excluded from the study.

General conditions and laboratory test indicators

We collected the patient's name, gender, disease severity, first symptom, basic diseases, urine routine, blood routine, erythrocyte sedimentation rate, glucose, biochemistry, coagulation, cytokines, and other indicators for the first admission test. Indicators with a missing value greater than 20% were not included in the analysis.

Statistical analysis

First, the indicators included in the analysis were analyzed by single factor analysis. According to the reference range of normal values, the quantitative variables were set as dichotomy or multiple categorization variables. Chi-square test and single-factor Cox regression were used to compare the negative conversion group and the control group. The test level was 0.05. To reduce the influence of the inclusion of variables on the stability of the model, the missing value of variables was filled, and the mean value method was used to fill. Then, the variables whose p values in the two single-factor test methods were both <0.05 were included in multivariate Cox regression analysis. The analysis software was IBM SPSS Statistics Version 24.0 and GraphPad Prism Version 8.2.1.

Results

The basic situation

It can be seen that the gender distribution was statistically significant between two groups ($p < 0.05$), while in the negative conversion group, the patients of non-severe disease occupied a large proportion (78.4%, $p < 0.001$). The median time for the negative conversion group was 17 days, and at the end of the observation period, the virus duration was 24 days ($p < 0.05$). The proportion of those older than 65 in the control group was larger ($p < 0.05$), as shown in Table 1.

Single factor analysis

Univariate analysis was performed for variables that were filled in missing values and converted into categorizing variables. A total of 55 variables were included, among which 30 variables were statistically different between the two groups, as shown in Table 1.

Then, to avoid collinearity among independent variables, which would affect the multi-factor analysis, collinearity diagnostics was made for quantitative variables with statistical significance, and the results are shown in Table 2.

As shown in Table 2, the VIF of calcium ion, HCO, interleukin (IL)-6, PCT, AST, and IL-8 were nearly or more than 10, which indicated the existence of collinearity. Since IL-6 and 8 had been widely reported in the previous studies [6], [7], [8], [9], [10], [11], [12], cytokine IL-10 was retained in this study to explore the influence of cytokine IL-10 on the negative transformation of COVID-19 virus. In addition, because we had enough variables, we deleted these variables as appropriate. After that, some variables were deleted because their VIF >4 and there were still variables of the same type. They were BU and eGFR.

After adjustment, there was no obvious collinearity between variables (Table 3). Although the VIF of TP is 3.132, we incorporated it into the analysis not to delete important variable. The screened variables were incorporated into Cox regression model for analysis. The analysis results were shown in Table 4.

Table 1: Results of single factor analysis

Variables	Group (%)		χ^2	p-value
	Control (n = 49)	Negative conversion (n = 222)		
Disease severity				
Non-severe	2 (4.1)	174 (78.4)	97.324	<0.001
Severe	47 (95.9)	48 (21.6)		
UPRO				
N	2 (4.1)	108 (48.6)	33.062	<0.001
P	47 (95.9)	114 (51.4)		
Gender				
Male	33 (67.3)	112 (50.5)	4.607	0.032
Female	16 (32.7)	110 (49.5)		
U-KET				
N	32 (65.3)	198 (89.2)	17.831	<0.001
P	17 (34.7)	24 (10.8)		
URO				
N	43 (87.8)	216 (97.3)	6.529	0.011
P	6 (12.2)	6 (2.7)		
WBC				
Normal	17 (34.7)	177 (79.7)	48.619	<0.001
Low	2 (4.1)	12 (5.4)		
High	30 (61.2)	33 (14.9)		
NEUT				
Normal	11 (22.4)	167 (75.2)	58.102	<0.001
Low	1 (2.0)	10 (4.5)		
High	37 (75.5)	45 (20.3)		
LC				
Normal	3 (6.1)	109 (49.1)	30.575	<0.001
Abnormal	46 (93.9)	113 (50.9)		
NT-PROBNP				
Normal	8 (16.3)	114 (51.4)	19.894	<0.001
High	41 (83.7)	108 (48.6)		
PCT				
Normal	1 (2.0)	91 (41.0)	27.158	<0.001
High	48 (98.0)	131 (59.0)		
Hypersensitive cardiac troponin				
Normal	17 (34.7)	170 (76.6)	32.921	<0.001
High	32 (65.3)	52 (23.4)		
AST				
Normal	16 (32.7)	162 (73.0)	28.950	<0.001
High	33 (67.3)	60 (27.0)		
TP				
Normal	24 (49.0)	183 (82.4)	24.902	<0.001
Abnormal	25 (51.0)	39 (17.6)		
Albumin				
Normal	7 (14.3)	105 (47.3)	18.040	<0.001
Low	42 (85.7)	117 (52.7)		
DBIL				
Normal	30 (61.2)	200 (90.1)	26.048	<0.001
Abnormal	19 (38.8)	22 (9.9)		
GGT				
Normal	30 (61.2)	172 (77.5)	5.587	0.018
Abnormal	19 (38.8)	50 (22.5)		
LDH				
Normal	0 (0.0)	60 (27.0)	17.009	<0.001
Abnormal	49 (100.0)	162 (73.0)		
Sodium				
Normal	26 (53.1)	183 (82.4)	29.732	<0.001
Low	9 (18.4)	28 (12.6)		
High	14 (28.6)	11 (5.0)		
Calcium ion				
Normal	7 (14.3)	95 (42.8)	13.898	<0.001
Abnormal	42 (85.7)	127 (57.2)		
BU				
Normal	24 (49.0)	145 (65.3)	41.100	<0.001
Low	1 (2.0)	51 (23.0)		
High	24 (49.0)	26 (11.7)		
HCO				
Normal	18 (36.7)	176 (79.3)	53.127	<0.001
Low	30 (61.2)	30 (13.5)		
High	1 (2.0)	16 (7.2)		
eGFR				
Normal	11 (22.4)	104 (46.8)	9.781	0.002
Abnormal	38 (77.6)	118 (53.2)		
PT				
Normal	12 (24.5)	170 (76.6)	49.376	<0.001
Abnormal	37 (75.5)	52 (23.4)		
INR				
Normal	24 (49.0)	194 (87.4)	37.638	<0.001
Abnormal	25 (51.0)	28 (12.6)		
Age (year)				
≤65	13 (26.5)	110 (49.5)	8.581	0.003
>65	36 (73.5)	112 (50.5)		
FIB				
Normal	18 (36.7)	67 (30.2)	14.199	0.001
Low	6 (12.2)	4 (1.8)		
High	25 (51.0)	151 (68.0)		
D-D dimer quantification				
Normal	1 (2.0)	59 (26.6)	14.018	<0.001
Abnormal	48 (98.0)	163 (73.4)		

(Contd...)

Table 1: *(Continued)*

Variables	Group (%)		χ^2	p-value
	Control (n = 49)	Negative conversion (n = 222)		
IL-2R				
Normal	4 (8.2)	111 (50.0)	35.554	<0.001
Low	1 (2.0)	16 (7.2)		
High	44 (89.8)	95 (42.8)		
IL-6				
Normal	2 (4.1)	106 (47.7)	31.930	<0.001
Abnormal	47 (95.9)	116 (52.3)		
IL-8				
Normal	35 (71.4)	216 (97.3)	35.604	<0.001
Abnormal	14 (28.6)	6 (2.7)		
IL-10				
Normal	19 (38.8)	177 (79.7)	33.636	<0.001
Abnormal	30 (61.2)	45 (20.3)		

UPRO: Urine protein; P: positive; N: Negative; U-KET: urine ket; URO: Urobilinogen; WBC: white blood cell count (normal: 3.50–9.50 low: <3.50 high: >9.50, 10^9/L); NEUT: neutrophil count (normal: 1.80–6.30 low: <1.80 high: >6.30, 10^9/L); LC: lymphocyte count (normal: 1.10–3.20 abnormal: <1.10 or >3.20,10^9/L); NT-PROBNP: amino-terminal pro-brain natriuretic peptide (normal: <241/285 (male/female) high: ≥241/285 (male/female), pg/mL); PCT: Procalcitonin (normal: 0.02–0.05 high: ≥0.05, ng/mL); Hypersensitive cardiac troponin (normal: ≤34.2/15.6 (male/female) high: >34.2/15.6 (male/female), pg/mL); AST: Glutamic oxalacetic transaminase (normal: ≤40/32 (male/female) high: >40/32 (male/female) U/L); TP: Total protein (normal: 64–83 abnormal: <64 or >83, g/L); Albumin (normal: 35–52 low: <35, g/L); DBIL: Direct bilirubin (normal: ≤8.0 abnormal: >8.0, μmol/L); GGT: Gamma-glutamyl transpeptidase (normal: 10/6–71/42 (male/female) abnormal: <10/6 or >71/42 (male/female), U/L); LDH: Lactic dehydrogenase (normal: 135–225/214 (male/female) abnormal: <135 or >225/214 (male/female), U/L); Sodium (normal: 136–145 low: <136 high: >145, mmol/L); Calcium ion (normal: 2.20–2.55 abnormal: <2.20 or >2.55, mmol/L); BU: Blood urea (normal: 3.6/3.1–9.5/8.8 (male/female) low: <3.6/3.1 (male/female) high: >9.5/8.8 (male/female), mmol/L); HCO: Bicarbonate radical (normal: 22.0–29.0 low: <22.0 high: >29.0, mmol/L); eGFR: Epidermal growth factor receptor (normal: >90 abnormal: ≤90, mL/min/1.73m^2); PT: Prothrombin time (normal: 11.5–14.5 abnormal: <11.5 or >14.5,s); INR: International normalized ratio (normal: 0.80–1.20 abnormal: >1.20); FIB: Fibrinogen (normal: 2.00–4.00 low: <2.00 high: >4.00, g/L); D-D dimer quantification (normal:<0.5 abnormal: ≥0.5,μg/mL FEU); IL-2R: Interleukin-2 receptor (normal: 223–710 low: <223 high: >710, U/mL); IL-6: Interleukin 6 (normal: <7.0 abnormal: ≥7.0, pg/mL); IL-8: Interleukin 8 (normal: <62 abnormal: ≥62, pg/mL); IL-10: Interleukin 10 (normal: <9.1 abnormal: ≥9.1, pg/mL).

Table 2: Collinearity diagnostics results

Model	Collinearity statistics	
	Tolerance	VIF
Age	0.492	2.032
WBC	0.567	1.765
LC	0.523	1.911
NT-PROBNP	0.483	2.070
Hypersensitive cardiac troponin	0.540	1.851
TP	0.244	4.105
DBIL	0.617	1.621
GGT	0.826	1.211
LDH	0.169	5.903
Sodium	0.159	6.270
Calcium ion	0.026	38.389
HCO	0.037	27.243
PT	0.528	1.893
INR	0.954	1.048
FIB	0.608	1.644
D-D dimer quantification	0.513	1.948
IL-2R	0.374	2.676
IL-6	0.028	35.273
NEUT	0.444	2.252
PCT	0.045	22.313
AST	0.096	10.420
Albumin	0.319	3.139
BU	0.205	4.879
eGFR	0.236	4.234
IL-8	0.030	33.805
IL-10	0.109	9.157

WBC: White blood cell count; LC: Lymphocyte count; NT-PROBNP: Amino-terminal pro-brain natriuretic peptide; TP: Total protein; DBIL: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; LDH: Lactic dehydrogenase; HCO: Bicarbonate radical; PT: Prothrombin time; INR: International normalized ratio; FIB: Fibrinogen; IL-2R: Interleukin-2 receptor 2; IL-6: Interleukin 6; NEUT: Neutrophil count; PCT: procalcitonin; AST: Glutamic oxalacetic transaminase; BU: Blood urea;; eGFR: Epidermal growth factor receptor; IL-8: Interleukin 8; IL-10: Interleukin 10.

Table 3: Collinearity diagnostics after adjusting variables

Model	Collinearity statistics	
	Tolerance	VIF
Age	0.712	1.404
WBT	0.599	1.670
LC	0.542	1.845
NT-PROBNP	0.789	1.267
Hypersensitive cardiac troponin	0.620	1.614
TP	0.319	3.132
DBIL	0.689	1.450
GGT	0.921	1.086
LDH	0.356	2.808
Sodium	0.428	2.336
PT	0.549	1.823
INR	0.970	1.031
FIB	0.710	1.409
D-D dimer quantification	0.555	1.801
IL-2R	0.474	2.109
NEUT	0.467	2.140
Albumin	0.358	2.793
IL-10	0.643	1.556

WBC: White blood cell count; LC: Lymphocyte count; NT-PROBNP: Amino-terminal pro-brain natriuretic peptide; TP: Total protein; DBIL: Direct bilirubin; GGT: Gamma-glutamyl transpeptidase; LDH: Lactic dehydrogenase; PT: Prothrombin time; INR: International normalized ratio; FIB: Fibrinogen; IL-2R: Interleukin-receptor 2; NEUT: Neutrophil count; IL-10: Interleukin 10.

Multivariate analysis results

The variables whose p < 0.05 in a single factor analysis and whose missing values were filled were included in Cox regression analysis, the method was forward: LR, with inclusion criteria of 0.05 and exclusion criteria of 0.10. We found that lactic dehydrogenase (LDH), age, fibrinogen (FIB), and disease severity were associated with delayed clearance of viral RNA in patients, as shown in Table 4. Then, drew the Kaplan and Meier curves and performed Log Rank test, as shown in Figures 1-4.

Table 4: Multivariate analysis results

Variables	B	SE	Wald	df	p-value	HR	95.0% CI for HR
Age	−0.302	0.137	4.824	1	0.028	0.739	(0.565,0.968)
Disease severity	−1.111	0.172	41.540	1	0.000	0.329	(0.235,0.462)
FIB normal			19.555	2	0.000		
Low	−0.657	0.530	1.537	1	0.215	0.519	(0.184,1.465)
High	−0.715	0.162	19.406	1	0.000	0.489	(0.356,0.672)
LDH	−0.532	0.161	10.952	1	0.001	0.587	(0.428,0.805)

FIB: Fibrinogen (normal: 2.00–4.00 low: <2.00 high: >4.00, g/L); LDH: Lactic dehydrogenase.

Discussion

We found that on the whole, men were less likely than women to undergo negative conversion of SARS-CoV-2 RNA (p < 0.05), which was consist with some other studies to some extent [13], [14], [15]. However, in our study, univariate Cox regression showed that gender was not related factor, so we did not include it. By the end of observation, the median duration of virus in the control group was 24 days that in the negative conversion group was 17 days; the difference was statistically significant (p < 0.05). It is very important to study the factors related to the negative transformation of the virus to shorten the duration of the virus and eliminate the virus in the body as soon as possible.

In our study, multivariate Cox regression showed that age was a relevant factor for viral nucleic

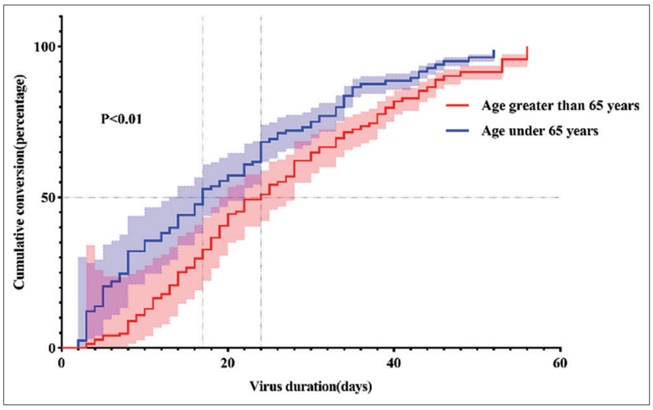

Figure 1: Negative conversion curves in coronavirus disease-19 patients according to age

acid negative transformation, and those younger than 65 years were more likely to have negative conversion than those older than 65 years (HR = 0.739, $p < 0.05$).

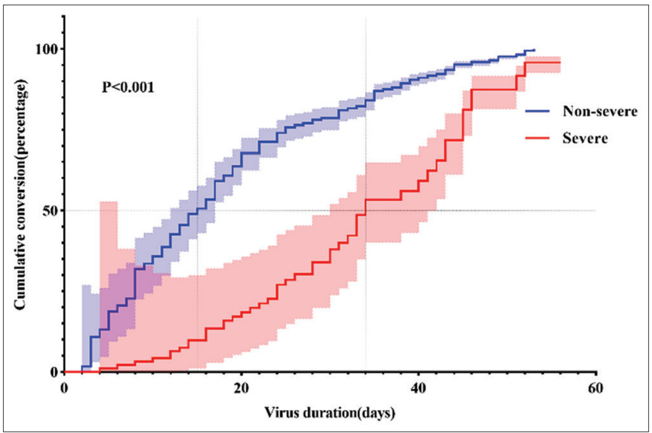

Figure 2: Negative conversion curves in coronavirus disease-19 patients according to disease severity

When the cutoff for age was set at 45 years as a related study did [16], we did not find this difference between the two age groups.

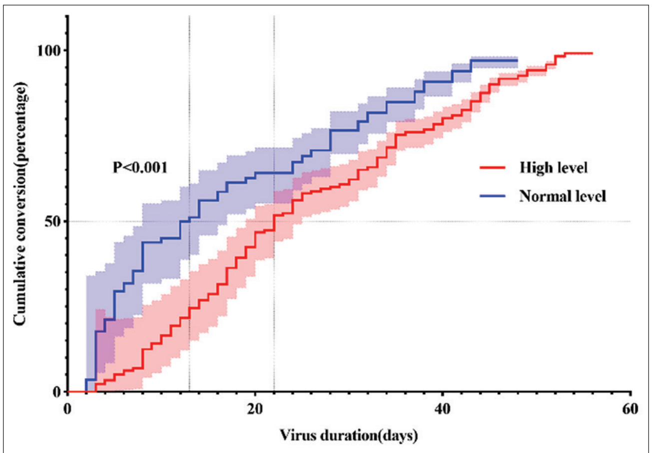

Figure 3: Negative conversion curves in coronavirus disease-19 patients according to fibrinogen

So we set the cutoff at 65 years as another research did [17] and found age > 65 years was a factor associated with viral negative conversion. First, older patients have a poorer prognosis as some studies showed [18], [19], [20]. Then, elderly patients are prone to systemic complications that may affect the clearance of SARS-CoV-2 [21]. In addition, it is generally believed that with age, immune system becomes weaker. Therefore, the risk of infection increases and the virus is difficult to remove from the body [22], [23].

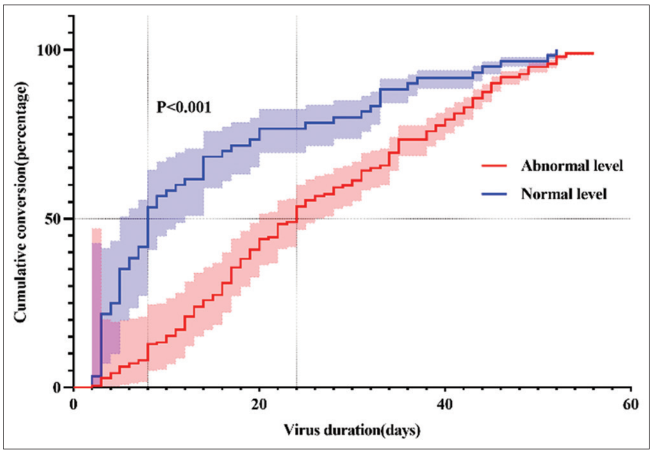

Figure 4: Negative conversion curves in coronavirus disease-19 patients according to lactic dehydrogenase

We found that the clearance of SARS-CoV-2 was associated with disease severity. It will be less conducive to virus removal if the illness at the time of admission is more serious. Ding Shi and other researchers have proved the same result [17]. The consensus view is that having severe COVID-19 symptoms affects the prognosis. As we all know, the more serious the disease is, the more critical complications may happen, which may affect the clearance of the virus in the body [24], [25].

Early studies have suggested that COVID-19 patients were easy to present with coagulopathy, disseminated intravascular coagulation, and other complications [26], [27], [28]. Based on this finding, our study has demonstrated that high levels of FIB were related to the delayed virus clearance. Although few studies have been consistent with our results, some researchers have confirmed that FIB seems to increase early in COVID-19 patients or severe patients and may be used as a risk stratification marker [29], [30]. As for the mechanism of clotting disorder, according to relative research, the endothelial glycocalyx is one of the important targets in the pathogenesis of virus-induced coagulopathy, while it still remains to be clarified whether similar mechanisms exist in COVID-19 or not. Besides, in a severer viral infection, both direct virus-induced cytotoxic effect and indirect injury may damage the host, pro-inflammatory cytokines and chemokines reported in COVID-19 were examples [31], [32]. For coagulation disorders, the corresponding treatment may indirectly help the virus to turn negative so as to improve the prognosis.

Meta-analysis showed that the laboratory indicator abnormality that COVID-19 patients were more likely to occur was the elevated LDH level and it had stronger correlations with COVID-19 mortality [20], [33]. In other studies, patients were divided into the severe group with diabetes and the group without diabetes, the cardiovascular disease group and the non-cardiovascular disease group. The results showed that the level of LDH in the former group was higher than that in the control group, which indicates the increase of LDH may be associated with cooccurring chronic diseases. These patients were more likely to suffer from multiple organ dysfunction syndrome [6], [34]. It has been reported that the cause of elevated LDH may be that the virus damages muscles and myocardial [35]. Increased LDH may cause the decrease of cytosolic pH and exacerbate muscle soreness [36]. Therefore, it is necessary to detect the LDH concentration in time and to determine the degree of damage to important organs in the body.

We studied the related factors from the perspective of virus negative conversion. It has been rarely studied in the previous research. In addition, variables with missing values greater than 20% were eliminated and other missing values were filled to ensure the stability of multi-factor analysis results. However, this study still has some shortcomings. Factors that may affect the lab indicators, such as comorbidities, were not included in the analysis because of the excessive lack of data and the causal relationship between laboratory findings and disease severity could not be determined.

Conclusion

Our study found that age older than 65 years, more severe disease; the elevated levels of LDH and FIB were not conducive to the negative conversion of SARS-CoV-2 RNA. Under the same conditions, the elevated group would prolong the virus clearance time. Therefore, in the treatment of COVID-19, attention should be paid to people over 65 years old and in critical condition and monitor these indicators, so as to control the inflammation and organ damage caused by viral infection, and help to improve the prognosis of patients.

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Knowledge, Attitude, and Behavior of Egyptian Medical Students Toward the Novel Coronavirus Disease-19: A Cross-Sectional Study

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Abstract

BACKGROUND: People in times of pandemics, crave after any medical field member (including medical students) to gain their knowledge and correct their behaviors.

AIM: We aimed to assess medical students' coronavirus disease (COVID)-19 related knowledge, attitude, and behavior (KAB).

METHODS: The study is an exploratory cross-sectional study, conducted among medical students using an online survey. Medical students were classified according to their current academic year into either early year's group (first 3 years in the medical school) or final year's group (past 3 years in the medical school).

RESULTS: A total of 2255 students completed the questionnaire**.** Regarding their COVID-19 related knowledge; 63.4% gave unsatisfactory responses (answered <75% of the questionnaire items correctly). Most of males (62.9%) and females (64.1%) gave unsatisfactory responses.

CONCLUSION: Most of students had unsatisfactory responses of the current pandemic; however, the final year's group had a significantly higher score in nearly all questionnaire (KAB) subsections than the early year's group. The majority of both groups significantly believed that there are undeclared numbers in Egypt. Facebook and other platforms were the most common sources of information.

Introduction

Coronavirus (CoV) disease (COVID-19), the new comer to the viral, droplet infectious disease family has aroused attention of millions of researchers and physicians all over the world [1].

Worldwide, since pneumonia of unknown cause detected in Wuhan, China; and up till now (Mid May 2020); 216 territories or countries have reported cases. The total confirmed cases are 4,248,389; the total recovered cases are 1,521,397, and finally the total deaths are 292,046 [2], [3].

Egypt, with more than 105 million citizens, is the most populous country in North Africa, Arab region, and the Middle East. This big number of citizens could be correlated with a grave, drastic risk of spread, and mortality [4]. In Egypt, the official figures brought out by Egyptian Ministry Of Health and Population (MOHP) exhibit that the total infected cases are 10,431, the total recovered cases are 2172, and finally the total deaths are 556 [5].

The epidemiological profile of COVID-19 is currently under vigorous investigations; starting from causative organism origin, prevention (General and specific), treatment, and finally control measures [6]. The WHO carefully monitors this emerging pandemic and information is updated continuously as more evidence becomes available [7].

Medical students are the future healthcare workers (HCWs) and the volunteers in times of need. Addressing their current knowledge, attitude, and behavior (KAB) of this newly emerging pandemic is a vital necessity, not only to be able to protect themselves but also to disseminate the correct information to their local communities [8]. People in times of pandemics, and sever fright crave after any medical field member (including medical students) to gain their knowledge and correct their behaviors [9], [10].

Infection Prevention and Control (IPC) recommendations can only be set after recognizing how HCW and in the heart medical students, perceive COVID-19 virus and translate their knowledge into practical guidelines to minimize risk of infection [11], [12]. That is why we urged to perform this survey among medical students to assess their COVID-19 related KAB.

Methods

Study design and setting

The study is an exploratory cross-sectional study, performed among medical students to assess their COVID-19 related KAB. An online survey through Google Form was created, and disseminated through the Facebook application, one of the most frequently utilized social media in Egypt. To attain a high response rate, groups with large numbers of medical students were approached by the researchers. To obtain permission to spread this survey, requests were sent to administrators of these groups. Then, the link of the survey with an encouraging statement including its purpose was posted by the researchers.

Sample size and sampling technique

A total of 2255 medical students were recruited by consecutive sampling technique during the study duration from March 1, 2020, to April 1, 2020. Participants were excluded from the study if they were not medical students.

Data collection tool

A pre-tested electronic questionnaire was used to collect data from the study participants. It included four sections:

Socio-demographic characteristics

Age, sex, education, university, and educational year.

Medical students involved in this study were classified according to their current academic year into either the early year’s group (first 3 years in the medical school) or final years group (last 3 years in the medical school).

Knowledge of study participants regarding COVID-19

Composed of a total of 30 items addressed modes of transmission, the symptoms, and complications (12 questions), and prevention and treatment (18 questions). The questions formatted in close-ended with yes, no, and do not know options. The questions were coded so that true answers were given a score of 1, while wrong answers or answering with I don’t know were given a score of 0. The total raw score (if all answers are correct) was 30. Percent score was calculated by dividing the raw score over 30 (maximum achievable score) and then multiplying the result by 100.

Knowledge status was classified into satisfactory and unsatisfactory

Satisfactory knowledge: considered when the students gave correct answers to 75% or more of the questionnaire items.

Questions used in this section were adopted from the available literature [13], [14].

For further assessment of study participants’ attitude toward COVID- 19; six questions were used to assess medical student’s attitude toward COVID-19. The questions formatted in close-ended with yes, no, and do not know options. Questions used in this section were adopted from the available literature [13], [14].

Attitude questions included inquiry on

Possibility to prevent infection by following the methods of prevention declared by the MOHP, undeclared numbers in Egypt, readiness to take corona vaccination if present, ability of government in Egypt to control the spread of the disease, if this virus is a biological warfare.

Five questions were used to assess behavior formatted in close-ended with yes, no. Questions used in this section were adopted from the available literature [13], [14].

Behavior questions included inquiry on

Worries that someone in family will be ill, wearing gloves, wearing masks in daily activities, using alcohol or sterile gel to cleanse hands constantly, washing hands many times a day, using diluted chlorine with water to cleanse the surfaces.

Sources of knowledge about COVID-19; using multiple options format, which included scientific websites, literature, colleagues and or health-care providers, television, internet, Facebook, WhatsApp, WHO website, CDC, MOHP, and others including Twitter, and Instagram.

A pilot test was performed to test the clarity of the questions by interviewing ten participants (not included in the study). The required modifications were applied. The content of the questionnaire was validated by four faculty members who are experts in public health and the required modifications were done. Reliability was tested using internal consistency and a Cronbach’s Alpha ranging from 0.59 to 0.80 was found for the 30 knowledge questions.

Statistical analysis

Statistical Package for the Social Science program (SPSS, version 24) was applied for data analysis. The median and interquartile range were utilized to sum up quantitative variables while frequency and percentage were utilized, to sum up qualitative variables. Chi-square test and cross-tabulations were done for bivariate analysis. Meanwhile, Mann–Whitney test was used for quantitative data analysis. p < 0.05 was considered statistically significant.

Ethical considerations

Study approval was acquired from the Research Ethics Committee, Faculty of Medicine, Cairo University under number F-15-2020.

Informed consent was attained directly from the study participants after clarification of the study aim and importance of the online-form before data collection. Only those who agreed were included and those who refused were excluded from the study by submitting empty form after answering “Not willing to participate.” All procedures for data collection were treated with confidentiality according to the Helsinki Declarations of biomedical ethics.

Results

A total of 2255 students completed the questionnaire; about half of them were males (44.9%). About two-thirds of the students (66.7%) belonged to the early year’s group. Regarding their response to the questionnaire item; 63.4% gave unsatisfactory knowledge responses. Most of males (62.9%) and females (64.1%) gave unsatisfactory responses (p = 0.564). Similarly, most of the early years group (67.1%) and the final years group (56.6%) significantly gave unsatisfactory responses (p < 0.001) (Figure 1).

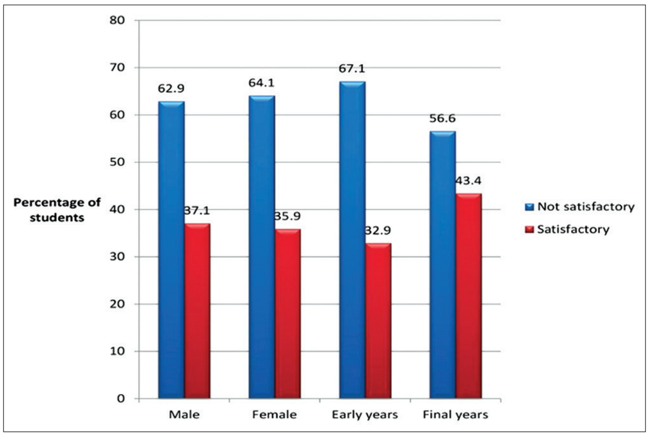

Figure 1: Summarization of the level of knowledge about coronavirus disease-19 among medical students, Egypt

Figure 2 shows that the Facebook was most common source of medical students’ information about COVID-19 virus regardless of their academic year, whereas TV (57.4%) and WhatsApp groups (18.7%) were significantly the major sources of information for early years group, the doctors (or colleagues) (54.7%), and the WHO (16.8%) were the major sources of information for final years group (p < 0.001).

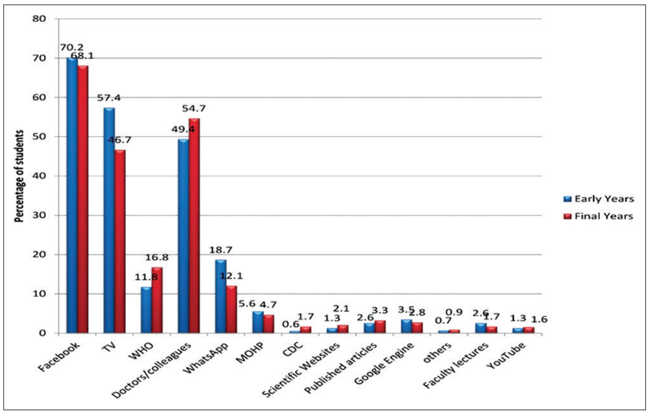

Figure 2: Source of information about coronavirus disease-19 among medical students, Egypt

Concerning students’ knowledge about COVID-19 transmission, symptoms, and testing; most of the final years group significantly and correctly responded to most of the questionnaire items; p < 0.001. Whereas most of the early years group responded significantly and correctly to only three questions as follows: Direct contact without protection with infected wild animals (60.1%), the possibility of infecting young people are less than the elderly (55.2%) and COVID-19 testing is done for returnees from traveling from countries with societal prevalence even without the appearance of symptoms (86.5%); p < 0.001. The difference in the median of the total knowledge score across the 12 items of this questionnaire section between the early and final year’s groups was not significant (Table 1).

As for students’ knowledge about COVID-19 prevention and treatment; most of the final year’s group correctly responded to almost all questionnaire items except for only five questions where the early year’s group surpassed them. The five questions were about: Eating more nutritious foods to strengthen the immune system (96.8%), covering nose and mouth during coughing (99.1%), abstinence from touching sick animal (79.6%), good cooking of meat and heating milk to avoid transmission of the disease (79.2%), and possibility to treat COVID-19 with regular cold medication in cases without complications (36.5%). The difference in the median of the total knowledge score across the 18 items of this questionnaire section between the early and final years groups was statistically significant; p < 0.001 (Table 2).

The attitude assessment section of the survey disclosed that the majority of both the final year’s group (84.8%) and the early year’s group (78.2%) believed that there are undeclared numbers in Egypt with a statically

Table 1: Comparison between early and final years medical students regarding COVID-19 related knowledge (Disease transmission, symptoms, and testing)

Disease transmission, symptoms, testing	Correct answer	Early years (n = 1503) No. (%)	Final years (n = 752) No. (%)	p-value*
Direct contact without protection with infected wild animals	Yes	903 (60.1)	343 (45.6)	<0.001*
The virus is transmitted between humans by droplets (sneezing)	Yes	1447 (96.3)	740 (98.4)	0.005*
The incubation period is from 2 to 14 days	Yes	1405 (93.5)	730 (97.1)	<0.001*
Fever, coughing, and shortness of breath are symptoms of infection with the new coronavirus	Yes	1483 (98.7)	748 (99.5)	0.081
COVID-19 symptoms could be self-limited?	Yes	1054 (70.1)	631 (83.9)	<0.001*
Complications of the disease are more severe in the elderly and people with chronic diseases such as diabetes	Yes	1471 (97.9)	745 (99.1)	0.040*
The possibility of infecting young people is less than elderly	Yes	829 (55.2)	357 (47.5)	0.001*
Is it possible for the patient to be infected without any symptoms?	Yes	1258 (83.7)	693 (92.2)	<0.001*
COVID-19 testing is done for contacts of positive cases without the appearance of symptoms?	No	273 (18.2)	169 (22.5)	0.015*
COVID-19 testing is done for contacts of positive cases when symptoms appear during active surveillance?	Yes	1035 (68.9)	543 (72.2)	0.102
COVID-19 testing is done for returnees from traveling from countries with societal prevalence even without the appearance of symptoms	Yes	1300 (86.5)	575 (76.5)	<0.001*
COVID-19 testing is done for suspected cases, provided symptoms occur	Yes	805 (53.6)	439 (58.4)	0.030*
Total score				
Median (IQR)		9 (8–10)	9 (8–10)	0.288

*p < 0.05. COVID: Coronavirus disease.

Table 2: Comparison between early and final years medical students regarding COVID-19 related knowledge (Disease prevention and treatment)

Disease prevention and treatment	Correct answer	Early year's (n = 1503) No. (%)	Final year's (n = 752) No. (%)	p-value
One of the methods to prevent spread is good ventilation living places	Yes	1230 (81.8)	662 (88.0)	<0.001†
Staying away from crowded places and keep safe distances	Yes	1497 (99.6)	750 (99.7)	0.616
Eating more nutritious foods to strengthen the immune system	Yes	1455 (96.8)	713 (94.8)	0.021†
Washing hands with soap and water helps to prevent transmission of the disease	Yes	1476 (98.2)	746 (99.2)	0.063
Covering nose and mouth during coughing	Yes	1489 (99.1)	740 (98.4)	0.164
Maintaining surfaces clean	Yes	1492 (99.3)	749 (99.6)	0.345
Abstinence from touching sick animal	Yes	1196 (79.6)	486 (64.6)	<0.001†
Good cooking of intentioned meat and heating milk to avoid transmission of the disease	Yes	1190 (79.2)	478 (63.6)	<0.001†
There is a vaccination for the new coronavirus	No	1229 (81.8)	682 (90.7)	<0.001†
COVID-19 can be cured	Yes	1286 (85.6)	679 (90.3)	0.002†
Antibiotics are the first means to treat disease	No	1013 (67.4)	631 (83.9)	<0.001†
Is it possible to treat COVID-19 with regular cold medication in cases without complications?	No	549 (36.5)	155 (20.6)	0.089
Confirmed cases should go to hospitals regardless the severity of symptoms	No	642 (42.7)	491 (65.3)	<0.001†
Home isolation must be done for contacts with confirmed cases	Yes	1233 (82.0)	681 (90.6)	<0.001†
Hospital quarantine must be done for contact with confirmed cases	No	375 (25.0)	349 (46.4)	<0.001†
Home insolation is done for positive cases	No	930 (61.9)	499 (66.4)	0.037†
Quarantine must be done for confirmed cases	Yes	1411 (93.9)	716 (95.2)	0.197
Hydroxychloroquine is a prophylaxis drug for COVID-19	No	436 (29.0)	387 (51.5)	<0.001†
Total score				
Median (IQR)		14 (12-15)	14 (13-15)	<0.001†

†p < 0.05. COVID: Coronavirus disease.

Table 3: Comparison between early and final year's medical students regarding COVID- 19 related attitude and behavior

Attitude and behavior	Early years (n = 1503) No. (%)	Final years (n = 752) No. (%)	p-value
Attitude			
Is it possible to prevent it by following the methods of prevention declared by the Ministry of Health			
Yes	1452 (96.6)	737 (98.0)	0.172
No	26 (1.7)	7 (0.9)	
I don't know	25 (1.7)	8 (1.1)	
If the corona vaccination is present, you will take it or not			
Yes	1350 (89.8)	665 (88.4)	0.596
No	84 (5.6)	47 (6.3)	
I don't know	69 (4.6)	40 (5.3)	
Do you think that there are Undeclared no. in Egypt			
Yes	1176 (78.2)	638 (84.8)	0.001‡
No	131 (8.7)	51 (6.8)	
Can the government in Egypt control the spread of the disease?			
I don't know	196 (13.0)	63 (8.4)	
Yes	610 (40.6)	222 (29.5)	<0.001‡
No	445 (29.6)	297 (39.5)	
I don't know	448 (29.8)	233 (31.0)	
Do you think this virus is a biological warfare?			
Yes	568 (37.8)	189 (25.1)	<0.001‡
No	615 (40.9)	376 (50.0)	
I don't know	320 (21.3)	187 (24.9)	
Behavior			
Are you worried that someone in your family will be ill?			
Yes	1360 (90.5)	706 (93.9)	0.006
No	143 (9.5)	46 (6.1)	
Do you wear gloves in your regular daily activities now?			
Yes	580 (38.6)	172 (22.9)	<0.001‡
No	923 (61.4)	580 (77.1)	
Do you wear masks in your daily activities now?			
Yes	681 (45.3)	288 (38.3)	0.002‡
No	822 (54.7)	464 (61.7)	
Do you use alcohol or sterile gel to cleanse hands constantly?			
Yes	1194 (79.4)	621 (82.6)	0.076
No	309 (20.6)	131 (17.4)	
Do you wash your hands many times a day?			
Yes	1442 (95.9)	742 (98.7)	<0.001‡
No	61 (4.1)	10 (1.3)	
Do you use diluted chlorine with water to cleanse the surfaces?			
Yes	1229 (81.8)	628 (83.5)	0.307
No	274 (18.2)	124 (16.5)	

‡p < 0.05. COVID: Coronavirus disease.

significant difference between early and final year's groups. Most of both groups either completely did not believe or did not know whether the government in Egypt could control the spread of the disease and whether this virus is a biological warfare or not; p < 0.001 (Table 3).

Regarding the behavior section of the survey disclosed the early year's group significantly outreached the final year's in wearing gloves (38.6%), and wearing masks (45.3%) in regular daily activities; p < 0.001. However, the final year's group significantly outreached them in washing their hands many times a day (p = 0.001) (Table 3).

Discussion

We assessed the (KAB) of some Egyptian medical students regarding COVID-19. Our study displayed that knowledge and attitude responses toward COVID-19 were not significantly different with regard to socio-demographic variables such as gender and years of experiences. Particularly, gender findings goes in accordance with a recent Egyptian COVID-19 survey among the general public which demonstrated similar and non-significant differences in the knowledge mean scores between male and female participants [15]. Furthermore, our gender findings go in consonance with the disclosures of a previous Malaysian survey among final year medical students which investigated their knowledge of mandatory notifiable infectious diseases (TD) [9]. In developing countries, this is particularly important because the students' future role as HCWs in the country's disease surveillance system is one of the major constituents to fight against TD.

The current study divulged that Facebook and other internet sources were the most widespread sources of students' information. Our findings are in accordance with many national studies which reported that more than seventy percent of participants used the Facebook as the main social media platform in Egypt [15], [16].

More than 75% of Facebook users in Egypt are in the youth age groups between 18 and 40 years including medical students. In 2019, Facebook platform users increased from 33 million in 2016 to more than 40 million [17].

In the same time, many international studies similarly reported social media and television as the chief information sources [18], [19], [20].

Meanwhile, this differs from the findings of a regional study in Saudi Arabia, where 50% of the participants relied on the official Ministry of Health website as the principal information source about Middle East respiratory syndrome (MERS) [10]. Taken together, these findings endorse the weightiness of using such platforms for propagation the health information and educational messages about COVID-19 transmission, prevention, and control. Due to increased awareness of policymakers about the importance of social media platforms, the Egyptian MOHP started recently using COVID-19 sponsored ads on Facebook [15]. Although social media platforms provide an affluent and at hand methods of obtaining information, likewise they can be an origin of misinformation. An eminent example includes fake news on Facebook about potential drugs, and vaccines [21]. Alertness while using these platforms must be regarded, to avoid the circulation of rumors and fabricated data.

As expected, the final years group had a significantly higher score in nearly all knowledge questionnaire (disease transmission, symptoms, and testing) subsections than the early years group. This goes in concordance with a recent Indian COVID-19 awareness survey among health care professionals, where the medical undergraduate students sub-group gave the highest percentage of correct responses (74.10%) [22]. Final year's group enjoys acceptable knowledge level due to multiple information sources starting from formal curricular teaching, self-directed learning, and informal bedside practice [23]. Moreover, other than formal curriculum teaching, the raised knowledge testified among final year's students may be on account of their previous knowledge regarding the outbreak of MERS-CoV which occurred in neighboring Gulf countries in 2015 [24], [25]. Meantime, the fact that more than half of the early year's students believed the possibility of infecting young people are less than the elderly, goes hand in hand with the Egyptian general public COVID-19 survey where great majority of participants believed that the disease complications are more severe in the elderly and people with chronic diseases as diabetes [15]. In China, many studies were published affirming these facts about the disease [26], [27].

Our results uttered that most of early years medical students had a lower level of knowledge about COVID-19 prevention and control subsections. These finding are matching with the disclosures of three analogous survey studies performed at different times in neighboring Saudi Arabia. They all investigated knowledge and information sources among medical students regarding MERS-CoV and ID control [13], [20], [23]. The first one investigated knowledge and attitudes toward (MERS-CoV) and exhibited that the majority of students had significantly lower knowledge compared with the physicians and nurses [13]. The second survey investigated knowledge, attitude, and practice of secondary schools and university students toward (MERS-CoV) epidemic in Saudi Arabia [20]. The third one which investigated medical students' (KAB) regarding standard precautions and infection control, at a Saudi university, were much subsidiary than expected [23]. Causes behind COVID-19 poor knowledge resides in the nature of the disease itself, being a newly emerging pandemic disease, information concerning threats of infection and control are still explored and investigated rigorously by many scientists in many parts of the world [28], [29].

Saudi Arabia and India had previously reported similar findings among medical students while investigating Zikavirus outbreaks which caused venerable morbidity and mortality in several countries since its epidemic started in Brazil in 2015 [18], [30]. With respect to staying away from crowded places and keep safe distances, almost all our students gave correct answer. This goes in conformity with the Indian COVID-19 awareness survey where the highest number of correct responses regarding correct definition of "close contact" was from the medical undergraduate students [22]. Awareness of the correct "close contact" definition (like the US CDC one) is particularly important for all paramedical personnel such as medical students or managerial staff [31]. Although these groups are not dynamically plunged in patient management, there is high potentiality of having patient contact at certain point in the health-care facilities and accordingly at hazard of contracting and propagation of the infection.

The fact that almost all early years group surpassed in their knowledge regarding the importance of general preventive measures such as covering nose and mouth during coughing (by wearing face masks), reflects the cautious wary among those students more than their older counter fellows. These matches with the Egyptian general public COVID-19 survey where about three quarters of participants believed that putting a face mask can protect from infection [15].

The CDC recently commended putting cloth face masks for the public, especially in regions where there is grave, exalted possibilities of community-based transmission [32]. During the current pandemic time, it is commended that preventive measures guidelines must be set by governments and local public health authorities. Although constant exploitation of masks creates a burden on the limited, available resources, the WHO commends the continuous use of medical masks by HCW and caregivers in areas of known or suspected community transmission regardless of whether direct care to COVID-19 patients is being provided or not [33], [34].

The majority of both early and final year's students correctly believed that home isolation not hospital quarantine must be done for contacts with confirmed cases. This disagrees with the findings of the Egyptian general public COVID-19 survey where nearly sixty percent were willing to stay in the hospital if they contacted an infected case [15].

Another strong predictor of a higher total knowledge score was accomplishment of an ID clinical round which is vital in adapting and retaining ID transmission, prevention, and control knowledge. Many of the early year's students who yielded unsatisfactory replies to questions of the survey lacked clinical experiences due to not yet obtaining their ID clinical rotation [35].

Meantime, the attitude questions where the early year's group significantly outreached the final year's group focused on using personal protective equipment (PPE) such as wearing masks and gloves. In the current study, the most well-distinguished spheres were the general concepts of standard precautions, hand hygiene, and PPE. This is because the medical curricula were rectified to maximize the highlighting of these spheres. Moreover, IPC conveyance is currently early commenced to health sciences students [23], [36], [37]. This goes in concurrence with the Indian COVID-19 awareness survey. For example, the highest number of correct responses regarding awareness of the right sequence for the mask application and hand hygiene was from the undergraduate medical students (42.2%) [22]. In our study, the majority of medical students significantly believed that there are undeclared numbers in Egypt. A finding of considerable concern which arises from inadequate, under reporting of COVID-19 cases. Due to a combination of insufficient diagnostic kits and tools provided by MOHP and/or the societal stigma associated with COVID-19 infection. Stigma arises due to fear from mortality and the high communicability which results in negative attitudes toward those infected. This can be worked out through meriting education, awareness, and transparency of health-care policies [38]. This goes in accordance with the Egyptian general public COVID-19 survey where 23% of participants thought the infection of the virus is associated with stigma [15]. Most of students either completely did not believe or did not know whether the government in Egypt could control the spread of the disease. Again, this could be explained by the increased effectiveness of the messages provided by the different social media platforms when used as a source of information. Sometimes, the negative assumptions dominate these platforms for example that media are exaggerating the COVID-19 risk [15]. In addition to, the ambiguity in distinguishing the validity and scientific purport of the official MOHP announcements as well as the likelihood of misinformation being expounded by local health departments [39]. Such departments behave in this way to minimize their responsibility over the disease spread in light of the minimal available resources (inadequately equipped hospitals, few diagnostic tools, and few HCW manpower) to combat COVID-19 spread. Again, most of students either completely did not believe or did not know whether this virus is a biological warfare or not. This goes hands in hands with the Egyptian COVID-19 survey among the general public where only quarter of their participants thought that the virus started as a biological weapon. This reflects the raising consciousness of the public when discussing controversial matters [15]. Many sounds lately have suggested that MOHP should temporarily permit senior grades medical undergraduates to treat COVID-19 patients. Such call has been previously made in developing country like India [40]. This initiative could help plugging up the insufficiency of HCW and conceivably provide care to larger numbers of people.

Conclusion

In this study, most of students had unsatisfactory responses of the current pandemic; however, the final year's group had a significantly higher score in nearly all questionnaire (KAB) subsections than the early year's group. The majority of both groups significantly believed that there are undeclared numbers in Egypt. Facebook and other platforms were the most common sources of information. During epidemic time, a safe tool for educational interventions and awareness campaigns about COVID-19, arranged by health-care authorities; is through conducting "periodic webinars" for managing health team which also include medical students.

Limitations

Our study was "online" limited to the students active on social media who reached the survey, thus the results displayed here may not be generalizable to the rest of the country. Participation bias is also of a concern. Therefore, rounding off further on ground large‐scale studies from other governorates (faculties of medicine and university hospitals) in Egypt is important to further inquire on (KAB) of medical students at the national level.

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An Online Survey: Assessing Anxiety Level among General Population during the Coronavirus Disease-19 Pandemic in Indonesia

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Abstract

BACKGROUND: Indonesia, the world's fourth-most populous country, is grappling with coronavirus disease 2019 (COVID-19) catastrophe as cases continue to rise. This situation induces uncertainties and changes in daily life, leading to uneasiness among the population, which may trigger anxiety symptoms.

AIM: This study aimed to analyze the factors associated with the anxiety level among the general population during the COVID-19 pandemic in Indonesia.

METHODS: A cross-sectional study was carried out among 267 adults from June 10, 2020, to June 15, 2020, the transition phase week after Large-scale Social Restriction of Indonesia. The survey was conducted online using a Google Form distributed through social media (WhatsApp, Instagram, Facebook, and Twitter). Respondents over 18 years old, who agreed to participate in this study, were asked to complete the questionnaire by clicking the link. The anxiety level was measured by the Hamilton Anxiety Rating Scale.

RESULTS: The results of this study showed a significant correlation between age (p = 0.010), education (p = 0.039), personal income (p = 0.034), media exposure (p < 0.01), physical activity (p < 0.01), and anxiety diagnosis (p < 0.01) with the anxiety level among general people. However, ordinal logistics regression revealed that only respondents living in the city (odds ratio [OR] = 2.476) and people with clinician-anxiety diagnosis (OR = 5.116) were more likely to experience anxiety symptoms during the COVID-19 pandemic in Indonesia.

CONCLUSION: According to the obtained results, age, education level, average income per month, media exposure, physical activity, and anxiety diagnosis correlated with anxiety incidence, whereas risk factors of anxiety included current residence and anxiety diagnosis.

Introduction

A novel coronavirus, designated as 2019-nCov, was identified with the first outbreak since December 2019 in Wuhan, Hubei Province, China [1]. The disease caused by the novel coronavirus was named coronavirus disease 2019 (COVID-19). This virus is affecting 213 countries and territories around the world, including Indonesia [2].

The first confirmed case of COVID-19 in Indonesia was announced on March 10, 2020. Since then, the cases have been increasing drastically. As of June 10, 2020, the government has reported 34,316 people with confirmed COVID-19. There have been 1959 deaths and 12,129 patients have recovered from the disease [3]. In response to this situation, the Indonesia government has made new public policy, such as mandatory isolation for individuals coming back from red zone-regions, working from home, school suspensions, shutdown of non-essential administrations, and large scale social restriction [4]. These policies are typically implemented during a pandemic for an uncertain period. Furthermore, since Indonesia is the fourth most populated country in the world, the COVID-19 pandemic is anticipated to endure enormously over a more extended timeframe compared to other less populated nations. Indonesians, like the rest of the world, are increasingly concerned about these changes. A case report of anxiety disorder-related COVID-19 outbreak in Indonesia showed that a 23-year-old female student initially experienced a feeling of anxiety symptoms such as heaviness in the chest, difficult breathing, and palpitation [5]. However, few investigations have detailed the effect of COVID-19 pandemic on anxiety levels among Indonesians despite that the pandemic has seriously influenced this country.

Anxiety, which may be defined as the pathological counterpart of normal fear, is identified by disturbance of mood, thinking, behavior, and psychological activity. It causes feelings of fear to predominate, out of proportion to any threat [6]. Everyone may experience anxiety at a different level and intensity; however, these different levels of anxiety and worry will be important when causing clinically significant distress or impairment in social, occupational, or other major areas of functioning. People with generalized anxiety disorder typically experience anxiety and worry alongside three or more of the following symptoms for at least 6 months: Muscle tension, early fatigue, restlessness, difficulty concentrating, irritability, and sleep disturbance [7].

The uncertainties and changes in daily life may lead to uneasiness among the population. The pandemic has provoked people to have stress and anxiety. During 2015–2016, large outbreaks of Zika virus occurred that increased anxiety [8]. The same trend holds for this pandemic; a recent study proved the association of the COVID-19 pandemic with an increase in stress among citizens in China [9]. This worry can be related to the continuing coronavirus spike. The general population has also been advised by authorities to decrease voyaging and stay at home as a fundamental method for constraining individuals' exposure to the virus. Unfortunately, the restriction on travel and directives on preventing participation in outdoor activities, including regular physical activity, would inevitably disrupt the routine daily activities. Since there is much uncertainty as to the current situation, people tend to feel plagued. Worrying refers to the psychological process of having rehashed negative and catastrophic considerations and is identified with discouragement and a few anxiety-related issues [10], [11].

Although staying at home provides safety during a pandemic, it may have unintended negative consequences. In general, there is an extended time sitting or resting for screening activities (playing games, watching television, and utilizing cell phones), which lessens normal physical movement [12], [13].

Another potential anxiety factor is media exposure. During the COVID-19 outbreak, more exposure to threatening news, for example, reading about the number of new deaths, data on social media, and so forth, would increase fear of the virus. A previous study showed that media news about COVID-19 could trigger high levels of worry among the community, and it might consequently be a risk factor for depression and anxiety [14]. Threat information has shown that the mass media may become a conduit that spreads negative consequences of community trauma beyond directly affected communities [15], [16].

Furthermore, the COVID-19 pandemic may be associated with exacerbating pre-existing mental illnesses, especially anxiety disorders [17]. Therefore, we examined the diagnosis of an anxiety disorder as one factor that may induce anxiety in a large general population survey.

Previous studies have examined anxiety using a questionnaire that has been adjusted to pandemic situations. On the other hand, the current study applied a validated questionnaire to measure anxiety levels using the Hamilton Anxiety Rating Scale (HAM-A). Several studies also correlated anxiety during the pandemic era to media exposure only without considering screen time increment. To the best of our knowledge, there is no previous study that investigated anxiety during the pandemic period in Indonesia. Thus, we considered current research is essential to analyze anxiety within multicultural society in Indonesia during this COVID-19 pandemic.

This study aims to investigate the association between predisposition variables (age, gender, education, occupation, income, and current living place), physical activity, screen time, media exposure, and history of anxiety with current anxiety levels among Indonesian people during pandemic.

Methods

Sample size determination

Participants for this research were selected through an online survey using Google Form shared through social media (e.g., Whatsapp, Facebook, and Instagram). A total of 354 respondents (all over 18 years old) consented to participate; however, 87 respondents did not fill out the survey correctly. As a result, the last sample size of 267 people (representing 10 different provinces in Indonesia) was used for the rest of the study based on an a priori power calculation [15].

Data collection started on June 10, 2020, and was culminated on June 15, 2020, since it met the initial target sample size.

Measures

Anxiety level

During the pandemic, the anxiety level was measured using the Indonesian version of the HAM-A which fulfills the criteria of reliable (Cronbach's alpha = 0.756) and valid (Pearson correlation ranged from 0.529 to 0.727) [18]. This questionnaire consists of 14 indicators, that is, anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior at interview. Respondents were asked to rate their frequency of experiencing the former symptoms on a 4-point scale: 0 (not present), 1 (mild), 2 (moderate), and 3 (severe). The total anxiety score could range between 0 and 56; an anxiety score <17 indicates mild severity, 18–24 stands for mild to moderate severity, and 25–30 denotes a moderate to severe level.

Media exposure

To measure voluntary exposure to news about COVID, respondents were asked to answer the following questions: "Have you looked for any extra information on the COVID-19 outbreak in any kind of media?" (with a yes or no answer). If they answered yes, they were also asked about the frequency of this action per week.

Physical activity

Physical activities during the COVID-19 pandemic were measured by the International Physical Activity Questionnaire-Short Form. Overall, the IPAQ questionnaires demonstrated strong validity (r = 0.72–0.82) and reliable (Cronbach's alpha = 0.63) [19]. This form includes open-ended questions about the individuals' last 7-day recall of any physical activity. The data processing and analysis of this measure resulted in three categories, including low, moderate, and high.

Screen time

Subjects were asked to provide information on two items about screen time; first, "Do they always work online or through screen devices before the pandemic? Second, How much time do they spend in front of a device for work per day?"

Anxiety diagnosis

Respondents were asked whether they have been diagnosed with depression by a doctor or psychotherapist (over the past 12 months).

Analytic approach

Data analysis was performed by SPSS v20 software, and the statistical significance level was set at $p < 0.05$. Demographic characteristics were split based on gender and summarized using descriptive statistics. Chi-square was employed to compare demographics associated with anxiety levels. Moreover, ordinal logistic regression analysis was performed to identify factors associated with anxiety by determining the odds ratio (OR) value.

Results

Demographic characteristics

Table 1 lists the demographic information of the respondents (267 participants in total; about 33.3% male and 66.7% female).

Table 1: Demographic information of the respondents

Variables	Total (n = 267)	Females (n = 178)	Males (n = 89)	p-value
Age				
18–29	168 (62.9)	113 (63.5)	55 (61.8)	>0.05
30–49	86 (32.2)	59 (33.1)	27 (30.3)	
50–69	13 (4.9)	6 (3.4)	7 (7.9)	
Education level				
Primary school education	1 (0.4)	0 (0)	1 (0.6)	<0.01
Secondary education	21 (7.9)	15 (16.9)	6 (3.4)	
Higher education	245 (91.8)	74 (83.1)	171 (96.1)	
Occupation				
Unemployed	7 (2.6)	3 (1.7)	4 (4.5)	>0.05
Full-time employed	235 (88.0)	161 (90.4)	74 (83.1)	
Part-time employed	25 (9.4)	14 (7.9)	11 (12.4)	
Current residence				
Urban	215 (80.5)	145 (81.5)	70 (78.7)	>0.05
Rural	52 (19.5)	33 (18.5)	19 (21.3)	
Income				
Decrease	78 (29.2)	50 (28.1)	28 (31.5)	<0.01
Stable	182 (68.2)	127 (71.3)	55 (61.8)	
Increase	7 (2.6)	1 (0.6)	6 (6.7)	

Based on the age demographics of the respondents, 62.9% of the respondents were 18–29 years old. Furthermore, 91.8% of the participants were university students, and 88% of the respondents were full-time employees. The current residence was categorized into urban and rural areas, showing that most respondents lived in urban areas (80.5%). From a financial viewpoint, compared to the time before the COVID-19 pandemic, 68.2% of the respondents had a stable income, 29.2% and 2.6% experienced decreases and increases in their incomes, respectively.

Anxiety level

Table 2 presents the anxiety level among the population. Overall, most of the respondents had mild anxiety (67.4%), and 11.6% only experienced severe anxiety.

Table 2: Anxiety level in frequency and percentage

Anxiety level	Frequency	%
Severe	31	11.6
Moderate	36	13.5
Mild	180	67.4
Normal	20	7.5

Table 3 lists the frequency distribution of anxiety levels based on the characteristics of the respondents.

The data attribute severe anxiety mostly to women, 18–29 years old, and higher education. Respondents with full-time work tended to experience severe anxiety more than others. Those living in an urban area with stable incomes were at risk of anxiety.

Anxiety level significantly correlated across age, education, and income ($p < 0.05$).

Table 3: Distribution of the respondents' anxiety levels

Characteristics	Anxiety level			
	Severe n (%)	Moderate n (%)	Mild n (%)	Normal n (%)
Gender				
Male	8 (25.8)	10 (27.8)	62 (34.4)	9 (45)
Female	23 (74.2)	26 (72.2)	118 (65.6)	11 (55)
Chi-square		>0.05		
Age				
18–29	23 (74.2)	30 (83.3)	107 (59.4)	8 (40)
30–49	7 (22.6)	5 (13.9)	62 (34.4)	12 (60)
50–69	1 (3.2)	1 (2.8)	11 (6.1)	0 (0)
Chi-square		0.010		
Education level				
Primary education	0 (0)	0 (0)	0 (0)	1 (5)
Secondary education	2 (6.5)	4 (11.1)	13 (7.2)	2 (10)
High education	29 (93.5)	32 (88.9)	167 (92.8)	17 (85)
Chi-square		0.039		
Occupation				
Unemployed	2 (6.5)	1 (2.8)	4 (2.2)	0 (0)
Full-time employed	27 (87.1)	30 (83.3)	160 (88.9)	18 (90)
Part-time employed	2 (6.5)	5 (13.9)	16 (8.9)	2 (10)
Chi-square		>0.05		
Current residence				
Urban	29 (93.5)	29 (80.6)	144 (80)	13 (65)
Rural	2 (6.5)	7 (19.4)	36 (20)	7 (35)
Chi-square		>0.05		
Income				
Decrease	14 (45.2)	17 (47.2)	42 (23.3)	5 (25)
Stable	17 (54.8)	18 (50)	133 (73.9)	14 (70)
Increase	0 (0)	1 (2.8)	5 (2.8)	1 (5)
Chi-square		0.034		

Media exposure

Based on the records, 94.4% of the participants experienced media exposure, and 39.7% of them updated the information on COVID-19 every day.

Table 4: Correlation of anxiety level with the frequency of media exposure per week

Variable	Total (n = 267)	Anxiety level			
		Severe n (%)	Moderate n (%)	Mild n (%)	Normal n (%)
Media exposure					
Yes	252 (94.4)	28 (90.3)	33 (91.7)	171 (95)	12 (60)
No	15 (5.6)	3 (9.7)	3 (8.3)	9 (5)	8 (40)
Chi-square		<0.01			
Frequency of media exposure about COVID-19 per week					
Everyday	106 (39.7)	13 (41.9)	11 (30.6)	73 (40.6)	6 (30)
5–6 days	15 (5.6)	2 (6.5)	1 (2.8)	10 (5.6)	2 (10)
3–4 days	60 (22.5)	3 (9.7)	12 (33.3)	42 (23.3)	1 (5)
1–2 days	71 (26.6)	10 (32.3)	9 (25)	46 (25.6)	4 (20)
None	15 (5.6)	3 (9.7)	3 (8.3)	9 (5)	7 (35)
Chi-square		<0.01			

As can be seen from Table 4, from 252 respondents exposed to media, 90.3% had severe anxiety, 91.7% had moderate anxiety, and 95% experienced mild anxiety. Statistically, there was a significant correlation between media exposure and anxiety level.

Among those intended to update COVID-19 news every day, 41.9% experienced severe anxiety groups, 30.6% moderate anxiety, and 40.6% mild anxiety. Chi-square test proved that the frequency of watching, reading, or listening to the news related to COVID-19 significantly correlated with the anxiety incidence among the population.

Screen time

Based on Table 5, 94% of the total participants spent their work time in front of electronic devices during the pandemic, 35.2% with the screen time of ≥8 h per day.

Table 5: Correlation of anxiety level with device screen-based work

Variable	Total (n = 267)	Anxiety level			
		Severe n (%)	Moderate n (%)	Mild n (%)	Normal n (%)
Device-based work					
Yes	251 (94)	31 (100)	34 (94.4)	169 (93.9)	17 (85)
No	16 (6)	0 (0)	2 (5.6)	11 (6.1)	3 (15)
Chi-square	0.181				
Approximate hours a day of screen					
≥8 h	94 (35.2)	16 (51.6)	10 (27.8)	59 (32.8)	9 (45)
6–7 h	58 (21.7)	5 (16.1)	9 (25)	41 (22.8)	3 (15)
4–5 h	44 (16.5)	7 (22.6)	5 (13.9)	29 (13.9)	3 (15)
2–3 h	36 (13.5)	1 (3.2)	6 (16.7)	27 (15)	2 (10)
<2 h	19 (7.1)	2 (6.5)	4 (11.1)	13 (7.2)	0 (0)
No screen time	16 (6)	0 (0)	2 (5.6)	11 (6.1)	3 (15)
Chi-square		0.395			

Most of the participants with severe, moderate, mild anxiety and even normal were found to work with devices a lot. However, the result of the Chi-square test showed values of 0.181 and 0.395, suggesting a negative correlation of device-based work and approximate hours of screen time per day with anxiety level.

Physical activity

Based on physical activity, the majority of respondents (62.2%) had a low intensity of physical activity. The correlation between anxiety and physical activity is presented in Table 6.

Table 6: Correlation of anxiety level with physical activity

Variable	Total (n = 267)	Anxiety level			
		Severe n (%)	Moderate n (%)	Mild n (%)	Normal n (%)
Physical activity					
Low	166 (62.2)	21 (67.7)	18 (50)	117 (65)	7 (35)
Moderate	75 (28.1)	8 (25.8)	10 (27.8)	51 (28.3)	5 (25)
High	26 (9.7)	2 (6.5)	8 (22.2)	12 (6.7)	8 (40)
Chi-square		<0.01			

The results revealed that the majority of people with severe anxiety (67.7%), moderate anxiety (50%), and mild anxiety (65%) had low physical activity. In contrast, 40% of normal respondents had a high intensity of physical activity.

The probability value of <0.01 indicated a significant correlation between anxiety level and physical activity.

Anxiety diagnosis

The history of anxiety disorder in each respondent was determined by asking for anxiety diagnosis over the last 6 months. Data collection showed that only 3% of the participants had anxiety diagnosis.

Based on the results presented in Table 7, 12.9%, 2.8%, and 1.7% of the participants with clinician-diagnosed anxiety showed severe, moderate, and mild anxiety symptoms, respectively. Chi-square analysis revealed that anxiety diagnosis was significantly associated with anxiety levels.

Table 7: Correlation of anxiety level with an anxiety diagnosis

Variable	Total	Anxiety level			
	(n = 267)	Severe n (%)	Moderate n (%)	Mild n (%)	Normal n (%)
Anxiety diagnosis					
Yes	8 (3)	4 (12.9)	1 (2.8)	3 (1.7)	0 (0)
No	259 (97)	27 (87.1)	35 (97.2)	177 (98.3)	20 (100)
Chi-square		<0.01			

Ordinal logistics regression

The ordinal logistics regression test, shown in Table 8, revealed that the current residence and anxiety diagnosis largely influenced anxiety among respondents. Urban people showed a higher estimated probability of being anxious compared to the rural group (OR = 2.476). People with previous anxiety diagnoses had a higher estimated probability of being anxious.

Table 8: Likelihood of anxiety level for individuals (ordinal logistics regression)

Individual characteristic	Odds ratio
Education	
Primary	ns
Secondary	ns
High	ns
Sex	
Male	ns
Female	ns
Age	
18–29	ns
30–49	ns
50–69	ns
Occupation	
Unemployed	ns
Full-time employed	ns
Part-time employed	ns
Current residence	
Urban	2.476*
Rural	
Personal income category	
Decrease	ns
Stable	ns
Increase	ns
Media exposure	
Yes	ns
No	ns
Frequency of media exposure in a week	
Everyday	ns
5–6 times	ns
3–4 times	ns
1–2 times	ns
None	ns
Device screen-based work	
Yes	ns
No	ns
Screen time during a pandemic	
≥8 h	ns
6–7 h	ns
4–5 h	ns
2–3 h	ns
<2 h	ns
None	ns
Physical activity	
Low	ns
Moderate	ns
High	ns
Anxiety diagnosis	
Yes	5.116*
No	

*p < 0.05.

Discussion

Sample characterization

The study was conducted during the early week of the transition phase after Large-scale Social Restriction in Indonesia, in which numerous individuals were encountering emotional distress and nervousness. Although the new normal phase has started, people are still at risk of anxiety since COVID-19 has not been eliminated yet. Based on the study, 67.4%, 13.5%, and 11.6% of the general population who participated in this research had mild, moderate, and severe anxiety, respectively. These findings are consistent with the investigations that showed approximately 25% of the overall public in China experienced moderate to extreme degrees of tension in response to COVID-19 [20].

In this study, most of the participants have lived in an urban area where they confer greater challenges and economic pressure compared to rural areas. Even though living in a metropolis can be exciting, there is also a downside. The statistical test found that current residence had a significant relationship with anxiety levels during the pandemic. Based on the ordinal logistics regression test, urban people showed a higher estimated probability of being anxious than the rural group. This result is consistent with a previous study that stated people living in cities are more likely to become mentally ill than people in rural areas due to its challenging and competitive atmosphere to survive [21]. More urban living situations are related to higher prescription rates for psychotropic medication for tension, depression, and psychological issues. Accordingly, living in an urban area can expose adults to social problems, lead them to be stressed, and contribute to poor health [22].

A recent study showed that youths living in cities often endure a high level of stressful life events, neighborhood issues, and family stress [23], [24], [25]. A meta-analysis also found that mental health conditions such as PTSD, anger management, and generalized anxiety disorder were more frequent among those living in urban areas [26]. Social issues and environmental stressors that might cause anxiety disorder are generally more prevalent in cities than in rural areas. However, it is important to keep in mind that there is no clear trend since we have a limited sample size, and there are indeed considerable risk factors, that is, poverty, social isolation, discrimination, and so forth [27]. Further insight into the association between spatial heterogeneity factors and anxiety tendency requires interdisciplinary research.

Media exposure

Media is one of the fundamental channels updating the COVID-19 data [28]. This study showed that more than 90% of participants reported being frequently exposed to COVID19-related media. Moreover, more than 90% of participants with anxiety issues, whether heavy, moderate, or low, always updated recent news about COVID-19 through any kind of media platform. Our study also revealed the probability value <0.01 for the relationship between media exposure of COVID-19 information and self-rated anxiety. This bivariate correlation also had a high OR (3.481), consistent with a previous study [15]. As to gender characteristics, women had a higher tendency to be COVID-19 news addicts, more frequent among respondents aged 18–29 years old with higher education living in cities.

Furthermore, the results indicated a significant correlation between the characteristics of individuals exposed to media with anxiety levels ($p < 0.01$). Different investigations have discovered a valid link between media access and an increased risk of depression, anxiety, loneliness, self-hurt, and even self-destructive considerations [29], [30]. As another important finding, social media as the most predominant source of information was related to COVID-19. Nowadays, social media is increasingly becoming a popular and key source of health information by connecting people with health contents, experts, support, and the latest news [31]. As a result, people can easily be exposed to an uncertain source of information [32].

At the end of April 2020, a study also reported that around seven out of 10 Americans chose to take breaks from news about coronavirus, and four of 10 felt more terribly desperate due to following the news [33]. This was because, during the outbreak, disinformation and false reports have bombarded any kind of media and stoked unfounded fears among users. Hence, watching, perusing, or listening to news about COVID-19 that makes people feel on edge need to be minimized. It is essential to seek information only from trusted sources (local authorities or WHO website) and reduce the media exposure frequency. Checking the features once a day is a reasonable objective by surfing the web or reading a daily news bulletin or government announcement. The frequency could be diminished to once per week for those with an elevated anxiety level. Urgently, it is also essential to select a trusted news website with an emphasis on realities rather than conjecture [33].

Screen time

During the pandemic, people tend to spend time at home, including work, following the government's recommendation to implement working from home. Consequently, an increasing proportion of adults' time at home is spent with screens, including smartphones, tablets, laptops, and other devices [33]. The results revealed that 94% of the respondents worked with devices; 35.2% of them spent ≥8 h per day. Although there is a general tendency for anxiety symptoms to be experienced by those who work with devices, statistically, there was no correlation between screen time and anxiety. This result agreed with that obtained by Twenge *et al*. [34] and Babic *et al*. [35], but contradicted the findings of Odgers [36], and Przybylski and Weinstein [37], who reported no correlation between screen time and anxiety. However, it is crucial to understand that screen time may have essential clinical implications for the mental and even physical health of children and adolescents [34]. As mentioned, the frequency or intensity of using screens, including gadgets for different reasons, will affect their mental and emotional development [38]. People with higher screen use were more likely to have anxiety or depression [34]. Thus, more research is needed for discussing the association of screen time with mental health.

Physical activity

This study found a significant correlation between physical activity and anxiety probability. Respondents who experienced severe, moderate, and low anxiety had a low intensity of physical activity. Like the rest of the world, Indonesians have seen drastic changes in their lives due to the large-scale social restriction as a part of the public health emergency response. It has affected the routine of their daily activities by restricting outdoor activities, except for urgent reasons. The policy of large scale restrictions may provoke new unhealthy habits while staying at home. Although the public health priority aims to protect Indonesians under such circumstances, the unintended outcomes may include decreased physical movement and expansion in inactive conduct that might lead to chronic health conditions [39].

Statistically, physical activity was not a risk factor for anxiety; however, it is true that grown-ups who are consistently physically active experience fewer symptoms of anxiety and depression [10], [12]. Furthermore, regular exercise brings physiological changes and adaptations in the human body. Studies have indicated that physical activity and exercise are successful treatments for the vast majority of interminable illnesses with direct impacts on both mental and physical well-being [20]. Exercise has proved to positively influence the surrogate measure of adult hippocampal neurogenesis such as β-endorphins, vascular endothelial growth factor, BDNF, and serotonin, all of which are thought to be the common pathophysiologic mechanism for anxiety disorder [40]. Thus, the inactive participants who were more dynamic or maintained their exercise levels demonstrated more elevated levels of social, emotional, and psychological health and lower levels of generalized anxiety [41], [42]. Accordingly, it is appropriate for citizens to do sports and other activities to preserve physical and mental health. These findings agree with the WHO recommendation to learn a simple daily exercise to perform at home in quarantine or isolation to keep up portability and diminish fatigue [2].

Anxiety diagnosis

Participants' report of a previously diagnosed depression or other mental health disorders by a health professional is frequently used to estimate the prevalence rate. In a large-scale health review, the prevalence of anxiety was surveyed by asking respondents whether they were diagnosed with anxiety by a health professional over the past year [16].

Based on the observations, 12.9%, 2.8%, and 1.7% of participants with clinician-diagnosed anxiety had symptoms of severe, moderate, and mild anxiety, respectively. Ordinal logistics regression showed that people with anxiety diagnoses had a higher estimated probability of being anxious than those without any anxiety history. These findings suggested that anxiety diagnosis may influence the result of such research. Besides, anxiety diagnosis was more common among women aged 18–29 years old. These results were consistent with the findings of McLean *et al*. [43], who showed the lifetime and 12 months male:female prevalence ratios of any anxiety disorders are 1:1.7 and 1:1.79, respectively. In general, women tended to have higher frequencies of affective disorders (such as depression and anxiety) than men. Furthermore, anxiety disorders are more disabling in women than in men [43].

Conclusion

This study proved that age, education, income, media exposure, physical activity, and anxiety diagnosis associated with anxiety levels. However, ordinal logistics regression revealed that only respondents living in the city and individuals diagnosed with anxiety disorders were more likely to experience anxiety symptoms during the COVID-19 pandemic in Indonesia (OR >1).

Limitation of the study

This study had limited access to rural respondents due to restricted internet access. As a result, the number of samples from villages was not representative enough. Moreover, the present study was cross-sectional research that could not help to determine cause and effect.

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Perception against COVID-19 Threat Affecting the Behavior of Indonesia People Three Months after the Outbreak

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Abstract

BACKGROUND: In Indonesia, a new behavior has been introduced in the community to prevent COVID-19 transmission following 3 months of the COVID-19 outbreak. The Ministry of Health, Republic of Indonesia, names this new concept as "the adaptation of new behavior." However, preventive measures and health protocols encouraged by the government have not yet yielded a significant impact on reducing the COVID-19 positivity rate. This unsuccessful outcome indicates that infective circulation is still occurring caused by incompliant to the health protocol.

AIM: This study aimed to measure community perceptions against COVID-19 at the individual level.

METHODS: A cross-sectional study with a total of 1687 respondents was performed. Questionnaires distributed thru sharing online links which contain questions on perception of vulnerability and severity of COVID-19. Chi-square test used in analysis to determine the difference in perception with respondents' behavior.

RESULTS: A total of 81.7% of respondents who had a perception of "susceptible to contract" performed behavior suited to recommendations and 81.2% study population had a perception of "COVID-19 is severe" executed behavior suited to the recommendation.

CONCLUSION: This study demonstrated the establishment of government recommendations for COVID-19 infection did not guarantee the actual health practice/behavior in the community. The existing misconception of the perspective of seriousness/severity and susceptibility would prevent the country from flattening the curve.

Introduction

COVID-19 has not only stopped in the China region, called Wuhan, in which the first case of this violent outbreak was reported. In a brief period, there is no continent free from the outbreak insurgence [1], resulting in the emergence of 85.959 cases reported by the World Health Organization (WHO) at the end of February 2020. COVID-19 outbreak has escalated 3 times for 1 month by infecting six million people in May 2020, and finally, more than 40 million people diagnosed with COVID-19 and more than a million deaths on October 21, 2020 [2].

WHO regional office in South-East Asia (SEARO) is also involved in the reporting of the outbreak. In early February, there were only 100 confirmed cases. Still, it rose to more than two million people infected in this region at the end of July and ranked South East Asia as the third position for the highest COVID-19 cases after America and Europe [2].

In Indonesia, the first case was officially reported by the Ministry of Health in early March 2020. After the first case, the outbreak became more vigorous in the incidence and attracted international concern. Three months after the first case's announcement, there were 26.473 cases with a six percent mortality rate related to COVID-19. Until last July 2020, more than 100.000 people contracted, and 4.975 deaths were confirmed with the infection [3].

New behavior has been introduced in the community to prevent COVID-19 transmission following 3 months of the COVID-19 outbreak [4]. The Ministry of Health, Republic of Indonesia, also names this new concept as "the adaptation of new behavior." The exemplification of these concepts starts from the recommendation to use facemasks when performing outdoor activities, proper hand-washing with soap or disinfectant frequently, keeping the distance, and avoiding mass gatherings. Furthermore, the government also encourages people to implement a healthy lifestyle by adequately consuming nutritious food and vitamins to boost the immune system [5].

Efforts to contain COVID-19 transmission need coordination for the national campaign by establishing the special task force. This task force works in the national until regional/city level all over Indonesia with the central vision of ensuring citizen compliance abided to the health protocol previously aired by the government from several routes such as social media and television. Until recently, the government has continued to deliver health communication, reminded the public to maintain discipline on government recommendations, and reported essential developments in preventing COVID-19 transmission.

However, all preventive measures and health protocols encouraged by the government have not yet yielded any significant impact on reducing the COVID-19 positivity rate. This unsuccessful outcome indicates that infective circulation is still occurring caused by incompliant to the health protocol.

Rule enforcement is necessary to create a supportive environment for implementation. Still, community perception against COVID-19 has more critical effects on producing good practice since positive perception would generally bear positive outcomes/ behavior [6]. Therefore, the evaluation of perception could be a beneficial approach.

Health belief model (HBM) is one of the concepts for the determination of community perception against COVID-19. In HBM, there are six things that drive a person's behavior, namely perceived susceptibility, perceived severity, perceived benefits, perceived barriers, perceived self-efficacy, and clues to action. With the HBM model, it is assumed that if a person has the view that he is susceptible to the severity of COVID-19, then he will interpret the recommended benefits more than the perceived barriers. Then, the person will have self-efficacy that he will act (clues to action). Thus, two basic things are important to know, namely, perceived susceptibility and perceived severity. Both of them are commonly mentioned as "threat perception" [7]. These two things will be used as indicators in carrying out this research.

Although the HBM concept has been used extensively in a variety of health studies, in the context of COVID-19, there is still very little theoretical guidance in this latest health issue [8]. The application of the HBM concept in conceiving community behavior against COVID-19 has been utilized previously. Therefore, extensification is necessary to adjust varied conditions existing in other regions/countries.

The application of the HBM concept in conceiving community behavior against COVID-19 has been utilized previously. Therefore, extensification is necessary to adjust varied conditions existing in other regions/countries.

Thus, measuring community perceptions against COVID19 at the individual level is essential. This study would supply feedback to the existing point that could represent the gap for COVID-19 health communication and disclosing consistency between perception and community behavior.

Materials and Methods

Sample

The study was designed cross-sectional, which was conducted through sharing online links. Respondents must exceed 17 years old and participated in the questionnaire filling for 4 weeks, between May 18, 2020, and June 19, 2020. A total of 1687 respondents (99.5%) respondents consent for study enrollment from 1696 respondents originated from all over Indonesia. The respondent data relating to name, address, or other personal identities were keep confidential and has been approved by the research committee.

Questionnaire

The questionnaire consists of a study explanation, informed consent, and questions. There are two sub-sections in the question section, such as identity/demography (gender, marital status, age, and source of information) and implemented-health practice. Questions about health practice were scrutinized in the previous 2 months. It includes asking hand-washing, facemasks, mass gatherings avoidance, hand-sanitizer application, and nutritious food/vitamin consumption (government recommendation).

The question regarding HBM asks two perceptions, namely perception of self-vulnerability and COVID-19 severity, and there are six questions for each perception. Thus, there are a total of 12 questions asked of each respondent. The time needed to complete the questionnaire was less than 1 min. The arrangement of questions was following three options such as "agree" would be scored two, one for "do not know," and zero for "disagree." The readability of the questionnaire was tested against 30 people before online dissemination.

The summation of scores in each primary perception would be grouped into two types of interpretations. Perceptions of self-vulnerability were divided into "susceptible to contract" for a total score of 8–10, and vice versa, "not susceptible" was indicated by 0–7 scores. Meanwhile, perception of severity was grouped into "COVID-19 is severe" for a minimum score of eight and "not severe" for a score ranging from zero and seven.

Six questions determined the interpretation of behavior, and each question consisted of answers with four options such as "always," "rarely," "when remembering," and "never." Under the government recommendations, everyone is obliged to implement three vital behaviors. It must be performed by respondents, including hand-washing with soap, using facemasks, and avoiding mass gatherings. Respondents abided to the three behaviors simultaneously would be stated as "suited to recommendations." Meanwhile, respondents who only applied one behavior, or even though they implement other health practices outside of the three mandatory behavior, would be categorized as "not suited to recommendations." The Cronbach's alpha for 12 questions is 0.783, indicates a high level of internal consistency for this questionnaire.

Platform

The questionnaire was designed and disseminated using a Google form since this platform was easy to access by respondents. Furthermore, a survey model using Google form is wide-spread in terms of both familiarity and reproducibility for online-based-survey. Google forms could also be distributed just in a brief period through rapid link sharing using copy-paste shortcuts to other social media platforms, including the WhatsApp group.

Data processing and statistical analysis

Data were analyzed descriptively in the form of a frequency distribution. The Chi-square test continued further analysis to determine the difference in perception with respondents' behavior, while the statistical significance degree used $p<0.05$ in the study.

Results

Demographic characteristics

A total of 67.8% of respondents was female from 1678 people approved for study enrollment. Table 1 depicts more than half of the respondents are married, and the largest proportion is in the age group of 21–30 years old (35.8%) and 31–40 years old (29.9%). Besides, respondent access for the information about COVID-19 varied, but the most familiar line is WhatsApp group/private lines, followed by television/radio, 83.5% and 80.6%, respectively.

Table 1: Demographic characteristics of respondents

Characteristics	n	%
Gender		
Male	544	32.2
Female	1143	67.8
Marriage status		
Unmarried	711	42.1
Married	949	56.3
Widow/-er	27	1.6
Age groups (years old)		
<20	182	10.8
21–30	604	35.8
31–40	505	29.9
41–50	315	18.7
51–60	74	4.4
>60	7	0.4
Information access about COVID-19		
TV/radio	1359	80.6
Newspaper/ print/online magazine	1197	71.0
WhatsApp group/ personal chat	1410	83.6
Facebook	1265	75.0
Other social media	1393	82.6

Practice/behavior

Table 2 shows the pattern of respondents' health practices as recommended by the government. Several behaviors were performed as "always" in the previous 3 months, dominated by the practice of using facemasks (92.9%) and hand-washing (90.2%). Meanwhile, vitamin consumption, using hand-sanitizer, and avoiding mass gatherings were only complied by 49.6%, 63.1%, and 88.4% of respondents.

Table 2: Respondents' health practice/behavior to prevent COVID-19 transmission

Implemented-behavior for the previous 3 months	Always (%)	Rarely (%)	When remembering (%)	Never (%)
Hand-washing with soap after performing outdoor activities	90.2	4.7	5.0	0.1
Using hand-sanitizer	63.1	26.9	7.6	2.4
Using facemasks	92.9	4.7	2.4	0.1
Avoiding mass gatherings	88.4	9.5	1.7	0.4
Nutritious food and vitamin consumption	49.6	35.4	11.9	3.1

Perception

In the study, there were two perceptions becoming the aims of the questions. First, respondents' perception of self-vulnerability contracting COVID-19 was demonstrated in Table 3. There were 71.4% of respondents who answered agree that self-vulnerability of getting COVID-19 is because of frequent interaction outside the home, but "agree" was answered for getting an infection because of not using a facemask by 56.3%. Meanwhile, only 47.2% of respondents stated that living in a similar region/city with sufferers also a source of self-vulnerability.

Table 3: Respondents' perception of self-vulnerability for contracting COVID-19

Variables	Agree	Do not know	Disagree
If not wearing facemasks	950 (56.3)	94 (5.6)	643 (38.1)
Because frequently interact outside the home	1205 (71.4)	110 (6.5)	372 (22.1)
Because living in similar places/ neighborhood with health workers	588 (34.9)	215 (12.7)	884 (52.4)
Because living in similar places/ neighborhood with died COVID-19 patients	734 (43.5)	178 (10.6)	775 (45.9)
In one region/city with COVID-19 patients.	797 (47.2)	194 (11.5)	696 (41.3)

The second perception was shown in Table 4, and the results for evaluation are more homogenous than the self-vulnerability perception. For instance, 90.0% of respondents agree for the fact that they could get infection involuntarily and vice versa, transmit the virus without prior knowledge of being infected, and 88.5% of respondents answered "agree" for the statement. A total of 85.4% of respondents agreed if the family and his-/herself could be contracted with COVID-19. Moreover, 86.7% of respondents realized that COVID-19 was more severe if its sufferers were ill with other comorbidities. The awareness of COVID-19 severity was reflected by the agreement of 83.6% of respondents if COVID-19 could cause fatality/deaths.

