

Clinical Manifestations of COVID-19 Involving the Gastrointestinal Tract

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease is a primarily respiratory illness transmitted among close contacts mainly via respiratory droplets and direct contact. It uses angiotensin-converting enzyme 2 (ACE2) receptor to enter into the cells of the respiratory epithelium and as ACE2 receptor is also expressed in gastrointestinal (GI) epithelial cells, some patients with coronavirus disease-2019 (COVID-19) have GI symptoms, such as abdominal pain, vomiting, nausea, and diarrhea. Patients with COVID-19 with GI and hepatic manifestations are at risk of severe disease as well as development of acute respiratory distress syndrome. Also, detection of SARS-CoV-2 viral RNA in stool samples of infected patients has raised possibility of GI tract being an additional site of infection as well as viral replication and further studies are needed to study the possibility of feco-oral transmission of COVID-19. This updated review discusses GI and pancreatic manifestations of COVID-19 and its clinical implications.

Keywords: Amylase, Coronavirus, Diarrhea, Pancreatitis, Pandemic, Vomiting.

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Coronavirus disease-2019 (COVID-19) is a viral illness caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ It was first reported in December 2019 in China and since then has evolved into a pandemic with widespread ramifications. Severe acute respiratory syndrome coronavirus 2 is a contagious disease transmitted among close contacts mainly via respiratory droplets and direct contact.² It uses angiotensin-converting enzyme 2 (ACE2) receptor to enter into the cells of the respiratory epithelium.³ As it primarily involves the respiratory tract, the majority of symptomatic patients present with fever, fatigability along with the respiratory symptoms, such as cough and respiratory distress.⁴ However, the ACE2 receptor is also expressed in gastrointestinal (GI) epithelial cells and many patients with proven COVID-19 illness manifest with GI symptoms, such as abdominal pain, vomiting, nausea, and diarrhea.⁵ Detection of SARS-CoV-2 viral RNA in stool samples of infected patients has also raised possibility of GI tract being an additional site of infection as well as viral replication.^{2,6-8} This updated review discusses GI and pancreatic manifestations of COVID-19 and its clinical implications. The hepatic manifestations will not be discussed in this review.

FREQUENCY OF GI SYMPTOMS

A number of studies have reported involvement of luminal GI tract, liver, as well as pancreas in patients with COVID-19. However, there is a significant variation in the reported GI symptoms in various studies. A systematic review reported that 15% patients (range: 11–79%) with COVID-19 had GI symptoms and 19% patients had evidence of hepatic injury.^{9,10} This meta-analysis also concluded that as severity of COVID-19 increases the severity of GI symptoms as well as liver injury becomes more pronounced. The pooled analysis reported that in contrast to 11.8% of patients with non-severe COVID-19 having GI symptoms (95% CI: 4.1–29.1), 17.1% of patients with severe illness had GI symptoms (95% CI: 6.9–36.7).¹¹ Importantly, ~10% patients have been shown to present with GI symptoms only without any respiratory symptoms leading on to delayed correct diagnosis. Patients with COVID-19 with GI and

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hepatic manifestations have to be carefully monitored as they are at risk of severe disease as well as development of acute respiratory distress syndrome.⁹ Studies have also reported stool samples testing positive for SARS-CoV-2 viral RNA in 30–50% patients and importantly, few patients tend to have positive stool samples even after the viral RNA was negative in the respiratory sample.^{10,12} Fecal shedding is an area of concern as analysis of a community cluster of SARS caused by SARS-CoV-1 in Hong Kong suggested that fecal shedding and air movement of contaminated bioaerosols was an important contributor to the outbreak.¹³ Although role of fecal transmission in COVID-19 is being debated, fecal bioaerosol transmission should be taken into account in hospital settings as part of infection control. The hospitals should advise staff and patients to cover toilets before flushing or using non-flushing commodes, and also ensure strict environmental decontamination protocols.¹³

GI SYMPTOMS

The GI symptoms in COVID-19 are insidious as compared to the respiratory symptoms and therefore can be easily ignored and missed. Diarrhea is the most common GI manifestation in patients with COVID-19 being reported in 3.8–34% patients.

Other GI symptoms reported are nausea with or without vomiting (3.9–10.1%) and abdominal pain (1.1–2.2%).¹⁴ GI symptoms like anorexia and dysgeusia (distortion of taste) have also been reported.^{4,7,9,14–23} These findings suggest that patient with COVID-19 with GI manifestations may mimic acute gastroenteritis and could lead to delayed diagnosis. Therefore, it is important to obtain a complete and detailed history of high-risk contact exposure, COVID-19 symptoms, such as fever, shortness of breath, cough, myalgias, sore throat, anosmia, dysgeusia, as well as other GI symptoms including abdominal pain, nausea, and vomiting in patients presenting with new onset acute diarrhea.¹⁵ Most of the patients with COVID-19 with GI manifestations will have classical symptoms, such as fever, and respiratory symptoms. However, few patients may present with GI manifestations preceding respiratory symptoms and fever by 1–2 days. These patients should be closely monitored for the development of COVID-19-related symptoms and in high COVID-19 prevalence setting should be offered COVID-19 testing despite absence of COVID-19-related symptoms.¹⁵ Also, hospitalized patients with COVID-19 should be carefully evaluated for the presence of GI symptoms as these patients have the tendency to develop severe illness as compared to patients without GI symptoms. Studies have shown that patients with preexisting GI diseases are not at an increased risk of developing severe disease but patients with new onset GI symptoms tend to develop severe illness.⁹

