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SARS-CoV-2 Reverse Transcription-Polymerase Chain Reaction Positivity and Seroprevalence among Health Care Workers in a Referral Cancer Institute: A Cross-sectional Study

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Abstract

BACKGROUND: During the ongoing coronavirus disease 2019 pandemic, healthcare workers (HCWs) are presumed to be at increased risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), transmitting the infection to vulnerable patients if they are not timeously isolated.

AIM: This study aimed to determine the point prevalence of SARS-CoV-2 infection in a cohort of HCWs providing oncology services.

METHODS AND RESULTS: HCWs in a large referral cancer hospital in Egypt were tested using real-time reverse transcription-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs, and immunochromatography-based rapid serological test (RST). Clinical and epidemiological data were collected. In 2020, 999 HCWs were screened, of whom 86 tested positive for SARS-CoV-2 by RT-PCR (8.6%) and 127 subjects were seropositive for antibodies against SARS-CoV-2 by RST (12.8%). Immunoglobulin M seroprevalence demonstrated considerable concordance with RT-PCR positivity (sensitivity 82.14% and specificity 96.71%). Most HCWs (>95%) reported adherence to personal protective equipment. Patient transporters/cleaner were the group with the highest frequency of positive RT-PCR (19%) whereas laboratory and radiology technicians displayed the lowest frequency. Fever, dry cough, rhinorrhea, shortness of breath, fatigue and diarrhea were significantly associated with RT-PCR positivity, with increased likelihood of being positive with the presence of five or six simultaneous symptoms.

CONCLUSIONS: The point prevalence of SARS-CoV-2 infection in screened HCWs is 8.6% by RT-PCR and seroprevalence is 12.8% by RST. Strict measures should be implemented to minimize transmission within healthcare settings and to the community. Our data support the importance of HCWs screening for SARS-CoV-2, taking in account the significant proportion of asymptomatic carriers.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in coronavirus disease 2019 (COVID-19), has posed major challenges to healthcare systems globally [1], as well as, locally with the first laboratory confirmed case of COVID-19 in Egypt declared on February 14, 2020 [2]. Healthcare workers (HCWs) worldwide have been on the frontlines fighting this pandemic, accounting for a substantial proportion of COVID-19 cases [3]. A study of more than 72,000 patients with COVID-19 by the Chinese Centre for Disease Control and Prevention showed that by early February around 3000 HCWs had become infected, accounting for 3.8% of all cases of COVID-19 [4]. In Europe, HCWs accounted for 8% of total cases in Italy in early March [5] rising to 10.5% in late April [6], whereas, 26% of confirmed COVID-19 infections in Spain, were HCWs [7]. As of April 9, a total of 9282 HCWs in the U.S. were confirmed to have COVID-19, as reported to the Centers for Disease Control [8]. Understanding risk factors of SARS-CoV-2 infection in HCWs is of utmost importance, as it helps policymakers to formulate appropriate infection control measures in the hospital setting [9].

The unprecedented burden of COVID-19 has important implications for cancer care [10]. Given the extrinsic factors of the current pandemic (e.g., high morbidity/mortality and resource constraints) and the intrinsic factors of patients with cancer (e.g., highly vulnerable population, immunosuppressed state caused by the cancer itself or its treatment), HCWs in cancer facilities face great responsibilities to navigate the

COVID-19 health crisis [11]. Oncology often requires a complex set of clinic visits, laboratory blood draws, imaging studies, infusion sessions, radiation therapy appointments and hospital admissions. Collectively, caring for patients with cancer requires numerous contact points, with resultant potential opportunities for SARS-CoV-2 transmission [12]. Major oncology societies have issued recommendations to guide HCWs on the proper measures to sustain timely, appropriate health services to cancer patients while protecting themselves from becoming infected with SARS-CoV-2 [13].

Although, several papers describe prevalence and outcomes of COVID-19 in patients with cancer, there is a paucity of studies describing its impact on HCWs providing services to this vulnerable group of patients. This study was conducted to determine the extent of SARS-CoV-2 infection by real-time reverse transcription polymerase chain reaction (RT-PCR) and an immunochromatography based rapid serological test (RST) among HCWs providing oncology services.