Table 4: Respondents' perception of COVID-19's severity

Variables	Agree	Do not know	Disagree
Family and his-/herself could be infected	1441 (85.4)	113 (6.7)	133 (7.9)
Infected involuntarily	1534 (90.9)	86 (5.1)	67 (4.0)
Severe if it was ill with comorbidity	1463 (86.7)	103 (6.1)	121 (7.2)
Could cause fatalities/deaths	1411 (83.6)	89 (5.3)	187 (11.1)
Could transmit involuntarily	1493 (88.5)	101 (6.0)	93 (5.5)

From Chi-square analysis, there were 81.7% of respondents who had a perception of "susceptible to contract" performed behavior suited to recommendations, as suggested by government. At the same time, a total of 81.2% study population had a perception of "COVID-19 is severe" executed behavior suited to the recommendation. Based on statistical analysis, perception of COVID-19 severity had a significant result in the behavior (p < 0.05), as depicted in Table 5.

Table 5: Statistical analysis for perception and behavior among respondents

Perception	Behavior		p
	Suited to recommendations	Not suited to recommendations	
Self-vulnerability			
Vulnerable	518 (81.7)	116 (18.3)	0.196
Not vulnerable	833 (79.1)	220 (20.9)	
COVID-19 severity			
COVID-19 is severe	1171 (81.2)	272 (18.8)	0.008*
Not severe	180 (73.8)	64 (26.2)	

Discussion

This study utilized the basic concept of HBM, threat perception so that it could unravel that perception of the family- and self-vulnerability as well as COVID-19 severity highly determine respondents' behavior. As depicted in Table 5, respondents who conceived that they were vulnerable to getting the infection and at the same time strictly abided to the government recommendation, such as hand-washing with soap, using facemasks, and avoiding mass gatherings; however, it was insignificantly related (p = 0.196). Other than that, if the respondents grasped the perspective that COVID-19 is severe, they also performed the recommendation (p < 0.05).

The two-factual basis demonstrated that perception has a strong association with health behavior or practices. In a study, there was also a significant relationship between the behavior of using health insurance and the perception of seriousness and susceptibility of developing several health conditions among young adults as its users [9]. Meanwhile, the suboptimal of health practices in the targeted-population was conversely related to several studies' adequate perception levels [10], [11]. Thus, this perception study does not only appear as the tools to scrutinize the current event for the behavior evaluation or the use of healthcare facilities, but it could also be used as a predictor for health behavior/practices in the future [7], [12].

In other words, the positive or good perception could attain the betterment of behavior/ practices. On the contrary, negative perception is complicated to the achievement of the desired behavior. Tackling COVID-19 needs implementation of new behaviors, but some people were reluctant to perform the behavior, or it has never been done before. For 3 months, people's behavior reflected that there was difficulty in enforcing the behavior. Indeed, this condition was also related to threat perception that is not present among every community member.

In addition, respondents' perceptions also represent some potential problems, and it needs prompt management with effective communication. Referring to Table 3, most respondents have insights that her-/himself would be more vulnerable if they were not using facemasks and having interaction outside the home. Nevertheless, both statements were agreed only by a percentage of 56.3% and 71.4% of respondents for each. Conversely, there were 38.1% of respondents disagree with the fact that using facemasks reducing transmissibility, and 22.1% of respondents also disagreed that self-vulnerability to contract from the infection occurred through frequent interaction outside the home. This condition demonstrated that the perspective against the importance of using facemasks and the people who had frequent interactions outside the home still need attention.

Furthermore, there was a significant mortality rate among COVID-19 patients in the country. Nevertheless, there were still about 40% of the respondents who disagree with the fact that a higher possibility of getting COVID-19 would ensue if they did not abide by the government recommendation. The negligence of the perception would become the primary source of problems since it let the people ignore the recommendation and, at the same time, increase the positivity rate in the community; the preventive measures only rely on the recommendations as it acknowledges that no vaccine is available until the mid-year of 2021.

However, perception of COVID-19 severity was evident, having higher coverage for "COVID-19 is severe"; all questions for this perception agreed by almost 80% of respondents. The statement for the respondents could be infected involuntarily was agreed by 91% of respondents. Nevertheless, 11.1% of respondents disagree with the severity of COVID-19 could cause deaths, and 8% of respondents also disagreed with the statement that she/he and her/his family could get the infection. This item of question would be related to most of the respondents' perception in Table 3 disclosed that they were not vulnerable to COVID-19 infection, although no facemasks were used and not in their home.

Moreover, identifying essential steps in alleviating the burden of COVID-19 transmissibility is inevitable, and findings for the information gap about COVID-19; therefore, this current study would answer those aims. The question structure given to the respondents disclosed several aspects that need urgent management by the government. Similar to previous studies [13], [14], assessment against aspects of individual perception would ease further intervention. For the people in the intervention targeted-group, assessment of item perceptions cautiously would yield more positive behavior [15]. A more advanced approach was performed in which the items of respondents' perception then put as the background for intervention, continued by comparison studies using the randomized controlled trial [16].

Following the study's context, respondents' perception of responding to this pandemic served as a genuine problem if they wrongly understood it. Still, it could be transformed by good deliverance of information to the people comprehensively and accurately, and it finally turns the community into becoming more knowledgeable. The current dissemination of any information is more convenient since a wide variety of platforms could be deployed (Table 1). More than 50% of respondents were also in the age group of 21–40 years old, who stated as the generation with easy exposure for information.

This research reveals only two basic ideas of HBM theory in the context of COVID-19, which some may consider weak. More thorough research on the HBM theory may produce better pictures of individual perception on COVID-19. In addition, analysis of other aspects outside HBM theory may explain a better formation of individual behavior. However, the information gathered from this study is very useful in changing people's perceptions which identified still inadequate after the COVID-19 pandemic occurred for almost a year. Although the study was conducted to picture a 3 months period after the pandemic occurred, it can be stated that there is no significant difference on the perceptions of COVID-19 since it is obvious there are no changes in people's behavior up to present.

Conclusion

Based on the author's knowledge, this is the first study conducted in Indonesia using "threat perception" as the main approach for revealing people's behavior. This study finally demonstrated the establishment of government recommendations, and several factual bases for COVID-19 infection did not guarantee the actual health practice/behavior in the community. The existing misconception of the perspective of seriousness/severity and susceptibility would prevent the country from "flattening the curve." Therefore, this study becomes evident that there is a need for the government to emphasize enforcing and encouraging for the changes in people's perspective and, lastly, behavior.

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COVID-19 Pandemic in ASEAN Region and Implication in Dentistry

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Abstract

The coronavirus disease (COVID-19) has spread globally and has influenced every aspect of life worldwide. In the ASEAN region, at present, many nations are still locked the academic organizations, shopping malls, events, and activities, and banks and airports are shut down to prevent the spread of the COVID-19 infection. COVID-19 has affected dental practice, and, in many countries, dentists are affected by COVID-19, leading to deaths. The dental treatments should be done with high standards of care and infection control by following proper recommendations. Personal protective equipment, patient screening, hand hygiene practices, mouth rinsing, disposable instruments, and use of rubber dam, reducing ultrasonic instruments use, treating suspected or confirmed COVID-19 patients in separate rooms, and disinfection of the inanimate surfaces helps in protecting clinicians and patients.

Introduction

The coronavirus (CoV) was first seen in Wuhan (China) and it is a form of severe acute respiratory syndrome CoV 2 (SARS-CoV-2) virus [1]. The World Health Organization (WHO) termed it COVID-19 [2]. Then, COVID-19 has spread globally and the WHO declared it pandemic [3], [4], [5]. The global distribution of COVID is shown in Figure 1. Until October 18, 2020, the CoV COVID-19 has affected 210 countries and there have been over 39,959,336 COVID-19 cases with over 1,114,633 deaths [6]. The geographic distribution of 14-day COVID-19 cases worldwide, as of October 17, 2020, is shown in Figure 1 [7]. The outbreak of COVID-19 has influenced every aspect of life worldwide. WHO has given details and various aspects of COVID and mentions that currently, there are no specific vaccines or other therapies for COVID-19 [8], [9]. Nevertheless, many ongoing clinical trials are evaluating potential therapies. In addition, no clear evidence of the treatment plan and the prevention and most data in the literature depending on personal experience only which is different from country to others [10].

At present, the COVID-19 outbreak is quick, many nations have locked down the academic organizations, shopping malls, events, and activities, and banks and airports are shut down to prevent its spread. Moreover, people are on self-quarantine to limit the spread of disease [11].

COVID-19 in ASEAN Region

In ASEAN countries, Singapore and Indonesia show the 1st and 2nd highest number of COVID-19 cases. The total COVID-19 cases in ASEAN countries compared to the USA, Korea, Japan, and China (Table 1).

Table 1: Total COVID-19 cases in ASEAN countries (listed according to the descending order of cases) compared to the USA, Korea, Japan, and China was of July 18, 2020 [6]

Countries	Total cases	Total deaths	Total recovered	Active cases
Indonesia	357,762	12,431	281,592	63,739
Philippines	354,338	6603	295,312	52,432
Singapore	57,904	28	57,789	9875
Malaysia	19,627	180	12,561	6886
Myanmar	34,875	838	16,370	17,667
Thailand	3686	59	3481	146
Vietnam	1126	35	1031	60
Cambodia	283	-	280	3
Brunei	147	3	143	1
Laos	23	-	22	1
USA	8,342,665	224,282	5,432,192	2,686191
China	85,672	4,634	80,786	252
Japan	92,063	1661	85,030	5372
South Korea	22,504	367	19,310	2827

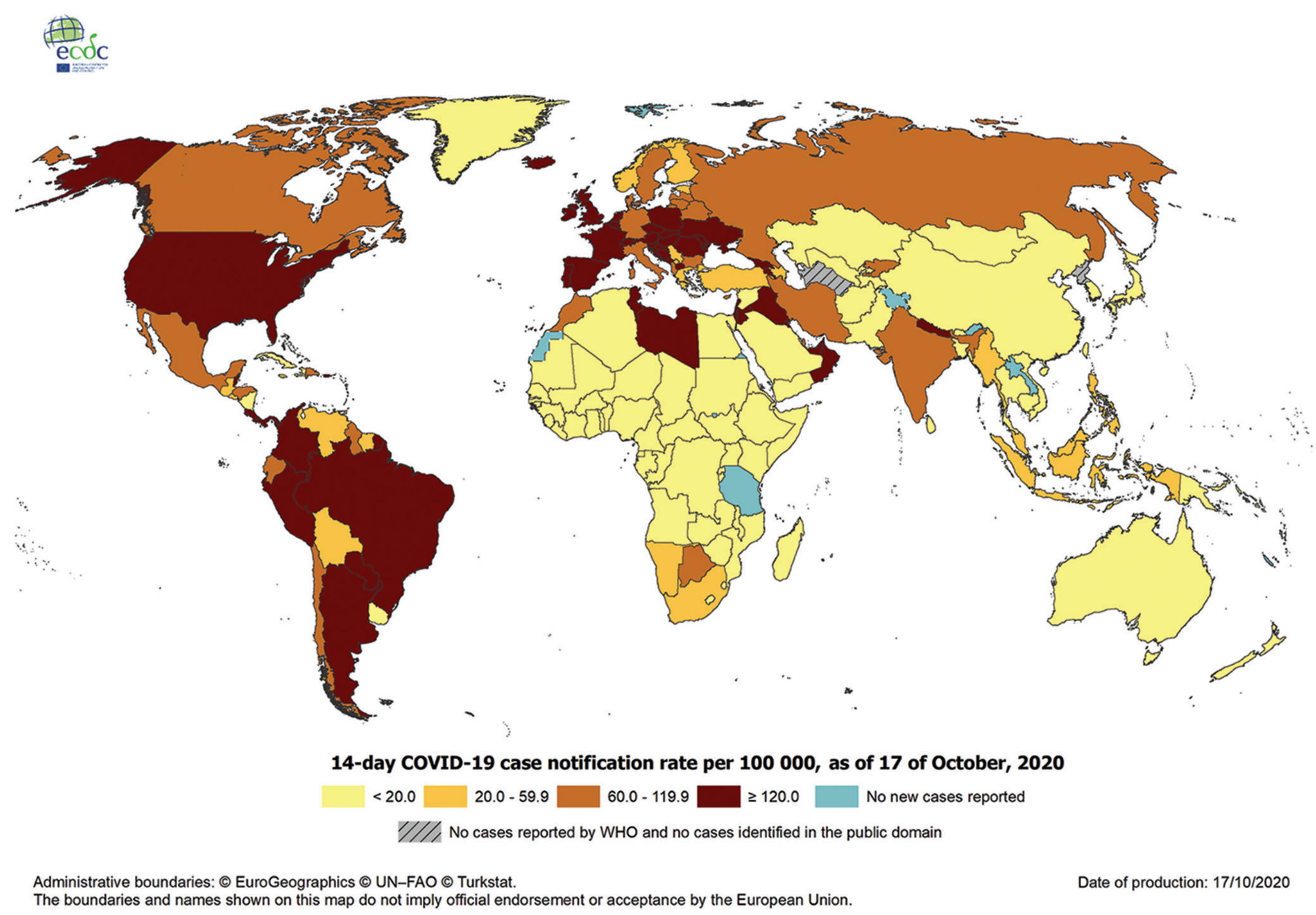

Figure 1: Geographic distribution of 14-day COVID-19 cases worldwide, as of October 17, 2020 [7]

In the ASEAN region, Indonesia and the Philippines show the greatest number of cases. In Indonesia, a total of 10,551 CoV cases were announced until May 1, 2020 [6]. It was found that the number of infections increased during the Ramadan period. There was a ban on Ramadan-related travel, but the government had opposed through the head of the Indonesian COVID-19 taskforce, assuring that people would have to undergo a 14-day quarantine following Ramadan [12]. Singapore shows the third greatest number of COVID-19 cases (57,904 cases) until May 1, 2020 [6]. Singapore is a small and top destination for business meetings and international travelers. In addition, Singapore's Changi airport is one of the most interconnected hubs in the world. At present, the Singapore authorities have increased the health alert and done strict lockdown. Malaysia, Thailand, Cambodia, and Brunei have controlled COVID-19 cases. Recently, more cases are increased in Myanmar and slightly increased in Vietnam. In Thailand, their biggest festival was also banned to prevent the spread of COVID infection. It was found that this festival could increase by 1.3–100 times more infected cases [13]. At present, Thailand has a total of around 3686 cases [6]. Laos has the least cases in the ASEAN region. This may be due to the less population and less travel movement.

Impact of COVID-19 Virus in Dentistry

As COVID-19 is a respiratory virus, the main clinical manifestations of the infection are fever, fatigue, respiratory symptoms (mainly dry cough), and the emergence of dyspnea. Most infected people show mild to moderate respiratory illness and recover. However, older people with underlying systemic diseases such as diabetes, cardiovascular disease, chronic respiratory disease, and cancer have a higher chance of developing severe illness and may result in mortality [9], [14]. The transmission of the virus can occur through contact with infected people through droplets infection from cough, sneeze, or saliva [15]. Infected people may be asymptomatic may be difficult to diagnose. Clinical diagnosis can be made by the presence of typical ground-glass opacities on chest computed tomography and contact tracing [2], [16].

COVID has an impact on dentists and dental practice. The consequences of anxiety, depression, and stress in people from the outbreak of COVID-19 may lead to temporomandibular disorders (TMD). Hence, the COVID-19 may be correlated with TMD as one of the major causes of TMD is stress and psychosocial impairment [17], [18].

In many countries, regular dental treatments are postponed, and only emergency treatment is done. It was found that a high number of dentists, 284 (70%), were affected by the financial burden and were not receiving a salary during this lockdown [19]. Patients receive dental treatments only from 10% of the dentists. Only 28 (7%) dentists think they should do the regular dental treatments, but 240 (59%) dentists think they should do emergency dental treatments for COVID-19 infected cases. It has been shown that some dentists are affected by COVID in Indonesia and Thailand. In Indonesia, 24 medical professionals, including six dentists, have died in the country from COVID-19 [20]. The reason for high COVID cases in medical and dental practitioners may be due to The Indonesian dental association had not advised dentists to close their practices or to postpone non-emergency treatment. After this incident, the Indonesian government has taken seriously on COVID-19 and advised the doctors and dentists to close their practices.

As other health workers, the dentists are at risk of COVID-19 infection due to exposure to hazards such as pathogen exposure, including long working hours, psychological distress, stigma, and fatigue [21]. The treatment component should be strengthened to reduce the case fatality [22].

General Recommendations on COVID Prevention

Although, the newly confirmed cases would continue to decline and the total confirmed cases will reach a peak around the end of February of 2020 under the current control measures [15]. But until now, the cases are increasing in many countries in America, Europe, and Asia. Hence, the timing of returning to work should be evaluated carefully, given a different strength of protection and control measures.

The best way of prevention of COVID-19 is well informed about the COVID-19 virus and its transmission. Washing hands or using an alcohol-based rub frequently and not touching our face can prevent its transmission [23]. In Thailand, people have followed social distancing of 1-2 meters in public places such as restaurants, shopping places, public transports, hospitals, elevators, banks, and on a motorbike taxi [Figure 2]. These all helped to reduce the number of new COVID-19 infected cases.

At this time, the academic institutions and schools are closed in ASEAN countries. The academic institutions can implement online lectures for the students for the prevention of COVID transmission [Figure 3]. For the prevention and treatment, the various vaccine is being tested but the efficacy needs to be verified for vaccine development against COVID-19 [24].

Recommendations on COVID-19 Prevention in Dentistry

Oral health is affected in the pandemic and disaster situations similar to the situation of the

Figure 2: The social distancing of 1-2 meters for COVID prevention in Thailand

COVID-19 pandemic [25], [26]. Hence, the dentist should manage oral health problems and prevent the spread of COVID-19 in dental practice. Figure 4 shows patient screening flow chat for COVID-19 and dental treatment [23]. A detailed medical history of the patients and their family members should be asked upon their arrival in the dental clinic, such as contact with COVID-19 infected people, history of fever, and travel history in the last 14 days.

Figure 3: Online delivery of lecture for prevention of COVID

The temperature of the patient must be measured using a non-contact thermometer. The temperature can be measured with a camera having infrared thermal sensors. Patients having a fever (38°C or >100.4°F) and/or symptoms of COVID-19 should be differed in his/her elective dental treatments for >2 weeks. The patients with suspected COVID-19 should be kept in a separate and well-ventilated waiting area farther than 6 ft from other people [27]. Patients should be instructed to wear a mask and cover the mouth and nose while coughing or sneezing [28]. After the patient's self-quarantine, they were instructed to contact the physician to rule out the COVID-19.

The dentists may need to manage various dental emergencies in the COVID-19 pandemic period. Emergency dental treatment might be needed for dental trauma and oral infections. The symptomatic irreversible pulpitis is the most common dental emergencies in a COVID-19 period [29]. In emergency cases, vital pulp therapy can be done, reducing treatment time and reducing the risk of further infection. The pharmacologic management (antibiotics and/or analgesics) may be an alternative in COVID-19 infected cases, and the patient can be referred to a suitable place for further treatment afterward. The dental practitioners should be aware of the following things:

- Dental practitioners must follow the guideline from the WHO or CDC, including personal protective equipment (PPE) and hand hygiene [21], [27]. It is advisable to use N95 marks and reuse
- A mouth rinse containing 0.2% povidone-iodine [30], [31] or 0.5–1% hydrogen peroxide [32] helps to reduce the CoVs; hence, they can be used before a dental procedure
- Disposable instruments such as mouth mirror, diagnostic probes, and syringes can be used to prevent cross-contamination [23]
- For intraoral radiographs, sensors can be a double barrier to avoid perforation and contamination [33]
- A rubber dam (covers the nose) can be used to minimize splatter generation [29]

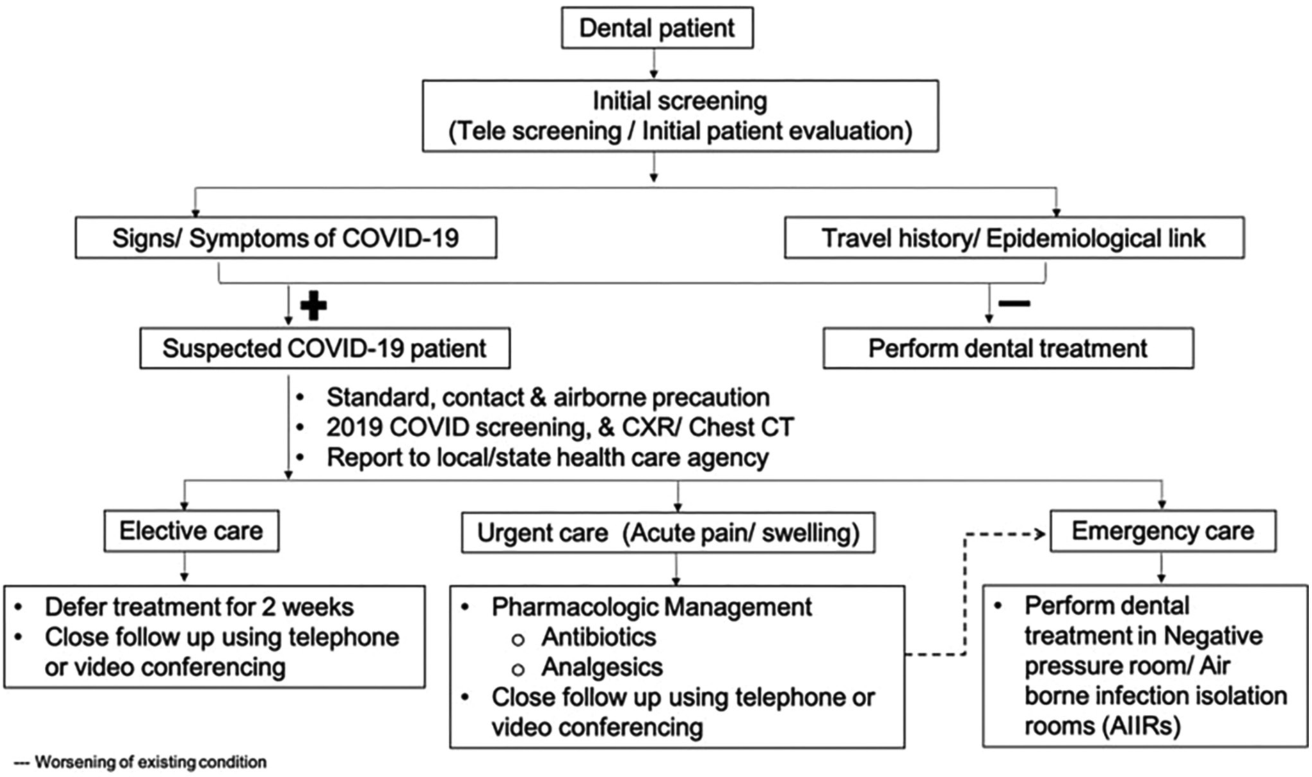

Figure 4: Patient screening for COVID and dental treatment [23]

- Reduce the use of ultrasonic instruments, high-speed handpieces, and 3-way syringes to prevent contamination from aerosols [23]
- The dental treatments of suspected or confirmed COVID-19 patients must be done in separate, airborne infection isolation rooms (AIIRs) or negative-pressure treatment rooms. Good knowledge and positive attitude of health-care staff toward COVID-19 and AIIRs can assist dentists in providing dental treatment [34], [35]
- SARS CoV-2 is viable in the air for about 3 days [36]. Therefore, the inanimate clinic surfaces must be disinfected using chemicals to prevent its spread.

Conclusions and Recommendations

In ASEAN countries, Singapore has the maximum number of COVID-19 infections cases followed by Indonesia. The dentist and dental practice are severely affected by the COVID-19 virus. Hence, the timing of returning to work should be evaluated carefully, given a different strength of protection and control measures. Dental professionals have the duty to treat dental treatment protecting the public. The dental procedures should be done with high standards of care and infection control by following proper recommendations. PPE, patient screening, hand hygiene practices, mouth rinsing, disposable instruments, and use of rubber dam, reducing ultrasonic instruments use, treating suspected or confirmed COVID-19 patients in separate rooms, and disinfection of the inanimate surfaces helps in protecting clinicians and patients.

Authors' Contributions

KS designed the manuscript. KS wrote the manuscript. Both KS and SW contributed to the final version of the manuscript. SW edited the manuscript.

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Epidemiological Characteristics of COVID-19 in Seremban, Negeri Sembilan, Malaysia

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Abstract

BACKGROUND: Coronavirus disease (COVID)-19 has become a global pandemic with an increasing burden on healthcare. Early recognition of the trend and pattern of the chain of transmission is necessary to slow down the spread.

AIM: Therefore, the study aimed to describe the epidemiology of COVID-19 at a local setting.

METHODS: A retrospective cross-sectional study was done to all COVID-19 cases registered in Seremban Health District. Statistical analysis, using Chi-square test, was employed to compare the sociodemographic characteristic of COVID-19 patients between the red zone area and the non-red zone area in Seremban.

RESULTS: As of April, a total of 214 number of COVID-19 cases reported in Seremban district alone. The trend of cases registered has changed as more asymptomatic infection outnumbered patients with clinical symptoms from the aggressive active case detection (ACD) activity. Majority of the cases affecting Malay ethnicity were due to a large religious gathering event held 1 month earlier than subsequently spread the infection within the community.

CONCLUSION: The first wave of COVID-19 cases in Seremban was sudden and unexpected, with a skewed distribution affecting a particular race group regardless red zone area and non-red zone area. Therefore, identifying the pattern of infection in the local community is important for a focused intervention strategy. ACD strategy, isolation of patients, quarantine the exposed, tracking down the close contact, and continuous health promotion and education will ultimately break the chain of transmission.

Introduction

Coronavirus disease (COVID)-19 is a global pandemic and has caused a significant impact to live, economic and social perspectives [1]. The disease transmission dynamic was beyond imagination as initial postulation centered around zoonosis etiology, but subsequent study confirmed human to human transmission [2]. Current recorded cases have surpassed three million cases worldwide, with the United States of America is on top of the chart. While vaccine development is still underway, many countries have employed containment strategy by ramping up testing, active contact tracing, isolating the exposed, as well as treating the positive case. Some countries go beyond hard policy change that limits gathering or imposing movement restriction, which has been predicted by machine learning to reduce infectivity rate by 7.8% [3].

In Malaysia, the earliest recorded cases were dated back in January 2020 and have closed contact with infected persons in Singapore. As of April 17, 2020, Malaysia has reported a total of 5251 number of cases with 86 deaths [4]. As for Seremban district, we reported the first case of COVID-19 about 3 months after the beginning of Wuhan epidemic and quickly become the top three districts with the highest number of cases in Malaysia. To date, almost all of the cases could be epidemiologically linked and pointed to a specific source of exposure. A thorough analysis to describe the characteristics of the COVID-19 case is vital to plan for focused and optimal intervention. Thus, this study provides an analysis of epidemiological data for the basis of the local prevention plan.

Methods

This was a retrospective record review cross-sectional study from February until April 2020 obtained from the Seremban Health District Crisis and Preparedness Respond Centre Surveillance System. Each of the registered COVID-19 cases was investigated thoroughly by the Health Inspector, and subsequently, a formal report was submitted containing all the demographics and epidemiological information. The definition criteria used were in accordance with the Ministry of Health (MOH) Malaysia guideline. A confirmed case was defined by a positive real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) from samples taken either through nasopharynx swab or oropharynx swab. An asymptomatic COVID-19 case was defined as a positive RT-PCR but without clinical symptom. A cluster of COVID-19 was defined as two or more confirmed cases or asymptomatic cases found with strong epidemiological linkage, that is, significant-close contact with positive cases or have travel history to an epidemic country (World Health Organization).

Statistical analysis

All the data were extracted and tabulated into Microsoft Excel 365 and licensed SPSS version 23.0 (borne by the author) was used in data analysis and producing relevant chart. The epidemiological characteristic and trend were described. Chi-square test was done to compare the sociodemographic difference between the red zone and non-red zone area.

Ethical approval

The study has been approved by the Medical Research and Ethics Committee of the MOH Malaysia and registered with the National Medical Research Register.

Result

COVID-19 incidence, mortality, and case-fatality rates (CFR)

As of April 10, 2020, a total of 214 number of COVID-19 cases were reported in Seremban district that account for 69.3% of the total number of cases for the whole state of Negeri Sembilan. However, these 214 cases were unevenly distributed among eight sub-districts; that is, sub-district Ampangan recorded the highest number of cases (76 cases) while sub-district Lenggeng only recorded 9 cases of COVID-19, Figure 1.

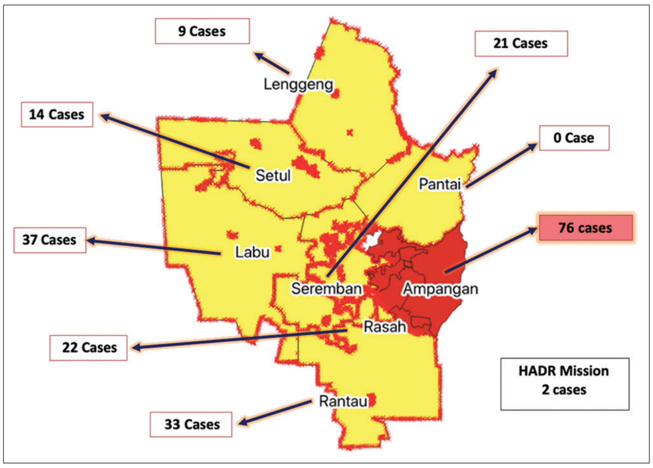

Figure 1: Distribution of coronavirus disease-19 cases in Seremban district as of April 10, 2020

Therefore, mapping of the area based on a number of cases has been used by the MOH Malaysia to allow stratification of the risk. By definition, sub-district with recorded more than 41 number of COVID-19 cases will be classified as a red zone area. The red zone area is considered high risk for the spread of COVID-19 as more than 41 COVID-19 cases were clustered in the area and have the potential to become a new epicenter of the outbreak if it is not well controlled. To date, only sub-district Ampangan was registered as a red zone area for the district of Seremban. The demographic and characteristic of all the cases were described in Table 1.

Table 1: Demographic and characteristic of COVID-19 patients

Variables	Red zone n=78 (%)	Non red zone n=136 (%)	χ^2	p-value
Age, y, mean (SD)	44.9 (17.6)	42.4 (17.6)	0.985	0.33*
Age, y, range			2.225	0.56
≤19	8 (10.3)	12 (8.8)		
20–39	19 (24.4)	46 (33.8)		
40–59	34 (43.6)	51 (37.5)		
≥60	17 (21.8)	27 (19.9)		
Gender			0.247	0.67
Male	42 (53.8)	78 (57.4)		
Female	36 (46.2)	58 (42.6)		
Ethnicity			14.162	0.001#
Malay	76 (97.4)	113 (83.1)		
India	0 (0.0)	12 (8.8)		
Chinese	2 (2.6)	3 (2.2)		
Non-citizen	0 (0.0)	8 (5.9)		
Co-morbidity			0.758	0.90#
None	57 (73.1)	100 (73.5)		
1 Co-morbid	9 (11.5)	15 (11.0)		
2 Co-morbid	9 (11.5)	18 (13.2)		
≥3 Co-morbid	3 (3.8)	3 (2.2)		
Symptoms			0.216	0.93
Asymptomatic	30 (38.5)	54 (39.7)		
Fever only	10 (12.8)	19 (14.0)		
Fever with any URTI symptom	21 (26.9)	33 (24.3)		
No fever but with URTI symptom	14 (17.9)	25 (18.4)		
Other symptoms	3 (3.8)	5 (3.7)		

*Independent t-test; #Fisher's exact test.

The incidence rate of COVID-19 in Seremban district for the first wave of outbreak as of April 10, 2020, was 311 cases per 1,000,000 population. There was 5 recorded death due to COVID-19, which makes the CFR of 2.3%. All mortality cases were Malaysian, Malay race, age range 41–64-year-old and had a significant co-morbidity of chronic disease.

Distribution of COVID-19 cases by onset and diagnosis

On 4th March marked the beginning of widespread of COVID-19 local transmission. Based on Figure 2, it is crystal clear to notice the earlier rapid rise in the number of onsets before the spikes in the number of detected cases. Nevertheless, toward the end of the phase, the number of cases has exceeded the number of onsets as a result of an extensive active contact tracing program conducted by the Seremban Health District Office. As per MOH guideline, all positive cases of COVID-19 will be admitted to the designated hospital and received standard treatment protocol based on severity classification.

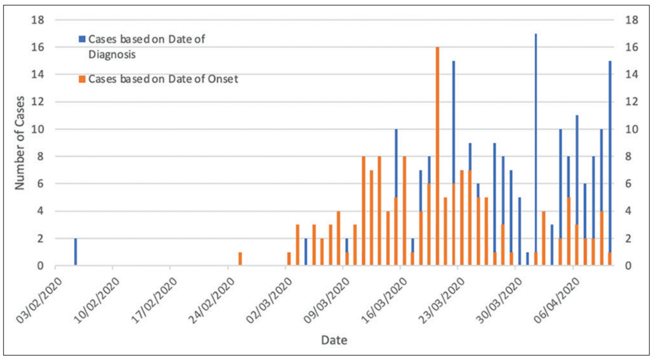

Figure 2: Epidemiology curve showing distribution trend of coronavirus disease-19 cases based on date of diagnosis and date of first symptom onset

Distribution of cases of COVID-19 by identified clusters

The two earliest recorded COVID-19 cases in Seremban district (based on Figure 2) were from Humanitarian Assistance and Disaster Relief mission that was aimed to retrieve the Malaysians which was stranded in Wuhan, the epicenter of the COVID-19 world pandemic. Both of them were treated in the Seremban General Hospital. A total of 107 passengers were brought home during the mission, and those with no acute illness and negative COVID-19 test has undergone 14-days of quarantine in a designated academy in Seremban. The first wave of local transmission began in early March arise from the cluster of multi-conglomerate cases. Only three registered cases in Seremban district were attributed to this cluster as those who involve were limited to the board members of the company. Hence, the circle of contact was scared. Immediately after, the ongoing transmission of local COVID-19 spread to date has been largely attributed to a cluster of Islamic congregations gathering at Sri Petaling that was assumed to house as many as 16,000 participants. This cluster accounted for 72.3% (157 cases) of the total registered cases in Seremban. Despite all this, only 8 cases of COVID-19 in Seremban district were attributed to healthcare worker (HCW).

Further analysis to compare sociodemographic differences among patients who live in red zone and non-red zone area revealed no statistically significant result for all the variables measure except for ethnicity. Malay race was particularly affected during the first wave of COVID-19 outbreak in Seremban district for both red zone and non-red zone area.

Discussion

Many nations employed total lockdown or massive restriction of movement approach to combat the unprecedented COVID-19 outbreak worldwide. Despite the health benefits in controlling the disease, it causes severe economic disruption to the nation that can lead to a recession. Hence, there should be a balance in employing public health countermeasures when striking COVID-19 pandemic. Early diagnosis will lead to early treatment and rapid isolation of the confirmed cases. Mass screening may not be possible during the early phase of an outbreak due to unpreparedness to handle such event. Thus, targeted screening approach is best suited to achieve the early detection goal. However, a set of criteria need to be established to ensure a suitable target group. This can be done by studying the epidemiology of the current outbreak and subsequently translate the findings to be used at ground zero (field).

One of the initial steps taken by the MOH in response to the growing outbreak is to stratify the district into three categories, namely red zone, yellow zone, and green zone (zero COVID-19 cases). Each zone received similar public health interventions, but the red zone areas were given more priority due to the highest potential risk of COVID-19 transmission. Furthermore, it was observed that the red zone area in Seremban is densely populated.

Our study found that a higher proportion of cases affected were adult group (mean aged 43 years) regardless of the zones. The finding is similar to other studies done before [2], [5], [6]. [7]. These groups of population are likely to be inactive and constant contact with the world due to their nature as the working population and the breadwinner of the family [8]. Hence, making them more susceptible to COVID-19 infection and subsequently passes on the transmission to other family members [9]. Despite the fact that the proportion of male is seen to be more than female who contracted COVID-19 for both zones, but it was not statistically significant. This could be due to the unspecific nature of virus pathophysiology with no selective gender preferences, as seen in other epidemiological studies [7], [10], [11], [12].

Apart from that, our study revealed that the risk of getting COVID-19 infection did not associate with the presence of co-morbidity of a person. Therefore, it should be an alarming feature for everyone to be more vigilant to look after themselves. Although the risk of infection is less affected by the variable, there is growing evidence that co-morbidity may lead to poorer outcome such as in severe cases and mortality cases; especially those with hypertension or diabetes [13], [14].

In Seremban district, Malay ethnicity represents a significant proportion of COVID-19 cases as compare to the others. The figure is not serendipitous as simple reasoning might be caused by a disproportionate population composition of the country. However, the main explanation was that the Malays ethnicity made up 100% of the participants in the major outbreak; Islamic congregation at Sri Petaling mosque. Hence, by applying the possible mean reproduction time (R0) and the secondary attack rate, the number may increase by at least a factor of 2 [15], [16]. Although COVID-19 cluster among HCW was very minimal, the fraternity must not be too complacent but continue to be vigilant to ensure uncompromised manpower. To ensure minimal exposure risk of the medical personnel, they must have abundant access to all the personal protective gear [17], [18] that is suitable for the threat that they are facing. Nevertheless, they need to be given sufficient education, training, and updated information about COVID-19.

Overall, there is no difference in terms of clinical presentation between the zones. Common presentations were fever and upper respiratory symptoms, which are similar findings in other studies [2] [11], [12], [19]. However, the proportion of asymptomatic patients was the highest in our study due to the extensive contact tracing program. The health authority will activate an active case detection protocol each time a COVID-19 test came back positive. Nevertheless, proactive action by the Seremban Health District conducting a continuous screening program at the entry border, regardless of symptom presentation, led to higher detection of asymptomatic cases [20].

The ultimate aim of early detection, early treatment, and rapid isolation of positive cases is to quickly break down the chain of transmission. The cost of such interventions is very much less if more population are infected with COVID-19 and ended up being treated in the hospital or intensive care unit. In response to the pandemic, the Malaysian health authority has been collaborating with other agencies to achieve the goals. Mobilization of human resources and utilizing vehicles from other departments to be used for targeted screening and isolating confirmed cases were made possible from good national leadership. Quarantine centers were set up to monitor the high-risk relatives or contacts to the positive cases. These people underwent COVID-19 testing after careful epidemiology links were established with the confirmed cases. As mentioned, early detection of COVID-19 cases before symptom development is key to flatten the epidemiology curve when there is evidence of pre-symptomatic transmission of the virus [21].

As mentioned, the factor that triggered the spread of COVID-19 infection within Seremban district in this first wave of the outbreak was related to a religious gathering. Despite no reported any ill attendee during the 3-day event, the resultant outcome of COVID-19 infection was still catastrophic. Combining the mode of transmission and the pre-symptomatic transmission of the virus, it would easily make one at risk for the infection by just being in close proximity with an index case. The situation will be made worse if no space available for social distancing, inadequate hand hygiene facility, or improper usage of face mask by those attending the event. Hence, it is recommended to postpone any informal activities involving huge gathering and held in a confined space until COVID-19 curve has flattened.

Our findings should be interpreted carefully due to some limitations. The primary limitation is that our data only limited to only 234 confirmed cases which were bounded to the set of culture and tradition of Seremban population. This single-center (district) study limits the number of samples. Finally, detailed clinical information was not available due to a lack of follow-up.

Conclusion

Based on our data analysis, COVID-19 infection was easily transmitted in Seremban district following the introduction of a potential source to a susceptible population. The first wave of local transmission occurred abruptly. The epidemiology of the outbreak was largely skewed toward a certain particular race group. A rapid and coordinated response by the health authority in collaboration with other relevant agencies has successfully made early detection of cases before symptom presentation. This strategy, together with the quarantine of those exposed with a negative result, as well as isolating and treating the positive cases, will ultimately break the chain of transmission. Nevertheless, individual and community must play their biggest part by keeping safe distance social distancing, frequent handwashing or sanitizing, and keeping good cough or sneeze etiquette.

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COVID-19 and the Fourth Burden of Women in Developing Countries: A Mini Review

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Abstract

It is known that women experience heavier physical and psychological burdens more than men. This is closely related to the traditional role of women because of the absence of women's authority in themselves. In the coronavirus disease (COVID)-19 pandemic situation, the role of women has increased, namely taking on a protective role. With this additional burden, the physical and psychological burden on women becomes heavier and has the potential to create health problems in the future. In this mini review, the authors discuss the potential impact of implementing the COVID-19's prevention protocol on women's lives. It was concluded that there were serious and very large potential consequences for women, in terms of physically, psychologically, or emotionally; thus, early anticipations are really needed.

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Introduction

It has been almost a year that coronavirus disease (COVID)-19 has caused suffering to all people in the world. Based on WHO data, until the middle of September 2020, COVID-19 has created suffering for about 30 million people in the world. Based on a report from Africa and South-East Asia region only, the number of people affected has reached 6.5 million [1]. Unfortunately, until now, there is no vaccine available even though vaccine trials are being carried out by various parties [2].

The immediate impact of COVID-19 is clear. At present, the number of deaths has reached 921,801 deaths [1]. Initially, there was concern about death in the elderly because their immunity is more vulnerable. However, recent data show morbidity rates in a much younger age group. For example, Indonesia notes that half of the positive cases are in the 19–45 year age group [3]. Meanwhile, in England, the 20–39 year age group has up to 10 times the risk of those over 70 years of contracting COVID-19 [4]. These facts show that the current mortality rate is no longer very different for all age groups.

The economic impact of COVID-19 is also visible [5]. The World Bank explained that there has never been a recession so severe, so fast, and so deep since 1990. In addition, this recession is predicted to bring tens of millions of people into extreme poverty [6]. The achievements of the global community during the last 15 years could be instantly collapse so that the global targets that have been formulated in the Sustainable Development Goals are likely to fail [7]. United Nations Development Programme has warned that COVID-19 is not only a health problem but has very serious consequences for the economy and social life [8].

However, one of the impacts that still escapes in-depth discussion is the burden on women. This article is a mini review that will discuss the impact of COVID-19 on women's lives, especially in developing countries, because, until now, there are still too few things about it. This is understandable because the impact of COVID-19 on women may only be felt for some time to come considering that the world community is now focusing on the direct impact of COVID-19. However, if this burden is not anticipated at an early stage, it is not impossible that serious consequences will occur in the lives of women.

Traditional Role

In many developing countries, women are often regarded as responsible parties in the traditional role, which are: Productive, reproductive, and social sectors [9]. This occurs because the practices of patrilineal norms do not provide space for women to have sufficient autonomy over themselves [10], [11]. This patrilineal norm maintains the ideal things that must be done by women throughout their life. This norm has been practiced for a long time so that it is not easy to release women from the responsibilities that have become their traditional roles. The norms that place a huge burden on women are no longer questioned so that they are considered the truth [12], [13].

These burdens then cause various health problems for women which can be seen from various indicators. The best example is maternal death. According to the WHO, in 2017, nearly 300 thousand women died during pregnancy and childbirth. That means that every day there are 810 cases of maternal deaths, and 90 percent of them occur in developing countries [14]. This means that in 1 h, about 33 pregnant women died. At this time, maternal mortality ratio in Indonesia is equal to 359/100,000 live births [15].

Maternal death represents a major impact of the women's traditional role. Apart from the direct cause, maternal death cannot be separated from the fact that women do not have autonomy over themselves. A pregnant woman is considered to have no right to herself so that even her own reproductive health decisions, including examining her own pregnancy, let alone recognize danger signs in pregnancy, and even deciding where to give birth, are not in her hands. The low health status of women [15], [16] producing delay after delay in every stage of the pregnancy process, due to decision making by parties outside the pregnant mother, causes pregnant women to experience fatal conditions [17], [18].

Gender inequality is also associated with another issue that has a major impact on women, namely mental health. One of the manifestations of mental disorders is depression, in which women are twice as likely as men [19], [20]. It has been proven that with gender roles that are not too different, the prevalence of mental health disorders in women is reduced [21]. This means that in developing countries where the traditional role of women is still very strong, women are more at risk of experiencing mental disorders because, in these countries, these women experience "structural gender inequity, measured at the macro or societal level" [22]. As explained by WHO, gender affects all structures of society, including in terms of differences in the occurrence of mental health impacts [20].

The two things above have adequately represented the manifestation of the impact of the traditional role of women which is still ongoing in developing countries. In other words, the persistence of the traditional role of women is one of the causes behind women's health problems. Unfortunately, this heavy burden is often maintained by state policies [23], including during the COVID-19's pandemic.

New Normal Policy

The new normal policy implies the enactment of various important provisions designed by the state to be obeyed by everyone. The provisions have a lot to do with activities from within the family. Among them are washing hands frequently, cleaning the house, consuming healthy food and drinks, including maintaining body immunity.

The Centres for Disease Control and Prevention (CDC) has provided very detailed guidance on preventing the transmission of COVID-19 in households. The guide explains that every house must apply two important principles, namely cleaning and disinfecting [24]. Both of these things must be done in all components of the house such as doors, tables, lamps, or kitchen apparatus. In addition, the CDC complements the manual with technical guidelines that contain detailed procedures necessary for household use [25]. The technical guidelines are also provided in full by WHO, according to the conditions suitable for the individual [26].

It is true that these guidelines are of course made to help everyone avoid the spread of COVID-19 because COVID-19 has now formed household clusters. As a new disease, of course, the entire guide seems very complete and detailed. However, as in the traditional context of roles above, given the very dominant role in the household, it is clear that this heavy burden inevitably ends up being carried by women. Guidelines for handling COVID-19 seem to be made to be implemented by none other than women.

In an atmosphere where every country in the world has entered "new normal," it is clear that women's burden is not lighter; instead, it is multiplying. Apart from the three burdens that had been affixed to her, women must now bear the fourth burden, namely the protective role. The protective task is the role of women in protecting family health to avoid the virus that causes COVID-19.

With a protective role, it is women who play a role in ensuring that the implementation of health guidelines for the prevention of COVID-19 is obeyed by family members. These good practices must be carried out obediently by all family members because the COVID-19 transmission currently relies on prevention through the family. This is where the protective role of women is seen. In this role, women must ensure that all family members carry out clean and good living arrangements and are able to protect the family.

To prevent COVID-19 transmission in the family, for example, according to the recommendation, every family member must no longer use clothes that have been worn from outside the home. The clothes must be removed immediately and then washed. It is the women who then wash the clothes of all family members, in addition to the routine of washing clothes that they usually do. In developing countries, the availability of clean water is not easy. Women usually have to transport clean water from its source, which is generally quite far away. Imagine how much more burden a woman has to do to protect her family's health.

In addition, women are also the ones who guarantee food and drink for their families. In developing countries, it is women who have a role in fulfilling family needs, including food hygiene and health.

To ensure that food and drinks from outside the house must be guaranteed cleanliness, it is often women who go directly to shop and interact with the traditional markets, where the COVID-19 cluster often occurs. Such activities put women at risk of exposure and or being a carrier. Likewise, to increase body immunity, family members must eat nutritious foods and take vitamins. Those who buy and regulate their use are generally women.

Ironically, for family members to stay healthy, women often choose to maintain the house alone, not wanting to be accompanied, thereby increasing the workload that must be completed alone. Hence, many to-do lists that must be made to be done by women.

This protective role activity clearly had a significant impact on the health of women's bodies, particularly housewives. Physically, women are overloaded because in addition to working on traditional roles, now they have to do new things that are very important and very draining, namely preventing their families from being exposed to COVID-19. Psychological impacts are also expected to occur, although they will only be seen in the future. Even though the COVID-19 guidelines state that everyone's immunity must be maintained in an effort to fight severe acute respiratory syndrome coronavirus 2 virus infection, but it seems that this recommendation does not apply to women. It is not surprising that, based on the survey in Asia Pacific continent, women experience a much higher level of stress than men [27]. This survey, although only represented by a few countries in the region, provides preliminary information on this issue in the world, particularly in developing countries.

With this fourth burden, women's position is getting heavier. Increasing the burden will be increasing women's health risks. This condition, unfortunately, is never be anticipated in implementing the new normal policy. Hence, it can be concluded that the new normal policy is a policy that has a negative impact on the women's lives today and in the future.

Conclusion

The COVID-19 pandemic is not yet over. Meanwhile, while the traditional roles of women still cause serious problems for women, now women have to bear the burden of protective roles. Great efforts are needed to prevent the impact of these major roles on women's physical and psychological health.

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Epidemiology, Prevention and Control Strategies of Coronavirus COVID 19 in Iran: A Systematic Review

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Abstract

BACKGROUND: Following the announcement of the World Health Organization (WHO) on January 30, 2020, of coronavirus disease (COVID)-19 as a global and emergency state of international health emergency; posing a serious threat to the physical health and lives of individuals transmitted through respiratory droplets and close contact. The virus causes respiratory symptoms and damages to other organs, sometimes leading to death in case of exacerbation of symptoms.

AIM: This study was conducted through reviewing various articles related to COVID-19 disease, with the purpose of reviewing the epidemiology, prevention and control strategies of COVID-19 coronavirus in Iran.

METHODS: In the present review study, the articles indexing in the Persian and Latin databases of SID, Magiran, PubMed, Scopus, Scholar, Web of Science, Embase, MedRxiv, and WHO were examined based on MESH keywords. Finally, 38 articles, 5 protocols and reports were reviewed.

RESULTS: According to the report of the WHO on July 22, 2020, 14,765,256 people worldwide have been infected and 612,054 people have died of this virus. Moreover, in Iran, according to the WHO report, 278,827 people were infected and 14,634 people died of the virus until July 22, 2020. Respiratory droplets are the main way of transmission and it can also be transmitted through close contact. According to research, 51% of patients with chronic disease show symptoms such as fever (83%), cough (82%), shortness of breath (31%), muscle pain (11%), fatigue (9%), headache (8%), sore throat (5%), had rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%). There is currently no specific antiviral treatment or vaccine for severe acute respiratory syndrome coronavirus 2, and clinical treatment for COVID-19 has so far been limited to prophylaxis and palliative care. Quarantine alone is not enough to prevent the spread of COVID-19. Basic health measurements to prevent the spread of the disease include frequent handwashing and the use of personal protective equipment such as masks.

CONCLUSION: Extensive research can be the key to solve the existing challenges in the prevention, control, diagnosis, and treatment of the disease. The best ways to fight the new corona disease include educating the people, providing accurate information, providing personal protective equipment, canceling meetings and emphasizing citizens homeliving and regular handwashing, observing social distancing, and finally identifying suspicious cases and quarantine.

Introduction

On January 7, 2020, the pathogen was identified as the new coronavirus, now novel coronavirus (nCOV)-2019, or coronavirus disease (COVID-19), which is a virus distinguished from both severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) is distinct [1], [2]. With the spread of this endemic disease in China, other cases of it were observed outside of China [3]. On January 30, 2020, the World Health Organization (WHO) declared it a public health emergency a International public health emergency in the world [4]. As of July 22, 2020, 14,765,256 people have been infected worldwide and 612,054 people have died of the virus. Furthermore, in Iran, according to the WHO report, as of July 22, 2020, 278,827 people were infected and 14,634 people died due to the virus [5].

According to current epidemiological research, the incubation period of the disease is 1–14 days (mostly 3–7 days) [6]. The virus is transmitted mainly through respiratory droplets and close contact and is observed in human respiratory epithelial cells for about 96 h, first invading the lungs and causing serous fluid, fibrin exudate, and the formation of a hyaline membrane in the alveoli. Becomes [7], which causes respiratory symptoms such as dry cough, dyspnea, fever and eventually pneumonia, acute respiratory failure, acute respiratory distress syndrome, and other multiple organ failures [8], [9]. Furthermore, many patients with COVID-19 have gastrointestinal symptoms such as anorexia, abdominal pain, nausea and vomiting, and diarrhea even before the onset of respiratory symptoms [10]. A study found that about 40% of cases suspected of having COVID-19 had symptoms. Anorexia, 10% had diarrhea, 8% had non-specific abdominal pain, and 8% had nausea and vomiting [11].

The highest mortality and morbidity occurred in the elderly and those with underlying disease. Children and infants are also vulnerable to this disease [12], [13]. According to the National Health Commission of China, the death rate in cases confirmed in China was 2.2% as of February 4 [14], and among hospitalized patients, the mortality rate was between 11% and 15% [6] [15]. To increase the safety of patients and to prevent cross-infection in respiratory infectious patients (such as influenza, COVID-19) can be used contact precautions, air precautions, and droplet precautions [16]. However, treatments supportive drugs are mainly used because there is currently no specific effective treatment [17] and currently the main focus is on the development of new drugs, including antivirals and vaccines [18]. Most people infected with or without mild symptoms can spread the virus and transmit it to others, which is very challenging to prevent the spread of COVID-19. Therefore, strict monitoring is very important to prevent sustainable transmission [19]. In the first period, the new coronavirus, many studies were published on the epidemiology, causes, manifestations, and clinical diagnosis and prevention and control of the virus. However, studies examining prevention and control measures have gradually increased. To minimize the impact of prevalence, it is necessary to study in this field [20].

Countries such as Taiwan and Vietnam have been able to control Corona by doing some strict hygiene measures, including invasive tests, quarantine, tracking contacts with polluted environment, and border monitoring. Likewise, Korea could decrease epidemy by applying invasive tests, quarantine, accompanied by physical distant measures. On the other hand, China could control the epidemy using some strategies such as compulsory quarantine and invasive tests [21]. Moreover, the hygiene system, as well as the community of Iran, has been greatly affected by this epidemy disease [22]. Regarding the severity of the disease, the hygiene system provides some plans to deal with the disease. However, because of the extensive dimensions of the disease, there would have been so much pressure on the hygiene care systems so much that it might not be able to compensate its loss regarding its different dimensions. These dimensions include financial problems, social tension, and hygiene system not responding to the patients. Therefore, cooperation and collaboration of the society with the health system would be influential in control and preventing the disease [23].

Since coronavirus 19 is the third most dangerous pandemic virus emerged in the 21st century and is one of the most prevalent diseases [19], [20] with high mortality and morbidity rate during the disease pandemic which has developed worldwide, although the effective vaccine to prevent it has not yet been made. In the current situation, the only logical way to control the disease and reduce its effects and mortality rate is to use ways to prevent the disease. Hence, the present study was conducted aiming at reviewing the epidemiology, prevention and control strategies relevant to coronavirus 19. Moreover, no similar systematic review study has not been conducted in Iran, this study has been done to review the epidemiology, preventive, and COVID 19 controlling strategies systematically.

Methods

The aim of this study was to review and classify the findings of Latin and Persian articles relevant to COVID-19 disease, epidemiology, symptoms, ways of control and prevention, as well as existing challenges by reviewing articles published by foreign and Iranian authors in international and local journals about COVID disease-19. In the present review study, articles indexed in Persian and Latin databases of SID Magiran, PubMed, Scopus, Scholar, Web of Science, Embase, MedRxiv, and WHO were examined. The search terms regarding the research topic, based on MESH and syntax, were: COVID-19, coronavirus, deltacoronavirus, SARS-CoV-2, MERS-CoV, SARS virus, prevention, and prevalence, prevention and control strategies. In total, throughout the present study, on the basis of the above-mentioned keywords, initially 525 articles, reports, and protocols of reputable health organizations were studied, as well as the entry and extract criteria of the articles were scrutinized. After studying the titles and abstracts of articles by the authors of the article and excluding the similar and unrelated items, the relevant items were selected as research items and 38 studies and 5 protocols and reports were reviewed based on the abstract and full text of the articles (Figure 1). Due to the widespread and increasing prevalence of the disease and the changes in the statistics related to the prevalence, the statistics presented in this study are until July 23, 2020. Criteria for selecting articles are:

1. Descriptive, analytical, interventional, and review articles published in the past 5 years.
2. Persian and English articles published in scientific research journals in and out of the country, the full texts of which were available.
3. Articles related to epidemiological studies, control strategies, and prevention of coronavirus 19.

Criteria for excluding articles were: Articles that did not have the full text, articles that did not have clear implementation methods, and articles that focused only on treating the disease rather than ways to prevent and control the disease.

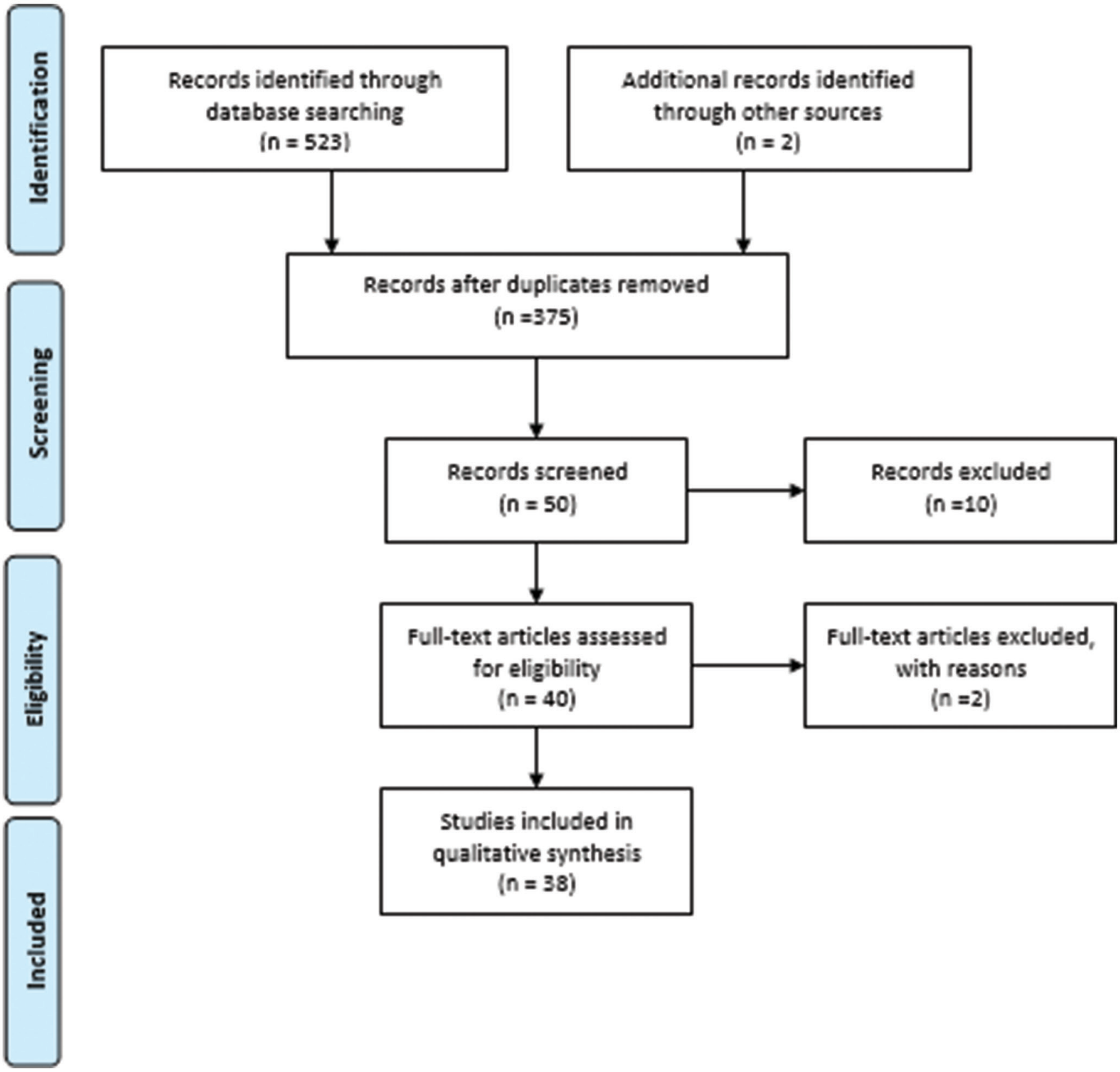

Figure 1: Flowchart for selection of studies

To investigate and analyze the papers elicited from searching databases, which were assessed and qualified according to input and output criteria determined in the methodology, four researchers participated in the research. The flowchart for the selection of studies was illustrated in Figure 1.

Results

Epidemiology

Throughout history, many infectious diseases such as HIV, Ebola, Zika, and H1N1 have been emerged [21]. In addition, the Ebola virus outbreak in 2014 and the Zika virus outbreak in 2015 both caused significant damages to countries [21]. The coronavirus is an RNA virus weighing 80–120 nm. It is divided into four types: Alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. The recombination rate of COV is high due to high transcription errors. Despite its high mutation, coronavirus has genetic pathogens that occur in humans and animals with a wide range of clinical symptoms from the asymptomatic period to the need for intensive care, infection of the respiratory, gastrointestinal, hepatic, and nervous systems [23]. Human coronavirus was neglected long before the onset of severe acute coronavirus syndrome (SARS-COV) in 2002, and in 2002, in 8096, cases with a 10% of mortality rate. Fortunately, public health measures, including isolation and quarantine, brought SARS to an end in the summer of 2003. After that, the

MERS-COV is another coronavirus that has been a constant global health threat since 2012. The disease was reported in South Korea due to an infected person traveling from the Middle East, where in 2015, 186 cases and 36 deaths were reported. As of November 2019, MERS-COV has infected 2944 people and killed 858 [22].

In December 2019, a new beta-coronavirus was temporarily renamed coronavirus 2019. It was later formally renamed as acute respiratory syndrome 2 (SARS-COV2) by the International Committee for the Classification of Viruses (ICTV). Coronavirus 2019 (COVID-19) was named SARS-COV-2 [24]. It is the seventh type of coronavirus that causes infection in humans after SARS-COV and MERS-COV and alike them is a beta subset of coronavirus [23]. On January 30, the WHO declared COVID-19 as an international emergency concern. nCOV-2019 is the third most dangerous pandemic virus that emerged in the 21st century. It is also one of the epidemic diseases [22].

In no time, scientists began researching the source of new coronavirus, and the first COVID-19 genome was extracted on January 10, 2020, by a research team led by Professor Zhang Zhang. The new virus spread across China within a month of the Chinese New Year. As of December 29, 2019, the first four cases of acute respiratory syndrome of unknown cause were reported in Wuhan, Hubei Province, China, among people associated with the local seafood market [20]. Most of the sufferers were at the exposure of wild animals offered at Wuhan Seafood Wholesale Market. Chickens, snakes, bats, and other domestic animals were also sold in this market. The scientists' findings showed that bats and minks may be two potential hosts for the new coronavirus, while bats were more similar to the new coronavirus in terms of infection pattern than mink. Thereafter, the China Center for Disease Control and Prevention surveyed seafood market products in southern China, concluding that the virus came from wild animals sold in the market. However, Lost's report on 41 infected patients challenged the finding that "no epidemiological link was found between the first patient and the next." The data showed that, in total, 13 of the 41 had no connection to the market. Person-to-person transmission of coronavirus was confirmed by Chan *et al*., who reported that one person infected five members of the family [25]. The new coronavirus outbreak occurred during the Spring Festival in China, China's most famous traditional festival, with nearly 3 billion people attending across China. These conditions have brought about proper conditions for the transmission of this highly contagious disease and severe problems in the prevention and control of the epidemic. The city of Wuhan has been the epicenter of the disease with a population of about 10 million [24]. From December 31, 2020, to January 3, 2020, a total of 44 cases of this new respiratory disease were reported by Chinese authorities to the WHO. As of July 22, 2020, 14,765,256 people have been infected worldwide and 612,054 people have died of the virus. Furthermore, in Iran, according to the WHO report, as of July 22, 2020, 278,827 people were infected and 14,634 people died due to the virus [26]. To date, the main source of infection has been patients with nCOV-2019. Respiratory droplets are the main way of transmission and can also be transmitted through close contact. Although many details, such as the source of the virus and its ability to spread among individuals, are yet unknown, an increasing number of cases indicate the transmission from human to human [27]. The researchers also detected SARS-COV2 in stool, saliva, and urine samples. Based on bioinformatics evidence, it was shown that the gastrointestinal tract could be a potential route for SARS-COV2 infection. In addition, SARS-COV2 was observed in the tear and conjunctival secretions of COVID-19 patients. Meanwhile, a retrospective study of 9 pregnant women with COVID-19 showed for the 1st time that the possibility of vertical intrauterine transmission between mothers and infants in late pregnancy was temporarily ruled out. However, research is not adequate and more research is needed in this regard [23]. The infection is transmitted through large droplets sent out by coughing and sneezing by symptomatic patients but may also be transmitted by asymptomatic individuals. These droplets can spread 1–2 m and remain on the surface. The virus can survive in suitable weather conditions for days but can be killed in less than a minute by common disinfectants such as sodium hydrochloride and hydrogen peroxide. The infection can be transmitted to a healthy person either by inhaling these droplets or touching the infected surface and then touching the nose, mouth, and eyes. Studies show that angiotensin 2 receptor acts as a receptor through which the virus enters the respiratory mucosa [28] (Table 1).

Symptoms

According to the current epidemiological study, the incubation period is generally from 3 days to 7 days and a maximum of 14 days. Unlike SARS-COV, nCOV-2019 is contagious during the commune period [27]. However, many different results have been reported on the incubation period of this disease. Coronavirus SARS-COV2 reproduces efficiently in the upper respiratory tract. Infected people produce a large amount of the virus in their upper respiratory tract during an introductory period, which leads to more spread of the virus to other people. Coronavirus SARS-COV2 also infects cells in the lower respiratory tract and multiplies in these organs, causing lesions in the lower respiratory tract. Infection with the new SARS-COV2 new coronavirus is initially associated with nonspecific and general symptoms such as nausea, fatigue, and body aches, fever, and dry cough. Patients with pre-fever may initially have symptoms of nausea and diarrhea. A small number of patients may also have headaches or vomiting of blood. It may even be asymptomatic. Respiratory failure, septic shock, and extrapulmonary organ failure may also occur in severe cases [29]. In a study conducted by Chen *et al.*, 51% of patients with chronic disease and symptoms such as fever (83%), cough (82%), shortness of breath (31%), muscle pain (11%), fatigue (9%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), diarrhea (2%), and nausea and vomiting (1%) were reported [15]. Patients with cardiovascular disease, chronic disease, and people aged 60 and over, and men have a higher risk of mortality than the rest of the population. Next clinical findings is including: increasing the number of white blood cells, mostly neutrophils, with a decrease in lymphocytes, platelets and red blood cells. This new coronavirus infection causes more severe illnesses in the elderly, pregnant women, people with chronic debilitating diseases such as diabetes, cardiovascular disease, and malignancy [31].

Prevention and Control

Lack of specific clinical features, diagnostic microbiological challenge of the new coronavirus outbreak, together with seasonal flu, make difficult COVID-19 to diagnose. Furthermore, clinical signs such as high fever and respiratory symptoms are very similar to previous features of coronavirus. There is currently no specific antiviral treatment or vaccine for SARS-COV2, and clinical treatment of COVID-19 has so far been limited to prophylaxis and palliative care [22]. In the absence of appropriate treatment measurements to overcome the virus, the best ways to deal with are to prevent the spread of infection and control the sources of infection. All sections of society, including employees, employers, and workers, must be fully prepared to repel the coronavirus, even if the corona epidemic has not yet reached that country or region [32]. Prevention of this disease, if divided into two levels, individual and social, will be as follows:

Individual Prevention

1. Use personal protective equipment such as masks [33]; 2. Do washing and disinfecting hands, especially after touching surfaces in public places; 3. Prevent the spread of respiratory droplets when coughing or sneezing with a mask and other protective equipment; 4. Avoid touching eyes, nose, and mouth; 5. Avoid attending in crowded places and close contact with people; 6. Disinfect the centers that are most exposed to touch [34]; 7. Stay at home when you feel disease; 8. Abstain from smoking and any action that causes damage to the lungs; 9. Follow the government guidelines [35]; 10. Do not share your personal items such as towels, bedding, either at home or at work [36]; 11. Wash your personal items with soap and water after using [37]; 12. Do not shake hands nor hug others when greeting in the workplace or home; 13. Avoid crowded public means of transportation and crowded centers such as hospitals, clinics, and any other public places; 14. Avoid physical contact with pets such as touching, petting, kissing, or eating together; 15. If animal care is necessary, wear a mask and wash your hands before and after touching pets; 16. Stay home for 14 days in case you are returning from areas with COVID-19 [36]; and 17. Wearing a simple surgical mask by patients [33].

Social Prevention

1. Restrictions on travel, especially international travel; 2. Screening of people in offices when entering and controlling for signs [34]; 3. Observance of the social distance of at least 2 m to reduce exposure and cut the transmission chain; 4. Cleaning and disinfecting infected surfaces and items in cities to eliminate and inactivate the virus [38]; 5. Quarantine and movement restrictions in infected areas; 6. Early identification of infected people; 7. Provide appropriate care for patients; 8. Identify and reduce transmission from animal resources; 9. Minimize social and economic impact through multispectral partnerships [30]; 10. School closures [41]; 11. Use of appropriate equipment, including N95 masks and protective clothing and goggles by health care providers [22]; 12. Preventing sick employees from entering the workplace; 13. Giving compulsory sick leave to sick or suspected employees; 14. Separating and isolating patients and suspects from other employees; 15. Establish proper ventilation systems in workplaces; 16. Use glass or plastic barrier between staff and clients or visitors; 17. Use of disposable tools and equipment; 18. Continuous training the employees regarding the observance of hygienic rules, handwashing, and how to use protective equipment; 19. Reducing staff working hours; 20. Reducing unnecessary missions and trips of employees; and 21. Restricting staff gatherings in sports and religious centers and holding remote meetings [32].

Quarantine alone is not enough to prevent the spread of COVID-19. A lot of countries have done controlling measurements, including a combination

Table 1: Research on epidemiology and prevention and control strategies of coronavirus COVID 19

Title	Authors	Year	Study selection	Samples	Results	Ref.
Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures	Wang *et al.*	2020	Review	92 articles	Majority of infected individuals with no or mild symptoms can release viruses and spread viruses to others, which is extremely challenging for preventing the spread of COVID-19. Active interventions, including nutrition supplement, symptomatic treatment, and antiviral treatment are critical for mild patients as well as severe patients. Prophylactic vaccination is highly demanded for future prevention of emerging coronavirus related epidemics or pandemics	[19]
Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review	Adhikari *et al.*	2020	Review	65 articles	This study shows a holistic picture of the current research in response to the outbreak of COVID-19. Most studies have focused on the epidemiology and potential causes. However, studies exploring prevention and control measures have begun to gradually increase. Studies in this domain are urgently needed to minimize the impact of the outbreak	[20]
Pandemic fear and COVID-19: Mental health burden and strategies	Ornell *et al.*	2020	Review	26 articles	It is extremely necessary to implement public mental health policies in conjunction with epidemic and pandemic response strategies before, during and after the event. Mental health professionals must be on the front line and play a leading role in emergency planning and management teams	[24]
2019 novel coronavirus (2019-nCoV) outbreak: A new challenge	Lupia *et al.*	2020	Review	225 articles	The new 2019-nCoV epidemic is mainly associated with respiratory disease and few extrapulmonary signs. However, there is a low rate of associated pre-existing respiratory comorbidities	[25]
A review of coronavirus disease-2019 (COVID-19)	Singhal	2020	Review	32 articles	Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors, the SARS-CoV and MERS-CoV, but has lower fatality	[26]
2019 novel coronavirus (COVID-19) outbreak: A review of the current literature	Sahin *et al.*	2020	Review	36 articles	Coronaviruses will cause spreads and outbreaks with different-mutant strains similarly in the coming years. With increased scientific collaboration, which is a result of globalization, we may have more powerful means of fighting against coronaviruses, in which we know the genome structure very well in the future	[27]
2019 novel coronavirus: Where we are and what we know	Cheng and Shan	2020	Review	32 articles	By fitting the number of infections with a single-term exponential model, we report that the infection is spreading at an exponential rate, with a doubling period of 1.8 days	[28]
A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia	Jin *et al.*	2020	Review	38 articles	This rapid advice guideline is suitable for the first frontline doctors and nurses, managers of hospitals and healthcare sections, community residents, public health persons, relevant researchers, and all person who are interested in the 2019-nCoV	[29]
A review of the 2019 novel coronavirus (COVID-19) based on current evidence	Wang *et al.*	2020	Review	73 articles	This review in the hope of helping the public effectively recognize and deal with the 2019 novel coronavirus (SARS-CoV-2) and providing a reference for future studies	[30]
Novel coronavirus disease 2019 (COVID-19): An emerging infectious disease in the 21st century	Tavakoli *et al.*	2020	Review	53 articles	The outbreak caused by the novel coronavirus is larger than the previous human coronaviruses; however, the mortality rate of COVID-19 is lower than that of other coronaviruses diseases such as SARS or MERS and other viruses. At present, due to the lack of an effective treatment and vaccine, the best way to deal with the COVID-19 disease is to prevent transmission and spread of the virus and to execute personal protective measures	[31]
COVID-19 and substance use disorders: Recommendations to a comprehensive healthcare response	Mokri *et al.*	2020	Review	128 articles	In this paper, an international group of experts on addiction medicine, infectious diseases, and disaster psychiatry explore the possible raised concerns in this issue and provide recommendations to manage the comorbidity of COVID-19 and substance use disorder (SUD)	[32]
Novel coronavirus 2019-nCoV: Prevalence, biological, and clinical characteristics comparison with SARS-CoV and MERS-CoV	Meo *et al.*	2020	Review	18 articles	The 2019-nCoV has epidemiological and biological characteristics, making it more contagious than SARS-CoV and MERS-CoV. Although the fatality rate of MERS-CoV was higher than them. The major clinical manifestations in coronavirus infections 2019-nCoV are fever, chills, cough, shortness of breath, generalized myalgia, malaise, drowsy, diarrhea, confusion, dyspnea, and pneumonia. Global health authorities should take immediate measures to prevent the outbreaks of such emerging and reemerging pathogens across the globe to minimize the disease burden locally and globally	[33]
Approaches for COVID-19 infection control in the workplace. Occupational Medicine. 2019	Rafeemanesh *et al.*	2019	Review	19 articles	All members of the society, including employers, employees and laborers, should be completely ready to overcome the virus, even if the epidemic has not been spreading in that country or area. This point can be effective on the reduction of lost workdays, work absenteeism, and prevent the spread of the virus in the community	[34]
Review on the symptoms, transmission, therapeutics options and control the spread of the disease of COVID-19	Irani	2020	Review	22 articles	The extensive functions have been carried out to reduce person-to-person transmission of COVID-19. In this review, the symptoms, epidemiology, transmission, pathogenesis, phylogenetic analysis, and future directions to control the spread of this fatal disease have been presented	[35]
A review of the new 21st century coronavirus (novel coronavirus-2019)	Ghaderi *et al.*	2020	Review	47 articles	Accordingly, it is considered a serious global threat and all necessary precautions should be taken in the event of any suspected case. Experiences from (MERS) and (SARS) highlight the importance of rapidly finding the source for 2019-nCoV to stem the ongoing outbreak	[36]
Coronavirus: Origins, signs, prevention, and management of patients	Hill	2020	Review	17 articles	It is important that, in these difficult times, nurses understand the symptoms of COVID-19, how to prevent its spread, and are up-to-date on the guidance on critical care	[37]
Coronavirus disease (COVID-19) outbreak and the strategy for Prevention	Sajed and Amgain	2020	Review	6 articles	Eradication of highly contagious SARS-CoV-2 virus that causing the ongoing deadly pandemic COVID-19 demands individual attention and awareness is necessary regarding the route and mode of transmission across the bounders throughout entire world. Proper handwashing, staying in-home, and maintaining the social distance are proved to be the most effective preventive measures which are immediate solution to save human being from this unseen enemy	[38]

(Contd...)

Table 1: *(Continued)*

Title	Authors	Year	Study selection	Samples	Results	Ref.
Modeling transmission and control of the COVID-19 pandemic in Australia	Chang *et al.*	2020	Review	58 articles	School closures are not found to bring decisive benefits unless coupled with high level of social distancing compliance. We report an important transition across the levels of social distancing compliance, in the range between 70% and 80% levels. This suggests that compliance of below 70% is unlikely to succeed for any duration of social distancing, while compliance at the 90% level is likely to control the disease within 13–14 weeks when coupled with effective case isolation and international travel restrictions	[39]
2019 novel coronavirus (COVID-19) pandemic: Built environment considerations to reduce transmission	Dietz *et al.*	2020	Review	96 articles	We hope this information can help to inform the decisions and infection control mechanisms that are implemented by corporate entities, federal, state, county, and city governments, universities, school districts, places of worship, prisons, health care facilities, assisted living organizations, daycares, homeowners, and other building owners and occupants to reduce the potential for transmission through BE-mediated pathways	[40]

of increasing hygienic acts, travel restrictions, case diagnosis, contact tracking, and remote activities. Their overall goal is to reduce the number of contacts of the population, thus preventing the transmission of infection [24]. While many common precautions are being taken to stop the spread of SARS-COV2, other less common transmission pathways should be considered and taken to reduce the spread [42]. The effectiveness of school closures is limited, although a 2-week delay in the peak of the epidemic does not have a significant effect on the peak size of the disease [41]. The greatest risk of COVID-19 is transmission to health care workers. At the outbreak of SARS in 2002, 21% of these people were affected by health care workers. Protecting the transmission of infection to other patients is important. Patients should be placed in separate rooms or next to each other. Negative pressure in rooms is generally not required [22].

Discussion

Research studies which assess the rate of COVID-19 interventions are limited and even if they are available, they either consider just one intervention, or they had been done in other fields of study. Therefore, the present study would be influential in dealing with disease by providing some major perspectives elicited from the collection of papers through investigating controlling, as well as personal and social preventive strategies.

Numerous features of the virus make it difficult to prevent, including non-specific features of the disease, infection even before the onset of symptoms during the incubation period, transmission from asymptomatic individuals, long incubation period, prolongation of the disease, and transmission even after its clinical improvement [26].

There is no single intervention to adequately control or reduce the epidemic of the disease. A combination of several influential measures such as keeping the social distance, doing several diagnostic tests, and identifying positive cases would probably decrease the burden of the epidemic. However, it is essential to start synergic treatment earlier and continue appropriately. If following social distance and strict measures to diagnose the cases and tracking them start earlier but stops in <6 months, the disease burden and mortality rate would increase again, growing the demand for receiving hygienic care. While in doing early, invasive and long interventions, it would be easier to control the disease for a longer time. It seems that diagnosing marked patients, separating, intervening proceeding is the footstone of each successful controlling strategy [23].

Regarding recent findings, almost half of disease transmissions maybe before the symptom occurrence phase [43]. Therefore, keeping the social distant and keeping schools off to reduce personal contacts are logical and important ways. While dealing with an uncontrollable disease, hygienic systems of the countries with limited sources are significantly under pressure; thus, the morbidity and mortality rate would be 2 times of expected amount. If an uncontrollable disease is updating itself, even adding the number of hospital beds significantly does not work to decrease the mortality rate [23].

Several challenges have been posed by the COVID-19 epidemic, one of which is that the true extent of COVID-19 and the scale of its possible prevalence are not known precisely, and the actual number of infected and suspected patients is not identifiable [44].

Extension of corona resulted in a decrease of enormous economic and social offices all over the world. To decrease the financial loss resulted from the disease, as well as to support the small, stricken careers, most countries consider protective acts such as grants and tax reductions [45]. The propose theory is that it is possible that people are tired of following the long intervention; moreover, doing social distance can result in unwanted hygienic, economic, and welfare consequences, the subject that would probably affect strongly on a lot of countries who do not care on following the social security principles [46], [47].

The mortality and transmission rate of patients with COVID-19 vary in different findings [48].

On the other hand, more studies should be done on the following: How the virus is easily transmitted among people? How can it affect vulnerable subgroups such as the elderly or people with chronic diseases? What is the source of the virus? And how can it spread worldwide in such a short period of time [49]. Another challenge is whether nCOV-2019 disease is transmitted directly from bats or through an intermediate host. Wang *et al.* stated that one of the challenges is that "time is so limited that we cannot fully account for all the clinical problems with this emergency; second, much of the evidence from data retrieval is indirect" [5]. One of the existing problems is social media. In addition to sharing content quickly, social media also quickly spreads rumors, misunderstandings, and intimidation [20]. Only extensive research can be the key to solving the existing challenges and we hope that future studies will focus on the development of COVID-19 vaccines and effective drugs to treat them to reduce mortality.

Conclusion

According to studies and reports, the best way to overcome new corona disease is to prevent new cases and control the disease. Given the unknown characteristics of COVID-19, it is recommended that all organizations work to prevent and control the disease and break the transmission chain. To achieve this goal, the best solution is to educate the community, provide accurate information, provide sufficient personal protective equipment, allocate funds to fight the disease, abolish all communities, and emphasize on citizens staying home and washing their hands regularly, observe social distance, providing adequate diagnostic and treatment facilities, establishing fever measuring rooms in all stations, airports and public places, and finally identify suspected cases and quarantining.

The uncontrollable epidemic of COVID-19 has the potential to lead to a huge amount of death, strengthening with unanswered demand to hygienic measures. Results indicate that the best strategy is to control facing epidemic is a combination of interventions aiming at diagnose, reducing the contact, through some physical actions, and doing quarantine for infected people. Restricting the measures would prevent the extension of the epidemic, but if additional control measures would not be implemented, it would probably low in value.

It is essential that all managers, employers, and business owners be provided with the necessary information and training on prevention and control of COVID 19 disease based on health guidelines and protocols to reduce the number of patients and prevent the spread of the disease in society.

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COVID-19 and COVID-like Patients: A Brief Analysis and Findings of Two Deceased Cases

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Abstract

BACKGROUND: The predominant pattern of lung lesions in patients affected by coronavirus disease (COVID-19) disease is diffuse alveolar damage with massive thromboembolism similar as described in patients infected with severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronaviruses. Hyaline membrane formation and pneumocyte atypical hyperplasia were frequent. Importantly, the formation of platelet–fibrin thrombi in small vessels was seen consistent with coagulopathy, which appeared to be a common feature in patients who died of COVID-19. However, many were the cases found with similar COVID-19 symptomatology though negative results from nasal-pharyngeal swab performed by reverse transcription-polymerase chain reaction (RT-PCR). This latter typology of patients, otherwise named COVID-like, showed analogous clinical signs with similar arterial blood gas, cell blood count and laboratory parameters, and same computed tomography (CT)-scan ground-glass opacities. Symptoms such as cough, fever, and difficulty breathing were highly similar as well. Both forms, COVID-19 and COVID-like, are primarily respiratory with multi-organ involvement and both revealed comparable incubation periods often with a rapid onset and unexpected decay.

CASE REPORT: In this brief paper, we described two cases regarding two deceased males, one confirmed COVID-19 (RT-PCR but not CT scan) and the second a COVID-like (negative for RT-PCR but positive to CT scan with ground-glass opacity) whom condition, disease patterns, and analysis were highly similar.

CONCLUSION: Improved investigation is mandatory, in which RT-PCR and CT scan procedures are completed by data from more detailed laboratory analysis, ABG analysis, BALF, and a deeper clinical assessment.

Introduction

At the beginning of the current year, Italy was suddenly involved in the current coronavirus disease (COVID)-19 pandemics, and many thousands of patients have been recorded [1]. Nowadays, the main accepted procedure to confirm the positivity to COVID-19 is based on the nasopharyngeal swab analyzed by reverse transcription-polymerase chain reaction reverse transcription-polymerase chain reaction (RT-PCR). However, the limits of this procedure in diagnosing the disease are well known. The main issue is related to the low specificity of the procedure in verifying the presence of both false negatives and false positives; the second issue is due to mistakes related to the manual procedure by the health personnel; and third the possibility that virus has moved downward and settled within lungs, generating negative swab results. In addition, specimen tested without proper internal control could bias the results [2], [3], [4].

In our experience, the presence of COVID-like patients represented an important number (n ≥ 60) (data not showed) and 2 patients out of 60 underwent bronchi-alveolar liquid test (bronchoalveolar lavage fluid [BALF]) resulting positive to severe acute respiratory syndrome coronavirus (SARS-CoV-2). Therefore, we do not exclude that among COVID-like patients may remain someone that was eventually infected by SARS-CoV-2 but resulted negative to the swab screen. Nevertheless, clinical and laboratory outcomes showed substantial similarities between SARS-CoV-2 and COVID-like patients which sharing pathophysiological features related to specific traits of severe and interstitial pneumonia with clinical presentation greatly resembling each other's [4], [5].

It follows that the RT-PCR negative results should not be conclusive of SARS-CoV-2 infection-free status and should not be used as solely indicator in the decision making treatment plan in suspected COVID-19 cases. Hence, we proposed a new diagnostic protocol that eventually includes the clinical observations, patient history, BALF, blood, and specimen results with thoracic computed tomography (CT) scan essential in making the final conclusion.

It should be also added that SARS-CoV-2, with more than twenty million individuals infected worldwide, still remains unknown in many aspects, which includes the way the virus spreads and cooperates with other pathogens affecting the lungs and different organs such as heart, kidney, liver, and brain. In-fact, metatranscriptomic sequencing performed on BALF obtained from COVID-19 affected patients exposed a significant presence of bacteria highly similar to those found in patients affected by non-COVID-19 pneumonia. In addition to SARS-COV-2 infection, it was seen to contribute to the overall complications and worsening condition of patients with pre-existing comorbidities such as diabetes, cardiovascular disease, cancers, and kidney deficit, often leading to death [6], [7], [8], [9].

In this study, we prepared a comprehensive evaluation of two deceased patients; first patient (negative to swab-RT-PCR) admitted to 118 Pre-Hospital and Emergency Department of SG Moscati Hospital of Taranto City in Southern Italy, which is one of the designated hospitals assigned by Italian Government for patients severely or critically ill with COVID-19. The second patient was a confirmed COVID-19 (positive to swab-RT-PCR) admitted to Emergency Department and then moved to ICU Department of Civic Hospital of Cantu' City in Northern Italy. We aimed to compare these two patients, COVID-19 and COVID-like, both presenting similar clinical features and symptomatology with tight superimposable laboratory and analysis findings, including arterial blood gas (ABG) results and cell blood count (CBC).

