ABSTRACT

Coronavirus disease 2019, caused by severe acute respiratory syndrome coronavirus 2, has recently become the number one problem affecting global health. Coronavirus disease 2019 is principally recognized by its respiratory manifestations; however, recent studies have shown an increasing number of patients with gastrointestinal complaints like diarrhea, nausea, vomiting, and abdominal discomfort. Severe acute respiratory syndrome coronavirus 2 infects the gastrointestinal tract via the angiotensin-converting enzyme II receptor, expressed on the ileum and colon enterocytes. Usually, gastrointestinal symptoms manifest later than respiratory symptoms. Concern for fecal-oral transmission has been raised following the detection of severe acute respiratory syndrome coronavirus 2 RNA in fecal samples for prolonged periods, even after respiratory clearance. In this review, we summarize the effects of severe acute respiratory syndrome coronavirus 2 on the gastrointestinal system.

Keywords: COVID-19, fecal-oral transmission, gastrointestinal system, liver, SARS-CoV-2

1 Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged in December 2019 from Wuhan, China, giving rise to the universal outburst of a respiratory disease called coronavirus disease 2019 (COVID-19) (1,2). The responsible agent is an enveloped, positive-sense, single-stranded RNA virus that belongs to the betacoronavirus genus along with the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (3,4). SARS-CoV-2 is rapidly transmitted through aerosols (5,6); its high transmissibility and the absence of immunity in the communities have led to the rapid spread of the virus worldwide (7), forcing the World Health Organization (WHO) to declare a public health emergency (8). The mortality rates varied widely among different cohorts, though the confirmed risk factors for the severe disease include elderly, underlying pulmonary disease, cardiovascular disease, smoking, chronic kidney disease, obesity, diabetes mellitus, malignancy, and chronic HIV infection (9–12).

The SARS-CoV-2, similar to SARS-CoV, can infect both the respiratory and gastrointestinal (GI) tracts (13–15). In this regard, researchers have reported GI manifestations alongside respiratory signs and symptoms since the onset of the SARS-CoV-2 outbreak (7,16). In fact, among the patients with COVID-19, roughly 40% show GI manifestations such as nausea, vomiting, diarrhea, and abdominal pain. Moreover, SARS-CoV-2 RNA has been detected in the fecal samples and rectal swabs in some COVID-19 patients...
Gastrointestinal Manifestations

Some viruses like rotavirus, calicivirus, adenovirus and cytomegalovirus (CMV) might infect the gastrointestinal tract and cause diarrhea and vomiting (23–25). Moreover, the gastrointestinal manifestations have also been reported in some COVID-19 patients during the recent SARS-CoV-2 outbreak (26). The ACE2 receptor enables SARS-CoV-2 to enter cells and use the host transcription and replication apparatus (27). The binding affinity of the SARS-CoV-2 spike protein to the ACE2 receptor is 10-20 times higher than that of SARS-CoV (28). Also, in vitro studies showed that the expression level of the ACE2 receptor in the intestinal cell lines is higher relative to the lung cell lines (29).

The origin of GI symptoms is not completely clear, but several phenomena might be involved. The ACE2 molecules play an important role in the intestine by regulating the amino acid homeostasis and microbiome balance (30). However, binding of SARS-CoV-2 to the ACE2 receptor reduces the ACE2 availability to the cells and alters the physiological function, causing dysbiosis and eventuating in a common COVID-19 symptom; diarrhea (31). On the other hand, the cytokine storms can inflict the injury to the GI duct cells. Moreover, autopsies of COVID-19 patients showed that ACE2-expressing cells produce inflammatory cytokines more than cells that do not express this enzyme (32). In addition, inflammation induced by the SARS-CoV-2 in the intestine could induce GI microbes to release inflammatory cytokines, which may spread to the circulatory system and cause systemic damage, with more severe consequences than a mere viral infection (33). Approximately, 80% of the COVID-19 patients showed mild to moderate clinical symptoms, 20% experienced severe disease, and only 5% developed a critical condition with multiple organ failure, septic shock, or respiratory arrest (34). The mean incubation period ranged from 5.2 to 6.65 days with 95% CI 4.4 to 5.9 and 95% CI 6.0 to 7.2, respectively (35).

