



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.

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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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