Case 1

The first case was a 51-year-old man, Caucasian admitted to 118 Emergency Hospital of SG Moscati Hospital in Taranto City, transported with "yellow code," in April 24, 2020. The symptoms were dyspnea, tachypnea accompanied by fever, and general malaise that commenced between 19th and 20th of April. At that time, the family Doctor prescribed steroids (betamethasone) and anti-histamines. The situation dramatically declined during the following days to the point had to be admitted into 118 Emergency Department (triage) in the early evening (20:00 pm), where he started receiving the adopted protocol of suspected COVID-19 composed of methylprednisolone, ceftriaxone, enoxaparin sodium, azithromycin, and oxygen therapy.

Of note, the ABG analysis (ABG) assessed the presence of pH alkalosis, with hypoxia and hypocapnia. The CBC revealed a clinical characterized of neutrophilia and lymphopenia associated with high levels of inflammatory markers such as C-reactive protein (CRP), interleukin 6, D-dimer, and troponin with a low level of e-GFR and vitamin D. The nasopharyngeal swab analyzed by RT-PCR was negative and the CT scan showed the ground-glass opacity (Table 1).

At the beginning, the patient responded positively to the therapy and doctors assessed amelioration, the patient was aware, responsive, and attentive; the breathing was also better and, the fever sloped as well. The revised trauma scores were optimal confirmed by the Cincinnati Prehospital Stroke Scale that was normal.

However, around 23:10 same evening, unexpectedly the patient's condition suddenly worsened while he was moving to the Imaging Department to receive a CT scan (Figures 1a and b). Within a short time, the patient started showing symptoms of severe respiratory distress with hypotension, tachypnea, and hypoxemia and almost immediately entered into an irreversible comatose state. The electrocardiogram (ECG) performed at that time showed a sign of tachycardia with right axial deviation suggestive of ongoing respiratory distress and associated with an ongoing myocardial infarction (QRS-T complex) (Figure 2).

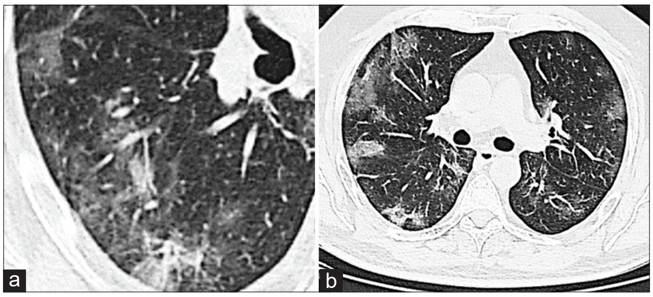

Figure 1: (a and b) Computed tomography scan of a coronavirus from a patient in SG Moscati showing ground-glass lesions in the lungs bilaterally soon before his situation worsened

The patients died soon after, the death was confirmed by the medical coroner at 00:10 AM of April 25, 2020.

Autopsy examination and findings in case 1

Autopsy was performed in accordance with Italian NIH protocol and instruction. The whole procedure was completed in a thorough airborne infection isolation autopsy room with the use of appropriate protective tools and shields [10].

The trunk and abdomen were covered by hyperemic patches in a layer-like distribution. The heart presented few abnormal features described as follow:

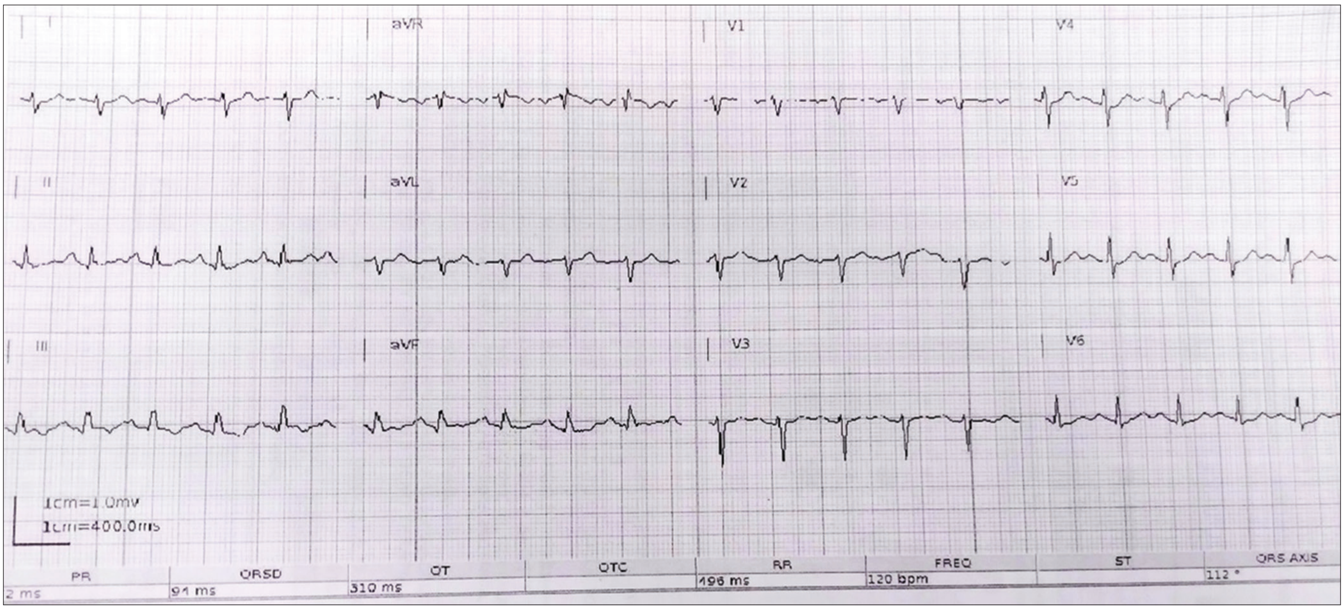

Figure 2: The electrocardiogram (ECG) performed at the time of the admission showed tachycardia with a right axis deviation and evident problem in the ventricular repolarization mechanism. The precordial V1-V6 was suggestive of myocardial infarction in process. In general, the ECG has confirmed a key tool in prognostic value in coronavirus disease (COVID)-19 patients showing a variety of underlying cardiovascular conditions, such as hypertension, offering a particularly attractive methodology current COVID-19 pandemic [9]

Table 1: The vital signs at the time of the entrance of patient n. 1 (COVID-like)

Patient 1 male 51 years	Vital signs – normal ranges	CT scan	RT-PCR swab
Arterial pulse	140/100	Ground glass	negative
Body temp.	37.5°C		
Heart rate	120/min		
Respiratory rate	22.min		
O_2 sat.	85%		
Glucose	119 mg/dL (74–100)		
ABG	pH 7.493 (7.35–7.45)		
	PO_2 52.4 (75–100)		
	PCO_2 25.3 (35–45)		
eGFR	83,73 ml/min (>90)		
Total bilirubin	2.20 mg/dl (0.50)		
Direct bilirubin	040 mg/dl (0.20)		
Indirect bilirubin	180 mg/dl (0.30)		
Fibrinogen	586 mg/dl (200–400)		
Troponin	54.400 ng/L (<14)		
CRP	28.2 mg/L (<3.5)		
D-dimer	13.30 mg/L (<0.5)		
25OH-vitamin D	23.1 ng/ml (>45)		
IL-6	222.3 pg/ml (<7)		
Total WBC	15.21 $10^3/mm^3$ (3.59–10)		
Neutrophilia	80.7% (35–75)		
Lymphopenia	114% (20–55)		

COVID: Coronavirus disease-19, CT: Computed tomography, RT-PCR: Reverse transcription-polymerase chain reaction, ABG: Arterial blood gas, CRP: C-reactive protein, IL-6: Interleukin.

Globular shape and manifestly enlarged; abnormal condition of the oval foramen was seen as well; right atrial was enlarged and presented a concentrically hypertrophy of ipsilateral ventricle (thickness 1.2 cm); it was also seen the stenosis of pulmonary valve consequent of partial fusion of either right or left cuspid valves.

The lungs were found pleura-parietal and pleura-diaphragmatic adherent synechiae with modest pericardial serum effusion of about 100 cc. Upon macroscopic evaluation, the lungs were heavily congested and edematous. Bilaterally, the lower lobes showed topographies with dark-red colors consistently with hemorrhagic events, upper lobes were pink with atelectasis facets. Features were suggestive of an exudative and diffuse alveolar damage due to massive thromboembolism found in the right pulmonary artery with multiple occlusions of pulmonary arteries bilaterally mainly seen in the lower lobes. Thus, clots were located in the larger branches as well as in the periphery which means the clots were either thrombotic or embolic. It was confirmed the presence of aortic atherosclerosis.

Case 2

The second case was an 86-year-old man, Caucasian admitted to 118 Emergency Unit of Civic Cantu' Hospital in Cantu' City Northern Italy. The patient was accepted in "yellow code," in March 17, 2020, at 15:37. The assessed symptoms were dyspnea (PaO_2 87%) with breathing difficulties, tachycardia, together with fever, asthenia, anosmia, and loss of appetite accompanied by diarrhea, the symptoms commenced March 10th. The patient was sent to receive CT scan and blood test analysis. The CT scan revealed multiple small patches of ground-glass opacities, while the blood count results were considered all within the normality ranges. The patient had a story of ischemic attack and benign prostate hyperplasia, he was under anti-coagulants and anti-prostatic medications, and he started receiving antibiotics ceftriaxone. The patient was reacting well to the first line of therapy and doctors assessed a slight amelioration, the patient was aware and attentive, the breathing was as well. However, at 18:37, the patient started worsening and was considered critical (PaO_2 67%); thus, he received the CPAP O_2 mask. Later that night, condition decline further and CPAP was removed and an MV at 50% was instead positioned to the patient. The day after, March 18th, at 9:00 in the morning patient was considered non-responsive. Around 02:19 in the early morning of March 21st the patient was eventually assessed deceased.

The vital signs at the time of the entrance were as follow

The patient was continuously monitored during the time of his hospitalization. The first total CBC performed March 11, 2020, showed only a few abnormal parameters (Table 2).

The CBC and vital signs at the entrance showed a not alarming situation, with an arterial pulse of 160/90, no fever 36.3°C, the heart rate was acceptable with 120 b/min and respiratory rate 22/min. The patient was considered alert and responsive to stimuli; the revised trauma scores were normal; the Cincinnati Prehospital Stroke Scale was also normal (Table 2 for other levels and signs). However, the patients were saturating very low with an O_2 level of 91% (AA), the ABG analysis confirmed a critical condition with typical signs of pH alkalosis 7.568, hypoxia PO_2 30.5, and hypocapnia PCO_2 18.1. The ECG performed at the time of admission confirmed a sinus tachycardia with typical signs of an ongoing MI prevalently seen in precordial V1-6 (QRS-T complex) (Figure 3).

The second total CBC performed March 17, 2020, showed a completely different clinical scenario all metabolic, chemistry, and inflammatory parameters were suggestive of a fast worsening condition (Table 2).

Table 2: Results obtained from patient n.2 (COVID-19)

Patient 2 male 86 years	Vital signs – normal range	CT scan	RT-PCR swab
First check			
Arterial pulse	160/90	Ground glass	positive
Body temp.	36.3°C		
Heart rate	120/min		
Respiratory rate	22/min		
O2 sat.	91		
Glucose	115 mg/dL (74–100)		
ABG	pH 7.568 (7.35–7.45)		
	PO_2 30.5 (75–100)		
	PCO_2 18.1 (35–45)		
eGFR	46.20 ml/min (>90)		
Creatine	1.15 mg/dl (0.6–1.3)		
Chlorine	99 mEq/L		
Second check	Vital signs – normal range		
Glucose	180 mg/Dl (74–100)		
eGFR	37.1 ml/min (>90)		
Fibrinogen	602 mg/dl (200–400)		
Urea	81 mg/dl		
Troponin	6337 ng/L (<14)		
CRP	225.7 mg/L (<3.5)		
Pro-BNP	18800 pg/ml (<450)		
D-dimer	51977 ng/ml (<0.5)		
p-PT/INR	1.55 (<1.1)		
total WBC	20.16 10^3/mm^3 (3.59–10)		
Neutrophilia	89.9% (35–75)		
Lymphopenia	5.3% (20–55)		
Potassium	3.20 mEq/L (3.5–5.2)		
AST	90 U/L (40)		
ALT	57 U/L (55)		
LDH	1095 U/l (100–245)		
CPK	418 UI/L (		
CK-MB	11.70 ng/ml		

COVID: Coronavirus disease-19, CT: Computed tomography, RT-PCR: Reverse transcription-polymerase chain reaction, ABG: Arterial blood gas, CRP: C-reactive protein, IL-6: Interleukin.

Thoracic CT scan

The CT scan findings of COVID-19 are those of atypical pneumonia or organizing pneumonia. Pulmonary hilar were congested and enlarged in appearance, it was seen a diffuse reticular-nodular with a parenchymal consolidation characterized by bilateral ground-glass opacities evidently the expression of active inflammation (Figure 4a and b).

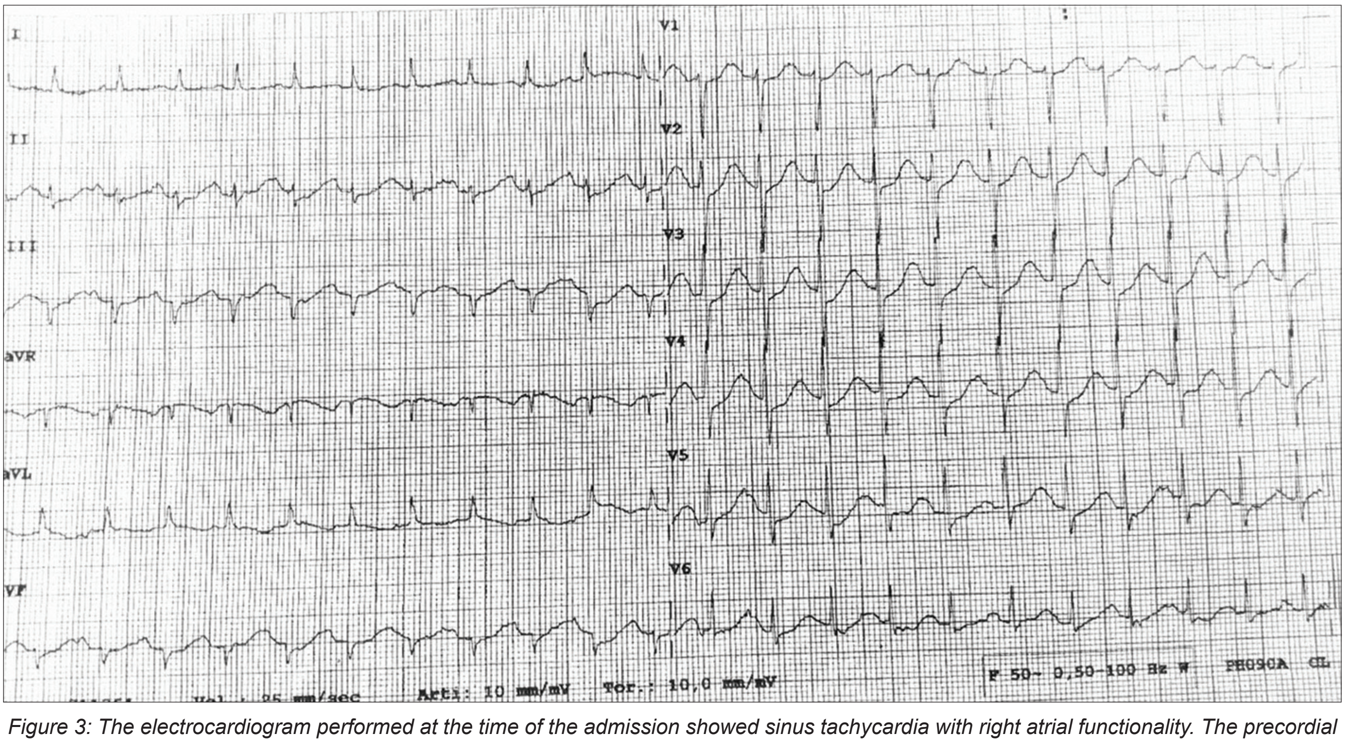

Figure 3: The electrocardiogram performed at the time of the admission showed sinus tachycardia with right atrial functionality. The precordial V1-V6 was indicative of myocardial infarction in process with ongoing angina. The patient died a few hours after for a massive severe cardiorespiratory collapse

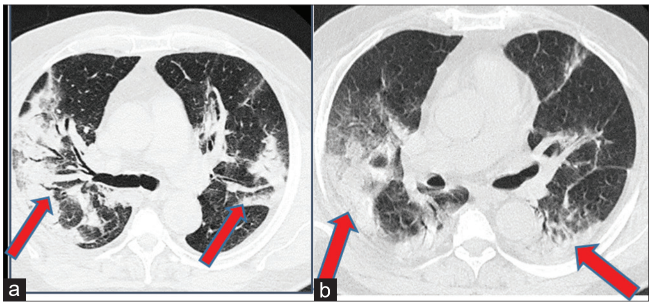

Figure 4: (a and b) Computed tomography scan obtained on illness day 1 shows a mixed pattern with an evident ground glass extent and atelectasis (red arrows) bilateral. The overall consolidation suggests the presence of organizing interstitial pneumonia

Discussion

Due to the rapid spread and the increasing number of COVID-19 infected patients, there is the need of more accurate evaluation of the virus to better control the sources of infection helping the population in preventing disease progression and spreading. Since December 2019, there have been considerable challenges especially in regarding the use of nucleic acid test (the nasal-pharyngeal swab by RT-PCR procedure), the CT scan, and the clinical physiognomies in trying to produce a standard orientation toward a more definitive diagnose of COVID-19 disease [11].

Nevertheless, at present, the diagnosis cornerstone remains in COVID-19 early-onset the positivity of RT-PCR and (only as secondary) the CT scan with the lung “ground glass” images and ABG analysis. This procedure would tend to exclude all those types of patients that we have titled COVID-like, which exhibit analogous symptoms and clinical picture of COVID-19 disease. The consequence of this diagnostic discrimination would eventually pose two fundamental and practical problems; first, the denial of having contracted the virus and thus being a potential contagious threat and second, the renunciation to consider the crucial results from the ABG and CT scan as predictive of more general worsening of the clinical condition due to virus infection.

The COVID-19 and COVID-like patients share many features, they manifest low-intensity symptoms that usually aggravate shortly before the admission to the hospital, commencing with unnoticeable episodes of increasing respiratory difficulties. Furthermore, the COVID-19 and COVID-like patients show also similar clinical and laboratory patterns, low fever, dry cough, and medium intensity headache; the ABG analysis shows an alkalotic pH, with low PaO_2 and low $PaCO_2$, low lymphocytes, high neutrophils, high fibrinogen, high troponin, high CRP, high D-dimer, low eGFR, and high ESR. Apparently, both types of patients seem to respond well to the preliminary therapy approach, and both types of patients reveal a similar sudden and unexpected deteriorating process that may end-up to severe hypoxia, hypocapnia, MOF, and then death.

In these short two case reports, our main aim was to highlight the similarities between COVID-19 and COVID-like deceased. COVID-like and COVID-19 share many common pattern of the infection much more than COVID-like would share with other pulmonary disease. Alarm has risen, especially after considering the deceptive good health of COVID-like individuals, which may become an exceptional contagious source. Important, the autopsy findings and post-mortem laboratory results performed on both COVID-19 and COVID-like deceased patients were all suggestive of a death consequent of an acute cardio-respiratory decay characterized by massive pulmonary thromboembolism accompanied by a considerable pulmonary hemorrhage as finally reported by few prominent published studies [13], [14], [15], [16].

Conclusion

While we are still learning and close to a second COVID-19 pandemic wave, there is still a lot that remains to be clarified about SARS-CoV-2. These short descriptive two case reports, which is just a part of wider and more extensive study yet to be published, are an attempt of comparing COVID-19 and COVID-like disease as we strongly believe that it would be of great importance to identify patients at very high risk of mortality as a result of an overlapping of risk factors that were separately reported in patients who died from COVID-19 or COVID-like. Subjects aged ≥45–90 years and suffering from pre-existing comorbidities such as diabetes, cardiovascular diseases, or kidney disorders are likely to be the elective target of prevention and diagnostic activities. This is the reason why an improved investigation is mandatory, in which RT-PCR and CT scan procedures are completed by data from more detailed laboratory analysis, ABG analysis, BALF, and a deeper clinical assessment.

Consensus

This brief report received an official written consensus from the family of the deceased patients.

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Section: *Narrative Review Article*

The Effectiveness of Probiotics against Viral Infections: A Rapid Review with Focus on SARS-CoV-2 Infection

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Abstract

Viral infections have gained great attention following the rapid emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic around the globe. Even with the continuous research on developing vaccines and antiviral agents against various viral infections, no specific treatment or vaccine has been approved for many enteric or respiratory viral infections; in addition, the efficiency of currently available treatments is still limited. One of the most reliable and recommended strategies to control viral infections is prevention. Recently, intense studies are focusing on a promising approach for treating/preventing various viral infections using probiotics. As per the World Health Organization (WHO), probiotics can be defined as "live microorganisms which, when administered in adequate amount, confer a health benefit to the host." The use of probiotics is a simple, cost-effective, and safe strategy to prevent viral infections, specifically; respiratory tract and intestinal ones, by different means such as stimulating the host's immune response or modulating gut microbiota. In this rapid review, we emphasize the protective effects of probiotics against viral infections and proposed mechanisms for protection that might offer a novel and cost-effective treatment against current and newly discovered viruses like SARS-CoV-2.

Introduction

The first scientific evidence regarding probiotics was made by Nobel laureate Metchnikoff, who sensed that the intake of non-pathogenic bacteria with yogurt had a positive influence on endogenous bacterial flora and gastrointestinal tract's functionality [1]. The term "probiotics" was first used in 1953 by Werner Kollath to describe inorganic and organic supplements of several foods used to improve the health of malnutrition patients [2]. In 1965, Lilly and Stillwell used the term "probiotics" to describe microorganisms that promote other microbial growth [3]. Later, FAO/WHO has defined probiotics as "live microorganisms which, when administered in adequate amount, confer a health benefit to the host [4]." Figure 1 illustrates some beneficial effects of probiotics on human health.

To be classified as a probiotic, the microorganism should have certain characteristics, such as having a human origin source, being non-pathogenic, being resistant to the intestinal environment, and having a beneficial effect on the immune system. The majority of the probiotic microorganisms are "generally recognized as safe, GRAS" [6]. Most lactic acid bacteria (LAB) and bifidobacteria have been described as probiotics [7], [8]. However, the most common probiotic microorganisms are listed in Table 1.

In addition to their important biological activities, the probiotics were previously defined to have antiviral activities. Ang *et al*. [38] have confirmed in this context that *Lactobacillus reuteri* is capable of protecting human skeletal muscles and colonic cell line against Coxsackievirus A and Enterovirus 71 infections. In addition, Galán *et al*. [39] have proven the antiviral activity of *Lactobacillus casei* and *Bifidobacterium adolescentis* against rotavirus infection. Moreover, *Bacillus subtilis* anti-influenza activity and *Lactobacillus gasseri* anti-respiratory sentential virus potential have also been proved by Starosila *et al*. and Eguchi *et al*., respectively. However, many other studies are being conducted to investigate the efficacy of probiotics against certain viral infections.

At the end of the year 2019, an etiological agent responsible for the outbreak of viral pneumonia was detected in Wuhan, Hubei Province, China, and spread rapidly around the world. Then, this new virus was named by the International Committee on

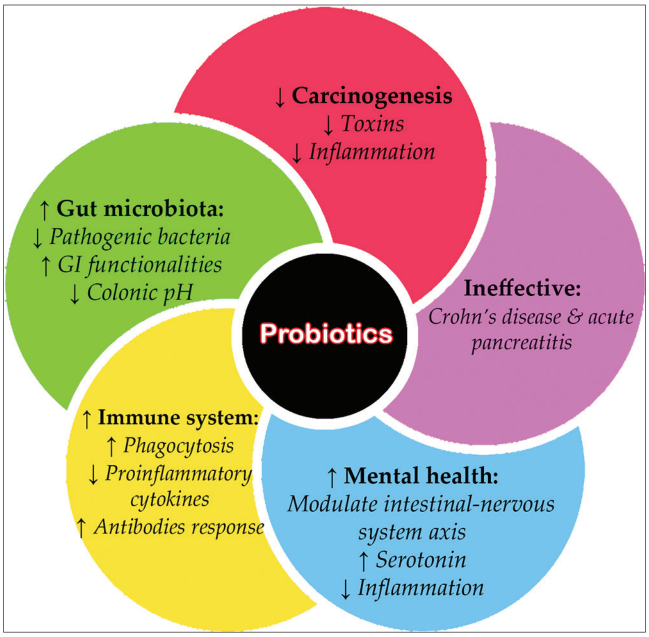

Figure 1: Probiotics' beneficial properties to human health [5]

Taxonomy of Viruses as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 19 (COVID-19) [42]. SARS-CoV-2 belongs to the Orthocoronavirinae subfamily of the Coronaviridae family in the order Nidovirales. Coronaviruses named after the distribution of crown-like spikes on the outer surface of the virus particle. In addition, the nucleic material of these viruses is a single-stranded, positive-sensing RNA (+ssRNA) [43], [44].

Table 1: Some major probiotic microorganisms

Microorganism	Genera	Probiotic strains	References
Bacteria	*Lactobacillus*	*L. acidophilus*	[9], [10], [11], [12], [13],
		L. amylovorus	[14], [15], [16]
		L. brevis	
		L. casei	
		L. crispatus	
		L. curvatus	
		L. delbrueckii subsp. *bulgaricus*	
		L. fermentum	
		L. gallinarum	
		L. gasseri	
		L. johnsonii	
		L. paracasei	
		L. plantarum	
		L. reuteri	
		L. rhamnosus	
		L. salivarius	
	Bifidobacterium	*B. adolescentis*	[17], [18], [19], [20], [21],
		B. animalis	[22]
		B. bifidum	
		B. breve	
		B. infantis	
		B. longum	
		B. thermophilum	
	Enterococcus	*E. faecalis*	[23], [24]
		E. faecium	
	Lactococcus	*L. lactis*	[25], [26]
	Leuconostoc	*L. mesenteroides*	[27]
	Pediococcus	*P. acidilactici*	[28]
	Sporolactobacillus	*S. inulinus*	[29]
	Streptococcus	*S. thermophilus*	[30]
	Bacillus	*B. cereus*	[31], [32]
		B. clausii	
		B. pumilus	
		B. subtilis	
	Escherichia	*E. coli* Nissle 1917	[33], [34]
	Propionibacterium	*P. freudenreichii*	[35]
Yeast	*Saccharomyces*	*S. cerevisiae*	[36], [37]
		S. boulardii	

SARS-CoV-2 genome encodes 27 proteins, including capsid (S) and envelope (N). The S-protein binds the angiotensin-converting enzyme 2 (ACE-2) receptor, which is widespread in many human tissues (including the lungs and gut) and can indirectly modulate nutrient transport to the intestine, reduce the bioavailability of vitamins and amino acids essential for the production of antibodies and immune regulation in general [45]. Clinically, SARS-CoV-2 is reported to cause respiratory and gastrointestinal tract symptoms. Although scientists around the world work hard and respond rapidly in developing a new vaccine or antiviral medication for SARS-2, no COVID-19 vaccine or new effective antiviral medicines are approved yet. In such circumstances, the most reliable and recommended strategy to control viral infections is prevention.

In this review, we sought to elucidate the mechanisms through which the probiotics exert their antiviral and preventive potential as well as the possibility of using them to improve the COVID-19 patient's health.

Possible Antiviral Mechanisms of Probiotics

The probiotics' antiviral effects may exert by several mechanisms, including the production of antiviral inhibitory substances, direct interaction with viruses, or by stimulating the immune system [46]. These proposed mechanisms are summarized below.

Production of Viral Inhibitory Substances

A wide range of antimicrobial compounds is produced by probiotics such as organic acids, bacteriocins, hydrogen peroxide (H_2O_2), exopolysaccharides (EPS), and diacetyl. These agents lead to control other microbial growth [47].

Organic acids

The important and characterized antimicrobial compounds produced by LAB are acetic, lactic acid, and formic acid [48]. The major end-product of sugar fermentation by LAB is lactic acid which used to inhibit microbial growth by stress resultant from the low pH, which, in turn, makes the environment unfavorable for some pathogenic and spoilage microbial growth [49], [50]. The microbial inhibitory effects of organic acids are mainly caused by their dissociated forms, which, by changing the environment into acidic, interfere with essential metabolic functions [51], [52]. The acidic pH has been reported inactivates human immunodeficiency virus (HIV) and herpes simplex virus 2 (HSV-2) [53], [54]. Such low pH may also participate in alleviating SARS-CoV-2 infectivity.

Bacteriocins

Bacteriocins are extracellular, low-molecular-weight proteins that can inhibit the microbial growth of various pathogens with distinct bacteriostatic and bactericidal effects [47], [55]. The majority of bacteriocins are heat stable and sensitive to certain proteolytic enzymes [56]. Many bacteriocins have accordingly been characterized and purified from LAB and used for a variety of industrial and biomedical applications such as food and biopreservation technology, cancer therapy, antimicrobials, and for maintaining human health [57]. Bacteriocins of LAB have some pivotal properties that gain considerable attention, such as (a) being GRAS, (b) non-toxic, (c) protease-inactivated with a slight effect on the gut microflora, (d) can tolerate pH and temperature ranges, (e) having the ability to inhibit many food spoilage bacteria and food-borne pathogens, (f) having bactericidal potential, and (g) they are usually plasmid-encoded [58].

In the past two decades, bacteriocins have been reported to have antiviral properties [59]. They can bind, at the cellular level, to the cell surface receptors [60]. This, in turn, could reduce the cytopathic effects and intracellular RNA of the virus at a pre-incubation condition [61]. Furthermore, bacteriocins and bacteriocin-like substances can interfere with the enzymatic reactions that are important for viral infection [62]. Wachsman *et al*. have proven the antiviral effect of entertain, a bacteriocin, against strains of HSV-1 and HSV-2 by inhibiting late stages of replication and effect on intracellular replication of the virus. *Lactobacillus delbrueckii* subsp. *bulgaricus* 1043 bacteriocin also has a virucidal effect on influenza virus [63]. Moreover, the virucidal effect of the bacteriocin subtilosin, produced by probiotic *Bacillus amyloliquefaciens* has also been reported against HSV and influenza virus [40], [64]. In this context, bacteriocins produced by probiotics may also have such antiviral activities against SARS-CoV-2.

Hydrogen peroxide

H_2O_2 is a compound with high reactivity at high concentrations and quite toxic to the biological systems [65]. In addition, H_2O_2 represents a strong oxidizing agent that has been shown to damage cellular membranes, DNA, and bacterial proteins [66] and have an inhibitory or lethal effect on microorganisms, depending on certain factors including concentration, temperature, pH, and other environmental factors [67]. LAB can produce H_2O_2 when grown in the presence of oxygen through electron-transporting by different mechanisms involving flavin [68] and because they are catalase-negative, H_2O_2 can accumulate to higher concentration [50]. The induction of stress proteins allows LAB to tolerate higher concentrations than the other types of bacteria [69]. Although H_2O_2 and superoxide radical (O^{2-}) are strong oxidant species and can increase the reactive oxygen species that lead to oxidative stress [70], a recent study by Singh *et al*. has revealed that H_2O_2 production by *Lactobacillus johnsonii* could promote epithelial restoration during colitis [71].

In regards to antiviral activities, H_2O_2, superoxide, and hydroxyl radicals are all suspected for inactivating pathogenic viruses [72]. A previous study has also shown that H_2O_2 has a significant anti-influenza virus activity [73]. Typically, H_2O_2 from *Lactobacillus* has a microbicidal effect in the vagina to protect the female genital tract from microbial infection. It also showed notable activities against type-1 and type-2 HIV [72], [74].

Exopolysaccharides

Polysaccharides are polymers composed of 20 to 10^7 units of monosaccharides. They range from linear to highly branched structures [75]. However, EPS are long-chain biological polysaccharides produced by microorganisms [76]. It was proven that EPS have important biological activities such as antibiofilm, antitumor, antioxidant, and immunomodulatory effects [77]. EPS from the probiotic *Lactobacillus plantarum* strain N4 (Lp) have been shown to have an inhibitor effect on the transmissible gastroenteritis virus [77]. Furthermore, Callahan *et al*. [78] reported that EPS could block HIV viral entry. Such EPS may also have a preventive or inhibitory role against SARS-CoV-2.

Direct virus-probiotic interaction

Inactivation of viruses by LAB could also occur through adsorption or trapping mechanism [46]. In this mechanism, the interaction between bacteria and viruses is a principal to exhibit the antiviral effect of probiotics [79]. Conti *et al*. (2009) have reported that *Lactobacillus* isolated from vagina have a protective effect against HSV through the adhesive ability of bacteria to reduce the absorption of the virus. Bacterial cells may directly interact with viral particles and lead to trapping them or competition for cell membrane receptors [62]. A previous study stated that the probiotics trap vesicular stomatitis virus (Indiana vesiculovirus) through interaction between *Lactobacillus* cells and the envelope of the virus directly [80]. Similarly, Mousavi *et al*. [81] reported the mechanisms for the antiviral effect of *L. crispatus* toward HSV-2 and concluded that these mechanisms include (a) formation of micro-colonies in the cell surface, cause blocking to the receptors and effect on the entry of virus into the cells and (b) trapping of viral particles by *L. crispatus* that interact directly with an envelope of the virus. Furthermore, *L. gasseri* inhibited HSV-2 through the trapping mechanism [82]. Furthermore, Wang *et al*. (2013) reported the inhibition of influenza viruses by *Enterococcus faecium* through direct interaction. However, such mechanisms may cease SARS-CoV-2 infection or decrease viral load which is a possible factor in the severity of the disease.

Stimulation of immune system

Lactobacilli have distinct antimicrobial and antiviral activities that play an effective regulator to the immune system [83]. Furthermore, they stimulate specific and non-specific responses, including the activation of natural killer (NK) cells, enhancement of the phagocytic activity of peripheral blood leukocytes, regulatory T cells, and interleukin-10. In this regard, the stimulation of nonspecific secretory and specific antibody responses to rotavirus has been recorded [84]. Recent work by Arena *et al*. (2018) has proven that probiotics can exert modulatory effects of the immune system by enhancing the immune defense against viruses such as induction of interleukins, T-helper cells, macrophages, NK cells, and immunoglobulins.

Several studies have evaluated the effect of some immunobiotics against enteric viruses, respiratory viruses, and pathogenic bacteria [85]. In 2010, the administration of *L. pentosus* to mice showed antiviral potential by activation of lung NK cells and decreased allergic reaction [86]. Heat-killed *Lactobacillus rhamnosus* strains administration has also exhibited IFN-α stimulation in respiratory syncytial virus (RSV) infection and decrease a viral load in mice lungs [87]. Moreover, Kawashima *et al*. (2011) have demonstrated that innate and adaptive immune systems are triggered by the probiotic strain, *L. plantarum*, isolated from traditional Japanese fermented food. In addition to its strong IL-12-inducing activity and IgA-inducing activity, viable *L. plantarum* has a high digestive juice resistance, leading to improved Th1 immune response and preventative activity against influenza virus infection. Too, reduction of H1N1 infection in mice by *Lactobacillus fermentum* has also been documented through the same mechanisms [88], [89]. Likewise, *Bifidobacterium longum* showed an anti-H1N1 activity by decreasing the pro-inflammatory cytokines [90]. Finally, enhancing the immune responses using probiotics' supplementation is a well-documented point; however, it may also be an effective way to alleviate COVID-19.

Probiotics and Enteric Viral Infections

The rotavirus, norovirus, adenovirus, and astrovirus are the most common viruses that cause gastroenteritis. The preventive role of probiotics against common types of viral enteritis is discussed below:

Rotavirus infection

The rotavirus infection is commonly responsible for diarrheal disease among children under 5 years of age, particularly in developing countries. Rotavirus infection is also associated with other symptoms such as vomiting, fever, and dehydration which can lead to death [91], [92]. In 2006, the US-FDA approved two oral live vaccines (RotaTeq and Rotarix) to prevent rotavirus infection in infants [93]. However, the rates of morbidity and mortality are still high [91]. In such circumstances, probiotics may consider promising cheap and safe preventive alternatives [94] to be administered to patients.

Many researchers have studied the preventive role of certain probiotics against rotavirus, such as *Bifidobacterium* and *Lactobacillus* affirmed their role in antagonizing rotaviruses [95]. Erdoğan *et al*. [96] have reported that the treatment of acute rotavirus gastroenteritis with *Bifidobacterium lactis* B94 and oral rehydration could significantly reduce the diarrheal period in children aged from 5 months to 5 years old. Later, in 2017, Park *et al*. [97] reach similar results after administering *B. longum* BORI and *L. acidophilus* AD031 to infants infected with rotavirus. A more recent study has proven that specific probiotic strains such as *Lactobacillus salivarius* PS2, *L. acidophilus* NCFM, *Bifidobacterium breve* M-16V, and *Lactobacillus helveticus* R0052 have the ability to reduce the severity of rotavirus infection [98].

Supporting the theory that probiotics can stimulate the host's immune system, Sindhu *et al*. [99] have mentioned that the consumption of *L. rhamnosus* (LGG) can modulate both innate and adaptive immune system's responses by increasing levels of serum IgG during infection with rotavirus. On the other hand, Fernandez-Duarte *et al*. [100] suggested that *B. adolescentis* and *L. casei* could block rotavirus adherence to the MA104 cells. While, a recent study indicated that non-protein components with low-molecular-weight derived from *B. longum* BORI act as anti-rotaviral substances [101]; however, more studies are required to specify active compound to completely elucidate the underlying mechanism of action.

Noroviruses infection

Human norovirus can also cause gastroenteritis and generally lasts for 2–3 days and accompanied by vomiting, nausea, and diarrhea [102]. Infants, elderly, and immunocompromised patients are the risk groups. Although acute diarrhea is generally self-limiting and may disappear within a few days [103], [104], dehydration in toddlers and young infants remains the major risk factor.

Developing vaccines and antiviral drugs against human norovirus are still under experiments [105]. Studies indicated that probiotics might act as adsorbents for P particle, a nano-scale sized particle in norovirus capsid and critical for the host's immune response and receptor binding [106]. For example, *Enterobacter cloacae* which are a commensal bacterium could bind to human norovirus through surface histo-blood group antigen and inhibit virus infectivity when tested in pigs [107], [108]. Another study showed that P particle attachment to epithelial cells could be inhibited by the presence of *L. casei* BL23 and *Escherichia coli* Nissle 1917 [109]. Accordingly, and to avoid developing severe forms of SARS-CoV-2, enhancing a healthy diet with probiotics may represent a good strategy.

Probiotics and Respiratory Viral Infections

While many researchers have concentrated on the use of probiotics to treat or prevent intestinal infections, recent research has focused on the effectiveness of probiotics on humans against respiratory viral infections [110], which are a serious cause of morbidity and mortality around the world [111]. The causative agents of respiratory viral infections in humans are over two hundred different types of pathogenic viruses, including RSV, human rhinoviruses (common cold), human enteroviruses, influenza viruses, adenoviruses, parainfluenza viruses, and coronaviruses. Symptoms of these infections vary from mild respiratory symptoms to severe diseases [112], [113], [114], [115]. Below, evidence-based probiotics' effects against common infections are highlighted below:

RSV infection

One of the most common respiratory viruses that almost all children are infected with by the age of 2 years is RSV. The symptoms can vary from mild symptoms to severe infection of the lower respiratory tract, bronchiolitis, and pneumonia with an increasing risk of developing asthma and persistent wheezing [116], [117]. Elderly and immunocompromised individuals are most at risk to be infected with RSV [118], [119]. No RSV vaccine has been approved so far, and specific antiviral medicines against RSV are still limited. Several probiotics are therefore proposed to prevent RSV infection as prophylactic or antiviral agents. For example, Tomosada *et al*. (2013) have found that TLR3/RIG-I antiviral respiratory immune response is modulated by intranasal administration of two different commensal strains of *L. rhamnosus* (*L. rhamnosus* CRL1505 and *L. rhamnosus* CRL1506) and increased infant mice resistance to RSV in comparison with a control group. In addition, recent research has shown that the RSV titer in the lungs can be significantly reduced with no weight loss in mice after viral infection when *L. gasseri* (LG2055) is administered orally [41].

Human rhinoviruses (HRV)

Rhinoviruses are the leading causes of common cold in humans [120]. Severe symptoms typically include irritation, pneumonia, bronchiolitis, asthma, and chronic obstructive pulmonary disease [121]. There is currently no approved antiviral treatment or vaccine for HRV infection. However, research articles have documented that various probiotics could reduce the risk of HRV disease. In a preterm population, the incidence of HRV infection was reduced significantly during the 1^{st} year of life through using polydextrose and *L. rhamnosus* [122]. Kumpu *et al*. [123] found that receiving *L. rhamnosus* GG (live or heat-inactivated) decreased the incidence and severity of common cold symptoms caused by rhinoviruses. However, the dose of probiotic bacterial strains, side effects, and accurate mechanism against HRV is inadequately reported and needs further investigation [124], [125].

Influenza virus infection

Another viral agent responsible for thousands of human and animal deaths annually is the influenza virus. Influenza viruses are a group of RNA viruses, which belong to the family Orthomyxoviridae. There are four types of influenza viruses A, B, C, and D. Mainly, humans are infected with type A and B [126]. Influenza A viruses are responsible for several pandemic outbreaks worldwide [127]. Although the vaccine is available but with new viral strains evolving rapidly and variations between circulating viruses and vaccines created, the efficiency of the influenza virus vaccine decreases [128], [129]. Therefore, the efforts rely on the use of probiotics to reinforce and improve the host's immune system against viral infection. The use of yogurt fermented by *L. delbrueckii* ssp. *bulgaricus* OLL1073R-1 (R-1) might prevent infection caused by respiratory or influenza viruses through polysaccharides secretion, which improves immune system's functions and activates the NK cells [130], [131]. In a mouse model, *L. acidophilus* can regulate NK T-cells and prevent influenza virus infection [132]. Furthermore, the *B. bifidum*'s effect on improving immune response to the influenza virus in a recent study on BALB/c mice infected with lethal influenza A (H1N1) has been evaluated by Mahooti *et al*.

[133]. Furthermore, findings revealed a strong induction of both humoral and cellular immunity, drop in the level of IL-6, and increased survival rate in mice receiving *Bifidobacterium* than those of the control group.

Adenoviruses infection

Adenoviruses represent group of Rowavirales that belong to the non-enveloped double-stranded linear DNA viruses. Adenoviruses can cause various clinical syndromes in humans in addition to keratoconjunctivitis, including gastrointestinal and urogenital infections [134]. Various antiviral drugs such as ribavirin, ganciclovir, and cidofovir have shown variable activities against severe human adenovirus infections especially in immunocompromised organ transplant recipients. However, the efficiency of these drugs is limited to the ability of the virus to develop resistant strains in addition to their side effects [135]. Therefore, it is safer to stimulate the immune system and increase resistance to adenovirus infections through probiotics and their metabolic products [136]. *In-vitro* MTT assay against human adenovirus type 5 was used to examine the cytotoxicity of six EPSs produced by various LAB. The results showed that EPS 26a produced by *Lactobacillus* sp. have a significant antiviral activity through the formation of non-infectious virus progeny [137].

Probiotics and COVID-19

In response to the emerging threat posed by SARS-CoV-2, the WHO announced a Public Health Emergency of International Concern a pandemic on March 11, 2020. Infection with SARS-CoV-2 causes coronavirus disease 19 (COVID-19), which has been characterized by fever, respiratory, and gastrointestinal symptoms, along with other less common symptoms [138]. No vaccine or antiviral drug for SARS-CoV-2 has been yet approved. However, faced with this pandemic, new answers and ways of addressing these problems are needed.

Strengthening the immune system is well-known to be an effective and successful way for a healthy lifestyle. This, in turn, oriented attention to the pivotal role of a healthy immune system to face SARS-CoV-2 infection [139]. Open literature search revealed that immune system function is largely improved by a healthy diet. Accordingly, a diversified diet with a broad nutrient profile may prevent and even reduce the vulnerability during COVID-19.

Adjuvants against COVID-19 could be healthy food choices, micronutrients, bioactive compounds, and probiotics [140]. In particular, the potential benefits of probiotics in other coronavirus strains were thoroughly documented [141]. Some probiotics may also play a positive role in the treatment of COVID-19 patients due to their antiviral activity, ability to modulate inflammation, restore gut microbiome, ready availability, generally safe, inexpensive, and easily administered [142]. There are no guidelines on strain, dose, and duration of the probiotics consuming yet. However, *Lactobacillus* and *Bifidobacterium* can be safely used in different clinical situations.

A recent study by Aanouz *et al*. (2020) [143] on computational and molecular dynamics obviously demonstrates the antiviral activity of plantaricins, a bacteriocin, which blocks viral entry by binding with RdRp, RBD, and ACE2 through multiple mechanistic approaches by metabolic product of *L. plantarum*. Blocking the main structural protein S is critical and can be one of the best targets since it plays a key role in the life cycle of SARS-CoV-2. Moreover, Anwar *et al*. (2020) [144] have suggested that plantaricin metabolites may be a preventive option before the latest antiviral medication specific to COVID-19 has been discovered. Other studies are being carried out across the globe to decide whether modifying the gut microbiota through the diet will contribute to our COVID-19 care, and in recent times, Baud *et al*. (2020) [145] have suggested certain probiotic strains that are evidence-based and that are important in reducing the pandemic burden. Apart from boosting the immune system, specific therapeutic strategies may be advised for the prevention of cytokine storm such as the use of probiotics for patients with gastrointestinal symptoms linked to COVID-19 and those with milder systemic symptoms [146].

Different patients' responses to infection may depend on variations in the composition of their microbiota and correction with probiotics may help to minimize the need for intensive care [147]. Dhar and Mohanty (2020) have identified the potential role of intestinal microbiota in determining better immune and respiratory function in such patients [148]. Too, number of authors discussed the idea of significant positive modulation of respiratory function by probiotics/synbiotics supplementation, starting from previous studies on the close associations between gut microbiota and lung function. In general, that finding indicates that probiotics are essential and useful supplements to patients and confirm the role of our microbiota in sustaining and eventually restoring a healthy quality of life.

For better understanding, the presented knowledge must be more deeply validated before they can be implemented in standard protocols for COVID-19 patients, assess also the true impact of SARS-CoV-2 on gut microbiota, and also take into account the possible role of gut virobiota, which seems to have a specific role in the homeostasis of gut microbiota [149]. Moreover, interactions between SARS-CoV-2 and the gut microbiome and resident virobiota could influence the ability of this new coronavirus to infect and disseminate the intestinal cells more easily and explain how probiotics could have a COVID-19 resistance [150].

In addition to their benefits to humans, probiotics may also participate in certain clinical presentations related to life-threatening outcomes such as bloodstream infections [151], [152]. However, neither mortality nor adverse health complications were ascribed to the clinical use of probiotics. Furthermore, additional studies are demanded to better understand their safety, behavior in the food matrix, and their survival and colonization in the gastrointestinal tract using expressly designed *in vivo* models.

Conclusions

With no approved vaccine or antiviral drugs for some viral disease, including COVID-19, establishing effective means to protect humans from viral infections still a bit challenging. Of the safest, affordable, and easy to consume, agents are probiotics. Enhancing the host immune system with probiotics is widely studied. They were known with their multifunctional effects, which can act as adjunctive therapy for the prophylaxis of a large number of viral infections. Finally, research needs to progress to establish probiotic scientific guidelines for the prevention and/or treatment of COVID-19.

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Authors' Contribution Statement

All authors have equally contributed to this work and approved it before submission.

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Autoimmune Hemolytic Anemia as a Novel Complication of COVID-19 Infection in Sanglah General Hospital Bali, Indonesia

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Abstract

BACKGROUND: Clinical manifestation of coronavirus disease (COVID-19) could be asymptomatic, mild to severe, even mortality. Although various hematological complications associated with COVID-19 infection have been reported, the finding of autoimmune hemolytic anemia (AIHA) is a novel case.

CASE REPORT: A 59-year-old woman was admitted to our emergency room because of a 5-day period of fever with cough and shortness of breath. At admission, she was takipnea, jaundice, and had an oxygen saturation of 60% on room air. Laboratory studies showed hemoglobin (Hb) 3.68 g/dL, high reticulocyte (14.4%), and hyperbilirubinemia. Chest X-ray showed bilateral pneumonia with positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test. Although she got packed red cell (PRC) transfusions in 7 days, her Hb remained low and bilateral infiltrate still increased. That's why we considered direct Coombs test and it returned positive. AIHA was diagnosed and treatment with hydrocortisone 100 mg IV twice daily was given for the first 72 h. The maintenance dose with methylprednisolone 16 mg twice daily was continued for 7 days admission. Then, Hb value increased to 11.03 g/dL and she was discharged home without any compliments.

CONCLUSION: In the current epidemiological situation, AIHA needs to be considered as a complication of COVID-19 infection in a patient who presents with jaundice and severe anemia without any underlying chronic disease, which is need blood transfusions, steroid medication use, or blood cancer.

Introduction

Unexplained pneumonia cases were reported by the People in Republic of China to the World Health Organization on December 31, 2019. This outbreak called coronavirus disease 2019 (COVID-19) that caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Indonesian Ministry of Health reported the total number of COVID-19 cases in the world as of July 20, 2020, was confirmed as many as 14,043,176 cases and infected 215 countries around the world. Of these, 597,583 people were reported dead. The mortality rate for COVID-19 in Indonesia is quite high (4.8%) when compared to the world average mortality rate of around 4.3% [2].

SARS-CoV-2 has spike protein which can strongly bound with an angiotensin-converting enzyme (ACE-2) in host cell. Mostly, ACE-2 is found in the lower respiratory tract, small bowel enterocyte, heart, vascular structure, and other parts of the body. That's why this virus called thousand faces disease. The clinical manifestation is vary, could be asymptomatic, mild to severe, even mortality. Diabetes, cardiovascular disease, chronic lung disease, malignancy, immunosuppression, obesity, and elderly are high-risk comorbidities which can make poor prognosis of this infection. Laboratory levels of lymphopenia, thrombocytopenia, and elevated D-dimer levels are associated with severe disease [3], [4].

We report a novel case of Autoimmune Hemolytic Anemia (AIHA) as a complication of COVID-19 infection at our institution, Sanglah General Hospital, Bali, Indonesia. AIHA is a disorder caused by the presence of autoantibodies that attack normal erythrocyte membranes, which triggers the hemolysis process and results in a shortening of erythrocyte age (normal erythrocyte age ranges from 100 to 120 days) [4], [5]. This condition exceeds the capacity of the bone marrow to produce new erythrocytes so that the level of reticulocytes in the blood will increase. The process of hemolysis can occur either inside the blood vessels (intravascular) or outside the blood vessels involving the reticuloendothelial system. The antigen on the erythrocyte membrane is recognized as foreign and destroyed in the spleen, liver, or bone marrow (extravascular) [6].

The incidence of AIHA reaches 1/100,000/year which can occur in all age groups, but the incidence increases with age. Diagnosis of AIHA is confirmed with a positive direct Coombs' test (direct antiglobulin test [DAT]) [7].

The mechanism of reducing hemoglobin (Hb) levels in COVID-19 patients is very limited. Liu *et al*. reported that the presence of spike-CD147 protein in the virus plays a role in the process of viral attachment to erythrocytes which causes the release of Hb from erythrocytes. The released Hb will be broken down into heme and globin. It reported that viral proteins such as Orflab, ORF3a, and ORF10 are able to bind to porphyrin in heme, which form a complex and causes the destruction of heme [8]. Angileri *et al.* also reported that molecular mimicry is thought to be a determinant factor in the incidence of AIHA in COVID-19 infection. Ankyrin-1 (ANK-1), a protein in the erythrocyte membrane, has the same antigenic epitope as the Spike protein in SARS-CoV-2 so that erythrocyte destruction is part of the patient's immune defense mechanism which can cause a decrease in Hb levels [9].

The mechanism underpinning autoimmunity in COVID-19 which can cause hemolytic anemia by autoantibodies has yet to be elucidated. Besides that, corticosteroids are recommended to use in a patient with COVID-19 who are experiencing critical acute respiratory distress syndrome (ARDS). However, its administration is still controversial due to unwanted side effects such as secondary infection, complications of long-term use, and delayed viral load reduction [3]. On the other side, first-line therapy in AIHA cases emphasizes the use of corticosteroids to suppress autoimmunity processes that affect hemolysis [7]. Here, we present a complete response (CR) case of AIHA as a new complication in COVID-19 patient in Sanglah General Hospital, Bali, Indonesia

Case Report

A previously healthy 59-year-old woman, a shopkeeper, was admitted to our emergency room because of a 5-day period of fever with the cough. She also felt shortness of breath from one a week before admission, then worsen in 5 days. Changing position could not relieve the symptoms. Besides that, she also felt fatigue, nausea, and vomiting. Three days before admission, she also got jaundice in her eye and melena. The patient denied of suffering gall stone, kidney disease, or gastric ulcer before. She also did not have any history of disease, such as asthma, cancer, diabetes mellitus, hypertension, or tuberculosis. There was not any medication which she was consumed regularly.

In the emergency room, she was tachypnea, tachycardia, and had an oxygen saturation of 60% on room air. Laboratory studies showed Hb 3.68 g/dL (13.5–17.5 g/dL) with microcytic hypochromic, leukocyte 11.600/μL (4.100–11.000/μL), and high reticulocyte (14%). The value of SGOT is 106.4 U/L (11–27 U/L), SGPT is 60.90 U/L (11–34 U/L), ureum 17.7 mg/dL (8–23 mg/dL), and creatinine is about 0.79 mg/dL (0.5–0.9 mg/dL). There was increment in bilirubin (total bilirubin 5.93 mg/dl; direct bilirubin 2.36 mg/dl, and indirect bilirubin 3.57 mg/dl). Besides that, prothrombin time/PT is 17.9 s (10–14.4 s) and activated partial thromboplastin time/APTT is 48.7 s (24–36 s). Feritin level as high as 6020 ng/mL (13–150 ng/mL) and total iron-binding capacity (TIBC) level is 228 g/dL (261–478 g/dL). Other laboratory studies showed serum iron 144.1 g/dL (50–170 g/dL), alkaline phosphatase 54 U/L (42–98 U/L), total protein 7.4 g/dL (6.4–8.3 g/dL), globulin 3.5 (3.2–3.7), and gamma-GT 31 U/L (7–32 U/L). HBsAg test and Anti-HCV were non-reactive. The chest X-ray showed bilateral pneumonia. Besides that, the polymerase chain reaction (PCR) test SARS-CoV-2 was positive through nasopharyngeal and oropharyngeal swab.

Blood gas analysis reported that she got hypoxemic respiratory failure (type I) with uncompensated metabolic acidosis. Peripheral blood smear showed severe anisopoikilocytosis hypochromic with giant thrombocyte only, another parameter blood smear was normal.

At admission, this patient got packed red cell (PRC) in 3 days and her hemoglobin increase becomes 7.47 g/dL, but in 2 days later, her Hb decreases in 6.35 g/dL. Transfusions were continued in 3 days later, so her Hb becomes 8.69 g/dL, but she felt fatigue and became more hypoxic, so she still dependent in oxygen supplementation. Her chest X-ray also showed much more infiltrate addition in both of her lungs than before. Because of this condition and the jaundice was still remained in her eyes, we considered to do serology test to see autoimmunity condition in this patient. Then, the results of direct Coombs test (DAT) were positive, and indirect Coombs test was negative. Hence, the diagnose of this patient was confirmed to be AIHA

During admission, she was given oxygen using face mask, intravenous (IV) fluid drip, cefoperazone 1 g IV twice a day, azithromycin 500 mg oral once daily, hyloquin 200 mg oral twice a day, acetylcysteine 200 mg oral 3 times a day, and Vitamin C 500 mg oral twice a day. Besides that, she got hydrocortisone 100 mg IV twice a day at the first 72 h after she confirmed as AIHA. She relieved her symptoms such as weakness, pale skin, and tiredness; then, she got a maintenance dose of methylprednisolone 16 mg oral twice a day in the next 7 days of her admission. After this treatment, her Hb becomes 11.03 g/dL and she does not have any compliments so she could discharge home.

Discussion

The COVID-19 pandemic has caused significant morbidity and mortality. The clinical manifestations of COVID-19 patients have a broad spectrum, ranging from symptoms (asymptomatic), mild symptoms, pneumonia, severe pneumonia, ARDS, sepsis, to septic shock [10]. Manifested clinical anemia, many times, have been reported in COVID-19 patients with severe disease [11].

Patient 59-year-old woman, with a history 5-day period of fever with cough, shortness of breath, felt fatigue, and she also got jaundice in her eye. There is no family history with hematology disease. Physical examination was tachypnea, tachycardia, and hypoxia. Laboratory studies showed severe anemia with high reticulocyte, increment in bilirubin, ferritin level, and TIBC level. Serum iron, alkaline phosphatase, total protein, globulin, and gamma GT was normal. The chest X-ray showed bilateral pneumonia. PCR test SARS-CoV-2 was positive through nasopharyngeal and oropharyngeal swab. Direct Coombs test was positive.

This patient is confirmed as COVID-19 based on the symptom in respiratory failure and positive results in PCR Test SARS COV-2. Recommendations from the First International Consensus Meeting reported about diagnostic criteria for AIHA are hemolysis sign accompanied by a positive DAT and exclusion of alternative causes [12]. In this patient, we got a sign of hemolysis such as jaundice, increment of hemolytic markers such as bilirubin and reticulocyte. Besides that, from the blood smear test, we found severe anisopoikilocytosis that shows hemolytic condition. Hence, she was confirmed to be AIHA through the positive result of DAT.

Besides that, her iron blood test showed normal serum iron, increase in ferritin value, and TIBC value was decline which could be excluded iron deficiency anemia. She also did not have any history of chronic disease which is need medication regularly, so there was not any chronic disease or drug that induced her anemia. HBsAg test and anti-HCV were non-reactive, so anemia caused by hepatitis can be ruled out. There was no obvious provoking factor to her AIHA condition and thus it was attributed to her COVID-19 infection, being the first case reported so far in Bali, Indonesia.

Our patient during 3 days of treatment since patient hospitalized, from May 24, 2020, to May 26, 2020, the patient was given four bags of PRC blood transfusions (1.000 ml PRC), the Hb level increased from 3.68 g/dL to 7.47 g/dL, but the decrease in Hb levels occurred again on May 28, 2020, to 6.35 g/dL with persistent weakness and tightness so that patients still need oxygen supplementation. The patient was again given PRC transfusions from May 29, 2020, to May 31, 2020, as much as five bags of PRC (1.250 ml PRC), with an Hb level of 8.69 g/dL; the patient still complained of persistent tightness and chest X-ray evaluation showed additional infiltrates in both lung fields compared to the chest X-ray previously. During treatment, the patient showed no clinical improvement as well as an increase in Hb levels according to the transfusion target.

Anemia that occurs in patients is suspected to be due to the presence of a hemolysis process caused by autoimmunity so that the patient is subjected to direct Coombs test, and the result was positive. Since the patient is diagnosed with AIHA with COVID-19, the management using 100 mg of hydrocortisone steroid therapy every 12 h for 3 days intravenously starting on June 01, 2020–June 04, 2020. The patient has experienced improvement after being given steroids both clinically, laboratory, and radiologically so that it is continued by administering methylprednisolone 16 mg every 12 h orally for 7 days of treatment. When discharged, the patient clinically had no complaints of respiration and laboratory results showed an improvement in Hb levels, bilirubin levels, and liver function.

AIHA is characterized by the destruction of red blood cells by autoantibodies, but the mechanism underlying the autoimmunity of SARS-CoV-2 infection has yet to be explained. To the best of our knowledge, this is the first case report of COVID-19 with AIHA infection in Indonesia. In another case report, seven patients from six hospitals in France and Belgium reported the emergence of AHAI during COVID-19 infection accompanied by previous comorbid diseases (hypertension, diabetes mellitus, and chronic renal failure). The mean time between the onset of Covid-19 symptoms and the onset of AHAI was 9 days (range 4 and 13 days) [11].

The mechanisms for reducing Hb levels in COVID-19 patients are very limited, two mechanisms currently reported are the Liu W and Angileri F studies in 2020. Liu *et al.* reported that the presence of spike-CD147 protein in the virus plays a role in the process of viral attachment to erythrocyte digestion and Angillery *et al.* reported that molecular mimicry ANK-1, a protein in the erythrocyte membrane, has the same antigenic epitope as the Spike protein in SARS-CoV-2 so that erythrocyte destruction as part of the patient's immune defense mechanism can cause a decrease in Hb levels [8], [9].

Liu *et al.* recently, it reports that the virus may first infect cells with ACE2 receptors, including immune cells. Immune cells produced antibodies and viral proteins. Antibodies and red blood cells generated immune hemolysis, or red blood cells were infected by Spike-CD147 pathway, by then, Hb was attached and then attacked produce toxic and inflammatory derivatives. This mechanism because of some viral proteins could combine to the porphyrin to form a complex, respectively. At the same time, orf1ab, ORF3a, and ORF10 proteins could coordinate attack the heme on Hb. Deoxyhemoglobin is more vulnerable to virus attacks than oxidized Hb. The attack will lead to less Hb to carry oxygen and carbon dioxide. Lung cells are toxic and inflammatory due to derivatives produced by the attack, which eventually resulted in ground glass appearance. Capillaries easily were broken due to inflammation. Proteins such as fibrinogen fill the capillaries cracks through the coagulation reaction [8].

Angilleri *e.al.* reported the hypothesis that molecular mimicry ANK-1, a protein in the erythrocyte membrane, has the same antigenic epitope as the Spike protein in SARS-CoV-2 so that erythrocyte destruction as part of the patient’s immune defense mechanism can cause a decrease in Hb levels. ANK-1 is an erythrocyte membrane protein for red cell differentiation and function, providing the primary connection between the membrane skeleton and the plasma membrane. They found that ANK-1 shares a putative immunogenic-antigenic epitope (amino acids LLLQY) with 100% identity with the SARS-CoV-2 surface glycoprotein named Spike protein. They are established that this epitope is part of Spike’s predicted immunogenic epitope 750-SNLLLQYGSFCTQL-763 for B cells using the immune epitope database and analysis resource [9].

Steroid administration in COVID-19 is given in accordance when a hypoxic condition occurs in the patient. Giving anti-inflammatory therapy too early is not recommended because it can inhibit the development of adaptive immune responses and even trigger viral replication [13]. This is in line with research by Lee *et al.* who reported that administration of corticosteroid therapy early in Coronavirus infection is associated with an increase in plasma viral load and should be avoided [14]. Steroids such as dexamethasone 6 mg given for 10 days indicated only for patients with acute hypoxemic respiratory failure (increased oxygen demand), requires mechanical ventilation, as well as in conditions that support the need for steroids (e.g., asthma with chronic obstructive pulmonary disease [COPD] and COPD exacerbations). Other corticosteroids that can be an option in the equivalent dose are betamethasone oral 6 mg, methylprednisolone oral or injection 32 mg, and prednisone or prednisolone 40 mg oral [15]. The recommended dose is hydrocortisone 200 mg/24 h or its equivalent, given in conditions of refractory shock or signs of ARDS. The administration of corticosteroid therapy is proven to provide benefits in the development of the patient’s condition so that the patient can avoid worsening that requires mechanical ventilation and achieve a CR in conditions of AIHA. Since corticosteroid can make false negative in direct Coombs test (DAT), it suggested that direct Coombs test should be performed before corticosteroid administration.

Conclusion

To the best of our knowledge, this is the first case report SARS CoV-2 could have triggered AIHA in adult in Bali, Indonesia. Her workup for other etiologies, including other diseases or another viral infection that causes hemolytic condition was unrevealing. During this current COVID-19 pandemic, it is necessary to consider the presence AIHA as new complications in COVID-19 infection. Hence, it is deemed necessary to carry out a DAT to rule out complications of AIHA in COVID-19 patients who present anemia accompanied by evidence of hemolysis to provide comprehensive therapy of the patient.

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Severe Encephalitis in Infant with COVID-19: A Case Report

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Abstract

BACKGROUND: Encephalitis is a serious condition that contains neurological dysfunction cause by inflammation of the brain tissue. Etiological factors for the occurrence of this condition include infectious and non-infectious causes.

CASE REPORT: We are presented 9-month-old infant referred to our clinic in convulsive status, fever, and disturbed consciousness. From anamnestic information, the infant has been febrile for 2 days with profuse vomiting initiating just before admission at the clinic. At the moment of admission in the clinic, the infant looked intoxicated with generalized tonic-clonic seizures, with shortness of breath and fever with a weakened reaction to painful stimuli. It was admitted in the Isolation Unit by the protocol of the clinic. Laboratory investigations were done. Due to the persistence of convulsive status, a computed tomography scan of the brain was performed with the finding of enlargement of the lateral ventricles, with intraventricular masses and pronounced internal hydrocephalus. The results of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) from the infant were positive as well as the grandmother. The infant was intubated immediately and put on mechanical ventilation SIPPV.

CONCLUSION: Our case report could suggest that SARS-CoV-2 infection may cause severe clinical symptoms, neurological manifestations, and encephalitis in infants.

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Introduction

Encephalitis is a serious condition that contains neurological dysfunction cause by inflammation of the brain tissue [1]. Etiological factors for the occurrence of this condition include infectious and non-infectious causes [2], [3]. The exact cause of this condition is often unknown, but the most common causes of infection are viruses. The viruses that can cause encephalitis include Varicella-Zoster virus, Epstein-Barr virus, Herpes simplex virus (type 1 and 2), enteroviruses, Rubeola, West Nile virus, and Rabies [2], [4]. Encephalitis can also be caused by a bacterial infection such as tuberculosis, syphilis, Lyme disease, or after an infection caused by parasites such as toxoplasmosis [5]. Non-infectious causes include an autoimmune reaction in the body and this occurs when the body's own immune system produces antibodies against brain tissue [6]. Diagnostic tests required to confirm the diagnosis include: Blood tests, BAL or sputum, urine and stool tests, electroencephalography, lumbar puncture, X-ray, computed tomography (CT) scan, and magnetic resonance imaging [7], [8]. Treatment of viral encephalitis consists of antiviral drugs, supportive therapy such as monitoring of cardiac and respiratory function and respiratory support, intravenous fluids, anti-inflammatory drugs, and anticonvulsant drugs [9], [10], [11].

Human coronaviruses (CoVs) can be found in human population, and they can cause respiratory, enteric, hepatic, and neurological diseases [12], [13]. A novel CoV first time appears in December 2019 in Wuhan, Hubei province of China, with severe pneumonia causes [14]. Severe acute respiratory syndrome CoV 2 (SARS-CoV-2) is the third human CoV known to co-opt the peptidase angiotensin-converting enzyme 2 (ACE2) for cell entry [15]. SARS-CoV-2 cell entry is dependent on its 180-kDa spike (S) protein, which mediates two essential events: Binding to ACE2 by the amino-terminal region and fusion of viral and cellular membranes through the carboxyl-terminal region [16]. Infection of lung cells requires host proteolytic activation of the spike at a polybasic furin cleavage site [17]. The lung pathology in severe disease is different from the earlier pneumonitis, with progressive loss of epithelial-endothelial integrity, septal capillary injury, and marked neutrophil infiltration, with complement deposition, intravascular viral antigen deposition, and localized intravascular coagulation [18]. The virus binds to the ACE2 receptor, located in epithelium of the small intestine, respiratory tract, kidney cells, respiratory tract, the vascular endothelium throughout the body, and widely throughout the central nervous systems. ACE2 receptor is expressed in astrocytes, oligodendrocytes, neurons and concentrated in ventricles, and posterior cingulate cortex, olfactory bulb, substantia nigra, and middle temporal gyrus. Most patients with SARS-CoV-2 manifest a respiratory infection followed by sore throat cough, fatigue, shortness of breath, and respiratory distress. In addition to these effects on organic systems, larger studies published by China and France show that as many as 36% of patients with this infection develop neurological symptomatology. SARS-CoV-2 can cause a wide range of symptoms from other organic systems such as the gastrointestinal tract, manifested by diarrhea and vomiting, blood clotting disorders, and heart damage [19], [20], [21].

Organ dysfunction can be life-threatening. Rapid clinical symptom in pediatric patients infected with SARS-CoV-2 and neurological damage may lead to endotracheal intubation and placement of this group of patients on mechanical ventilation [22], [23], [24].

Case Report

We are presented 9-month-old infant referred to our clinic in convulsive status, fever (temperature 38.2), and disturbed consciousness. From anamnestic information, the infant has been febrile for 2 days with profuse vomiting initiating just before admission at the clinic. Epidemiological survey for COVID-19 was a false negative. At the moment of admission in the clinic, the infant looked intoxicated with generalized tonic-clonic seizures, with shortness of breath and fever with a weakened reaction to painful stimuli. It was admitted in the isolation unit by the protocol of the clinic. The seizures were treated with an intravenous benzodiazepine. The test of SARS-CoV-2 was done. Laboratory investigationes were made: Complete blood count: Hemoglobin = 105 g/l, erythrocytes = 4.45 × 10*12/l, leukocytes = 10.69 × 10*9/l, thrombocytes = 242 × 10*9/l, hematocrit = 31.8%, neutrophils = 45.5%, lymphocytes = 43.5%; C-reactive protein = <0.2 mg/l; glycemia = 13.46 mmol/l; sodium = 133 mmol/l, potassium = 4.3 mmol/l, calcium = 2.13 mmol/l, phosphor = 1.72 mmol/l, magnesium = 0.77 mmol/l, chloride = 106 mmol/l; total bilirubin = 1.8 umol/l; direct bilirubin = <1.8 umol/l; AST=54 U/L; ALT = 29 U/L; LDH = 314 U/L; GGT = 10 U/L; creatinine = 41 umol/l; urea = 3,3 mmol/l; total protein = 56 g/l, albumin = 42 g/l; CK= 206 U/L; CKMB = 49.12 U/L; ABS: pH = 7.38; pCO_2 = 34.1 mmHg; pO_2 = 90.5 mmHg; HCO_3 = 19.7 mmol/l; BE = −4.9 mmol/l; and sO_2 = 96.1%. Urinalysis parameters were normal. Due to suspected encephalitis, a lumbar puncture was indicated. We consult an ophthalmologist who performs fundus oculi examination and no changes were detected. We perform a lumbar puncture, liquor was obtained under pressure, clear, without elements, with proteinuria and glycorrhachia. Liquor biochemical analysis: Lactates = 1.70 mmol/L, glucose 5.08 mmol/L, and proteins = 2027 mg/L. Film array meningitis/encephalitis (ME) panel was not isolated from the liquor a causative agent. From blood culture was isolated Staphylococcus with film array blood culture identification panel qualitative multiplexed nucleic acid-based *in vitro* diagnostic test. The infant was put on dual antibiotic therapy with third-generation cephalosporin and aminoglycoside, antiviral drug, anticonvulsant drug, and anti-edematous therapy. Due to the persistence of convulsive status, a CT scan of the brain was performed with the finding of enlargement of the lateral ventricles, with intraventricular masses and pronounced internal hydrocephalus (Figure 1).

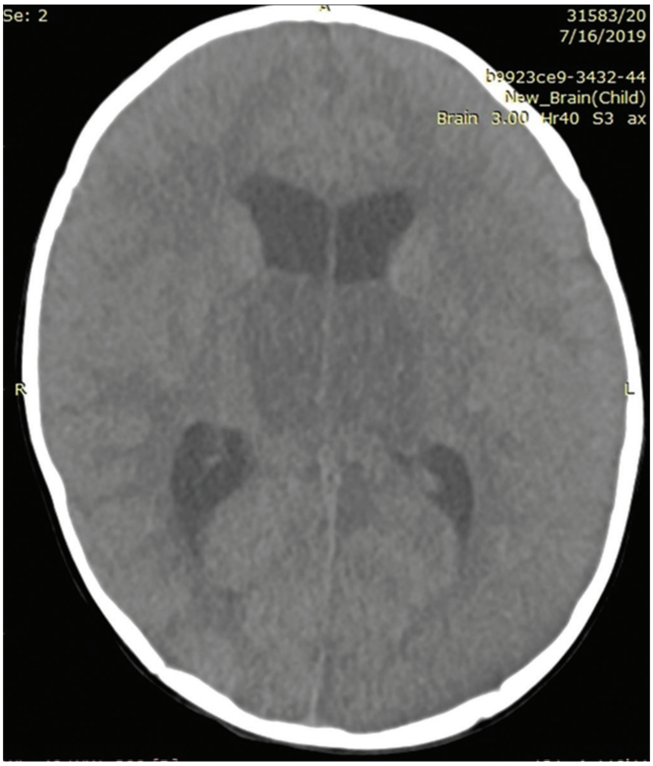

Figure 1: Computed tomography scan of the brain-enlargement of the lateral ventricles, with intraventricular masses and pronounced internal hydrocephalus

Late that day we have gotten the results of SARS-COV-2 from the infant that was positive as well as the grandmother that has actually taking care of the infant during the past 2 weeks. We have made a teleconference with Geneva Children's Hospital due to the fact that the infant had Swiss citizenship. They suggested, according to the fact that they might transfer the infant in their country and come by fly ambulance, but before that to intubate. That actually happened immediately after a few minutes with cardiac arrest and no breathing. The infant was intubated immediately and put on mechanical ventilation SIPPV. After a couple of hours, the plane came and the child by all means of protocols for COVID-19 pandemic was transferred safely in Geneva.

Discussion

By all means, infants are before getting encephalitis due to viral infection. Symptoms of viral encephalitis in infants usually start with mild flu-like symptoms, such as fever, fatigue, weakness, headache, and aches in muscles or joints. The symptoms can be much more severe and include: Seizures, confusion, loss of sensation and paralysis, agitation or hallucinations, muscle weakness, loss of consciousness, and coma. In young children and infants, symptoms, and signs encountered: Tense fontanels, poor feeding, irritability, nausea, and vomiting [25]. Timely diagnosis and treatment are important because it is difficult to predict how encephalitis will affect each individual. Given the heterogeneity of the disease, epidemiological, laboratory, clinical, and radiographic examinations are required to make a diagnosis and prepare the therapeutical protocol. According to previous studies from around the world, more than a third of patients with SARS-CoV-2 develop neurological symptoms, convulsions, loss of sense of smell and taste, hallucinations, disorientation, confusion, movement disorders [26], [27], [28]. SARS-CoV-2 virus can result with: Encephalitis, brain edema, stroke, neurological disorder, and Guillain-Barré syndrome, where the immune system responds to SARS-CoV-2 infection with attacks nerve cells that lead to muscle weakness and paralysis [29], [30]. Once in the bloodstream, the brain barrier replicates and causes neurological involvement. Although most patients in the pediatric population are asymptomatic or have a mild clinical picture, in some of them, the clinical picture may deteriorate rapidly and lead to acute respiratory distress or respiratory failure. Some pediatric patients could occur severe clinical manifestations with myocardial injury or heart failure, hypoxic encephalopathy, coagulation dysfunction, shock, and acute kidney injury. In this case report, the fast-moving of the poor child health and aggressive progression of the disease with proven SARS CO2 19 virus we were absolutely engaged with the information of this child as having severe inflammatory reaction SIRS that progressively made meningoencephalitis affecting all areas of the brain (we could not predict how long it has been taken in the child body) because of poor information of the family but we suppose that it has probably taken longer than 2 days (with fever). Encephalitis is something that has made an infant in very bad condition and stops circulation and breathing [22], [23], [24]. Talking and sharing the experience with the colleagues from Swiss, we could have expected this to happen and we have performed all the procedures, including monitoring mechanical ventilation and drug therapy. No any specific drug for COVID-19 has been given.

Conclusion

In our study (in this case report study), we have presented 9-month-old infant with COVID-19 encephalitis who was referred to our clinic in convulsive status, fever (temperature 38.2), disturbed consciousness, severe clinical symptoms, and CT scan of the brain with the finding of enlarge lateral ventricles, intraventricular masses, and internal hydrocephalus. Our case report could suggest that SARS-CoV-2 infection may cause severe clinical symptoms, neurological manifestations, and encephalitis in infants.

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Effectiveness of the Use of Dexamethasone in Treatment of Coronavirus Infections: A Systematic Review

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Abstract

BACKGROUND: WHO declared the coronavirus disease (COVID)-19 outbreaks as a worldwide pandemic in March 2020. More than 1,500,000 confirmed cases have been diagnosed in more than 130 countries and regions, estimated to cause 93,000 deaths so far recorded on April 10, 2020. There is no vaccine or antiviral treatment for coronavirus.

METHODS: The literature sources from the research were obtained by searching for national and international journals. The journal is indexed in Google Scholar, PubMed, Science Direct, e-books, and others. Five journals were obtained, including a literature review, systematic review, and randomized controlled trials (RCT) discussing the use of dexamethasone in COVID-19 therapy, Middle East respiratory syndrome, and severe acute respiratory syndrome.

RESULTS: A study from Oxford University compared 2100 COVID-19 patients who received low and moderate potential dexamethasone at a dose of 6 mg/day for 10 days with 4300 COVID-19 patients who only received standard treatment for coronavirus infection. The results obtained in patients using ventilator mortality decreased from 40% to 28%, and patients using oxygen, the mortality rate decreased from 40% to 20%. The dexamethasone RCT study can reduce the death rate of 1 in 3 COVID-19 patients who received mechanical ventilation therapy and 1 in 5 patients who received oxygen therapy without mechanical ventilation but did not reduce patients' mortality rate who did not receive therapy oxygen.

CONCLUSION: The use of dexamethasone with oxygen therapy and mechanical ventilation can reduce mortality patients with COVID-19.

Introduction

Coronavirus (CoV) is an RNA virus of 120–160 nm particulate size. This virus infects mostly wildlife, including bats and camels. CoV is contagious with six types: Alphacoronavirus 229E, alphacoronavirus NL63, OC43 beta CoV, HKU1 beta-CoV, severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East Respiratory CoV Syndrome (Middle East respiratory syndrome [MERS]-CoV) [1], [2].

In December 2019, due to an unknown virus, some patients in Wuhan, Hubei, China, were diagnosed with secondary pneumonia. From December 31, 2019, to January 3, 2020, there was a significant increase in cases marked by 44 cases reported. This disease has spread in separate provinces in China, Thailand, Japan, and South Korea for <1 month [3], [4].

The sample studied shows the etiology of a new type of CoV. The name of this disease was originally the 2019 novel CoV (2019-nCoV). The WHO revealed a new name on February 11, 2020, CoV Disease (COVID-19), which was caused by the CoV-2 (SARS-CoV-2) extreme acute respiratory syndrome virus [5], [6].

In March 2020, the WHO proclaimed the COVID-19 epidemic a global pandemic. In more than 130 countries and regions, more than 1,500,000 confirmed cases are diagnosed, expected to cause 93,000 casualties as recorded on April 10, 2020 [7].

SARS-CoV-2 can cause various symptoms, including fever, fatigue, dry cough, myalgia, and difficulty breathing. There is evidence that SARS-CoV-2 variations have been produced from humans by respiratory outlets triggered by cough and sneezing [8]. There is no vaccine or antiviral treatment for CoV. Therefore, it is imperative to determine the treatment plan as soon as possible for the COVID-19 outbreak [9], [10], [11].

Dexamethasone is a corticosteroid preparation. Corticosteroids have an outstanding inhibitory effect on inflammatory factors and are typically used as an alternative treatment for viral pneumonia. Glucocorticoids are steroid hormones with anti-inflammatory properties that block pro-inflammatory genes encoding cytokine, chemokine, cellular adhesion molecules, inflammatory enzymes, and inflammatory process receptors [12].

Dexamethasone was shown to be the first drug to prevent CoV deaths in more than 430,000 patients worldwide, based on a randomized controlled clinical trial (randomized controlled trials [RCT]) study in the United Kingdom. Dexamethasone can decrease mortality by around one-third in patients with CoV infection ventilators in these tests [13], [14], [15]. Based on these problems, we are interested in conducting a literature review on the effectiveness of using dexamethasone in the treatment of CoV infections.

Methods

This literature uses the method of literature review. Sources from the research were obtained by searching for national and international journals. The journal is indexed in Google Scholar, PubMed, Science Direct, e-books, and others. Five bulletins were obtained, including a literature review, systematic review, and RCT discussing the use of dexamethasone in COVID-19 therapy, MERS, and SARS.

Results

In a recovery trial study in March 2020 conducted at Oxford University, a RCT tested various potential therapies. The research compares 2100 patients receiving low to moderate potential 6 mg a day dexamethasone for 10 days, with 4300 patients getting normal CoV treatment only. The findings found that dexamethasone had the most extraordinary effect relative to mildly ill people in seriously ill patients who used ventilators. The results of using dexamethasone in patients using a ventilator can reduce the risk of death from 40% to 28%. Dexamethasone also has an effect on patients taking oxygen therapy but not on the ventilator; an increase in mortality decreased from 40% to 20% [16].

Based on studies conducted by Chen *et al*., corticosteroids were administered to 401 SARS patients, in which there were 152 patients in the critical category. The results showed that corticosteroids reduced mortality and treatment time in acute SARS patients. Dose offered for <7 days is low-moderate (to 0.5–1 mg/kg body weight or equivalent of methylprednisolone) [17].

Built upon the RCT dexamethasone report, the mortality rate was reduced by 1 in 3 COVID-19 patients receiving mechanical ventilation and by 1 in 5 COVID-19 patients receiving oxygen therapy without mechanical ventilation, but mortality rates were not reduced in those without oxygen therapy [18], [19].

Table 1 shows the use of dexamethasone in the preliminary report and some guidelines that have used dexamethasone as a therapy in the treatment of COVID-19.

Discussion

Since the first study was released in December 2019, COVID-19 has gained worldwide interest because of its similarity to SARS-CoV and MERS-CoV in causing fatal respiratory illnesses and possibly contributing to significant human infections and their economic effects. The use of corticosteroid treatment is still under consideration in patients with SARS and MERS that are close to COVID-19 [24], [25].

Corticosteroid therapy of patients with SARS is used regardless of the early anecdotal knowledge,

Table 1: Using dexamethasone

References	Year	Drug	Trial and clinical experience	Dosage
Horby Peters [20]	2020	Dexamethasone intravenous	A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75–0.93; p<0.001) In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51–0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72–0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91–1.55)	6 mg once daily for up to 10 day
Guidelines CHKD [21], [22]	2020	Dexamethasone intravenous and peroral	Dexamethasone should not be used in COVID-19 (+) patients who are: a) Otherwise healthy and do not require respiratory support Dexamethasone should be utilized in COVID-19 (+) patients with: a) Respiratory support (oxygen or invasive mechanical ventilation) b) An underlying condition requiring chronic steroid treatment, steroids should be continued c) An additional diagnosis where steroid therapy is appropriate	0.15 mg/kg once daily (Max: 6 mg)
Raymond [23]	2020	Dexamethasone	In the RECOVERY trial, dexamethasone was beneficial for participants treated seven or more days into the symptomatic phase, with the onset of hypoxemia. Importantly, there was a non-significant trend (P=0.14) toward possible harm affecting participants without hypoxemia and not on mechanical ventilation. RECOVERY findings, therefore, support use of dexamethasone only for patients with hypoxemia, not those with milder disease. The data do not support the use of dexamethasone or other corticosteroids in the outpatient setting	6 mg/day

and it is comparable of patients with acute respiratory distress syndrome (ARDS) to radiological and histologic observations in essential diseases [26], [27]. In March 2003, the proposed high dose glucocorticoids should be used based on Chinese SARS treatment trials if the patient has a fever for more than three days or if radiological reports are indicative. Persistent pulmonary activity or gradual decline In Bronchiolitis obliterans, the radiographic picture with pneumonia and likeness of the histologic features to those of early ARDS in postmortem studies have prompted doctors in china use corticosteroids in combination with ribavirin for the treatment of SARS. In ARDS and particularly in Bronchiolitis obliterans with organizing pneumonia, corticosteroid therapy with ribavirin has been used with some success in the resolution of fever and lung opacities within two weeks [28].

Recovery trials conducted at Oxford University show that at the dose of dexamethasone tested, steroid treatment benefits may outweigh the potential harm posed. This research did not find any remarkable medication side effects. According to Anthonia, a deformed or hyperactive inflammatory reaction in patients with a ventilator leads to morbidity, mortality, and clear viral effects [13].

The corticosteroid partnership in SARS management may be complicated with acute lung injury (ALI)/ARDS. Excessive systemic inflammation has been identified in ARDS and B emission factors may lead to glucosteroid tolerance, which is related to relative adrenal insufficiency and further degradation of ARDS. Use methylprednisolone, which can be used to solve problems by recovering systemically. The present opinion thus indicates that ARDS steroid therapy can only be done on the basis of relative loss due to systemic inflammation and targeted at increasing systemic inflammation. The length of the steroid depends on the inflammatory length. In summary, appropriate advice for ALI/ARDS steroid administration involves the initialization of a sufficient steroid dosage at a time of relative adrenal insufficiency, discussed in terms of steroid application. Steroids need not, however, be delayed until ARDS continues [17], [29], [30].

Corticosteroids will dramatically reduce the concentrations of interleukin (IL)-8, monocyte protein-1, and induced protein-10 from days 5 to 8 after treatment. In further analysis, IL-10, IL-6, and tumor necrose (tumor necrosis factor [TNF]) levels were higher than average before intake. Corticosteroid treatment still decreases IL-10 but not IL-6 and TNF. The data show the benefits of steroid therapy in reducing the lungs’ reserve response and protection [28], [31].