The first intestinal autopsy study of COVID-19 was done on an 85-year-old man. The pathological examination of the small intestine showed segmental dilatation and stenosis. Various grades of gastrointestinal mucosa degeneration, necrosis, and shedding were also found histologically in another patient who died from this disease (36). On the other hand, Xiao et al., found no obvious mucosal epithelial damage on microscopic analysis of the esophagus, duodenum, colorectal, and stomach of the COVID-19 patients with H&E staining (22). However, histology studies have indicated lymphocytic infiltration in esophageal squamous epithelium as well as high infiltration of plasma cells and lymphocytes with interstitial edema in the stomach, duodenum, and rectum lamina propria (37). Moreover, pathological staining revealed that ACE2 was expressed mainly by the gastric and intestinal epithelial cells, infrequently being observed in esophageal squamous epithelial cells (21,38). The viral nucleocapsid protein was also identified in the cytoplasm of gastric, duodenal, and rectal glandular epithelial cells, though not in the esophageal epithelium, suggesting that the GI symptoms of COVID-19 are caused by the direct viral attack and the immune response (39).

Although early studies of COVID-19 described a low percentage of the patients with GI symptoms, evidence for the enteric involvement is on the rise (40). The first COVID-19 patients manifested GI symptoms in the United States (US) had nausea, vomiting, and abdominal pain with loose bowel movements (34). Notably, a multicenter study in China showed that GI symptoms were common among COVID-19 patients (2). Also, Redd et al., found that almost two-thirds of the hospitalized patients had at least one common GI symptom. They stated that one-third of the COVID-19 patients had anorexia or diarrhea, while 10-25% had nausea, abdominal pain, vomiting, or weight loss (41). In a cross-sectional, multicenter study, researchers verified that nearly 50% of the patients experienced GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain (34). In the patients with anosmia and ageusia (believed to be related to COVID-19), significantly higher rates of nausea and anorexia were observed (41). Interestingly, no association has been reported between the GI symptoms and the patient demographics, laboratory parameters, medical history, or other clinical signs of COVID-19 (41).

In COVID-19, the onset of GI symptoms appears to be delayed by nearly two days compared to the respiratory symptoms (2). In a large clinical study of the COVID-19 patients, digestive symptoms were seen in 48.5% of the patients; they included anorexia (84%), vomiting (0.8%), diarrhea (29%), and abdominal pain (0.4%) (16). In that study, seven patients with only GI symptoms had prolonged disease durations compared to the patients with respiratory symptoms. The
authors warned that in COVID-19 patients, GI symptoms are common and non-specific, thus, many patients may have the virus in the GI system for a long time, contributing to the further spread of SARS-CoV-2 (16).

In a January 2020 study, Huang et al., described the clinical features of 41 COVID-19 patients, including 13 intensive care unit (ICU) and 28 non-ICU cases. Their initial symptoms were fever, cough, dyspnea, fatigue, and myalgia. Diarrhea was seen in 4.8% (2 of 41) of the patients. At the same time, Chen et al., reported 99 older males suffering from COVID-19 pneumonia, some with GI symptoms like diarrhea (5 patients) and nausea or vomiting (1 patient) (42). In one study, approximately 10% of COVID-19 patients showed GI symptoms, including nausea, diarrhea, and abdominal pain earlier than the classic respiratory symptoms (16). In a study from Wuhan, China, out of 206 patients with mild COVID-19, 48 had GI manifestations only, 69 had both GI and respiratory manifestations, and 89 had only respiratory manifestations. Overall, 117 patients had GI symptoms. The SARS-CoV-2 RNA was detected in the stool specimens of the majority (73%) of the patients; these patients took longer to clear the virus. Hence, the authors agreed that the virus probably infects the GI tract (16).

