

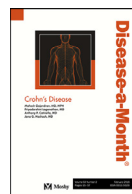


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COVID-19 extrapulmonary illness – special gastrointestinal and hepatic considerations

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ABSTRACT

Coronaviruses have caused three global outbreaks in the last 20 years, which include Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (SARS-CoV-1), Middle East Respiratory Syndrome (MERS) by MERS-CoV and Coronavirus Disease-2019 (COVID-19) due to SARS-CoV-2. These outbreaks share many similarities, including clinical presentation, transmission, and management. Although respiratory manifestations are responsible for most of the morbidity and mortality in these conditions, extra-pulmonary manifestations such as gastrointestinal symptoms are also increasingly recognized as important symptoms. Important gastrointestinal symptoms include nausea, vomiting, anorexia, diarrhea, and abdominal pain. Hepatic manifestations such as abnormal aminotransferases are also noted in these patients. Early identification of GI symptoms is crucial as some patients can present only with GI manifestations in the absence of pulmonary symptoms. Furthermore, patients with diarrhea have tested positive for viral RNA in the stool. This has been reported even after the resolution of respiratory symptoms and

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can extend up to many days from the onset of symptoms. Because of this phenomenon, there is a theoretical risk of fecal-oral transmission and the potential spread of the disease. Though GI symptoms are frequently observed, understanding the pathogenesis of these symptoms is crucial, as it can not only of public health importance but could also identify infected patients early in the spread. Understanding the different GI and hepatic manifestations with underlying mechanisms of symptoms can assist in the therapeutic management of these patients. In this article, we summarize various GI and hepatic manifestations with their prevalence, underlying pathophysiology with emphasis on stool positivity.

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Introduction

Coronaviruses (CoV) are the largest group of viruses under Nidovirales order with spike-like projections, which led to the name “Coronavirus.” They have caused three global outbreaks in the last 20 years, which include Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV (SARS-CoV-1), Middle East Respiratory Syndrome (MERS) by MERS-CoV and Coronavirus Disease-2019 (COVID-19) due to SARS-CoV-2. These outbreaks share many similarities, including clinical presentation, transmission, and management. Although respiratory manifestations are responsible for most of the morbidity and mortality in these conditions, extra-pulmonary manifestations such as gastrointestinal (GI) symptoms are also common.^{1–3} The GI manifestations have implications on clinical manifestation, mechanism of spread, and infection-control measures. In this article, we seek to discuss the epidemiology, pathogenesis, and clinical features related to GI manifestations in COVID-19, SARS, and MERS.

Coronavirus disease-2019 (COVID-19)

Coronavirus disease-2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) identified for the first time in Wuhan, China.⁴ It originally presented as a cluster of pneumonia-like cases. In a few months, COVID-19 spread across multiple nations and led to a pandemic of global health concern.⁵ As of June 20, 2020, COVID-19 has affected 185 countries with 8.7 million cases and 461,000 deaths.⁶ While respiratory symptoms dominate the presentation, GI manifestations such as nausea, vomiting, abdominal pain, diarrhea, loss of appetite, dysgeusia, and abnormal liver chemistries are increasingly being reported, especially in hospitalized COVID-19 patients.^{4,7–12} In addition, there have been reports of GI bleeding, colitis, acute pancreatitis, and exacerbation of prior GI diseases (inflammatory bowel disease).^{12–15} What follows are key GI findings:

Diarrhea

Diarrhea is the most common GI manifestations in COVID-19 patients. Although multiple studies have reported diarrhea in COVID-19, a strict definition is missing.^{16,17} Only a few studies have noted the severity and type of diarrhea. Studies included loose or watery stools ranging from 2 to 10 bowel movements per day. In addition, some of the symptoms are not present at hospital admission, making it difficult to ascertain if the diarrhea is from the direct effect of SARS-CoV-2 or indirect effects (such as antiviral medications, antibiotics, altered gut flora). Ideally, if diarrhea is attributed to SARS-CoV-2 infection by its direct cytopathic effect, symptoms should be present at the hospital admission, and the stool should be positive for nucleic acid.