They observed that corticosteroids, large doses of 2019-nCoV pneumonia such as secondary infections, long-term complications, and extended-release of the virus were likely based on corresponding research. However, severe inflammation and cytokine-related lung injuries can rapidly cause progressive pneumonia in critically ill patients. Doctors of the Chinese Thoracic Community have formed a consensus of experts on pneumonia corticosteroids 2019-nCoV. Under the expert’s agreement on the basics of use with corticosteroids to be discussed;(1) The role of corticosteroids in suppressing the production of dysregulated cytokines patient with pneumonia in 2019-ncoV (2) Corticosteroid must be used with caution in a critically diseased patient with pneumonia in 2019-ncoV; (3) with hypoxia patients [32].

Conclusion

The use of dexamethasone with oxygen therapy and mechanical ventilation can reduce mortality patients with COVID-19.

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Fighting against COVID-19 and Fighting against Stigma: A Mini-review

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Abstract

COVID-19 is a new global disease. Over time, COVID-19 shows itself not only as a disease that causes illness, death, and economic downturn but also social impacts. In this mini-review, the authors will discuss how stigmatization has occurred following the occurrence of COVID-19 and has afflicting not only patients and their families but also medical personnel who are struggling to save those affected. It is recommended that stigmatization must be stopped because if this continues that it will worsen the situation of the COVID-19 pandemic by organizing mentoring health services for patients, providing accurate and credible information, and, at the same time, encouraging the community's social cohesion to care for others.

Introduction

COVID-19 is sweeping the world so fast. In only about 8 months, millions of people have been infected. The WHO said that globally more than 40 million people currently have been infected, with the number of deaths reaching more than 1 million people [1]. The global response continues to be carried out to find a vaccine which, unfortunately, has not been produced yet [2].

In accordance with the findings of health experts that COVID-19 is a disease that attacks multiple organs, the impact of COVID-19 is increasingly visible in many aspects. Apart from the economic impact, COVID-19 also shows another significant impact that is also dangerous, namely, social stigma. Sadly, this social stigma affects not only patients but also health workers and even COVID-19 survivors [3].

Therefore, the current world struggle is not only against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus but also against the stigma that accompanies the presence and spread of the virus. If, at this time, the SARS-CoV-2 virus could be identified by its method of spread, the social stigma would not be easy to overcome because it spreads through the social system in society.

Social Context

The definition of social stigma raised by Goffman explains the social situation that occurs by the presence of stigma. By stigmatization, there is an event that discredits a person from their usual condition, to be "a tainted, discounted one" [4]. As a social dimension, stigma does not occur in empty space but social interactions in a society. One of the causes of stigma is an excessive fear of something, which is not only due to physical things but also on the labeling of something/someone [5]. In other words, stigma cannot be separated from the ongoing social framing.

Since the onset of this pandemic, the emphasis on isolating patients has been voiced by the WHO [6]. The quarantine procedure is carried out to prevent the transmission of COVID-19 to healthy groups of people.

Evidence-based treatment measures recommend that at least isolate the patient if placement in a special quarantine location is not possible.

However, unfortunately, the limitation on these patients has become a framing that has resulted in social stigma. Patients are labeled dangerous so that unconsciously efforts to prevent disease transmission have created excessive fear and encouraged social stigma [7]. Although the WHO has provided an early warning that the current enemy of humans is not only the virus that causes COVID-19 but also stigmatization [8], this stigma has spread everywhere and created a huge impact that was never previously anticipated.

Apart from framing the sufferer, one of the causes of this stigma lies in human psychology. It is normal for humans to develop protection for themselves [9]. This desire encourages humans to bring up self-defense mechanisms from something outside themselves. When people with COVID-19 are perceived to have a virus that can threaten someone's safety, then automatically, other people will do something, including showing social stigma. As warned by the WHO that in an outbreak situation, "people are labeled, stereotyped, discriminated against, treated separately, and/or experience loss of status due to a perceived link with a disease" [10].

Impacts

As a social problem, stigma has a very significant serious impact as does other diseases such as tuberculosis [9], [10], [11] or HIV/AIDS [12], [13], [14], [15]. At least, due to the stigma that exists, people who are exposed to COVID-19 tend to hide their illness. As a result, they will not immediately seek treatment when it is really needed. In the end, they will not make behavioral changes, which should be needed in the appropriate conditions [16]. The Indonesian Ministry of Health stated that the high number of deaths due to COVID-19 was influenced by the delay in handling patients due to this social stigma [17]. These conditions are clearly very dangerous because the transmission of COVID-19 in the community will be hidden, like an iceberg phenomenon. COVID-19 will spread silently in society and cause tragic deaths.

The big impact of stigma that is still continues to occur is also seen in the occurrence of injustice to a person or community group [18]. The Jakarta Post, in its August 30, 2020 edition, reveals the story of a young woman who recovered from Covid-19. She experienced a social stigma that is so obvious. When she returned to her place of work, her friends greeted her so coldly, her coworkers avoided her, even some of them no longer wanted to have lunch with her. Sadly, she was blamed for the infection of some of her colleagues [19].

The public's fear of COVID-19 infection can be seen from the stories of the Westerdam passengers, as reported by the New York Times. When one passenger was found positive, more than 1500 others had to be tested. While waiting for the test results, not a single country was willing to accept the ship due to fears of the spread of COVID-19. Some of the ship's passengers, who then got off the ship with negative test results, actually received rejection and even hate speech from their own neighbors [20].

Stigmatization also seems to eliminate our human feelings. Facts show that many patients who died due to COVID-19 were refused burial by the public. People still think that the bodies of people who died due to COVID-19 are still dangerous, so they do not want burials in their residential areas [21]. The rejection of the patients who died due to COVID-19 is not much different from the rejection of those who are detected positive for COVID-19 even though they survived the disease.

The fear of this disease is, indeed, natural, and considering that this virus is still not well recognized at the beginning of its occurrence. Experts and the public do not have a clear understanding of this virus, including the method of spread and its effects. Hence, it is no wonder at the beginning of the outbreak of COVID-19; this stigma spreads so fast. However, it is very unfortunate that, over time, the stigma that occurs, which does not decrease, it even affects health workers [22].

Medical personnel who serve patients in hospitals experience a stigma that is sometimes so terrible because they are thought to be transmitting the disease. Therefore, in many places, they dare not wear their medical clothes due to the pressure that appears on them. Even nurses and doctors not only accept social pressure, even violent behavior [23].

This is clearly a very big problem. At present, the whole world needs medical personnel. In some places, the government has even been forced to take emergency measures by sending medical students who have not yet completed their education to serve the increasing number of patients. Health workers are exhausted due to the number of cases they have to handle, while the equipment available is very limited. There are even doctors who kill themselves because they are unable to see the suffering in their patients [24]. However, it is during times of crisis as well, stigma occurs on health workers and exacerbates emergency situations like this.

Seven months after the first case was reported, the stigma was still emerging. In West Java, Indonesia, for example, the houses of COVID-19 patients are fenced off by neighbors. Neighbors think that they can get the virus [25].

Against Stigma

The presence of COVID-19 has presented a huge challenge to policymakers in the field of public health. The COVID-19 pandemic has opened our minds to various problems that we never imagined would happen. The consequences of this stigma should encourage us to start thinking about mental health development efforts, far beyond what has been considered the traditional area of mental health. At present, the mental health of patients is considered very important. Many health facilities have developed mentoring efforts with patients to prevent the impact of this stigma on their mental health. However, people’s mental health is something that cannot be ignored [26]. Of course, the stigma begins with people’s insufficient knowledge of COVID-19. Therefore, after 10 months have passed, even though something is still unknown about this disease, more adequate information should be able to be conveyed to the public. Fighting the stigma caused by COVID-19 also means fighting the circulation of incorrect and even misleading information, especially relating to patients and their families, and even medical personnel [16], [24].

The government must provide a special information channel about COVID-19. This has been taken by many countries by providing important information regarding the prevention and handling of COVID-19 from the household level [25], [26], [27]. However, the government should also routinely enter into citizens’ social media channels by conveying accurate information and countering misleading information circulating in the community. In situations where restrictions are imposed, social media is the community’s top choice, and the problem of stigma unfortunately often originates there.

Instead of allowing the public to just accept misinformation, the health authorities should also encourage efforts to increase the social strength of the community. The community must be motivated so that they are actively motivated to help, pay attention, and give respect to their neighbors, their acquaintances and even anyone affected by COVID-19 because maybe they will need the same thing in the future. Increasing the social cohesion of the community is also a challenge that requires consistency and seriousness of the government in overcoming this stigma.

Therefore, involving community and religious leaders is essential [28], [29], [30], [31]. Their involvement will accelerate the eradication of this stigma. They can tell the public not to give negative labels to patients; they can even convey correct information for the public to know. They can also spread the right message about COVID-19 so that people know what is right and what they should avoid. In one region in Indonesia, for example, food and basic necessities for positive patients are even provided by religious groups. This created positive support for the patients [32]. Inevitably, there are too many opportunities to raise our awareness of the dangers that follow COVID-19.

Conclusion

Stigma is a serious problem that greatly affects efforts to control and handle COVID-19. Therefore, various efforts must be made to prevent the stigmatization of patients, health workers, and people infected with COVID-19.

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Response Times of Motorcycle Ambulances during the COVID-19 Pandemic

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Abstract

BACKGROUND: Motorcycles (motorlance) are often deployed as ambulances to the scene of an emergency to reduce response time. The COVID-19 pandemic has affected emergency medical services (EMS) in Thailand in many respects, and this study was conducted to examine its effect on motorlance operation time.

AIM: The aim of the study was to examine motorlance operation time during the COVID-19 pandemic in comparison to normal periods.

METHODS: This cross-sectional study examined all EMS motorlance operations dispatched from Srinagarind Hospital (Thailand). Data were collected from the Srinagarind Hospital EMS operation database and hospital information database system. Data from June 1, 2018, to December 31, 2019 (normal period) were compared with those from January 13 to April 21, 2020 (COVID-19).

RESULTS: Eight hundred seventy-one EMS operations were examined over two periods. Mean patient age during the COVID-19 pandemic was 41.5 ± 6.2 years, and 54.6% (n = 59) were male. Average response time was 6.20 ± 1.35 min during the normal period and 3.48 ± 1.01 min during the pandemic ($p = 0.021$). Transport time was also significantly shorter during the latter period (2.35 vs. 5.20 min).

CONCLUSIONS: Motorlance response and transport time during the COVID-19 pandemic were significantly shorter than usual.

Introduction

Motorcycles (motorlance) are often deployed as ambulances to the scenes of emergencies in large cities with traffic problems or during rush hour to reduce response time [1]. They allow for rapid access to patients, reduced waiting times, and increased response to emergency expectations [2]. The motorlance can also be used to deliver patients with mild symptoms or pregnant women from primary care units to the hospital [3], [4]. In Scandinavian countries, motorlances are used in cases of cardiac arrest outside the hospital or severe accidents to allow for rapid access to the scene [5], [6]. In addition, a previous study found that the costs of using a motorlance were lower than those of van ambulances [7]. Motorlances can be used in both basic and advanced emergency situations, including those requiring a defibrillator [8]. In South Korea, there is a 5-min time limit to reach patients with out-of-hospital cardiac arrest (OHCA). In the United States, the time allowed to reach a trauma patient is no more than 9 min [9]. Because of this, various efforts have been made to reduce the time it takes to reach patients [10], [11], [12], [13].

The COVID-19 (novel coronavirus 2019, 2019-nCoV) pandemic, announced by the world health organization in mid-March 2020 and continuing into the present [14], [15], [16], [17], [18] has affected health services [19], [20], socioeconomics, and people's lifestyles, all of which are factors that impact emergency medical services (EMS). However, there have yet been no studies of motorlance response time during the COVID-19 pandemic. This study was thus conducted to compare EMS operation time through motorlance during the pandemic versus normal periods.

Methods

The present study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (HE631278). The requirement for informed consent from the patients was waived since patient confidentiality protection had been guaranteed by identifying them using a unique study number, rather than by name.

Study population and design

This cross-sectional study examined all motorlance operations dispatched from Srinagarind Hospital through Thailand's emergency telephone services (number: 1669). Cases in which the patients were under 18 years of age or for which there were missing data were excluded from this study. Data were recorded using the operation national standard checklist for EMS in Thailand. Data were collected from the Srinagarind Hospital EMS operation database and hospital information database system.

Definitions

Motorlance service during the COVID-19 pandemic was defined as operations in which a motorlance was deployed between January 13 and April 21, 2020 (the date of the first confirmed case of COVID-19 in Thailand according to the Ministry of Public Health and day 100). We used the period from June 1, 2018, to December 31, 2019, as a normal period for comparison. Activation time was defined as the time from dispatch to resources being en route, response time was defined as time from 1669 center call receipt to arrival on scene, on-scene time was defined as the time between the responding ambulance arriving on location and its departure with the patient to the emergency department, and transport time was defined as the time from the scene of the emergency to arrival at the hospital. Time from dispatch to the arrival of the automated external defibrillator (AED) on scene was defined as AED waiting time.

Statistical analysis

The sample size was calculated based on the number of motorlance deployments from Srinagarind Hospital EMS by Apiratwarakul [13]. To achieve a significance level of 5% and power of test of 0.8, we determined that a sample size of 871 would be required. Statistical analysis was performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as percentages, and continuous data were presented using mean and standard deviation. Univariable analysis was performed using a two-sample t-test for numerical data and a Pearson's correlation for data relationships between the two groups.

Results

Eight hundred seventy-one EMS operations were examined over the two periods of the study, 108 (12.4%) of which were conducted during the COVID-19 pandemic. The characteristics of the subjects and services are shown in Table 1. The mean age of patients who received motorlance service during the pandemic was 41.5 ± 6.2 years, and 54.6% (n = 59) were male. Operations in both groups were most commonly performed on non-holidays (68.3% during the normal period and 59.3% during COVID-19). Most cases in both groups involved non-trauma patients. The severity of patients' signs and symptoms were classified by color according to the Thai criteria-based dispatch (CBD) triage system. During the COVID-19 pandemic, CBD codes were red in 11.1% of cases, yellow in 48.1%, and green in 40.8%.

Table 1: Characteristics of the subjects

Characteristics	Normal period (n = 763), n (%)	COVID-19 pandemic service (n = 108), n (%)	p-value
Age (years) Mean ± SD	38.4 ± 5.2	41.5 ± 6.2	0.202
Sex: male	398 (52.2)	59 (54.6)	0.852
Operation day			
Non-holiday	521 (68.3)	64 (59.3)	0.651
Holiday	242 (31.7)	44 (41.7)	0.752
Type			
Non-trauma	548 (71.8)	82 (75.9)	0.810
Trauma	215 (28.2)	26 (24.1)	0.740
EMS triage level			
Red	103 (13.5)	12 (11.1)	0.650
Yellow	375 (49.1)	52 (48.1)	0.742
Green	285 (37.4)	44 (40.8)	0.785

Activation times during the normal period and the COVID-19 pandemic were 0.58 ± 0.20 and 0.56 ± 0.12 min, respectively (p = 0.680; Table 2), and response times were 6.20 ± 1.35 and 3.48 ± 1.01 min, respectively (p = 0.021). Transport time during the pandemic was significantly lower than in the other period (2.35 vs. 5.20 min).

Table 2: Operation time in motorlance

Operation time (min) Mean ± SD	Normal services (n = 763)	COVID-19 pandemic service (n = 108)	p-value
Activation time	0.58 ± 0.20	0.56 ± 0.12	0.680
Response time	6.20 ± 1.35	3.48 ± 1.01	0.021*
On-scene time	6.41 ± 1.20	6.33 ± 1.17	0.577
Transport time	5.20 ± 0.58	2.35 ± 1.01	0.010*

*Statistical significance.

Motorlances were dispatched to cardiac arrest patients a total of 38 times. Response times during the normal period and the COVID-19 pandemic were 7.11 ± 0.42 min and 4.01 ± 0.20 min, respectively (p < 0.001; Table 3). Mean AED waiting time during the pandemic was also significantly lower than in the normal period (3.20 vs. 5.20 min), but the mortality rates of the two groups were similar.

Table 3: Motorlance services for cardiac arrest patients

Procedures	Normal services (n = 33)	COVID-19 pandemic service (n = 5)	p-value
Response time (min) Mean ± SD	7.11 ± 0.42	4.01 ± 0.20	<0.001*
AED waiting time (min) Mean ± SD	5.20 ± 0.26	3.20 ± 0.36	<0.001*
Mortality, n (%)			
Survived	4 (12.1)	1 (20.0)	0.068
Did not survive	28 (87.9)	4 (80.0)	0.055

*Statistical significance.

Discussion

This study is a comparison of EMS motorlance operation during the COVID-19 pandemic versus normal circumstances. Motorlance response and transport time during the pandemic were significantly lower than during the normal period [13], [21], [22], [23]. This is likely due to reduced traffic as a result of workplaces and schools being closed and more people staying home in general. The most important function of a motorlance is to reach the scene quickly, assess symptoms, and provide the necessary treatment. Less important is its role in delivering patients to the hospital, which is usually carried out using a traditional ambulance. However, in many African countries, the Motorlances play a greater role in patient transport, mostly because of shortages of other types of ambulance. Previous studies have found correlations between national economic indicators and EMS response time [15], [16], [17], [18].

We also found decreases in response and AED waiting times (when the AED is attached to a motorlance) for patients with OHCA during the COVID-19 pandemic. In addition, response time was lower than in previous studies, which has varied from 5 to 15 min depending on the country, but in most countries, it was 8 min. These findings demonstrate the efficiency of the EMS unit in terms of notification of the incident, response of EMS members, and management of the vehicle en route. It may also be due to the fact that the area for which Srinagarind Hospital EMS is responsible is relatively small, including only a university and the surrounding communities. In addition, the small roads in the area are more suitable for motorcycles than larger vehicles. Although response and AED waiting times for OHCA patients were lower during the pandemic, there was no significant difference in mortality rate between the two periods.

The present study was limited in that data were gathered from only one EMS center and that the study design was retrospective, which may have resulted in incomplete data collection [24], [25].

Conclusions

The motorlance response and transport times during the COVID-19 pandemic were significantly lower than normal, both overall and in cases of OHCA.

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An Old Therapy, Convalescent Plasma, for Coronavirus Disease-19: Do We Have All the Answer?

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Abstract

BACKGROUND: Coronavirus (CoV) disease (COVID-19) has become a global health pandemic by early 2020; it has pushed the health-care system to its limit. From the initial estimates, 15% of COVID-19 patients caused by severe acute respiratory CoV 2 syndrome present with severe symptoms and requires hospitalization or even intensive care. There is no specific treatment against COVID-19, particularly for those with severe symptoms. Desperation caused by COVID-19 has driven clinicians to try an alternative therapies with little or even no-evidence previously. Convalescent plasma therapy (CPT) has emerged as a promising COVID-19 therapy.

AIM: We aimed to review current state of convalescent plasma therapy.

METHODS: We summarize the historical CPT, COVID-19 pathology and evaluate potential of CPT for COVID-19; raising the question regarding routinely administrating CPT to the COVID-19 patients, whether it is safe and effective.

RESULTS: From cases in Indonesia and other countries, there is bunch of examples that healthcare workers being negatively stigmatized in case of COVID-19. They lost their rights to have a normal life in this pandemic era. A reasonable basis is found in many literatures to advocate the CPT. Convalescent plasma from COVID-19 patients who had been recovered with high neutralizing antibody titers was reported to be effective on transfusion to other COVID-19 patients.

CONCLUSION: CPT is one good option to treat COVID-19 patients, but it not without risk; many potential candidate treatment that promising in theory but somehow fall apart when translated into clinical study; only time will tell, including our ongoing CPT clinical study.

Introduction

Coronavirus (CoV) disease (COVID-19) is currently a global health problem, but until recently, there is no specific therapy for COVID-19 [1]. Since December 2019, pneumonia cases caused by severe acute respiratory syndrome-CoV-2 (SARS-CoV-2) until May 24, 2020, have reported total 5,429,234 cases with 344,448 deaths and 2,259,882 recovered, with a percentage of case fatality rate (CFR) in the world of 6.48% [2]. The most cases were found in the USA with 1,667,284 cases, followed by Brazil with 349,113 cases then Russia with 344,481 cases, while the Republic of China, where the virus originated, was in the 14 ranks with 82,974 cases. The highest death cases were in the USA which was 98,691 people, followed by the UK with 36,675 people and Italy 32,735 people; while deaths in the Republic of China reached 4,634 cases [2]. In Indonesia, as of May 24, 2020, there were 22,271 reported cases, with a total of 1372 deaths and 5402 recovered [3]. Since March 11, 2020, the World Health Organization (WHO) has established pandemic status for the COVID-19 case [4].

The COVID-19 case was first identified in Indonesia in early March 2020, which infected two patients, then spread to all provinces in Indonesia [5], [6]. The CFR rate in Indonesia reached 6.21%, surpassing the Republic of China with 5.52% or even almost equal with the world (6.48%). Patients who were confirmed positive, most came from Jakarta, which reached 6515 cases, East Java Province ranks second with 3596 cases, followed by West Java Province with 2045 cases [3]. There were 2045 positive confirmed cases in West Java Province, with recovered of 471 people and a death toll of 127 [3]. Until May 22, 2020, Dr. Hasan Sadikin Hospital (RSHS), Bandung, West Java, had treated 308 patients in monitoring (PIM) cases, with confirmed COVID-19 positive of 75 cases; there were 57 PIM death cases, with confirmed COVID-19 positive of 23 cases [7]. The therapy used in RSHS refers to the COVID-19 therapy protocol from the Indonesian Lung Association, including chloroquine phosphate, oseltamivir, and other supportive therapies [8].

Globally, all health authorities are planning (and constantly scrambling) for the increased growing number of hospitalized patients. With the absence of any detectable natural immunity to this CoV in the population, and no known therapy or vaccinations, management has been largely supportive to date [9]. Nevertheless, a number of therapies are being investigated and implemented by researchers and clinicians. Those clinical trials including: Retroviral drugs such as lopinavir/ritonavir and remdesivir, combination of hydroxychloroquine and azithromycin, and anti-malarial drug chloroquine [10]. The other modality that has been investigated and advocated for alternative treatment of COVID-19 is convalescent plasma therapy (CPT) in the world, as well as in Indonesia [1], [11].

CPT has been known and used to preventing viral diseases such as mumps, measles, and poliomyelitis [12], [13]. This therapy also has been used effectively in the treatment of H5N1 avian influenza [14], H1N1 influenza [15], SARS [16], and Middle East respiratory syndrome (MERS) [17], in which CPT has been found to be both safe and effective. Our center in Bandung, has just started to begin the CPT clinical trial for patients with severe COVID-19 (Ethical approval No. LB.02.01/X.6.5/94/2020).

SARS-CoV-2

CoV disease 2019 (COVID-19) is a form of respiratory illness caused by severe acute respiratory syndrome CoV 2 (SARS-CoV-2); CoV is a capsule-positive, single-stranded RNA virus, included in the *Coronaviridae* family belong to the *Orthocoronavirinae* subfamily, and has a "crown-like" in its surface area [18]. CoV is included in the genus beta-CoV as (SARS; emerged in China in 2003), (MERS; appeared in Saudi Arabia in 2012) but has different biological and virulence characteristics [19]. Bats are considered as the natural host reservoir of SARS-like CoV. However, the origin or natural host for the 2019-nCoV is not clear, it might come from a kind of wild life [20]. SARS-CoV-2 is as big as 125 nm in diameter; they are also relatively large for the viruses that use RNA to replicate; with 30,000 genetic bases, the largest genomes of all RNA viruses. SARS-CoV-2 has 29,891 nucleotides which encode 9860 amino acids [18]. Their genomes are more than 3 times as big as those of HIV and hepatitis C, and more than twice influenza's [21]. SARS-CoV-2 is so far estimated to have a rate of <25 mutations per year, compare to influenza's 50 [22]. The fatality rates of both SARS and MERS are much higher, 9.6% and 34.4%, respectively [23], [24]. Infographic comparison of the three major genus beta-CoV, SARS, and MERS compared to COVID-19 is shown in Figure 1.

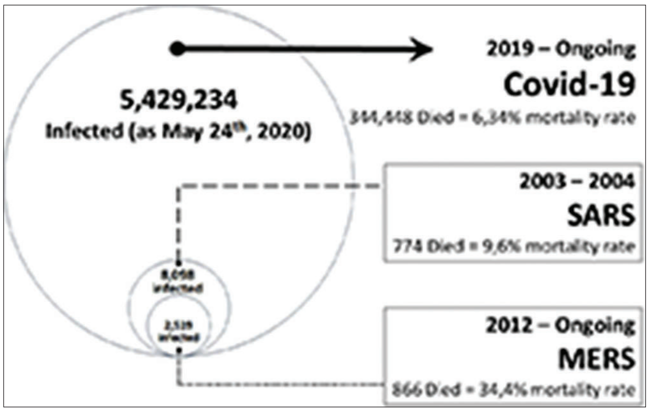

Figure 1: Infographic comparison of the three major genus beta-coronavirus, namely: severe acute respiratory syndrome (emerged in China in 2002), Middle East respiratory syndrome (appeared in Saudi Arabia in 2012) and coronavirus disease 2019 (COVID-19; appeared in China in late 2019)

All CoVs contain very specific genes in open reading frame 1 (ORF1) downstream regions that encode proteins for viral replication, nucleocapsid, and spikes formation [25]. The glycoprotein spikes on the outer surface of CoVs are responsible for the attachment and entry of the virus to host cells. The receptor-binding domain (RBD) is loosely attached among virus; therefore, the virus may infect multiple hosts [26], [27]. SARS-CoV-2 possesses the typical CoV structure with spike protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins [28], [29]. The 394 glutamine residue in the RBD region of SARS-CoV-2 is recognized by the critical lysine 31 residue on the human angiotensin converting enzyme 2 (ACE2) receptor [30]. According to current evidence, SARS-CoV-2 is primarily transmitted between the people through respiratory droplets and contact routes.

Although SARS-CoV-2 shares 79% of its genome with SARS-CoV, it presumably more contagious [31]. As recently Indonesia submitted three full sequence genome (ID: EIJK2444, EIJK 0141 and EIJK 0317) to Global Initiative on Sharing AvIan flu Data (GISAID); interestingly, all COVID-19 in Indonesia is originated from the Republic of China and been mutated as non-synonymous. For EIJK2444, travel from the Republic of China to Australia and Japan, finally arrived in Indonesia; it mutated in the amino acid Threonine at position 76, converting it to Isoleusin in the amino acid sequence of protein S. For EIJK0141, travel from the Republic of China to United Kingdom and United State, and finally arrived in Indonesia; it mutated in the amino acid Serine at position 2103, converting it to Phenilalanine in the amino acid sequence of protein ORF1a. For EIJK0317, travel from the Republic of China to United

Kingdom, United State and United Arab Emirates, and finally arrived in Indonesia; it mutated in the amino acid Isoleucine at position 461, converting it to Valine in the amino acid sequence of protein ORF1a [32].

Both of SARS-CoVs enter the host cells through ACE2 receptor [30]. The SARS-CoV-2 predominantly infects the lower airways and binds to ACE2 on surface alveolar epithelial cells. Both viruses are potent inducers of inflammatory cytokines. The cytokine storm or cytokine cascade is the postulated mechanism for organ damage. The virus activates immune cells, induces the secretion of inflammatory cytokines and chemokines into pulmonary vascular endothelial cells [33]. There were 14 cytokines that significantly elevated on admission in COVID-19 cases. Moreover, IP-10, MCP-3, and IL-1ra were significantly higher in severe cases and highly associated with the PaO_2/FaO_2 and Murray score [34].

Pathology of COVID-19

The S protein on CoV surface specifically recognizes the spike protein in ACE2 of the exposed cell and after binding, the virus enters the cell thereby infected the cell [30]. Unfortunately, the ACE2 receptor is widely distributed on the human cells surface, especially at AT2 (alveolar cell type II) of the lungs. ACE2 receptors are also abundantly found in the heart, liver, digestive organs, and kidneys. In fact, almost all endothelial and smooth muscle cells in our organ express ACE2; therefore, once virus enters the blood circulation, it spreads widely in the body [35]. All tissues and organs expressing ACE2 could be "the battlefield" of the CoV against immune cells. Based on Huang *et al*., (2020), most COVID-19 patients presented with dry cough, fever, dyspnea, and bilateral ground-glass opacities on chest computed tomography scans [20]. These COVID-19 infection characteristics bear a certain resemblance to SARS and MERS infections [36], [37] However, few patients with COVID-19 infection had prominent upper respiratory tract signs and symptoms (such as rhinorrhea, sneezing, or sore throat), indicating that the target cells may be located in the lower airway. Based on Indonesian task force for COVID-19, most death cases related to airway problem (cough 17.3% and breathing difficulties 14.7%) [3]. Further, COVID-19 patients rarely developed intestinal signs and symptoms (like diarrhea), whereas about 20–25% of patients with SARS or MERS infection had diarrhea [20], [37]; in Indonesia about 7.6–8.2% [3]. In severe form of COVID-19, CoV infection stimulates a cytokine storm that lead to acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection that lead to generalized sepsis thus multiorgan failure, which eventually lead to death [38]. Avoiding

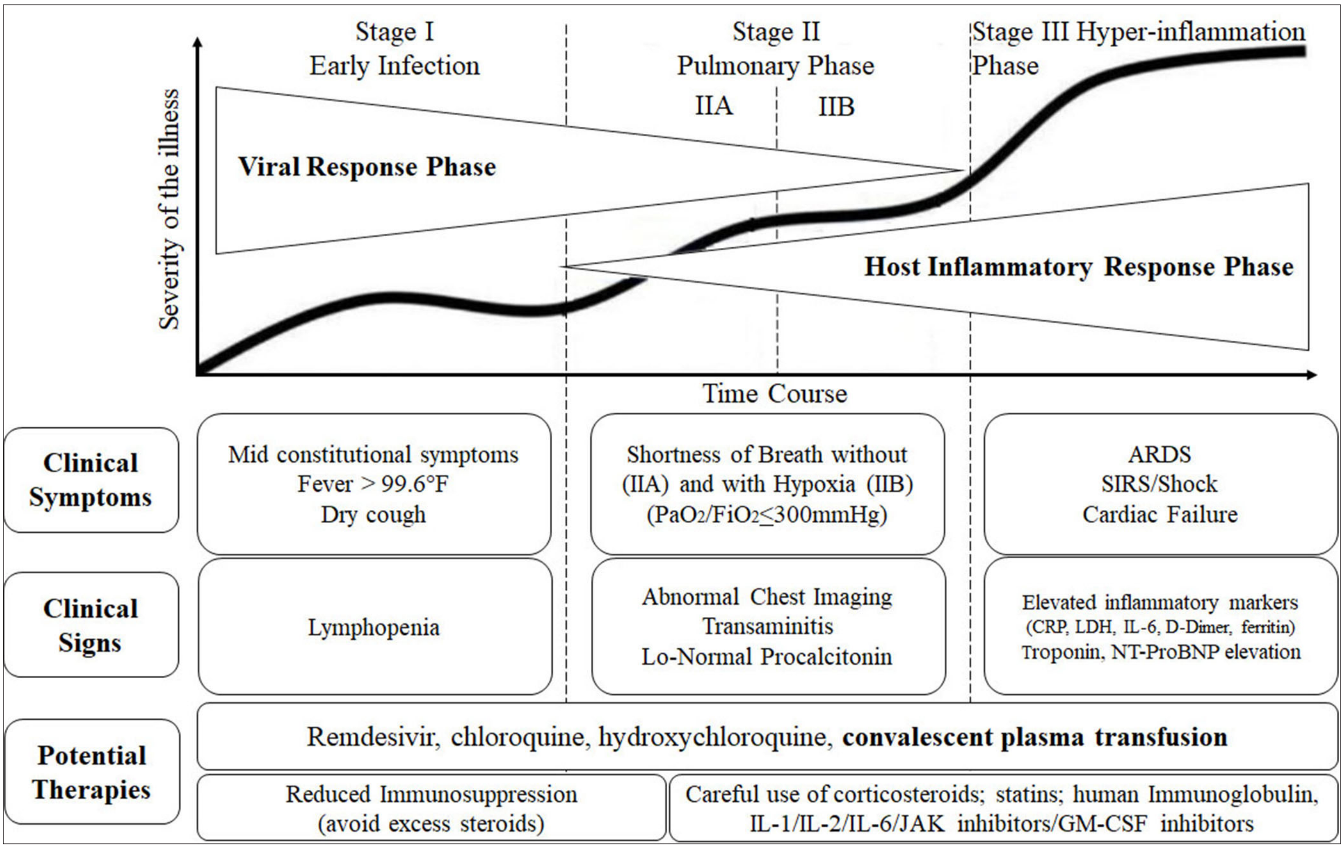

Figure 2: Three-stage classification system proposed by Siddiqi HK and Mehra MR [39], recognizing that coronavirus disease-19 illness exhibits three grades of increasing severity, which correspond with distinct clinical findings, response to therapy, and clinical outcome

or modulating the cytokine storm maybe the key for treatment of severe/critical patients with COVID-19 summarized in Figure 2 [39].

CPT

Desperation caused by COVID-19, the high mortality rate caused by ARDS that has not been successfully cured with conventional therapy and the increasing need for intensive care unit due to its accelerating number of ARDS sufferers has driven clinicians to try an alternative therapies with little or even no-evidence therapy previously (e.g., herbal medicine, cell-based therapy, and CPT). Convalescent plasma is a treatment that known for more than 100 years ago that the 1st time described in JAMA in 1893, when the German scientists used the serum from animal immunized against diphtheria to treat patients with the disease [21]. CPT also had been used against the 1918 Spanish flu pandemic, measles, MERS, Ebola, and SARS [21]. CPT is considered as out-of-dated approach for modern diseases, such as COVID-19, compared with all the advanced technologies in medicine and the entire novel breakthrough in molecular biology that we know today.

CPT has emerged as a potential therapy for patients with severe COVID-19. The principle of CPT is to use antibodies from the healthy people who had recovered from COVID-19 (a.k.a convalescent); as antibody-rich in their plasma to provide neutralizing effects for high viral load and to calm down the cytokine storm in patients with severe COVID-19. CPT is particularly encouraged to utilize in patients with severe COVID-19 (ARDS) those have no other “effective” treatment. CPT are useful against emerging infectious agents if the latter induces neutralizing antibodies [40]. The effectiveness of CPT appears to differ depending on the pathogen and treatment protocols (e.g., timing, volume, and dosing of administration) [41]. CPT is not a novel concept. It has been applied to the prevention and treatment of many infectious diseases. The successful of CPT to treat the severe acute viral respiration infections brings optimism in the management of the COVID-19 [12]. A meta-analysis from 32 studies of SARS and severe influenza showed a statistically significant reduction in the pooled odds of mortality following CPT, compared with placebo or no therapy (odds ratio, 0.25; 95% CI) [40]. In 2014, the WHO suggested the use of CP obtained from patients recovering from Ebola virus disease (EVD) as an empirical treatment during outbreaks [42]; unfortunately, CPT was not associated with a significant improvement in survival for EVD. Recently, in 2019, there was published one report for randomized clinical trial (RCT) of 140 children and adults with influenza treated either CPT with high level of anti-influenza antibodies or to standard plasma. Those double-blind study concluded that the anti-influenza CPT coffered no significant benefit superior versus standard plasma [43].

The Principle of Convalescent Blood Products Administration

After 10–14 days of infections usually followed by the clearance of viremia, this was the principle of convalescent blood products administration that usually performed after the initial symptoms to maximize efficacy [16]. Concurrent treatments might synergize or antagonize CPT efficacy (e.g., polyclonal intravenous immunoglobulins or steroids) [44]. Since the virological and clinical characteristics share similarity among SARS, MERS, and COVID-19, CPT might be a promising treatment option for COVID-19 rescue. The most critically ill patients show prolonged viremia (strongly correlated with serum IL-6 levels) which leaves room for the therapeutic intervention with antivirals and immunoglobulins even in late stages [45]. Viral shedding in survivors can be as long as 37 days, mandating SARS-CoV-2 RNA screening in CP donors [46]. Appearance of serum IgM and IgA antibody in COVID-19 occurs since day 5 after symptom onset, while IgG is detected since day 14 but universally detected since day 20 [47], [48]. Severe female patients generate IgG earlier and higher titers [49]. The reason remains unknown but this could be detrimental consequences clinically; more chance of having transfusion-related acute lung injury (*TRALI*). Hence, the patients with resolved SARS-CoV-2 viral infection will develop significant serum antibody response (IgG) to different viral epitopes of the SARS-CoV-2 virus and some of these developed antibody responses in the host system will be likely to have the potential to neutralize the virus [12]. There is, currently, no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection, as reported in china that seven cases of COVID-19 (three children and four adults) who was readmitted to hospital after recovered from COVID-19 [50]; as such issue rising the important to determining the efficacy of CPT.

The high level of antibody titers produced by the host immune system against the SARS-CoV-2 virus significantly reduces the chances of getting re-infected [12]. Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of CPT (1). However, duration of anti-SARS-CoV-2 antibodies in plasma remains unknown, though for other beta-CoVs immunity typically lasts 6–12 months [51]. Hence, a suitable donor could donate 600 mL plasma (equivalent to three therapeutic doses) every 14 days for a minimum of 6 months. In contrast to EVD, SARS, and MERS, most of COVID-19 patients exhibit few or no symptoms and do not require hospitalization, suggesting that the majority of convalescent donors are best sought after in the general population [52]. Based on Indonesian COVID-19 CPT Task Force 2020, the appropriate donor [53], [54] and recipient [55] must meet the following conditions:

Donor	Recipient
a) Tested positive COVID-19 through the results lab. examination and >3 weeks after the onset of COVID-19 symptoms	a) Positive COVID-19 results
b) Complete symptom resolution at least 14 days before donation plasma	b) Having severe COVID-19 at least one of the signs: Dyspnea, respiratory frequency ≥30 breaths/min, blood O_2 saturation ≤93%, ratio arterial O_2 partial pressure to inspired O_2 fraction (PaO_2/FiO_2) <300, and/or lung infiltrates > 50% in 24 or 48 h
c) Age: 18–55 years old, and weight for male ≥50 kg, for female ≥45 kg	c) Having critical COVID-19 at least one of the following circumstances: Respiratory failure (ratio of arterial O_2 partial pressure to inspired O_2 fraction (PaO_2/FiO_2) <200), septic shock, and/or multiple organ dysfunction failure
d) No history of blood-transmitted diseases	d) Can be given immediately to treated patients who complain shortness of breath
e) Female donor must be negative towards HLA antibody (if not available HLA antibody tests can be from women who not ever pregnant) or male donors	e) Not indicate for patients with mild COVID-19 (without symptoms of breath shortness, does not meet the criteria of severe or critical COVID-19)
f) Negative COVID-19 results	f) Informed consent
g) Determine the SARS-CoV-2 neutralizing antibody titer, if the examination can be performed (the optimal antibody titer is greater than 1:320)	
h) Eligible donors must be assessed by clinicians according to treatment	

Based on Pei *et al*., (2020), CP was collected using fully automatic apheresis machine or a fully automatic blood cell separator (refer to technical operation procedure of blood station). The plasma volume taken was around 200–400 mL that the exact volume should be assessed by clinicians. The interval between plasma collections should be more than 2 weeks. The plasma was stored at 2–6°C for 48 h, while for long-term storage; it should be rapidly frozen at −20°C.

CPT, Do We Have All the Answer?

The first published report of CPT against COVID-19, a preliminary communication posted online on March 27, 2020, in JAMA for five seriously ill patients in China. Shen *et al*., (2020), reported in all five patients, who were critically ill with COVID-19, after treated with CPT shown the body temperature normalized within 3 days in four of five patients, the Sequential Organ Failure Assessment score decreased, and PaO_2/FiO_2 increased within 12 days (around 172–276 before treatment and 284–366 after treatment) [56]. Furthermore, viral loads decreased and became negative within 12 days of transfusion and SARS-CoV-2-specific ELISA and neutralizing antibodies titers increased after the transfusion (around 40–60 before treatment and 80–320 after treatment on day 7). Furthermore, at 12 days after transfusion, ARDS was resolved in four patients. Within 2 weeks of treatment, three patients were weaned from mechanical ventilation. From five patients, three patients have been discharged from hospital (length of stay: 53, 51, and 55 days) and two patients are in stable condition at 37 days after transfusion. Two more reports from Wuhan, published on April 6 and April 15, 2020, respectively [1], [57]. All those reported the therapy save lives and looking for continuing with randomized controlled trial to confirm the results.

The US Food and Drug Administration (FDA) first announce on March 24, 2020; in more details on April 3, and April 13, 2020, respectively, that FDA would facilitate access to CP for treating COVID-19. The FDA cautioned "It is therefore important to determine through clinical trials, before routinely administrating CPT to the patient with COVID-19, that it is safe and effective." CPT is one good option, but it not without risk. The COVID-19 may cause increasing clotting; Plasma is rich with clotting factors and typically used to reverse bleeding problems, so theoretically CPT could increase clotting risk in patients with COVID-19 without any promise of benefit (plasma also promote anti-coagulation) [58]. In additional, plasma transfusion is also associated with adverse event, ranging from mild fever and allergic reaction (e.g., plasma protein, sodium citrate, or selective IgA deficiency) to life-threatening bronchospasm, *TRALI* (male donors are usually preferred to avoid the risk of transfusing anti-HLA/HNA/HPA antibodies from parous women; as anti-HLA/HNA/HPA antibody screening should be performed), and antibody-dependent enhancement that will leads to enhanced infection and transfusion associated circulatory overload (TACO) such as in patients with cardiorespiratory disorder, old age, or renal impairment [59]; also chance the risk of transfusion-transmitted infectious (TTI), as pathogen inactivation combine with nucleic acid testing can reduced TTIs.

There is a lack of RCTs investigating CPT as a potential therapy for COVID-19, though observational studies have reported some promising benefits. There were two RCTs [60], [61], that were published after being terminated early. The first RCT was conducted in Wuhan, China, February to April 2020. It was comparing the standard treatment (n = 52) versus the effect of CPT (n = 51); with two patients reported an adverse events [60]. Ultimately, there was no significant effect of CPT on the primary outcome of time to clinical improvement within 28 days [60]. The second RCT, conducted in the Erasmus MC, Netherlands [61]. It was comparing the standard treatment (n = 43) versus the effect of CPT (n = 43); hence, somewhat unsurprisingly, there was no effect of treatment on mortality, hospital length of stay or disease severity [61].

In addition, an initial safety assessment of 5000 patients who received CPT in the USA demonstrated a 0.08% mortality, 0.14% TACO, 0.22 TRALI, and 0.06% severe allergic transfusion reaction; with over all <1% rate of serious adverse events immediately following treatment, indicating that the risks of CPT are likely not excessive relative to the risks of severe COVID-19 [62]. Another larger study of 138 CPT patients who were compared with 1430 patients receiving standard therapy showed promising benefits such as reduced mortality and reduced proportion of patients exhibiting shortness of breath, somehow there were three patients experienced minor allergic [63]. Despite the above studies reporting positive and negatives outcomes, pro versus contra; it is clear that additional RCTs and global action are required.

Conclusion

There are so many of potential candidate treatment that are so promising in theory but somehow fall apart when translated into real-clinical study; only time will tell, including our ongoing CPT clinical study. All of these CPT against a massively COVID-19 infection is "imperfect Science," and YES, we do not have all the answer; but its' worth to trying rather than dying doing nothing.

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Availability of Data and Materials Section

The datasets gathered and shown in this review is available as an open access data as cited in our references; the corresponding author will make it available on reasonable request.

Authors' Contributions

AF, RA, WW, YH, NNH, and ABH design the discussion directions. AMA and JKA gathering all the data and references. All authors took part on writing and approved of the final manuscript.

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Changes in Orthopedic Services in Two Indonesian Tertiary-referral Hospitals during the Coronavirus-19 Pandemic

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Abstract

BACKGROUND: Many countries report decreasing on the number of hospital visit even on the emergency cases.

AIM: This study aims to reveal the important data on how big the impact of coronavirus-19 pandemic on orthopedic services in two Government's tertiary-referral hospitals.

METHODS: This research is a comparison study to measure the trend of orthopedic services, the monthly orthopedic surgical load and outpatient visit were examined during the period of March to May 2020 (the early pandemic period) then compared to the same period in the 2019.

RESULTS: The lowest number of outpatient visits occurred during May 2020 with 715 total number of outpatient visit. The lowest number of orthopedic surgery occurred during May 2020 with 167 total number of orthopedic surgery. Significant decrease of outpatient visits is recorded in 3 months of early pandemic period compared to the same period in 2019 ($p < 0.005$). Regarding the orthopedic surgical loads, the data show significant decrease in number of orthopedic surgeries in early pandemic period compared to those months in 2019 ($p < 0.005$). The largest declines were in visits for post-operative control patient (–179), spinal problem (–127,33), and osteoarthritis (–91,33).

CONCLUSION: There was a significant difference in outpatient visit and orthopedic surgery number in the early pandemic period compared to the period before the pandemic occur.

The largest drops in outpatient visit were in visits for post–operative control patient and spinal problem.

Introduction

Coronavirus disease (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS–COV2). Coronaviruses have a history of causing public health threats in the past; they previously caused outbreaks of SARS in China and Middle East respiratory syndrome in Saudi Arabia. The first case of COVID–19 was confirmed in December 2019 in Wuhan, China [1]. COVID-19 is a respiratory pathogen with the most common symptoms being common cold-like syndrome, fever, dry cough, shortness of breath, and SARS in severe cases. The less common symptoms are productive cough and gastrointestinal problems [2]. In early March 2020, the WHO declared COVID–19 a pandemic. Later in March, the president of Indonesia signed the Government Regulation Number 21/2020 to exercise the large-scale social restriction approach to control the spread of the disease. Non-essential activities were restricted, and only essential public places were allowed to remain open, such as grocery shops, gas stations, pharmacy shops, and hospitals. The measures undertaken in Indonesia were less rigid than those undertaken in China, the epicenter of the disease, where extreme measures were implemented, including a lockdown [3].

Dr. Soeradji Tirtonergoro Central General Hospital and Dr. Saiful Anwar General Hospital, which are located in Central Java and East Java Province, respectively, are categorized as type A hospitals in Indonesia, which are designated as tertiary referral hospitals by the Government of Indonesia provide healthcare for up to 70,000 people annually. The orthopedics and traumatology department in the hospitals provides subspecialty services, such as adult reconstruction, sport, hand and microsurgery, spine surgery, pediatric orthopedic, and musculoskeletal oncology, along with advance musculoskeletal trauma service.

Since the COVID–19 outbreak, many countries have reported decreasing numbers of hospital visits [4]. The Austrian, Chinese, and Italian health centers report downward trends in the number of hospital visits, even in emergency cases [5], [6], [7]. Moreover, US centers have reported that emergency department visits dropped more than 50% during this pandemic [8].

This study aimed to reveal important data highlighting the impact of the COVID–19 pandemic on orthopedic services in two Government's tertiary referral hospitals. The study results can be valuable to health policy makers during this pandemic.

Materials and Methods

To evaluate the trend of orthopedic services, the monthly orthopedic surgical load and outpatient visits were examined during the period from March to May 2020 (the early pandemic period), in comparison with the same period in 2019 and analyzed separately.

The change in mean visits per month between the early pandemic period and the respective period from the previous year was calculated as the mean difference in total visits for a diagnostic category between the two periods, divided by 3 months. The visit prevalence ratio was calculated for each diagnostic category as the proportion of outpatient visits during the early pandemic period divided by the proportion of visits during the prior year. The same method is used for the analysis of differences in the number of orthopedic surgeries.

Statistical data were analyzed using an independent sample t–test. The analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0, manufactured by IBM in New York USA. The results of the difference between the number of outpatient visits between the two groups were considered statistically significant if $p < 0.05$. The same method was used to analyze the differences in the number of orthopedic surgeries.

Results

Data taken from Dr Soeradji Tirtonergoro Central General Hospital (Hospital X) and Dr Saiful Anwar General Hospital (Hospital Y) were analyzed.

The average monthly number of outpatient visits in those two hospitals during the early pandemic period was 1181 visits per month, compared to the 1972 visits during the period in comparison. The lowest number of outpatient visits occurred during May 2020 with 715 total outpatient visits. The monthly number of outpatient visits is shown in Figure 1.

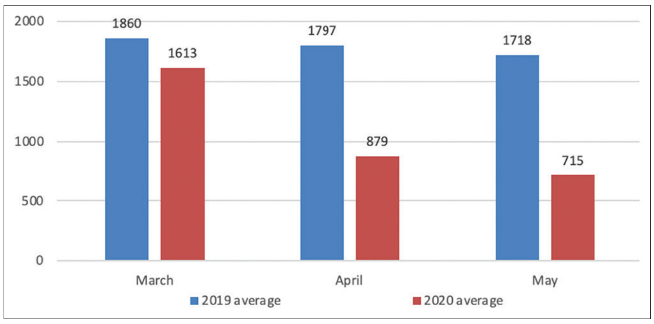

Figure 1: Outpatient Visit Number

The monthly orthopedic surgical loads also decreased. From the data collected, there were 221 surgeries per month in 2020, compared to 362 per month 1 year prior in those two hospitals. The lowest number of orthopedic surgeries occurred during May 2020 is 167. The monthly number of orthopedic surgeries is shown in Figure 2.

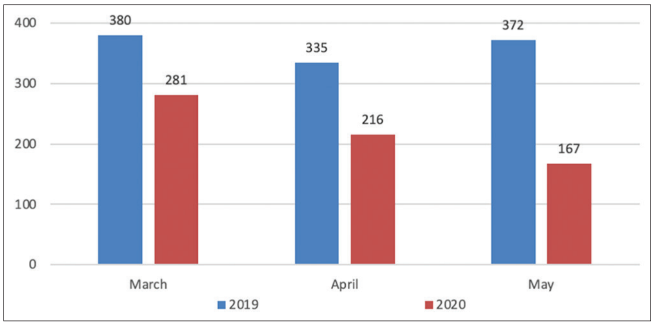

Figure 2: Orthopaedic Surgery Number

A significant decrease in outpatient visits was recorded in the 3 months of the early pandemic period compared to the same period in 2019 ($p < 0.005$), as shown in Table 1.

Table 1: Outpatient number

Month	Year	Outpatient number	p value
March	2019	1860	0.000
	2020	1613	
April	2019	1797	0.000
	2020	879	
May	2019	1718	0.000
	2020	715	

Regarding the orthopedic surgical loads, the data showed a significant decrease in the number of orthopedic surgeries in March, April, and May 2020 (early pandemic period) compared to those months in 2019 ($p < 0.005$), as shown in Table 2.

Table 2: Orthopedic surgery number

Month	Year	Patients	p value
March	2019	380	0.014
	2020	281	
April	2019	335	0.000
	2020	216	
May	2019	372	0.000
	2020	167	

The largest declines were in visits for post-operative control patients (–179), spinal problems (–127,33), and osteoarthritis (–91,33). In terms of the number of monthly orthopedic surgeries, spine surgery, and fracture/dislocation surgery have the biggest decline with (–20) change in mean number (Tables 3 and 4).

Table 3: Differences in mean monthly numbers of outpatient visits for diagnostic categories

Diagnostic category	Change in mean no of monthly outpatient visits	Prevalence ratio (95% CI)
Post–operative control	–179	1.16
Spinal problem	–127.33	0.67
Osteoarthritis	–91.33	0.78
Sport	–24	0.78
Other arthritis	–16,33	0,92
Fracture (Trauma)	–13,66	1.05
Arthroplasty	–10.33	1.41
Nerve/muscle problem	–6	0.99
Others	–4.66	0.007
Neoplasm	–4.33	0.007
Dislocation	–4,33	0.86
Congenital/acquired deformity of the limbs	–4.33	1.13
Bone/joint infection	–3.66	1.15
Open wound	–1	0.43

Discussion

Our findings show that during the early 3 months interval in the COVID–19 pandemic, there was a significant decrease in outpatient visits in each month compared to outpatient visits during the comparison period ($p < 0.05$). Furthermore, our data revealed that orthopedic surgical loads decreased significantly in March, April, and May 2020 (early pandemic period) compared to those periods a year before ($p > 0.05$).

Table 4: Differences in mean monthly numbers of orthopedic surgery

Surgery	Change in mean no of monthly average orthopedic surgery numbers	Prevalence ratio (95% CI)
Spine	–20	0.35
Fracture/Dislocation (Trauma)	–20	1.11
Sport	–5.66	0.71
Arthroplasty/Adult Reconstruction	–2.66	1.01
Neoplasm	–0.33	0.66
Nerve Procedure	–0.33	0.66
Infection	0.33	1.40
Congenital Abnormality	0	1.36
Others	2.66	1.94

Our findings are similar to those of an Austrian study conducted by Metzler *et al* [6]. who reported that there had been a significant decline in hospital patient admissions in Austria since the outbreak of COVID-19. A study in Hong Kong by Tam *et al* [7]. supports this finding with the same conclusion that there is a significant decrease in the number of visits in the emergency department compared to the same period in the year before, even in emergency and life-threatening situations such as acute coronary syndrome.

Another study that supports our findings is the paper by Lazzerini *et al* [5]. in Italy that reports a significant decrease in the number of visits to pediatric emergency departments, even in acute infection and trauma cases.

A US center study by Hartnett *et al* [4]. and Wong *et al* [8]. also reported a decrease in the number of visits to the emergency department that reached 50% drop nationwide.

A study from England by Thornton [9] reports that there is a 25% decrease in emergency department visits during the COVID-19 pandemic. On the other hand, only pneumonia cases increased in number since the lockdown due to the COVID-19 pandemic began.

Significant differences in the number of outpatient visits and orthopedic surgeries may be due to some of the following reasons. First, the government regulation that exercised the large-scale social restriction was just signed by the president in March 2020. The non-essential activities were restricted, and only essential services were excluded, such as grocery, gas station, pharmacy, and hospital. Other activities, such as school, concert, and other public crowds, were prohibited.

Another factor that may be a cause of the decreasing number of outpatient visits and surgery loads is the appeal by the Indonesian Orthopaedic Association in response to large-scale social restrictions by the government. They urged the patients to postpone their visits to the orthopedist or hospital unless there was an emergency situation such as fracture, either open or closed, joint dislocation, and bone or joint infection that is marked by joint swelling and fever, severe pain that did not subside with analgesics, sudden motor, or sensory loss in a limb that is accompanied by bladder or bowel incontinence following any fall or injury, and post-operative control patient.

Future studies will help to make further statements about the proportion of the decline in outpatient visits and orthopedic surgery that were not preventable or avoidable, such as those for limb-threatening or life-threatening conditions, those that could be managed at primary care, and those that need regular observation for special conditions.

The findings in this report are subject to some limitations. First, the diagnosis is based on the specific code in the hospital, which may limit the variability of the diagnosis and may differ from other hospitals. Later, more than two center studies may be needed to enhance the quality and strength of the study and to enrich the data variability.

The strength of this study is that it used primary data sources, and the hospitals where the study was taken are the highest referral hospitals for COVID-19 patients.

Conclusion

There was a significant difference in the number of outpatient visits and orthopedic surgeries in the early pandemic period compared to the period before the pandemic occurred.

The largest drops in outpatient visits were in visits for post–operative control patients and spinal problems. In terms of the number of monthly spine surgeries and trauma surgery have the biggest decline in mean number.

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Authors' Contribution

Sholahuddin Rhatomy and Faiz Alam Rasyid conceived the study, collected the data, analyzed data. Sholahuddin Rhatomy prepared and drafted the manuscript. KrisnaYuarno Phatama edited manuscript. Edi Mustamsir visualized the data into table and graph. Sholahuddin Rhatomy and Faiz Alam Rasyid reviewed and revised the manuscript.

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Patient with Antineutrophil Cytoplasmic Antibody Associated Small Vessel Vasculitis, Acute Renal Failure, and Coronavirus Disease-19 Pneumonia: A Diagnostic and Therapeutic Challenge

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Abstract

BACKGROUND: Antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) has a predilection for the kidney and more than three quarters of patients have renal involvement with rapidly progressive glomerulonephritis. Small-vessel systemic vasculitis may present as pulmonary-renal syndrome and is characterized by necrotizing glomerulonephritis and pulmonary hemorrhage. Diagnosis and therapy for AAV in coronavirus disease (COVID) COVID-19 pandemic require multi-disciplinary collaboration due to the affection of multiple systems and risks associated with immunosuppressive medications.

CASE REPORT: A 69-year-old non-smoker, non-diabetic female presented in the outpatient unit at the department of pulmonology with dry cough, malaise, and sub-febrile temperature, lasting for 1 month. The patient had a high suspicion of severe pulmonary-renal syndrome, ANCA-AAV, and acute renal failure requiring hemodialysis. She was treated with corticosteroids, cyclophosphamide, and plasma exchange. The treatment led to temporary improvement. Infections with COVID-19, *Enterococcus* in the urine, and Acinetobacter in the tracheal aspirate further complicated the clinical picture and despite antibiotic treatment, use of tocilizumab and convalescent plasma, the outcome was lethal.

CONCLUSION: It is important to establish the diagnosis and distinguish accurately between vasculitis and infection to provide adequate and timely therapy.

Introduction

Antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) is a rare group of multisystem disorders, affecting 13–25 people per million population in Europe [1]. It is characterized by inflammation, destruction of small and medium-sized blood vessels, and presence of circulating ANCA's. Clinical disease phenotype includes granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, and renal-limited vasculitis [2]. ANCA-AAV has a predilection for the kidney and more than three quarters of patients have renal involvement with rapidly progressive glomerulonephritis [3]. Small-vessel systemic vasculitis may present as pulmonary – renal syndrome and is characterized by necrotizing glomerulonephritis and pulmonary hemorrhage [4].

Diagnosis of a patient with de-novo ANCA-AAV during coronavirus disease (COVID)-19 pandemic is a challenge [5]. Clinical presentation of patients with AAV may overlap with manifestations of COVID-19 infection [6]. Pulmonary affection and acute kidney injury may occur as a result of AAV or as a presentation of COVID-19 infection [7]. Furthermore, cytokine-release syndrome, as a systemic inflammatory response which may occur in COVID-19 disease, may mimic vasculitis [8]. It is important to distinguish accurately between vasculitis and infection to provide adequate and timely therapy. Therapy for AAV in COVID-19 requires multi-disciplinary collaboration due to the risks associated with immunosuppressive medications.

Case Report

A 69-year-old non-smoker, non-diabetic female, presented in the outpatient unit at the department of pulmonology with dry cough, malaise, and sub-febrile temperature, lasting for 1 month. She was treated with a combination of two antibiotics (azithromycin and ceftriaxone) without improvement of the situation. There was no positive family history. She gave a history of allergy to non-steroidal anti-inflammatory drug and a history of sensorineural hearing loss, needing a hearing aid for 2 years. Dry, age-related macular degeneration was diagnosed in 2017 and she had a history of pneumonia in 2017 and 2019. Chest examination at check-up revealed an auscultation finding of vesicular respiration with bronchial crackling sounds bilaterally in the basal parts.

Due to persistent symptoms, a chest X-ray and computed tomography (CT) scan were performed with a finding of parenchymal consolidation on the basis of the right lobe in continuity with the lower part of the right hilum and pronounced peri-bronchial changes bilaterally. The heart, aorta, and major blood vessels and central pulmonary arteries were patent without evident emboli. Four tests for COVID-19 were made, all negative.

The patient was admitted in the department of pulmonology. The microbiological results from sputum were negative and tests such as anti-nuclear antibodies HEp-2 (indirect fluorescence assay), anti-double-stranded deoxyribonucleic acid, and c-ANCA were all negative. p-ANCA immunological test was positive, pneumonia panel plus test was negative, hantavirus immunoglobulin (Ig) IgM was negative, rapid test for *Mycobacterium tuberculosis* was negative on two separate occasions, and the Löwenstein–Jensen medium was negative. Procalcitonine level was 0.4 ng/ml (ref. value 0, 15 ng/ml).

Due to the rapid increase of serum creatinine from 65 umol/l to 695 umol/L and serum urea 13 mmol/L (normal range of serum creatinine 45–109 umol/L and serum urea 2, 7–7, 8 mmol/L) on the 7th day of the hospitalization, a femoral venous catheter was placed, and the next day the first dialysis was performed. Urinary analysis showed proteins and blood in the urine. Affection of multiple systems and ANCA positivity implied the use of Birmingham vasculitis activity score (BVAS) as an index of severity of disease and it was 17.

All efforts to obtain tissue biopsy failed. Invasive lung investigations were not possible due to the overall estimation of risk as very high. Renal biopsy was not possible due to prolonged bleeding time. Nasal endoscopy was indicated. Unfortunately, no granulomatous disease-associated lesions in the nasal cavities were found and biopsy was not done.

The patient was transferred to our department of nephrology on the 9th day of the hospitalization at the department of pulmonology, with high suspicion of pulmonary-renal syndrome, ANCA-AAV, and acute renal failure requiring hemodialysis.

On transfer, the patient still complained of shortness of breath and had hematuria. General examination of the patient revealed an alert and conscious patient with pale skin. On admission, the patient was hypertensive (165/90 mmHg), tachycardic (123 bpm), and hypoxic (oxygen saturation on room air 85%) and had no visible swelling on the lower extremities. Chest examination revealed an auscultation finding of vesicular respiration with bronchial crackling sounds bilaterally in the basal parts. Examination of other systems was unremarkable. The BVAS score in our department was calculated as 33.

The blood tests on admission demonstrated renal impairment with a creatinine of 364 umol/L, an ongoing acute inflammatory response with C-reactive protein (CRP) 205 mg/L, leukocytosis 17.5 (10^9/L), lymphocytopenia 8.2%, anemia red blood cell (RBC), hemoglobin (HGB), (RBC 2.5; HGB 72; hematocrit 0.2), serum albumins 27 g/L, and total protein 56 g/L. Urinalysis demonstrated blood and protein on dipstick testing. Proteinuria of 3.5 g/dU was confirmed. Immunological status of the patient: IgM, IgE, IgG, IgA, C3, and C4 levels were normal. Anti-glioblastoma was negative. COVID-19 polymerase chain reaction (PCR) test at admission at the department was negative. Viral markers for hepatitis B and C were negative.

An ultrasound of the kidneys and urogenital tract was performed with the following finding: Both kidneys with normal ultrasound shape and placement with no pathological findings, urinary bladder unremarkable.

A CT lung scan on the day of admission in our department was indicated and revealed an evident progression of finding demonstrated with diffuse centrilobular ground-glass opacities dominantly in upper lobes and an alveolar consolidation, as well as in apicobasal and in the right basal segments with patchy nodular lesions. On the right side, there was an anterior subsegmental and posterobasal consolidation and small pleural effusion. Findings were suggestive for alveolar hemorrhage consistent with autoimmune disease-vasculitis (Figure 1).

Immediately upon transfer of the patient at the department of nephrology, patients' oxygen saturation dropped to 70%. Oxygen therapy was commenced and continued throughout her stay in the hospital. After obtaining the CT scan finding, induction therapy was started for the treatment of ANCA positive AAV.

Several diagnostic tests were done out of the hospital building. The patient received intravenous pulse methylprednisolone therapy in a dosage of 500 mg per day for 3 days, continued with oral prednisolone, slowly tapered to 60 mg per day. An intravenous drip of cyclophosphamide 500 mg was administered. Due to the alveolar hemorrhage, plasmapheresis treatment was started. Seven sessions were planned, but only 4 were performed due to further aggravation of the situation. Plasmaphereses and hemodialysis sessions were performed on an alternate day. With this treatment and oxygen support, saturation started to rise and reached 90%. In addition to this treatment an antihypertensive drug (a calcium antagonist) and an inhibitor of the gastric proton pump were administered. Urine culture revealed Enterococcus and treatment was started with amp. tazobactam a 4, 5 g/12 h, according to an antibiogram.

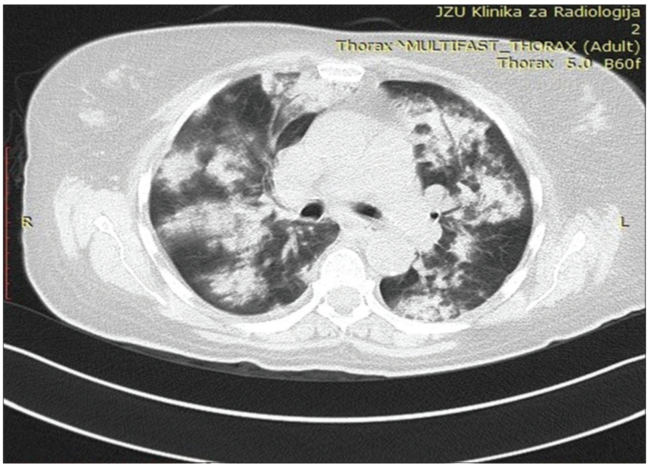

Figure 1: Findings of computed tomography lung scan at admission in the department of nephrology were suggestive for diffuse alveolar hemorrhage

Due to activated fibrinolysis (elevated levels of D-dimer - 9024), low molecular dose of heparin (amp. Clexane a 40 mg per day) was started. Two units of RBCs were administered during the hospitalization.

After 11 days of hospitalization in our unit, the inflammatory markers of the patient were in decline: CRP 20 mg/L; white blood cell 11, 5, but there was persistent anemia even after transfusion with two doses of RBC (HGB 95; RBC 3, 2). During the hospitalization period, the patient was afebrile and circulatory stable.

After 12 days of hospital treatment and a requirement to repeat the cycle of cyclophosphamide at the 14^{th} day, and a newly stated complaint of pharyngeal dryness and drop of HGB to 72 g/l, a control nasal swab for PCR test was taken for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), which turned out positive. Serological IgM and IgG tests for SARS-COV-2 were negative. Plasma exchanges were discontinued due to the co-infection with COVID-19.

According to the protocol, the patient was transferred to a COVID-19 hospital. Discharge diagnosis included pulmorenal syndrome, acute renal failure stage 3, treatment with hemodialysis, ANCA-AAV, alveolar hemorrhage treated with plasmapheresis, anemic syndrome, urinary infection with Enterococcus, and infection with COVID-19.

The patient was first transferred to the infectious diseases unit in the general city hospital and diagnosed with COVID-19 pneumonia. Another reverse transcription PCR (RT-PCR) test for SARS-COV-2 taken upon admission was also positive. Initial laboratory tests were made on admission and revealed persistent anemia and hypoalbuminemia.

There the hemodialysis treatment continued. CT angiography of the pulmonary truncus showed bilateral diffuse zones of interstitial consolidation (Figure 2). Multiple lymph nodes were seen in the mediastinum. Visualization of the main pulmonary truncus (Figure 3) and pulmonary arteries showed no alterations in the hemodynamic flow and no endo-luminal thrombotic masses. No alterations of the blood flow were seen in the segmental pulmonary branches, but subsegmental branches were not visible because of massive consolidation.

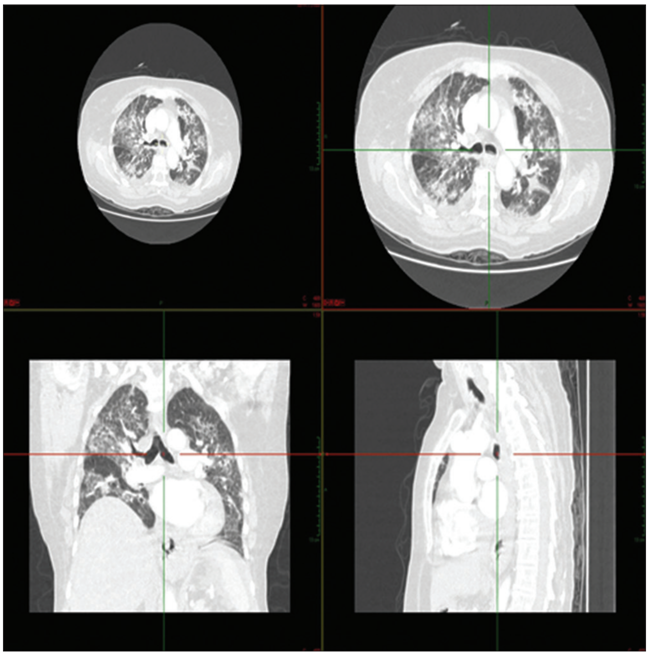

Figure 2: Bilateral diffuse zones of consolidation

Pulmonary X-ray showed massive zones of parenchymal consolidations in the apical, middle, and basal parts of both lungs.

Because of the severe general health condition, the patient was transferred to the intensive care unit, was intubated, and put on a mechanical ventilator. She was oligoanuric and under continuous inotrope stimulation. The laboratory tests revealed an increase in interleukin 6 (IL-6) (30 pg/ml); ferritin> 612; and procalcitonin 2, 13 ng/ml.

Acinetobacter was identified in the tracheal aspirate. She was treated with triple antibiotic therapy (Meropenem, Linezolid, and Colistin). An infectious disease specialist was consulted and tocilizumab was added to the medication list. The patient was also treated with packed RBCs, fresh frozen plasma, convalescent plasma, ozone therapy, anticoagulant, and gastroprotective therapy. In spite of treatment and used measures for cardiopulmonary resuscitation, death occurred on the 33rd day of her first hospitalization.

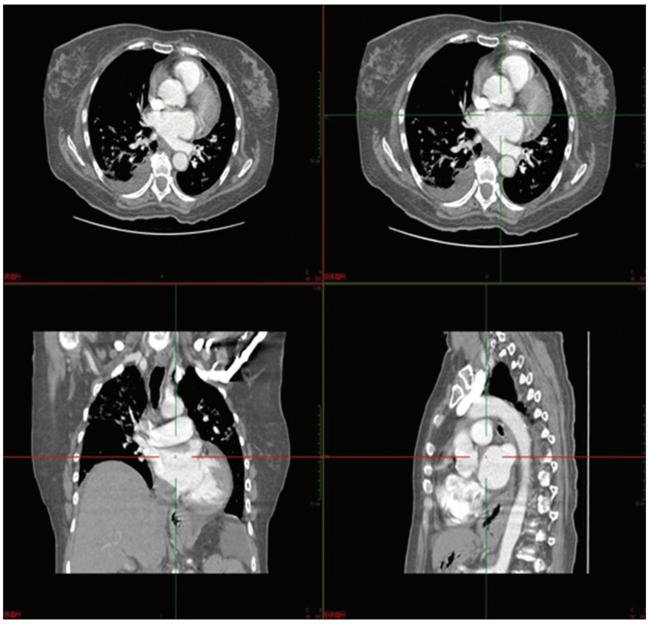

Figure 3: Absence of thrombotic masses

Discussion

Our patient had a pulmonary-renal syndrome and severe ANCA-associated renal involvement, complicated with COVID-19 pneumonia.

The exact clinical phenotype of the AAV could not be determined, since tissue biopsy was cancelled, due to the severity of the general condition and prolonged bleeding time. A 3-year history of sensorineural loss of hearing, macular degeneration, pneumonia, and allergies may imply isolated affection of several organs as part of vasculitis. There were no signs of highly active disease in her medical history. Although an uncommon finding, these findings were suggestive of microscopic polyangiitis in the absence of granulomas and more destructive local changes [9].

For at least a month before hospitalization, there were non-specific constitutional presentations such as malaise, low-grade temperature, and diarrhea. Progression of the pulmonary and kidney injury, with alveolar hemorrhage and rapid progressive glomerulonephritis, together with the myeloperoxidase (MPO) positivity and high score of disease activity BVAS, led to diagnosis of AAV. Microscopic polyangiitis was the most probable phenotype in our patient. This finding is not unexpected, according to a study which reported that in a 20-year population-based cohort of patients with AAV-glomerulonephritis, 65% had microscopic polyangiitis, and 74% were MPO-ANCA positive [10].

Recent reports showed that ANCA antibodies are not only a biomarker of AAV but are involved in the pathogenesis of the renal involvement in AAV. Binding of MPO or proteinase 3 antibodies to autoantigens activates neutrophils, that degranulate and release reactive oxygen species [11]. Neutrophil extracellular traps (NETs) are released to contain infections, but if they are not properly regulated, they damage the endothelium and activate complement, thus provoking inflammation and microvascular thrombosis, explained as ANCA-cytokine sequence theory [12], [13]. Unregulated NETs are also involved in COVID-19 pneumonia and lead to a very fast progression of lung destruction [14].

According to the grading recommended by the European vasculitis study group, the patient had a high index of activity of the disease, with life-threatening diffuse alveolar hemorrhage [15]. Severity of disease implied immediate commencement of therapy. Standard of care for induction therapy in severe AAV includes a combination of glucocorticoids with either cyclophosphamide or rituximab [2]. Although autoimmune patients receiving immunosuppressive therapy may be prone to COVID-19 infection, it is contraindicated to delay therapy [16]. The management of glomerular diseases in the COVID-19 era is changing, and there are issues whether intravenous cyclophosphamide should be substituted with peroral or rituximab should not be used at all due to long-term depletion of B cells [17]. There are recently some case reports where rituximab was used successfully in patients with AAV [18]. The most recent paper for treatment of AAV during COVID pandemics recommends plasma exchange, oral glucocorticoids, and intravenous cyclophosphamide 500 mg every 2–3 weeks in 6 doses for COVID-19 negative patients, with several options in COVID-19 positive patients [19].

Single intravenous dose of cyclophosphamide and pulse methylprednisolone for 3 days was administered in our patient. Plasma exchange was instituted based on the findings of serum creatinine above 500 μmol/l and diffuse intraalveolar hemorrhage on CT scan, according to the recommendations of the MEPEX trial [20]. Plasma exchange removes the pro-inflammatory cytokines, complement, and coagulation factors, and dilutes ANCA titers, and may decrease progression to end-stage renal disease [21].

Inflammatory markers, such as CRP, were very high at the beginning of the hospitalization and decreased after induction therapy with corticosteroids and cyclophosphamide. The clinical condition of the patient improved significantly.

Later on in the hospitalization, nasal RT-PCR

SARS-COV 2 test was positive, and COVID-19 pneumonia soon emerged. We found only one report of false-positive SARS COV 2 RT-PCR test in a patient with AAV, potentially due to cross-reactivity [22]. This was not the case with our patient because a positive RT PCR test was confirmed twice and the disease progressed with worsening of the clinical and radiological features.

There is a link between infection and autoimmunity – a higher disease activity may predispose to developing infections. We believe that the high disease activity index predisposed our patient to infection with COVID-19, as well as to urinary infection with Enterobacter. Worsening of the condition was confirmed by an increase in the inflammatory markers, CRP and procalcitonin, and high IL6. Procalcitonin is normal in patients with autoimmune disease and when higher levels are confirmed, it is associated with infection [23]. IL 6, CRP, erythrocyte sedimentation rate, serum ferritin were positively associated with the severity of COVID-19, as suggested in literature [24]. High circulating level of D-dimers correlated with the inflammatory markers, representing a hypercoagulable state, associated with the AAV and also with COVID-19 infection [25], [26].

COVID-19 may be responsible for cytokine release syndrome (CRS), as a systemic inflammatory response [27]. SARS-CoV-2 binds to alveolar epithelial cells and results in the release of a large number of cytokines, including IL-6. Treatment of the cytokine storm has become an important part of rescuing severe COVID-19 patients. Tocilizumab as a IL-6 receptor blocker was used as salvage therapy in this patient. Tocilizumab was tried in patients with a severe form of COVID-19 and cytokine storm yet with no significant difference in survival [28].

Although radiological findings of nodules, consolidation, and ground-glass opacities were consistent first with alveolar hemorrhage in vasculitis, the findings progressed into massive zones of consolidation at the next radiological imaging (CT angiography) which was highly suggestive of COVID-19 pneumonia, confirmed by two positive SARS COV2 PCR tests [29].

One of the diagnostic challenges in COVID-19 infection is that it may provoke acute kidney injury and may mimic vasculitis. It was reported that 36.6% of patients hospitalized for COVID-19 had acute kidney injury, with 14.4% requiring a registered respiratory therapist. Acute renal failure was registered in patients with respiratory failure on mechanical ventilation and was a predictor of poor outcome [30]. Renal failure may be due to prerenal failure and collapsing glomerulopathy [31]. Recent reports object to the SARS-COV2 nephropathy as a separate entity, as there was an absence of viral genetic material in renal biopsy specimens and no histologic proof for cytopathic effects of the virus [32].

Unfortunately, the severe form of AAV, renal failure, and infections, despite all therapeutic efforts, were predictors of a poor outcome in the patient.

Conclusion

ANCA positive vasculitis is a rare disease which needs fast and prompt diagnosis and responds well to aggressive treatment with plasmapheresis, pulse dose of corticosteroids, and immunosuppressive drugs. COVID-19 infection is still a rather new and unknown disease, but the CRS that it causes can have a lethal outcome in the complications of the primary disease. Infections are common in immune-compromised patients and the risk is increased with every prolonged stay in the intensive care unit. In COVID-19 pandemic, it is important to diagnose AAV timely and to provide induction therapy as well as to provide treatment for concurrent infections.

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Investigating the Causes of Elderly People Leaving Home during Coronavirus Disease-19 Epidemic

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Abstract

BACKGROUND: Coronavirus disease-19 (COVID-19) disease affects all age groups, especially the elderly, and regarding the high mortality rate among the elderly, preventive measures are needed to reduce mortality in the elderly.

AIM: This study was conducted to investigate the causes of in elderly people leaving home in time of COVID-19 epidemic.

METHODS: The present study is a descriptive-analytical study performed on 1656 elderly people in Urmia, Iran, by simple random sampling method. The data collection tool in this study was a researcher-made questionnaire that included demographic characteristics, a questionnaire on the causes of the elderly leaving home during the COVID-19 epidemic. Data were analyzed using Chi-square and Fisher tests using SPSS 23 software.

RESULTS: The results revealed that the highest concern of the elderly to leave home was to receive health services (45.89%) such as visiting the doctor or the caregiver, receiving medication, and so on. As the second priority, buying daily necessities such as bread, food, clothes … (42.75%) was one of the reasons for the elderly to leave home. Furthermore, education, gender, age, underlying diseases, occupation, and living conditions of the elderly were related to the needs of health services and living necessities and this relationship was statistically significant ($p < 0.05$).

CONCLUSION: Effective interventions should be designed based on the causes of the elderly leaving home, including the use of home distance care and health ambassadors to estimate the needs and causes of leaving home. Therefore, the elderly would be protected from this disease and its mortality.

Introduction

The World Health Organization (WHO) claimed coronavirus disease-19 (COVID-19) disease as an epidemic, and a new, different one from other viruses of severe acute respiratory syndrome, Middle East respiratory syndrome, and influenza [1]. The morbidity rate and mortality rate of the COVID-19 are growing and the economic damage resulting from the disease is highly increasing, estimated to overpass the capacity of both developed and developing countries in forthcoming months [2]. Elderly people are one of the high-risk groups with a high possibility of morbidity and mortality, due to old age as well as high statistics of underlying diseases. Therefore, elderly people are at higher risk of catching the disease and death from the COVID-19 more than other groups of society [3]. Studies on the elderly showed that they not only face a higher risk of catching the disease but also are at a greater risk of death of the disease. However, the reason of the fact that old people with underlying diseases are at higher risk of the disease is unknown [4]. The results of a study in China showed that 92% of the people affected by COVID-19 were elderly over 72, while more than 42% of the death from COVID-19 were of them. It is also reported to have 82% of the deaths from COVID-19 among elderly over 60 in the U.S [5], [6]. Old people are more susceptible of the disease because underlying diseases such as renal failure, diabetes, high blood pressure, arthritis, heart diseases, and chronic obstructive pulmonary disease are more common among the elderly. Recent research revealed that the high rate of morbidity among the elderly is due to diagnostic disorders, immune system deficiency, underlying diseases, malnutrition, taking multiple drugs, and social problems. Thus, in developing countries, the number of elderly people affected from and died of COVID-19 outnumbers other age groups [7]. Weak preventive measurements among the elderly indicate they have not taken the significance of the issue seriously and have not considered COVID-19 as a threat to their health. To diagnose the preventive measurements and to control the spread of the COVID-19, the determinants and contributory factors on preventive behavior from the disease should have been identified [4].

Regarding the ways of transmission for this disease, home quarantine is one of the main influential ways in removing the transmission cycle of the disease [8]. Staying at home and not commuting out would reduce the elderlies' contact with each other, as well as the environment, therefore, decreases the transmission of the disease from one person to the other or to the environment [9].

Findings of the studies conducted by Daoust in 27 countries were dramatically clear and alarming: Despite the fact that the probability of death from COVID-19 is much higher among the elderly, they seldom regard preventive measures like staying at home [10]. Therefore, the behavior of the elderly in preventing the disease and staying home is crucial toward advancing home-quarantine policies. However, the needs of the elderly should be noticed for their home quarantine. The elderly people often have complicated and unknown needs, and besides their physical disorders, they have psychological, social, environmental, protective, and health-relevant problems [11]. Daily needs of the elderly are of important factors in preventing COVID-19, for their leaving home. Therefore, it is of vital importance to identify the daily needs of the elderly and providing them to prevent their home-leaving. The purpose of the present study is to identify the reasons of the elderly people home leaving during the coronavirus epidemic in Urmia, Iran.

Materials and Methods

The present study is a descriptive-analytical one, aiming at investigating the reasons of the elderly people home-leaving in time of coronavirus epidemic in 1399 (2020), conducted in Urmia, Iran. Regarding the population of the elderly in Urmia (51000), of which, 3.25% was chosen as the sample to study, and 1656 persons were included in the study. Using simple random sampling from 30 health centers of Urmia, 3.25% of the elderly people were selected in the proportion of the population of each health center. Data collection instruments of the present research study were researcher-made, including the demographic specifications of the participants and the Elderly Home-Leaving Questionnaire. The items of the determined consequences were selected through the literature review, and to meet the reliability and validity of the questionnaire, the methods of content validity and Cronbach-alpha were implemented respectively. To indicate the reliability of the questionnaire, it was sent to 10 experts in health education and elderly science, and the comments were applied according to their opinions. The reliability of the questionnaire was more than 80%. To measure the validity, the questionnaire was completed by 30 elderly people who were not included in the group under study. Using the Cronbach-alpha method, reliability coefficient of the health and therapeutic questions 0/77; referring to the banks and offices 0/78; living necessities 0/28; social and recreational interactions 0/80; and being in ceremonies and occasions 0/83 were reported.

To assess the above-mentioned dimensions in 24 questions which were provided as Yes/No choices and the Yes ones were pointed as 1, while the No answers were pointed as 0. The points were varied from 0 to 24; as the health-therapeutic dimension had 4 questions, referring to the banks and offices 6 questions, living necessities 5 questions, social and recreational interactions 4 questions, and being in ceremonies and occasions 5 questions.

Health-care providers communicated with the elderly through phone calls and the purpose of the study was elaborated to all the participants. Then, the questionnaire was completed through phone interviews by elderly people. In addition, the time range of the home-leaving was considered as 1 week before. The criteria for taking part in the study were age over 60, capability of answering through phone, not abiding in nursery home, while the items of not satisfaction, not being inclined to contribute in the research were excluded from the study. The descriptive data were analyzed in terms of frequency (in percent), and analytical data through Chi-square and Fisher tests using SPSS 23 software.

Results

The average age of the elderly people participated in the study was 66/4 ± 8/87, while the biggest age group was 60–65 (33%). Most of the elderly were women (51/1%), being housewives (49/2%). The living conditions indicated that most of the elderly people under study live with their spouses (79/7%). Moreover, most elderly people were illiterate (45/7%), and 72/5% of them were suffering from a chronic disease (cardiovascular, respiratory, diabetes, blood pressure, etc. diseases) Table 1.

The findings of the reasons of elderly home-living indicated that their biggest concern of going out of home was to receive health-therapeutic service like visiting the doctor or the caregiver, and medication (45/89%). The second priority of the elderly home-leaving reason was to buy daily necessities such as bread, food supplies, clothing, and so on (42/75%). Besides, 21/02 percent of the elderly people leave home to pay their electricity, gas, and phone bills, as well as to get their payrolls. Taking part in social and recreational interactions was of weak reasons of their home-leaving of the elderly (Table 2).

Table 1: Frequency and the distribution percentage of the demographic features of the elderly under study

Variables	Number	Percent
Age		
60–65	547	33
65–70	497	30
70–75	414	25
80–75	198	12
Sex		
Male	809	48.9
Female	847	51.1
Job		
Housewife	815	49.2
Employed	278	16.8
Retired	563	34
Living condition		
With spouses	1320	79.7
Alone	112	6.8
With children	224	13.5
Education		
Illiterate	757	45.7
Elementary	577	34.8
Diploma and postgraduate	211	12.7
	111	6.7
History of chronic diseases		
Yes	1201	72.5
No	455	27.5

The results of Chi-square and Fisher test revealed that home-leaving of elderly to receive health-therapeutic services, going to the banks and offices, buying living necessities, and social-recreational interactions were more among elderly people with higher education. Moreover, elderly women had home-leaving to receive health and therapeutic services more than men. In contrast, elderly men leave home to go to banks and offices, to buy living necessities, and social, recreational interactions more than women with a

Table 2: The frequency and the distribution percentage of the home-leaving elderly under study

Variables of the elderly home-leaving	Yes		No	
	Frequency	Percent	Frequency	Percent
Social/recreational interactions	823	12/42	5801	87/58
Going to parks	131	7/91	1525	92/09
Being in streets, sectors	371	22/40	1285	77/60
Visiting relatives and friends	196	11/84	1460	88/16
In/out city communities	125	7/55	1531	92/45
Being in ceremonies and occasions	195	2/36	8085	97/64
Visiting the patients	53	3/20	1603	96/80
The obit, funeral	74	4/47	1582	95/53
The birthday parties	14	0/85	1642	99/15
The wedding parties	28	1/69	1628	98/31
The religious ceremonies	26	1/57	1630	98/43
Referring to the offices and banks	2089	21/02	7847	78/98
To unbound and free Edalat stocks	198	11/96	1458	88/04
To pay bank installment	318	19/20	1338	80/80
To pay bills of gas, electricity,	365	22/04	1291	77/96
To get money from ATM	550	33/21	1106	66/79
To receive payrolls	234	14/13	1422	85/87
To receive subsidy and livelihood	424	25/60	1232	74/40
Health-therapeutic issues	3040	45/89	3584	54/11
Doing tests and risk assessments	632	38/16	1024	61/84
Receiving Medications	737	44/50	919	55/50
Doctor visiting	949	57/31	707	42/69
Referring to the caregivers	722	43/60	934	56/40
To buy living necessities	3540	42/75	4740	57/25
Buying clothing	532	32/13	1124	67/87
Buying sanitary fittings (shampoo, soap)	756	45/65	900	54/35
Buying home appliances	450	27/17	1206	72/83
Buying food	902	54/47	754	45/53
Buying bread	900	54/35	756	45/65

significant meaning statistically (p < 0/05). On the other hand, older people leave home mostly to receive health-therapeutic services, while elderly with lower age heave home to buy living necessities, and this difference was more meaningful among age groups home-leaving (p < 0/05). The findings of investigating the relationship between underlying diseases and the reasons of elderly home-leaving revealed that the elderly people with underlying diseases refer more to the health centers, while leave homeless for providing living necessities and official or bank affairs. Employed elderly leave home more than other groups in all dimensions but attending the ceremonies and occasions. Living alone was the other reason of the elderly home leaving. All above-mentioned reasons were significant statistically (p < 0/05) Table 3.