Previous reports showed that in 10.6% of the cases infected with SARS-CoV-2 and up to 30% of the cases infected with MERS, the symptoms were non-specific, and some had GI symptoms such as diarrhea (43). Out of 30 medical staff in China suffering from coronavirus pneumonia, 30% had GI symptoms, including diarrhea and nausea (16). In another study, a subset of patients who had GI symptoms experienced considerably higher rates of fever, shortness of breath, fatigue, and headache (34). In a Chinese study, 11.4% of the patients with an average age of 46.1± 8.6 years presented at least one GI symptom such as vomiting, nausea, or diarrhea (44). A meta-analysis in Greece showed that the pooled incidence rate for the GI symptoms was 8.9%, while the distinct rates were 9.6% for diarrhea, 5.8% for abdominal discomfort/pain, and 6.6% for nausea/vomiting. In the subgroup investigation in adult patients, these rates were 8.7%, 9.6%, 5.8%, and 6.5%, respectively. Among children, the pooled figures were 9% for all symptoms, 6.8% for nausea/vomiting, and 9% for diarrhea. Additionally, the incidence of GI symptoms in the patients with severe type of COVID-19 was greater than those with mild disease (16.6% vs. 11.7%, respectively) (7). Among non-medical staff, women appear to be more likely to develop GI symptoms with higher levels of inflammatory markers. However, no notable correlation was established between the GI symptoms and clinical features of COVID-19 among medical staff (8).

Tian et al., reviewed the GI manifestations of COVID-19 and assessed the occurrence of the specific GI symptoms in both children and adults. The most common symptom was diarrhea in both children and adults lasted almost 4 days. Notably, a lower proportion of adults exhibited vomiting compared to the children. Other prominent GI symptoms were anorexia (39–50%), vomiting (4–66%), abdominal pain (2–6%), nausea (1–29%), and GI bleeding (4–13%) (26).

It is essential to note that adults and children infected with SARS-CoV-2 without respiratory manifestations may show digestive symptoms (34). Published data in Ireland from 230 COVID-19 patients (129 men and 101 women) with the median age of 47.5 years from January to March 2020 showed that the prominent symptoms were fever (84%), cough (69%), and sputum production (43%). Diarrhea was also observed in 21% of the patients; these individuals were older and more likely to have comorbidities than those without diarrhea. Moreover, 43% (9 of 21) of the patients admitted between February and March 2020 had diarrhea, suggesting that as the outbreak progressed, a greater proportion of the patients admitted to the hospital presented diarrhea (2).

Institutional review boards from the Sun Yat-sen University and participating hospitals indicated that the most common GI manifestations were diarrhea and loss of appetite, possibly related to an inflammatory state, liver dysfunction, hypoxia, depression, or adverse reactions to the therapeutic drug (45). Diarrhea might also be related to different causes; one proposed etiology is an assault to the digestive tract, supported by finding the viral nucleocapsid protein in the epithelial cells (39). Moreover, antiviral drugs or herbal medicines might be involved in inducing nausea and diarrhea (39). Finally, antibiotics — by eliminating microbial probiotics — might be a third important factor contributing to diarrhea in COVID-19 patients (45). The GI symptoms caused by SARS-CoV-2 may also be associated with other mechanisms. The first is related to the expression of the ACE2 cell receptor. The second mechanism is the virus direct attack to the GI tract, triggering an inflammatory response and potentially leading to malabsorption, unbalanced intestinal secretion, and diarrhea secondary to the activation of the enteric nervous system (34).

During the epidemic of SARS-CoV in 2003, approximately 20% of the patients displayed GI symptoms (46,47). Not only was SARS-CoV RNA readily detectable in the stool specimens of the patients (48), but also dynamic viral replications were observed using electron microscopy on the biopsy/autopsy specimens of the small and large intestines (47). Interestingly, GI manifestations were also noted in
11.5-32% of the MERS-CoV patients (7). During the current pandemic, the Centers for Disease Control and Prevention (CDC) suggested that the risk of COVID-19 transmission is resolved after two negative breath tests (45). However, some important questions remain: Can SARS-CoV-2 be transmitted through the fecal-oral pathway? Also, how long does the virus persist in the GI system after the clearance of the respiratory tract?