Prevalence: Studies have shown that the prevalence of diarrhea could range from 2% to 50% of the cases.¹⁷ However, the overall pooled prevalence of diarrhea in COVID-19 based on multiple studies is 5–10%.^{17,18} Luo et al. identified 68 patients among 1141 cases with a prevalence of 6% (95% CI, 4.7%–7.5%).¹⁶ In one of the large studies conducted by Xu et al. in the Hubei province of China, 130 out of 355 patients developed diarrhea with a prevalence of 36.6% (95% CI, 31.6%–41.9%).¹⁹ Hajifathalian et al. noted 234 cases with diarrhea among a large cohort of 1059 patients with a prevalence of 22.1% (95% CI, 19.6%–24.7%).²⁰ Though the prevalence varied among these studies, few aspects need consideration before evaluating the prevalence of diarrhea. As noted above, a strict definition of diarrhea is not prevalent in most studies. Furthermore, the recognition of symptoms increased as the disease spread across the nations, prevalence varied by the country, and if patients were treated either outpatient or on an inpatient basis. For example, the studies from China report an overall lower prevalence of diarrhea of 5.8% (95% CI, 5.3%–6.4%) compared to non-Chinese studies with a prevalence of 18.3% (95% CI, 16.6%–20.1%).¹⁸ It is unclear if this is due to a lack of recognition of symptoms during early in the pandemic or due to epidemiological differences. Similarly, the pooled prevalence of diarrhea among outpatient COVID-19 patients was 4% (95% CI, 3.1%–5.1%), which was lower as compared to the individuals who were admitted in the hospital 10.4% (95% CI, 9.4%–10.7%).¹⁸ This is expected because the number of patients presenting on an outpatient basis was quite low during the pandemic, especially if symptoms were not severe.

Pathogenesis: Understanding the mechanisms of diarrhea in COVID-19 patients is crucial to develop strategies to mitigate the spread of the disease. It is well recognized that the functional receptor for SARS-CoV-2 entry is angiotensin-converting enzyme-2 (ACE-2).²¹ The abundance of ACE-2 in the epithelium of the GI tract makes it vulnerable to the SARS-CoV-2 entry. Studies have shown increased ACE-2 expression in the mucosa of the tongue, esophagus, gastric mucosa, ileum, and rectum.^{22,23} Though gastric acid can significantly reduce the life of the virus, SARS-CoV-2 can still potentially make its way to the duodenum and distal small bowel, making them a target for viral cytopathic effect.²⁴ Once the virus enters the epithelium, replication and synthesis occur at a rapid rate resulting in cytopathic changes evidenced by intracellular staining of viral nucleocapsid protein. It remains to be studied if the presence of SARS-CoV-2 in the stools of these patients is the cause of diarrhea or if the virus is just a bystander. This explains the need for stool RNA testing in patients with diarrhea not only to assess for infectivity but also to assess the potential cytopathic effects.

In addition to the above mechanisms, gut flora has been shown to be altered in the patient's severe disease state with the use of antimicrobials, and enteral nutrition.²⁵ Hyperinflammation noted in COVID-19 patients (cytokine storm syndrome) can release a number of cytokines such as interleukins (IL-2, 7), granulocyte monocyte colony-stimulating factor (GM-CSF) and tumor necrosis factors (TNF- α) which not only alter the gut motility but also affects the GI flora, increasing the risk for diarrhea.²⁶ Multiple antiviral and antibiotics are used in the management of COVID-19 patients, which can directly induce diarrhea as a part adverse effects of these medications.²⁷ Fecal calprotectin is elevated in COVID-19 patients who have diarrhea lasting for more than 48 h.¹⁴ Furthermore, ACE-2 activity is overexpressed in inflamed gut tissue, especially in inflammatory bowel disease (IBD).²⁸ This signifies the role of gut inflammation in these patients. It is unclear if an isolated mechanism or a combination of factors plays a role in diarrhea in COVID-19 patients.²⁹ Nevertheless, identification of these pathways might be used for potential therapeutic drug targets for treatment for the symptoms in the future.

Stool Testing: As SARS-CoV-2 gains entry through the mucous membranes and can affect the GI epithelium, it is expected that stools can be positive for viral RNA particles. A systematic review of 12 studies showed a pooled prevalence of 48.1% (95% CI, 38.3%–57.9%) for stool RNA positivity.³⁰ Few aspects need consideration to identify the importance of stool positivity and fecal shedding. In patients with SARS-CoV-2 infection, viral replication occurs in different organ systems, including the GI tract. A study conducted in Hong Kong among 59 patients with COVID-19, nine patients (15.3%) had positive stool viral RNA.³⁰ In the same study, patients without diarrhea were also tested positive for the stool viral RNA, but a lower rate. The median fecal

viral RNA load was higher in individuals with diarrhea compared to without diarrhea ($5.1 \log_{10}$ copies/ml vs. $3.9 \log_{10}$ copies/ml; $p = 0.06$).³⁰