Discussion

Since no study has been conducted on the issue so far, the viewpoints, approaches, and suggestions were most discussed in this study. The results showed that the biggest mental concern of the elderly leaving home is health and therapeutic issues. It seems that elderly people with more physical problems refer to health centers for treatment. In studies conducted in Iran [12], Turkey [13], and Uganda [14], the reported level of health for the elderly was weak. The reason can be related to the increasing frequency of the various concurrent diseases in the elderly. On the other hand, the assessment of the relationship between demographic variables with the elderly home leaving to provide sanitary fittings was meaningful. According to the report of WHO, the elderly were at higher risk of getting the coronavirus [15]. Since the mortality rate is high among old people, it is suggested in to reduce the elderly commuting and encountering the virus, medical care be done through tele home care (THC), so better management of the elderly with underlying diseases such as cardiovascular diseases, COPT, diabetes, and so on resulted elderly people less home leaving to receive health care services. THC increases the access to health and sanitary services, particularly when the importance of the need of the elderly for in-home care increases. Moreover, THC can help establish the service network between hospitals and first-aid providers, through which will facilitate the opportunity of better accessibility of the elderly to the services. In addition to the improvement of the management of the chronic condition as well as the increasing availability of health care, THC believes that it would decrease the health care expenses as well [16], [17]. Eventually, it should be noted in THC, the prioritizing THC, implemented according to the meaningful relationship of the demographic variables with health and sanitary needs. For instance, women and lonely elderly people who leave home more than other groups to receive health and therapeutic services should be prioritized.

Other findings of the present study indicated the amplitude of daily needs (buying bread, food, sanitary fittings, etc.), as well as referring to the banks and offices, as the reasons of home leaving. Daily necessities are mentioned as part of major environmental needs of

Table 3: Investigating the relationship between demographic variables with the home-leaving of the elderly

Demographic variables	Health issues (%)		Going to banks and offices (%)		Buying living necessities (%)		Social and recreational interactions (%)		Going to ceremonies and occasions (%)	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Education										
Illiterate	1320 (43/6)	1708 (56/4)	621 (13/7)	3921 (86/3)	1167 (30/8)	2618 (69/2)	353 (11/7)	2675 (88/3)	80 (2/1)	3705 (97/9)
High school	1089 (47/2)	1219 (52/8)	903 (26/1)	2559 (73/9)	1474 (51/1)	1411 (48/9)	319 (13/8)	1989 (86/2)	81 (2/8)	2804 (97/2)
Diploma	433 (51/3)	411 (48/7)	388 (30/6)	878 (69/4)	575 (54/5)	480 (45/5)	87 (10/3)	757 (89/7)	18 (1/7)	1037 (98/3)
Academic studies	198 (44/6)	246 (55/4)	177 (26/6)	489 (73/4)	324 (58/4)	231 (41/6)	64 (14/4)	380 (85/6)	16 (2/9)	539 (97/1)
p value	0/000		0/000		0/000		0/012		0/105	
Gender										
Male	1419 (43/9)	1817 (56/1)	1529 (31/5)	3325 (68/5)	2318 (57/3)	1727 (42/7)	468 (14/5)	2768 (85/5)	92 (2/3)	3953 (97/7)
Female	1621 (47/8)	1767 (52/2)	560 (11)	4522 (89)	1222 (28/9)	3013 (71/1)	355 (10/5)	3033 (89/5)	103 (2/4)	4132 (97/6)
p value	0/001		0/000		0/000		0/000		0/636	
Age groups										
60–65	1618 (44)	2058 (56)	1171 (21/2)	4343 (78/8)	2070 (45)	2525 (55)	463 (12/6)	3213 (87/4)	116 (2/5)	4479 (97/5)
65–70	251 (40/5)	369 (59/5)	472 (20/9)	1784 (79/1)	448 (43/5)	582 (56/5)	168 (11/2)	1336 (88/8)	36 (1/9)	1844 (98/1)
70–75	424 (51/5)	400 (48/5)	271 (21/9)	965 (78/1)	778 (41/4)	1102 (58/6)	117 (14/2)	707 (85/8)	30 (2/9)	1000 (97/1)
>75	747 (49/7)	757 (50/3)	175 (18/8)	755 (81/2)	244 (31/5)	531 (68/5)	75 (12/1)	545 (87/9)	13 (1/7)	762 (98/3)
p value	0/000		0/321		0/000		0/194		0/165	
Underlying diseases										
Have	2491 (51/7)	2325 (48/3)	1432 (19/8)	5792 (80/2)	2406 (40)	3614 (60)	600 (12/5)	4216 (87/5)	148 (2/5)	5872 (97/5)
Not have	549 (30/4)	1259 (69/6)	657 (24/2)	2055 (75/8)	1134 (50/2)	1126 (49/8)	223 (12/3)	1585 (87/7)	47 (2/1)	2213 (97/9)
p value	0/000		0/000		0/000		0/891		0/311	
Job										
Retired	285 (12/7)	1967 (87/3)	1053 (31/2)	2325 (68/8)	1503 (53/4)	1312 (46/6)	285 (12/7)	1967 (87/3)	59 (2/1)	2756 (97/9)
Housewives	348 (10/7)	2912 (89/3)	478 (9/8)	4412 (90/2)	1121 (27/5)	2954 (72/5)	348 (10/7)	2912 (89/3)	96 (2/4)	3979 (97/6)
Employed	190 (17/1)	922 (82/9)	558 (33/5)	1110 (66/5)	916 (65/9)	474 (34/1)	190 (17/1)	922 (82/9)	40 (2/9)	1350 (97/1)
p value	0/027		0/000		0/000		0/000		0/290	
Living condition										
With spouses	2345 (44/4)	2935 (55/6)	212 (15/8)	1132 (84/2)	347 (31)	773 (69)	122 (13/6)	774 (86/4)	34 (3)	1086 (97)
Alone	471 (52/6)	425 (47/4)	1741 (22)	6179 (78)	267 (47/7)	293 (52/3)	651 (12/3)	4629 (87/7)	148 (2/2)	6452 (97/8)
With children	224 (50)	224 (50)	136 (20/2)	536 (79/8)	2926 (44/3)	3674 (55/7)	50 (11/2)	398 (88/8)	13 (2/3)	547 (97/7)
p value	0/000		0/000		0/000		0/395		0/266	

the elderly in other various studies, and speculated their environmental need different according to their residence [18], [19], [20]. Due to the fact that it is inevitable for the elderly to provide daily needs and to refer to the banks, the elderly have to leave home to provide them. In this regard, the family and relatives should help the elderly, do the out of home activities for them. Educating families so that one of the close people to the elderly takes the responsibility of providing his/her necessities is an important issue, of which media play an important role in this regard. Therefore, it is suggested to implement Health Ambassadors to provide the elderly necessities and to pay their bills. The ministry of health has initiated training Family Health Ambassadors since 1393 (2014), who is a young member of the family with at least 8 years of school studies, taking responsibility of conveying health-related learned issues, as well as active care of himself, his family members, and society voluntarily. Volunteer Health Ambassador is trained for every family without any competent member [21], [22]. The Family Health Ambassador can act as a link between health system and the families under coverage, to receive the sanitary data about coronavirus in person or electronically, and convey them to the families to provide self-care. Of other activities supposed for family, health ambassador is buying daily necessities of the elderly and paying their bills. Consequently, the elderly would not have to leave home and the young, informed person of the ways and possibilities of transmission of the coronavirus would do them instead. For families without such a person, a volunteer health ambassador from other families would be employed to do this. It is worthy of noting that demographic features such as age, gender, and education are related to the frequency of home leaving to provide daily needs and to pay the bills, thus should be taken into account in administrating the provision of the daily needs of the elderly by the health ambassadors.

Fortunately, having social and recreational interactions was one of the weak reasons of the elderly going out. However, most of the affected and hospitalized patients in corona wards usually attended in family gatherings, wedding and funeral ceremonies, as well as gathering places 2 weeks before getting the disease. Thus, it is of vital importance to educate and sensitize the elderly in terms of not attending in ceremonies and highly crowded places such as parks, streets, as well as visiting and traveling. It should be prioritized, particularly for the men and employed elderly who have a higher frequency of home leaving to meet their social and recreational needs.

Conclusion

Regarding the findings of the present study, it is suggested to design precise planning for the elderly people on the basis of their home leaving reasons, like using THC, and Health Ambassadors, which are influential in estimating the home leaving reasons and preventing the elderly from getting the disease and associated death.

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Worden's Task-Based Model for Treating Persistent Complex Bereavement Disorder During the Coronavirus Disease-19 Pandemic: A Narrative Review

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Abstract

BACKGROUND: A wide range of studies has shown that the coronavirus disease (COVID)-2019 pandemic could cause many deaths on the global scale by the end of 2020 because of the high speed of transmission and predicted case-fatality rates.

AIM: This paper is a narrative review aiming to address the treatment of persistent complex bereavement disorder (PCBD) during the COVID-19 crisis using Worden's task-based model.

MATERIALS AND METHODS: Related papers published from 2000 to 2020 were searched in the EMBASE, PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases. Bereavement, COVID-19, pandemics, and Worden's task-based model constituted the search terms. A narrative technique was implemented (including reading, writing, thinking, interpreting, arguing, and justifying) for material synthesis and creating a compelling and cohesive story.

RESULTS: A few studies have specifically addressed the grief experiences within the COVID-19 crisis. They managed to identify some potential obstacles to grieving during the pandemic, namely, "anticipatory grief" and "multiple losses." This study tried to use Worden's task-based model to address the treatment of PCBD during the pandemic.

CONCLUSIONS: Despite the paucity of information, Worden's task-based model seems to have a considerable impact on the reduction of the PCBD symptoms. Nonetheless, further research is needed to perceive the effect of this approach on PCBD during the COVID-19 pandemic.

Introduction

Dying could be assumed as a developmental concomitant of living and a part of the birth-to-death continuum [1]. Life could involve a number of tragic deaths. Bereavement and grief implicate the mental reactions of the survivors of a significant loss [2]. The expression "bereavement" stands for a universal experience of losing or loss, especially after the death of a loved one. Grief means an emotional, cognitive, physical, and behavioral reaction of a person to bereavement [3]. Recent trajectory studies [4], [5], [6] have challenged the traditional "grief work" view of emotion during bereavement [7], [8]. These studies revealed that a recovery pattern could not merely characterize how to cope with loss (i.e., high chronic distress levels or initial escalated distress post-loss followed by a noticeable decrease). Actually, the most common response has been found to be a resilient pattern (i.e., low levels of stable distress) [4], [5], [6]. However, following the natural death (e.g., an illness-induced death) of a significant other, a total of 10–20% of individuals show chronic complaints, including depression, disturbed grief reactions, and/or posttraumatic stress disorder (PTSD) [5], [6]. These disturbed grief reactions that bring about high levels of life distress and impairments are called persistent complex bereavement disorder (PCBD) in the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [9] and frequently comorbid with depression and PTSD [10].

In recent months, the coronavirus disease (COVID)-2019 pandemic has disrupted the usual process of mourning by delaying the funerals and burials, the impossibility to embrace the deceased warmly, and missing the opportunity to say goodbye before death [11], [12], [13]. According to several studies, by the end of 2020, this pandemic could cause millions of deaths due to high transmission speed and current estimated case-fatality rates (3:4) all around the world [14]. Grieving for such deaths is often more difficult due to some special features, including the sense of unreality about the bad death, exacerbation of feelings of guilt, need to blame others, frequent involvement of medical and legal authorities, sense of helplessness, obvious uneasiness attributable to a sudden increase in levels of adrenalin and other hormones, the unfinished business (including what they did not speak and the deceased related stuff they never managed to do, and an increased need for understanding and meaning [13], [15], [16]. Moreover, the "multiple losses" and "anticipatory grief" (i.e., grieving prior to the actual loss) may add to the complexity of grief [16], [17]. In this regard, multiple losses during the COVID-19 crisis could lead to a more severe bereavement that would leave the person on their own with a sense of repeated survivor. These survivors, assuming that the bigger society is not willing to know about their feelings, often doubt whether to express them [16], [18]. Furthermore, the spread of COVID-19 and the enforcement of social isolation programs, such as physical distancing, quarantine, self-isolation, and limiting or banning the physical presence of visitors in hospitals, have affected the possibility of PCBD occurrence [12], [13], [19]. Although all of the survivors are not at risk of PCBD, it is incumbent on the therapist to specify how the current pandemic could cause PCBD after the death of a significant person [12].

Materials and Methods

Search strategy

Based on the search terms (i.e., bereavement, COVID-19, pandemics, and Worden's task-based model), related English papers published from 2000 to 2020 were searched in the EMBASE, PubMed, Web of Science, Scopus, Cochrane Library, and Google Scholar databases. Fundamental studies on PCBD during the COVID-19 crisis were examined, and the entire relevant literature was included. Quality appraisal assessed if the material exhibited an almost correct and reasonable argument for the presented themes. Eventually, the narrative technique was applied so that the material synthesis included creating a compelling and cohesive story. This depends on MacLure's [20] description of how a researcher engages with the material, that is, reading, writing, thinking, interpreting, arguing, and justifying. We used these data attempting to discuss critical topics in this realm, such as (1) diagnosing PCBD; (2) Worden's task-based model; (3) tasks of mourning; (4) mediators of mourning; (5) grief counseling versus grief therapy; and (6) pharmacotherapy.

Results

Diagnosing PCBD

Worden [21] provided four definitions for PCBD, or as he calls it "complicated mourning:" (1) Chronic grief reaction (a reaction that drags on for a long time and would not yield a satisfactory result); (2) delayed grief reactions (when emotional reactions do not fit the loss, and the experience of grief symptoms for a subsequent loss would be intensified in the future); (3) exaggerated grief reactions (feeling overwhelmed or resorting to maladaptive behaviors following the loss, while the person is aware of the association of these symptoms with the grief); and (4) masked grief reactions (where the patients experience specific symptoms and behaviors but they are not aware of their association with the loss).

During the COVID-19 pandemic, multiple losses could delay mourning attributable to the weight and burden of bereavement overload [12], [22]. Such delayed reactions could occur not only following a subsequent loss but also by encountering other survivors or watching a movie/TV show/other media events about loss [23]. This process is consistent with Bowlby's view [23], which states that "earlier attachment figure" could revive the pain of the earlier loss as though it is being felt for the 1st time.

However, in 2013, the American Psychiatric Association made five major alternations in DSM-5 that affected the definitions of grief, bereavement, and PCBD [9]. First, the simultaneous diagnosis of PTSD in the two 1st months after the loss became possible. Second, the grief as an exclusive criterion was removed from the diagnostic category of adjustment disorders. Third, the separation anxiety disorder term was permitted to be applied to adults as well. In the fourth alternation, the diagnosis of PTSD was maintained as a manifestation of PCBD after the observation or awareness of a traumatic event (i.e., a sudden death). In the last alternation, the suggestive criterion of PCBD, that was applied to refer to the more than 1 year lasing mourning, was included in DSM-5 [9], [24], [25]. Although this clinical condition has not been officially confirmed by DSM-5 as a disorder, it might pave the way for the provision of a higher research budget as well as the coverage of health-care insurance [25].

Lazare [26] introduced an excellent taxonomy of clues to identify an unresolved grief reaction that can help diagnose PCBD during the COVID-19 pandemic (Table 1). Although these clues are not sufficient for a diagnostic conclusion, in case, each one of them is identified in a patient, the therapist should consider the possibility of the PCBD [25]. However, diagnostic decisions about bereavement should be conservative during the COVID-19 pandemic to prevent iatrogenic complications attributed to professional interventions (as well as consequential side effects) and interference in a normal human process [27].

Worden's task-based model

The very first grief theories became disfavored due to their extreme rigidity. However, new models

Table 1: Diagnostic clues of persistent complex bereavement disorder [26]

Clue 1.	Inability to talk about the deceased without experiencing an intense and fresh grief
Clue 2.	Intense grief reaction following some relatively minor loss events
Clue 3.	Observing themes of loss during a clinical interview
Clue 4.	Unwillingness to move the material possessions belonging to the deceased
Clue 5.	Suffering the physical symptoms similar to those experienced by the deceased before his/her death
Clue 6.	Creating radical changes in lifestyle by avoiding friends, family members, or activities associated with the deceased
Clue 7.	A long history of subclinical depression that could be identified as persistent guilt, lowered self-esteem, and false euphoric feeling
Clue 8.	A compulsion to imitate the deceased, which is caused by one's need to make up for the loss by feeling sympathy with the deceased
Clue 9.	The existence of self-destructive impulses
Clue 10.	Unaccountable sadness occurring at a certain time each year
Clue 11.	A phobia about death caused by a specific illness got by the deceased
Clue 12.	Avoid paying the gravesite a visit or taking part in death-associated activities or rituals

manage to identify specific relations and patterns in the idiosyncratic and complicated grief experience. One of the most applicable and inclusive grief theories is the task-based model, established by Worden [25]. The task-based model provides both clients and counselors with frameworks for guiding interventions and improves clients' self-efficacy and self-awareness. Worden [25] recognized grieving as an active process that engages the following four tasks: (1) Accepting the reality of loss; (2) processing the pain of grief; (3) adapting to a world without the deceased (involving internal, external, and spiritual adjustments); and (4) finding a long-lasting connection with the deceased while starting a new life. Furthermore, Worden proposed seven mourning mediators critical to appreciate the client's experience. These mediators are as follows: (1) The character of the deceased; (2) the attachment of the bereaved to the deceased; (3) how the person died; (4) historical antecedents; (5) personality variables; (6) social mediators; and (7) concurrent stressors. Their assessment casts light on the protective factors introduced by the literature. They also create a required context to understand the grief experience's idiosyncratic nature. Further, some other issues need to be considered, such as the strength and style of the bereaved's attachment to the deceased, as well as the level of ambivalence and conflict with the deceased. Death-related factors, namely, degrees of violence or trauma, physical proximity, or death without body recovery, can have significant impacts on the bereaved [25]. In what follows, the Worden's model is detailed.

Tasks of mourning

Grief is defined as a cognitive process that requires facing and rebuilding views about the deceased, grief experience, and the changing world, wherein the survivor has to live now. This process, called grief work, comprises basic tasks that the survivor should accomplish to adapt to the loss (Table 2) [23], [25], [28], [29], [30], [31]. However, it is notable that these tasks are not similarly challenged in any death loss [32]. Certain features need to be taken into account as to the survivors of patients infected by COVID-19, who suffer from PCBD [12], [22]. Usually, unexpected death makes survivors have unreal feelings about the loss, which may last a long time. In such conditions, numbness, walking around in a daze, and experiencing nightmares and intrusive images are not uncommon [25]. Another special feature of survivors with PCBD is an increased need for understanding, which is typically accompanied by blame [25]. In fact, the first question that arises in the minds of COVID-19 survivors after an unexpected loss is "why this happened?" [12]. In such cases, there would be a strong need to find meaning, which should be seriously incorporated in the third mourning task [25].

Table 2: Tasks of mourning [23], [25], [28], [29], [30], [31]

Task 1: Accept the reality of the loss
This task involves the attempt of therapists to help the survivors believe in the impossibility of reunion, at least in this life. The searching behavior that has been widely investigated by Bowlby and Parkes is directly related to this task. In this task, important considerations comprise denying the facts of the loss, mummification, selective forgetting, denying the irreversibility of death, religion spiritualism (i.e., the hope for a reunion with the deceased), and "middle knowledge" as implicated by Avery Weisman (i.e., knowing and not knowing the loss at the same time)
Task 2: Process the pain of grief
The survivor should process the pain of loss to complete the process of pain and avoid suppressing or neglecting this pain. Not feeling, geographic cure, idealizing the deceased, preventing the reminders of the deceased, and using drugs or alcohol are all among the ways whereby the survivors avoid facing this task. If this task is not sufficiently met, it could later lead to a more difficult return and pass the pain that has been avoided
Task 3: Adjustment to a world without the deceased
In this task, three types of adjustment should be considered after a loss, including external adjustments (the effect of the loss on the everyday functioning of an individual), internal adjustments (the effect of the loss on the sense of self od any individual), and spiritual adjustments (the impact of the loss on an individual's values, beliefs, and assumptions about the universe)
Task 4: Help the survivors find an appropriate place for the deceased in their emotional life
The purpose of this task is to provide a place that helps the survivors to lead a fruitful life in the world. William Worden has interpreted this task as "finding a way to remember the deceased while embarking on the rest of one's journey through life."

Mediators of mourning

Among many people experiencing an unexpected loss, there is a broad spectrum of symptoms involved in four general categories, including feelings, physical sensations, cognitions, and behaviors (Table 3) [3], [25]. Although it is incumbent on a therapist to know about this process, regardless of their viewpoint on it (such as stages, phases, or

Table 3: Symptoms of grief under four general categories [3], [25]

Feelings	Anger, sadness, blame, anxiety, guilt and self-reproach, loneliness, helplessness, fatigue, shock, emancipation, yearning, relief, numbness
Physical sensations	Hollowness in the stomach, tightness in the chest, tightness in the throat, oversensitivity to noise, depersonalization, breathlessness, muscle weakness, loss of energy, dry mouth
Cognitions	Confusion, disbelief, preoccupation, sense of presence, hallucinations
Behaviors	Sleep disturbances, eating disturbances, distracted and absentminded behavior, dreams of the deceased, social withdrawal, sighing, avoiding reminders of the deceased, restless hyperactivity, crying, visiting places or carrying objects that remind the survivor of the deceased, treasuring the objects belonging to the deceased

tasks), it is not adequate for effective grief counseling [25]. The grief varies among people according to its intensity and duration [33]. Among most people with PCBD in the time of the COVID-19 pandemic, for example, feelings of guilt, anger, helplessness, shock, numbness, disbelief, sleep disturbances, and restless hyperactivity are more severe and require special attention [16]. Therefore, it is essential to perceive the way of moderating these tasks through different factors to realize why people manage tasks of mourning differently, which is more significant when facing PCBD [12], [25].

As already stated, Worden [25] introduced seven key mourning mediators that influence the tasks of mourning. The kinship relationship with the deceased, as the first mediator, plays a prominent role in the response of these people to the loss. For instance, parents (especially mothers), widows, and the sisters of the deceased are more affected than adult children, widowers, and brothers [25]. The second mediator is the nature of the survivor's attachment to the deceased [25]. In this regard, the intensity of love for the deceased, the degree of the effectiveness of the presence of the deceased in the survivor's sense of well-being, ambivalence about the deceased, conflict with the deceased, and dependent relationships (like pre-loss marital dependence) could affect the reaction to grief [34], [35]. The third mediator is how the person died [17], [25], [36]. In COVID-19 crisis, the remoteness of the deceased at the moment of death, suddenness or unexpectedness of the death, and multiple losses could alter the process of grief [12]. The forth mediator is the historical antecedents, including the quality of the survivor's reaction to the prior losses, that is, whether he/she has mourned adequately and properly or has added the previous unresolved grief to the new loss [25]. The fifth mediator is personality variables [25]. The previous studies have demonstrated that grief reaction intensifies for the cases of preexisting mood and anxiety disorders, preexisting trauma (particularly childhood trauma), maladaptive coping styles, insecure attachment styles, rumination, and negative cognitive styles [37], [38]. The sixth mediator involves social variables [25]. Since mourning is a social phenomenon, the degree of perceived emotional and social support from family or others has a significant role in the mourning process, which has been highly affected by the COVID-19 pandemic [19]. Fear of contagion, stigma, and subsequent lack of social support are some of the challenges faced by therapists during the COVID-19 pandemic [12]. The last mediator is the concurrent losses and stresses [25]. It includes issues such as complicated economic problems (as a result of business restrictions during quarantine or loss of family head due to COVID-19), substance use, and inability to follow usual cultural practices of death and mourning [12], [13], [19]. Furthermore, these mediators have been classified into three main categories, namely, loss-related factors (mediators 1, 2, and 3), pre-loss risk factors (mediators 4 and 5), and periloss factors (mediator 7) [39].

According to Wortman and Silver's view [40], the distress levels of survivors are conspicuously affected by various mediators. Accordingly, therapists should seriously consider these mediators during the grief process, grief counseling, and grief therapy.

Grief counseling versus grief therapy

The occurrence of a wide range of grief reactions following a loss is a normal experience [41]. Some of the people, including individuals bereaved by COVID-19, might experience high levels of distress that leads them to seek counseling [12]. In such cases, grief counseling usually could help people adapt to the loss more efficiently [13]. In this regard, there are particular purposes based on the four mourning tasks, including (1) elevating the loss realism, (2) helping the survivors manage both behavioral and emotional pains, (3) providing the survivors with the ability to handle different impediments to readjustment (external, internal, and spiritual) after the loss, and (4) helping the survivors establish an approach to remembering and/or maintaining an emotional connection with the deceased while moving forward to reinvest in life [25].

A recent meta-analysis has shown that the preventive grief counseling (unlike treatment interventions) is not effective and could even be harmful [42]. However, in some cases, it is better to begin grief counseling as soon as possible but not in the first 24 h after the loss, unless the survivor and the therapist have been pre-connected [25]. This counseling process could be performed in a professional setting, informal setting (home environment), or through telephone contacts [12]. However, Parkes and Prigerson [43] stated that counseling processes in professional settings and through telephone contacts are the most and the least effective approaches, respectively. The grief counseling principles and procedures are illustrated in Figure 1 using Worden's task-based model [25]. Notice that grief counseling needs to follow a theoretical insight into human behavior and personality, not only according to mere settings of techniques [25]. In this regard, some techniques such as evocative language (using tough words to evocate the survivor's feelings like using the term "your son died" instead of "you lost your son"), use of symbols (using pictures or the belongings of the deceased), writing (writing a letter to the deceased and expressing the feelings and thoughts by the survivor), drawing (painting pictures reflecting the sentiments of an individual as well as what he/she experienced with the deceased), role-playing (helping the survivor to role-play various situations he/she fears), cognitive restructuring (particularly concerning covert thoughts and self-talk), memory books (creating a memory book for the deceased), directed imagery (helping the survivor visualize the deceased in an empty chair with closed eyes; then provoking the survivor to talk about what he/she needs to

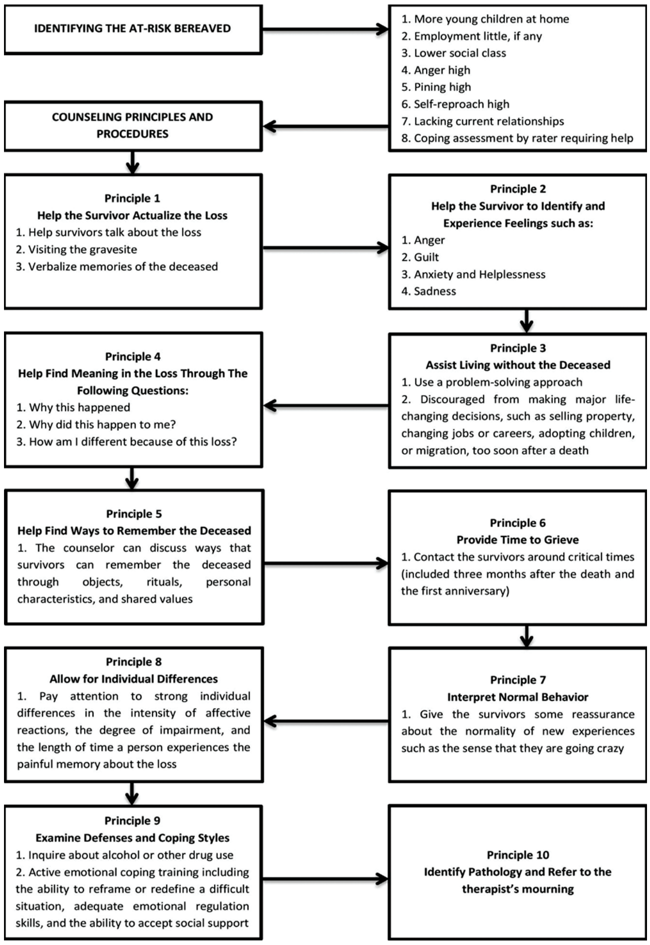

Figure 1: The stages of grief counseling during coronavirus disease-19 pandemic [25]

say to the deceased), and metaphors (a more acceptable symbolic representation of grief such as phantom pain and amputation related to the former image of loss) could provide an efficient grief counseling [25], [44], [45]. However, the aim of grief therapy is different from that of grief counseling to some extent [25]. Grief counseling aims to facilitate the grief tasks concerning the recent bereavement so that the survivor better adapts to the loss, whereas grief therapy aims at identifying and resolving the separation conflicts [25]. These conflicts prevent the completion of mourning tasks for those people suffering from PCBD [25]. Resolving these conflicts requires the experience of thoughts and feelings avoided by the patient. On this subject, the therapist would provide the patient with the opportunity to mourn through giving the social support required for a successful grief process, that is, an opportunity that might not be accessible at the moment of the death, which implicates a suitable therapeutic band [25]. One way to bolster this band is recognizing the difficulties that people might experience when dealing with a long-lasting intense grief. As the conflicts concerning the deceased become a more fundamental issue, the resistance to discovering painful feelings and thoughts increases. Hence, in any therapy, the resistances are always observed carefully and addressed as a component of the therapy process [25]. Grief therapy is mostly performed in a professional setting lasting from 2 to 20 sessions (depending on the types of treatment interventions) [46]. The therapeutic procedures for grief are briefly illustrated in Figure 2 using Worden's task-based model [25].

Pharmacotherapy

Although the psychological insight into the bereavement has been enhanced, there is still not an appropriate basis for biological interventions, except in cases with a serious psychiatric disorder such as major depressive disorder, post-traumatic stress disorder, and psychotic disorders [25]. Despite different viewpoints regarding the management of PCBD, there is an agreement on the treatment of anxiety and insomnia (not depressive symptoms) with low doses of medications [47], [48]. Prescribing antidepressants for people suffering from acute grief reactions due to the COVID-19 pandemic are not common for two reasons. First, these medications would work in long term and could hardly ever sedate acute grief reaction symptoms, aside from major depressive episodes [25]. Second, drug interactions have raised concerns among COVID-19 survivors [49]. In this respect, duloxetine, fluvoxamine, fluoxetine, phenelzine, sertraline, and vortioxetine are the only antidepressants that have the least interaction with the therapeutic regimens used in COVID-19 infection [50], [51].

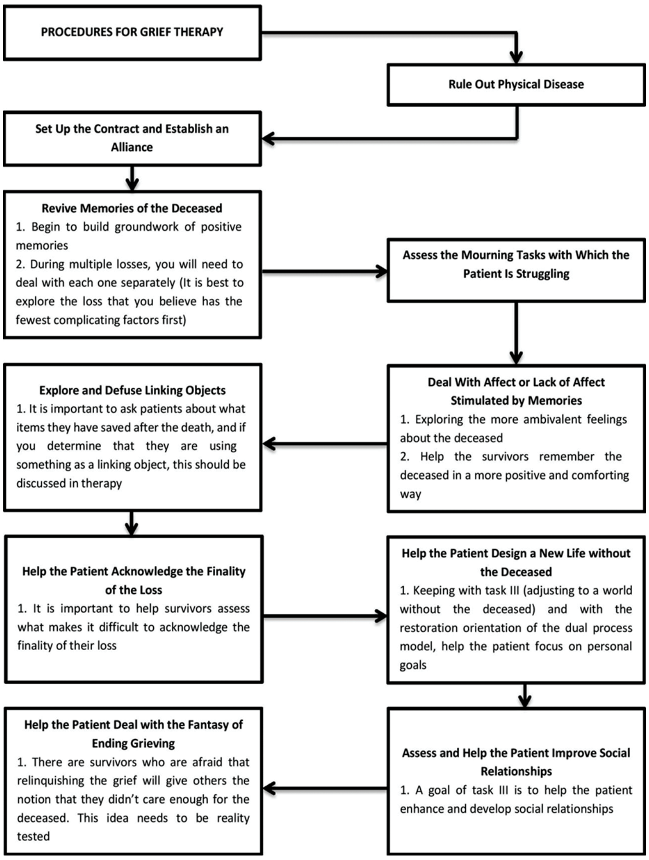

Figure 2: The stages of grief therapy during coronavirus disease-19 pandemic [25]

Conclusions

The COVID-19 crisis will proceed with influencing more people. Loss and grief, as the most encompassing themes, interweaves many facets of people's life in different context. Thus, it is necessary to improve accessibility to evidence-based interventions, in both face-to-face and online formats, during the COVID-19 crisis [52], [53], [54]. It seems that Worden's task-based model may be effective in reducing the symptoms of PCBD. However, further investigations in this field need to be carried out through longitudinal empirical study.

Authors' Contributions

Mohsen Khosravi designed the study, collected the data, and drafted the manuscript. Furthermore, he read, revised, and approved the final manuscript.

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Impact of Coronavirus Disease-19 Lockdown on Egyptian Children and Adolescents: Dietary Pattern Changes Health Risk

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Abstract

BACKGROUND: Lockdown and school closure related to the coronavirus disease 2019 (COVID-19) have unfavorable effects on children and adolescents.

AIM: This study was conducted to survey the changes in dietary pattern and related health factors in Egyptian children and adolescents during the COVID-19 outbreak closure.

MATERIALS AND METHODS: Data were collected through a dietary pattern, eating behavior, and physical activity electronic questionnaire conducted through social media sites, targeting parents of children and adolescents after two whole months of lockdown and school closure in Egypt.

RESULTS: This study included 765 participants, 31.8% noted increased appetite, 45.6% reported increased sweets and unhealthy food consumption, and 37.6% showed increased frequent snacking between meals. Alongside 53.1% showed increase in late snacks during night after COVID-19 closure. The majority of our participants 82.0% noted associative change in eating behavior with boring and 94.6% revealed increased usage of electronics and screen time. This study showed significant positive correlation between increased appetite and mobile screen time, laptop screen time, and video gaming. Increased sweets and unhealthy food consumption was positively correlated with TV watching and mobile screen time. A significant positive correlation was revealed between uncaring about eating fruits and vegetables and increase screen time for each of mobile, and laptop and remote learning. Furthermore, there was positive correlation between decreased protein serving intake and each of mobile screen time and remote learning. TV watching and laptop screen times showed positively significantly association with frequent snacking between meals. Mobile screen time, TV screen time, and video gaming were positively significantly correlated with late night snacking.

CONCLUSIONS: The present study concluded prolonged lockdown leads to changes in eating patterns, related to contributing factors of physical inactivity and prolonged screen time.

Introduction

Acute respiratory infections are one of the prevalent pediatric diseases. Coinfections of respiratory viruses and atypical bacterial respiratory pathogens are common [1]. Coronavirus disease 2019 (COVID-19) is considered one of the most pathogens which targets the human respiratory system causing atypical pneumonia and severe acute respiratory syndrome (SARS) [2].

Numerous patients admitted to hospitals with pneumonia and SARS accompanied by rising deaths reported daily which overwhelms the health-care systems worldwide. Yet no specific treatment or vaccine has been developed for COVID-19 disease despite of high infectivity and rapid transmission, World Health Organization declared COVID-19 outbreak as global pandemic [3].

A constellation of Egyptian governmental restrictions has been released to control the spreading and transmission of the disease. Curfew, lockdown, and stay-at-home orders have been applied to support social distancing and separation [4].

COVID-19 pandemic quarantine and school closure have unfavorable effects on families especially children and adolescents. It is recognized that when children are off of school such as in weekend's vacations and summer breaks, they are physically less active, spend more screen time, have irregular pattern of sleep, and less healthy diets, resulting in excess weight gain, and loss of cardiorespiratory fitness [5].

Physical activity of children and adolescents is tightly adherent to school-related activities, active movement, and sport practicing [6]. In addition, stay-at-home instructions reduce the opportunities for physical activity among children, particularly for those that living in urban areas or in small apartments [7].

Prolonged screen time is associated with experiencing overweight and obesity in childhood, which is more likely attributed to sedentary time and the association between screen time and frequent snacking [8].

Excess weight gained during the lockdown may not be easily reversible and might contribute to excess adiposity during adulthood [9].

Many challenging and stressor effects are facing children and adolescents that confined with prolonged home stay duration, inadequate information, lack of friends and classmates contact, absence of home personal space, fears of infection, frustration, and monotony, in addition to family financial burdens [10].

Breaking of daily activity caused by the curfew and lockdown could result in boredom and monotony [11]. Furthermore, continuous talking and hearing about the COVID-19 from media or family members can be stressful. Stress is leading attitude toward too much eating especially toward comfort food which contains excess sugar [12]. Comfort food contains sugar and simple carbohydrate increased serotonin release that helps in decrease stress and ameliorate mood and temper [13].

Home environment and child raising attitude are the most important factors that touch food behavior through joint interaction [14]. Parents may affect their children's eating behaviors, as they may habitually use food to control or regulate their children upset or negative emotions and the children acquired it as learnt behavior [15].

This study aimed at surveying changes in dietary pattern and related health factors in Egyptian children and adolescents in order to highlight the collateral hidden threats during the COVID-19 outbreak closure.

Methods

A cross-sectional questionnaire was conducted during the lockdown and curfew to survey the changes in dietary pattern, eating behavior, and physical activity in Egyptian children and adolescents. An electronic questionnaire designed through Google forms was distributed through social media sites to parents or caregivers targeting children and adolescents aged 4–16 years old of both sexes. It was started on the 12th of May, 2020, after two whole months of governmental restrictions; school closure, community activity limitations, curfew, and quarantine measures, in addition to public health instructions and awareness of social distancing. The questionnaire was available online for 2 weeks.

Ethical approval was taken from the Medical Ethical Committee of the National Research Center. All respondents provided informed consent, which explained the aim of the study, the privacy policy, time consumed by the participant, and the benefits risk issues. The Parent/caregiver could only continue the questionnaire after agreement on participation.

This electronic questioner was designed to include:

- Sociodemographic data as age, gender, residence, father, and mother education level
- Information about regular activities before COVID-19 pandemic, following strict quarantine measures, and night sleeping hours after lockdown
- Eating habits changes which included questions about alteration in eating habits during the lockdown. It was reviewing change of appetite, change pattern of food types such as eating proteins, fruits and vegetables, and unhealthy food, and change of some eating habits such as more frequent snacking and late night meals. Beside determination if these changes were associated with the pandemic lockdown or not. Moreover, reporting the association between change of eating desire and specific mood condition such as boredom, frustration, or anger
- Screen time survey which includes questions about alteration in screen time and frequency of electronics usage.

After successful submitting, the parent/caregiver receives an acknowledge note for participation and a link if he/or she would like to respond for another child.

All the data were converted automatically to Google sheets and inspected carefully from the team to exclude any error or mistaken data.

Results

The analytic sample of this study was 765 participants with age ranged between 4 and 16 years old. They are of matched sex groups. They are classified according to their age group into; 211 children were <6 years (27.6%), 440 children were 6–12 years old (57.5%), and 114 children were above 12 years old (14.9%) (Table 1).

Most of their parents were highly educated as 735 (96.1%) of the children's fathers and 739 (96.6%) of the children's mothers were highly educated (Table 1).

Descriptive reviewing about change lifestyle and behavior revealed 505 children (66.0%) followed strict quarantine measures; about 426 children (55.7%) were performing physical activity before quarantine measures. Three hundred thirty-four children (43.7%) were practicing for more than 3 h/week. About 354 children (46.3%) showed number of night sleeping hours more than 6–8 h daily (Table 1).

The analytic data about change of eating patterns and habits showed that 243 children (31.8%)

have increased appetite after COVID-19 closure. About 349 children (45.6%) have increased sweets and unhealthy food consumption after COVID-19 closure. On the other hand, 288 children (37.6%) showed increased frequent snacking between meals after COVID-19 closure, and about 406 children (53.1%) showed increase in late snacks during night after COVID-19 closure. These changes of eating patterns were clear in the 6–12 years age group. Moreover, 627 children (82.0%) revealed that the change in eating behavior was usually associated with boring (Table 2).

Reviewing the data about effect of quarantine and lockdown on electronic and screen time usage showed that 724 children (94.6%) have increased usage of electronics and screen time (Table 3).

Children and adolescence were exposed to different types of media consumption TV watching, mobile and tablets' screens, laptops, and videogame playing. Categorizing daily extra screen time exposure of our sample revealed that 483 children (63.1%) used mobile screen time over 3 h/day, 417 children (54.5%) used TV watching over 3 h/day, and 233 children (30.5%) were playing video games more than 3 h/day, while only 124 children (16.2%) were laptop users. That alongside of 434 children (56.7%) shifted to home schooling and distant learning (Table 3).

Correlating analysis of changes of eating pattern and extra screen time usage during curfew and lockdown showed that significant positive correlation between increased appetite and mobile screen time, laptop screen time, and video gaming. Increased sweets and unhealthy food consumption was positively correlated with TV watching and mobile screen time. Our study also showed significant positive correlation between uncaring about eating fruits and vegetables and increase screen time for each of mobile, and laptop

Table 1: Socio-descriptive data of the studied sample

Item (n = 765)	Category	Frequency	Percent	Chi-square	p-value
Sex	Male	408	53.3	3.400	0.065
	Female	357	46.7		
Age stage	<6 years	211	27.6	219.773	0.000
	6–12 years	440	57.5		
	More than 12 years	114	14.9		
Education stage	Nursery	229	29.9	422.425	0.000
	Primary	407	53.2		
	Preparatory	83	10.8		
	Secondary	46	6.0		
Follow strict quarantine measures	Yes	505	66.0	913.844	0.000
	No	260	34.0		
Father educational level	Higher qualification	735	96.1	910.624	0.000
	Secondary school	30	3.9		
Mother educational level	Higher qualification	739	96.6	819.957	0.000
	Secondary school	26	3.4		
Regular activities before lockdown	No	131	17.1	654.340	0.000
	Physical activity	426	55.7		
	Drawing and arts	20	2.6		
	Other activity	79	10.3		
	Several activities	109	14.2		
Number of activity hours before lockdown	<3 h/week	232	30.3	203.392	0.000
	More than 3 h/week	334	43.7		
	<3 h/day	96	12.5		
	More than 3 h/day	103	13.5		
Number of night sleeping hours after lockdown	<6 h	178	23.3	63.584	0.000
	6–8 h	233	30.5		
	More than 8 h	354	46.3		

p ≤ 0.005 (highly significant), ≤ 0.05 (significant), > 0.05 (insignificant).

Table 2: Change of eating pattern categorized by age group

Change in eating pattern	Category	Age stage (%)			F	p one-way	Total		
		<6 years	6–12 years	More than 12 years		ANOVA	No (%)	Chi-square	p-value
Decrease or loss of appetite	No	87 (41.2)	259 (58.9)	72 (63.2)	9.484	0.000	418 (54.6)	185.953	.000
	Preexisting before lockdown	39 (18.5)	57 (13.0)	16 (14.0)			112 (14.6)		
	Occurred after lockdown	85 (40.3)	124 (28.1)	26 (22.8)			235 (30.7)		
Increase of appetite	No	161 (76.3)	226 (51.4)	59 (51.8)	21.801	.000	446 (58.3)	269.278	.000
	Preexisting before lockdown	18 (8.5)	49 (11.1)	9 (7.9)			76 (9.9)		
	occurred after lockdown	32 (15.2)	165 (37.5)	46 (40.4)			243 (31.8)		
Increase sweets and unhealthy food	no	59 (28.0)	137 (31.1)	44 (38.6)	2.037	0.131	240 (31.4)	60.008	.000
	Preexisting before lockdown	47 (22.3)	104 (23.6)	25 (21.9)			176 23.0)		
	occurred after lockdown	105 (49.8)	199 (45.2)	45 (39.5)			349 (45.6		
Does not care about eating vegetables and fruits	No	104 (49.3)	201 (45.7)	41 (36.0)	.192	0.826	346 (45.2)	91.082	.000
	Preexisting before lockdown	69 (32.7)	158 (35.9)	56 (49.1)			283 (37.0)		
	Occurred after lockdown	38 (18.0)	81 (18.4)	17 (14.9)			136 (17.8)		
Decrease in his regular protein intake	No	76 (36.0)	170 (38.6)	42 (36.8)	.192	0.826	288 (37.6)	52.306	.000
	Preexisting before lockdown	78 (37.0)	190 (43.2)	47 (41.2)			315 (41.2)		
	Occurred after lockdown	57 (27.0)	80 (18.2)	25 (21.9)			162 (21.2)		
Snacks between meals	No	69 (32.7)	136 (30.9)	38 (33.3)	.446	0.640	243 (31.8)	6.565	.000
	Preexisting before lockdown	69 (32.7)	135 (30.7)	30 (26.3)			234 (30.6)		
	Occurred after lockdown	73 (34.6)	169 (38.4)	46 (40.4)			288 (37.6)		
Late snacks during night	No	79 (37.4)	131 (29.8)	29 (25.4)	1.507	0.222	239 (31.2)	469.609	.000
	Preexisting before lockdown	28 (13.3)	67 (15.2)	24 (21.1)			119 (15.6)		
	Occurred after lockdown	104 (49.3)	241 (54.8)	61 (53.5)			406 (53.1)		
When is change in eating behavior	No change	12 (36.4)	16 (48.5)	5 (15.2)	6.806	0.001	33 (4.3)	23.396	.001
	With severe depression	22 (38.6)	26 (45.6)	9 (15.8)			57 (7.4)		
	With severe anger	25 (52.1)	19 (39.6)	4 (8.3)			48 (6.3)		
	With boring	152 (24.2)	379 (60.4)	96 (15.3)			627 (82.0)		

p ≤ 0.005 (highly significant), ≤0.05 (significant), >0.05 (insignificant).

Table 3: Lockdown effect on electronic screen time usage

n = 765	Category	Frequency	Percent	Chi-square	p-value
Lockdown effect on electronics and screen use	Yes	724	94.6	609.790	0.000
	No	41	5.4		
Mobile extra screen time	No use	104	13.6	316.525	0.000
	<3 h/day	178	23.3		
	More than 3 h/day	483	63.1		
TV extra screen time	No use	155	20.3	157.208	0.000
	<3 h/day	193	25.2		
	More than 3 h/day	417	54.5		
Laptop extra screen time	No use	519	67.8	409.984	0.000
	<3 h/day	122	15.9		
	More than 3 h/day	124	16.2		
Video game extra screen time	No use	426	55.7	203.631	0.000
	<3 h/day	106	13.9		
	More than 3 h/day	233	30.5		
Remote learning	Yes	434	56.7	13.868	0.000
	No	331	43.3		

p ≤ 0.005 (highly significant), ≤0.05 (significant), >0.05 (insignificant).

Table 4: Correlation between change of eating patterns and each of screen time and sleeping hours

Change of eating pattern n = 765	Electronic screen time usage					No. of sleeping hours after lockdown
	Mobile extra screen time	TV extra screen time	Laptop extra screen time	Video game extra screen time	Remote learning	
Decrease or loss of appetite						
r	0.012	0.072*	−0.139**	−0.023	0.112**	−0.044
p	0.736	0.047	0.000	0.534	0.002	0.221
Increase of appetite						
r	0.125**	0.043	0.162**	0.123**	−0.065	0.027
p	0.001	0.234	0.000	0.001	0.073	0.460
Increase sweets and unhealthy food						
r	0.074*	0.114**	0.022	0.047	0.001	−0.076*
p	0.041	0.002	0.551	0.196	0.979	0.036
Does not care about eating vegetables and fruits						
r	0.093*	0.024	0.102**	0.045	0.097**	−0.131**
p	0.010	0.503	0.005	0.214	0.007	0.000
Decrease in his regular protein intake						
r	0.106**	0.047	0.015	0.031	0.075*	−0.139**
p	0.003	0.197	0.673	0.396	0.038	0.000
Frequent snacks between meals						
r	0.059	0.076*	0.198**	0.065	−0.083*	−0.003
p	0.104	0.035	0.000	0.071	0.022	0.942
Late snacks during night						
r	0.158**	0.090*	0.069	0.087*	0.041	−0.032
p	0.000	0.013	0.058	0.016	0.262	0.381

r: Spearman's correlation test. **p ≤ 0.005 (highly significant), *p ≤ 0.05 (significant), >0.05 (insignificant).

and remote learning. Furthermore, there was positive correlation between decreased protein serving intake and each of mobile screen time and remote learning (Table 4).

TV watching and laptop screen time were positively significantly associated with frequent snacking between meals. However, remote learning was inversely related to frequent snacking between meals (Table 4).

Mobile screen time, TV screen time, and video gaming were significantly positively correlated with late night snacking (Table 4).

This study noted significant negative correlation between night sleeping hours and increased sweet and unhealthy food ingestion and carelessness of eating fruits and vegetables and protein serving intake; less night sleeping hours is related to more sweet and unhealthy food ingestion, more increase in the carelessness of receiving fruits and vegetables and protein servings (Table 4).

Linear stepwise regression analysis of change of eating patterns revealed association between increased appetite and increase each of age stage group, mobile screen time and TV screen time (Table 5).

Regression analysis of predicting factors for frequent snacking between meals denoted significant association with increased laptop screen time and TV screen time (Table 6).

Late night snacking was significantly associated with increased mobile screen time, TV screen time, and video gaming (Table 7).

Table 5: Linear stepwise regression analysis of predicting factors for increase of appetite

Predicting factors	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0.053	0.172		0.308	0.758
Age stage	0.401	0.077	0.189	5.232	0.000
Laptop extra screen time	0.150	0.044	0.121	3.375	0.001
TV extra screen time	0.080	0.038	0.074	2.093	0.037

p ≤ 0.005 (highly significant), ≤0.05 (significant), >0.05 (insignificant).

Table 6: Linear stepwise regression analysis of predicting factors for frequent snacking between meals

Predicting factors	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	1.151	0.086		13.359	0.000
Laptop extra screen time	0.209	0.041	0.179	5.036	0.000
TV extra screen time	0.079	0.036	0.078	2.201	0.028

p ≤ 0.005 (highly significant), ≤0.05 (significant), >0.05 (insignificant).

Statistical analysis

Data were collected, verified, coded, and analyzed using the Statistical Package for the Social

Table 7: Linear stepwise regression analysis of predicting factors for late night snacking

Predicting factors	Unstandardized coefficients		Standardized coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	1.174	0.123		9.506	0.000
Mobile extra screen time	0.178	0.041	0.154	4.310	0.000
TV extra screen time	0.105	0.039	0.097	2.714	0.007
Video game extra screen time	0.072	0.033	0.079	2.178	0.030

$p \leq 0.005$ (highly significant), ≤ 0.05 (significant), >0.05 (insignificant).

Science (SPSS) version 26 (SSPS Inc., Pennsylvania, USA). Qualitative data presented as number and percentages. The comparison between two groups with qualitative data was done by using Chi-square test. Spearman's test correlation analysis was used to assess the relationship between two ordinal parameters in the same group. All tests were two-tailed, with a significance level of $p \leq 0.05$ and highly significance at $p \leq 0.005$. Linear stepwise regression analysis was used to detect the predictors of the dietary change variable.

Discussion

Lockdown and school closure created large domestic leisure time; nevertheless, children have not been allowed to use regular playgrounds, prevented from social group activities and sports clubs, strict implication for social distancing, and limited contact to peers [16].

Our findings suggest that with respect to 2 months of quarantine and curfew measures a constellation of collateral eating pattern changes and their related hazardous alterations in children and adolescents life style. About 66% of our studied group was following strict quarantine and lockdown measures which mean long staying at home, more exposure to life style alterations such as less physical activity, more usage of electronics, long screen time exposure, and unhealthy change of the food patterns and eating behaviors.

As reviewing the dietary and eating patterns of our participants under COVID-19 lockdown, the main noticed dietary pattern changes were increased appetite (31.8%), increased sweets and unhealthy food consumption (45.6%), frequent snacking between meals (37.6%), and increased late night snacks (53.1%). These poor eating patterns seemed to be adherent to each other as frequent snacking between meals and late night snacks need easily available rapid food such as sweet and most of unhealthy food types in presence of increased appetite.

The main age group showed eating patterns affection was children aged 6–12 years old, which may be explained by that this age group can be obligated and forced to follow the strict quarantine measures and stay at home orders. However, to some extent, they are self-dependable and can prepare easy rapid snacks alone and frequent snacking between meals without help.

Besides, school environments offer schedule and routine about mealtimes, physical activity, and sleep time. These three crucial lifestyle aspects are implicated in obesity risk [17]. Hence, school closure related to COVID-19 pandemic distributed this routine and omitted this privilege.

An online trans-continental survey done to determine the effect of COVID-19 pandemic confinements on multiple life style behaviors reviewed a negative effect on all grades physical activity even walking, poor eating patterns included frequent snacking, increased late night snacking, increased numbers of main meals, eating out of control, and high unhealthy food consumption [18].

In favor to our study, an Italian public survey study about change in dietary habits during COVID-19 lockdown reported that an increase in comfort unhealthy food consumption (sweets, desert, and salty snacks), in addition this increase was attributed to psychological state of anxiety toward pandemic [19].

Another Italian survey reported third the studied sample eat less healthy food (fruit, vegetables, nuts, and legumes). Alongside body mass index was positively associated to the increased appetite and junk food consumption while less age was directly associated to night snacks and junk food consumption [20].

Moreover, an experience dietary study from Poland during COVID-19 lockdown revealed more eating and frequent snacking during pandemic quarantine. Notably, increased weight was related with reduced consumption of vegetables, fruit, and legumes during quarantine, and frequent providing of meat, dairy, and fast-foods [21].

Paralleling a collaborative multinational study involved Spain, Italy, Brazil, Colombia, and Chile compared average food intake before and during COVID-19 lockdown in children and adolescents 10–19 years old reported significant increase in fried and sweet food average intakes during COVID-19 lockdown comparing to that before pandemic lockdown [22].

The majority of our participants 82.0% noted associative change in eating behavior with boring. Boredom is a distinct individual feeling perceived due to lack of meaning and dissatisfaction in the present life state, circumstances, and actions [23].

Eating is poor coping mechanism to reduce the intensity of different negative stressors associated with pandemic, school closure, and lockdown [24]. Foods preferred and usually consumed in response to negative emotions are commonly rich in sugar and/or fat. These foods are palatable delivering hedonic pleasure and immediate instant reward that may distract from the experience of negative emotions [25]. However, overeating in children and adolescents is expressed by an eating behavior associated with frequent snacking, eating high energy-dense foods greater total caloric intake, and overweight [15].

Our findings were supported by a large consecutive sequential study done by Moynihan *et al*. at 2015 [11] about the relationship between boredom and eating behavior changes, it showed that boredom state predicted more calorie and food nutrients consumption. In addition, it increased the desire for snacking with preference of unhealthy food intake to escape the individual awareness with state of boredom.

The notable increase in sweets and unhealthy food consumption in our study may be explained by the resulting release of serotonin and tryptophan hormones that related to elevated mood which may improve the adverse feeling of boredom [13]. Meanwhile, these types of food are accessible and almost ready to prepare. On the other hand, increased frequent snacking between meals and late night snacking may be attributed to prolonged screen time and delayed sleeping time.

Saunders *et al*. [26] reported several foods types in the unhealthy diet such as fast foods, ice cream, fried food, French fries, potato chips, cakes, and sugar-sweetened sodas that are ready to eat and are easily available.

In this study, 55.7% were performing physical activity before quarantine measures. Furthermore, 43.7% were practicing for more than 3 h/week. Physical activity of children and adolescents is tightly adherent to school-related activities, active movement, and sport practicing [6]. Unfortunately, COVID-19 confinements were included schools, clubs, playgrounds, and gyms closure, prevented children from outdoor physical activity.

Sedentariness and inactivity are directly playing a role in many health outcomes such as obesity, metabolic syndrome, and cardiovascular diseases. Screen time, including watching television and playing electronic games, is considered as alternative indicators of Inactivity.

Digital electronic media usage represents fundamental part in children and adolescents lives, continuous rise of digital media leads to rise of time adherence and screen stickiness usage [27]. Besides, the benefits related to rapid access to information and rapid mass communication, screen exposure cause many health and psychological problems among children and adolescents [28].

This study reported 94.6% have increased usage of electronics and screen time after pandemic lockdown. About 63.1% had mobile screen time over 3 h/day, 54.5% were TV watching over 3 h/day, and 30.5% were playing video games more than 3 h/day, while only 16.2% were laptop users. That alongside 56.7% shifted to home schooling and electronic distant learning.

Our study suggested highly significant positive correlation between increased appetite and mobile screen time, laptop screen time, and video gaming ($p \leq 0.005$). Increased sweets and unhealthy food consumption were significant positively correlated with TV watching ($p \leq 0.05$) and mobile screen time ($p \leq 0.005$). Our study also showed high significant positive correlation between uncaring about eating fruits and vegetables and increase screen time for each of mobile, and laptop and remote learning ($p \leq 0.005$). Furthermore, there was positive correlation between decreased protein serving intake and each of mobile screen time ($p \leq 0.005$) and remote learning ($p \leq 0.05$).

TV watching and laptop screen time were positively significantly associated with frequent snacking between meals ($p \leq 0.05$) and ($p \leq 0.005$), respectively. However, remote learning was inversely related to frequent snacking between meals ($p \leq 0.05$).

Mobile screen time, TV screen time, and video gaming were positively significantly correlated with late night snacking ($p \leq 0.005$, ≤ 0.05, and ≤ 0.05, respectively).

The relationship between electronic screen time and change of eating patterns was backboned by linear stepwise regression analysis showed: Age stage group, increased laptop screen time, and increased TV screen time were significantly associated with increased appetite ($p \leq 0.005$, ≤ 0.005, and ≤ 0.05, respectively). Increased laptop screen time and TV screen time were significantly associated with frequent snacking between meals ($p \leq 0.005$) and ($p \leq 0.05$), respectively. Increased mobile screen time, TV screen time, and video gaming were significantly associated with late night snacking ($p \leq 0.005$, ≤ 0.005, and ≤ 0.05, respectively).

This agrees with other studies, children who watch TV during two or more meals per day receive less portions of healthy food, more processed meat, and extra junk food than children who prevented from watching TV during mealtimes or only allowed for one meal per day [29], [30], [31].

Ruiz-Roso *et al*. [22] study done during COVID-19 lockdown 2020 elucidated TV watching during mealtimes is associated to fewer intakes of vegetables and fruits during the COVID-19 lockdown and a higher fried food, sweet food, and sugar sweetened beverages consumption in children and adolescents aged 10–19 years.

Enlarged screen time usage in childhood is considered a contributing risk factor for obesity and delayed development of the child which is intensely associated with decrease outdoor activity and increase body mass index and overweight [32].

Many studies have been denoted similar results, in a study done on children aged 10–12, there was a direct relationship between inactivity and overweight. Consuming more screen time on TV watching, mobile using, and video gaming was greater risk for obesity and overweight [33].

Jalo *et al*. [34] carried out an international study at 2019, which involved 12 sites representing different cultural and environmental aspects that revealed positive association between behavioral eating and an unhealthy diet pattern, moderate physical activity, and TV viewing.

Lockdown and stay at home commands have increased consumption of electronic entertainment especially online gaming; excessive gaming has negative influences including harm to mental health, sleep patterns, or physical health [35].

The present study revealed significant negative correlation between night sleeping hours and increased sweets and unhealthy food ingestion ($p \leq 0.05$) and carelessness of eating fruits and vegetables and protein serving intake ($p \leq 0.005$) that means less night sleeping hours is correlated to more sweet and unhealthy food ingestion, more increase in the carelessness of receiving fruits and vegetables and protein servings.

Deficient sleep and reduced sleep time is a strong risk factor for obesity in children. Cross-sectional studies have indicated that late sleeping time increases the possibility of obesity [36].

These poor related vicious circus that started with lockdown confinements, stay at home, decreased physical activity, prolonged screen time, late sleeping time, then consequentially unhealthy food patterns, and eating habits.

Conclusion

COVID-19 pandemic has more threats that cross beyond those of direct viral infection that unfavorably affect children and adolescences. Prolonged lock down and home confinement leads to change of eating pattern and poor eating habits that associated with reduced physical activity and prolonged screen time. These are contributing factors causing excess weight gain and increased adiposity health risks later in life. Revising our requirements and resources regarding such overwhelming cries are a must. Allowing cooperative network and plan to face quarantine and lockdown physical health impacts affect children and adolescents.

Recommendations

This quick surveying study provides the privilege of focusing on management of poor dietary patterns and eating habits, and their related hazardous alterations of children and adolescent's lifestyle during pandemic lockdown. Here, some insights and recommendations that may help in managing the problem:

Eating well-balanced meals, having adequate servings, sticking to home-cooked food, avoid irregular snacking, and keeping shared family mealtimes.

Practice indoor activity breaks (such as stretch breaks or dance breaks). Provide physical education sessions either in the contexts of school schedule or media programs.

Receiving adequate night sleeping, schedule suitable time for night going to sleep and morning waking up.

Teach children that media has a beginning and an end; watching is not an all day mission.

Create schedule for online and offline times, let children sharing in setting limits on their screen usage, create a space for family gathering, talking, playing games, and reading books.

Watch out the media content to outfit the child age. Provide creative exciting content for the screen time such as touring the sights of our country or other countries handling wonders and curiosities around the world. Co-watching or watching together is effective.

Allow them contact their friends, relatives, and family members through phone or video chats.

Limitations of the study

This study facing several limitations; there is limited available resources and time-sensitivity of the COVID-19 pandemic, the strategy of snowball sampling was accepted which was not based on a random sample selection so the study could not reflect the real exact pattern of general population, besides biased results as the number of participants do not reflect the society.

This study was limited to availability of internet and social media activity usage. Subjective evaluation and self-reported levels, as no availability of face to face interaction by physical health professionals due to distancing circumstances and pandemic emergency state. Similarly, respondents might have provided socially desirable responses in terms of the satisfaction with the health information received and precautionary measures.

Another limitation is the evaluating scale has to be modified and shortened to encourage participation and avoid fidgets and quit the questioner so, it became less informative. Lastly, no supportive data about before lockdown dietary patterns was available to help in more comparative analysis.

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Correlation between Local Eid-al-Fitr Homecoming (Mudik) with Coronavirus Disease-19 during Ramadhan Season Amidst Large-scale Social Distancing in Indonesia

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Abstract

BACKGROUND: In anticipation of coronavirus disease (COVID)-19's transmission peak, *Eid-al-Fitr* homecoming (*mudik*) has officially been banned by the Indonesian government interlocal but not local in welcoming this religious Muslim celebration. This local Mudik is held by traveling among regional provinces and is still allowed by each local government, including Java, which has the highest transmission of COVID-19 in Indonesia.

AIM: This study aims to present the difference between COVID-19 status before and during local Mudik on Java during *Ramadhan* with the implementation of large-sale social distancing applied in Jakarta, Indonesia.

METHODS: This research was employed by secondary data analysis that was obtained from surveillance data from related authorities, including the Ministry of Health and all local governments of Java, which consisted of four provinces and Jakarta. Incidence and suspect statuses of COVID-19, which were examined in the study, were presented in daily rates with before and during local Mudik in four provinces: Jawa Barat, Yogyakarta, Banten, and Jawa Tengah.

RESULTS: The number of positive confirmed patients differed significantly with before and during local Mudik ($p < 0.05$; mean difference = −/negative values).

CONCLUSION: This study's findings showed that the local Mudik increased the number of COVID-19 cases in four provinces in Java, which these provinces were designated as *Mudik* destinations by travelers coming from Jakarta during the end of Ramadhan season.

Introduction

Coronavirus disease (COVID)-19 is a well-known infectious disease that is borne rapidly across the globe [1], [2]. When COVID-19 cases were first reported China was celebrating the Chinese New Year, an event that potentially drove the disease around the world [3], [4]. The many people travelling home from around the world enabled mass gatherings of big families, which transmitted the virus from where they lived [5]. This also happened in the hajj [6] and the *Eid-al-Fitr* celebration after the month of *Ramadhan* for Muslims in Indonesia.

The *Eid-al-Fitr* homecoming (*mudik*) is a routine and temporary migration in Indonesia, a country known for having the largest Muslim population in the world [7]. This migration is massive and done by long and short-distance travelers in celebrating the Eid-al-Fitr with family [8], which mass gathering is also potentially happening at this circumstance [9]. Mudik season usually lasts from the 1st day of *Ramadhan* until day one before (D-1) the month of *Syawal,* which has the *Eid-al-Fitr* celebration on the Islamic calendar of *Hijr*.

There are four provinces that are usually designated as Mudik destinations in Indonesia, all of which are located on Java [10]. Jawa Barat, Special Region of Yogyakarta (DIY), Banten, and Jawa Tengah experienced more than 50% of all *Mudik* travelers, leaving from the capital city of these provinces – including Bandung (Jawa Barat), Yogyakarta City (DIY), Tangerang (Banten), and Semarang (Jawa Tengah) [11] – to the center of COVID-19 pandemic in Java. In fact, these capitals contributed the most Mudik travelers to the area known as the capital and the center of business in each province, as well as Indonesia. These capitals of the provinces were also designated as *Mudik* destinations by travelers coming from other Indonesian regions, as well as from travelers and repatriations from abroad [11].

Since this Indonesian religious custom is a mass gathering that risks the spread of COVID-19, the Indonesia government banned all *Ramadhan* celebration activities using large-sale social distancing (LSSD) measures in this region. Although it was banned nationally, local Mudik was still allowed [12]. Since local Mudik potentially blew up COVID-19 transmission, evidence of it related to COVID-19 incidence rate is essential to know, particularly during this hardest time of the COVID-19 pandemic.

Methods

Study area

Four provinces have become local Mudik destinations in Java, Indonesia: Jawa Barat, Yogyakarta, Banten, and Jawa Tengah. These regions, including all Indonesian territories, face *Mudik* season, which started on 1st *Ramadhan* 1442 in the Islamic calendar of *Hijriah* – or April 24, 2020. This temporary travelling lasted until the end of *Ramadhan* or day one before (D-1) Eid-al-Fitr, which on this year falls on May 24, 2020.

Instead of applying "lockdown," a policy that consists of the full closure of all activities and entry-exit in a territory to cut down the transmission of COVID-19 [13], [14], the Indonesian government is applying LSSD. LSDD defined as massive restrictions in response to the COVID-19 pandemic that is followed by public place closures, public transportation restrictions, and a travel ban on leaving or entering a region. Other restrictions also include the disallowance of online-ordered motorcycle taxis (*ojek*) from carrying passengers (they are only allowed to carry food and goods), restricted dine-in at food cafes/restaurants (only takeaway is allowed), and the closure of all shops and workplaces except for those supplying basic needs. Places being shut down also include schools, worship places like mosques, and entertainment sites. LSSD measures consist of public transportation operating at 50% capacity [12]. This policy is still being carried out in several regions, particularly those with a high index of transmission, including Jakarta and most territories on Java.

Data collection

A COVID-19 dataset that ran from 6 March to May 16, 2020 was derived from each provincial authority, namely, Jawa Barat, Yogyakarta, Banten, and Jawa Tengah. In this study, local *Mudik* was measured in the month of *Ramadhan* based on the Islamic calendar, ranging from 24 April to May 2, 2020. The daily incidence and suspected cases of COVID-19 came from the local government public data for COVID-19. These data were collected according to LSSD, which started on April 10, 2020. This means that before LSSD implementation ranged from March 2 to April 9, 2020, while on-going LSSD was implemented starting on April 10, 2020, of the dataset.

Data analysis

An independent sample t-test was performed to analyze the mean difference according to normality data distribution (p value of Kolmogorov–Smirnov test > 0.05). The test was performed to present the mean difference between continue/numeric and discrete/categorical variables with two-tailed 95% confidence interval or 5% alpha and 80% power of tests. The difference between the before and during local *Mudik* season in *Ramadhan* season, while LSSD was implemented was assumed when there was a mean difference between these groups in determining the number of COVID-19 positive cases and suspected cases.

Results

According to Figure 1, both incidence and suspected cases of COVID-19 increased from before and during the local Mudik in Java during *Ramadhan*, while LSSD was applied in Jakarta. This shows that both incidence and suspected cases of COVID-19 increased daily since LSSD was first implemented in Jakarta.

Table 1 shows that suspected cases of COVID-19 did significant from before and during local Mudik in Yogyakarta Province. Meanwhile, incidence cases of COVID-19 did significant from before and during local Mudik in all provinces in Java, Indonesia.

Table 1: Independent-t-test's mean difference between before and during local Mudik in Java, Indonesia

COVID-19 status	Independent-t-test's mean difference
Jawa Barat Province	
Incidence	−21.041*
Suspect	−23.940
Yogyakarta Province	
Incidence	−2.852**
Suspect	−511.712**
Banten Province	
Incidence	−4.622**
Suspect	6.538
Jawa Tengah Province	
Incidence	−14.915**
Jawa Barat Province	
Incidence	−21.041*
Suspect	−23.940
Yogyakarta Province	
Incidence	−2.852**
Suspect	−511.712**
Banten Province	
Incidence	−4.622**
Suspect	6.538

*Difference is significant at the 0.05 level (2-tailed); **Difference is significant at the 0.01 level (2-tailed). COVID: Coronavirus disease.

Discussion

Being the region with the biggest Muslim population in the world, Indonesia has the potential to massively spread COVID-19 during the Mudik season [15]. In this period of time, Java usually has

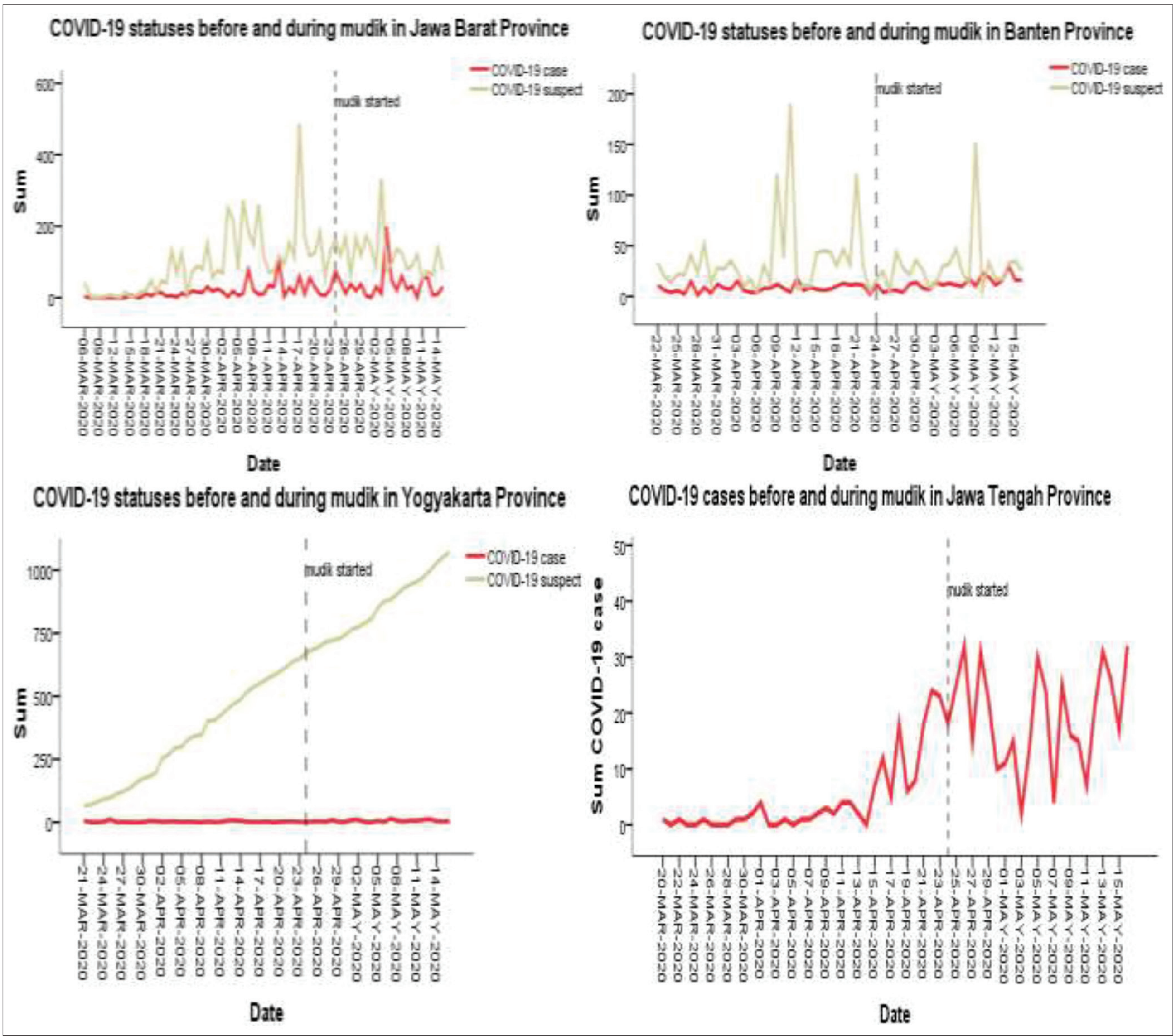

Figure 1: Coronavirus disease-19 statuses before and during local Mudik in four provinces in Java

a high number of local Mudik travelers who could potentially increase the number of COVID-19 incidence this season [11]. In fact, most of Java's local Mudik travelers come from pandemic centers, including each of the province capitals, as these are the entry point areas for those travelling from abroad [16].

In this study, we found that the local *Mudik* season was related to more cases of COVID-19 among this population (negative value of mean difference). This result is in line with previous evidence that traditional celebration is associated with the spread of COVID-19, which increases COVID-19 incidence rates [3], [4], [17]. At the same time, in other related circumstances in the Middle East, Iraq, has reported higher COVID-19 incidence rate than Saudi Arabia and Kuwait, but lower than Iran, Turkey, and Jordan. This scenario can help us improve the pandemic incidence rate when we welcome the *Eid-al-Fitr* [18].

Sitting in the western part of Indonesia, Java has the most complete, hybrid, and multiple modes of transportation than any other part of Indonesia [19], [20]. Zones included in this area contain three provinces that are namely Jawa Barat, Banten, and Jawa Timur. People that originate from these buffer regions are able to travel around the regions, particularly leaving and entering the capital city of these provinces [21], [22].

Since they are easily connected to these zones, people who originated from around Java traveled home when Mudik started to apply on April 27, 2020. This Muslim tradition is a time to seek forgiveness from relatives, especially from core families, and then welcoming the victory day as *Eid-al-Fitr* day [23]. Local Mudik not only attracted travelers for the *Eid-al-Fitr* celebration, but they also enjoyed a vacation with their visit to their hometown [24].

Despite the significant finding of how local Mudik during LSSD in Jakarta during is related with COVID-19 incidence rates, this study has limitations. The incident rate of COVID-19 could be affected by the effectiveness of travel bans, which varied by the district and by how provincial local governments applied the LSSD. In addition, the travel ban has not optimally applied before implementation of LSSD, as it allowed travelers to go back to their hometown permanently due to the joblessness created by the COVID-19 pandemic.

Conclusion

This study shows that *Mudik* was significantly associated with COVID-19 incidence among the population in Java, Indonesia, during *Ramadhan* with LSSD implementation in Jakarta. This preliminary study needs to be further developed, as *Mudik* could potentially increase COVID-19 incidence not only in Indonesian Muslims but also in other countries, religions, and cultures, especially in homecoming travel traditions during this pandemic.

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Sex Differences in Patients with COVID-19: A Retrospective Cohort Study and Meta-analysis

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Abstract

BACKGROUND: Accumulated evidence revealed that male was much more likely to higher severity and fatality by SARS-CoV-2 infection than female patients, but few studies and meta-analyses have evaluated the sex differences of the infection and progression of COVID-19 patients.

AIM: We aimed to compare the sex differences of the epidemiological and clinical characteristics in COVID-19 patients; and to perform a meta-analysis evaluating the severe rate, fatality rate, and the sex differences of the infection and disease progression in COVID-19 patients.

METHODS: We analyzed clinical data of patients in Changchun Infectious Hospital and Center, Changchun, Northeast China; and searched PubMed, Embase, Web of Science, and Cochrane Library without any language restrictions for published articles that reported the data of sex-disaggregated, number of severe, and death patients on the confirmed diagnosis of adult COVID-19 patients.

RESULTS: The pooled severe rate and fatality rate of COVID-19 were 22.7% and 10.7%. Male incidence in the retrospective study was 58.1%, and the pooled incidence in male was 54.7%.

CONCLUSION: The pooled severe rate in male and female of COVID-19 was 28.2% and 18.8%, the risky of severe and death was about 1.6folds higher in male compared with female, especially for older patients (> 50 y).

Introduction

On December 2019, the outbreak of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China [1]. The clinical presentations of COVID-19 greatly resembled with viral pneumonia, and patients could be infected both in hospitals and in family or public settings [2]. Previous studies have demonstrated that SARS-CoV-2 has a high homology with severe acute respiratory syndrome coronavirus (SASR-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) that they might have similar clinical characteristics [3], [4]. World Health Organization (WHO) has declared COVID-19 as a public health emergency of international concern and a pandemic successively. As of April 4, 2020, the laboratory-confirmed cases had climbed above 1 million and deaths over 50,000 all around the world [5]. With the first confirmed case occurred on January 31, 2020 in the US, the number of patient surge rapidly in the US and exceeded all reported cases in China and Italy in a short term [6]. Although the detailed data of severity and mortality all over the world were limited, especially in western countries, there were a large variation of severe rate and case-fatality rate of COVID-19 among different population [2], [7], [8], [9], [10].

Timely identification of risk factors for the infection and severe or critical cases is of critical importance [11]. Previous studies found that older age, higher d-dimer concentrations, high sequential organ failure assessment (SOFA) score, and pre-existing underlying disease were the potential risk factors for the infections and poor progression and prognosis in COVID-19 patients [12], [13], [14], [15], [16]. Meantime, accumulated evidence revealed that male was much more likely to higher severity and fatality by SARS-CoV-2 infection than female patients [10], [11], [14], [15], [17], [18], [19], but few studies and meta-analyses have evaluated the sex differences of the infection and progression of COVID-19 patients. Therefore, we performed the first retrospective cohort study to compare the sex differences of the epidemiological and clinical characteristics on

COVID-19 patients in Changchun, Northeast China; and a comprehensive meta-analysis to evaluate the severe rate and the sex differences of the infection and disease progression in COVID-19 patients.

Materials and Method

Retrospective cohort study

Data were collected from Changchun Infectious Hospital and Center for Disease Prevention and Control in Jilin Province, Northeast China. All 43 patients were hospitalized from January 20, 2020, to February 14, 2020, and discharged from February 19, 2020, to March 9, 2020. The study was approved by the ethical committee of Jilin University School of Public Health (ethical code: 2020-03-011), and written informed consent was obtained from all cases.

Meta-analysis

We searched and identified all relevant articles through following electronic databases: PubMed, Embase, Web of Science, and Cochrane Library without any language restrictions to limit the language bias (up to April 2020). We also evaluated the reference lists of all identified references for additional relevant studies by manual retrieval. We combined the following search terms: COVID-19, 2019 novel coronavirus, SARS-CoV-2, 2019-nCoV, and novel coronavirus-infected pneumonia. After removing duplicate citations and screening the title and abstracts, we downloaded and assessed the full texts in accordance with the following criteria for eligibility. Two authors (ZJ Li and LQ Deng) independently evaluated the screened articles for eligibility and any disagreements were adjudicated by the third author (Q Yu). The meta-analysis was performed and reported on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

Any relevant studies that reported the data of sex-disaggregated, number of severe cases on the confirmed diagnosis of adult COVID-19 patients were included in the meta-analysis. The exclusion criteria were described as follows: (1) Data not provided or unavailable or duplication; (2) children or pregnant population; and (3) non-human studies, abstract, case reports, methodological report, review, or meta-analysis. Two authors (Li and Deng) independently performed data extraction and assessed the methodological quality of eligible studies, and any discrepancies were adjudicated by discussion with third author (Yu). The following information was extracted: Author, publication year, study design, date of collection, location, age, total patients, number of severe cases, and sex distribution of COVID-19 patients.

Assessment of risk bias

The quality of eligible studies was assessed using 11-item checklist criteria which recommended for cross-sectional study by Agency for Healthcare Research and Quality (AHRQ). Each item was answered by “Yes” “No” “Unclear,” only answered “Yes” that would score 1.

Statistical analysis

All analyses were processed on R 3.6.1 software, and $p \leq 0.05$ was considered to be statistically significant. Median with interquartile and the number of illness and its percentages were used to summarize continuous and categorical variables. The Chinese management guideline for COVID-19 (6.0) was used to separate patients into general and severe or critical cases. Mann–Whitney U test, Chi-square test, and Fisher’s exact test were used to compare the differences between general and severe or critical cases. All meta-analyses were performed by *meta* package and *metaprop module* of R 3.6.1. Heterogeneity among studies were evaluated by I^2 statistics and Q test, the random-effect model was used to compute the pooled results when $I^2 > 50\%$ and $p < 0.05$ of Q test; otherwise, the fixed-effect model was used. Subgroup analysis, sensitivity analysis, and meta-regression were performed to assess the sources of heterogeneity. Funnel plot asymmetry and *peters* test were used to evaluate the publication bias among studies.