Nearly a couple of decades ago, detection of the SARS-CoV RNA in the intestinal biopsy and stool specimens of SARS patients confirmed the tropism of the virus to the GI tract (47). Similarly, SARS-CoV-2 RNA was detected in the stool samples of the first COVID-19 cases in the US (40). Moreover, Yang et al., found that the stool samples of 3 out of 7 COVID-19 patients remained positive for SARS-CoV-2 RNA after a negative nasopharyngeal swab test. In one review, the authors noted that 36-53% of the stool samples were positive for the SARS-CoV-2 RNA (39). Also, a meta-analysis discovered that SARS-CoV-2 RNA was detected in 30.3% of the stool samples among COVID-19 patients (7). Another study found the virus in 55% of the stool specimens (39).

In terms of virus detection, variable test window periods have been reported according to the type of specimen. For example, the stool test reportedly remained positive longer in COVID-19 patients treated with corticosteroids compared to the non-treated ones (49). Also, one study reported that stool specimens became positive for the viral nucleic acid for 2-5 days after the positivity of the nasopharyngeal specimens, and remained positive in 23%-82% of the patients despite negative results from nasopharyngeal samples (39). In further confirmation, Cipriano et al., mentioned that the virus was detectable in the stool specimens of 24% of the patients, even after negative nasopharyngeal tests (7). Another research group reported that stool samples became positive 2-5 days after respiratory samples, and remained positive for about 1-11 days longer than the sputum samples (49). The virus can also be identified through the rectal swabs (16), and it is even detected in the feces of asymptomatic subjects for as long as 17 days (50).

Findings from the previous epidemics suggest that the GI tract viral shedding may continue after the resolution of clinical symptoms as viral RNA was detected for as long as 30 days in the stools of the patients with SARS-CoV infection (49). It should be noted that the behavior of SARS-CoV-2 in the GI system is not well understood and may not be identical to the SARS-CoV behavior in the respiratory tract (51–53). It is worth noting that the positivity of the stool samples does not affect the severity of COVID-19 (49,54).

### Hepatic Manifestations

In addition to the viral hepatitis viruses such as HBV and HCV, SARS-CoV-2 has also been reported to infect liver cells/tissue (55,56). Clinical studies suggest that elevated levels of interleukin (IL)-6, ferritin, and C-reactive protein (CRP) associated with the systemic inflammation might be involved in liver injury (57,58). The IL-6 is produced by endothelial cells, fibroblasts, and hepatocytes; it fulfills a vital role in inducing systemic inflammation and liver damage. Researchers have shown a direct relationship between the raised AST levels and increased levels of IL-6 and acute phase proteins (59,60).

Liver function may become impaired in the COVID-19 patients who develop GI symptoms. Metabolic disorders augment the absorption of harmful metabolites, which affect the central nervous system function via the gut-brain axis, giving rise to dizziness and fatigue. Disorders of intestinal metabolism lead to the increased production of harmful metabolites that damage hepatocytes. Moreover, moderate microvesicular steatosis with mild lobular and portal inflammatory activity has been reported in the autopsy of a COVID-19 patient, which might be related to the direct attack of SARS-CoV-2 to the liver (45).

According to the American College of Gastroenterology (ACG), liver enzymes abnormalities are seen in 20–30% of the COVID-19 patients (34). Cholankeril et al., reported that 40% (26/65) of the COVID-19 patients showed abnormalities in the liver function tests, including ALT, AST, and total bilirubin levels. Notably, 84% (22/26) of these patients had normal baseline ALT and AST levels. Moreover, all four patients with abnormal baseline enzyme levels experienced a two-fold elevation during their COVID-19 course. Interestingly, COVID-19 severity was related to the AST levels at the time of presentation (45).

A study in China reported that 50.7% of the 148 confirmed SARS-CoV-2 infected patients had abnormal liver enzyme levels at admission (61). Abnormalities in liver function tests have been seen in other studies as well (34). Although severe liver damage can also occur during the course of COVID-19, most liver injuries are mild and transient (62). People with severe COVID-19 might experience severe liver damage, which can be ameliorated by administering the hepatoprotective drugs (34).