Subjects and Methods

This study was approved by the Research Ethics Committee of the National Cancer Institute (NCI). Informed consent was obtained from all HCWs for data collection and SARS-CoV-2 testing. Participants reported demographic and medical history, exposure to a patient or another co-worker with suspected or confirmed SARS-CoV-2 infection, in addition to symptoms compatible with COVID-19 in the 14 days preceding SARS-CoV-2 testing. Nasopharyngeal swabs on a viral transport media and whole blood samples collected from participants were sent to the virology and immunology unit, cancer biology department, NCI to detect SARS-CoV-2 RNA using real-time RT-PCR and anti-SARS-CoV-2 immunoglobulin M (IgM) and IgG antibodies using RST.

SARS-CoV-2 RST

Igs were detected by COVID-19 rapid IgM-IgG combined antibody test (BioMedomics Laboratories, North Carolina, USA). This is a lateral flow immunoassay used to detect anti-SARS-CoV-2 IgM and IgG antibodies in human serum, plasma, or whole blood *in vitro*. 50 ul of whole blood and 100 ul of buffer were added to sample well and the results were read after 10 min, with a 96.7% sensitivity and a 97.1% specificity as reported by the manufacturer.

Detection of SARS-CoV-2 RNA in nasopharyngeal swabs

The genesig real-time PCR COVID-19 CE IVD (Genesig kit, primer design, United Kingdom) is intended to be used to achieve qualitative detection of COVID-19 viral RNA extracted from nasopharyngeal swabs, oropharyngeal swabs using applied Biosystems 7500 fast. For detection of SARS-CoV2 RNA, a total of 250–300 μL of each nasopharyngeal swab sample was used for viral RNA extraction using the QIAMP VIRAL RNA mini kit (Qiagen, Hilden, Germany) with an internal PCR control according to the manufacturer's instructions. The extracted viral RNA was used directly for amplification using Genesig real-time PCR Detection Kit using two primers/probe. One primer and TaqMan probe labeled at the 5'-end with the reporter molecule 6-carboxyfluorescein (FAM) for SARS-Cov-2 detection and the other primer/probe for internal extraction control detection labeled at the 5'-end with the reporter molecule Hexachloro-fluorescein for the test validation.

Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were described as mean ± standard deviation (SD). Chi-square testing was done as appropriate for comparison of features between positive and negative groups. $p < 0.05$ was considered statistically significant. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated, along with the 95% confidence interval (CI).

Results

A total of 999 HCWs were enrolled in the study. The mean age of participants was 37.79 ± 8.87 and 52.6% were females. Around half of the screened HCWs (52.3%) were administrative employees, 22% were nurses and 10.2% were physicians. Exposure to suspected or confirmed COVID-19 cases in the preceeding 2 weeks was reported by 136 participants (13.6%), whereas, only four HCWs (0.4%) reported travel during the preceding month.

Overall, 86 HCWs tested positive for SARS-CoV-2 by RT-PCR (8.6%). The characteristics of these individuals are summarized in Table 1. The age, sex, travel history, smoking habits and co-morbidities except diabetes, did not show any significant association with RT-PCR positivity to SARS-CoV-2. The proportion of positive RT-PCR ranged from 19% (16/84) among patient transporters/cleaners to 11.4% (25/220) among nurses, 7.6% (40/522) among administrative employees and 3.9% (4/102) among physicians with minimal frequencies among laboratory and radiology technicians (1/52 and 0/19 respectively). Approximately, 44.2% of the positive RT-PCR individuals reported exposure to COVID-19 cases in the preceeding 2 weeks. Most

participants (>95%), even in RT-PCR positive group, confirmed that they adhered to personal protective equipment (PPE), by wearing masks as recommended. Meanwhile, a total of 127 subjects were seropositive for antibodies against SARS-CoV-2 by RST (12.8%). Of those, 91 were positive for IgM only (9.1%), 28 were positive for IgG only (2.8%), and 8 showed simultaneous IgM and IgG positivity (0.8%).