Results

As of March 9, 2020, 43 patients with SAS-CoV-2 infections were discharged. Baseline of demographic characteristic, clinical features of COVID-19 patients were presented in Table 1. The median of age was 41.0 years and 25 (58.1%) patients were male. Most patients (88.4%) were classified as general pneumonia, 11.6% as critical or severe (Table 1). Age, severity of pneumonia, exposure history, and comorbidities were comparable between female and male ($p > 0.05$). As for occupation, half of female cases were retired or unemployed and most male (72.0%) were employee or professional technical ($p < 0.05$). The majority of female were family cluster cases ($p < 0.05$). Comorbidities were non-significant higher in female than that in male. History of hypertension and diabetes in male was higher than female, but COPD, CVD, bronchitis, and asthma in male were lower than female (Table 1). The initial symptoms

Table 1: Baseline of demographic characteristic, clinical features of COVID-19 patients

Characteristics	Total (n = 43)	Female (n = 18) (%)	Male (n = 25) (%)	p value
Age, median(IQR), y	41.0 (33.0–52.0)	41.0 (30.0–53.0)	42.0 (33.0–85.0)	0.730
Severity				1.000
General	38 (88.4)	16 (88.9)	22 (88.0)	
Critical or severe	5 (11.6)	2 (11.1)	3 (12.0)	
Occupation				0.012
Agricultural worker	2 (4.7)	2 (11.1)	0	
Employee	19 (44.2)	4 (22.2)	15 (60.0)	
Professional technical	6 (14.0)	3 (16.7)	3 (12.0)	
Retired	9 (20.9)	5 (27.8)	4 (16.0)	
Self-employed	3 (7.0)	0	3 (12.0)	
Unemployed	4 (9.3)	4 (22.2)	0	
Exposure history				0.680
Exposure to Wuhan	7 (16.3)	2 (11.1)	5 (20.0)	
Exposure to confirmed or suspected people	36 (83.7)	16 (88.9)	20 (80.0)	
Cluster patients	35 (81.4)	16 (88.9)	19 (76.0)	0.284
Single case	8 (18.6)	2 (11.1)	6 (24.0)	0.013
Family cluster	28 (65.1)	16 (88.9)	12 (48.0)	
Working cluster	7 (16.3)	0	7 (28.0)	
Comorbidities	22 (51.2)	10 (55.6)	12 (48.0)	0.760
Hypertension	7 (16.3)	2 (11.1)	5 (20.0)	0.680
Diabetes	5 (11.6)	1 (5.6)	4 (16.0)	0.380
Malignancy	3 (7.0)	2 (11.1)	1 (4.0)	0.562
Hypothyroidism	3 (7.0)	3 (16.7)	0	-
Chronic obstructive pulmonary disease	2 (4.7)	2 (11.1)	0	-
Coronary heart disease	2 (4.7)	1 (5.6)	1 (4.0)	-
Bronchitis	2 (4.7)	0	2 (8.0)	-
Neurodegenerative disease	2 (4.7)	2 (11.1)	0	-
Asthma	1 (2.3)	1 (5.6)	0	-
Symptoms				
Fever	33 (76.7)	14 (77.8)	19 (76.0)	0.892
Highest temperature, °C	38.0 (37.3–38.4)	37.9 (37.1–38.4)	38.0 (36.9–38.4)	0.961
Cough	35 (81.4)	16 (88.9)	19 (76.0)	0.284
Expectoration	31 (72.1)	12 (66.7)	9 (36.0)	0.047
Myalgia or fatigue	23 (53.5)	9 (50.0)	14 (56.0)	0.736
Chest tightness	20 (46.5)	9 (50.0)	11 (44.0)	0.763
Nasal congestion or sneezing	15 (34.9)	5 (27.8)	10 (40.0)	0.782
Diarrhea	8 (18.6)	1 (5.6)	7 (28.0)	0.111
Nausea or vomiting	8 (18.6)	3 (16.7)	5 (20.0)	0.782
Incubation period, median(IQR), d	8.0 (5.0-11.0)	9.0 (5.8–12.0)	7.0 (4.0–11.0)	0.459
Onset of illness to, median(IQR), d				
Hospital admission	6.0 (2.0–8.0)	5.0 (2.0–6.0)	6.0 (3.0–9.0)	0.143
Discharge	22.0 (18.0–24.0)	22.5 (16.0–24.0)	22.0 (18.0–28.0)	0.387
Duration of viral shedding, median(IQR), d	19.0 (14.0–22.0)	19.0 (12.0–21.2)	19.0 (15.0–25.2)	0.393
Hospitalization time, median(IQR), d	17.0 (11.0–20.0)	18.0 (10.8–20.0)	17.0 (11.0–21.0)	0.961
Laboratory results				
White blood cell count, ×109/L	5.3 (4.1–6.4)	4.0 (3.1–6.3)	5.8 (5.0–7.1)	0.005
Neutrophil count, ×109/L	3.7 (2.8–4.9)	2.9 (1.6–4.5)	4.0 (3.4–5.1)	0.008
Lymphocyte count, ×109/L	1.1 (0.8–1.6)	1.1 (0.8–1.5)	1.0 (0.8–1.7)	0.790
Monocyte count, ×109/L	0.3 (0.2–0.5)	0.26 (0.19–0.32)	0.30 (0.27–0.60)	0.031
Haemoglobin, g/L	144 (130–157)	133.0 (126.0–143.5)	151.5 (139.5–159.5)	0.002
C–reactive protein, mg/L	10.9 (2.5–33.4)	11.5 (2.4–24.0)	10.5 (3.2–63.6)	0.626
Platelet count, ×109/L	183 (161–223)	180.0 (163.0–211.5)	201.0 (159.2–240.0)	0.424
Prothrombin time, s	12.0 (11.6–12.9)	11.8 (11.3–12.7)	12.6 (11.7–13.3)	0.104
Activated partial thromboplastin time, s	32.6 (30.5–35.4)	32.2 (26.0–33.8)	34.7 (30.6–36.4)	0.158
Fibrinogen, g/dl	2.2 (2.0–3.5)	2.2 (1.9–3.6)	2.2 (2.0–3.6)	0.601
Thrombin time, s	15.8 (15.2–16.7)	16.2 (15.3–20.9)	15.7 (15.0–16.4)	0.327
Alanine aminotransferase, U/L	25.0 (19.0–45.0)	28.0 (19.7–47.5)	24.0 (19.0–44.0)	0.931
Aspartate aminotransferase, U/L	26.0 (22.0–32.0)	26.5 (24.0–35.5)	23.0 (21.0–31.5)	0.153
Albumin, g/L	44.2 (42.0–46.1)	44.3 (42.4–44.9)	44.2 (41.4–46.4)	0.905
Total bilirubin, mmol/L	7.9 (6.7–10.4)	6.9 (6.0–7.8)	8.8 (7.6–11.3)	0.006
Cholinesterase, U/L	7575 (6084–9029)	6898.5 (5600.8–8958.8)	7899.0 (6711.0–9071.5)	0.207
Creatine, μmol/L	69.2 (62.1–77.3)	61.0 (55.8–67.6)	76.3 (69.2–80.4)	<0.001
Creatine kinase, U/L	79 (12–24)	71.0 (54.0–96.5)	109.0 (65.5–157.0)	0.047
Creatine kinase–MB, U/L	16 (12–24)	17.5 (11.8–24.2)	15.0 (12.0–23.0)	0.521
Lactate dehydrogenase, U/L	210 (185–269)	220.0 (184.0–263.0)	210 (182.5–285.0)	0.730
Myoglobin, ng/mL	69.7 (20.3–118.6)	24.4 (19.2–72.4)	26.8 (21.4–153.4)	0.151
Glucose, mmol/L	6.5 (5.7–8.0)	6.4 (5.6–7.6)	6.6 (5.9–8.5)	0.233
Cardiac troponin I, pg/mL	1.7 (1.2–7.4)	1.6 (1.2–3.7)	1.8 (1.2–8.4)	0.415
CT imaging features				
Bilateral distribution of patchy shadows or ground glass opacity	31 (72.1%)	13 (72.2%)	18 (72.0%)	0.987

were mainly fever, couth, expectoration, myalgia or fatigue, and chest tightness, but the expectoration in female was higher than in male ($p < 0.05$). Median incubation period in female (9 days) was non-significant longer than that in male (7 days).

The serum WBC, neutrophil count, monocyte count, hemoglobin, total bilirubin, creatine, and creatine kinase were higher in male than that in female ($p < 0.05$) (Table 1). Leukopenia only occurred in 6 cases (33.3%) of female. C-reactive protein was elevated in 10 cases (55.6%) in female and 15 (60.0%) in male (Table 1). Lymphopenia occurred in 7 cases (38.9%) of female and 10 (40.0%) of male, aspartate aminotransferase was increased in each 3 cases of female (16.7%) and of male (12.0%), and lactate dehydrogenase was increased in 12 cases (66.7%) of female and 16 (64.0%) of male (Table 1). The typical CT findings of COVID-19 patients were bilateral distribution of patchy shadows or ground glass opacity, and no significant differences between female and male ($p > 0.05$). Complication of leukopenia in female was higher than in male ($p < 0.05$), but there were no significant differences on treatment between female and male ($p > 0.05$) (Supplementary data: Table S1).

Meta-analysis

The detailed inclusion and exclusion steps of the potentially relevant articles are presented in Figure 1. Finally, a total of 76 studies involving 90,475 patients were included in analyzing the proportion of male in patients with COVID-19, including our current retrospective study. The characteristics and quality assessment results of eligible studies are summarized in Supplementary data: Table S2. The pooled male proportion of COVID-19 patients was 54.7% (95% CI: 0.522-0.572, I^2 = 96.9%), which was slightly higher than female (Supplementary data: Figure S1). Subgroup analyses suggested that the pooled morbidity of older male patients (>50-year) was 58.0% (95% CI: 0.532-0.628, I^2 = 97.8%) and 51.5% (95% CI: 0.489-0.541, I^2 = 89.9%) in ≤50-year patients.

Thirty-two articles were in analyzing the severe rate of patients, 21 in each male and female. The pooled severe rate and case-fatality rate of COVID-19 were 22.7% (95% CI: 0.195–0.259) and 10.7% (95% CI: 0.092-0.122, I^2 = 98.8%) (Figures 2 and 3).

The pooled severe rate in male and female of COVID-19 was 28.2% (95%CI: 0.23-0.333, I^2 = 86.7%) and 18.8% (95%CI: 0.149-0.226, I^2 = 78.6%), correspondingly (Figure 4). Subgroup analyses showed that the severe rate and case-fatality rate of older patients (> 50 y) (30.4%, 95%CI: 0.248-0.36, I^2 = 94.0%; 20.5%) were significant higher than younger patients (16.7, 95%CI: 0.134–0.200, I^2 = 93.9%; 1.3%).

Twenty-one studies involving 4213 patients and 12 studies involving 53,695 cases were included analyzing the sex differences of the disease severity and mortality of COVID-19 patients (Table 2) [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49]. The pooled risk of disease severity and mortality in male was statistically significant higher than in female (OR: 1.60, 95% CI: 1.37–1.87, I^2 = 25%; OR: 1.57, 95%CI: 1.42–1.74, I^2 = 34%), respectively (Table 3, Figure 5).

Subgroup analyses suggested that the severe risky of older male patients had 1.94 folds higher compared with female. However, the mortality risky of younger male patients had 1.7 folds higher compared with female. Sensitivity analyses by omitting one individual study every time showed that there was no study significantly affected the pooled results (Figure S2-S7). In the meta-regression, there were significant correlation between age and log odds of sex and disease severity and mortality of COVID-19 patients (disease severity-correlation coefficient: 0.013, p = 0.001 and mortality-correlation coefficient: −0.02, p = 0.029) (Figure 6). In addition, there was no publication bias in the study, all that indicated that the results were credible in the meta-analyses (Figure S8-S13).

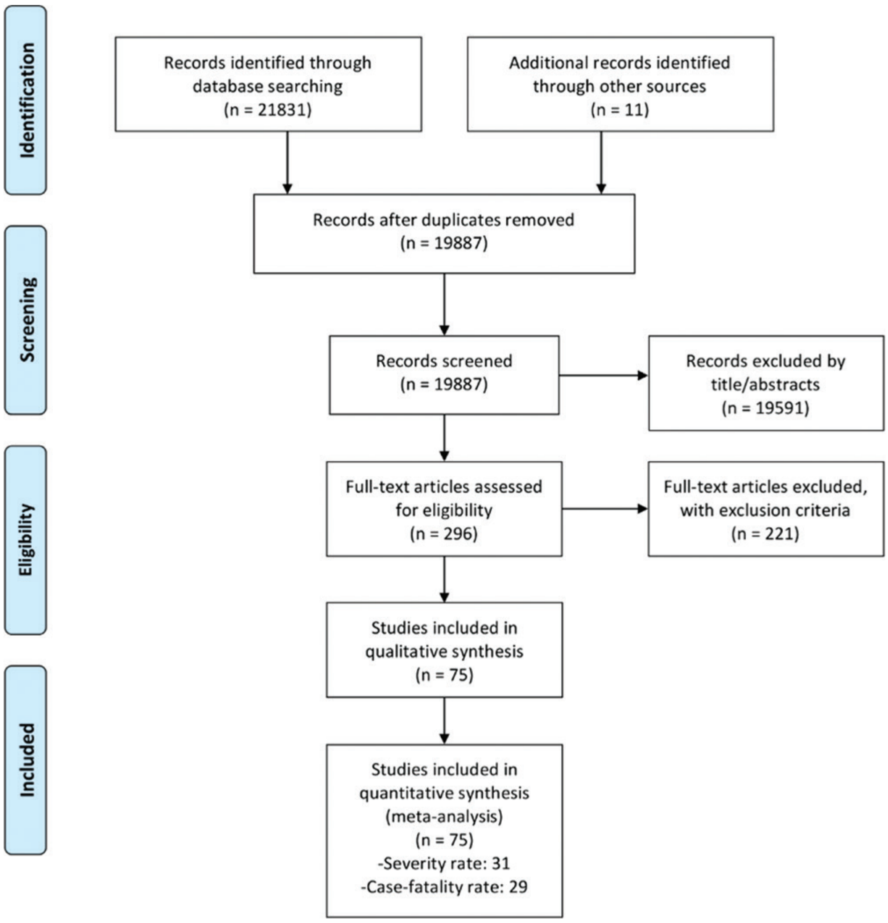


Figure 1: Flowchart of the study selection procedure

Study	Events	Total	Proportion	95%−CI	Weight (fixed)	Weight (random)
Cai QX et al	58	298	0.19	[0.15; 0.24]	0.4%	3.6%
Cao JL et al	18	102	0.18	[0.11; 0.26]	0.2%	3.2%
Chen C et al	24	150	0.16	[0.11; 0.23]	0.2%	3.4%
Chen G et al	11	21	0.52	[0.30; 0.74]	0.0%	1.4%
Chen J et al	22	249	0.09	[0.06; 0.13]	0.7%	3.7%
Chen L et al	14	29	0.48	[0.29; 0.67]	0.0%	1.7%
China CDC	8255	44672	0.18	[0.18; 0.19]	65.9%	3.9%
Dong XC et al	62	135	0.46	[0.37; 0.55]	0.1%	3.0%
Goyal P et al	130	393	0.33	[0.28; 0.38]	0.4%	3.6%
Guan W et al	173	1099	0.16	[0.14; 0.18]	1.8%	3.8%
Huang C et al	13	41	0.32	[0.18; 0.48]	0.0%	2.2%
Jin X et al	64	651	0.10	[0.08; 0.12]	1.6%	3.8%
Lei SQ et al	15	34	0.44	[0.27; 0.62]	0.0%	1.9%
Li KH et al	25	83	0.30	[0.21; 0.41]	0.1%	2.8%
Liu W et al	8	78	0.10	[0.05; 0.19]	0.2%	3.3%
Livngston E et al	6731	22512	0.30	[0.29; 0.31]	23.9%	3.9%
Peng YD et al	16	112	0.14	[0.08; 0.22]	0.2%	3.3%
Qian GQ et al	9	91	0.10	[0.05; 0.18]	0.2%	3.4%
Shi HS et al	3	81	0.04	[0.01; 0.10]	0.5%	3.6%
Shi Y et al	49	487	0.10	[0.08; 0.13]	1.2%	3.8%
Tian S et al	46	262	0.18	[0.13; 0.23]	0.4%	3.6%
Wan SX et al	40	135	0.30	[0.22; 0.38]	0.1%	3.2%
Wang DW et al	36	138	0.26	[0.19; 0.34]	0.2%	3.2%
Wu CM et al	84	201	0.42	[0.35; 0.49]	0.2%	3.3%
Wu J et al	3	80	0.04	[0.01; 0.11]	0.5%	3.6%
Xie HS et al	28	79	0.35	[0.25; 0.47]	0.1%	2.7%
Xu YH et al	13	50	0.26	[0.15; 0.40]	0.1%	2.5%
Yao N et al	22	40	0.55	[0.38; 0.71]	0.0%	2.0%
Zhang GQ et al	55	221	0.25	[0.19; 0.31]	0.3%	3.4%
Zhang JJ et al	58	140	0.41	[0.33; 0.50]	0.1%	3.1%
Zhao W et al	14	101	0.14	[0.08; 0.22]	0.2%	3.3%
Current study	5	43	0.12	[0.04; 0.25]	0.1%	2.9%
Fixed effect model		**72808**	**0.21**	**[0.21; 0.21]**	**100.0%**	**--**
Random effects model			**0.23**	**[0.20; 0.26]**	**--**	**100.0%**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0070$, $p < 0.01$

0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 2: The pooled severity rate of COVID-19 patients

Study	Events	Total	Proportion	95%−CI	Weight (fixed)	Weight (random)
Arentz M et al	11	21	0.52	[0.30; 0.74]	0.0%	0.4%
Cai QX et al	3	298	0.01	[0.00; 0.03]	0.9%	5.1%
Cao JL et al	17	102	0.17	[0.10; 0.25]	0.0%	2.4%
Chen C et al	11	150	0.07	[0.04; 0.13]	0.1%	3.7%
Chen NS et al	11	99	0.11	[0.06; 0.19]	0.0%	2.8%
Chen T et al	113	274	0.41	[0.35; 0.47]	0.0%	2.9%
Cheng JL et al	11	1079	0.01	[0.01; 0.02]	3.1%	5.2%
China CDC	1023	44672	0.02	[0.02; 0.02]	57.9%	5.3%
Dong XC et al	3	135	0.02	[0.00; 0.06]	0.2%	4.6%
Guan W et al	15	1099	0.01	[0.01; 0.02]	2.4%	5.2%
Guo T et al	43	187	0.23	[0.17; 0.30]	0.0%	2.8%
Huang C et al	6	41	0.15	[0.06; 0.29]	0.0%	1.4%
KIDS	22	4212	0.01	[0.00; 0.01]	23.5%	5.3%
Lei SQ et al	7	34	0.21	[0.09; 0.38]	0.0%	1.0%
Liu K et al	16	137	0.12	[0.07; 0.18]	0.0%	3.1%
Livngston E et al	1625	22512	0.07	[0.07; 0.08]	9.7%	5.3%
Peng YD et al	17	112	0.15	[0.09; 0.23]	0.0%	2.6%
Ruan QR et al	68	150	0.45	[0.37; 0.54]	0.0%	2.1%
Tang N et al	21	183	0.11	[0.07; 0.17]	0.1%	3.5%
Tian S et al	3	262	0.01	[0.00; 0.03]	0.7%	5.1%
Wan SX et al	1	135	0.01	[0.00; 0.04]	0.5%	5.0%
Wang DW et al	6	138	0.04	[0.02; 0.09]	0.1%	4.1%
Wu CM et al	44	201	0.22	[0.16; 0.28]	0.0%	3.0%
Yang XB et al	32	52	0.62	[0.47; 0.75]	0.0%	1.0%
Yuan ML et al	10	27	0.37	[0.19; 0.58]	0.0%	0.6%
Zhang GQ et al	12	221	0.05	[0.03; 0.09]	0.1%	4.4%
Zhou F et al	54	191	0.28	[0.22; 0.35]	0.0%	2.7%
Goyal P et al	40	393	0.10	[0.07; 0.14]	0.1%	4.4%
Richardson S et al	553	2634	0.21	[0.19; 0.23]	0.5%	5.0%
Fixed effect model		**79751**	**0.02**	**[0.02; 0.03]**	**100.0%**	**--**
Random effects model			**0.11**	**[0.09; 0.12]**	**--**	**100.0%**

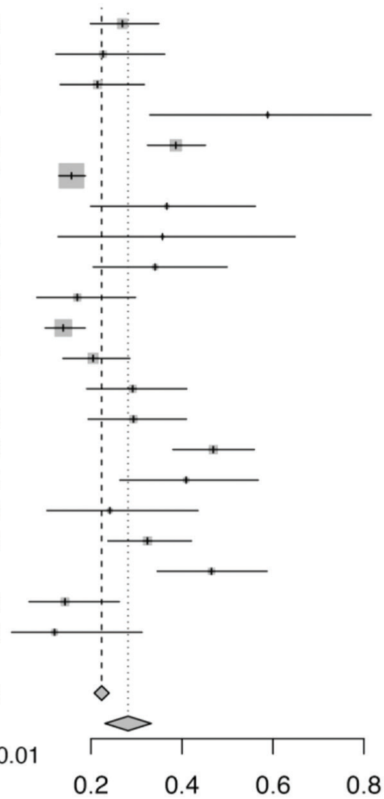
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.0011$, $p = 0$

0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 3: The pooled case-fatality rate of COVID-19 patients

Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Cai QX et al	39	145	0.27	[0.20; 0.35]	5.2%	5.5%
Cao JL et al	12	53	0.23	[0.12; 0.36]	2.1%	4.8%
Chen C et al	18	84	0.21	[0.13; 0.32]	3.5%	5.3%
Chen G et al	10	17	0.59	[0.33; 0.82]	0.5%	2.7%
Goyal P et al	92	238	0.39	[0.32; 0.45]	7.1%	5.7%
Guan W et al	100	637	0.16	[0.13; 0.19]	34.0%	6.1%
Huang C et al	11	30	0.37	[0.20; 0.56]	0.9%	3.6%
Lei SQ et al	5	14	0.36	[0.13; 0.65]	0.4%	2.5%
Li KH et al	15	44	0.34	[0.20; 0.50]	1.4%	4.2%
Peng YD et al	9	53	0.17	[0.08; 0.30]	2.7%	5.0%
Shi Y et al	36	259	0.14	[0.10; 0.19]	15.3%	6.0%
Tian S et al	26	127	0.20	[0.14; 0.29]	5.5%	5.6%
Wan SX et al	21	72	0.29	[0.19; 0.41]	2.5%	4.9%
Wang DW et al	22	75	0.29	[0.19; 0.41]	2.6%	5.0%
Wu CM et al	60	128	0.47	[0.38; 0.56]	3.6%	5.3%
Xie HS et al	18	44	0.41	[0.26; 0.57]	1.3%	4.1%
Xu YH et al	7	29	0.24	[0.10; 0.44]	1.1%	3.9%
Zhang GQ et al	35	108	0.32	[0.24; 0.42]	3.5%	5.3%
Zhang JJ et al	33	71	0.46	[0.35; 0.59]	2.0%	4.7%
Zhao W et al	8	56	0.14	[0.06; 0.26]	3.2%	5.2%
Current study	3	25	0.12	[0.03; 0.31]	1.7%	4.5%
Fixed effect model		**2309**	**0.22**	**[0.21; 0.24]**	**100.0%**	**--**
Random effects model			**0.28**	**[0.23; 0.33]**	**--**	**100.0%**

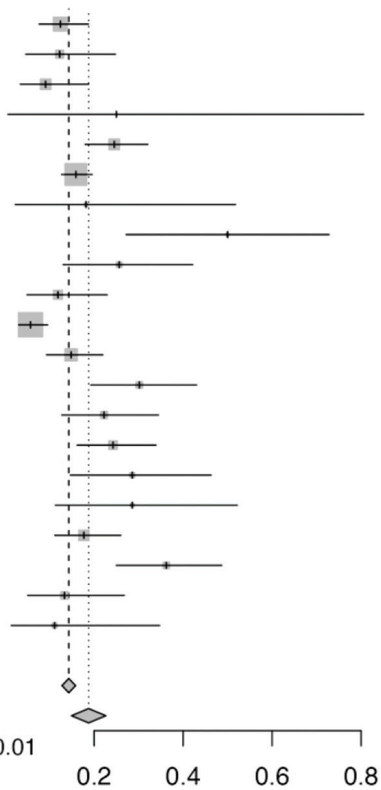
Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.0109$, $p < 0.01$



a

Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Cai QX et al	19	153	0.12	[0.08; 0.19]	8.6%	6.6%
Cao JL et al	6	49	0.12	[0.05; 0.25]	2.8%	5.3%
Chen C et al	6	66	0.09	[0.03; 0.19]	4.9%	6.1%
Chen G et al	1	4	0.25	[0.01; 0.81]	0.1%	0.8%
Goyal P et al	38	155	0.25	[0.18; 0.32]	5.1%	6.1%
Guan W et al	73	459	0.16	[0.13; 0.20]	21.0%	7.1%
Huang C et al	2	11	0.18	[0.02; 0.52]	0.5%	2.1%
Lei SQ et al	10	20	0.50	[0.27; 0.73]	0.5%	2.2%
Li KH et al	10	39	0.26	[0.13; 0.42]	1.3%	3.9%
Peng YD et al	7	59	0.12	[0.05; 0.23]	3.5%	5.6%
Shi Y et al	13	228	0.06	[0.03; 0.10]	26.0%	7.2%
Tian S et al	20	135	0.15	[0.09; 0.22]	6.6%	6.4%
Wan SX et al	19	63	0.30	[0.19; 0.43]	1.8%	4.6%
Wang DW et al	14	63	0.22	[0.13; 0.34]	2.2%	4.9%
Wu CM et al	24	99	0.24	[0.16; 0.34]	3.3%	5.6%
Xie HS et al	10	35	0.29	[0.15; 0.46]	1.1%	3.6%
Xu YH et al	6	21	0.29	[0.11; 0.52]	0.6%	2.6%
Zhang GQ et al	20	113	0.18	[0.11; 0.26]	4.8%	6.0%
Zhang JJ et al	25	69	0.36	[0.25; 0.49]	1.8%	4.6%
Zhao W et al	6	45	0.13	[0.05; 0.27]	2.4%	5.0%
Current study	2	18	0.11	[0.01; 0.35]	1.1%	3.7%
Fixed effect model		**1904**	**0.14**	**[0.13; 0.16]**	**100.0%**	**--**
Random effects model			**0.19**	**[0.15; 0.23]**	**--**	**100.0%**

Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.0052$, $p < 0.01$



b

Figure 4: The pooled severity rate in Male (a) and Female (b) of COVID-19 patients

Table 2: Characteristic of severe and deceased patients with COVID-19

Author	Date	Location	Age	Total patients (M/F)	Severe (M/F)	Mortality (M/F)	Quality
Arentz *et al.* [21]	Feb 20–Mar 5,2020	USA	70 (IR 43–92)	21 (11/10)	–	11	8
Cai *et al.* [14]	Jan 11–Feb 6,2020	Shenzhen, China	47 (IQR 33–61)	298 (145/153)	58 (39/19)	3	8
Cao *et al.* [22]	Jan 3–Feb 1,2020	Wuhan, China	54 (37–67)	102 (53/49)	18 (12/6)	17	6
Chen *et al.* [23]	Jan–Feb,2020	Wuhan, China	59 (SD 16)	150 (84/66)	24 (18/6)	11	9
Chen *et al.* [24]	Dec,2019–Jan 27,2020	Wuhan, China	56 (IQR 50–65)	21 (17/4)	11 (10/1)	–	8
Chen *et al.* [15]	Jan 20–Feb 6,2020	Shanghai, China	51 (IQR 36–64)	249 (126/123)	22	–	9
Chen *et al.* [25]	Jan 14–Jan 29,2020	Wuhan, China	56 (IR 26–79)	29 (21/8)	14	–	8
Chen *et al.* [16]	Jan 1–Jan 20,2020	Wuhan, China	55.5 (SD 13.1)	99 (67/32)	–	11	9
Chen *et al.* [26]	Jan 13–Feb 12,2020	Wuhan, China	62 (IQR 44–77)	274 (171/103)	–	113 (83/30)	9
Cheng *et al.* [7]	Feb 19,2020	Henan, China	46 (SD 24)	1079 (573/505)	–	11 (7/4)	7
China CDC[8]	Feb 11,2020	China	50	44672 (22981/21691)	8255	1023 (653/370)	8
Dong *et al.*. [27]	Jan 7–Feb 24,2020	Tianjin, China	48.6 (SD 16.8)	135 (72/63)	62	3	8
Goyal *et al.*. [28]	Mar 3–Mar 27,2020	USA	62.2 (IQR 48.6–73.7)	393 (238/155)	130 (92/38)	40	7
Guan *et al.*. [2]	Dec 11,2019–Jan 31,2020	China	47 (35–58)	1099 (637/459)	173 (100/73)	15	9
Guo *et al.*. [29]	Jan 23–Feb 23,2020	Wuhan, China	58.5 (SD 14.66)	187 (91/96)		43	9
Huang *et al.*. [19]	Dec 16,2019–Jan 2,2020	Wuhan, China	49 (41–58)	41 (30/11)	13 (11/2)	6	9
Jin *et al.*. [30]	Jan 17–Feb 8,2020	Zhejiang, China	45	651 (331/320)	64	–	8
KSID [10]	Jan 19–Mar 2,2020	Korea	43	4212 (1591/2621)	–	22 (13/9)	8
Lei *et al.*. [31]	Jan 1–Feb 5,2020	Wuhan, China	55 (IQR 43–63)	34 (14/20)	15 (5/10)	7	9
Li *et al.*. [32]	Jan–Feb,2020	Chongqing, China	45.5 (SD 12.3)	83 (44/39)	25 (15/10)	–	7
Liu *et al.*. [33]	Dec 30,2019–Jan 24,2020	Hubei, China	55 (SD 16)	137 (61/76)	–	16	8
Liu *et al.*. [34]	Dec 30,2019–Jan 15,2020	Wuhan, China	38 (IQR 33–57)	78 (39/39)	8	–	9
Livingston *et al.*. [9]	Mar 15,2020	Italy	64	22512 (13462/9050)	6731	1625	3
Peng *et al.*. [35]	Jan 20–Feb 15,2020	Wuhan, China	62 (IQR 55–67)	112 (53/59)	16 (9/7)	17	8
Qian *et al.*. [36]	Jan 20–Feb 11.2020	Zhejiang, China	50 (IQR 36.5–57)	91 (37/54)	9	–	7
Ruan *et al.*. [37]	–	Wuhan, China	57.7	150 (102/48)	–	68 (49/19)	6
Richardson *et al.*[6]	Mar 1–Apr 4,2020	USA	63 (IQR 52–75)	2634 (1499/1135)	–	553 (337/216)	9
Shi *et al.*. [3]	50(IQR 36.5–57)	Wuhan, China	49.5 (SD 11)	81 (42/39)	3	–	9
Shi *et al.*. [17]	Feb 17,2020	Zhejiang, China	46 (SD 19)	487 (259/228)	49 (36/13)	–	6
Tang *et al.*. [38]	Jan 1–Feb 3,2020	Wuhan, China	54.1 (SD 16.2)	183 (98/85)	–	21 (16/5)	7
Tian *et al.*. [39]	Jan 20–Feb 10.2020	Beijing, China	47.5 (1–94)	262 (127/135)	46 (26/20)	3	7
Wan *et al.* [40]	Jan 23–Feb 8,2020	Chongqing, China	47 (IQR 36–55)	135 (72/63)	40 (21/19)	1	8
Wang *et al.*. [41]	Jan 1–Jan 28.2020	Wuhan, China	56 (42–68)	138 (75/63)	36 (22/14)	6	9
Wu *et al.*. [13]	Dec 25,2019–Jan 26,2020	Wuhan, China	51 (IQR 43–60)	201 (128/99)	84 (60/24)	44	9
Wu *et al.*. [42]	Jan 22–Feb 14,2020	Jiangsu, China	46.1 (SD 15.42)	80 (39/41)	3	–	9
Xie *et al.*. [43]	Feb 2–Feb 23,2020	Wuhan, China	60 (IQR48–66)	79 (44/35)	28 (18/10)	–	8
Xu *et al.*. [44]	Jan–Feb,2020	Beijing, China	43.9 (SD 16.8)	50 (29/21)	13 (7/6)	–	7
Yang *et al.*. [45]	Dec,2019–Jan 26,2020	Wuhan, China	59.7 (SD 13.3)	52 (35/17)	–	32 (21/11)	9
Yao *et al.*. [46]	Jan 12–Feb 21,2020	Shaanxi, China	53.87 (SD 15.84)	40 (25/15)	22	–	7
Yuan *et al.*. [47]	Jan 1–Jan 25,2020	Wuhan, China	60 (IQR 47–69)	27 (12/15)	–	10 (4/6)	7
Zhang *et al.*. [18]	Jan 2–Feb 10,2020	Wuhan, China	55 (IQR 39–66.5)	221 (108/113)	55 (35/20)	9 (7/2)	9
Zhang *et al.*. [48]	Jan 16–Feb 3,2020	Wuhan, China	57 (IR 25–87)	140 (71/69)	58 (33/25)	–	8
Zhao *et al.*. [49]	–	Hunan, China	44.4 (SD 12.3)	101 (56/45)	14 (8/6)	–	7
Zhou *et al.*. [12]	Dec 29–Jan 31,2020	Wuhan, China	56 (IQR 46–67)	191 (119/72)	–	54 (38/16)	9
Current study	Jan 20–Feb 14,2020	Changchun, China	41 (IQR 33–52)	43 (25/18)	5 (3/2)	–	8

Table 3: Meta-analysis on risk of disease severity and mortality patients with COVID-19 between male and female

	Study	Total patients	OR	95%CI	Heterogeneity		P for pooled	Publication Bias
					I^2(%)	P for I^2		
Severity	21	4213	1.604	1.373 – 1.873	25	0.145	<0.001	0.535
≤ 50 y	10	2596	1.358	1.098 – 1.678	38.0	0.105	0.005	0.885
> 50 y	11	1617	1.942	1.546 – 2.44	0.0	0.742	<0.001	0.536
Mortality	11	53695	1.571	1.422 – 1.736	34	0.1266	<0.001	0.678
≥ 50 y	3	49962	1.696	1.494 – 1.926	0.0	0.721	<0.001	0.910
> 50 y	8	3732	1.382	1.175 – 1.625	33.0	0.164	<0.001	0.973

Discussion

It has been suggested that gender may play a role in the infection, severe or fatality of COVID-19 patients [11], [13], [15]. This is the first retrospective study to compare the sex differences of the epidemiological and clinical characteristics in COVID-19 patients, we included 43 patients with COVID-19, the morbidity of male (58.1%) was higher than female (41.9%), which was consistent with previous results [6], [15], [26], [31], [48]. There were no significant sex differences on severity, comorbidity, complication, and treatments. Previous studies found that male was more prone to SAS-Cov-2 infection and more severe symptoms [12], [15], [44], but the severity of COVID-19 patients was comparable between males and females in our study, that might be due to the small sample, comparable ages between males and females and mostly general or mild patients. The initial symptoms between female and male were similar that were consistent with previous studies [16]. We found that male was more have underlying comorbidities, and higher levels of WBC, neutrophil count, monocyte count, hemoglobin, total bilirubin, creatine, and creatine kinase compared with female. Previous studies suggested that the severity of COVID-19 had a positive correlation with the inflammatory response and cytokine storm [14], [15], [19], [24], [48].

To the best of our knowledge, this comprehensive meta-analysis including the largest cases from December 2019 to April 2020 was the latest to analyze the sex differences of morbidity, and the severe rate of COVID-19 patients. Our meta-analysis results confirmed that sex play an important role in SARS-CoV-2 infection, male of all 90,475 COVID-19 patients showed slightly higher incidence than female. Previous studies have demonstrated that males might be more susceptible to SAS-Cov-2 infection than females, and elder with more underlying comorbidities were associated with the severity of

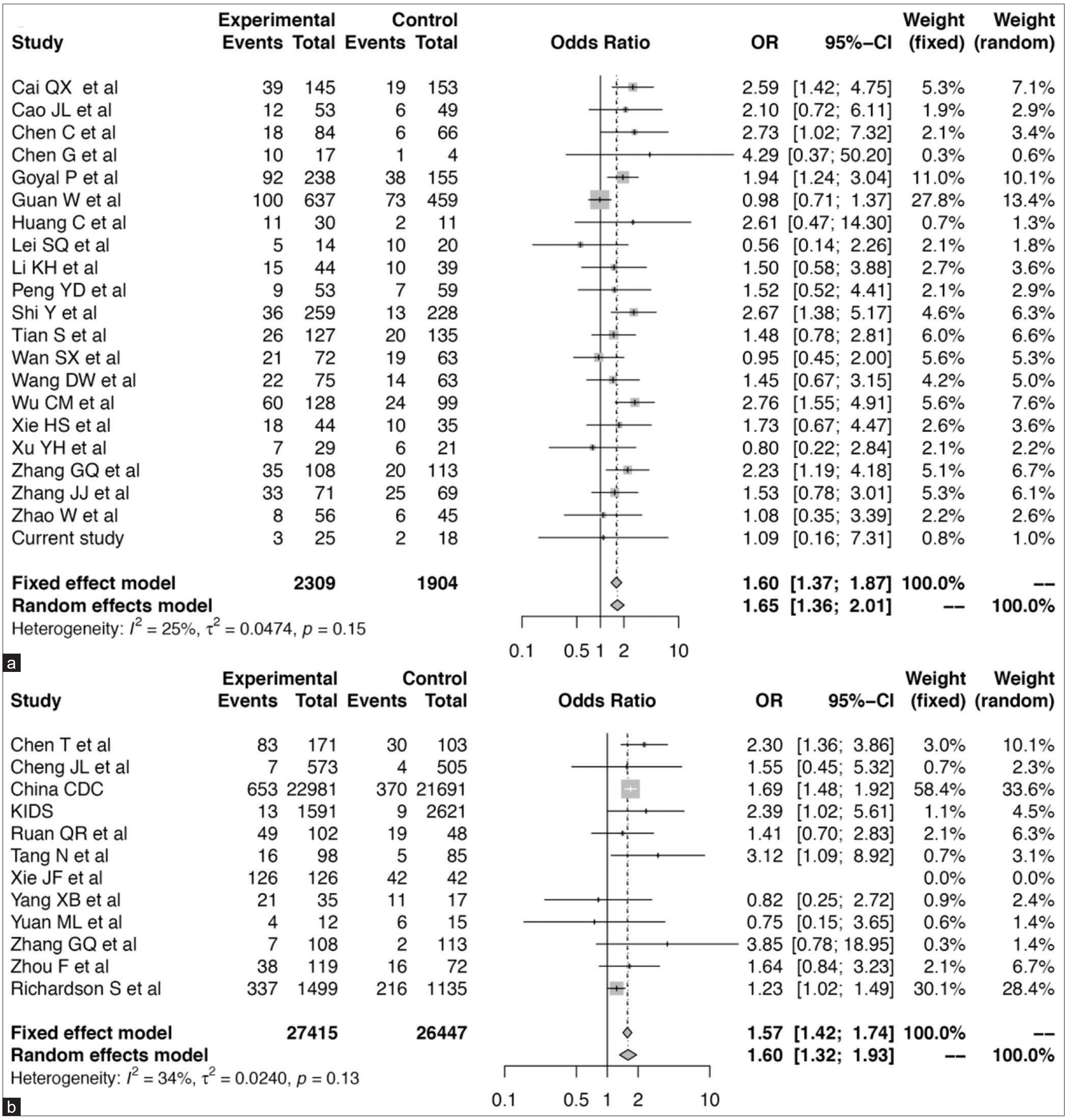


Figure 5: Risk of Severity (a) and Mortality (b) between male and female in COVID-19

COVID-19 patients [41], [50]. Our study showed that the severe rate and the fatality rate of COVID-19 reached 22.7% and 10.7%, which were higher than the rates of SARS-CoV [51]. The risky of severe and death of COVID-19 in male were significantly higher than female, male has 1.6 folds higher compared with female. Moreover, the risky in older male had 1.94 folds higher compared with female and 1.7 folds higher in younger. It might due to the number of study and limited time so far, data collection of severe or death patients is still incomplete, and most of the studies did not analyzed sex differences in severe or death patients. However, there was significant heterogeneity among eligible studies, which might be potential from age and location of patients. However, the meta-analysis results were stable and reliable that no individual study significantly affects the pooled results after performing subgroup, sensitivity analyses, and meta-regression. Besides, funnel plot asymmetry and peters test results showed that there was no publication bias in our meta-analysis.

Men might be more vulnerable to infection with SARS-CoV-2, and poor progress and outcomes [14], [15], [41]. However, the pathogenesis of

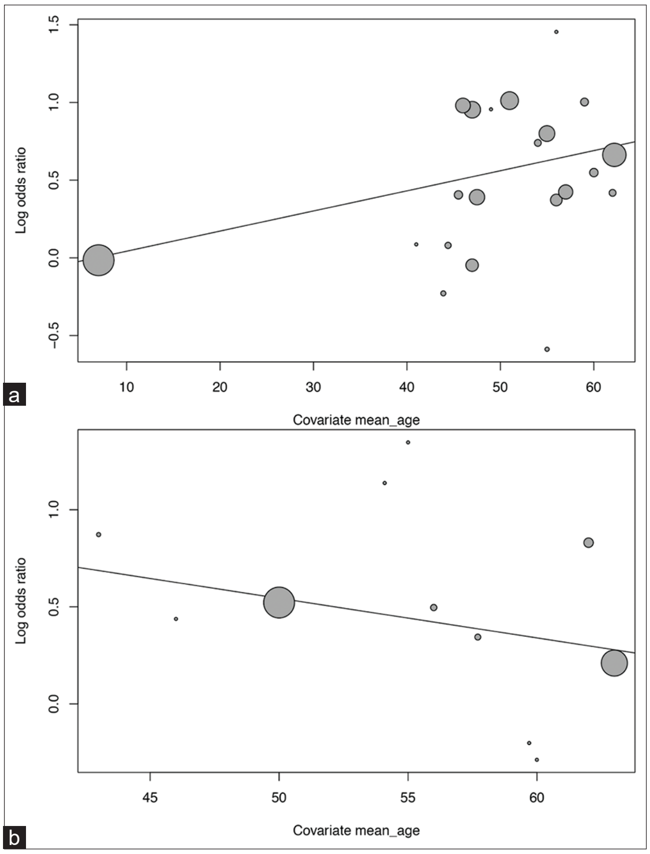


Figure 6: Meta-regression of age and log odds of Sex and Severity (a) or Mortality (b) in COVID-19

sex differences of COVID-19 patients is still unknown. Previous studies have revealed that biological and genetic structure differences, lifestyle, and behavior factors might play a major role for the sex differences of SAS-CoV-2 infection [52]. Previous studies suggested that the innate antiviral immune responses to a variety of virus infections of female was appropriate and greater than male and estrogen would increase the antiviral response of immune cells [16], [24], [53]. Moreover, female have two X-chromosome while male only one, which have encoded many genes that regulate the immune response system [53]. Compared with male, female has better lifestyle and behavior and is more likely to follow public health advice and seek medical attention. Previous studies found that smoking was a risk factor of COVID-19 progression, the prevalence of smoking in severity or death patients was significantly higher than mild or asymptomatic patients [2], [26]. Male smoking prevalence is significantly higher than female, which is the risk factor of many chronic non-infectious diseases. SARA-CoV-2 might directly force bind to ACE2 positive cholangiocytes, which is located on the X-chromosome, and male had higher expression of ACE2 than female [14], [54]. The more underlying comorbidities and higher expression of ACE2 in male patients would prolonged clinical course, cause worse complications and clinical outcomes [24], [55].

Our retrospective cohort study and meta-analysis had several limitations. First, retrospective study results limited by smaller sample, some briefly or incomplete documentation, and not all same laboratory variables were tested in all cases. Second, heterogeneity existed in our meta-analysis, which might relate to large variation of sample variation, different data collection and follow-up time, age, and location of patients. Third, the statistics reported by different countries to estimate overall and sex differences of fatality rate were incomplete and limited, so general conclusions of comparison with fatality rate between different countries should be caution.

Conclusion

The pooled severe rate and fatality rate of COVID-19 were 22.7% and 10.7%. Male incidence in the retrospective study was 58.1%, and the pooled incidence in male was 54.7%. The pooled severe rate in male and female of COVID-19 was 28.2% and 18.8%, the risky of severe and death was about 1.6 folds higher in male compared with female, especially for older patients (> 50 y).

Authors' Contributions

ZJL, LQD, and QY designed the study, ZJL, LNF, and LQD analyzed the data and wrote the first draft. WYC, JZ, YXH, YHZ, FT, DLW, BNC, and HW contributed to analysis and discussion. All authors interpreted the results and wrote the manuscript.

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Supplementary Tables and Figures

Table S1: Complications and treatments in hospitalization of COVID-19 patients

	Total (n = 43) (%)	Female (n = 18) (%)	Male (n = 25) (%)	p value
Complications				
Liver damage	19 (44.2)	7 (38.9)	12 (48.0)	0.756
Metabolic acidosis	8 (18.6)	5 (27.8)	3 (12.0)	0.247
Hypoxemia	8 (18.6)	4 (22.2)	4 (16.0)	0.701
Respiratory failure	6 (14.0)	2 (11.1)	4 (16.0)	0.648
Leukopenia	6 (14.0)	6 (33.3)	0	0.003
Acute cardiac injury	5 (11.6)	2 (11.1)	3 (12.0)	0.929
Treatment				
Antiviral therapy	43 (100.0)	18 (100.0)	25 (100.0)	-
Lopinavir/ritonavir+ Interferon alpha inhalation	40 (93.0)	17 (94.4)	23 (92.0)	0.756
Antibiotics	36 (83.7)	15 (83.3)	21 (84.0)	0.953
Moxifloxacin	30 (69.8)	12 (66.7)	18 (72.0)	0.747
Moxifloxacin+Xuebijing Injection	13 (30.2)	6 (33.3)	7 (28.0)	0.747
Corticosteroids	23 (53.5)	9 (50.0)	14 (56.0)	0.763
Oxygen therapy	25 (55.8)	11 (61.1)	13 (52.0)	0.756
Traditional Chinese medicine therapy	42 (97.7)	18 (100.0)	24 (96.0)	-

Table S2: The characteristics of eligible studies of COVID-19

Author	Date	Location	Age	Total	M/F	Severity	Mortality	Quality
Arentz *et al*. [1]	February 20-March 5, 2020	USA	70 (IR 43-92)	21	11/10	21	11	8
Bernheim *et al*. [2]	January 18-February 2, 2020	China	45.3 (SD 15.6)	121	61/60	-	-	9
Cai *et al*. [3]	January 11-February 6, 2020	Shenzhen, China	47 (IQR 33–61)	298	145/153	58	3	8
Cao *et al*. [4]	January 3-February 1, 2020	Wuhan, China	54 (37–67)	102	53/49	18	17	6
Chang *et al*. [5]	January 16-January 29, 2020	Beijing, China	34 (IQR 34–48)	13	10/3	-	-	7
Chen *et al*. [6]	January-February, 2020	Wuhan, China	59(SD 16)	150	84/66	24	11	9
Chen *et al*. [7]	December 2019-January 27, 2020	Wuhan, China	56 (IQR 50–65)	21	17/4	11	-	8
Chen *et al*. [8]	January 20-February 6, 2020	Shanghai, China	51 (IQR 36–64)	249	126/123	22	-	9
Chen *et al*. [9]	January 14-January 29, 2020	Wuhan, China	56 (IR 26–79)	29	21/8	14	-	8
Chen *et al*. [10]	January 1-January 20, 2020	Wuhan, China	55.5 (SD 13.1)	99	67/32	-	11	9
Chen *et al*. [11]	January 13-February 12, 2020	Wuhan, China	62 (IQR 44–77)	274	171/103	-	113	9
Chen *et al*. [12]	January 20-February 17, 2020	Zhejiang, China	43 (SD 17.2)	98	52/46	-	-	8
Cheng *et al*. [13]	February 19, 2020	Henan, China	46 (SD 24)	1079	573/505	-	11	7
China CDC [14]	February 11, 2020	China	30–69	44672	22981/21691	8255	1023	8
Chuang *et al*. [15]	January 18-January 27, 2020	China	51 (SD 14)	21	13/8	-	-	7
Australia [16]	January 13, 2020	Australia	43 (IR 8–66)	15	9/6	-	-	5
NERC [17]	February 14, 2020	Korea	42.6 (IR 20–73)	28	15/13	-	-	6
Dong *et al*. [18]	January 7-February 24, 2020	Tianjin, China	48.6 (SD 16.8)	135	72/63	62	3	8
Easom *et al*. [19]	January 29-February 24, 2020	UK	42.5 (IR 0.5–76)	68	32/36	-	-	9
Goyal *et al*. [20]	Mar 3-Mar 27, 2020	USA	62.2 (IQR 48.6–73.7)	393	238/155	130	40	7
Grasselli *et al*. [21]	February 20-March 18, 2020	Italy	63 (IQR 56–70)	1591	1304/287	1591	405/1581	9
Guan *et al*. [22]	December 11-January 31, 2020	China	47 (35–58)	1099	637/459	173	15	9
Guo *et al*. [23]	January 23-February 23, 2020	Wuhan, China	58.5 (SD 14.66)	187	91/96	-	43	9
Huang *et al*. [24]	December 16, 2019-January 2, 2020	Wuhan, China	49 (41–58)	41	30/11	13	6	9
Huang *et al*. [25]	December 21, 2019-January 28, 2020	Wuhan, China	56.24 (SD 17.14)	34	14/20	-	-	7
Jin *et al*. [26]	January 17-February 8, 2020	Zhejiang, China	45	651	331/320	64	-	8
KSID [27]	January 19-March 2, 2020	Korea	20–50	4212	1591/2621	-	22	8
Lei *et al*. [28]	January 1-February 5, 2020	Wuhan, China	55 (IQR 43–63)	34	14/20	15	7	9
Li *et al*. [29]	January-February, 2020	Chongqing, China	45.5 (SD 12.3)	83	44/39	25	-	7
Li *et al*. [30]	December-January 22, 2020	Wuhan, China	59(IR 15–89)	425	240/185	-	-	9
Li *et al*. [31]	December 28-February 10, 2020	Southwest, China	47 (SD 15)	131	63/68	-	-	8
Liu *et al*. [32]	December 30, 2019-January 24, 2020	Hubei, China	55 (SD 16)	137	61/76	-	16	8
Liu *et al*. [33]	December 30-January 15, 2020	Wuhan, China	38 (IQR 33–57)	78	39/39	8	-	9
Livngston *et al*. [34]	March 15, 2020	Italy	64	22512	13462/9050	9	1625	3
Mizumoto *et al*. [35]	February 5-February 20, 2020	Japan	-	634	321/313	-	-	8
Pan *et al*. [36]	January 12-February 6, 2020	Wuhan, China	40(SD 9)	21	6/15	-	-	8
Pan *et al*. [37]	December 30-January 31, 2020	Wuhan, China	44.9 (SD 15.2)	63	33/30	-	-	7
Peng *et al*. [38]	January 20-February 15, 2020	Wuhan, China	62 (IQR 55–67)	112	53/59	16	17	8
Qian *et al*. [39]	January 20-February 11, 2020	Zhejiang, China	50 (IQR 36.5–57)	91	37/54	9	-	7
Richardson *et al*. [40]	March 1-April 4, 2020	USA	63 (IQR 52–75)	5700	2263/3437	-	553/2634	9
Ruan *et al*. [41]	-	Wuhan, China	46–70	150	102/48	-	68	6
Shi *et al*. [42]	December 20-January 23, 2020	Wuhan, China	49.5 (SD 11)	81	42/39	3	-	9
Shi *et al*. [43]	February 17, 2020	Zhejiang, China	46 (SD 19)	487	259/228	49	-	6
Song *et al*. [44]	January 20-January 27, 2020	Shanghai, China	49 (SD16)	51	25/26	-	-	8
Sun *et al*. [45]	January 31, 2020	China	46 (IQR 35–60)	507	281/201	-	-	7
Su *et al*. [46]	January 13-January 31, 2020	Taiwan, China	56.6	10	7/3	-	-	5
Sun *et al*. [47]	January 26-February 16, 2020	Singapore	42 (IQR 34–54)	54	29/25	-	-	8
Tang *et al*. [48]	January 1-February 3, 2020	Wuhan, China	54.1 (SD 16.2)	183	98/85	-	21	7
Tian *et al*. [49]	January 20-February 10, 2020	Beijing, China	47.5 (1–94)	262	127/135	46	3	7
Wan *et al*. [50]	January 23-February 8, 2020	Chongqing, China	47 (IQR 36–55)	135	72/63	40	1	8
Wang *et al*. [51]	January 1-January 28, 2020	Wuhan, China	56 (42–68)	138	75/63	36	6	9
Wang *et al*. [52]	January 16-February 17, 2020	Wuhan, China	45 (SD 14)	90	33/57	-	-	7
Wu *et al*. [53]	December 25, 2019-January 26, 2020	Wuhan, China	51 (IQR 43–60)	201	128/99	84	44	9
Wu *et al*. [54]	January-February, 2020	Chongqing, China	44 (SD 11)	80	42/38	-	-	8
Wu *et al*. [55]	January 22-February 14, 2020	Jiangsu, China	46.1 (SD 15.42)	80	39/41	3	-	9
Wu *et al*. [56]	February 9-February 15, 2020	Hubei, China	68 (IQR 53–67)	38	25/13	-	-	9
Xie *et al*. [57]	February 2-February 23, 2020	Wuhan, China	60 (IQR48–66)	79	44/35	28	-	8
Xie *et al*. [58]	January 21-January 30, 2020	Wuhan, China	70 (IQR 64–78)	168	126/42	-	168	5
Xu *et al*. [59]	January 23-February 4, 2020	Guangdong, China	50 (IR 18–86)	90	39/51	-	-	7
Xu *et al*. [60]	January 10-January 26, 2020	Zhejiang, China	41 (IQR 32–52)	62	36/27	-	-	8
Xu *et al*. [61]	January-February, 2020	Beijing, China	43.9 (SD 16.8)	50	29/21	13	-	7
Yang *et al*. [62]	January 17-February 10, 2020	Zhejiang, China	45.11 (SD 13.35)	149	81/68	-	-	7
Yang *et al*. [63]	December 2019-January 26, 2020	Wuhan, China	59.7 (SD 13.3)	52	35/17	52	32	9
Yao *et al*. [64]	January 12-February 21, 2020	Shaanxi, China	53.87 (SD 15.84)	40	25/15	22	-	7
Young *et al*. [65]	January 23-February 3, 2020	Singapore	47 (IR 31–73)	18	9/9	-	-	8
Yuan *et al*. [66]	January 1-January 25, 2020	Wuhan, China	60 (IQR 47–69)	27	12/15	-	10	7
Zha *et al*. [67]	January 24-February 24, 2020	Wuhan, China	39 (IQR 32–54)	31	20/11	-	-	8
Zhang *et al*. [68]	January 2-February 10, 2020	Wuhan, China	55 (IQR 39–66.5)	221	108/113	55	12	9
Zhang *et al*. [69]	January 16-February 3, 2020	Wuhan, China	57 (IR 25–87)	140	71/69	58	-	8
Zhang *et al*. [70]	January 13-February 26, 2020	Wuhan, China	65 (IQR 56–70)	28	17/11	-	-	8
Zhang *et al*. [71]	January 18-February 3, 2020	Beijing, China	36 (IR 15–49)	9	5/4	-	-	6
Zhang *et al*. [72]	January 17-February 8, 2020	Zhejiang, China	45.4	645	328/317	-	-	8
Zhao *et al*. [73]	-	Hunan, China	44.4 (SD 12.3)	101	56/45	14	-	7
Zhou *et al*. [74]	December 29, 2019-January 31, 2020	Wuhan, China	56 (IQR 46–67)	191	119/72	-	54	9
Zhou *et al*. [75]	January 16-January 30, 2020	Wuhan, China	52.8 (SD 12.2)	62	39/23	-	-	8
Current study	January 20-February 14, 2020	Changchun, China	41 (IQR 33–52)	43	25/18	5	-	8

Study	Events	Total	Proportion	95%−CI	Weight (fixed)	Weight (random)
Arentz M et al	11	21	0.52	[0.30; 0.74]	0.0%	0.8%
Bernheim A et al	61	121	0.50	[0.41; 0.60]	0.1%	1.4%
Cai QX et al	145	298	0.49	[0.43; 0.54]	0.3%	1.6%
Cao JL et al	53	102	0.52	[0.42; 0.62]	0.1%	1.4%
Chang D et al	10	13	0.77	[0.46; 0.95]	0.0%	0.7%
Chen C et al	84	150	0.56	[0.48; 0.64]	0.2%	1.5%
Chen G et al	17	21	0.81	[0.58; 0.95]	0.0%	1.0%
Chen J et al	126	249	0.51	[0.44; 0.57]	0.3%	1.6%
Chen L et al	21	29	0.72	[0.53; 0.87]	0.0%	1.0%
Chen NS et al	67	99	0.68	[0.58; 0.77]	0.1%	1.4%
Chen T et al	171	274	0.62	[0.56; 0.68]	0.3%	1.6%
Chen ZH et al	52	98	0.53	[0.43; 0.63]	0.1%	1.4%
Cheng JL et al	573	1079	0.53	[0.50; 0.56]	1.2%	1.7%
China CDC	22981	44672	0.51	[0.51; 0.52]	47.9%	1.8%
Chuang M et al	13	21	0.62	[0.38; 0.82]	0.0%	0.8%
Australia	9	15	0.60	[0.32; 0.84]	0.0%	0.6%
NERC	15	28	0.54	[0.34; 0.72]	0.0%	0.9%
Dong XC et al	72	135	0.53	[0.45; 0.62]	0.1%	1.5%
Easom N et al	32	68	0.47	[0.35; 0.60]	0.1%	1.3%
Goyal P et al	238	393	0.61	[0.56; 0.65]	0.4%	1.6%
Grasselli G et al	1304	1591	0.82	[0.80; 0.84]	2.9%	1.7%
Guan W et al	637	1099	0.58	[0.55; 0.61]	1.2%	1.7%
Guo T et al	91	187	0.49	[0.41; 0.56]	0.2%	1.5%
Huang C et al	30	41	0.73	[0.57; 0.86]	0.1%	1.1%
Huang YH et al	14	34	0.41	[0.25; 0.59]	0.0%	1.0%
Jin X et al	331	651	0.51	[0.47; 0.55]	0.7%	1.7%
KSID	1591	4212	0.38	[0.36; 0.39]	4.8%	1.7%
Lei SQ et al	14	34	0.41	[0.25; 0.59]	0.0%	1.0%
Li KH et al	44	83	0.53	[0.42; 0.64]	0.1%	1.3%
Li Q et al	240	425	0.56	[0.52; 0.61]	0.5%	1.7%
Li XM et al	63	131	0.48	[0.39; 0.57]	0.1%	1.5%
Liu K et al	61	137	0.45	[0.36; 0.53]	0.1%	1.5%
Liu W et al	39	78	0.50	[0.38; 0.62]	0.1%	1.3%
Livngston E et al	13462	22512	0.60	[0.59; 0.60]	25.1%	1.8%
Mizumoto K et al	321	634	0.51	[0.47; 0.55]	0.7%	1.7%
Pan F et al	6	21	0.29	[0.11; 0.52]	0.0%	0.8%
Pan YY et al	33	63	0.52	[0.39; 0.65]	0.1%	1.2%
Peng YD et al	53	112	0.47	[0.38; 0.57]	0.1%	1.4%
Qian GQ et al	37	91	0.41	[0.30; 0.51]	0.1%	1.4%
Richardson S et al	2263	5700	0.40	[0.38; 0.41]	6.4%	1.8%
Ruan QR et al	102	150	0.68	[0.60; 0.75]	0.2%	1.5%
Shi HS et al	42	81	0.52	[0.40; 0.63]	0.1%	1.3%
Shi Y et al	259	487	0.53	[0.49; 0.58]	0.5%	1.7%
Song FX et al	25	51	0.49	[0.35; 0.63]	0.1%	1.1%
Su YJ et al	281	507	0.55	[0.51; 0.60]	0.5%	1.7%
Sun KY et al	7	10	0.70	[0.35; 0.93]	0.0%	0.5%
Sun Y et al	29	54	0.54	[0.40; 0.67]	0.1%	1.2%
Tang N et al	98	183	0.54	[0.46; 0.61]	0.2%	1.5%
Tian S et al	127	262	0.48	[0.42; 0.55]	0.3%	1.6%
Wan SX et al	72	135	0.53	[0.45; 0.62]	0.1%	1.5%
Wang DW et al	75	138	0.54	[0.46; 0.63]	0.1%	1.5%
Wang YH et al	33	90	0.37	[0.27; 0.47]	0.1%	1.4%
Wu CM et al	128	201	0.64	[0.57; 0.70]	0.2%	1.6%
Wu J et al	42	80	0.52	[0.41; 0.64]	0.1%	1.3%
Wu J et al	39	80	0.49	[0.37; 0.60]	0.1%	1.3%
Wu P et al	25	38	0.66	[0.49; 0.80]	0.0%	1.1%
Xie HS et al	44	79	0.56	[0.44; 0.67]	0.1%	1.3%
Xie JF et al	126	168	0.75	[0.68; 0.81]	0.2%	1.6%
Xu X et al	39	90	0.43	[0.33; 0.54]	0.1%	1.3%
Xu XW et al	36	62	0.58	[0.45; 0.70]	0.1%	1.2%
Xu YH et al	29	50	0.58	[0.43; 0.72]	0.1%	1.1%
Yang WJ et al	81	149	0.54	[0.46; 0.63]	0.2%	1.5%
Yang XB et al	35	52	0.67	[0.53; 0.80]	0.1%	1.2%
Yao N et al	25	40	0.62	[0.46; 0.77]	0.0%	1.1%
Young BE et al	9	18	0.50	[0.26; 0.74]	0.0%	0.7%
Yuan ML et al	12	27	0.44	[0.25; 0.65]	0.0%	0.9%
Zha L et al	20	31	0.65	[0.45; 0.81]	0.0%	1.0%
Zhang GQ et al	108	221	0.49	[0.42; 0.56]	0.2%	1.6%
Zhang JJ et al	71	140	0.51	[0.42; 0.59]	0.2%	1.5%
Zhang L et al	17	28	0.61	[0.41; 0.78]	0.0%	0.9%
Zhang MQ et al	5	9	0.56	[0.21; 0.86]	0.0%	0.4%
Zhang XL et al	328	645	0.51	[0.47; 0.55]	0.7%	1.7%
Zhao W et al	56	101	0.55	[0.45; 0.65]	0.1%	1.4%
Zhou F et al	119	191	0.62	[0.55; 0.69]	0.2%	1.5%
Zhou SC et al	39	62	0.63	[0.50; 0.75]	0.1%	1.2%
Current study	25	43	0.58	[0.42; 0.73]	0.0%	1.1%
Fixed effect model		**90475**	**0.53**	**[0.53; 0.54]**	**100.0%**	**--**
Random effects model			**0.55**	**[0.52; 0.57]**	**--**	**100.0%**

Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.0090$, $p = 0$

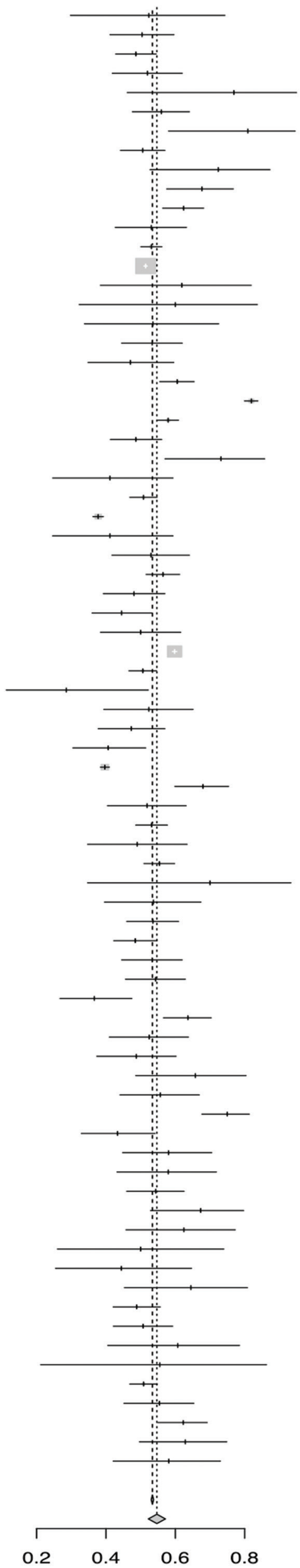

Figure S1: The pooled morbidity of male with COVID-19

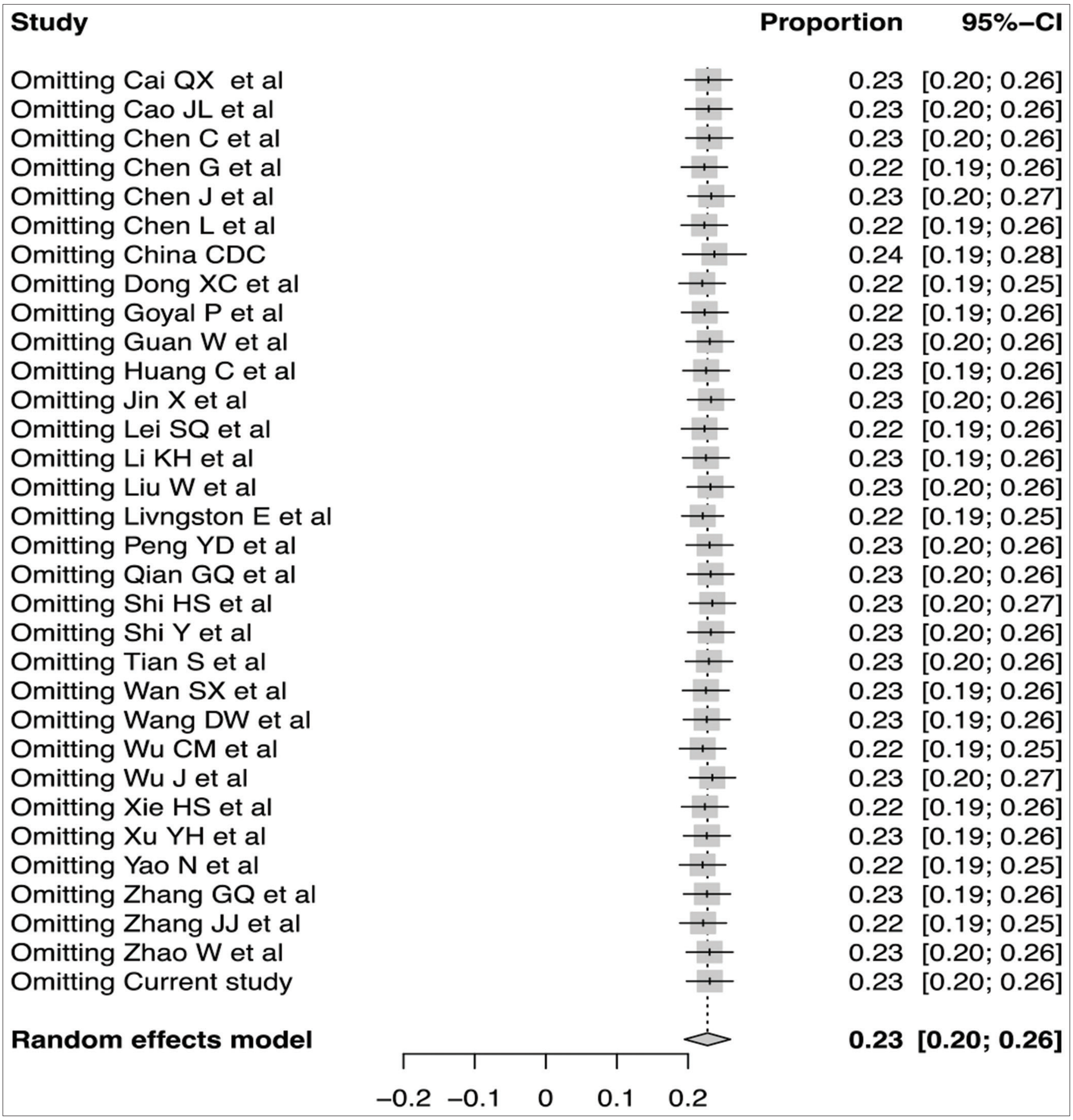

Figure S2: Sensitivity analysis of pooled severe rate in COVID-19

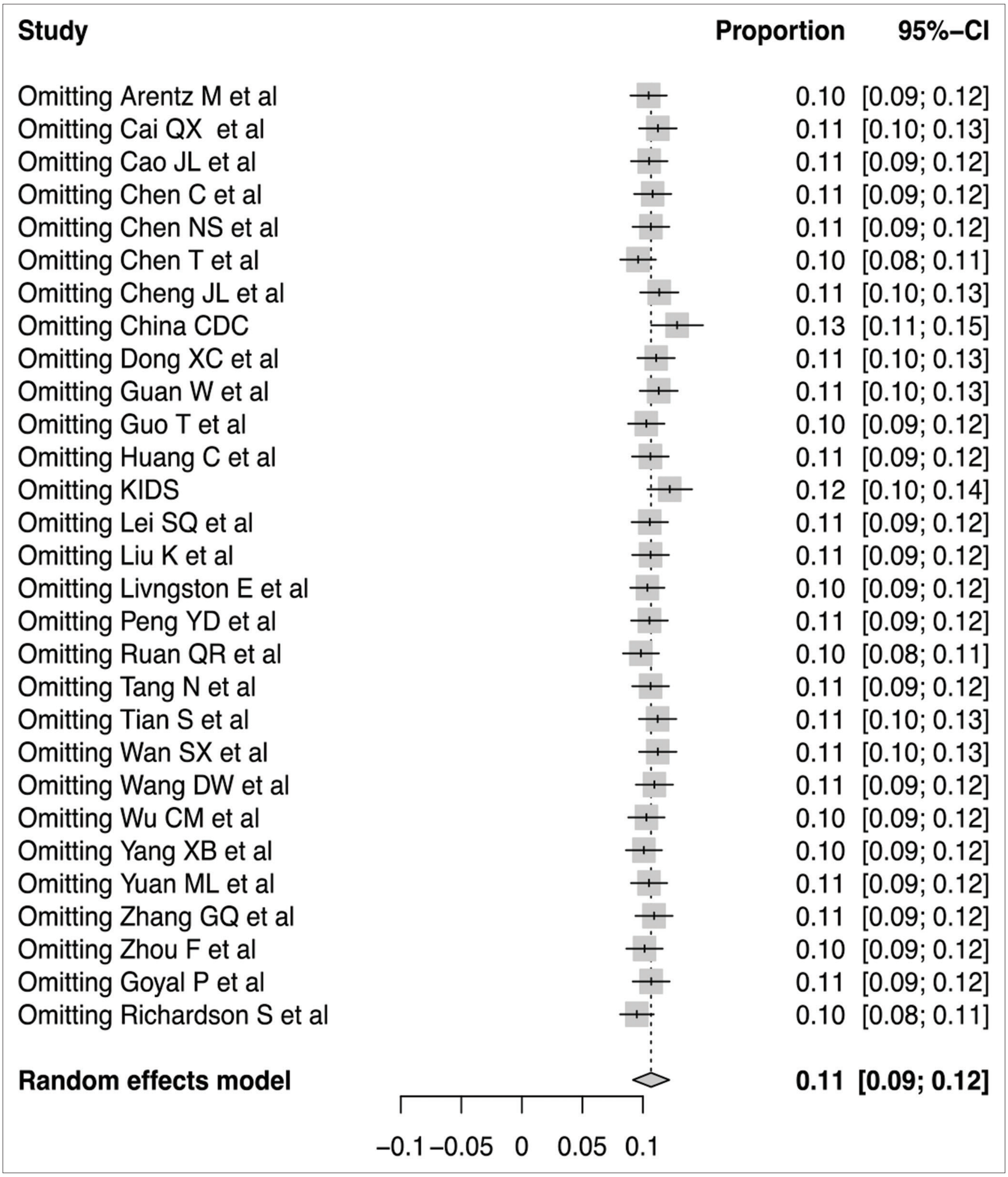

Figure S3: Sensitivity analysis of pooled fatality rate in COVID-19

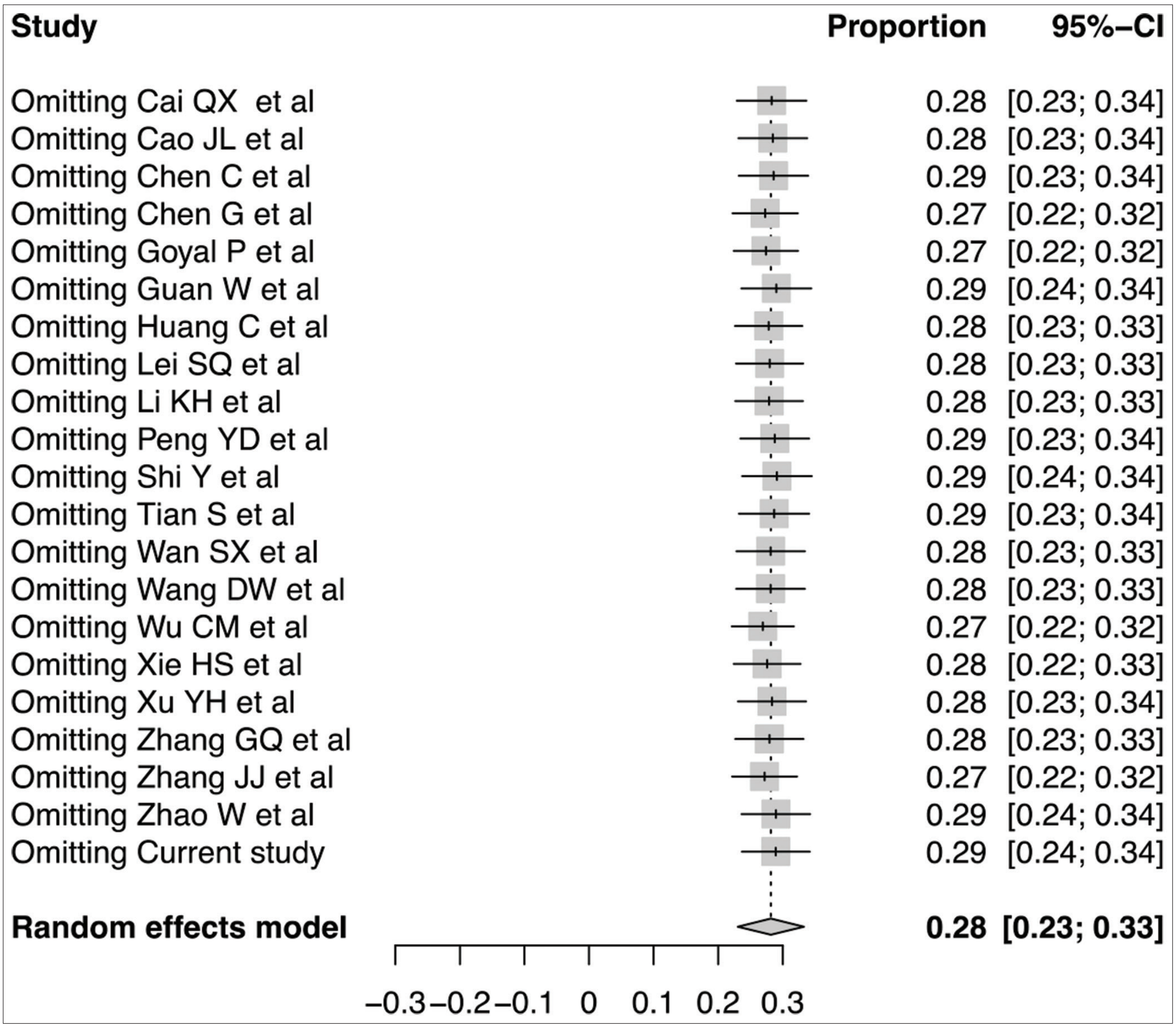

Figure S4: Sensitivity analysis of pooled severe rate of male in COVID-19

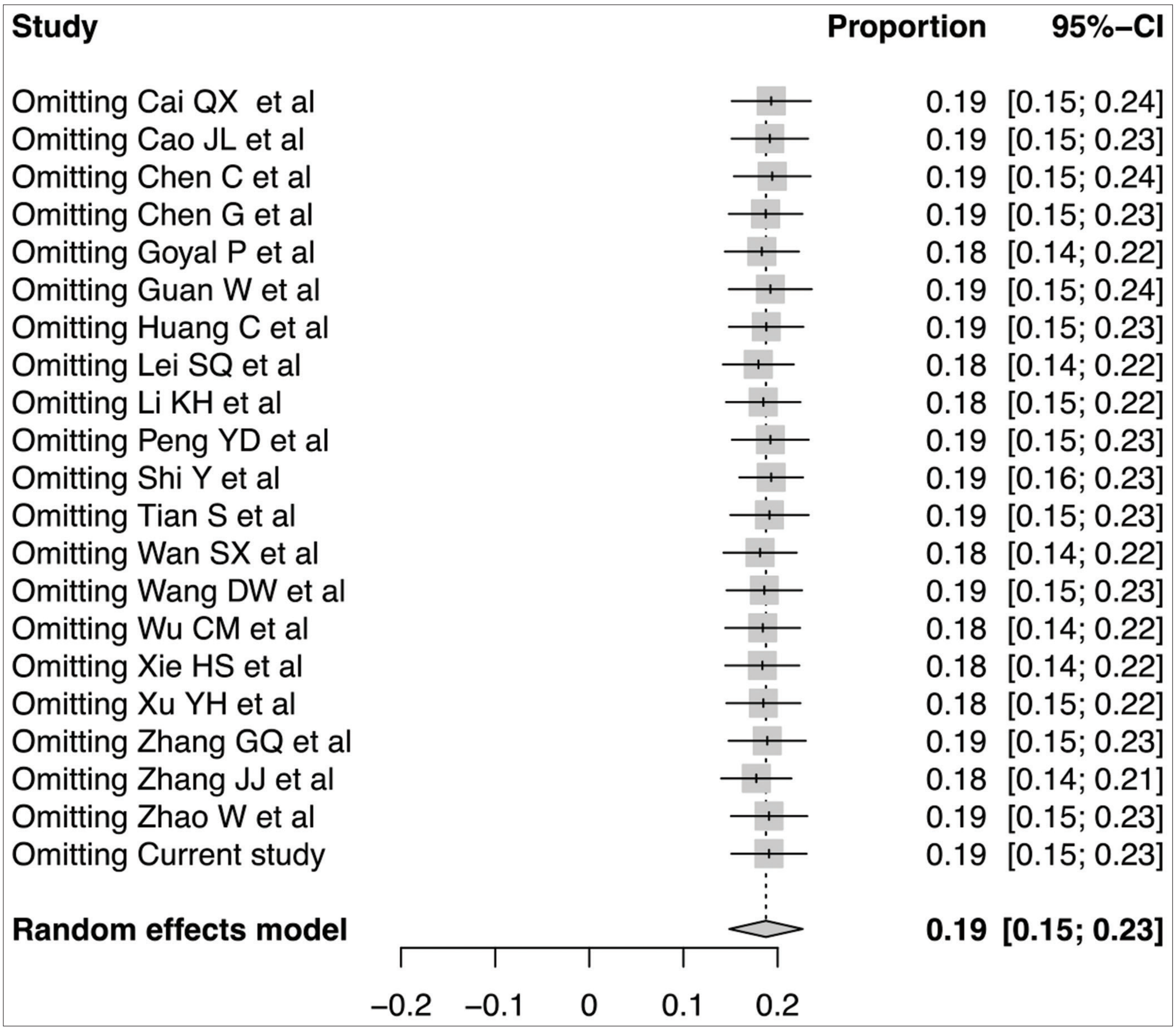

Figure S5: Sensitivity analysis plot of pooled severe rate of female in COVID-19

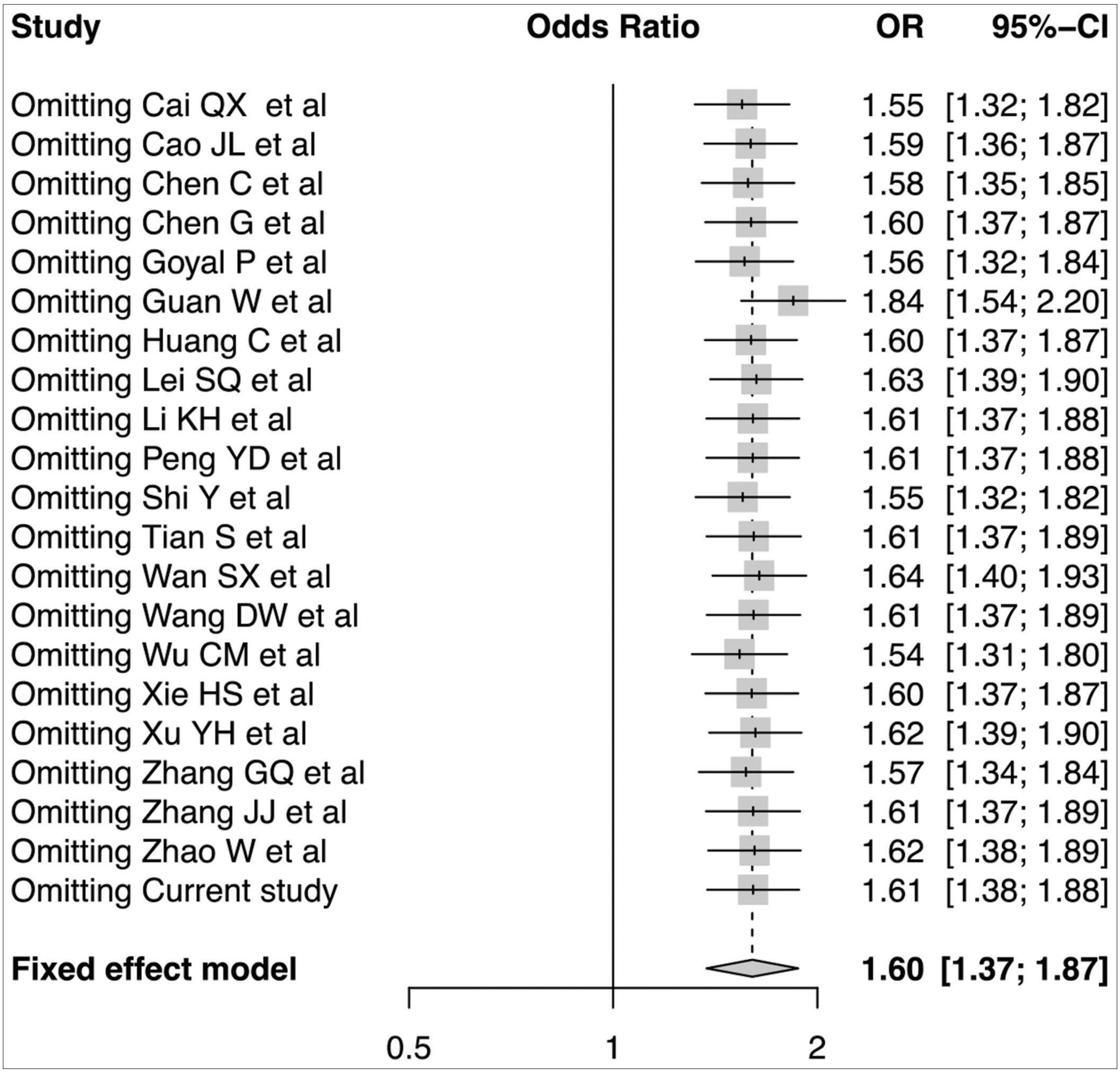

Figure S6: Sensitivity analysis plot of pooled risky between sex and severity in COVID-19

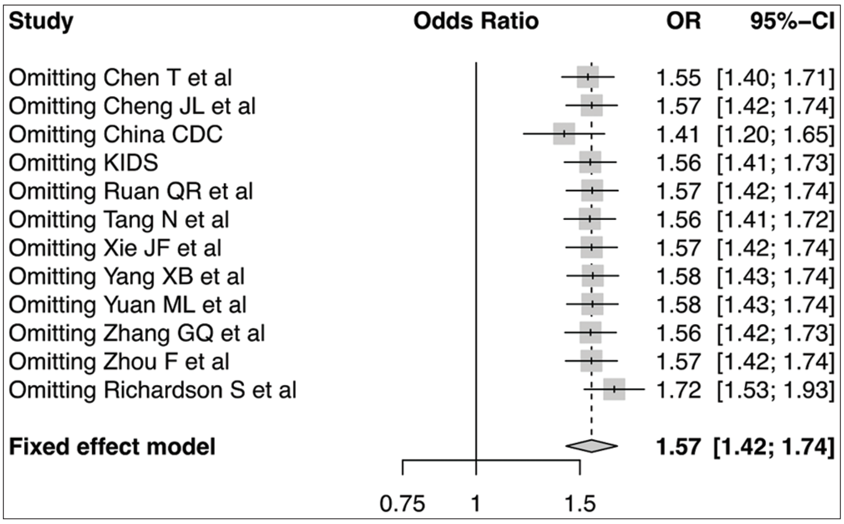

Figure S7: Sensitivity analysis plot of pooled risky between sex and mortality in COVID-19

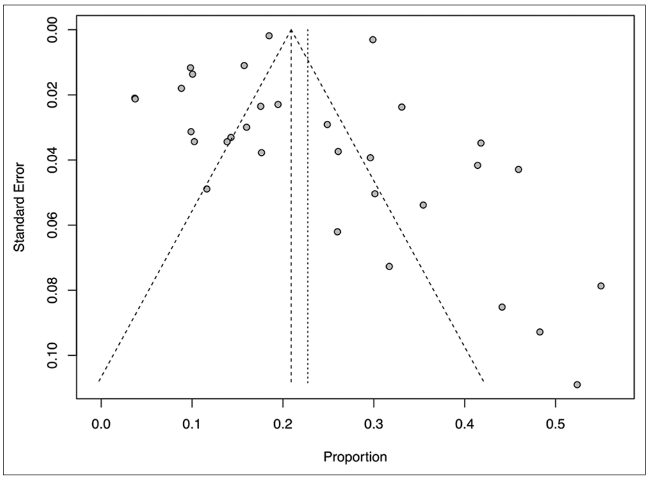

Figure S8: Funnel plot of pooled severe rate in COVID-19

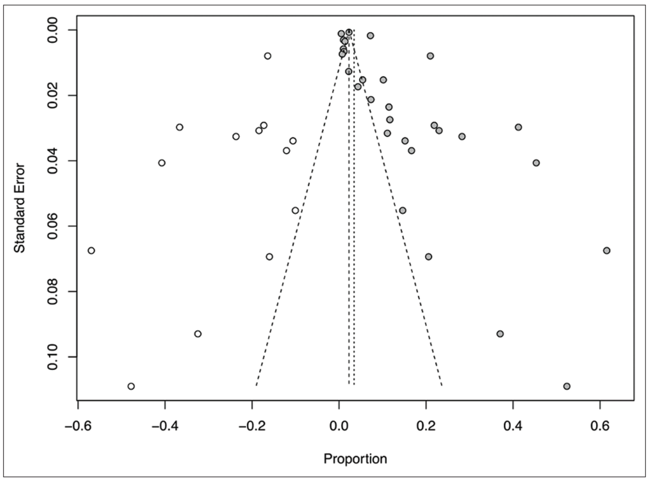

Figure S9: Funnel plot of pooled fatality rate in COVID-19 (trim-fill method)

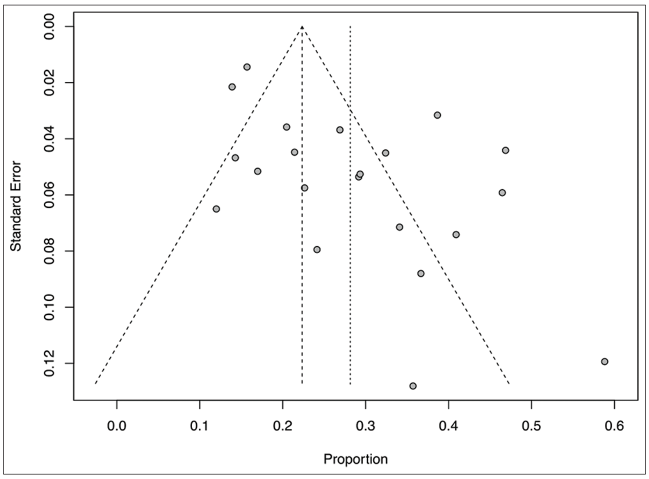

Figure S10: Funnel plot of pooled severe rate of male in COVID-19

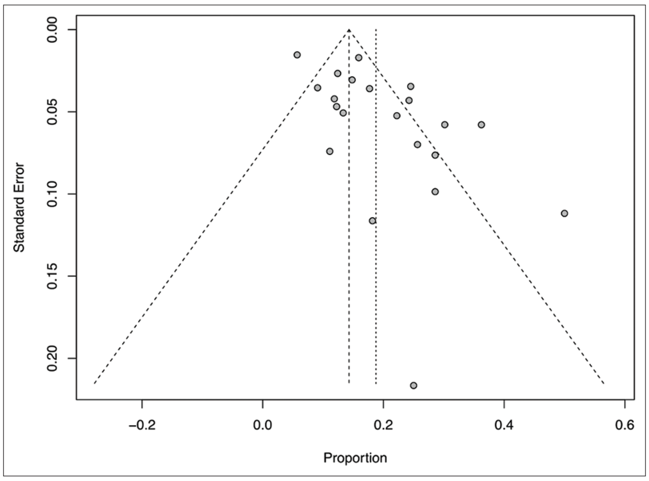

Figure S11: Funnel plot of pooled severe rate of female in COVID-19

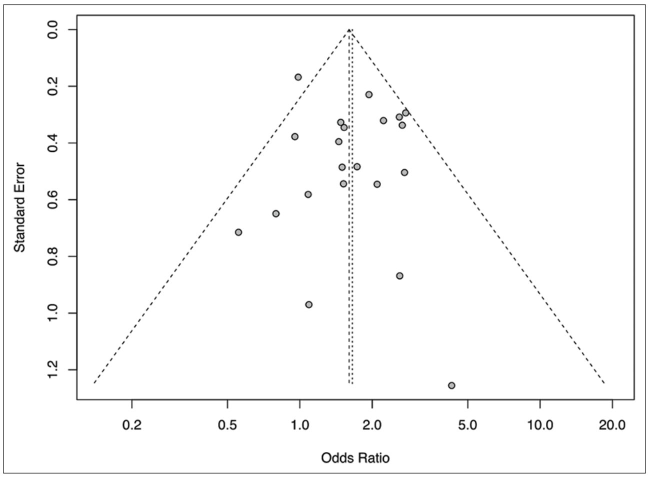

Figure S12: Funnel plot of pooled risky between sex and severity in COVID-19

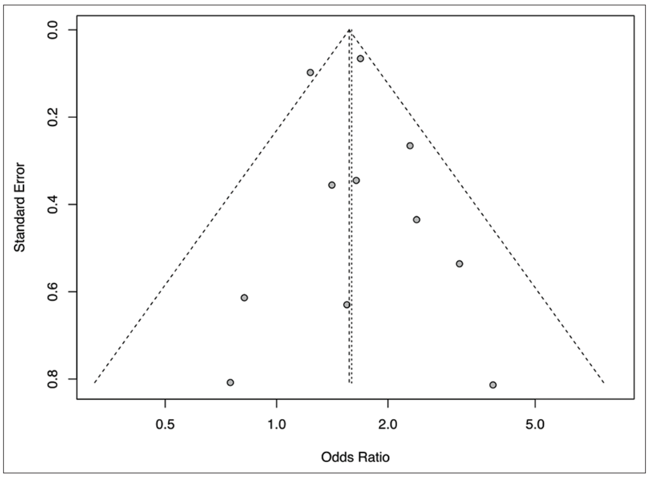

Figure S13: Funnel plot of pooled risky between sex and mortality in COVID-19

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Excess Mortality in a Nephrology Clinic during First Months of Coronavirus Disease-19 Pandemic: A Pragmatic Approach

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Abstract

BACKGROUND: Excess mortality is defined as mortality above what would be expected based on the non-crisis mortality rate in the population of interest.