Various pathogenic mechanisms have been proposed for the GI manifestation observed in patients with COVID-19. These manifestations could be due to either direct viral cytopathic effects on the GI epithelium as well as injury to the epithelium by the inflammatory response. Moreover, the destruction of enterocytes can lead to malabsorption, increased intestinal secretion, and activated enteric nervous system leading to diarrhea.^{18,19} Medications, such as chloroquine and hydroxychloroquine, can also have GI adverse effects including nausea and vomiting and therefore, a detailed drug history should be obtained from patients with COVID-19 presenting with GI symptoms.

PANCREATIC DISEASES

Angiotensin-converting enzyme 2 receptor is also expressed in pancreatic islets and elevated amylase/lipase has been reported in 17% of patients with COVID-19.²⁴ Moreover, 66% patients with elevated pancreatic enzymes had elevated blood sugars suggesting acute islet cells injury. The authors hypothesized that pancreatic injury could be either caused by direct cytopathic effect of the virus on the islet cells or could be a consequence of immune response triggered by the virus. In the previous outbreak of SARS caused by SARS-CoV infection, acute diabetes caused by the damage of islets has been reported.²⁵ Most of the patients with COVID-19 have asymptomatic mild elevation of pancreatic enzymes and symptomatic acute pancreatitis has been reported rarely in the literature.²⁶

INVESTIGATIONS

There are no specific investigations required for the evaluation of COVID-19 patients presenting or having GI symptoms. However, it is important to exclude GI diseases presenting with abdominal pain, nausea/vomiting, or diarrhea. According to the clinical scenario, patients presenting with abdominal pain and nausea/vomiting should undergo ultrasound abdomen, abdominal X-ray, and serum

amylase/lipase. As mentioned earlier, asymptomatic elevation of pancreatic enzymes can be seen in up to one-fifth of the patients with COVID-19. Therefore, patients presenting with significant abdominal pain should be further evaluated by imaging including ultrasound abdomen or computed tomography to exclude clinically significant acute pancreatitis. Patients presenting with diarrhea should undergo stool examination to exclude GI bacterial/protozoal infection as well as *Clostridium difficile* infection.

ROLE OF FECAL SARS-CoV-2 VIRAL RIBONUCLEIC ACID DETECTION

As mentioned earlier, 30–50% patients with COVID-19 have viral shedding in their stool samples and this raises the possibility of feco-oral transmission of SARS-CoV-2.²¹ However, detection of viral RNA in stool sample has been shown to be independent of GI symptoms and its correlation with disease severity, duration, and recurrence is unclear.^{5,27} Therefore, testing of viral RNA has limited clinical utility at present. However, results of the studies that have shown that fecal shedding of the viral RNA persists even after clearance from nasopharyngeal epithelium raises concern of transmission of disease from these apparently recovered COVID-19 patients.^{4,8,11,12,16,19} Despite detection of viral RNA in stool samples, there are no data that have looked into infectivity as well as duration of viability of virus in feces.⁶ Wang et al. evaluated viral RNA in various clinical specimens of patients with COVID-19 and found that 32% pharyngeal swabs and 29% fecal specimens were positive for viral RNA.²⁸ Moreover, the authors were able to culture as well as detect live virus using electron microscope in fecal samples. Although the evidence is accumulating that suggests fecal excretion of viral RNA, further studies are needed to determine the exact epidemiological role of fecal shedding of SARS-CoV-2.

TREATMENT OF GASTROINTESTINAL MANIFESTATIONS

No specific treatment except for supportive treatment is needed for the management of COVID-19 patients having GI manifestations.²⁹ Symptoms, such as vomiting and nausea, are conservatively managed with antiemetics and abdominal pain should be treated with analgesics (preferably non-narcotic analgesics) and antispasmodics. Symptomatic dehydration is rare in COVID-19-related diarrhea and standard principle of dehydration assessment and treatment are to be followed. Also, effective sanitation and infection control measures should be in place, especially because of the concerns of prolonged fecal shedding of viral RNA.

CONCLUSION

Gastrointestinal manifestations are not uncommon in patients with COVID-19 having severe illness more likely to develop GI symptoms. Nausea/vomiting, diarrhea, and abdominal pain are the common GI manifestations in patients with COVID-19. Many facets of GI involvement with SARS-CoV-2 are unclear and future studies are required to better understand the pathogenesis as well as clinical implications of COVID-19 GI manifestations.

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