Table 1: Demographic, epidemiological and clinical characteristics of total healthcare workers screened for SARS-CoV-2, including individuals with positive RT-PCR test

Characteristic	Total		Negative PCR		Positive PCR (n = 86)		p-value**
	n (±)*	%	n (±)	%	n	%	
Age (years), mean ± SD	37.79 ± 8.87		37.70 ± 8.91		38.76 ± 8.51		0.29
Gender							
Male	474	47.4	436	47.8	38	44.2	0.53
Female	525	52.6	477	52.2	48	55.8	
Smoking							
Current	115	11.6	105	11.6	10	11.6	0.13
Former	12	1.2	9	1.0	3	3.5	
No	865	87.2	792	87.4	73	84.9	
Exposure to case	136/859	13.6	98/811	10.8	38	44.2	<0.01
Wearing mask	968/31	96.9	885/28	96.9	83	96.5	0.83
Travel history	4/959	0.4	4/873	0.5	0	0.0	0.53
Occupation							
Physician	102	10.2	98	10.7	4	4.7	<0.01
Nurse	220	22	195	21.4	25	29.1	
Reception/ Administrative clerk	522	52.3	482	52.8	40	46.5	
Laboratory technician	52	5.2	51	5.6	1	1.2	
Radiology technician	19	1.9	19	2.1	0	0	
Patient transporter/ Cleaner	84	8.4	68	7.4	16	18.6	
Co-morbidities							
Asthma	87/906	8.8	84/823	9.3	3	3.5	<0.05
COPD	39/960	3.9	33/880	3.6	6	7	0.13
Diabetes	110/888	11.0	93/819	10.2	17	19.8	<0.01
Hypertension	116/882	11.6	106/806	11.6	10	11.6	0.99
Coronary heart disease	36/955	3.6	32/873	3.5	4	4.7	0.59
Rheumatic heart disease	5/993	0.5	4/908	0.4	1	1.2	0.36
Chronic liver disease	23/993	2.3	19/894	2.1	4	4.7	0.13
Cancer	1/996	0.1	1/910	0.1	0	0.0	0.76
Immunodeficiency	62/937	6.2	53/860	5.8	9	10.5	0.08
Symptoms							
Any symptom at time of swab	331/668	33.1	295/618	32.3	36	41.9	<0.05
Fever	22/977	2.2	7/906	0.8	15	17.4	<0.001
Dry cough	74/925	7.4	60/853	6.6	14	16.3	<0.001
Productive cough	51/932	5.2	46/851	5.1	5	5.8	0.78
Sore throat	58/940	5.8	50/862	5.5	8	9.3	0.15
Rhinorrhea	69/927	6.9	54/856	5.9	15	17.4	<0.001
Headache	119/879	11.9	110/802	12.1	9	10.5	0.66
Dyspnoea	48/949	4.8	37/874	4.1	11	12.8	<0.001
Myalgia/arthralgia	72/927	7.2	63/850	6.9	9	10.5	0.22
Diarrhea	55/943	5.5	46/866	5.0	9	10.5	<0.05
Fatigue	54/944	5.4	42/870	4.6	12	14.0	<0.001
Conjunctival congestion	92/906	9.2	81/831	8.9	11	12.8	0.23

*Number of positive versus negative, **From Chi-squared test, COPD: Chronic obstructive pulmonary disease, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, RT-PCR: Reverse transcription-polymerase chain reaction.

Participants in this study were divided into two groups: those with positive RT-PCR (n = 70) findings for SARS-CoV-2 and those with negative RT-PCR (n = 79) results for SARS-CoV-2.

As shown in Figure 1, amongst the 86 HCWs with RT-PCR positive samples, the RST detected 75 seropositive (89.3%) HCWs, either to IgM (n = 61, 72.6%), IgG (n = 6, 7.1%) or both (n = 8, 9.5%). On the contrary, only 5.7% of the subjects with negative RT-PCR were seropositive (n = 52). Performance

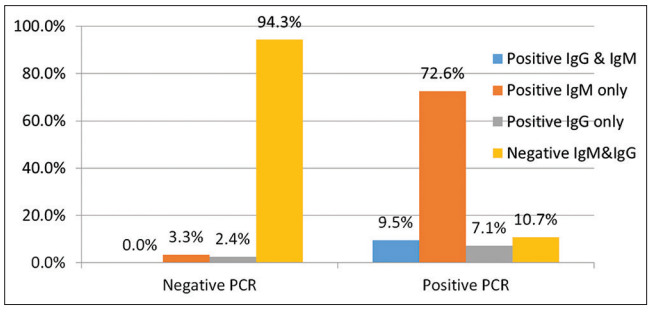

Figure 1: Seroprevalence of anti-severe acute respiratory syndrome coronavirus 2 immunoglobulin M and immunoglobulin G antibodies by rapid serological test in reverse transcription-polymerase chain reaction (RT-PCR)-positive and RT-PCR-negative healthcare workers

characteristics of RST compared to RT-PCR are shown in Table 2. In the current study, the sensitivity of IgM was 82.14% (95% CI: 72.26–89.65) and the specificity was 96.71% (95% CI 95.33–97.77). The PPV and the NPV of were 69.70% and 98.33%, respectively. When calculated for IgG, the sensitivity became 16.67% (95% CI: 9.42–26.38) and the specificity, PPV and NPV being 97.59% 38.89% and 92.70%, respectively.