Although drug hepatotoxicity, immune-mediated injury, and direct infection of hepatocytes by SARS-CoV-2 have been suggested to be related to the liver injury, the exact mechanisms behind liver damage in COVID-19 are unclear (34). In this regard, it has been suggested that high expression of ACE2 receptors in the gastrointestinal epithelial cells results in infection...
of cholangiocytes by the virus, possibly leading to the liver dysfunction (51,52,53).

The liver is an unlikely target for the infection, because hepatocytes do not express high levels of ACE2. However, a pilot study showed a high level of ACE2 expression in the cholangiocytes, suggesting the cholangiocyte dysfunction as an indirect source of the liver enzymes elevation (65). Interestingly, alkaline phosphatase is not elevated in COVID-19 patients. In addition, Yao et al., provided evidence that SARS-CoV-2 does not infect hepatocytes (66), clarifying that SARS-CoV-2 is unlikely to cause direct liver damage (36). However, viral components have been seen in the histological examination of liver biopsies from the deceased COVID-19 patients (62,64). In severe COVID-19 patients, liver failure or hepatocellular damage may cause pneumonia-associated hypoxia and a cytokine storm (62). Lastly, elevated levels of liver enzymes can be due to the toxicity of drugs like hydroxychloroquine (34). Another study lists acetaminophen as a possible culprit since it is frequently used to control fever in the COVID-19 patients (36).

Although liver enzymes levels abnormality may be associated with the higher risk of severe disease, routine liver function tests may not be warranted. In most patients with mild elevation in the liver enzymes, this issue is resolved as the patient clinically improves (67,68). To date, just one case of COVID-19 with the presentation of acute liver failure has been reported. The most common causes of death in SARS-CoV-2 infections are respiratory failure and sepsis (69). It is essential for the clinicians not to be distracted by minimally elevated liver enzyme levels because no effective hepatoprotective treatments are currently available (68). Moreover, Chornenky et al., found mild focal hepatitis seen histologically in the most deceased COVID-19 patients (70).

Pre-existing Liver/Bowel Disease

One of the most important groups of the patients needing more attention is those with pre-existing liver diseases (cirrhosis, cancer, etc.), who might be more prone to developing severe COVID-19 due to their immune system status (36). Moreover, patients with primary biliary cholangitis (PBC) need careful attention as they may be at increased risk of cholestasis; They should be closely monitored for their gamma-glutamyl transferase (GGT) and alkaline phosphatase levels. Furthermore, the role of glucocorticoids in the management of COVID-19 patients with autoimmune hepatitis is still unclear (62). In a study, 2% (23/1099) of the COVID-19 patients who had chronic hepatitis B infection showed more severe disease than others (2.4% vs. 0.6%) (71). Due to their immunodeficient status, patients with liver cirrhosis or cancer may be more likely to develop a severe SARS-CoV-2 infection. Therefore, patients with pre-existing liver disease are an important group requiring extra attention (34). Singh et al., compared the results among the patients with and without liver disease in a large group of 2,780 COVID-19 patients in the US. They reported elevations in the liver function test indices in the vast majority of the patients, which may indicate liver damage in the SARS-CoV-2 infection. They also stated that patients with pre-existing liver disease were at higher risk of mortality compared to those without liver disease, and the relative risk was considerably higher in the cirrhotic patients (72).

The expression of ACE2 receptors is likely in both bile duct and liver cells (73). In previous studies, abnormalities in transaminase enzymes have been reported in 14-53% of the COVID-19 patients. They also remarked elevations in the liver function tests, suggesting possible liver damage associated with the SARS-CoV-2 infection. As a common COVID-19 complication, hypoxia can diminish cellular activity and induce free oxygen radicals – a potential pathway for contributing to the liver damage and failure (62,74). Furthermore, persistent systemic inflammation and immune deficiency (revealed by the activated circulating immune cells and up-regulated serum levels of pro-inflammatory cytokines) in the patients with progressive liver disease can prompt uncontrollable pro-inflammatory cytokine production (75,76).