AIM: In this study, we aimed to access weather the coronavirus disease (COVID)-19 pandemic had impact on the in-hospital mortality during the first 6 months of the year and compare it with the data from the previous years.

METHODS: A retroprospective study was conducted at the University Clinic of Nephrology Skopje, Republic of Macedonia. In-hospital mortality rates were calculated for the first half of the year (01.01–30.06) from 2015 until 2020, as monthly number of dead patients divided by the number of non-elective hospitalized patents in the same period. The excess mortality rate (p-score) was calculated as ratio or percentage of excess deaths relative to expected average deaths: (Observed mortality rate–expected average death rate)/expected average death rate *100%.

RESULTS: The expected (average) overall death mortality rate for the period 2015–2019 was 8.9% and for 2020 was 15.3%. The calculated overall excess mortality in 2020 was 72% (p_{score} 0.72).

CONCLUSION: In this pragmatic study, we have provided clear evidence of high excess mortality at our nephrology clinic during the 1st months of the COVID-19 pandemic. The delayed referral of patients due to the patient and health care system-related factors might partially explain the excess mortality during pandemic crises. Further analysis is needed to estimate unrecognized probable COVID-19 deaths.

Introduction

The World Health Organization (WHO) has recognized the spread of coronavirus disease (COVID)-19 as a pandemic in March 2020 [1]. Authorities worldwide have implemented preventive measures, restrictions, lockdowns, and facility closures to slow the spread of the disease. Still, over 690,000 deaths worldwide were registered [2]. Excess mortality is defined by WHO [3] as: "Mortality above what would be expected based on the non-crisis mortality rate in the population of interest. Excess mortality is, thus, mortality that is attributable to the crisis conditions. It can be expressed as a rate (the difference between observed and non-crisis mortality rates), or as a total number of excess deaths." It is used to measure the mortality impact of a crisis when not all causes of death are known.

Hospital mortality has been used to assess the quality of care in our University Clinic of Nephrology (UCN). The annual in-hospital mortality rate which is being regularly referred to as the Ministry of Health (MOH), has been stable around 6% in the previous several years [4]. This healthcare unit is providing nephrology tertiary care for around two million citizens. It treats over 20000 outpatients per year and more than 2300 in-hospital patients. It provides over 500 emergency dialysis sessions, over 1500 vascular access interventions covering complications for almost all hemodialysis patients in the country [5]. Annually hundreds of renal [6], [7] and prostate biopsies are performed as elective or urgent procedures. Almost all Macedonian chronic kidney disease (CKD) patients initiate chronic hemodialysis program at our clinic and referred to local dialysis centers thereafter. Annually that number is around 300 patients [8].

The COVID-19 pandemic did not spare Macedonia. The first recognized case was known to be imported from Italy and laboratory confirmed on 26th of February 2020 [9]. The MOH closely monitored and prevented the spreading of the virus with implemented strict protocols in the social area and the health care system. Patients were informed and medical doctors instructed to refer patients to tertiary level only in emergency. Substantial behavioral restrictions have been imposed mostly because of the decision to prioritize preventing clusters from spawning. Even though, in the end of June, more than 6000 people were infected and 298 patients had died [2]. In this period at our hospital, starting from March, all previously scheduled out-patient referrals and elective in-hospital diagnostic (biopsies) or vascular access interventions (arteriovenosus fistula/tunnelled catheter creations) were cancelled or postponed. Patients with nephrology emergency were referred from all over the country and screened for COVID-19 at admission by clinical examination and epidemiological questionnaire. Patients with high risk were isolated and tested with the polymerase chain reaction (PCR) technique. If positive, those were transferred to the dedicated COVID-19 hospitals. Hospital policy applied written protocol measures for prevention of spreading the disease and adequate stuff and patents protective equipment used according to the current MOH recommendations on COVID-19 disease. In hospital, mortality was monitored and notified.

In this study, we aimed to access whether the COVID-19 pandemic had an impact on in-hospital mortality during the first 6 months of the year and compare it with the data from the previous years.

Methods

A retro-prospective study was conducted at UCN Skopje, Republic of Macedonia. A pragmatic approach was used to determine in-hospital mortality rates for the first half of the year (01.01–30.06) from 2015 until 2020. The mortality rates were estimated as monthly number of dead patients divided by the number of non-elective hospitalized patents in the same period. The data were extracted from the hospital registry, the National Integrated Health Information System–My Term (Moj Termin) [10], and the diagnosis-related group system [11], both based on a central database of all public health services in the country for the hospital patients. All the patients that were registered for hospitalization at our clinic for any reason in the 6 years were analyzed; no patients were excluded from the study. Elective in-hospital procedures (programmed creation of permanent vascular access – AV fistula or tunneled central venous catheter, prostate biopsy, renal [native or transplant] biopsy, potential kidney donor, and recipient evaluations) were canceled during pandemic, which resulted in minimizing the number of hospitalizations. Furthermore, minor vascular access interventions were performed as single day ambulatory procedures. Therefore, the mortality rates for the previous years were also estimated only for non-elective hospitalizations. In addition, deaths were analyzed by time frame of occurrence in <24 and 48 h from admission. The number of initial hemodialysis patents was calculated per state population [5], [12].

The real-time reverse transcriptase-PCR (RT-PCR) technique was used to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasopharyngeal and oropharyngeal swabs as specimen from each patient. All tests were performed at the Laboratory for Virology, Institute of Public Health (IPH) according to protocols available on the WHO website [13]. Patients were tested at the discretion of the clinicians if clinical criteria or/and epidemiological linkage to COVID-19 disease were positive for close contact, prior, at admission, or during the hospital stay.

Statistical analysis was performed with SPSS 16.0 for Windows: Continuous variables are shown as mean values and categorical as percentages. The excess mortality rate (p-score) was calculated as ratio or percentage of excess deaths relative to expected average deaths: (Observed mortality rate–expected average death rate)/expected average death rate × 100%. The observed mortality rates were from 2020 and the expected from the period 2015 to 2019.

Results

During the previous 5 years, there were more than 1000 patients admitted each year in the first 6 months of the year (Table 1). The hospitalizations due to any elective procedure ranged from 20% to 38% and the rest (60–80%) were for urgent or other nephrological treatment. The half-annual all-cause mortality rates in non-elective cases were stable at 7.4–10.9%. Deaths in the first 24 h of admission ranged between 2.8% and 4.2% and in the first 48 h from 2.8% to 5.3%. In the current year of 2020, the admissions were rather halved in the first 6 months (497), including only 7% of elective cases. Almost exclusively (93%) were patients admitted for urgent or other non-delayable treatments. In 2020, the mortality rates raised up to 15.3% for all non-elective admissions, almost doubling for the 24 h deaths (6.0%) and for the deaths in the first 48 h (9.9%). As for the surviving patients, the number of incident dialysis patients through the period of all 6 years was stable around 150 patients or 75×10^{-6} per state population.

The expected (average) overall death mortality rate for the period 2015–2019 was 8.9%. For the patients that died in the first 24 h of admission, the average mortality rate for the same 5 years period was 3.3% and for the dead in the first 48 h 4.0%. The calculated overall excess mortality was 72% (p_{score} 0.72), then 79% (p_{score} 0.79) for mortality in the first 24 and 102% (p_{score} 1.02) in the first 48 h, respectively, for 2020 (Figure 1). Out of all 71 dead patients, 28 (40%) died in the first 24 h and 46 (65%) in the first 48 h in 2020.

Table 1: Admissions, mortality rates, and incident dialysis patients in the first 6 months from 2015 to 2020

Year (01th January–30th June)	2015	2016	2017	2018	2019	2020
All hospitalizations	1191	1250	1286	1061	1132	497
Non-elective (%)	757 (64)	856 (68)	819 (64)	659 (62)	905 (80)	463 (93)
Elective (%)	434 (36)	394 (31)	467 (36)	402 (38)	227 (20)	34 (7)
Mortality rates in non-elective cases (%)	60 (7.9)	74 (8.6)	61 (7.4)	72 (10.9)	88 (9.7)	71 (15.3)
Death cases (first 24 h) (%)	28 (3.7)	24 (2.8)	23 (2.8)	28 (4.2)	29 (3.2)	28 (6.0)
Death cases (first 48 h) (%)	31 (4.1)	30 (3.5)	23 (2.8)	35 (5.3)	39 (4.3)	46 (9.9)
In-hospital incident dialysis patients (per state population × 10^{-6}) (%)	149 (74)	157 (78)	168 (84)	147 (73)	160 (80)	149 (74)

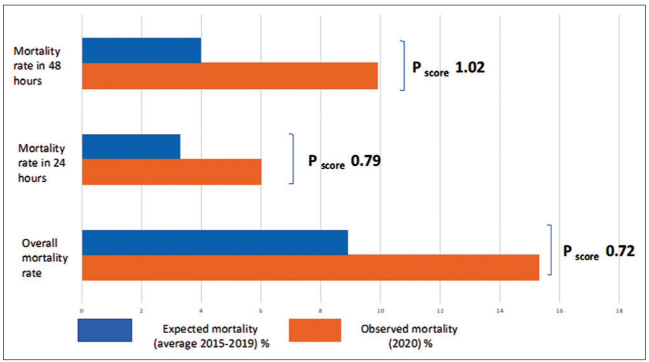

Figure 1: Excess mortality p-scores for 2020 regarding average mortality for 2015–2019.

Figure 2 compares the monthly in-hospital death rates for non-elective admissions in 2020 (red line), against each of the five preceding years. Soon after the detection of the first COVID-19 community case (26th of February), death rates increased rapidly. In <4 weeks, they almost doubled from 14.8% in March to 28.3% in April. In the following 2 months, the death rates were higher than 20%, exceeding the average rates in the same months in the previous 5 years (Table 2).

Table 2: Increasing monthly mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%)	January	February	March	April	May	June
2015	9.6	9.1	4.1	8.0	8.8	8.1
2016	11.4	9.8	8.1	8.4	7.2	6.9
2017	11.0	3.0	6.5	5.7	7.6	11.1
2018	5.8	12.5	13.7	14.0	8.4	10.6
2019	7.4	10.6	12.2	6.6	15.0	7.2
Mean ± STDV (2015–2019)	9.0 ± 2.4	9.0 ± 3.6	8.9 ± 4.0	8.5 ± 3.2	9.4 ± 3.2	8.8 ± 2.0
2020	8.7	11.4	14.5	28.3	20.0	21.9

Figure 3 compares the monthly in-hospital first 48 h death rates for non-elective admissions in 2020 (red line) against each of the five preceding years. Death rates increased rapidly and achieved the pick in April, followed by numbers much higher than average ones in the preceding years (Table 3).

Table 3: Increasing monthly first 48 h mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%) first 48 h	January	February	March	April	May	June
2015	5.6	3.3	3.3	2.7	6.9	3.5
2016	7.1	3.5	3.4	3.9	0.8	2.1
2017	4.9	0.6	3.9	3.4	2.3	1.7
2018	3.8	5.8	6.9	8.6	3.2	3.8
2019	3.9	3.5	5.2	2.9	7.1	3.2
Mean ± STDV (2015–2019)	5.1 ± 1.21	3.3 ± 1.64	4.5 ± 1.37	4.3 ± 2.19	4.0 ± 2.52	2.8 ± 0.81
2020	4.7	6.8	9.6	19.6	10.9	12.5

Figure 4 compares the monthly in-hospital first 24 h death rates for non-elective admissions in 2020 (red line) against each of the five preceding years. The curve climbed above 6% from February and maintaining Plato in the following months above 8%. Death rates were much higher than average ones in the preceding years (Table 4).

Table 4: Increasing monthly first 24 h mortality rates in 2020 versus average death rates in 2015–2019

Mortality (%) first 24 h	January	February	March	April	May	June
2015	4.0	4.1	3.3	1.8	5.8	2.9
2016	6.4	3.5	2.7	2.6	0.0	1.4
2017	4.3	4.2	1.3	3.4	2.3	3.4
2018	3.0	5.3	6.0	6.0	3.0	3.2
2019	3.1	3.0	5.0	2.7	5.7	3.4
Mean ± STDV (2015–2019)	4.2 ± 1.24	4.0 ± 0.78	3.6 ± 1.67	3.3 ± 1.45	3.4 ± 2.19	2.9 ± 0.76
2020	1.6	6.8	7.2	8.7	9.1	7.8

The number of hospital admissions in the first 2 months of 2020 was above 100 (Figure 5). A significant decline was observed from March, exceeding the lowest number in April (45). On the opposite, the RT-PCR testing for SARS-CoV-2 detection began at the beginning of April and raised along with the number of admitted patients.

From April 2020, the testing rate of the hospitalized patients was above 30% (Table 5). The patients that died we also partly tested in April 38%, May 27%, and 57% in June.

Table 5: Admissions, rates of RT-PCR tests for SARS-CoV-2 in all and the dead patients

2020	January	February	March	April	May	June
All admissions	134	104	91	45	55	64
All SARS-CoV-2 RT-PCR tests (rate)	0	0	0	15 (33%)	17 (31%)	25 (39%)
All deaths	11	10	12	13	11	14
SARS-CoV-2 RT-PCR tests in dead patients (rate)				5 (38%)	3 (27%)	8 (57%)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RT-PCR: Reverse transcriptase-polymerase chain reaction

In the first 6 months of 2020, there were 28 patients that died in the first 24 h of the hospital stay and only 2 (7.1%) were being tested for SARS-CoV-2 (Figure 6). Out of 46 patients that have died in the first 48 h of the hospital stay, 10 (21.7%) have been tested, and only one patient was positive. Other four positive patients were transferred to dedicated COVID-19 hospitals.

Discussion

During the COVID-19 pandemic, excess mortality was observed in many European countries [14] and reported in recent publications from all over the world [15], varying by states and regions. The analyzed data on excess mortality (the numbers of deaths over

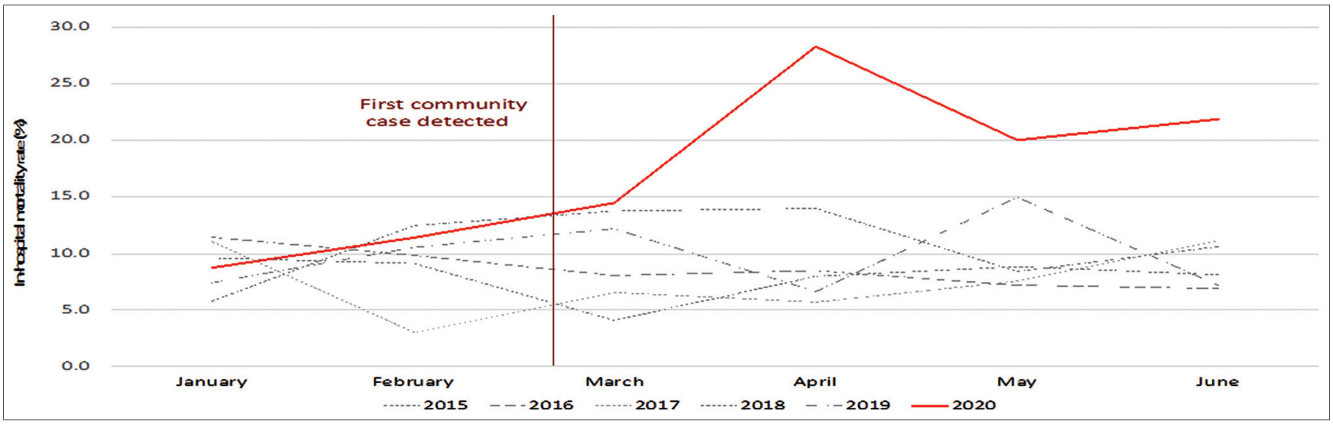

Figure 2: Monthly death rates in 2020 compared to the five preceding years for non-elective admissions

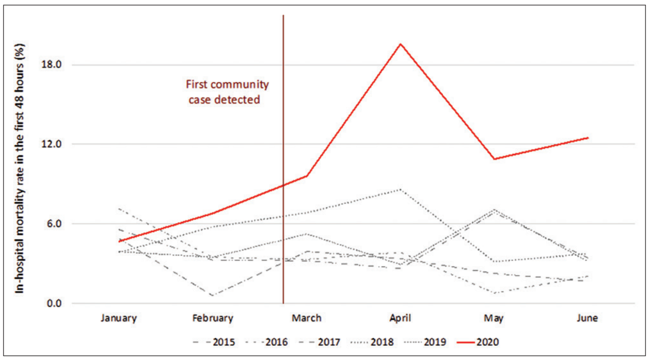

Figure 3: Monthly death rates in the first 48 h 2020 compared to the five preceding years for non-elective admissions

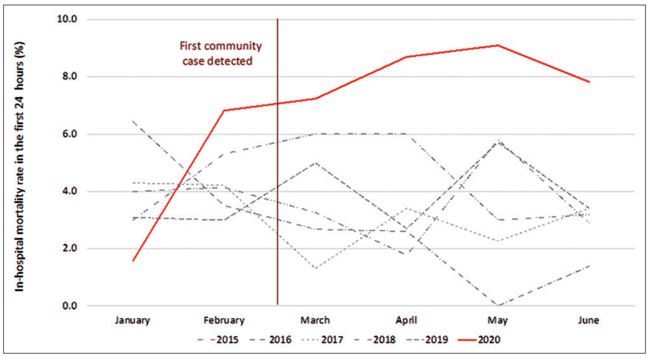

Figure 4: Monthly death rates in the first 24 h 2020 compared to the five preceding years for non-elective admissions

and above the historical average) across the globe have shown that numbers of deaths in some countries were more than 50% higher than usual [14]. In many countries, these excess deaths exceed reported numbers of COVID-19 deaths by large margins. In New York State, all-cause mortality rose from 2- to 7-fold above baseline at the peak of the pandemic, whereas 26% were unattributed to COVID-19 [16].

In this study, we have compared the in-hospital mortality rates in one nephrology clinic from the previous 5 years to the current year of 2020. The excess mortality exceeded 70%, resulting from sudden divergence from the excepted pattern, including decline in patients' hospitalizations and higher fatalities. This

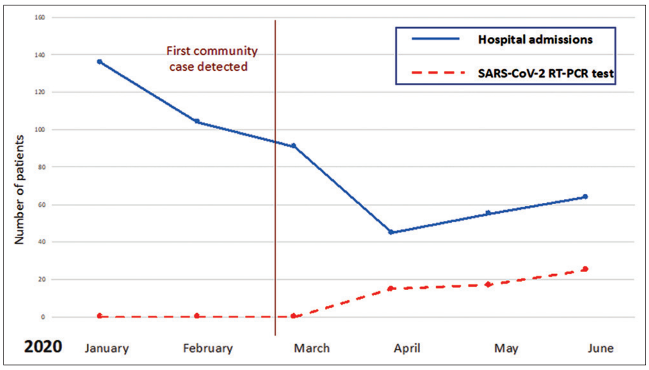

Figure 5: Hospital admissions and polymerase chain reaction testing for severe acute respiratory syndrome coronavirus-2 detection in hospitalized patients in 2020

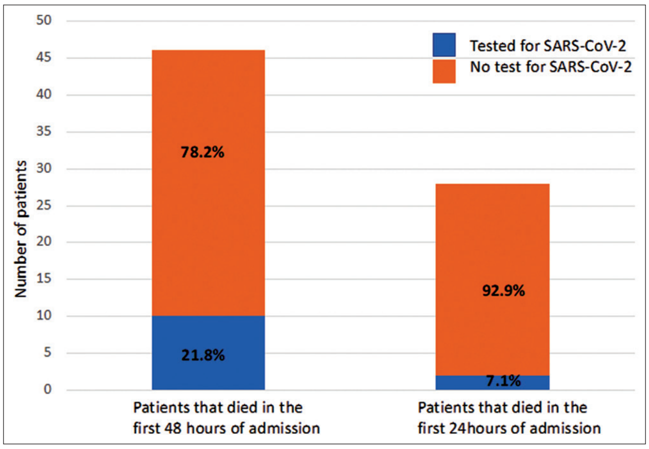

Figure 6: Proportions of performed severe acute respiratory syndrome coronavirus-2 tests regarding the time of the death

high mortality might be explained by several factors: Stress, avoidance of the health care system considering potential COVID-19 infection, delayed or unrecognized symptoms of kidney function deterioration with late admissions, and diagnostic uncertainties. We also have to account for the health care organizing changes.

Crises are generating stress to the general and populations with chronic diseases. During COVID-19 pandemic, WHO addressed the issue on global mental health and psychosocial considerations [17]. Stress implications for CKD initiation, progression, complications, and premature mortality are also well known [18]. Global lockdown, fear, lack of family connections, and low educational level of symptoms recognition might have caused delayed hospitalizations of patients with severe conditions. Our previous 5 years mortality study showed that more than 40% of dead patients from CKD were not aware of the disease or referred to a nephrologist ever [4]. Despite all the provided information about COVID-19, more than one-third of deaths from COVID-19 infection in our country occurred in the first 1–5 days after admission at hospitals and this high mortality was most probably due to the late referral or previous patients' reluctance for timely hospitalization [19]. However, patients educated and followed for CKD at our clinic, and those initiated on dialysis were timely referred even during COVID-19 lockdowns. This can be observed from the stable number of patients starting dialysis in the previous 5 years and during 2020. At best of our knowledge, there is no other publication on specific nephrology patients' mortality during this crisis to compare our data with and that is one limitation of our study. On the other hand, a dramatic hospital admission reduction for patients with acute myocardial infarctions has been witnessed in Asia [20], Europe [21], [22] and North America [23], associated with a parallel increase in hospital fatality and complication rates [24]. Those studies explained this phenomenon also by patients' related factors as stress, health care system reorganizations, and unrecognized COVID-19 deaths, referring to the need of education as prevention [25].

The highest pick of mortality at our clinic was observed in April, which is in line with mortality picks in nearly all European countries suffering from the outbreak in March 2020 and global lockdown [14]. Furthermore, 64% of all deaths occurred in only 48 h after admission. Considering the limited time before death, the number of first and repeated tests performed and sensitivity of the tests, there have might been a number of deaths caused by the virus that were not counted. One reason might be the detectability and clearance of the viral RNA [26]: Patients with mild symptomatology do not refer to the doctor in a timely fashion for being tested; also, the virus may be detectable in the upper respiratory tract 1–3 days before the onset of symptoms with the highest concentration around the time of symptom onset, and clearance of the virus for several days in some patients, while in other patients it can be detected for several weeks even months. As a limitation of our study, many patients were not tested, and in those that were tested, only one test was performed because of death. According to literature [26], [27] and the "National guidance for interpretation of the COVID-19 test results" published by the IPH since March 2020 [28], subsequent testing is recommended for firstly negative patients as well as considering other types of samples, not only from the upper respiratory tract. Recent systematic reviews of the accuracy of SARS-CoV-2 tests reported false-negative rates of between 2% and 29% (equating to sensitivity of 71–98%), based on negative RT-PCR tests which were positive on repeat testing [29], [30]. Furthermore, accuracy of viral RNA swabs in clinical practice varied depending on the site and quality of sampling [31], especially in patients with intestinal form of COVID-19 infection [32], where the respiratory infection was not confirmed by nasal swabs detection. Considering all these findings, we speculate that there might be some unrecognized or unconfirmed probable COVID deaths [33] among our patients, which implies a need of further analysis. If some of the patients were recognized with COVID-19 infection, part of them might be transferred to dedicated COVID-19 clinics, and the mortality rate would be lower, which also limits our study.

Nevertheless, the importance of our study is in the pragmatic approach by seeing the real striking data on the higher mortality rates during the pandemic from the registry data which elucidates the need of more knowledge about the novel virus and global pandemic circumstances.

Conclusion

In this study, we have provided clear evidence of high excess mortality at our nephrology clinic during the 1st months of the COVID-19 pandemic. Severely ill patients mostly died in the early 48 h of admission, limiting the time for diagnostic and therapeutic options. The delayed referral of patients due to the patient and health care system-related factors might partially explain the excess mortality during pandemic crises. Education of patients in recognizing symptoms of life-threatening conditions and seeks appropriate care on time remains crucial during the COVID-19 pandemic. Further analysis is needed to estimate unrecognized probable COVID-19 deaths.

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Acute Ischemic Stroke as Complication in COVID-19 with Acute Respiratory Distress Syndrome in Intensive Care Unit: A Review

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Abstract

Coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has broad spectrum of manifestation ranging from asymptomatic cases to multi-organs failures. Cerebrovascular disease COVID-19 patients are still a big issue among neurologist. Neurologic manifestations are shown to be the first or late presentation in patients with SARS-CoV-2 infection. Ischemic stroke had happened majority than hemorrhage stroke in patients hospitalized with severe COVID-19 and comorbid such as hypertension, diabetes mellitus, or cardiovascular disease. Acute respiratory distress syndrome is predictable complication of COVID-19 that will ended with prolonged hospitalization and comprehensive management in intensive care unit (ICU). Anticoagulant is believed to have proven advantage to prevent this thrombogenesis. Patients with acute ischemic stroke as COVID-19 have poorer prognosis. Managing patients with ischemic stroke within the ICU are challenging due to prior use of anticoagulant as preventive of thrombosis that increase the risk of intracranial hemorrhage.

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) is a devastating pandemic that being a significant threat to international health with more than 27 million confirmed cases and more than 800 confirmed death until September 2020 [1]. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a beta-coronavirus that associated with SARS and Middle East respiratory syndrome [2]. SARS-CoV-2 is an enveloped, positive sense, single stranded RNA virus and discovered in human, bats, and other wild animals [2]. In late December 2019, the virus was related to clusters of patients with pneumonia linked to seafood and wholesale market in Wuhan, Hubei Province, China [2]. The clinical spectrum of the disease forms asymptomatic infection, mild symptoms (fever, dry cough, and fatigue) to severe complications that ended with mortality [3], [4], [5]. Multiple organ failures are severe complications of COVID-19 includes acute respiratory distress syndrome (ARDS), arrhythmia, and acute heart injury, which is need transferred to intensive care unit (ICU) [3], [4], [6].

COVID-19 patients whom hospitalized with respiratory manifestation with appearance of viral pneumonia at first admission, they may develop to ARDS about 8 days from the first symptoms [6], [7]. Shortness of breath or dyspnea is the sign of lacking of oxygen, so the need of high-flow oxygen therapy or invasive ventilation in ICU are needed for ARDS patient with COVID-19 [6], [8]. The lung involvement shows in chest computed tomography (CT) scan showing ground-glass opacity with shadows of consolidation or cord like in multiple lung lobes [3], [4], [5]. Huang *et al*. [3] reported that consolidated bilateral multiple and subsegmental areas of the lungs are typical findings on the chest CT scan of ICU patients within first admission. Patients with refractory hypoxemia and ARDS needed high flow oxygen theraphy such as invasive ventilation or even extracorporeal membrane oxygenation [6].

Besides the respiratory symptoms, the neurological symptoms also happened in patients with COVID-19 [9]. The symptoms are headache, hyposmia, hypogeusia, dizziness, altered consciousness, seizure, encephalopathy, neuromuscular injury, or cerebrovascular disease [9]. Thrombosis in the lung, limbs, heart, and brain has been reported in patients with COVID-19 [10], [11], [12], [13]. Both microvascular and large vessel thrombosis occur in severe COVID-19 with the manifestation of venous thromboembolism, cardiovascular infarction, and pulmonary embolism [14]. Ischemic stroke is a potential condition related by the

COVID-19 [15], [16]. The identification of ischemic stroke is related with acute ARDS [17]. Patients hospitalized with severe COVID-19 in ICU show the sign of coagulopathy with serious consequences in mortality and morbidity [18]. Patients with stroke associated with COVID-19 have more severe outcomes and higher mortality than non-COVID-19 ischemic stroke [19]. We will discuss the mechanism COVID-19 with ischemic stroke in hospitalized patients with ARDS in ICU.

COVID-19 Patients with ARDS in ICU

The most common symptoms appeared in patients with COVID-19 are fever, fatigue, dry cough, myalgia, and dyspnea [3], [6], [20], [21]. Patients with older age have more comorbidities such as hypertension, diabetes, cardiovascular disease, and cerebrovascular disease so they are profound to develop severe manifestation and organ damage [6], [20], [22], [23]. Wang *et al*. [6] reported that 26% patients with COVID-19 were admitted and transferred to the ICU due to organ dysfunction development including ARDS, arrhythmia, acute cardiac injury, and shock. ICU-patients with COVID-19 and ARDS received high-flow oxygen therapy, non-invasive ventilation, and invasive ventilation to support the high oxygen demand [6].

SARS-CoV-2 infects mostly in respiratory and damages directly or indirectly the lungs by abrupt systemic inflammatory response [24]. The main cause of COVID-19 cause ARDS is damage of the alveolar epithelial cells and endothelial cells of blood vessels in all organs [24]. Chen *et al*. [22] showed that 17% patients with COVID-19 and ARDS had symptoms of dyspnea and hypoxemia. The mismatch of oxygen ventilation-perfusion or shunts intrapulmonary results a hypoxic respiratory failure condition [24]. Modalities to diagnose COVID-19 ARDS must include the Berlin 2012 ARDS diagnostic criteria of acute hypoxemic respiratory failure; presentation of worsening respiratory symptoms within 1 week; bilateral airspace disease on chest X-ray, CT, or ultrasound that is not fully explained by effusions, lobar or lung collapse, or nodules; and cardiac failure is not the primary cause of acute hypoxemic respiratory failure [25], [26]. Parameters for determine the patients with clinical condition leads to ARDS are respiratory rate and SpO_2 [25]. If the patients fits to any one of the following conditions, respiratory rate ≥30 breaths/min; $SpO_2 \leq 92\%$; and $PaO_2/FiO_2 \leq 300$ mmHg; they may have severe COVID-19 and require further evaluations [25]. These patients had worsening from the first common symptoms to dyspnea and ARDS in 8–12 days, then they need oxygen therapy afterward [6], [23], [24].

Abnormalities of laboratory results such as neutrophilia, lymphocytopenia, elevated end-organ indices (aspartate serum transaminase, urea, lactate dehydrogenase) elevated inflammation indices (high sensitivity C-reactive protein and serum ferritin), and elevated coagulation function-related indicators (pro-thrombin time [PT] and D-dimer) may leads to higher risk of ARDS to develop [23]. Spiezia *et al*. [27] reported the increased of hypercoagulable state in COVID-19 patients with respiratory failure than consumptive coagulopathy (disseminated intravascular coagulation [DIC]). Infection increases the level of fibrinogen and fibrin polymerization, then promote fibrin formation and deposition of D-dimer [28]. DIC is found in patient with sepsis and organ dysfunction as a result of activated monocytes and endothelial cells to the point release of cytokines [28], [29].

Severe COVID-19 Relations with Acute Ischemic Stroke

The spread of COVID-19 worldwide with various clinical symptoms related to the systemic infection of the SARS-CoV-2 virus within the body may also impact the central nervous system besides the respiratory system. With the evidence of ischemic stroke in patients in New York, United states, during hospitalization with COVID-19, about 0.9% patients had ischemic stroke [30]. Qin *et al*. report the cohort study of COVID-19 patients with a history of stroke in China is 2.7% [31]. The median age patients with stroke and COVID-19 are 63 years with hypertension and cardiovascular diseases as concomitant [31]. Elderly people have more comorbidities so they are more likely to be infected and to develop more severe symptoms in COVID-19 [31]. Yaghi *et al*. [30] reported from the 32 patients with ischemic stroke with COVID-19, 56.2% developed the ischemic stroke during hospitalization for COVID-19 respiratory symptoms. The patients with history of stroke and COVID-19 have higher risk of poor outcome due to increased risk for ARDS with the need of mechanical ventilation support and intensive care admission [31].

Hypercoagulable state in patients with COVID-19 shows abnormally laboratory findings of high D-dimer concentrations, prolonged PT, thrombocytopenia, and elevation fibrinogen level [32]. Those are final product of unregulated hyperinflammation immune response to SARS-CoV-2 [3], [33]. The pro-inflammatory cytokines in serum such as interleukin (IL) 1β, IL12, interferon (IFN) γ, IFN-γ-induced protein 10, and monocyte chemoattractant protein-1 that leads the activation of T-helper (Th) 1 cell response are increased [3]. The Th2 cytokines (IL4 and IL10) increase by the initiation of SARS-CoV-2 that suppresses inflammation [3]. As response to the infection, the excessive inflammation often ended in impairment to down regulate the activated macrophages and lymphocytes. This condition called hemophagocytic lymphohistiocytosis (HLH)-like syndrome [33]. COVID-19 may suppress the CD4+ T cell IFN-γ production by secondary HLH [33].

The role of platelets in viral clearance is by interacting with leucocytes to trigger recruitment and tissue infiltration [33]. The critically ill patients have thrombocytopenia and multi-organ failure related to this mechanism. The strong stimulation of neutrophils and other monocytes and eosinophils, release extracellular traps (ETs) in a process known NETosis [33]. Tissue neutrophil ETS (NETs) cause activation of platelet that induces platelet aggregation through toll-like receptors on platelets and other cells [33]. Platelet aggregation happened after the activation of platelet signaling through major adhesion receptor, integrin αIIbβ3 [33]. Factor XII (FXII) is activated into XIIa by the endogenous activator (nucleic acids RNA/DNA, NETs, polyphosphate, and heparin) then activates the intrinsic coagulation pathways [34]. Thrombin activation and fibrin generation is the last product after the activation of FXI into the FXIa in intrinsic pathway [34].

SARS-CoV-2 infects the host using the angiotensin converting enzyme-2 receptor as portal of entry, which these receptors are expressed in several organs such as lungs, heart, kidney, and intestine [35]. The receptor also expressed in endothelial surfaces that viral invasion of the vascular endothelium triggers initiation of thrombotic and inflammatory cascades leading into internal organ injury [34]. The viral inclusion in the endothelial cells is associate with accumulation of inflammatory cells, then results in apoptotic bodies in the related organ [35]. The induction of endotheliitis as a result of SARS-CoV-2 infection is triggering the thrombotic and inflammatory cascades that lead to internal organ injury [35]. This microcirculatory dysfunction is happened as result to endothelial dysfunction in more vasoconstriction state with ischemic organ, inflammation and tissue edema, and procoagulant state [35]. Von Willebrand Factor (VWF) is active after endothelial injury that impaired the vascular integrity and aggregates platelets [33]. Ultra-large VWF fibers are formed after inflammation process and became immobilized within endothelial cells that very adhesive under shear conditions [33]. The thrombosis may involve in all vascular beds including the microvascular circulation and large vessel after the inflammation and the coagulation process [33], [34]. White thrombus and red thrombus which has more platelets and red blood cells trapped in the fibrin strands as a result of high shear stress [36]. The relationship between hyperinflammation and hypercoagulation state in COVID-19 is shown in Figure 1.

Treatment Approach of Acute Ischemic Stroke in ICU with COVID-19

Recommendation from guidelines for early management of patients with acute ischemic stroke in 2019 [37], the early management for patients with mild stroke but disabling symptoms can be treated with recombinant-tissue plasminogen activator (r-TPA), also known as alteplase, within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. The use other fibrinolytic agents other than alteplase or tenecteplase is not recommended because of no shown benefit [37]. Bleeding risk should be considered within the given r-TPA by checking any abnormal platelet component [37]. Clearance of r-TPA is in the liver, then hepatic dysfunction in will result in high concentration of r-TPA in the serum and increase the risk of intra-cerebral hemorrhage [38]. Increased prothrombin time (PT), international normalized ratio (INR), and thrombocytopenia are associated with this coagulopathy due to liver dysfunction [38]. The dilemma in this situation related to patients in ICU with COVID-19 is the use of anticoagulant as massive thrombosis prevention [27]. The current guidelines to use r-TPA in patients with the history of warfarin use are may be considered on a case-by-case basis as long the INR $\leq$ 1.7 and/or PT < 15 s [37]. The use of low-molecular weight heparin in previous 24 h as prophylactic or treatment doses is harmful for r-TPA procedure [37].

Ntaios *et al*. [19] wrote about the outcome patients in COVID-19 ischemic stroke has higher mortality than non-COVID-19 ischemic strokes. In his report “characteristics and outcomes in patients with COVID-19 and acute ischemic stroke,” about 19.7% patients with alteplase administration had complication hemorrhagic transformation of the infarct and malignant brain edema [19]. Potential explanation in this complication is related to vasculopathy induced by viral infection [19]. Otherwise, prognosis after r-TPA administration in acute ischemic stroke in COVID-19 and ARDS in ICU has been reported by Co *et al*. [39] by the improvement of National Institutes of Health Stroke Scale (NIHSS). The use of antithrombotic after 24 h of r-TPA administration and fluid management is the key in successful treatment in this situation [39].

Mechanical thrombectomy can be a treatment choice with suspicion of large vessel occlusion from non-invasive vessel imaging evaluation such as CT angiography (CTA) or magnetic resonance angiography [37]. This procedure is suitable in patients with internal carotid artery or proximal middle cerebral artery (identified by CTA) occlusion, NIHSS score $\geq$ 6, Alberta Stroke Program Early CT Score $\geq$ 6, no extensive ischemic changes in head CT scan, and treatment can be initiated within 6 h of symptoms onset [37]. The challenges within COVID-19 pandemic are the patient cannot be transferred rapidly to angiographic suite form

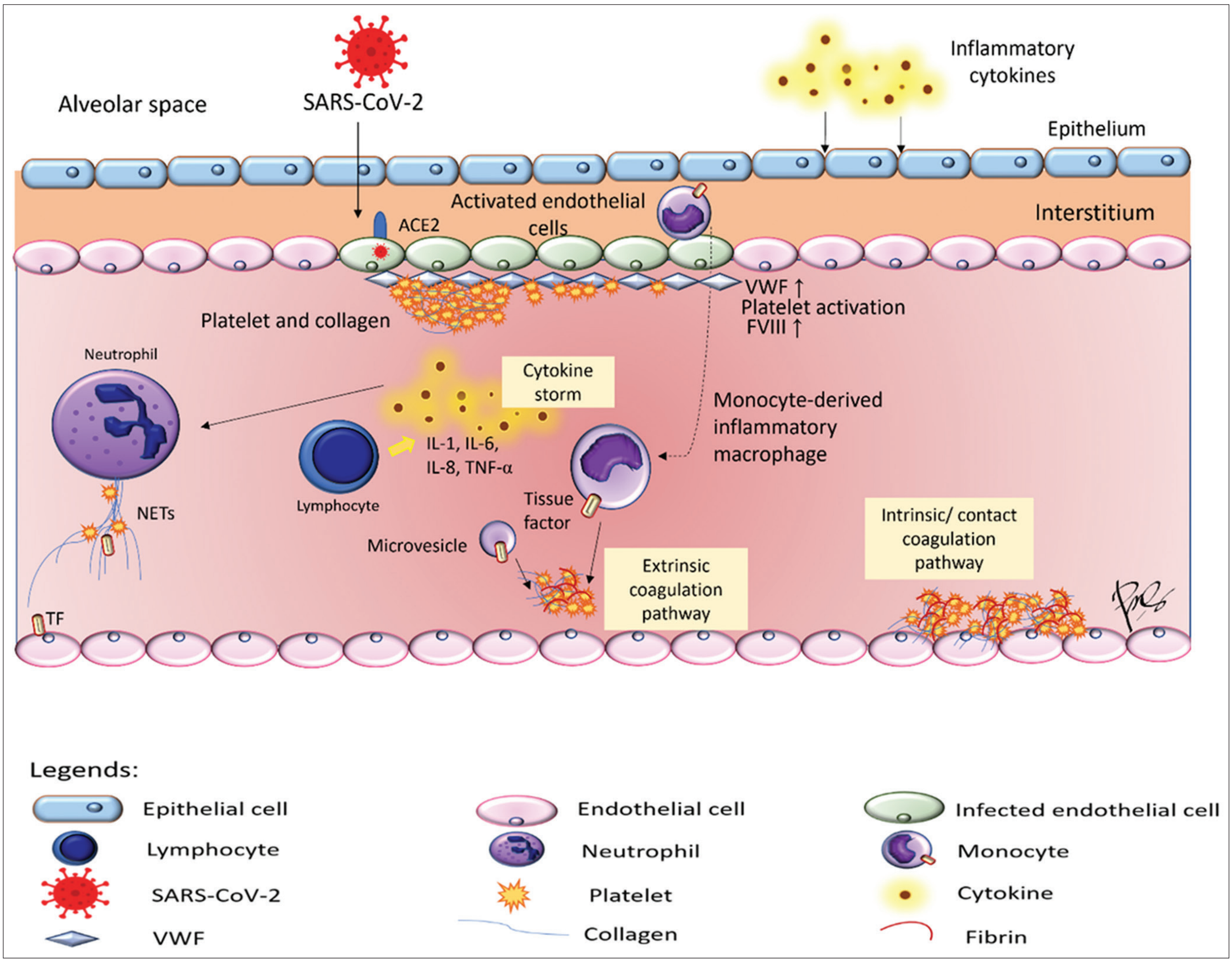

Figure 1: Pathophysiology of hyperinflammation and hypercoagulable state in coronavirus disease-2019

emergency department or from outside hospital due to added requirements [38].

Minor ischemic stroke or transient ischemic attack treatment should be immediate administration of aspirin or a combination of aspirin and clopidogrel [37]. The initial aspirin dose is 160–300 mg with flexible administration through oral (swallow), nasogastric tube, or rectal [37]. The safety and usefulness of urgent anticoagulant are not well established and not recommended to preventing early recurrent stroke of patients with AIS [37]. The report in anticoagulant in acute ischemic stroke with COVID-19 is still limited. Dogra *et al*. reports hemorrhage stroke happened by the using of anticoagulant for prophylaxis or therapeutic dose in COVID-19 [40]. The use of anticoagulant therapy should be considered due to risk of intra cranial hemorrhage [40]. Future studies should compare the outcomes in patients with anticoagulant or antiplatelet in AIS with COVID-19.

Corticosteroid is commonly used in treating patients with severe COVID-19 due to their mechanism by inhibiting effect on inflammatory factors [41]. Fadel *et al*. [42] reported about the efficacy of using early corticosteroids to prevent progression of the disease and improve outcomes. ARDS patients that received corticosteroid had shortened ventilation times and increase the number of ventilator-free days. Specific use of dexamethasone in patients with COVID-19 may reduce the days of hospitalization than those in the usual care group [43]. Incidence of death in COVID-19 patients receiving invasive mechanical ventilation and receiving oxygen without invasive mechanical ventilation is lower in the usual care group in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial [43]. Treatment for the patient COVID-19 with respiratory support that receives dexamethasone at a dose of 6 mg once daily for up 10 days may reduce the 28-day mortality [43].

Availability of Data and Material

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

All the authors contributed equally in this study and during preparation of this manuscript.

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Tele Education in Diabetic Patients during Coronavirus Outbreak

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Abstract

The number of cases of infection to coronavirus disease (COVID)-19, human casualties and economic losses are increasing, and one of the high-risk groups in which the risk of infection and death is high is diabetics. People with diabetes experience severe symptoms and complications if they are infected by COVID-19. One way to control and prevent the spread of the coronavirus is to stay home, avoid daily physical interactions, and quarantine at home. Due to the high prevalence of diabetes and the importance of long-term follow-up, Tele education in diabetic patients is one of the methods that provide care using communication means. As the quality of information received by diabetic patients improves, their awareness of treatment goals and, consequently, their acceptance of treatment methods will increase, which in turn will lead to greater effectiveness and better treatment outcomes. Finally, Tele education reduces contact between diabetics and physicians, therapists, and health care providers, thereby reducing the risk of disease.

Statement of the Problem

World Health Organization announced coronavirus disease (COVID)-19 as an epidemic, a new illness which is different from other viruses such as severe acute respiratory syndrome, Middle East Respiratory Syndrome, and influenza [1]. The number of cases of infection to COVID-19 and its human casualties are increasing worldwide; along with the economic losses resulting from the illness is much higher, estimated to go beyond the capacity of the developing and developed countries in coming months [2]. One of the high-risk groups in which the risk of infection and death is high is diabetics, in which the mortality rate out of COVID-19 is reported to be %9/2 among diabetics while it is %1/4 for normal healthy people [3]. People with diabetes experience severe symptoms and complications if they are infected by COVID-19. If the diabetes is controlled properly, the risk of experiencing acute symptoms of COVID-1 infection would be the same as common people, while if it is not controlled along with fluctuation in blood sugar, the person would encounter the complications and difficulties resulting from diabetes. As other infectious illnesses, heart disease as well as other disease together with the diabetes increases the risk of illness severity of COVID-19. Infectious diseases also cause the increase in internal inflation, because the ability of the body is reduced in fighting against infection. The reason of this complication is the high rate of blood sugar leading to incidence of more severe problems and complications [4]. The need to self-care and self-control to prevent and control the spread of the coronavirus is of vital importance. One way to control and prevent the spread of the coronavirus is to stay home, avoid daily physical interactions, and quarantine at home [1]. The crisis caused by this virus affects the patients' education system of all countries including Iran, leading to shut down of attendance courses of the patients [5]. In addition to education programs, it seems necessary to protect patients suffering from diabetes who have self-care problems with the administration of the follow-up program with the purpose of promoting the awareness, as well as improving the performance and attitudes. Although it is possible to follow the treatment through regular in-person attendance of the patient or visiting at home, there should be other low-cost and applicable methods for a large number of the patients due to the highly growing spread of the diabetes and the importance of its long-term follow-up. Today, Tele education makes the health-care provider able to evaluate, educate, collect data, intervene, and protect the patient's family [6]. Among the media used in Tele education, phone is regarded as the highly accessible tool for the majority of people.

Tele Education

One of the implications of tele medical services is tele education. It is one of the ways that provides health care using some media as videos, Internet, and phone. Throughout this technique, health care providers communicate with the patients or the medical centers using camera, video conferencing, phone and videos, attempting to educate and advise [7]. This technology leads to quick access of the individual to the health advisory services, reduction in cost, and accessibility to the most appropriate specialized skills, as well as an inclusive improvement in the quality of life. In addition, it makes people to attend virtually, instead of in person attendance over the long distance, so it would pass a great mass of information in short time from far distance, therefore, reduced the expenses [8].

Tele Education for the Diabetics

Education is one of the most important aspects of health service providing. Patients are highly interested in receiving information on their hearth status. When the quality of the received information by the diabetic patient increases, his/her awareness on the therapeutic goals, and consecutively, the acceptance of the treatment intervention would increase, leading to more effectiveness and better therapeutic results. Reaching to higher level of patient satisfaction is another achievement of patient education. COVID-19 pandemic not only put the health care providers under great pressure but also strongly changed the way of patients' education and their access to the hearth care services. COVID-19 pandemic highlights the importance of tele-education to prevent the infection caused by direct contact. Without any vaccine or effective treatment, the only satisfactory substitutes for in-person hearth care services are quarantine and observance of social distances. Tele education is an attractive, efficient, and affordable option in fighting against coronavirus for patients suffering from the diabetes.

Tele education for the diabetics in corona outbreak can de classified into two groups: (1) Diabetes self-care and (2) COVID-19 self-care.

Some instances of diabetes self-care tele education are education on consuming low volume meals more times, observing the program of health dish, consuming foods with low glycemic index such as vegetables and whole grains, drinking 6–8 glasses of liquids daily, using two to three units of fruits daily, avoiding too much use of fried and fast foods and sweets, consuming dairies, especially probiotics and enriched ones with Vitamin D daily, using low-fat proteins such as chicken, fish, meat, beans, and eggs. Dietary carbohydrate restriction, because it reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to the reduction or elimination of medication. On the other hand, since obesity is a highly prevalent comorbidity in severe cases of COVID-19, a decrease in body mass index has a significant effect on reducing the risk of developing COVID-19 disease or reducing the severity of symptoms in case of infection. All documents reported that there are currently no known supplements to prevent COVID-19 so we emphasize that there is no need to avoid different supplements [9].

It is recommended that diabetic patients have a hemoglobin A1C (HbA1C) test, 3–4 times a year and then consult with their doctor about the treatment process. HbA1C <7% indicates diabetes control and the values above 8% indicate that the patient should reconsider the treatment of diabetes. Therefore, the goal of successful diabetes treatment is to reduce the HbA1C level to <7% [10].

Another way to control your blood sugar is to exercise. Exercise for diabetics will cause glucose and glycogen to be burned and consumed within the muscles. During and after exercise, blood sugar enters the muscles and glucose levels are regulated in the body. In this way, exercise helps diabetics treat and control their diabetes [9]. Thus, doing light aerobics exercises weekly and keeping the optimal weight, taking the diabetes medicines regularly, doing blood sugar checkup test at home, keeping the optimal blood sugar, asking one of young and healthy family members' help for medicine prescriptions, home visiting and tele home care if possible, following the instructions of the doctor, regular contact with the doctor, regular examination of the health status of the feet, avoiding smoking, and controlling stress, anxiety, and tension.

Some instances of tele education on COVID-19 self-care are as follows: education on avoiding to contact with people suffering from symptoms similar to coronavirus and influenza, wearing masks while going out, avoiding to kiss or shake hand, keeping the social distance (at least one meter and a half), washing hands regularly with soap for 20 s, using alcohol disinfectants for hands out of home, avoiding to touch the public utilities and surfaces in crowded places and public means of transportation, avoiding to touch eyes and face, especially out of home, avoiding big parties and mass gatherings, and staying at home as much as possible.

Regarding the above-mentioned tips as well as the present condition of the country encountering COVID-19 illness, implementing Tele education for diabetic patients would be significantly beneficial in following ways:

1. Reducing treatment expenses with a decrease in symptoms and preventing sever complications
2. Preventing the consequences and severity of the illness
3. Improving the quality of the care and enabling the patient and family in their self-care
4. Reducing the time of hospitalization and the rate of re-hospitalization of the patient
5. Increasing the patient’s observance of the treatment procedure and needed follow-ups
6. Assisting the patient and his/her family in gaining independence and self-sufficiency (self-management and self-care)
7. Reducing stress, anxiety, and mental problems
8. Improving the patients’ quality of living
9. Increasing the satisfaction of the patient and his/her family
10. Reducing the unnecessary contact of the diabetic patients with doctors, therapists, and health care providers, leading to the decrease in encountering the illness
11. Improving the awareness level of the diabetic patients of their body and soul health, using the active participation of the patient in his/her own health control.

Conclusion

Tele education can be influential in prevention and control COVID-19 illness. The education which is performed with peace, concentration effortlessly can result in significant learning. Since tele education is done at home, it would be possible for diabetic patients to control their illness with more concentration and peace. Obviously, there are some inhibiting factors that prevent the diabetic patients from benefiting from this type of education properly. However, tele education can be influential for the diabetic patients more likely to encounter COVID-19, because of being attractive, efficient, and influential.

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Complications of Coronavirus Disease-19 in a Hospitalized Patient: A Case Report

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Abstract

BACKGROUND: Coronavirus (CoV) disease (COVID)-19 infection is a major public health issue worldwide with no specific therapy or vaccine.

CASE REPORT: COVID-19-positive patient was hospitalized due to a dry irritating cough that has persisted for 3 days. The polymerase chain reaction test to severe acute respiratory syndrome-CoV-2 was positive. Computed tomography (CT) scan of the lungs showed massive bilateral consolidation. The patient was set to oxygen support (6 L/min). Two hours after referring the patient's condition worsened with shortness of breath, suffocation, wheezing, and decreased saturation (77%). The patient was given mechanical support with continuous positive airway pressure mask. Therapy included azithromycin 500 mg and ceftriaxone 2 g. On the 3rd day of hospitalization, there was a sharp deterioration of the condition and a decrease in saturation (40%). The patient was intubated and immediately placed on intermittent positive pressure ventilation. Azithromycin was now combined with meropenem 3 × 1 g. The next morning patient's condition further worsened with decrease in saturation and heart rate. The resuscitation was unsuccessful.

CONCLUSION: COVID-19 is primary a respiratory infection, but the virus also affects other organs with poor outcome.

Introduction

The coronavirus (CoV) disease (COVID)-19 infection is a major public health issue worldwide. By September 10, more than 27,700,000 cases were registered worldwide, of which there were over 899,000 deaths. Over 18,000,000 cases have been recovered [1]. In our country, until now, there are more than 15,000 cases, resulting in more than 600 deaths. Over 12,000 cases have been recovered [2].

It all started in December 2019, in Wuhan. No one expected a global pandemic to occur shortly thereafter. On December 31, the World Health Organization (WHO) was informed about a case of pneumonia of unclear etiology in Wuhan. Then, on January 7, 2020, Chinese authorities identified the cause as a new type of COV, which was temporarily labeled as "2019-nCoV." CoVs are a large family of viruses that can cause a wide range of illnesses in humans, from the common cold to the severe illness. The new nCoV had not been identified in humans until February 11, 2020, and it was referred to as "COVID-19 virus" or CoV-2 of severe acute respiratory syndrome-CoV-2 (SARS-CoV-2). In a short time, there was a massive increase in the number of cases in China that was the reason for the declaration of a world pandemic on March 11 by the Director-General of the WHO [3].

In Republic of Macedonia, the first case of the new virus was identified on February 26. It was detected in a patient who returned from Italy which, at that time, was a hotspot of CoV in Europe. The patient was immediately hospitalized at the Clinic for Infectious Diseases and Febrile Conditions.

Those patients who are infected with COVID-19 show different symptomatology. However, the most common symptoms are fever and cough. The temperature can vary up to about 37°C in some patients. Other patients experience high fever, which can be over 40°C. The cough is usually dry, but can also be productive. In the same patient, the symptoms may change during the course of the disease. Other symptoms that may occur are joint and muscle pain, as well as shortness of breath. In some patients, the loss of sense of smell (anosmia) and the loss of sense of taste (dysgeusia) are the most prominent findings. Although the majority of patients are complaining on the most common respiratory symptoms, a significant number of patients also experience gastrointestinal symptoms, such as loss of appetite, nausea, vomiting, and diarrhea. Dizziness and headache can be found in certain cases. There are also patients who are asymptomatic. Most often, however, patients present with a mild clinical course or a moderately severe clinical course. The cause is unknown, but in a certain proportion of patients, there is a severe clinical course that progresses into an acute respiratory distress syndrome. Finally, it is not uncommon situation when the COVID-19 patients experience the following conditions: Septic shock, blood clots, cytokine storm, or multiorgan failure [4], [5], [6].

The incubation period of COVID-19 lasts about 4–5 days. Symptoms are usually clinically manifested from 2 to 7 days after contact with the infected person. It is evident that SARS-CoV-2 is transmitted by direct contact, indirect contact with contaminated objects or surfaces, or close contact with infected people through mouth and nose secretions (saliva, respiratory secretions, or secretion droplets) that are released when an infected person coughs, sneezes, speaks, or sings. People may become infected by touching objects and surfaces with infected droplets on them and then touching their eyes, noses or mouths before cleaning their hands [7]. Therefore, the WHO recommends a social distance of 1 m [8]. On the contrary, the US Centers for Disease Control and Prevention has different opinions and they recommend a social distance of 2 m [9]. According to the recommendations of the WHO, protective masks and frequent hand washing should also be worn [8].

The standard detection of the disease is through polymerase chain reaction (PCR) testing [10]. The test is performed by taking a nasopharyngeal swab. The test results are usually ready in 4 h–2 days. Antibody testing is less commonly used. The reason is that antibodies do not always appear during the period when the patient is infectious. Serological tests are most useful after 3 weeks of the onset of symptoms in patients. Computed tomography (CT) thorax is usually used in COVID-19 patients, but it is not a standard diagnostic method [11].

There is still no specific drug or vaccine to treat the disease. Numerous clinical trials are underway. Antiviral drugs are the most commonly used which are ritonavir and chloroquine or its derivative hydroxychloroquine (HCQ) [12]. HCQ showed significant antiviral activity against COVID-19 within *in vitro* experiments and some small human studies [13], [14], [15], [16], [17], [18]. The bacterial macrolide azithromycin is also used for COVID-19 treatment [18], [19], [20], [21]. It is, therefore, recently analyzed in numerous studies. The mechanisms of action of azithromycin have not yet been studied in detail but it is thought to have great antiviral activity. Furthermore, according to some experiments, the macrolide azithromycin has a significant effect against the inflammatory response that occurs in the lungs [20], [22], [23].

Case Report

Within the actual case report, we are presenting a case of COVID-19-positive patient and the clinical investigations and hospital care in that patient. A 62-year-old male patient has presented for examinations due to a dry irritating cough that has persisted for 3 days. The patient was diabetic and he has been treated with an oral antidiabetic therapy (repaglinide and metformin). Using the detailed medical history, we have obtained information that he has been subfebrile (body temperature of 37.5°C) during the previous day. Due to the current situation with the CoV pandemic, taking into consideration, the diagnostic suspicion that the same patient could be possible infected with SARS-CoV-2, he was referred to the City General Hospital 8th September, Skopje, as a country COVID-19 center.

The patient was checked up at the triage center of the City General Hospital 8th September. The measurement of the body temperature showed 37.1°C and after that the physical examination was performed. The blood pressure was 140/90 mmHg and electrocardiogram at rest revealed sinus rhythm, heart rate 90/min, as well as normal axis and ST segment without any changes in morphology and conductivity. Auscultation of the lungs showed pulmonary vesicular breathing with prolonged expiration and the breathing sounds were almost silent at the basal parts of the lungs, bilaterally. On auscultation, crackles were also detected at the basal pulmonary parts.

Oxygen saturation (SaO_2) (that measures the percentage of hemoglobin binding sites in the bloodstream occupied by oxygen) was 94%. Laboratory tests and CT thorax have been performed. Laboratory analyses showed these findings: White blood cells (WBCs) 4 × 10^9/L, hemoglobin 13.6 g/dL, hematocrit 40.2%, platelets (PLTs) 203 × 10^9/L, percentage of lymphocytes 50%, C-reactive protein (CRP) 20 mg/L, aspartate aminotransferase (AST) 68 U/L, and alanine aminotransferase (ALT) 75 U/L. The PCR test for SARS-CoV-2 was positive.

Figure 1 demonstrates the CT scan of the lungs in our patient and it shows massive bilateral consolidation.

The patient was hospitalized and set to oxygen support with an oxygen mask (6 L/min). Two hours after hospitalization, the patient’s condition worsened with manifestation of a shortness of breath, suffocation, and wheezing, while oxygen saturation dropped to 77%. The patient was put on a mechanical support with a continuous positive airway pressure (CPAP) mask. CPAP is a type of positive airway pressure ventilation. During this type of ventilation, a constant level of pressure that is higher than the atmospheric pressure is continuously applied to the upper airways. In addition, we have performed arterial blood analysis. Gas analyzes revealed the following results: pH

Figure 1: Computed tomography scan of the lungs showing massive bilateral consolidation in the case presented

7.50, $PaCO_2$ 30 mmHg, and PaO_2 110 mmHg, clearly demonstrating respiratory alkalosis.

In this patient, we have started a therapy with azithromycin 500 mg and ceftriaxone 2 g. We have also ordinate fluids, Amp. Urbason 80 mg, Amp. Gastrosol 40 mg, and Amp. Fraxiparine 0.4 mL (sc). The patient was not taking any foods or drinks. Therefore, he has received parenteral nutrition through a central venous catheter (CVC) on the right vena jugularis interna because of the possibility of aspiration due to non-invasive ventilation. Parenteral nutrition solutions have high osmolality. Because of the high osmolality, it requires placement of a CVC. A CVC is a form of venous access that is usually applied in critically ill patients and patients who spend many days in hospital to administer medications and/or fluids. We usually apply these catheters in vena jugularis interna, vena subclavia, or vena femoralis.

On the next day, the condition of the patient was stable. He has been receiving the same therapy. The non-invasive mechanical ventilation was also used. The following vital parameters have been determined: Blood pressure 140/95 mmHg, heart rate 85/min, PaO_2 95%, and diuresis 2300 mL.

On the 3rd day of the hospital care, despite the application of non-invasive ventilation, there was a sharp deterioration of the condition and a decrease of oxygen saturation to 40%. The patient was intubated and immediately put on mechanical ventilation with intermittent positive pressure ventilation (IPPV). IPPV is a type of mechanical ventilation using endotracheal or tracheostomy tube.

Control CT scan and control laboratory analyzes were performed. It has been observed that the consolidation was minimally resolved. The following laboratory results were obtained: WBC 8.8 × 10^9/L, CRP 360 mg/L, hemoglobin 13.6 g/dL, PLT 80 × 10^9/L, urea 20 mmol/L, creatinine 300 mmol/L, Na 140 mEq/L, and K 5.5 mmol/L. The patient had a diuresis of 600 mL. Dialysis has been taken into consideration but it was decided to wait and include diuretics in the therapy. Antibiotic therapy was changed. Azithromycin was still applied, and ceftriaxone was changed with meropenem 3 × 1 g. The next day there was worsening of the condition, a further decrease in saturation, and a decrease in the heart rate. Approached resuscitation was unsuccessful and the patient died.

Discussion

The COVID-19 pandemic is still increasing and every medical specialty is interested in the research aimed at effective diagnosis, treatment, and prevention of the disease and its clinical manifestations. The efforts of world leading medical centers are oriented toward detecting the best medical treatment of symptomatic COVID-19 disease as well as toward finding effective vaccine.

COVID-19 affects different people in different ways. Most infected people (about 80%) will develop mild–to-moderate illness and recover without hospitalization. In one out of five people, COVID-19 becomes serious condition and the affected people develop difficult breathing [24]. It is clearly shown that certain COVID-19 cases will develop severe viral pneumonia with respiratory failure, multiorgan and systemic dysfunctions in terms of sepsis and septic shock, and death [6], [25], [26]. However, the management of SARS-CoV-2 infection in those cases could be disadvantageous because of the abovementioned multiorgan response and failure.

The actual case report includes diagnostics and treatment of COVID-19-positive patient with severe clinical manifestation. Despite the combined antibiotic, corticosteroid, and supportive treatment, the condition of the patient has rapidly declined with minimally resolved consolidation. Since no vaccines or drugs for prevention and treatment have been approved so far, except remdesivir that has been authorized for use in several countries [19], [27], the team has used the combination of azithromycin with other antibiotics. It has been shown that azithromycin has significant immunomodulation and antiviral properties [19], [28], [29], [30], [31] and there are different aspects supporting its therapeutic effectiveness in SARS-CoV-2 infection.

In our case, what was the probable cause of death and how does COVID-19 act on the different organs?

Lungs

If COVID-19 progresses into a more severe clinical picture, the first organs to be affected are the lungs. The entrance of the virus in the human body is mainly though the respiratory system. Fecal-oral transmission has been only speculated. After entering the nose, the virus multiplies in the cells of the mucosa and then reaches the lungs through the trachea. The most frequent, serious manifestation of COVID-19 is found to be pneumonia, characterized by bilateral lower zone infiltrates displayed on radiographic chest imaging [6], [32].

The patient presented in this paper had pneumonia that was diagnosed by the CT scan of the thorax. The team has prescribed a combination of azithromycin with other antibiotics. The subsequent CT scan of the thorax showed minimally resolved consolidation, but there is still not enough evidence and knowledge whether this CT resolution was a result of the effects of azithromycin or not. It has yet to be confirmed in a large cohort of COVID-19 patients.

Kidneys

Some of the patients infected with SARS-CoV-2 could have impaired renal function even though they have not had any kidney problems previously [6], [33]. It is suggested that the pathogenesis of kidney involvement in COVID-19 infection and acute tubular necrosis could be a result of sepsis, multiorgan failure, and shock [34]. Another hypothesis is that the kidney cells do not get enough oxygen due to a lung disorder. According to some studies, COVID-19 increases the hypercoagulability that results from the formation of blood clots able to occlude the renal blood vessels.

The similar thing happened in the patient currently presented. When his health condition has deteriorated, there was a significant decrease in diuresis and an increase in degradation products. The patient was also a diabetic, so it is not clear whether the renal impairment was a consequence of COVID-19 or diabetes.

Liver

Mild and transient or severe liver damage can also occur in COVID-19 patients [6]. An increase in AST and ALT transaminases is a common finding in patients infected with SARS-CoV-2 [35]. According to most studies, however, liver damage is secondary and transient and it is not clear if the increase in AST and ALT is associated with COVID-19 or it is a result of the hepatotoxicity of the drugs used.

Thrombocytopenia

Thrombocytopenia is also a common finding in patients with COVID-19. In the last laboratory result, the PLT in our patient were 80×10^9/L. The mechanism by which it occurs is not yet known, but there is some speculation according to several studies. According to some studies, the virus directly attacks the bone marrow, preventing the formation of PLT. Others’ opinion is that PLT self-destruction is caused by the cytokine storm caused by the virus. Another possible cause is the PLT aggregation in the lungs and the formation of microthrombi.

Conclusion

COVID-19 is primary a respiratory infection and SARS-CoV-2 enters the body through the respiratory system, but the virus also affects other organs and, therefore, the disease in certain cases has a poor outcome. No cure or vaccine has been found yet, although numerous studies are being done. Therefore, at the moment, it is the most important to follow the recommendations that include maintaining social distance, frequent hand washing, and personal hygiene as well as wearing personal protective equipment, both at the workplace and in community.

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Coronavirus Disease-19 and Dentistry: A Review

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Abstract

Novel coronavirus (nCoV) is a novel form of virus with a new strain identified recently in humans. Common clinical signs and symptoms primarily consist of fever, cough, and breathing difficulties. In severe cases, it can results in pneumonia, severe acute respiratory syndrome, kidney failure, and even death. It is important to follow all infection control measures in prevention of the nCoV from spreading and controlling the epidemic situation. The risk of cross infection can be high between dental practitioners and patients due to the features of dental clinical settings. Here, we are summarizing the nCoV related information and infection control measures to be followed in dental practice.

Introduction

The pandemics of coronavirus disease (COVID-19) started from Wuhan, China, last December and Chinese Center for Disease Control and Prevention [1] on January 8, 2020, officially announced a novel form of coronavirus (nCoV) as the causative agent. It was first named as 2019-nCoV, but later officially as severe acute respiratory syndrome nCOV 2 (SARS-CoV-2) [2]. Now, it has become a major health problem not only for China but also majority of countries around the world [3]. The World Health Organization on January 30 announced that COVID-19 outbreak is a public health emergency of international concern [2], [4].

Characteristics of Virus

SARS-CoV-2 is a zoonotic virus [2]. nCoVs are from the family of *Coronaviridae*, of the order *Nidovirales*. It has genome of large, single, and plus-stranded RNA [5], [6]. There are four genera of nCoVs, namely, α-CoV, β-CoV, γ- CoV, and δ-CoV. The α-CoV and β-CoV mainly infect the respiratory, gastrointestinal, and central nervous system of humans and mammals, while γ-CoV and δ-CoV mainly infect the birds [7].

SARS-CoV and the Middle East respiratory syndrome CoV explored in 2002–2003 and in 2012, respectively, belong to the β-CoV. The virus explored in Wuhan, SARS-CoV-2, also belongs to the β-CoV11. The genome nucleotide sequence uniqueness was 96.2% between nCoV detected in the bat *Rhinolophus affinis* from Yunnan Province, China, and SARS-CoV-2, indicating the natural host of SARS-CoV-2 is the *R. affinis* bat [7].

However, the genome sequence similarity was 99% to the nCoV isolated from pangolins, indicating that these as the most likely intermediate host of SARS-CoV-2 [2], [7].

Incubation Period

An average of 5–6 days is the estimated incubation period of COVID-19. There is evidence that it might be as long as 14 days, which is now the universally adopted duration for medical surveillance and quarantine of potentially exposed or exposed persons [2].

People at High Risk of Infection

1. Peoples of all ages are usually susceptible to COVID-19. Healthcare workers and other individuals who are in close contact with patients of symptomatic and asymptomatic COVID-19 are at higher risk of SARS-CoV-2 infection [2]
2. Patients with most severe disease were more likely to have hypertension respiratory disease and cardiovascular disease [8]
3. In other studies, obesity and smoking were associated with increased risks [9], [10].

Common Symptoms

The characteristics symptoms of the patients were fever, cough, and myalgia or fatigue with abnormal chest computed tomography (CT). The less common symptoms were sputum production, headache, hemoptysis, and diarrhea [7].

Oral Manifestations

Ulcerations (unilateral palatal ulcerations) or blistering in the oral cavity	Reported as possible signs and symptoms in confirmed case of COVID-19 by Sinadinos and Shelswell [11]
52% – changes in taste sensation 56.25% – dry mouth 11% – pain in muscles of mastication	Reported as major changes in study by Biadsee *et al.* [12]
Necrotizing periodontal disease	Patel and Woolley in their letter to the editor proposed this can be an oral manifestation in patients with COVID-19 [13]
Oral reddish lesions and ulcerations	Soares *et al.* [14] and Chaux-Bodard *et al.* [15] in their letter to the editor marked in patients of COVID- 19
Smell and taste loss (chemosensory dysfunction)	Reported by Pedrosa et al. [16]

Source of Transmission

1. Patients with symptomatic COVID-19 have been the main source of transmission [2]
2. Asymptomatic patients in their incubation period [2].

Epidemiology

- Interpersonal transmission occurs mainly through respiratory droplets and contact transmission [2], [7]
- Studies have suggested that 2019-nCoV may be airborne through aerosols produced during medical procedures. However, the aerosol transmission route and the fecal–oral transmission route worried by the public still required to be further studied and confirmed [2], [7].

Spread in Dental Clinics

Eyes, nose, and oral cavity as the "T" zone in the maxillofacial region being the main entry for the virus into an individual, alerts all dental professionals while doing any procedures [17].

Dental care settings invariably carry the increased risk of 2019-nCoV infection due to the following reasons (Table 1 and Figure 1).

Table 1: Risk factors in dental clinic settings

Risk factors
Have more face-to-face communication with patients [2],[7]
Everyday exposure to saliva, blood, and other body fluids [2],[7]
Handling of the sharp instruments [2],[7]
Contact with droplets and aerosols [18]
Direct contact with patient materials [19]
Indirect contact with contaminated instruments and/or environmental surfaces [20]

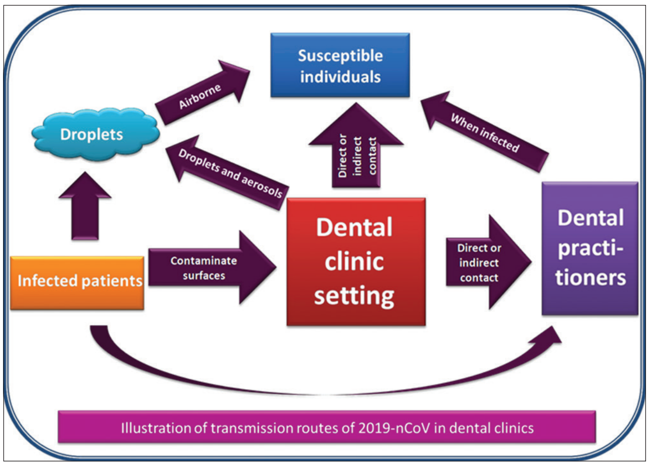

Figure 1: Illustration of transmission routes of 2019-nCoV in dental clinics

Infection Control in Dental Practice

In the early stages of COVID-19, the viral load in the saliva was constantly found high than that in the region of oropharynx. The SARS-CoV-2 viral load in the saliva can be effectively reduced for a short period of time with chlorhexidine mouthwash [21].

Alharbi *et al*. [22] classified therapeutic dental procedures into five groups: Emergencies, emergencies manageable through invasive or non-invasive procedures (minimum aerosol), non-emergencies, and elective treatments, depending on the dentist.

Following are the suggested measures to avoid spread of infection in dental clinics (Table 2).

Table 2: Infection control in dental practice

Infection control in dental practice
Patient evaluation: Identify a suspected case of COVID-19 [7]
Measurement of the body temperature: Should be measured in the first place using a contact-free forehead thermometer [7]
Screening: With the help of questionnaire [7]
Mouth rinse: preoperational antimicrobial mouth rinse with 1% hydrogen peroxide or 0.2% povidone is generally believed to reduce the number of oral microbes [7]
X rays: Orthopantomographs (OPG) or lateral oblique views may be considered instead of intraoral radiographs (IOPA) when required [23]
Hand hygiene: Good hand hygiene is of the utmost importance [7]
Dental professionals should avoid touching their own eyes, mouth, and nose [7], [24]
PPE: Protective eyewear, masks, gloves, caps, face shields, and protective outwear, is strongly recommended [7]
Dispensing instruments and materials: Should be done just before treatment. This prevents particles from settling on the surfaces [25]
Rubber dams: Significantly minimize the production of saliva- and blood- contaminated aerosol or spatter [7]
Anti-retraction high-speed dental hand piece: Can significantly reduce the backflow of oral microorganisms into the tubes of the hand piece and dental unit as compared with the hand piece without anti-retraction function [7], [26]
Impression making: Very sensitive patients may be anesthetized or sedated before taking impressions to control gag reflex [27], [28]
High volume evacuation: To remove infectious droplets at the source as soon as they are emitted. This minimize or prevent their dispersion in the air [29]
Disinfection of surfaces: Effective and strict disinfection measures using hospital-grade disinfectants after each patient in clinic setting [7], [30]
Sterilization of instruments: Is must for all the instruments [7]
Public areas such as door handles, chairs, and desks and elevators should be frequently disinfected [7]
Management of medical waste: Double-layer yellow color medical waste package bags and "gooseneck" ligation should be used [7]

Diagnosis and Laboratory Tests

1. The diagnosis of COVID-19 can be based on a combination of [31]
   - Clinical symptoms
   - CT imaging findings (seen in severe infection patients), and
   - Laboratory tests: For example, reverse transcriptase polymerase chain reaction (RT-PCR) tests on respiratory tract specimens using nasopharyngeal, oropharyngeal, and blood samples.
2. It should be mentioned that a single negative RT-PCR test result from suspected patients does not rule out infection. Clinically, we should be alert of patients with an epidemiologic history, COVID-19-related symptoms, and/or positive CT imaging results [31]
3. Saliva was found to be even more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs [32].

Treatment

In the present scenario, there has been no confirmation from randomized controlled trials to suggest any particular anti-nCoV treatment. Thus, the management consists of measures such as controlling the source of infection; lower the risk of infection transmission; and also provide early diagnosis, isolation, and supportive care for affected patients [9].

Conclusion

Although dental clinics have been closed during the epidemic, a large number of emergency patients need dental treatment. We have summarized the virology of 2019-nCoV, possible transmission routes and its control in dental clinics.

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Are the Obese Patients and Patients with Severe Malnutrition at Increased Risk of Severe Coronavirus Disease 2019 during Hospital Admission?

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Abstract

BACKGROUND: Recently, authorities highlighted the need for nutritional management of individuals with severe acute respiratory syndrome coronavirus 2 infection.

AIM: The aim of the study was to evaluate the use of body mass index (BMI) and nutrition risk index (NRI) on hospital admission for detecting patients at risk for malnutrition and obesity and their association with patients' outcomes (disease type, length of hospital and home stay, and inflammatory markers).

METHODS: The study of 100 patients with confirmed diagnosis Coronavirus Disease-19 (COVID-19). Assessment of patients took place at City General Hospital 8th September, Skopje, transformed into main COVID-19 Center during pandemic. Primary outcomes were NRI and BMI scores, while secondary ones: length of home and hospital stay, number of symptoms, presence of co-morbidities, type of disease, serum albumin, and C-reactive protein (CRP).

RESULTS: Patients were classified according to BMI and NRI scores. Increased BMI and NRI were associated with a severe type of disease. Most of the patients with severe disease were: obese (83.3%) and patients with risk for malnutrition (53.3%). Obese patients had a longer length of home stay and higher CRP levels, but the level of albumin was lower in a group with a risk for malnutrition.

CONCLUSION: Future studies are needed to identify and quantify specific screening tool for nutrition deficiency in patients with COVID-19 infection.

Introduction

On the April 12, 2020, Macedonian health authorities reported 854 people with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Few months later, coronavirus disease-2019 (COVID-19) is still a major health challenge for healthcare workers. Symptoms, laboratory, and radiology findings are the main targets of diagnosis [1]. Recently, European Society for Clinical Nutrition and Metabolism (ESPEN) published practical guidance for nutritional management of individuals with SARS-CoV-2 infections [2]. Hospitalized patients are at high risk of obesity or malnutrition upon hospital admission, even in the absence of chronic disease [3], [4], [5]. The underlying disease may directly decrease the dietary intake and to impair the appetite [6]. Furthermore, increased metabolism due to the stress of acute disease results in immune dysfunction, loss of fat-free mass and can lead to further inadequate dietary intake and deterioration of patients, as well as their nutritional status.

Nutrition deficiency represented by malnutrition and obesity, also, adversely affect clinical outcomes: Complications, length of stay (LOS), and mortality [7]. Nutritional deficiency is preventable and mostly reversible with adequate nutritional therapy. Therefore, it is important to perform nutrition risk screening systematically in all patients at the hospital admission in order to find those patients who are at risk. At present, there is no universally accepted gold standard for the assessment of nutrition status [8].

There are at least 33 different screening tools for nutrition risk [9]. In the present study, we applied two of them, namely nutrition risk index (NRI) and body mass index (BMI). We also measured serum albumin in each patient.

NRI is an easily applicable tool for detecting protein depletion. We can use this formula for its determination:

NRI=1.519 × serum albumin in g/L + (41.7 × present weight in kg/usual weight in kg)

For easier analysis, the calculator by Buzby can be used for its calculation.

BMI is calculated as the patient's weight in kg divided by the square of her/his height in meters.

We hypothesized that nutrition changes because of an acute illness or inadequate intake would affect the length of hospital stay LOS and the type of the disease.

Aim

The aim of this study was to evaluate the use of nutrition screening tools: BMI and NRI on hospital admission for detecting patients at risk for malnutrition and obesity and their association with patients' outcomes (type of disease, length of hospital and home stay, and inflammatory markers). Nutrition status of the patients was categorized into no risk and severe risk of malnutrition according to NRI. According to BMI, the patients were divided into either the normal group or in obese group. The actual study was a prospective observation study analyzing the need for evaluation of patients' nutrition status on hospital admission in City General Hospital 8th September in Skopje, Macedonia. We also wanted to assess whether the patients were obese or malnourished on hospital admission. Ethics approval was obtained by the Ethics Committee for the emerging infection of the hospital.

Patients and Methods

Nutrition screening tools were implemented in the COVID-19 Emergency Unit in City General Hospital 8th September in Skopje to enable screening of the nutritional status. A group of 100 adult patients affected by SARS-CoV-2 infection (aged 59 ± 60 years). A diagnosis of COVID-19 was confirmed according to the following criteria: History of epidemiological exposure, clinical symptoms of COVID-19-like pneumonia, positive result of a polymerase chain reaction (PCR) test, and pulmonary imaging changes with ground glass infiltration or consolidation. Our hospital become the main regional COVID-19 hospital in Macedonia and it was designed to accept all susceptive cases of COVID-19, but only patients with the confirmed diagnosis have been included in the study. Patients were analyzed at the hospital admission for demographics data, type (severity) of disease, symptoms, and co-morbidities.

Body fat and protein assessment were performed within 48 h of admission using measure of height and weight, as well as specific proteins in serum: albumin, globulin, and total proteins. Nutrition and dietary status of each patient were assessed by BMI, NRI, and serum levels of albumins and total proteins. NRI was calculated by an online calculator (https://www.mdcalc.com/nutritional-risk-index-nri) using serum albumin and recent body weight. BMI was also calculated using online calculator (https://www.calculator.net/bmi-calculator.html), entering patients' weight and height.

According to the NRI values, patients were classified into two groups: Nutritional risk group (NRI<83.5) and normal group without severe risk (NRI ≥83.5). According to the BMI, patients were classified into: Normal group (BMI ≤25), pre-obesity, and obese group, respectively. Pre-obesity and obese groups were merged into one group (BMI >25). Inflammatory status was also assessed within 48 h of admission using laboratory markers CPR and globulin. Lengths of hospital and home stay were filled latter, after hospitalization using medical records.

Results

A total number of 100 patients with COVID-19 were enrolled in the study. Patients' characteristics according to BMI groups are shown in Table 1.

There was no difference between the two BMI groups according to age ($t = -0.073$, $p = 0.942$), gender ($\chi^2 = 2.979$, $p = 0.084$), presence of co-morbidities ($\chi^2 = 0.004$, $p = 0.948$), level of albumin ($t = 0.102$, $p = 0.919$), and number of symptoms ($t = -0.18$, $p = 0.857$). Significantly more obese patients were detected in the group with severe COVID-19 (83.3%) than in the group with mild COVID-19 (53.2%) ($\chi^2 = 7.583$, $p = 0.023$). The length of hospital stay was longer in the group with normal BMI (15.09 ± 10.19 vs. 11.33 ± 5.97), but the difference was not significant ($t = 1.981$, $p = 0.054$). The length of home stay before hospitalization was longer in the group with obese patients (4.73 ± 4.4 vs. 2.88 ± 2.68) ($t = -2.217$, $p = 0.029$). The level of C-reactive protein (CRP) was significantly higher in obese patients (130.14 ± 80.6) than in group with normal BMI (88.11 ± 63.79) ($t = -2.643$, $p = 0.006$).

Patients' characteristics according to NRI groups are shown in Table 2.

Table 2 demonstrates significant differences between groups of patients with different risk for malnutrition, where the group of patients with severe risk for malnutrition (NRI <83.5) had significantly lower levels of albumin (24.01 ± 3.48 vs. 31.91 ± 3.81) ($t = 10.68$, $p < 0.001$) and total proteins (64.42 ± 5 vs. 67.37 ± 5.78) ($t = 2.69$, $p = 0.008$), as well as significantly higher level of globulin (40.2 ± 5.75 vs. 35.87 ± 5.8) ($t = -3.709$, $p < 0.001$).

Table 3 shows the correlation coefficient between BMI and NRI.

Table 1: Patients' characteristics according to BMI groups

Variable	Normal group BMI ≤25 (n = 34)	Obese group BMI>25 (n = 66)	Statistic, p-value
Age (years) (mean ± SD)	59.68 ± 16.43	59.91 ± 11.83	t = -0.073,p = 0.942
Gender - n (%)			
Male (n = 65)	26 (40)	39 (60)	χ^2 = 2.979, p = 0.084
Female (n = 35)	8 (22.9)	27 (77.1)	
Type of disease - n (%)			
Mild (n = 47)	22 (46.8)	25 (53.2)	χ^2 = 7.583, p = 0.023
Moderate (n = 23)	7 (30.4)	16 (69.6)	
Severe (n = 30)	5 (16.7)	25 (83.3)	
With co-morbidities - n (%)	24 (70.6)	47 (71.2)	χ^2 = 0.004, p = 0.948
Length of hospital stay (days) (mean ± SD)	15.09 ± 10.19	11.33 ± 5.97	t = 1.981, p = 0.054
Length of home stay before hospitalization (days) (mean ± SD)	2.88 ± 2.68	4.73 ± 4.4	t = −2.217, p = 0.029
Albumin (mean ± SD) (g/L)	28.26 ± 6.02	28.15 ± 5.06	t = 0.102, p = 0.919
Globulin (mean ± SD) (g/L)	37.64 ± 5.67	38.17 ± 6.33	t = −0.404, p = 0.687
Total proteins (mean ± SD) (g/L)	65.96 ± 4.37	66.13 ± 6.21	t = −0.152, p = 0.880
Number of symptoms	2.44 ± 1.11	2.48 ± 1.17	t = −0.18, p = 0.857
CRP (mean ± SD) (mg/L)	88.11 ± 63.79	130.14 ± 80.6	t = −2.643, p = 0.006

BMI: Body mass index; SD: Standard deviation; CRP: C-reactive protein.