A study by Wolfel et al. noted that stool specimens could be positive for 11 days in individuals presenting with diarrhea as an initial symptom.³¹ In addition, the use of steroids and immunosuppressive medications could prolong the stool viral RNA shedding.^{32,33} Furthermore, studies have shown that the stool viral RNA continues to be positive even after respiratory symptoms resolve. Ling et al. reported that 82% (95% CI, 70.4%–90.2%) of the patients had persistent stool viral RNA positivity after viral respiratory clearance.³⁴ Additionally, the median fecal viral load to establish infectivity from infected patients to non-infected individuals is essential.³⁰ Regardless of diarrhea, identification of stool positivity is vital in all patients as they can potentially spread the virus to a non-infected individual. Previous outbreaks of SARS in 2003, the sewage system was a significant source of infection.^{35,36} Similarly, testing of waste-water treatment plants showed positivity for SARS-CoV-2 as well.³⁷ These studies uncovered the potential of the fecal-oral route of transmission of SARS-CoV-2.

Early identification of GI manifestations is not only crucial in the management but also of public health importance.^{36,38} The presence of SARS-CoV-2 in stool, especially in patients with diarrhea, makes it a potential route of transmission. This can put the endoscopists and the ancillary staff at the risk of acquiring the infection via direct contact GI secretions.³ Moreover, the generation of aerosols because of suctioning during endoscopies carry a further risk of transmission to the hospital staff members.^{3,39,40} Patients with only GI symptoms involved in professions such as food handling, restaurant staff carry the risk of super-spreaders of the disease.⁴¹

Nausea or vomiting

Patients with COVID-19 can develop nausea and vomiting during the initial presentation of the disease. While this could imply a viral prodrome, the persistence of symptoms could herald potential GI involvement. A pooled analysis of 5955 patients with COVID-19 showed a prevalence of nausea or vomiting in 7.8% (95% CI, 7.1%–8.5%) of the patients.¹⁸ Similar to diarrhea, the prevalence of nausea or vomiting in Chinese studies was low (5.2%; 95% CI 4.4%–5.9%), probably due to decreased awareness of GI manifestations early in the pandemic.¹⁸

The mechanism of nausea or vomiting in COVID-19 is unclear. It is suspected that the interaction between the gut and central nervous system may play a potential role in the pathophysiology of these symptoms. The release of pro-inflammatory cytokines in COVID-19 can alter the gut-brain axis involvement of vagal nerve or through vascular/ lymphatic system.²⁵ Lateral hypothalamic nuclei are closely involved pathogenesis of nausea and vomiting.⁴² Neurological manifestations in COVID-19 patients can range up to 36.4%, and symptoms increase with age and underlying comorbidities.⁴³ If the involvement of the hypothalamus directly or indirectly plays a role in these GI symptoms remains to be studied. Furthermore, viral replication in the GI tract can interfere with neurohormonal signaling, which can induce nausea and vomiting.⁴⁴ Further studies are needed to elucidate the precise mechanism of these symptoms.

Loss of appetite

Loss of appetite is a common GI manifestation in COVID-19. However, due to its non-specific nature, it is typically combined with other GI symptoms for its relevance. Individual studies have reported a prevalence of 12.2% to 50.2% in patients with COVID-19.^{45–47} Among 18 studies, the pooled prevalence of loss of appetite was 26.8% (95% CI, 16.2%–40.8%). Though this is higher than the prevalence of diarrhea, it is unclear if they are isolated without other GI symptoms (abdominal pain, nausea/vomiting, or diarrhea). Mechanism of anorexia is probably related to nausea and vomiting, but assessing the literature to evaluate the precise pathophysiology is not available.

Abdominal pain

Patients with COVID-19 reports abdominal pain on an infrequent basis. The prevalence of abdominal pain is lower compared to diarrhea, nausea, or vomiting, or anorexia. Luo et al. noted abdominal pain prevalence as 3.9% with 45 events among 1141 patients (95% CI, 2.9%–5.2%).¹⁶

Chen et al. in Hubei, China reported prevalence as 6.9% with 19 events among 274 patients (95% CI, 4.2%–10.6%).⁴⁸ Studies performed in the USA had a higher frequency of abdominal pain. For instance, Hajifathalian et al. reported a prevalence of 6.8% (95% CI, 5.4%–8.5%) in 72 patients with abdominal pain among 1059 patients and Cholankeril et al. reported a prevalence of 8.6% (95% CI, 4.2%–15.3%) in ten patients with abdominal pain among 116 patients.^{20,49} Similar to other GI symptoms, the prevalence of this symptom is lower in Chinese studies 2.7% (95% CI, 2.0%–3.4%), whereas the non-Chinese studies report a prevalence of 5.3% (95% CI, 4.2%–6.6%).¹⁸ Few aspects of abdominal pain need consideration. Symptoms can range from generalized abdominal pain or epigastric pain or just non-specific abdominal discomfort. Furthermore, COVID-19 induced pancreatitis has been reported with symptoms of abdominal pain.^{12,50,51} Though elevated levels of lipase are noted in COVID-19, it remains unclear if they indicate a low-level of ongoing pancreatic injury or non-pancreatic causes such as gastritis or enteritis.⁵² The duration of these symptoms in the studies was missing. Although abdominal discomfort (from cramps) is frequently noted in viral infection, it is unclear if it correlates with the severity of GI involvement. If abdominal pain corresponds to the viral cytopathic effect and involvement of the enteric nervous system is yet to be studied.