Table 2: Performance characteristics of rapid serological test in comparison to RT-PCR

Measure	IgM and/or IgG		IgM		IgG	
	Value (%)	95 CI	Value (%)	95% CI	Value (%)	95% CI
Sensitivity	89.29	80.63–94.98	82.14	72.26–89.65	16.67	9.42–26.38
Specificity	94.29	92.58–95.71	96.71	95.33–97.77	97.59	96.37–98.48
PPV	59.06	52.30–65.48	69.70	61.47–76.83	38.89	25.28–54.48
NPV	98.96	98.09–99.44	98.33	97.38–98.94	92.70	92.02–93.33
Accuracy	93.87	92.19–95.28	95.48	93.99–96.68	90.75	88.78–92.48

IgM: Immunoglobulin M, IgG: Immunoglobulin G, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, RT-PCR: Reverse transcription-polymerase chain reaction.

Finally, the performance of VivaDiag COVID-19 IgM/IgG Rapid Test LFIA was tested in 50 patients at their first access at emergency room department with fever and respiratory syndrome (34 M/16 F; median age, 61.50; range, 33–97 years) in comparison with results of nasal swab molecular screening.

The association between selected symptoms and RT-PCR results is shown in Table 1. Thirty three percent of participants (n = 331) reported symptoms concomitant with COVID-19 at the time of swab. Among those HCWs, the frequency of positive molecular tests was 10.9%, while among asymptomatic HCWs the frequency was slightly lower (7.5%). Among the 86 RT-PCR positive subjects, 50/86 (58.1%) were asymptomatic at the time of testing with RT-PCR, whereas, 36 HCWs had at least one symptom associated with COVID-19 (41.9%). SARS-CoV-2 positive HCWs reported several symptoms more frequently than those with negative assays: fever (17.4% vs. 0.8%), rhinorrhea (17.4% vs. 5.9%), dry cough (16.3% vs. 6.6%), fatigue (14% vs. 4.6%), dyspnoea (12.8 vs. 4.1%) and diarrhoea (10.5% vs. 5%). Total symptoms reported at time of swab ranged from 0 to 7, with increased likelihood of being RT-PCR positive in case of presence of five or six simultaneous symptoms (Table 3).

Table 3: Association between number of symptoms and proportion of RT-PCR positivity among healthcare workers tested for SARS-CoV-2

Number of symptoms	Subjects	Positive test	%	p-value*
No symptoms	668	50	7.5	<0.001
One symptom	190	10	5.3	
Two symptoms	60	9	15	
Three symptoms	33	3	9.1	
Four symptoms	19	3	15.8	
Five symptoms	10	5	50	
Six symptoms	6	3	50	
Seven symptoms	12	3	25	

**From Chi-squared test, RT-PCR: Reverse transcription-polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Finally, we observed a mean time from first positive RT-PCR test to a negative test being 2.83 ± 1.68 days (Figure 2) with the majority of cases becoming negative within 2 days. However, 2/76 subjects were still positive 7 days after first positive test.

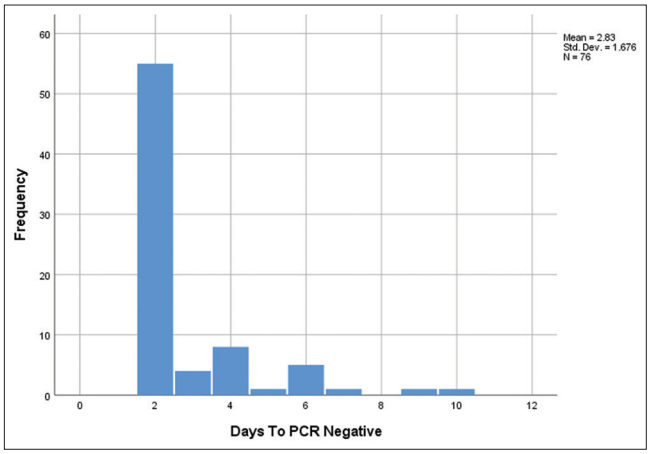

Figure 2: Duration to first negative test result among 76 reverse transcription-polymerase chain reaction positive healthcare workers