Pancreatic Manifestations

Pancreatic islet cells express high levels of the ACE2 receptors. Theoretically, they can become infected by SARS-CoV-2, resulting in the islet injury and acute diabetes (34). In this regard, researchers used vesicular stomatitis virus (VSV)-based SARS-CoV-2 pseudoviruses and hPSC-derived pancreatic islets to demonstrate that SARS-CoV-2 can infect alpha and beta cells in pancreas (77). Recent studies showed acute hyperglycemia and transient diabetes in the COVID-19 patients without any history of type II diabetes, which may indicate pancreatic damage (78). In one study, abnormal blood sugar levels were seen in 66.6% (6/9) of the COVID-19 patients due to pancreatic damage (34). Also, Liu et al., reported elevated serum amylase and lipase levels in the patients with severe COVID-19 (79). In some patients, computed tomography scans showed focal pancreatic enlargement and dilation of the pancreatic duct (79).

Other mechanisms that might contribute to the pancreatic damage include indirect systemic and immune-mediated cellular responses, direct cytopathic effects of SARS-CoV-2 infection, and toxicity induced by antipyretic drugs (34,80). In this regard, Wang et al., reported that out of 52 COVID-19
patients, 17% experienced abnormalities in amylase or lipase levels, suggesting the pancreatic damage. However, they did not show any clinical signs of the severe pancreatitis (81). Moreover, a recent study reported abnormal amylase and lipase levels due to pancreatic injury in the COVID-19 patients, with no exhibiting clinical symptoms (82).

Gastrointestinal Infection and Its Impact on SARS-CoV-2 Transmission

SARS-CoV-2 is detectable in the respiratory tract secretions of the COVID-19 patients one to two days before and up to two weeks after the resolution of the clinical manifestations (83). Historically, SARS-CoV was detected in urine, stool, whole blood, and serum specimens (83). Cai et al., showed that the frequency of SARS-CoV-2 in the stool specimens of pediatric patients was higher relative to adults (84). The prolonged shedding of viral RNA in feces for as long as a month and even more has been confirmed, suggesting that the GI tract acts as another site for the viral replication and shedding (84). This observation provoked scientists to suggest that viral RNA testing on feces by RT-PCR might help to control the SARS-CoV-2 infections (22). A study in China revealed that 53.4% (39/73) of the COVID-19 patients aged 1 to 78 years had positive stool test results while their respiratory test was negative (22). Additionally, the presence of the viral nucleocapsid protein in biopsy specimens of the gastric, duodenal, and rectal epithelium has been reported, indicating the replication of SARS-CoV-2 in the GI system (22).

Another critical issue regarding the GI system infection by the SARS-CoV-2 is the probability of disease transmission via fecal microbiota transplants. In this regard, some experts have stated that donors who have recently (within 30 days) made a trip to areas of high SARS-CoV-2 prevalence are at higher risk of transmitting the infection (85). As asymptomatic carriers might transmit the virus, all stool donors should be screened, regardless of the risk factors (36).

With bearing in mind that the presence of SARS-CoV-2 RNA in the stool has not correlated with the GI manifestations or the severity of pneumonia (86). It provided an opportunity to develop stool-based diagnostic tests for the SARS-CoV-2 infection (36), and fecal-oral transmission must be considered. On March 15, 2020, the gastroenterology societies in the US proposed a guideline recommending their members to use N95 masks or N99 or powered air-purifying respirator masks instead of surgical masks for all the endoscopy delaying all elective procedures and use N95 (or N99 or powered air-purifying respirator) masks instead of surgical masks for all endoscopy procedures as part of their personal protective equipment. The guideline also suggests using negative pressure rooms and double gloves when available (36).

2. Conclusion

SARS-CoV-2 is a new coronavirus that can lead to acute respiratory disease, with a high morbidity and mortality rate. In COVID-19 patients, in addition to respiratory manifestations, gastrointestinal (GI) symptoms have been seen frequently. The ACE2 receptor is present on GI tract cells, facilitating GI infection by SARS-CoV-2 in up to 8.9% of COVID-19 patients. Additionally, hepatic and pancreatic injuries have been evident in a subset of patients. As fecal shedding is well-established, greater attention should be directed toward the fecal-oral transmission of SARS-CoV-2.

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The authors declare any conflict of interest.

Reference


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38. Hikmet F, Méar L, Edvinsson Å, Miché P, Uhlén M, Lindskog C. The protein expression profile of