Other GI symptoms

Although GI symptoms such as diarrhea, anorexia, nausea or vomiting, and abdominal pain are commonly reported, few cases of gastrointestinal bleeding, colitis, and secondary bacterial infections were reported.⁵³ Lin et al. reported episodes of GI bleeding in severe COVID-19 patients with gastroduodenal ulceration.²³ Multiple round herpetic erosions were noted with positive SARS-CoV-2 in the esophageal samples. It remains unclear if it is directly related to viral cytopathic effect or due to other causes.^{53,54} Furthermore, *clostridium difficile* infections have been reported in COVID-19 patients, probably due to altered gut flora and the use of multiple antimicrobial agents.^{15,55} Though patients with COVID-19 have altered flora and increased cytokine release, studies showed that IBD patients are not at risk of COVID-19 and related mortality.⁵⁶

Ageusia/Dysgeusia

Altered taste (ageusia/ dysgeusia) has been reported as high as 49.8% (95% CI: 8.2% - 91.5%).⁸ It is unclear if taste changes can precede the development of anorexia, nausea, or diarrheal symptoms.

Hepatic manifestations of COVID-19

The most common hepatic manifestations include asymptomatic elevation of liver chemistries. However, worsening of underlying liver disease presenting with significant elevation of liver chemistries have also been documented.^{57–59} Abnormal liver chemistries can be present in 14%–53% of COVID-19 patients.⁶⁰ The pattern of derangement in liver chemistries is predominately hepatocellular.^{7,59,61,62} A systemic review showed a pooled prevalence of elevated aspartate transaminase [AST] and elevated alanine transaminase [ALT] in 15% (95% CI, 13.6%–16.4%) of the COVID-19 patients. Similarly, any elevation of bilirubin was reported in 16.7% (95% CI, 15.0%–18.5%) of the patients.¹⁸ Hajifathalian et al. reported that the presence of acute liver injury at admission is associated with a higher risk of intensive care unit (ICU) admission and death.²⁰ A few aspects need consideration in COVID-19 patients with elevated liver chemistries. Any viral infection can cause transient and mild elevation (<2 Upper Limit of Normal) of liver chemistries. Furthermore, evaluation of the prior history of liver disease and baseline liver chemistries is important to consider. Post-liver-transplant recipients are a specialized subset of populations who are at higher risk of COVID-19 infection due to their use of immune suppression.^{4,63} Immune-mediated organ damage is noted in COVID-19 patients, and suppression of the immune system might be protective in these individuals. In addition, the use of immunosuppression can mitigate the effects of the cytokine storm seen in COVID-19 patients.

The precise mechanism of liver involvement in COVID-19 patients is unclear. Multiple mechanisms have been proposed. ACE-2, the functional receptor of SARS-CoV-2, is expressed in higher amounts in the biliary epithelium (20 times compared to hepatocytes). As SARS-CoV-2 enters the mucous membranes, it can access the biliary system via the portal vein. SARS-CoV-2 can cause direct immune damage to hepatocytes (cytopathic effect). Direct viral cytopathy with microvesicular steatosis, mild lobular, or portal involvement has been reported.^{61,64} Cytokine storm noted in COVID-19 patients can lead to excess inflammatory burden and potential immune-mediated damage. Immunosuppressive medications such as calcineurin inhibitors reduce the Interleukin-2 and mycophenolic acid inhibits IL-17, which interferes with T-cell function. Furthermore, passive congestion due to increased use of positive pressure ventilation, drug-induced liver injury from medications (antiviral and antibiotics) commonly used during the course of illness are real possibilities.^{60,65}

Severe acute respiratory syndrome (SARS)

The first case of severe acute respiratory syndrome (SARS) was reported in China on November 16, 2002, and it spread to more than 30 countries. Overall, 8098 cases were reported with 774 deaths caused by SARS-CoV-1.^{66,67} In July 2003, WHO declared the end of the SARS epidemic. As the name suggests, it is primarily a disease of the lower respiratory tract. However, enteric involvement is also common in SARS.