Discussion

HCWs have been hard-hit by the COVID-19 pandemic with several reports of resultant morbidity, posing a risk to vulnerable patients and fellow workers in addition to potential propagation of hospital-to-community transmission [14]. Previously, nosocomial outbreaks of SARS-CoV and Middle East respiratory syndrome coronavirus played an important role in their spread [15]. Nonetheless, characterization and quantification of healthcare personnel infected with SARS-CoV-2 are under-studied [16]. To our knowledge, this is the first study to describe the real-life situation of SARS-CoV-2 among HCWs in a large referral institute providing oncology services to the particularly vulnerable cancer patients.

In this study, a total of 86 SARS-CoV-2 cases were confirmed by positive RT-PCR (8.6% of screened HCWs). This proportion is comparable to the 6% described by Kluytmans-van den Bergh *et al*. in a Dutch cohort of 1353 HCWs [17], and the 8.8% described by Lombardi *et al*. in an Italian cohort of 1573 HCWs [18], whereas it is significantly lower than the 38% reported by Folgueira *et al*. in a Spanish cohort of 2085 HCWs [19].

Despite being the current standard to diagnose SARS-CoV-2 due to its high specificity, molecular testing via nucleic acid amplification has limitations such as relatively longer time and the need for laboratories with specific expertise [20]. It is also highly dependent on the timing and quality of respiratory sample collection with suboptimal sensitivity in some reports [21], [22].

Therefore, adding serological assays for the presence of antibodies against SARS-CoV-2 might allow better capture of the SARS-CoV-2 situation in a population, especially in epidemiological studies [23]. IgM antibodies are produced short term after infection, whereas IgG are produced in a more delayed timescale and are likely to persist for a longer time after viral clearance [24]. In our study, antibodies could be detected by RST in 127/999 HCWs (12.8 %), raising the number of HCWs with at least one positive test (RT-PCR and/or RST) to 138 (13.8% of screened HCWs). In a similar study in a tertiary reference hospital in Belgium, among 326 HCWs, 41 SARS-CoV-2 cases were confirmed by RT-PCR and/or serology representing an overall rate of 12.6% [23]. On the other hand, 525 HCWs were screened for SARS-CoV-2 with a different RST in a cancer institute in Bari. Six subjects (1.1%) resulted with positive IgM, none of whom had positive oropharyngeal swabs upon RT-PCR testing [25].

Advantages of immunochromatography based RST include ease of performance without specific laboratory equipment, simple interpretation, and rapid results [26]. However, its results should be interpreted cautiously until sufficiently validated to determine their reliability [20]. When compared to the reference method, the RST demonstrated substantial concordance with the RT-PCR. Of the 86 HCWs who did test positive in the RT-PCR test, 82.1% were seropositive to IgM, and, most HCWs with negative RT-PCR were also negative for both IgG and IgM (94.3%). The sensitivity of the IgM by RST was 82.14% and the specificity was 96.71%.

For HCWs with discordant results of IgM detected by RST while negative at nasopharyngeal swabs (3.3% in our study), the possibility of falsely positive RST or falsely negative nasopharyngeal swab should be considered, with the latter of epidemiological concern, as missed infections could further spread SARS-CoV-2 unnoticed.

IgG seroprevalence in our cohort was 19%, but only 2.5% had negative concomitant RT-PCR. Negative results by RST are unreliable to exclude COVID-19 in acute-care settings because antibody production might be undetectable during the early phase of infection, limiting its sensitivity (as in our study) and underestimating the true prevalence rate of the disease [27]. Initial reports suggest that following infection with SARS-CoV-2, the immune system takes 6–21 days to produce IgM and IgG antibodies [28]. Therefore, follow-up of antibody titer changes over time might be required to estimate more accurate

cumulative infection rates in HCWs. Importantly, the correlation between seropositivity and protection against reinfection, as well as the duration of protective immunity, remain to be clarified [16]. Therefore, even health personnel with anti-SARS-CoV-2 antibodies should adhere to PPE.