Table 2: Patients' characteristics according to NRI groups

Variable	Not severe risk for malnutrition (NRI≥ 83.5) (n = 51)	Severe risk for malnutrition (NRI< 83.5) (n = 47)	Statistic, p-value
Age (years) (mean ± SD)	60.2 ± 13.38	59.19 ± 13.96	t = 0.364, p = 0.717
Gender- n (%)			
Male (n = 63)	36 (57.1)	27 (42.9)	χ^2 = 1.840, p = 0.175
Female (n = 35)	15 (42.9)	20 (57.1)	
Type of disease - n (%)			
Mild (n = 45)	27 (60)	18 (40)	χ^2 = 2.165, p = 0.339
Moderate (n = 23)	10 (43.5)	13 (56.5)	
Severe (n = 30)	14 (46.7)	16 (53.3)	
With co-morbidities - n (%)	40 (78.4)	30 (63.8)	χ^2 = 2.555, p = 0.110
Length of hospital stay (days) (mean ± SD)	11.51 ± 6.26	13.85 ± 9.28	t = −1.474, p = 0.144
Length of home stay before hospitalization (days) (mean ± SD)	4.38 ± 3.17	3.66 ± 4.71	t = 0.866, p = 0.389
Albumin (mean ± SD) (g/L)	31.91 ± 3.81	24.01 ± 3.48	t = 10.68, p < 0.001
Globulin (mean ± SD) (g/L)	35.87 ± 5.8	40.2 ± 5.75	t = −3.709, p < 0.001
Total proteins (mean ± SD) (g/L)	67.37 ± 5.78	64.42 ± 5	t = 2.69, p = 0.008
Number of symptoms	2.37 ± 1.18	2.55 ± 1.12	t = −0.775, p = 0.440
CRP (mean ± SD) (mg/L)	118.57 ± 78.5	113.66 ± 78.7	t = 0.309, p = 0.758

BMI: Body mass index; SD: Standard deviation; CRP: C-reactive protein; NRI: Nutrition risk index.

Graphical representation of the correlation between BMI and NRI is shown in Figure 1.

Table 3: Analysis of correlation between BMI and NRI

Bivariate analysis	BMI	NRI	p-value
BMI	1	0.303*	0.002

*Pearson r; BMI: Body mass index; NRI: Nutrition risk index.

Previous table and graph demonstrate a significant positive correlation between BMI and NRI (r = 0.303, p = 0.002), or higher the BMI, higher the NRI.

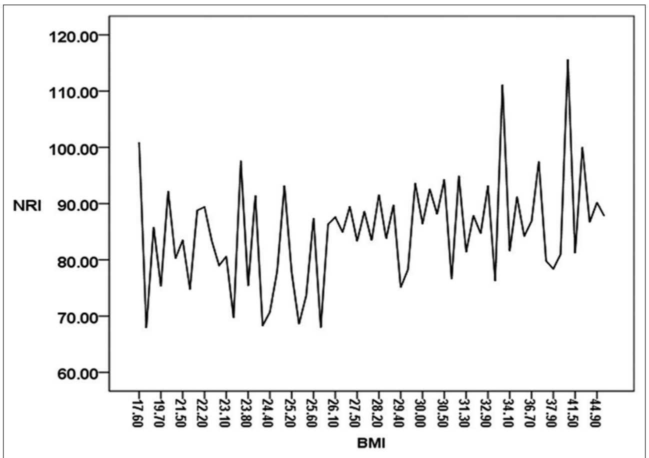

Figure 1: Graphical representation of the correlation between body mass index and nutrition risk index

Results of our study are showing that obese patients impose a higher risk for worse outcome according to the findings that significantly more obese patients were detected in the group with severe COVID-19, the length of home stay was longer in obese patients, and the level of CRP was significantly higher in this group of patients. Despite the detected correlation between BMI and NRI, we have found that there were no significant associations between NRI and other variables analyzed.

Discussion

ESPEN emphasizes the need to manage the diet of patients with COVID-19 infection. Inadequate dietary intake is one of the main reasons for the increased risk of infection [10]. Furthermore, inadequate dietary intake can lead to rapid obesity or malnutrition [11], [12]. Malnutrition and obesity are common findings of hospital dependencies for surgical patients [13], but the situation with patients infected with COVID-19 is unclear, especially if the patient has severe symptoms. Some studies demonstrated that obesity measured as BMI, and malnutrition defined as hypoalbuminemia or decline of serum albumin, were associated with an increased risk of developing severe pneumonia in COVID-19 [14], [15], [16].

The reported incidence of a severe type of disease of the patients in our study was 30%. Our data also showed that obese and NRI risk group patients had a severe type of disease in respect to non-obese and normal NRI group.

In the course of severe progress of COVID-19, the major component is hyper-inflammation [17]. Many nutrients have a role in supporting the immune system to defend against pathogens. Hence, regarding to COVID-19 infection, it is important to evaluate the nutrition status of each patient. Furthermore, nutrition deficiency needs to be considered in severe cases of COVID-19.

Body fat is biologically active and a source of pro-inflammatory factors, so bone marrow infection leads to a further increase in the production of pro-inflammatory cytokines [18]. In our study, even the normal BMI group showed an incidence of increased CRP. In patients classified according to NRI, the CRP was almost identical. It was, therefore, difficult to conclude whether malnutrition was a result of inflammation alone and not of inadequate dietary intake. However, given the significant reduction in albumin and high BMI, malnutrition is thought to be related to the severity of COVID-19. Further studies are needed to determine the screening tool to detect the cause of malnutrition.

Many studies have aimed to predict the number of hospital beds required for COVID-19 [19].

Several studies have shown a close relationship between LOS and dietary status [20], [21], [22]. In our study, the risk group had a longer LOS compared to those who were not at risk. Among obese patients, LOS at home before hospitalization was longer than that of patients with a normal BMI. This suggests that obesity affects breathing difficulties even before inflammation sets in [23]. Due to obesity, the patient always had difficulty breathing. His/her dyspnea he/she thought that was related to obesity and not to COVID-19 infection. We suppose that this is the reason why he/she is consulting the physician later on. Further research is needed, including other factors, such as demographics, laboratory analyses, and particularly the LOS at home.

In our study, increased BMI was associated with a higher disease rate, longer stay at home, and higher CRP levels. In contrast, no difference was observed between the two BMI groups for albumin level and number of symptoms. Increased NRI was associated with a serious form of the disease, longer hospital stay, and lower albumin levels. There appears to be a slight difference in CRP seen in a group of patients at different risk of malnutrition.

Our study has some limitations, but the fact that our hospital was the Main Regional COVID-19 Center brought us pleasure because we have the opportunity to collect data and to be the first to do that in the country.

Patients very often came late in the course of their illness, so they were not included because their weight and height could not be measured. When we collected the data retrospectively, we could not get all the information. For example, a patient due to respiratory discomfort, he/she refused to talk about eating properly, or LOS was affected by the PCR test results, even if he/she felt well.

Conclusion

BMI and NRI are well-established screening tools for the assessment of nutritional status on hospital admission. Nutritional care plans should be developed and implemented to maintain and improve patients' nutritional status. This study opened the question: Can we manage the acute illness easily with a better outcome if patients' examination starts with nutrition assessment, initially? Further investigations are also needed for the factors affecting the length of home stay, especially during a pandemic when the number of hospital beds is limited and the number of patients rapidly increases.

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Findings of Serial Computed Tomography Imaging in Patients with Coronavirus Disease-19

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Abstract

AIM: We investigated the serial changes of chest computed tomography (CT) in patients with coronavirus disease-2019 (COVID-19) presenting with viral-induced lung damage on follow-up CT.

METHODS: We evaluated 66 patients with confirmed COVID-19, who had undergone at least two chest CTs from February 24 to April 21, 2020. Nine patients also had a third CT. All patients demonstrated viral-induced lung damage (organizing pneumonia-like pattern) on second CT. The involvement pattern of each lobe and the extent of infiltration (based on CT score) were assessed on serial CTs to determine changes throughout the disease course. Patients' demographic and clinical data and final outcome were also recorded.

RESULTS: Mean age (standard deviation [SD]) of patients was 56.04 (15.2) years old; 51.5% were male. About 93.9% of patients had survived. Mean (SD) interval between the first and second CT and second and third CT was 7.6 (5.9) and 16.8 (8.3) days, respectively. The extent of total lung involvement was significantly higher in the second CT compared with the first CT ($p < 0.001$) and also increased non-significantly in the third CT ($p = 0.29$). The right lower lobe persistently had the highest CT score through the disease course.

CONCLUSION: Evaluation of serial CT imaging can reveal information regarding the stage of COVID-19, thus providing help for appropriate treatment planning.

Introduction

The diagnosis of coronavirus (CoV) disease-2019 (COVID-19) is confirmed through real-time reverse transcriptase-polymerase chain reaction assay (RT-PCR) of upper respiratory tract specimens [1], but imaging modalities have also proved to be helpful for the diagnosis of COVID-19. In particular, computed tomography (CT) imaging is capable of monitoring disease progression and clinical response in COVID-19 [2], [3].

It is currently evident that COVID-19 is mainly associated with respiratory distress and acute lung injury; however, the long-term sequelae of COVID-19 on the lung parenchyma and pulmonary function are not yet clear. A study on patients recovered from nosocomial severe acute respiratory syndrome (SARS) infection showed that even after 15 years of follow-up, chest CT abnormalities were not completely resolved, and residual lesions still existed on imaging [4]. Organizing pneumonia (OP) is a radio-histologic pattern commonly formed subsequent to lung damage in patients with focal or diffuse lung injury [5]. Many etiologies contribute to the secondary OP, among them, viral pneumonia such as H1N1 influenza, SARS-CoV, and Middle East respiratory syndrome-CoV [6], [7], [8]. Several studies have already reported the presence of viral-induced lung damage (OP-like pattern) in patients infected with SARS-CoV-2 [9], [10]. A diverse range of clinical outcomes is observed in patients with viral-induced lung damage (OP-like pattern), ranging from complete resolution of lesions to more severe progressive consequences such as pulmonary fibrosis [11], [12]. Hence, in patients who have developed viral-induced lung damage (OP-like pattern), CT is useful for determining the outcomes of lung involvement and defining patients' long-term prognosis. Herein, we aimed to evaluate serial changes of CT imaging in hospitalized patients with confirmed COVID-19 who had manifested with viral-induced lung damage (OP-like pattern) on their second CT scan.

Materials and Methods

Study design and participants

In this retrospective study, we evaluated 66 adult patients (age >18 years old) with a laboratory-confirmed diagnosis of COVID-19, who were hospitalized in our referral hospital from February 24 to April 21, 2020, and had underwent at least two CT scans. All of the enrolled patients had imaging findings consistent with viral-induced lung damage (OP-like pattern) on their second CT scan. COVID-19 diagnosis was confirmed with positive RT-PCR assay for SARS-CoV-2 obtained from a nasopharyngeal swab specimen and diagnosis of viral-induced lung damage (OP-like pattern) was based on consistent imaging findings on CT.

All patients underwent the second CT scan due to clinical indication. In nine patients, a third CT scan had also been performed. According to national COVID-19 guidelines, non-contrast low-dose CT was performed for all patients with reconstructions of the volume at 3 mm–5 mm slice thickness. CT images were reviewed by two board-certified radiologists with 4 and 10 years of experience. Both radiologists were blinded to the lab data, clinical features, and patients' diagnosis. Imaging findings were first interpreted independently and in case of disagreement, final decision was reached by consensus. For reporting imaging features, international standard nomenclature defined by the Fleischner Society was used [13]. The involvement pattern of each specific lobe on the first, second, and third CT was recorded to determine serial changes of imaging. Furthermore, the extent of lobar involvement was assessed using a scoring system as follows: a numerical score was assigned to each of the five lobes based on the percentage of infiltration in each lobe: 0 (none), 1 (1–5%), 2 (6–25%), 3 (26–49%), 4 (50–75%), and 5 (>75%); total score was obtained by summing the scores of all lobes for each patient. In addition to imaging findings, patients' demographic and clinical data and final disease outcome were also collected.

Statistical analysis

Categorical variables are reported as number (percentages) and continuous variables are expressed as mean (standard deviation [SD]) and range. Normality tests were used to assess distribution. Continuous data were compared between the groups using t-test and categorical variables were compared using Chi-square or Fisher's exact test. Statistical tests were performed by SPSS v.23 (IBM Inc., Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Ethics approval

This study was approved by the ethical review board of our institution (Ethics code: IR.SBMU.MSP.REC.1399.084) and Helsinki Declaration of 1975, as revised in 2000. Written informed consent was waived due to retrospective nature of study.

Results

Table 1 presents patients' demographic and clinical data. The mean age (SD) of patients was 56.04 (15.2) years old; 51.5% were male. The most common clinical manifestation was respiratory distress (93.9%) followed by fever (45.4%). The mean (SD) interval from symptom onset to presentation was 7.50 (4.11) days and the median hospitalization time was 5 days; however, this duration varied from 1 to 34 days. Considering patients' final outcome, 93.9% had survived and six patients had experienced death. Seven patients (10.6%) had leukocytopenia (leukocyte <4 × 10^9/L) and elevated CRP level (>50 mg/dL) was observed in 22/66 (33.3%) patients. More than half of patients had co-existing morbidities (51.5%) with hypertension and diabetes being the most prevalent (Table 1).

Table 1: Demographic and clinical data of patients (n = 66)

Variable	Result
Age, years	56.0 (15.2) 23–93
Gender	
Male	34 (51.5)
Female	32 (48.5)
Duration of hospitalization, days	9.65 (7) 1–34
Symptom onset to presentation, days	
0–4	9 (13.6)
4–14	51 (77.3)
>14	6 (9.1)
Outcome	
Ward	54 (81.8)
Intensive care unit	8 (12.1)
Death	4 (6.1)
Lab data	
C-reactive protein (mg/dL)	55.6 (48.4)
Lymphocyte (× 109/L)	1.46 (1.6)
Leukocyte (× 109/ L)	7.29 (6.6)
Comorbidities	
Diabetes	18 (27.2)
Hypertension	23 (34.8)
Hyperlipidemia	9 (13.6)
Ischemic heart disease	6 (9.1)
Chronic kidney disease	2 (3)
Other	2 (3)
Presenting symptoms	
Fever and chills	30 (45.4)
Respiratory distress	61 (93.9)
Neurologic involvement	7 (10.6)
Gastrointestinal involvement	17 (25.7)
Time from first to second CT (days)	7.6 (5.9) 2–30
Time from second to third CT (days)	16.8 (8.3) 7–30

Continuous data are represented as mean (SD) and range. Categorical data are reported as n (%). [a]This includes patients presenting with cough or dyspnea. CT: Computed tomography, CI: Confidence interval, RUL: Right upper lobe, RML: Right middle lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lobe. SD: Standard deviation

The mean (SD) interval between the first and second CT was 7.6 (5.9) days; this duration was 16.8 (8.3) days for the second and third CT. Table 2 shows the extent of lung involvement in each lobe on first, second, and third CT. As shown, through different time

Table 2: Extent of lung involvement based on CT score

Lobe	First CT score (n = 66)	Second CT score (n = 66)	p-value (95% CI)[a]	Third CT score (n = 9)	p-value (95% CI)[b]
RUL	1.98 (0.92)	2.45 (8.98)	<0.001 (0.26–0.68)	2.33 (1.00)	0.44 (−0.61–1.27)
RML	1.58 (0.95)	2.02 (0.92)	<0.001 (0.23–0.65)	2.44 (1.24)	0.51 (−0.52–0.96)
RLL	2.33 (1.03)	2.89 (0.82)	<0.001 (0.29–0.83)	2.78 (0.83)	0.68 (−0.71–0.49)
LUL	1.94 (1.13)	2.53 (0.95)	<0.001 (0.33–0.84)	2.67 (0.71)	0.28 (−0.99–0.33)
LLL	2.11 (0.99)	2.76 (0.82)	<0.001 (0.40–0.91)	2.56 (1.01)	0.45 (−0.86–0.48)
Total score (range)	9.93 + 3.77 (0–18)	12.65 + 3.07 (4–19)	<0.001 (1.75–3.66)	15.55 + 4.03 (11–22)	0.29 (−1.63–4.75)

Data are reported as mean (SD). [a]p-value (95% CI) represents the statistical difference between first and second CT. [b]p-value (95% CI) represents the statistical difference between second and third CT. CT: Computed tomography, SD: Standard deviation.

points, the right lower lobe was involved at a greater extent compared with other lobes. More importantly, the results of our study showed that the CT score of all lobes was significantly higher in the second CT compared with the first CT. Furthermore, in patients who had undergone a third CT, it was shown that there was a greater amount of lung involvement as compared with the second CT, although not statistically significant.

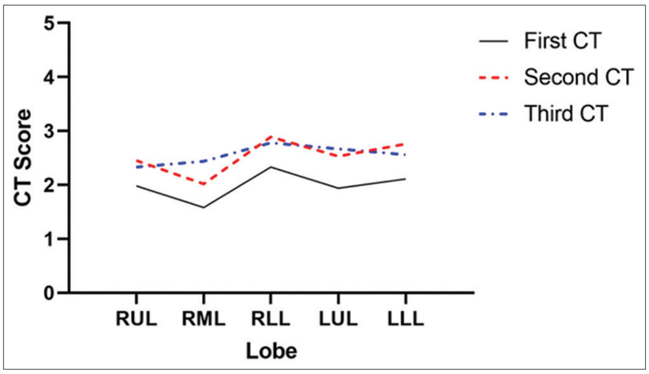

Figure 1: Mean computed tomography (CT) score of each lung lobe on first, second, and third CT

Figure 1 shows the median CT score of each specific lobe on first, second, and third CT scan. Figure 2 shows the total CT score based on the time from admission.

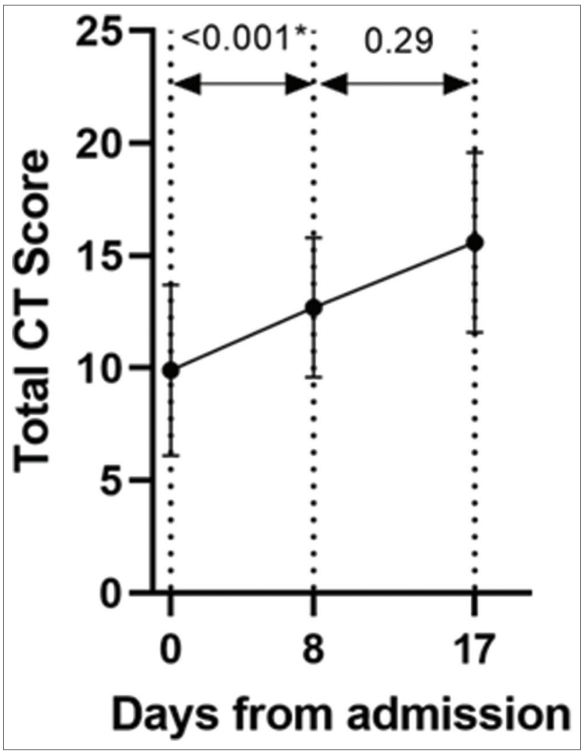

*Figure 2: Serial changes of total computed tomography score after admission (*p-value statistically significant)*

Table 3 shows in detail the serial changes in the involvement pattern of each specific lobe. On the first CT, ground-glass opacity (GGO) was the main involvement pattern in all lobes. The presence of this pattern ranged from 56.1% in the right middle lobe to 75.7% in the right upper lobe. As a show, the pattern of viral-induced lung damage (OP-like pattern) tended to remain in the majority of patients who had third CT. Regarding the changes in lesion distribution, in the first and second CT, peripheral distribution was the most common; however, there was a shift towards a diffuse pattern of involvement in the third CT (Table 4). When comparing the presence of other abnormal findings (Table 5), there was a substantial increase in the number of patients with pleural effusion in the second CT compared with the first (1.5% vs. 19.7%).

Discussion

In this study, we aimed to investigate the changes in serial chest CT imaging of patients with confirmed COVID-19 who, due to clinical indications, underwent a second or third follow-up chest CT during hospitalization and had developed viral-induced lung damage (OP-like pattern) on second CT. In a retrospective observation, we found that the total CT score as well as the CT score of all five lobes was significantly higher in the second CT scans compared with that of the initial CT scans, and also those from the third CT scans were higher, although not significant, than the second CT scans. In both the first and second CT scans, the right lower lobe and left lower lobe had the highest extent of involvement. This is consistent with previous studies that reported a basal predominance of pulmonary lesions among patients with COVID-19 [14], [15]. Furthermore, viral-induced lung damage (OP-like pattern) was most frequently seen in the right and left lower lobes, supporting the previously described predominance of lower lobes in viral-induced lung damage [16].

Viral pulmonary infections can cause a pattern of lung injury that is characterized by fibroblast proliferation. This pattern, which is seen in the organizing phase of diffuse alveolar damage and OP, has both histological and radiological manifestations [17]. Based on the current evidence, COVID-19 infection can similarly result in secondary

Table 3: Serial changes in CT involvement pattern

Lobe	First CT (n = 66)	Second CT (n = 66)	Third CT (n = 9)
RUL			
Primary pattern			
GGO	50 (75.7)	14 (21.2)	2 (22.2)
Consolidation	12 (18.2)	11 (16.7)	1 (11.1)
Crazy-paving	1 (1.5)	4 (6.1)	-
Reversed-halo	1 (1.5)	11 (16.7)	-
Smooth round GGO/consolidation	7 (10.6)	1 (1.5)	-
Non-specific pattern of GGO/consolidation	7 (10.6)	2 (3)	-
Irregular round GGO/consolidation	8 (12.1)	2 (3)	-
Viral-induced lung damage (OP-like pattern)	-	40 (60.6)	6 (66.7)
Sub-pleural band	-	12 (18.2)	1 (11.1)
PBV opacity	-	8 (12.1)	1 (11.1)
Bronchial dilation	-	10 (15.2)	-
Air space nodule	-	4 (6.1)	-
Sub-pleural consolidation	-	1 (1.5)	-
Fibrosing interstitial network	-	3 (4.5)	1 (11.1)
Reticulation	-	-	4 (44.1)
Complete resolution	-	-	1 (11.1)
RML			
Primary pattern			
GGO	44 (66.7)	14 (21.2)	4 (44.4)
Consolidation	12 (18.2)	9 (13.6)	1 (11.1)
Crazy-paving	1 (1.5)	2 (3)	-
Reversed-halo	-	-	-
Smooth round GGO/consolidation	7 (10.6)	-	-
Non-specific pattern of GGO/consolidation	9 (13.6)	5 (7.6)	-
Irregular round GGO/consolidation	5 (7.6)	2 (3)	-
Viral-induced lung damage (OP-like pattern)	-	41 (61.2)	5 (55.5)
Sub-pleural band	-	5 (7.6)	-
PBV opacity	-	5 (7.6)	-
Bronchial dilation	-	19 (28.8)	-
Air space nodule	-	11 (16.7)	1 (11.1)
Sub-pleural consolidation	-	-	-
Fibrosing interstitial network	-	1 (1.5)	1 (11.1)
Reticulation	-	5 (7.6)	3 (33.3)
Complete resolution	-	-	-
RLL			
Primary pattern			
GGO	37 (56.1)	2 (3)	3 (33.3)
Consolidation	22 (33.3)	6 (9.1)	1 (11.1)
Crazy-paving	-	2 (3)	-
Reversed-halo	-	2 (3)	-
Smooth round GGO/consolidation	10 (15.2)	-	-
Non-specific pattern of GGO/consolidation	7 (10.6)	-	-
Irregular round GGO/consolidation	6 (9.1)	-	-
Viral-induced lung damage (OP-like pattern)	-	56 (84.8)	7 (77.7)
Sub-pleural band	1 (1.5)	25 (37.9)	4 (44.4)
PBV opacity	-	9 (13.6)	-
Bronchial dilation	-	17 (25.7)	-
Air space nodule	-	1 (1.5)	-
Sub-pleural consolidation	-	3 (4.5)	1 (11.1)
Fibrosing interstitial network	-	7 (10.6)	1 (11.1)
Reticulation	-	9 (13.6)	9 (100)
Peri-lobular pattern	-	4 (6.1)	-
Complete resolution	-	-	-
LUL			
Primary pattern			
GGO	45 (68.2)	13 (19.7)	3 (33.3)
Consolidation	10 (15.2)	9 (13.6)	1 (11.1)
Crazy-paving	1 (1.5)	2 (3)	-
Reverse-halo	-	2 (3)	-
Smooth round GGO/consolidation	6 (9.1)	-	-
Non-specific GGO/consolidation	11 (16.7)	5 (7.6)	-
Irregular round GGO/consolidation	4 (6.1)	2 (3)	-
Viral-induced lung damage (OP-like pattern)	-	39 (59.1)	-
Sub-pleural band	-	11 (16.7)	6 (66.7)
PBV opacity	-	10 (15.2)	2 (22.2)
Bronchial dilation	-	9 (13.6)	-
Air space nodule	-	3 (4.5)	-
Sub-pleural consolidation	-	2 (3)	-
Fibrosing interstitial network	-	1 (1.5)	-
Reticulation	-	7 (10.6)	-
Peri-lobular pattern	-	-	3 (33.3)
Complete resolution	-	-	-
LLL			
Primary pattern			
GGO	38 (57.6)	1 (1.5)	2 (22.2)
Consolidation	20 (30.3)	6 (9.1)	-
Crazy-paving	1 (1.5)	2 (3)	-
Reversed-halo	-	2 (3)	-
Smooth round GGO/consolidation	7 (10.6)	-	-
Non-specific pattern of GGO/consolidation	11 (16.7)	1 (1.5)	-
Irregular round GGO/consolidation	6 (9.1)	-	-
Viral-induced lung damage (OP-like pattern)	-	57 (86.4)	9 (100)
Sub-pleural band	1 (1.5)	29 (43.9)	5 (55.5)
PBV opacity	-	7 (10.6)	-
Bronchial Dilation	-	10 (15.2)	-
Air space nodule	-	4 (6.1)	2 (22.2)
Sub-pleural consolidation	-	3 (4.5)	1 (11.1)
Fibrosing interstitial network	-	7 (10.6)	1 (11.1)
Reticulation	-	9 (13.6)	2 (22.2)
Peri-lobular pattern	-	1 (1.5)	-
Complete resolution	-	-	-

CT: Computed tomography, GGO: Ground-glass opacity.

Table 4: Serial changes in axial distribution of lung lesions

Lobe	First CT (n = 66)	Second CT (n = 66)	Third CT (n = 9)
RUL			
Diffuse	18 (27.2)	22 (33.4)	5 (55.5)
Peri-bronchovascular	9 (13.6)	8 (12.2)	1 (11.1)
Peripheral	39 (59.1)	36 (54.5)	2 (22.2)
RML			
Diffuse	19 (28.8)	21 (31.8)	5 (55.5)
Peri-bronchovascular	6 (9.1)	7 (10.5)	1 (11.1)
Peripheral	41 (62.1)	38 (57.5)	3 (33.3)
RLL			
Diffuse	18 (27.2)	21 (31.8)	6 (66.7)
Peri-bronchovascular	6 (9.1)	6 (9.1)	-
Peripheral	42 (63.6)	39 (59.1)	3 (33.3)
LUL			
Diffuse	19 (28.8)	23 (34.8)	6 (66.7)
Peri-bronchovascular	7 (10.5)	6 (9.1)	-
Peripheral	40 (60.6)	37 (56.1)	3 (33.3)
LLL			
Diffuse	16 (24.2)	20 (30.3)	6 (66.7)
Peri-bronchovascular	7 (10.5)	5 (7.5)	1 (11.10
Peripheral	43 (65.1)	41 (62.1)	2 (22.2)

Data are reported as n (%).

OP [18], [19], [20]. Although the majority of cases with OP resolve, irreversible fibrosis occurs in some instances [17]. Limited evidence is currently available on the pulmonary sequela and residual radiologic abnormalities in those who have survived. On the other hand, as indicated by studies from previous pandemics, resolution of pulmonary imaging abnormalities may take several months to even several years [4], [21], [22]. In a recently published study by Liu *et al.*, the cumulative percentage of complete radiological resolution at 3-weeks post-discharge was 53%. They concluded that COVID-19-associated pulmonary lesions may resolve approximately 2 weeks after discharge. In addition, 3 weeks after discharge, GGO, and fibrous stripe were the most common radiologic findings on CT [23]. Another study investigating the time course of chest CT changes during COVID-19 recovery found that gradual resolution of consolidation occurs ≥14 days after symptom onset. In this stage, also known as the absorption stage, the chest CT scores began to decrease [24]. This is in contrast with our study in that the total CT score of the third CT scan, which was performed approximately 17 days after initial CT, was higher than that of the first and second CT scans. Earlier studies on patients with COVID-19 reported that maximum lung involvement occurs approximately 10 days after the onset of initial symptoms [1], [24]. However, in a case report by Duan and Qin, GGOs in the right and left lower lobes started to resolve at day 7 after admission, while GGOs in the right lower lobe completely resolved at day 13 after admission [25]. These varying findings prompt further follow-up studies in convalescent patients after COVID-19.

Table 5: Serial changes in abnormal findings of chest CT

Imaging finding	First CT (n = 66)	Second CT (n = 66)
Cardiomegaly	6 (9.1)	6 (9.1)
Atherosclerotic plaque	23 (34.8)	22 (33.3)
Pleural effusion	1 (1.5)	13 (19.7)
Pericardial effusion	-	1 (1.5)

Data are reported as n (%). CT: Computed tomography.

Several factors, including patient's age, duration of hospitalization, presence of comorbidities, and severity of lung disease, have been proposed to determine the risk of residual lung abnormalities among survivors of viral pulmonary infections [21], [26], [27]. The mean age of patients in our study was 56 years; previous studies have shown that OP usually presents within the fifth and sixth decades of life [28]. In this study, patients had a 10-day hospital length of stay, similar to previous reports [29], [30]. In addition, 27% and 35% of the patients had diabetes and hypertension, respectively, which is higher than the prevalence of diabetes and hypertension among the general population with COVID-19 [31], [32], [33]. Follow-up studies are needed to verify whether these factors contribute significantly to the development of residual fibrosis in patients with COVID-19.

Our results showed that after approximately 8 days, GGO, the main imaging finding on initial CT, had been replaced by viral-induced lung damage (OP-like pattern). The axial distribution of pulmonary lesions did not change between the initial and second CT scans; the majority of lesions had a peripheral distribution, in line with previous reports in patients with COVID-19 [1]. Along with viral-induced lung damage (OP-like pattern), sub-pleural band, bronchial dilation, and reticulation were the most common patterns observed on second CT scans and were predominantly observed in the lower lobes. These patterns that may be a manifestation of OP-associated fibrosis have been reported to be predominantly lower-lobe dependent in other studies [34], [35]. In patients with SARS, reticular changes were observed nearly 2 weeks after the onset of initial symptoms and remained stable after 4 weeks in more than half of the patients. Bronchial dilation was also evident in a few patients after the 4^{th} week [36]. Our study showed that in patients who had undergone a third CT scan, reticulation was more commonly observed compared with previous CT scans. Furthermore, the observation of these patterns on chest CT, as well as other findings such as reversed-halo sign can provide a clue about the stage of the disease and guide physicians to select the most appropriate treatment strategy that is most beneficial in the post-acute phase of the disease. This will help in optimizing resource allocation and avoiding unnecessary acute-phase treatments to patients.

Based on our results, while pleural effusion was only evident in one initial CT, 13 patients had pleural effusion on the second CT. In a systematic review, Salehi *et al*. found that pleural effusion is one of the less common imaging findings associated with COVID-19 that may be seen with disease progression [1]. Of the four patients in our study who experienced death, three patients had atherosclerotic plaques on imaging, and two had concomitant cardiomegaly and pleural effusion.

In terms of management of patients with the secondary OP, the treatment of OP mainly consists of corticosteroid therapy, as well as treating the underlying disease [17], [28]. Most recently, preliminary results from the RECOVERY trial showed that dexamethasone has the potential to reduce mortality by 30% in critically ill patients with COVID-19 [37]. This could be due to the effect of corticosteroids on the degradation of fibroblastic plugs in those patients with OP pattern on chest imaging, thereby reducing mortality.

Conclusion

In this study, we showed that the total CT scores of patients with COVID-19 who developed an OP –like pattern on CT imaging during hospitalization had a steady rise from 1st day of admission to approximately 17 days later, and the right lower lobe had the highest involvement at all-time points. In addition, observation of imaging findings such as the reversed halo sign, which indicates that the viral response phase has already occurred, should prompt physicians to use medications other than antivirals since they are less likely to provide any benefits to the patient in the later phases of disease. Taken together, serial CT imaging renders helpful information that could be implemented in the management of patients with COVID-19.

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Personal Protective Equipment in Health Workers during Coronavirus Disease-19 Outbreak

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Abstract

BACKGROUND: Coronavirus (CoV) disease (COVID)-19 pandemic has put immense pressure on the healthcare systems worldwide.

AIM: The aim of the actual study was to assess the availability of personal protective equipment (PPE) in health workers (HWs) during an outbreak.

METHODS: The study was conducted in April-May 2020 using an on-line questionnaire. Completed surveys were returned by 560 HWs (297 physicians, 79 nurses/technicians, 78 dentists, 9 pharmacists, and 97 other HWs).

RESULTS: High proportion of HWs was using one surgery mask for two or more times or not using it at all when contacting patients who were self-isolated (35.3%) or severe acute respiratory syndrome CoV (SARS-CoV)-2 positive (19.3%). More than 90% of participants were using surgery masks and gloves every time or almost every time while working with patients who were self-isolated or SARS-CoV-2 positive. High frequency of participants reported: No isolation zones at the workplace (61.2%), no triage of patients at the entrance (33.4%), and not attended a training course about the correct usage of PPE (72%).

CONCLUSION: The data obtained can be used in the creation of specific interventions in healthcare settings aimed at providing high-quality PPE through the development of a national healthcare strategy that can lead to the prevention of COVID-19 in HWs.

Introduction

The current coronavirus (CoV) disease (COVID)-19 pandemic has put immense pressure on the healthcare systems worldwide. Due to the eruptive spread of the disease, health workers (HWs) were placed on the frontline of the battle.

As crucial assets in every healthcare system, HWs are essential in maintaining adequate patient care and keeping the healthcare system functioning. During this public health emergency, the overburdened healthcare capacities, long working hours, staff shortages, and the immense psychological and physical pressure make HWs one of the most vulnerable groups of workers [1], [2], [3], [4].

The occupational risk to which the HWs are exposed is obvious. Examples exist from the early onset of the pandemic – the infection of around 3000 HWs in the Hubei province, China and the death of Dr. Li Wenliang from Wuhan, who was one of the first who raised awareness for the severe acute respiratory syndrome CoV (SARS-CoV)-2 infection [5]. The latest updates report a proportion of 23% of infected HWs among confirmed cases from 15 countries in the EU/EAA and the UK [6], [7]. In Republic of Macedonia, from all confirmed cases until now, 891 (5.6%) COVID-19 cases and 6 deaths were reported among HWs [8].

The constant changes in the working environment, together with many unknown elements and uncertainties about the disease, the close contacts with contagious patients, the fear for themselves and their families, highly affects the wellbeing of the HWs. Furthermore, very often HWs without any previous expertise and training in dealing with patients with infectious diseases were recruited because of the shortage of qualified staff [2], [5].

All these factors emphasize the paramount need for ensuring safe workplaces for health-care providers. Three groups of preventive controls currently exist:

1. Administrative (e.g., early recognition of the disease, epidemiological surveillance, and control, providing effective training for HWs)

2. Engineering controls (e.g., use of isolation rooms for patients, appropriate ventilation in the hospital settings), and
3. Availability of adequate personal protective equipment (PPE) – considered essential and effective measures that can prevent the transmission of the virus and reduce the risk that HWs are exposed to Park [4].

Having in mind that no form of PPE can completely protect from transmission, the combination of all three levels of control is crucial for the safety of HWs during the COVID-19 pandemic. Different forms of PPE exist, including surgical masks, respirators, gloves, goggles, glasses, face shields, gowns, and aprons. For every HW, the choice of proper PPE should match their individual risk level of exposure to COVID-19 and the possible ways of transmission [9], [10].

Three modes of transmission of COVID-19 are currently known: Through droplets (from coughing or sneezing), by direct contact (touching or being in contact with body parts contaminated with contagious material) – both originating from direct care with infected patients; and airborne mode (risk for aerosol exposure in HWs who are involved in aerosol-generating procedures [AGPs] [e.g., bronchoscopy and putting the patient on mechanical ventilation]) [11], [12].

Surgical masks, mainly used for patients' protection, are proven to protect HWs from droplet mode of transmission, as well, for utmost of 8 h. They are considered the most common way of protection. For higher levels of protection, respirators are recommended. Based on their filter performance for particles with certain dimensions, three types exist – >0.3 μm: Filtering facepiece (FFP)1 (>80%), FFP2 (>94%), and FFP3 (>99%) [12].

According to WHO, HWs caring for COVID-19 patients should use surgical masks and eye protection (goggles or face shields) for droplet protection, long-sleeved water-resistant gowns, and gloves for contact protection, and when the risk of aerosol exposure exists, the use of respirators (N95, FFP2, FFP3, or equivalent) and water-resistant gowns or aprons is highly recommended [9], [13].

Finally, to prevent exposure and transmission of COVID-19, HWs must correctly use the chosen PPE. Previous epidemic spreads, like the Ebola outbreak, showed that the inappropriate removal or doffing of PPE can lead to infection of HWs [16]. Taking into consideration the aforementioned experiences, providing active and practical training for correct use, doffing, and disposal of PPE, as well as proper assessment of the potential risks for infection at the workplace, are vital in the prevention strategy [14], [10].

In times when adequate COVID-19 vaccination and treatment are not available, putting HWs safety as a priority, by supplying adequate protection and emphasizing the importance of their role in the community, can establish stronger healthcare systems and better chances in fighting with the COVID-19 pandemic [3], [6].

Objective

The aim of the actual study was to assess the availability of PPE in HWs during COVID-19 outbreak, depending on the contacts of HWs with patients who were SARS-CoV-2 positive or self-isolated, and to propose activities toward improvement of detected shortcomings.

We also had an objective to determine: The frequency of daily changing of PPE, the satisfaction of HWs with the available PPE, the available triage of patients at the entrance of the health care facility, as well as available trainings for HWs about the usage of PPE.

Methods

The study was conducted during April-May 2020 after the announcement of the COVID-19 pandemic in Republic of Macedonia. A self-administered questionnaire prefaced with an invitation letter and information about the study was sent to HWs in our country employing electronic communication through different platforms and social media. The invitations were sent on a weekly basis. For this purpose, we used all available social media, such as LinkedIn and Twitter. The communications with professional organizations of HWs were used to increase the number of respondents. Participation in the study was voluntarily and anonymously.

We used an on-line questionnaire that was created following the WHO and CDC recommendations on the usage of PPE in HWs during an actual pandemic. The study instrument was developed through the collaboration of Institute of Occupational Health of RM, WHO CC, Skopje, Republic of Macedonia with the WHO CC for Occupational Health within the Faculty of Medicine, University in Zagreb, Croatia.

The survey instrument contained items about the availability of PPE (e.g., masks, respirators, gloves, goggles, face shields, scrubs, aprons, and gowns) in HWs during COVID-19 pandemic, the frequency of daily changing of PPE, the satisfaction of HWs with the available PPE, the available triage of patients at the entrance of the health-care facility, as well as available trainings for HCWs about the usage of PPE.

During survey development, we have validated the study instrument. Semi-structured interview was employed since the questionnaire used was not a standardized instrument. A small group of HWs (n = 10) was interviewed in order to modify the questionnaire and to assess the relevance, adequacy, and understandability of the proposed items by using a Likert scale and scores from 1 (not relevant at all, not adequate at all, or not understandable at all) to 5 (very relevant, very adequate, or very understandable).

Completed surveys were returned by 560 HWs – 297 physicians (187 specialists, 110 residents), 79 nurses/technicians, 78 dentists, 9 pharmacists, and 97 other HWs. Participants were 69.5% female (n = 389). They had an average age of 40.3 (SD = 9.2) years and they worked in total for an average of 14.2 (SD = 9.4) years. Most of the participants have university degree (n = 330, 58.9%), while others have finished high school (n = 44, 7.9%), have bachelor degree (3 years of university education) or similar (n = 46, 8.2%), or have obtained Master or PhD degree (n = 84, 15%) or other level of education (n = 56, 10%).

Results

The participants, who were involved in the survey (n = 560), reported that during COVID-19 outbreak:

- Had contacts with patients who were self-isolated (n = 50, 8.9%)
- Had contacts with patients who were SARS-CoV-2 positive (n = 45, 8.1%)
- Had contacts with both patients who were self-isolated and patients who were SARS-CoV-2 positive (n = 117, 20.9%), or
- Had no contacts with neither self-isolated nor SARS-CoV-2 positive patients (n = 348, 62.1%).

Table 1 shows the usage of masks and gloves in HWs during the COVID-19 outbreak, depending on the contacts of HWs with patients who were SARS-CoV-2 positive or self-isolated.

Table 1: Different usage of masks and gloves in HWs during COVID-19 outbreak, depending on the contacts of HWs with patients who were SARS-CoV-2 positive or self-isolated

Variable	Contacts with patients who were self-isolated (n = 167) n (%)	Contacts with patients who were SARS-CoV-2 positive (n = 166) n (%)
Use of one surgery mask		
Once	108 (64.7)	134 (80.7)
Two or more times	53 (31.7)	28 (16.9)
Not using	6 (3.6)	4 (2.4)
Using surgery mask while working with patients		
Every time	153 (91.6)	159 (95.8)
Almost every time	8 (4.8)	2 (1.2)
Sometimes	3 (1.8)	1 (0.6)
Almost never	1 (0.6)	1 (0.6)
Never	2 (1.2)	3 (1.8)
Use of one pair of gloves		
Once	147 (88.02)	153 (92.2)
Two or more times	15 (8.98)	12 (7.2)
Not using	5 (3)	1 (0.6)
Using gloves while working with patients		
Every time	149 (89.2)	158 (95.2)
Almost every time	10 (6)	4 (2.4)
Sometimes	4 (2.4)	2 (1.2)
Almost never	3 (1.8)	1 (0.6)
Never	1 (0.6)	1 (0.6)

COVID: Coronavirus disease, HWs: Health workers, SARS-CoV: Severe acute respiratory syndrome coronavirus.

Table 1 data demonstrate that a high proportion of HWs was using one surgery mask for two or more times or not using at all when contacting patients who were self-isolated (35.3%) or patients who were SARS-CoV-2 positive (19.3%). The frequencies of HWs using one pair of gloves for two or more times or not using at all when contacting patients who were self-isolated (11.98%) or patients who were SARS-CoV-2 positive (7.8%) were lower. However, more than 90% of participants were using surgery mask every time or almost every time while working with patients who were self-isolated (96.4%) or who were SARS-CoV-2 positive (97%) and using gloves every time or almost every time while working with patients who were self-isolated (95.2%) or who were SARS-CoV-2 positive (97.6%).

Table 2 shows the usage of goggles/face shields, scrubs/aprons/gowns in HWs during the COVID-19 outbreak while contacting patients who were SARS-CoV-2 positive.

Table 2: Different usage of goggles/face shields, scrubs/aprons/gowns in HWs during COVID-19 outbreak while contacting patients who were SARS-CoV-2 positive

Variable	Contacts with patients who were SARS-CoV-2 positive (n = 166) n (%)
Use of one goggle/face shield	
Once	56 (33.7)
Two or more times	107 (64.5)
Not using	3 (1.8)
Using goggle/face shield while working with patients	
Every time	144 (86.7)
Almost every time	16 (9.6)
Sometimes	4 (2.4)
Almost never	1 (0.6)
Never	1 (0.6)
Use of one scrub/apron/gown	
Once	100 (60.2)
Two or more times	55 (33.2)
Not using	11 (6.6)
Using scrub/apron/gown while working with patients	
Every time	121 (72.9)
Almost every time	17 (10.2)
Sometimes	11 (6.6)
Almost never	4 (2.4)
Never	13 (7.8)

COVID: Coronavirus disease, HWs: Health workers, SARS-CoV: Severe acute respiratory syndrome coronavirus.

Table 2 data show that a high proportion of HWs was using one goggle/face shield (66.3%) or one scrub/apron/gown (39.8%) for two or more times or not using at all when contacting patients who were SARS-CoV-2 positive. High frequencies of participants were using goggle/face shield (96.3%) and scrub/apron/gown (83.1%) every time or almost every time while working with patients who were SARS-CoV-2 positive.

The participants reported that while contacting patients who were SARS-CoV-2 positive (n = 166) have been using the following masks/respirators:

- N95 (Every time 39.8%, almost every time 10.2%, sometimes 13.3%, almost never 3%, never 4.8%, and not available in the healthcare institution 28.9%)
- FFP2 (every time 21.7%, almost every time 9.6%, sometimes 13.3%, almost never 3.6%, never 10.8%, and not available in the healthcare institution 41%), or

- FFP3 (every time 14.5%, almost every time 1.2%, sometimes 9%, almost never 2.4%, never 19.9%, and not available in the healthcare institution 53%)
- The above data are clearly demonstrating that N95, FFP2, and FFP3 masks/respirators were frequently not available in the healthcare institution (N95 – 28.9%, FFP2 – 41%, and FFP3 – 53%) for work with patients who were SARS-CoV-2 positive
- HWs have reported that while working with patients who were SARS-CoV-2 positive (n = 166), they used one mask/respirator in aerosols-producing procedures:
  - Once – 57.2% (n = 95)
  - Two or more times – 39.2% (n = 65), and
  - Did not use masks/respirator – 3.6% (n = 6).

It is shown that a high frequency of HWs (42.8%) was using one mask/respirator for two or more times or not using at all in aerosols-producing procedures with patients who were SARS-CoV-2 positive.

In addition, HWs participating in the survey (n = 560) have been answering on two questions that have been focused on their satisfaction with the availability and the quality of the PPE at their workplace. Likert scale (from 0 = not satisfied at all to 10 = totally satisfied) was used. Concerning their satisfaction with the availability of the PPE at their workplace, 176 (31.4%) were promoters (satisfied), 118 (21.1%) were passives (neutral), and 266 (47.5%) were detractors (not satisfied). Graphical representation could be found in Figure 1.

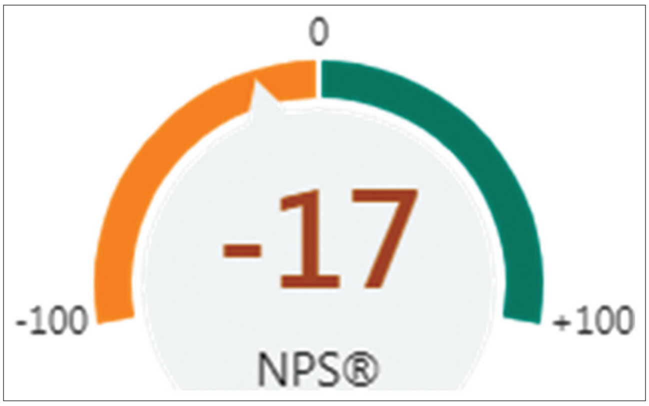

Figure 1: Satisfaction of HWs with the availability of the personal protective equipment at their workplace (in relative numbers)

The data in Figure 1 demonstrates that more HWs were not satisfied than satisfied with the availability of the PPE at the workplace. Concerning HWs' satisfaction with the quality of the PPE at their workplace, 168 (30%) were promoters (satisfied), 124 (22.1%) were passives (neutral), and 268 (47.9%) were detractors (not satisfied). Graphical representation could be found in Figure 2.

Figure 2: Satisfaction of HWs with the quality of the personal protective equipment at their workplace (in relative numbers)

The data in Figure 2 show that more HWs were not satisfied than satisfied with the quality of the PPE at the workplace. Overall, participants (n = 560) reported that during the working hours, they were using one mask:

- <4 h and then using another one – 234 (41.8%),
- Longer than 4 h – 297 (53%), or
- Not using mask – 29 (5.2%).

The above data are clearly demonstrating that a high frequency of HWs (58.2%) was using one mask longer than 4 h or not using mask at all. Concerning the organization of the working space into isolation zones (e.g., "Contaminated," "Potentially contaminated," and "Clean zone") aimed at reducing the spread of SARS-CoV-2, 342 (61.1%) study participants answered that there are no isolation zones in their health care facility. Triage of patients at the entrance of the health care facility was not reported by 187 (33.4%) of evaluated HWs. Of all 560 participants, only 157 (28%) reported that they have attended a training course about the correct usage of PPE. Finally, 144 (25.7%) HWs did not know what to do after unwanted contact with blood or other secretions from a COVID-19 patient.

It is demonstrated that high frequency of participants reported: No isolation zones at the workplace (61.2%), no triage of patients at the entrance (33.4%), not attended a training course about the correct usage of PPE (72%), and did not know what to do after unwanted contact with blood or other secretions from a COVID-19 patient (25.7%).

Discussion

Starting from December 2019, SARS-CoV-2 and COVID-19 became a global health threat [15]. Having in mind the community transmission from asymptomatic individuals, disease burden is expected to rise, resulting in an urgent need for front-line HWs in treating patients. Hence, their work requires close personal exposure to patients with SARS-CoV-2 front-line HWs are at high risk of infection, contributing to its further spreading [1]. It is estimated that HWs may account for 10–20% of all COVID-19 cases [16], [17].

Consistent use of PPE is important to reduce nosocomial transmission, at least based on experience with other respiratory viruses [18]. UK and USA guidelines recommend wearing the mask for HWs caring for people with COVID-19 [19], [20]. Global shortages of masks, respirators, face shields, and gowns, caused by surging demand and supply chain disruptions, however, have led to efforts to conserve PPE through extended use or reuse. Furthermore, disinfection protocols have been developed, for which scientific consensus on best practice is scarce [21], [22], [23]. Addressing the needs of front-line HWs during the COVID-19 pandemic is by default a high priority [16], [24]; nevertheless, data to inform such efforts are still insufficient.

The prospective observational cohort study conducted in the UK and the USA within the general community, including front-line HWs, using self-reported data from the COVID Symptom Study smartphone application [25], assessed the risk of COVID-19 by practice location. The results showed that compared with the risk for the general community, risk for front-line HWs was increased in all healthcare settings, but it was highest for those working in inpatient settings (adjusted HR 24.30, 95% CI 21.83–27.06) and nursing homes (adjusted HR 16.24, 95% CI 13.39–19.70). Furthermore, HWs in nursing homes most frequently (16.9%) reported inadequate PPE, whereas inpatient providers reported reuse of PPE most often (23.7%). Front-line HWs had a threefold increased risk of reporting a positive COVID-19 test and predicted COVID-19 infection, compared with the general community, even after exclusion of other risk factors. Among front-line HWs, both reuses of PPE or inadequate PPE were associated with an increased risk of COVID-19. Increased susceptibility to SARS-CoV-2 infection was evident even among those HWs reporting adequate PPE, although the highest risk of infection was registered in those caring for patients with COVID-19 who reported inadequate PPE. The greatest risk, however, was noticed among frontline HWs who worked in inpatient settings (where providers most frequently reported PPE reuse) and nursing homes (where providers most frequently reported inadequate PPE).

Our study showed that a high proportion of HWs reported reusing surgery masks and goggles/face shields or not using them at all when contacting patients who were self-isolated or SARS-CoV-2 positive. In addition, high frequency of HWs in the actual study reported reusing masks/respirators in aerosols-producing procedures with patients who were SARS-CoV-2 positive. It is also noteworthy that in this study, at the beginning of the COVID-19 outbreak, more HWs were not satisfied with the availability and quality of the PPE at the workplace.

The Lancet study [25] also provides evidence that sufficient availability of PPE, quality of PPE, or both usually reduce the risk of COVID-19. The participants included in the actual study reported that N95, FFP2, and FFP3 masks/respirators were frequently not available in the healthcare institution for work with patients who were SARS-CoV-2 positive. However, the reuse of PPE or inadequate PPE might confer comparably increased risk, which is in accordance with findings from one of the first studies to specifically investigate PPE reuse [26]. The greater risk associated with PPE reuse could be related to either self-contamination during repeated application and removal of PPE or breakdown of materials from extended wear. Of note, during the period of this study, disinfection protocols before PPE reuse were not widely available [13], [21]. An assessment of the PPE supply chain and equitable access to PPE should be a part of the deliberate and informed decision making about resource allocation.

In addition, even with adequate PPE, HWs who cared for COVID-19 patients remained at increased risk, stressing the importance of not only ensuring quality and availability of used PPE but also other aspects of its appropriate use and removal in practice. Furthermore, the obtained data underline the possibility for community spread of the infection by HWs, particularly when asymptomatic or mildly symptomatic, and urge to increase testing to decrease hospital-based transmission [1]. One fact that is important is a significant difference in risk for HWs in the UK compared with the USA, which could be attributable to country-specific or region-specific variation in density of population, socioeconomic circumstances, overall availability and/or quality of PPE, and type of healthcare settings. However, the study also reported that HWs in the UK were at higher risk of a positive test and also at greater risk of developing COVID-19 symptoms, which is not related to access to testing. The higher risk which is noted in UK could be associated with a higher infection rate due to differences in the quality and appropriate use of PPE [27] or differences in PPE use for HWs and the general population [28], [29].

The Pakistan study dealing with the preparedness of the healthcare personnel against the COVID-19 outbreak showed that there was a significant improvement in their knowledge about correct methods to make use of PPE which can afterward minimize their chances of getting infected [9]. Having in mind that PPE and testing kits are mostly in shortage in Pakistan, better understanding on these measures will not only be able to make appropriate use of available resources but also reduce costs and the growing economic burden [30], [31]. Therefore, such interventions may and will facilitate local implementation of international guidance that may contribute to flattening the curve. Our study clearly demonstrated that only a third of examined HWs reported that they have attended a training course about the correct usage of PPE, while a quarter of participating HWs did not know what to do after unwanted contact with blood or other secretions from a COVID-19 patient.

Meanwhile, TV and media images of HWs show a large variety of PPE being used, in many cases being worn incorrectly and compromising its effectiveness. On the other hand, every cough and sneeze from infected patient results in a spray of droplets and aerosol containing virus particles. The subsequent effect of this aerosol emission depends primarily on the size of the droplets, larger ones either impact or fall onto surfaces, but smaller ones remain airborne for some extended time periods [32], especially when there is potential exposure from AGPs. In this case, the use of medical (surgical) masks is sufficient in the circumstances where COVID-19 patients are present [33].

Within these circumstances, the healthcare sector needs to be more innovative in seeking out "novel" interventions to prevent infection in HWs. PPE might be an effective control measure but should never be the prime control because it is dependent on the worker's knowledge and skills to use the equipment properly to control this workplace hazard.

It is necessary to make the systems for the protection of workers from infectious risks as efficient as can be. In general, three choices of respiratory protective equipment, suitable for use in health and social care settings, are available nowadays: Surgical masks and disposable FFP, respirators with a face shield, and reusable powered air-purifying respirators (PAPRs). The first two are now commonly used and rely on the wearer fitting the device as closely as possible to the face and mouth. Two relevant standards are available in Europe: FFP2 (nominally reduces exposure by at least 75%) and FFP3 (with a nominal 95% reduction in inhaled particles concentration). FFP respirators better fit to the face, being an important reason why they provide a better protection level compared to surgical masks. The research with fine dust suggests that wearing a surgical mask might on average reduce aerosol concentrations by ~70%, whereas FFP respirators should reduce concentrations inhaled by >95%, on average [34]. PAPRs, however, should provide a more consistent fit and a higher degree of protection (>99.9% reduction in aerosol concentration inhaled) [35]. Brosseau [36] reports a precautionary approach to be provided for healthcare workers exposed to infectious aerosols, but also to receive training on the use of respirators with high protection factors, such as PAPRs. However, until obtaining effective control, the proposed hierarchy of provisional inhalation exposure control measures, able to balance the risk reduction with the availability of supplies is strongly recommended (healthcare workers where infected patients may be present: A visor and FFP3 respirator; healthcare workers in the vicinity of AGPs: Minimum FFP3 and visor, but preferably a PAPR) [37].

Findings of the actual study should be adopted and interpreted with caution as answering bias could rise because it is possible that more affected HWs tended to respond. Furthermore, we have to take into consideration that cross-sectional design is limited with regard to causality. Additional limitations also include the fact that the analyses were based on self-reporting from questionnaires. Future research has to be focused on the differences in the availability and usage of PPE in HWs during the COVID-19 outbreak according to certain demographic (gender, age, and education) and job (profile, tenure, and type of healthcare institution) characteristics.

At the end, we can conclude that we have found several deficiencies in the availability and inconsistencies in the use of PPE in healthcare settings at the beginning of COVID-19 pandemic. The current situation is not unique for our context, as many authors from different countries are reporting such issues. However, the data obtained can be used in the creation and implementation of specific interventions in healthcare settings aimed at providing high-quality PPE. Providing adequate workplace safety through a national healthcare strategy can lead to the prevention of COVID-19 in HWs and contribute positively to a higher quality of patient care.

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Effect of Coronavirus Disease-19 Pandemic to the Volume of Total Hip and Knee Arthroplasty Surgical Service: Experience from a Single Tertiary Orthopedic Hospital in Indonesia

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Abstract

The difficult situation of the coronavirus disease (COVID)-19 pandemic may affect to hip and knee arthroplasty service. Retrospective study was performed to patients who received elective total hip/total knee arthroplasty (THA/TKA) from January to September 2020 at Prof. Dr. R. Soeharso Orthopaedic Hospital, Surakarta, Indonesia. There were a total of 64 THA and 227 TKA from January to September of 2020. There was an extreme decrease in the number of TKA surgery during April, May, and June in 2020. The effect of coronavirus disease-19 pandemic to the decrease of arthroplasty service was mainly in the first 3 months period.

Introduction

The COVID-19 pandemic has been affecting orthopedic services all around the world [1]. Almost all aspects of orthopedic field include emergency service, outpatient service, inpatient service, and elective surgical service, have been significantly altered [2]. Recommendations to postpone elective surgical service have been announced by the national orthopedic society to reduce the COVID-19 spreading [3]. This difficult situation of course also affects the surgical hip and knee arthroplasty service [4]. Although there has been an increasing number of arthroplasty in Indonesia in the previous year [5], the COVID-19 pandemic may also affect to hip and knee arthroplasty service in Indonesia in the recent situation.

Several authors propose some recommendations to optimize the safety of elective surgical services while limiting the spread of COVID-19 [6], [7]. The recommendation manages all aspects of the service include: patients, staff, facilities, surgery, and post-operative management [6]. Another author also recommends an algorithm for resuming elective surgical service in the pandemic situation [7]. With the use of strict screening rules before surgery, elective surgical service may still be possible to perform. In this study, we tried to evaluate the effect of the COVID-19 pandemic to hip and knee arthroplasty surgical service in our institution.

Materials and Methods

This was a retrospective descriptive study of patients who received elective total hip/total knee arthroplasty (THA/TKA) during the period of January to September 2020 (9 months) at Prof. Dr. R. Soeharso Orthopaedic Hospital, Surakarta, Indonesia. All elective THA/TKA during the period were included in the study. We collect the demographic data, total number of surgery, number of surgery at each month, and patient's origin. We also evaluate similar data during the period of January to September 2019 (non-pandemic period) for comparison. Further, we also evaluate trends data of THA/TKA service at our institution during the past 6 years period (2014–2019).

Pre-operative screening at the outpatient clinic was performed on all patients who will receive THA/TKA surgery includes history and clinical examination, laboratory examination, chest radiograph, rapid COVID-19 test, and polymerase chain reaction (PCR) swab test. Internist performed the decision to proceed with elective surgery at our institution. Patients with confirmed COVID-19 based on PCR swab were referred to a special referral hospital of COVID-19 for further care. There were a total of four active arthroplasty surgeons at the division of adult reconstructive surgery at our hospital: Three senior arthroplasty surgeons and one junior arthroplasty surgeon. Among the three senior arthroplasty surgeons, two are aged more than 60 years old. Posterolateral approach was the most commonly used approach for THA at our institution. Medial parapatellar approach was the most commonly used approach in TKA. We did not differentiate between primary or revision arthroplasty surgery in the data presented as the number of revision surgery was very small and predicted to have no special impact in this recent study.

Results

There were a total of 64 THA and 227 TKA from January to September of 2020. The number of TKA was increased compared to the similar period at 2019 with 175 TKA surgeries. A similar number of THA surgeries were performed in 2019 and 2020. No difference in mean of age and proportion of gender between 2019 and 2020 was found [Table 1].

Table 1: Demographic data (January–September)

Parameters	2019	2020
Mean age	57,39	58,27
Male/female	74/165	78/213

There was an increasing number of THA/TKA surgery since the past 6 years, from 2014 to 2019 at our institution (Figure 1).

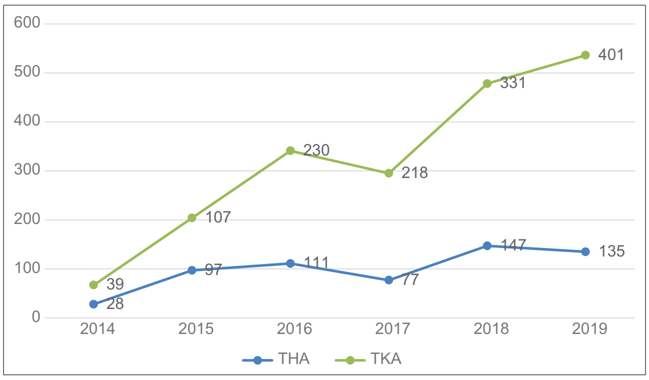

Figure 1: The trend of the total number of total hip and knee arthroplasty by year (2014–2019)

TKA was still predominantly performed surgery compared to THA. In 2019, the peak number of THA-TKA surgeries occurred in April. Conversely, there was an extreme decrease of the number of THA-TKA surgery during April, May, and June in 2020. The number of THA-TKA surgeries regaining its number from July to September 2020 (Figure 2).

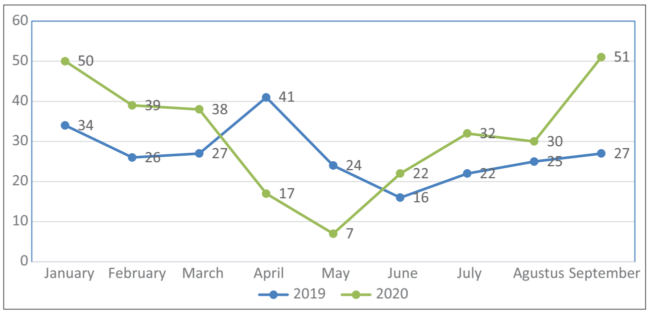

Figure 2: Comparison of total number of total hip arthroplasty during 2019 and 2020 (January–September)

There were only 13, 7, and 14 TKA during April, May, and June 2020. In comparison, the total number of TKA reaches its peak at April 2019 with 41 surgeries (Figure 3).

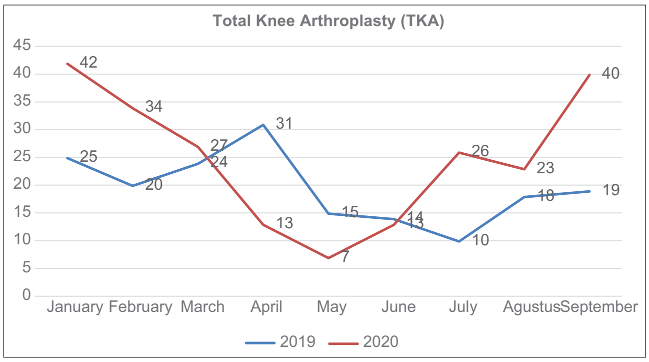

Figure 3: Comparison of the total number of TKA during 2019 and 2020 (January–September)

THA surgeries showed more fluctuated data in the number of surgeries both in 2019 and 2020. However, during the period of April and May 2020, the number of THA surgery was very small (Figure 4).

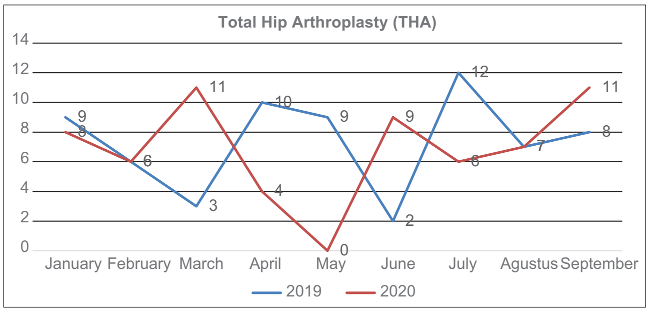

Figure 4: Comparison of the total number of total hip arthroplasty during 2019 and 2020 (January–September)

Patient's origin evaluations showed that patients who came from outside the city but still in the same province were the predominant patient's origin both in 2019 and 2020 (Figures 5 and 6). This is followed by patients who came from the outside province in early 2020 (January, February, and March). However, none of the patients come from another province in May

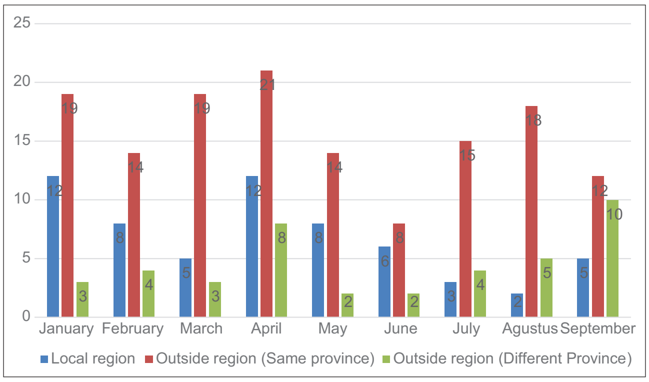

Figure 5: Origin of patients from January to September 2019

2020. Patients who come from outside of the province regain its number in July, August, and September 2020.

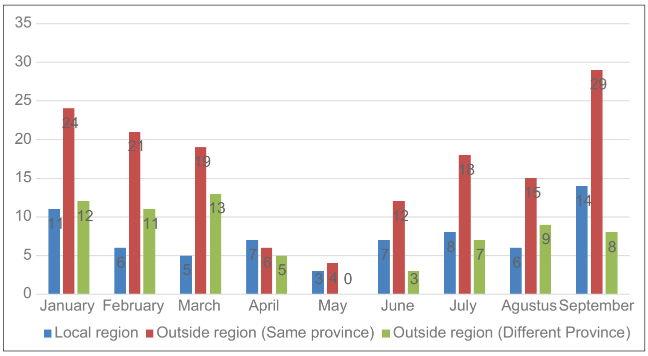

Figure 6: Origin of patients from January to September 2020

Discussion

Since the first confirmed case of COVID-19 in Indonesia in early March 2020, all aspects of medical services in Indonesia have been affected [8]. It is ranged from primary care service until surgery service [9], [10], [11]. There were several previous papers that reported the effect of the COVID-19 pandemic to THA/TKA surgical service from other countries [12], [13]. To the best of our knowledge, this is the first study to report the effect of the COVID-19 pandemic on THA/TKA surgical service in a single institution in Indonesia.

The results of this study showed that the number of THA-TKA surgeries was decreased during the early period of the pandemic, especially in the first 3 months (April, May, and June 2020). In this period, the majority of elective surgeries were canceled and rescheduled to prevent the possibility of severe acute respiratory syndrome-CoV-2 spreading. One of the senior arthroplasty surgeons who aged >60 years old was also advised to be out of duty during April, May, and June 2020 due to the previous history of health problems and categorized as high-risk personal. On the other hand, all aspects of the hospital medical service also in the phase of mitigation and preparation for the possibility of facing the COVID-19 were fulfilled. The availability of personal protective equipment (PPE) was another difficult problem in the early phase of the pandemic in Indonesia. The price of PPE was high and difficult to find in the early period pandemic.

A study in the United States showed that patients with hip/knee arthritis suffering from the pain and continue to struggle with pain due to the disease end-stage during the COVID-19 pandemic. About 90% of patients still want to have surgery as soon as possible [14]. We found a similar situation in which the patient's expectation of receiving THA/TKA surgery was still high at our institution. As the hospital preparedness to face the pandemic situation was better compared to the first 3 months period, the number of THA-TKA surgeries was regained its number starting from July until September 2020. A complete patient screening system combined with the availability of level-3 PPE gives a perception of safety to the person involved in elective surgical service. A recent short-term study at a national referral hospital in Indonesia showed that elective orthopedic surgery might not be associated with increased cases of COVID-19 cases [9]. However, further study is needed to confirm its findings.

The decision in resuming elective surgical service, especially THA/TKA, needs a focused strategy that depends on local condition of the hospital [15]. Our hospital is not a referral hospital for COVID-19 cases. Patients with confirmed COVID-19 based on PCR swab will be referred to a referral hospital of COVID-19 for further care. Recommendations related to the safety of resuming THA/TKA surgical service have been released by several organizations [16], [17]. Several authors reported that the decrease of THA/TKA surgery volume resulted in an economic burden to all involved stakeholders includes patients, physicians, and hospitals/health-care organizations [13], [14], [15]. The burden will be higher, especially for a special orthopedic hospital like in our institution, as orthopedic service is the only core of service in the hospital. Resuming THA/TKA service may give an opportunity for economic recovery while still ensuring the safety of patients and health-care providers [18], [19].

The patient's origin is another issue to discuss in this study. We found that the patient's origin was predominantly from another city but inside the same province. The situation was similar to the previous year 2019. The government of Indonesia did not apply a total whole country "lockdown" during the COVID-19 pandemic. However, restriction of people mobilization and transportation has been applied through a more local restriction program at each city or province, namely "*Pembatasan Sosial Berskala Besar* (PSBB)" [20]. The program started in April 2020 in several regions of Indonesia. This also affected the number of patients who visit our institution during the same period.

There were limitations to this study. This was a descriptive retrospective study, which may have its own weakness. The data were only obtained from a single orthopedic hospital, where the local situation can be different compared to another institution, such as in a general hospital. The period of evaluation was also only 9 months and the local situation of the hospital can be dynamically change with regard to the pandemic situations. However, we believe that this study could give some insight into the early effect of COVID-19 pandemic to THA/TKA surgical service in our institution.

Conclusions

The COVID-19 pandemic has an effect on the volume of THA/TKA service at our institution. The effect was mainly in the first 3-month period. Comprehensive patient screening and complete level-3 PPE should be available before proceed to resume elective THA/TKA service.

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Determinants of COVID-19 Prevention Behavior in the Elderly in Urmia: Application of Health Belief Model

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Abstract

BACKGROUND: COVID-19 disease effects on all age group and sex, especially the elderly, due to the high mortality rate, it is very impressive and the protective measures can reduce mortality in the elderly.

AIM: The present study was conducted to find the determinants of COVID-19 prevention behavior in the elderly in Urmia by emphasizing on the health belief model.

METHODS: The present study was a cross-sectional study on 1400 elderly people in Urmia, Iran in 2020 and the sample selection was *by simple random sampling* by simple random sampling. The data collection tool was a researcher-made questionnaire in this study that included demographic characteristics, health belief model questionnaire, and COVID-19 prevention behaviors. Data were analyzed using ANOVA and linear regression tests using SPSS 23 software.

RESULTS: The results showed that the COVID-19 prevention behavior score has been increased by increasing age rate and this behavior was higher in older women than men ($p = 0.02$). Furthermore, linear regression test showed the most predictive constructs as knowledge ($B = 0.38$), perceived susceptibility ($B = 0.29$), perceived intensity ($B = 0.25$), and perceived self-efficacy ($B = 0.21$, respectively) and these structures were statistically significant ($p < 0/05$).

CONCLUSION: Effective interventions based on the health belief model and emphasizing on promoting knowledge, perceived susceptibility, severity, and perceived self-efficacy can prevent the elderly from developing this disease and its complications.

Introduction

The COVID-19 pandemic disease has devastated the global economy and financial markets, and it forced the governments to take drastic public health measures to decrease the effects of the disease [1]. The virus has caused panic throughout the world and has affected on all age and sex groups. Elderly are one of the most at risk groups and according to epidemiologists, age is the most important factor in reducing the survival of COVID-19, especially after 65 years [2], [3]. Thus, targeting the elderly and try to persuade them to follow public health precautions are the strategies of governments around the world [4]. According to the high mortality rate among the elderly and the clear goal of governments around the world, it is only reasonable to expect elderly to be more conscientious than young people in preventing COVID-19. However, the results of the Daoust's study in 27 countries were unfortunately alarming and worrying in 2020, and despite the fact that elderly are much more likely to die from COVID-19 disease than other age groups, they are less likely to follow preventative guidelines such as staying at home [5].

Poor preventive measures in the elderly show that, they do not understand about the importance of the issue and do not think about COVID-19 disease as a threat to their health. Determinants and affecting factors on the preventive behavior of the disease must be identified to find preventive measures and control of COVID-19 disease [6]. Evidence also suggests that identifying determinants and protective measures as effectively and accurately as possible requires the use of patterns and theories of behavior change [7]. One of the models which were used to prevent the disease is the Health Belief Model (HBM). The HBM model is a well-accepted psychosocial model for behavior change and is used to describe the relationship between belief and behavior. HBM assumes that people's involvement in the prevention, early detection, and treatment of related measures to a particular health problem depends on their understanding in which they are at risk of the disease even if they do not suffer from its symptoms perceived susceptibility). Moreover, they should know that the disease is a health problem which can lead serious complications (perceived severity); they should believe that the benefits of the proposed preventive measures (perceived benefits) are more than the anticipated barriers (perceived barriers). In addition, they should believe that they are motivated and able to lead a healthy lifestyle and the capacity to do protective behaviors (self-efficacy). In addition, HBM hypothesizes that guidance for action can increase interaction in preventive behavior as an internal and external behavioral stimulus [8], [9].

According to the necessity of performing protective behaviors against COVID-19 infection and strict observance of health protocols among the elderly, the determinants of COVID-19 prevention behavior among these groups in designing and implementing appropriate educational interventions to promote protective behaviors are promising the beneficial effects. Therefore, considering the role of HBM model in preventing behaviors that protect against disease, the present study was conducted to find the determinants of COVID-19 prevention behavior in the elderly in Urmia with emphasis on the health belief model.

Materials and Methods

Study design and population

This cross-sectional study was conducted to investigate the determinants of coronavirus (COVID-19) prevention in the elderly based on the health belief model in health centers in Urmia, Iran in 2020.

Study tool

Data collection tools in this study were a researcher-made questionnaire that included demographic characteristics of the subjects, coronavirus knowledge questionnaire, coronavirus prevention behaviors questionnaire, and health belief model questionnaire.

Knowledge assessment was in the form of 16 questions, which was prepared in the form of “Yes”, “I do not know”, options, the “Yes always” option was given a score of 2, the “I do not know” option was given a score of 1, and the “No” option was given a score of 0. Scores of knowledge questionnaire range from zero to 32. Questions and scores of health belief model structures is based on the Likert scale of five options (strongly agree, agree, have no opinion, disagree, strongly disagree) that the score of “totally agree” option is 5 and the score of “strongly disagree” option is 1. Each structure had 6 questions and minimum and maximum scores were 6-30 points. 12 questions with three options “always,” “sometimes,” “never” were used to assess COVID-19 prevention behavior. The score of “always” option was 2 points, the score of “sometimes” option was 1 point, and the score of “never” option was 0 point. Scores for coronavirus prevention behavior questions range from zero to 24.

Validation and pilot study

The items of each desired outcomes were selected by reviewing the literature and for the validity and reliability of these questionnaires, content validity methods, and Cronbach’s alpha test were used, respectively, it was sent to 10 health education specialists and geriatrician to find the validity of the questionnaire. Based on the opinions of these experts, the necessary amendments were made to the questionnaire. The validity of the questionnaire was higher than 80%. To measure reliability, the questionnaire was completed by 30 elderly people who were not part of the intervention and control group, and reliability coefficient of knowledge questions 0.76, perceived susceptibility 0.77, perceived severity 0.80, comprehension barriers 0.81, guideline for action 0.84 perceived benefits 0.86, and self-efficacy 0.78 coronavirus prevention behavior was calculated 0.73 using Cronbach’s alpha test.

Data collection

Healthcare providers contacted elderly families by telephone, and the study goals were explained to all participants in the study. The questionnaires were then completed by telephone interview for the elderly. Inclusion criteria were age group over 60 years, ability to answer by phone, non-resident of nursing home, and exclusion criteria were the dissatisfaction and unwillingness to continue answering the questionnaires.

Sampling

According to the elderly population of Urmia (51,000 people), 2.8% of this population was considered as the study population which about 1,400 people entered the study. By simple random sampling method, 2.8% of the elderly were selected from 30 health centers in Urmia in proportion to the population of each health center.

Statistical analysis

Descriptive statistical methods were used to summarize data on sociodemographic characteristics. Data were summarized as frequencies (n) and percentages (%) for categorical variables. The ANOVA tests were used to find the relation between mean COVID-19 prevention behavior and sociodemographic variables. In the case of a significant ANOVA test, post hoc analysis (LSD) was performed for multiple comparisons between each two categories. Furthermore, the linear regression test was used to predict coronavirus prevention behavior in the elderly. All data analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 23.

Results

The mean age of the elderly was 66. 6± 4.97 years. The highest age group was in the age group of 60–65 (33%). Most of the elderly were housewives (49%) and marital status indicates that most of the elderly in the study were married (70%). Furthermore, most of the elderly were illiterate in terms of education (51%). In terms of economic situation, most of the elderly had poor economic status (41.5%). The elderly suffered from chronic disease were 72.5% (cardiovascular, respiratory, diabetes, and hypertension) (Table 1).

Table 1: Frequency and percentage of distribution of demographic characteristics of the studied elderly

Variables	Number	Percent
Age		
60–65	462	33
65–70	420	30
70–75	350	25
80–75	168	12
Sex		
Male	686	49
Female	714	51
Job		
Housewife	686	49
Employed	224	16
Retired	420	30
Out of work	70	5
Marital status		
Married	980	70
Single	196	14
Divorced/widow	224	16
Education		
Illiterate	714	51
Elementary	490	35
Diploma and Postgraduate	196	14
History of chronic diseases		
Yes	1015	72.5
No	385	27.5
The economic situation		
Weak	581	41.5
Moderate	514	36.7
Good	305	21.8

The results of ANOVA test showed that the score of COVID-19 prevention behavior increased by increasing age and this difference was significant (p = 0.02). Furthermore, in women, the COVID-19 prevention behavior score was higher than men and was statistically significant (p = 0.03). On the other hand, the score of COVID-19 prevention behavior in single elderly (single, divorced/deceased spouse) was lower than married elderly (p = 0.04). Another result of the study indicates that people who have at least one chronic disease (cardiovascular, respiratory, diabetes, hypertension, etc.) have a more unfavorable preventive behavior than other people (p = 0.01) (Table 2).

Table 2: Demographic information and its relationship with COVID-19 prevention behavior in the studied elderly

Variables	Mean and standard deviation of COVID-19 preventive behavior score	p-value
Age		
60–65	16 (1.8)	0.02*
65–70	15 (2.7)	
70–75	16 (2.2)	
<75	18.4 (2.4)	
Sex		
Male	15.8 (3.9)	0.03*
Female	18.2 (38)	
Job		
Housewife	16.2 (4.2)	0.2
Self-employed	15.6 (2.1)	
Retired	16.5 (1.7)	
Out of work	15.8 (28)	
Marital status		
Married	18.4 (2.6)	0.04*
Divorced	16.6 (1.3)	
Widow/widower	15.8 (3.1)	
Education		
Illiterate	16.39 (2.9)	0.08
Elementary	17.73 (3.3)	
Junior	17.9 (2.1)	
Diploma and Postgraduate	16.4 (1.7)	
History of diseases chronic		
Yes	15.1 (2.1)	0.01*
No	18.8(3.5)	
The economic situation		
Weak	17.2 (3.1)	0.08
Moderate	15.6 (2.3)	
Good	16.8 (3.2)	

According to the linear regression test to predict coronavirus prevention behavior in the elderly, respectively, the most predictive construct was knowledge (B = 0.38), the second construct was perceived susceptibility (B = 0.29), and the third construct was perceived severity (B = 0.25) and the fourth construct was perceived self-efficacy (B = 0.21) and these constructs of the health belief model are statistically significant in predicting the coronavirus prevention behavior of the elderly (p < 0.05) (Table 3).

Table 3: Findings of linear regression model in predicting COVID-19 preventive behaviors in the elderly

Independent variables	ß (regression coefficient)	SE	Beta	t	p-value
Knowledge	0.38	0.097	0.32	3.961	0.001
Perceived susceptibility	0.29	0.087	0.18	2.6	0.02
Perceived severity	0.25	0.085	0.16	2.5	0.03
Perceived benefits	0.04	0.045	0.06	1.21	0.7
Perceived barriers	−0.02	0.07	−0.09	2.02	0.6
Cues to action	0.06	0.08	0.07	1.05	0.9
Perceived self-efficac	0.21	0.083	0.15	2.15	0.04

Discussion

The results showed that elderly had higher disease prevention behavior. In fact, these people thought about the COVID-19 threat and believed that the threat was related to them. According to the WHO, elderly are at higher risk of the disease [10]. Iran's media and health care system provide significant programs to show that the risk of elderly is too high about the disease. This may have led elderly to learn that they are more susceptible to the disease and should consider more on preventive behavior.

In this study, it was found that older women had better COVID-19 prevention behaviors than men.

The results of Bell *et al*.'s study (2005) showed that women with diabetes had better self-care behaviors than men [11]. Gender differences in disease prevention behaviors can be derived from differences in knowledge, perceived susceptibility, and perceived severity of the disease and its duration, as well as the other diseases in men and women [12]. On the other hand, the results showed that there is a significant relationship between marital status and COVID-19 prevention behavior in the elderly. So that disease prevention behavior is more in married elderly. These results are consistent with the results of the study of Seow *et al*. that divorced and single people had uncontrolled hypertension [13]. Adoption of disease-preventing behaviors is more common among people who are in daily contact with their partner, and these behaviors are mostly through direct social control such as reminding, encouraging, monitoring, or even threatening [14], [15]. Furthermore, the existence of social support such as family can play an effective role in adopting preventive behaviors among the elderly.

The study found that people with at least one chronic illness (cardiovascular, respiratory, diabetes, or high blood pressure) had poorer preventive behaviors than others. This unfavorable attitude toward the prevention of this disease can indicate that these people are more at risk. Jahangiry *et al*. showed that people who did not have any chronic disease were more sensitive and had efficacy than those with a history of chronic disease, and their fear of COVID-19 was higher [16]. It can be considered that people who have an underlying disease, due to a more unfavorable attitude than other people, have a denial of a severe disease in themselves and believe that severely occurring this disease in them is less. The results of linear regression showed that there is a statistically significant relationship between the four variables of knowledge, perceived susceptibility, perceived severity, and perceived self-efficacy with the variable of coronavirus prevention behavior.

Knowledge structure was the most predictive of COVID-19 prevention behavior. Elderly people with high knowledge of COVID-19 had more coronary preventive behaviors. The study of Mahmoodabad *et al*. [17] showed that there was a significant correlation between knowledge and prevention behavior of falls in the elderly. An effective step can be taken in the prevention of this disease by increasing knowledge of the disease and ways of transmission, ways of prevention and affecting factors on COVID-19 disease. However, studies have shown that preventive behaviors cannot be improved by increasing knowledge alone. Therefore, to meet long-term self-care, creating attitudes and motivating people is more important than knowledge alone [18], [19].

In the present study, there was a significant relationship between perceived susceptibility variable and COVID-19 prevention behavior. High perceived susceptibility of people seems to lead to better performance in performing preventive behaviors. Raamkumar emphasized the role of perceived susceptibility in maintaining physical distance during COVID-19 outbreaks [20]. The high perceived susceptibility of the people indicates that they believe they are at higher risk of the disease. Therefore, the presence of this high perceived susceptibility will cause them to take the lead in performing preventive behaviors. The results show that there is a significant relationship between perceived intensity constructs and COVID-19 prevention behavior variable. This can be due to the knowledge of serious risks such as shortness of breath and extreme fatigue, neurological problems, including dizziness and impaired sense of smell and taste, the possibility of renal infarction and consequently the possibility of irreversible damage to other organs, brain dysfunction, stroke, or meningitis is one of the most important factors in raising the level of perceived severity in this regard. A study by Lin *et al*. showed that there is a significant relationship between the severity and perceived threat of AIDS and the reduction of high-risk behaviors [21]. Therefore, if the elderly are aware of the complications of COVID-19 and they fear that they may have these complications after contracting the disease; most of them will follow COVID-19 prevention behaviors.

Self-efficacy is a person's judgment of his or her ability to prevent COVID-19. In the present study, self-efficacy was one of the predictors of disease prevention behavior, which is consonant with Conn's study in which that self-efficacy was considered as the most important predictor of physical activity in the elderly [22] and with the study of Mahmoodabad *et al*. in which self-efficacy has been mentioned as a reason in promoting fall prevention behavior [17]. It seems that the elderly should work to improve their self-efficacy in adopting COVID-19 prevention behaviors.

Conclusions

The promotion of knowledge, perceived susceptibility, severity, and perceived self-efficacy can prevent the elderly from developing this disease and its complications. We recommend that careful educational planning for the elderly was strong predictors of COVID-19 prevention behavior which it was based on the health belief model on the structures of knowledge, perceived susceptibility and perceived severity and perceived self-efficacy to prevent the elderly from contracting this disease and its complications.

Limitations of the Study

The distribution of the survey through the phone allowed only those who can answer and have phone access to take part. This represents a major limitation of this study.

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of the Islamic Azad University with code (IR.IAU.TABRIZ.REC.1399.110).

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