Diarrhea was the most common GI symptoms observed in patients with SARS.^{68, 69} In a retrospective study by Leung et al., 20% of patients had watery diarrhea at the time of presentation, and 38% of the patients developed diarrhea overall during the course of the illness.⁷⁰ Some patients presented with fever and diarrhea, without the presence of respiratory symptoms. Diarrhea lasted for an average of 3.7 days and resolved spontaneously in the majority of cases. However, SARS-CoV-1 RNA was detected in the stool for up to ten weeks after the onset of symptoms.⁷¹ Diarrhea was also reported in other SARS outbreaks. In a study from Toronto, the prevalence of diarrhea was 23.6%, whereas another study from Hong Kong reported diarrhea in 70% of their patients.^{72, 73} The higher prevalence of diarrhea was attributed to the different modes of transmission. The mode of transmission from the Hong Kong study was linked to a faulty sewage system resulting in fecal-oral transmission, whereas in other studies, droplet transmission is the main mode of transmission.

Reactive hepatitis has also been reported in SARS. In a study of 294 SARS patients, 24% had elevated ALT on admission, and 69% developed ALT elevation during the course of hospitalization.⁷⁴ In patients with elevated ALT, further worsening of the liver chemistries was noted with systemic corticosteroid and ribavirin treatment.⁶⁹ Spontaneous improvement in ALT was noticed in correlation with the overall clinical improvement. The cytokine release from inflammatory cells was postulated to be the most likely cause of the ALT elevation, although a precise etiology was not determined the probable culprit.⁷⁴ Other laboratory abnormalities that were associated with abnormal transaminases include elevated creatinine, elevated creatinine kinase, and thrombocytopenia.⁷⁵

Middle eastern respiratory syndrome (MERS)

MERS-CoV was first reported in Saudi Arabia on September 20, 2012.⁷⁶ MERS became an epidemic with 2521 laboratory-confirmed cases and 919 deaths (case fatality rate 36%).⁷⁷ MERS-CoV cases are predominately reported from the Arabian Peninsula, with around 84% from Saudi Arabia.⁷⁷ Twenty-seven countries have reported cases of MERS so far. All cases outside the Arabian Peninsula had either history of travel to the region or contact with someone who traveled to the region.^{77, 78} Dromedary camels (*Camelus dromedarius*) are major reservoir/intermediate hosts for MERS-CoV. Although there are cases of human-to-human transition, especially in health care

settings due to close contact while delivering unprotected care to a patient, the virus does not pass easily from the human-to-human.⁷⁹ In an epidemiological study of 47 patients with MERS from Saudi Arabia, 26% had diarrhea, 21% had vomiting, and 17% had abdominal pain.⁸⁰ Hepatic abnormalities are not common with AST elevations in only 15% of patients and ALT elevations in about 11% of the patients.⁸¹ Similar to SARS, other laboratory abnormalities in MERS include leukopenia, thrombocytopenia, elevated lactate dehydrogenase levels, and elevations in creatinine.^{78, 82, 83}

GAPS in knowledge

GI and hepatic manifestations are increasingly being recognized due to an increase in the number of cases. Although anorexia, nausea, vomiting, and diarrhea are being noted as common manifestations, risk of heterogeneity among pooled estimates, geographical location, the publication of bias is inherently present. Potential confounder such as the use of antiviral, antibiotics, enteral feeding can cause nausea, vomiting, anorexia, and diarrhea by themselves and change the prevalence of these symptoms in affected patients. The use of sound methodology with evaluating the cause of these symptoms, along with these confounders, can provide the precise prevalence of the GI and hepatic manifestations.

Conclusion

COVID-19 is the latest of the coronavirus outbreaks in Humans, and it has already caused a devastating impact in the world. It is predominately a respiratory disease with pneumonia, severe acute respiratory distress syndrome, and multiorgan failure. However, non-pulmonary symptoms are increasingly being recognized. Anorexia, nausea, vomiting, diarrhea, and abdominal pain are the common GI symptoms noted in these patients. Patients with diarrhea can precede the development of respiratory symptoms, and in a small proportion of cases, it can be the only presenting symptom. Diarrhea can contribute to fecal-oral transmission and could of public health importance in developing mitigation strategies. Abnormal liver chemistries are noted in 10–15% of cases in COVID-19 patients and frequently involve elevated AST and ALT. As this unprecedented global pandemic unfolds, it is expected that mechanism of GI and hepatic manifestations can further improve in the future.

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