In our study, we found that SARS-CoV-2 acquisition was unrelated to sex or age. When stratified according to occupation, positive test frequencies were highest among subgroups not directly involved in clinical care (e.g. patient transporters/cleaners), which might be explained by lower perception of risk leading to less careful practices and higher risk of acquiring the infection. Consequently, screening of these personnel and increasing their awareness of proper infection control measures should be stressed. In our study, 44.2% of positive cases reported contact with suspected or confirmed cases. However, we cannot exclude un-recognized household exposure as an added source of infection among HCWs. During a pandemic, rates of SARS-CoV-2 infection among HCWs might rather reflect general community transmission than nosocomial exposure [19]. Consistent adherence to PPE is necessary to reduce SARS-CoV-2 transmission among HCWs [24]. In our study, the majority of HCWs (>95%) confirmed adherence to mask. However, even with adequate PPE, HCWs remain at higher risk, highlighting the importance of additional risk mitigation strategies [29].

It is well-recognized that COVID-19 individuals with co-morbidities, have a worse prognosis [30]. However, only diabetes showed significant association with RT-PCR positivity to SARS-CoV-2 in our cohort. Previous studies have shown a relationship between hemoglobin A1c and risk of hospital admission for respiratory tract infections [31]. However, diabetes does not seem to increase the risk of acquiring COVID-19 according to published literature, although diabetes is a risk factor for developing severe forms of COVID-19, emphasizing the importance of blood glucose monitoring and control [32]. On the contrary, HCWs with history of asthma in our study were siginificantly lower in SARS-CoV-2 positivity. Theoretically, asthmatic patients should have increased susceptibility and severity for SARS-CoV-2 infection due to a deficient antiviral immune response and the tendency for exacerbation by respiratory viruses [33]. However, existing studies show no clear evidence of this higher risk [34]. Certain aspects of type 2 immune response, including eosinophils and specific cytokines, in addition to anti-asthmatic drugs, might provide protective effects against COVID-19 by enhancing antiviral defense [33].

Thirty three percent of participants had at least one symptom associated with COVID-19 when tested with the swab. The frequency of positive RT-PCR among them (10.9%) is <18% and 24% frequencies reported by Keeley *et al*. and Lombardi *et al*. in 1533 and 503 symptomatic HCWs, respectively [18], [35]. In our cohort of HCWs, the individual symptoms significantly associated with positivity of nasopharyngeal swab for SARS-CoV-2 were fever, rhinorrhea, dry cough, fatigue, dyspnoea and diarrhoea. It is well established that fever along with respiratory symptoms represent the common symptoms of COVID-19 [36], but gastrointestinal symptoms, including diarrhoea have been increasingly documented in COVID-19 [37]. This should raise the index of suspicion when HCWs present with digestive symptoms rather than waiting for respiratory symptoms to emerge. Also, the likelihood of being RT-PCR positive increased with the presence of five or six simultaneous symptoms reported.

Although the World Health Organization advocates widespread testing for SARS-CoV-2 [38], national capacities differ considerably, restricting SARS-CoV-2 testing in most hospitals to HCWs who are symptomatic or have symptomatic household contacts. One of the strengths of our study was expanding SARS-CoV-2 screening to asymptomatic HCWs. It should be underlined that, despite the low relative frequency of positive RT-PCR among asymptomatic HCWs (7.5%), their number was high in absolute terms (n = 50), meaning that more than half of those infected could be missed with a screening strategy based on symptoms only. Therefore, taking in consideration available resources, screening all HCWs irrespective of symptoms, seems to be the best approach to limit intra-hospital spread [39].

Finally, we observed a mean time from first positive test to a negative test of 2.83 days, which is shorter than many published reports [18], [40]. The duration of viral replication and shedding has important implications in guiding isolation period after exposure to a confirmed case and the best time to re-perform a nasopharyngeal swab [41]. In some individuals, the RT-PCR can remain detectable for up to 6 weeks, however, in most of cases, they represent inactive genetic material without significant transmission [24].

Conclusions

In conclusions, the point prevalence of SARS-CoV-2 infection in our cohort of HCWs in the cancer institute was 8.6% as determined by RT-PCR on nasopharnygeal swabs. Seroprevalence detected by RST was 12.8% with a substantial concordance of results. Our data illustrate the need for additional measures to reduce SARS-CoV-2 transmission in healthcare settings during the current pandemic, including screening of HCWs regardless of presence of COVID-19 symptoms

Compliance with Ethical Standards

Informed consent was obtained from all individual participants included in the study.

Availability of Data and Material

Data is available upon request by reviewers but not to be published due to the Egyptian low of data security and privacy.

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