

## SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant

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### Abstract

The current pandemic due to the severe acute respiratory syndrome coronavirus 2 has caused an extreme burden for health care systems globally, and the number of cases is expected to continue to increase, at least in the immediate future. The virus is estimated to have infected more than 1.5 million individuals. The available reports suggest that gastrointestinal (GI) involvement in coronavirus disease 2019 (COVID-19) is common and in some cases the GI symptoms may precede the respiratory symptoms. In addition to direct effects of severe acute respiratory syndrome coronavirus 2, the infected patients remain at risk for the complications commonly managed by gastroenterology and hepatology consultants. The most commonly reported GI manifestation of COVID-19 is diarrhea, which is reported in a third to up to more than half of the patients. Mild to moderate elevation of the liver enzymes are also common, although no case of acute liver failure has been reported so far. Many of the medications used for treatment of COVID-19 can also be associated with GI symptoms or liver injury and can be included in the differential diagnosis in these patients. Although the diagnosis of the infection is currently based on RNA analysis in respiratory samples, the available literature on fecal shedding of this virus suggests that fecal RNA testing might prove to be a useful diagnostic test. It is reasonable to delay all non-urgent endoscopic procedures during the peak of the pandemic and use additional protective equipment such as N95 respirators during endoscopy while most patients can be considered high risk for having been exposed to the virus.

**Key words:** SARS-CoV-2; COVID-19; Gastroenterology; Hepatology; Liver

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the 21<sup>st</sup> century, engaging the health care providers in almost all countries around the world. Similar to previous coronavirus infections such as severe acute respiratory syndrome coronavirus, the COVID-19 is associated with a high prevalence of gastrointestinal (GI) and liver manifestations and abnormalities. Here we present a comprehensive summary of the available evidence on GI involvement of COVID-19 and its implications for the GI consultants.

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## INTRODUCTION

Since its emergence in December 2019, the coronavirus disease 2019 (COVID-19) has spread to over 146 countries and has been declared a pandemic by the World Health Organization (WHO). The virus that causes COVID-19, designated the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is estimated to have infected more than one million individuals and has resulted in more than 59000 deaths to date<sup>[1]</sup>. Community transmission of the virus has now been confirmed across all inhabited continents and emergency measures have been taken to further curb the transmission of the disease.

SARS-CoV-2 is a positive-sense single-stranded RNA betacoronavirus sharing sequence homology with other pathogenic coronaviruses including Middle East respiratory syndrome coronavirus (MERS-CoV, 2012), and severe acute respiratory syndrome coronavirus (SARS-Cov-1, 2003). The virus is thought to have emerged from animal reservoirs, namely horseshoe bats. The COVID-19 infection varies widely in severity, but primarily manifests as pneumonia. The median age of COVID-19 patients is reported to be in the fifth decade of life, with male predominance, less than 1% of cases occurring in patients younger than 10 to 15 years of age, and higher risk of severe disease in elderly or those with underlying medical comorbidities<sup>[2]</sup>. SARS-CoV-2 is thought to be transmitted mainly through contact with respiratory droplets and potentially airborne route; however presence of the virus in the stool of infected patients has suggested the fecal-oral route as a possible mode of transmission<sup>[3,4]</sup>.

The first case of COVID-19 was detected in Wuhan, Hubei Province, China, in early December 2019, and the first cohort of patients have been linked to a local live animal market, suggesting the emergence of this virus from animal reservoir. Unlike MERS-CoV and SARS-CoV where widespread international transmission was limited by high case fatality rates and more limited person-to-person transmission (in some instances happening to a large extent in health-care and research facilities), SARS-CoV-2 has shown a relatively lower case fatality rate and easy person-to-person transmission, potentially even during the asymptomatic phase of the disease, leading to a rapid global spread and causing the first known coronavirus pandemic<sup>[5]</sup>.

Although the available information on transmission, pathogenesis, clinical presentations, and management of COVID-19 is limited by the novelty of this new pandemic, it is still important to review the available literature in preparation for an ongoing increase in the number of infected patients over the next several weeks, and potentially months. Here we present a narrative review of the available literature regarding the involvement of the liver and digestive system in patients infected with SARS-CoV-2 infection.

## LITERATURE SEARCH

The MEDLINE database was searched through PubMed using a search query constructed with the following medical subject heading (MeSH) terms: (("severe acute respiratory syndrome coronavirus 2" [Supplementary Concept]) OR "COVID-19"[Supplementary Concept]) OR "coronavirus 2019"[Title/Abstract] OR "sars-cov-2"[Title/Abstract] AND ("Gastroenterology"[Mesh])) as well as with addition of different keywords to increase the sensitivity and specificity of the search (*e.g.*, "Signs

and Symptoms, Digestive"[Mesh] OR "GI" OR "gastro\*" OR "liver" OR "hepat\*" OR "digestive" OR "diarrhea" OR "nause\*" OR "vomit\*" OR "abdomen\*" OR "bowel" OR "colon" OR "bile" OR "bilial\*" OR "dyspep\*" OR "stomach" OR "gastr\*" OR "esophag\*" OR "duoden\*" OR "jejun\*" OR "ile\*" OR "transamin\*"). A similar search was performed in Google Scholar engine. The reference list of the papers, Websites of leading gastroenterology and hepatology journals, as well as WHO, and Center for Disease Control and Prevention publications were reviewed manually by the authors. The full texts of articles were reviewed by the authors to extract the relevant information and was constructed into a narrative review. Literature review was limited to the sources available in English. Fifty-five studies were selected for full-text review by the authors.

## RESULTS

### ***Clinical manifestation and complications***

Pneumonia is the most common serious clinical manifestation of COVID-19, with fever, fatigue, myalgia, and dry cough being the most common features<sup>[6]</sup>. Other common symptoms include the anorexia, headache, dyspnea, as well as sore throat and rhinorrhea. Gastrointestinal (GI) symptoms present less commonly, and include diarrhea, liver test abnormalities, nausea, and abdominal pain.

### ***Diarrhea***

In a report of 41 patients from Wuhan hospitalized with COVID-19, diarrhea was present in 3% of cases<sup>[7]</sup>. Interestingly, none of the patients with severe disease needing intensive care unit (ICU) care had diarrhea and all the cases of diarrhea happened in patient with less severe disease in this study. A study of 18 COVID-19 cases in Singapore similarly reported diarrhea in 25% of patients who did not need supplemental oxygen, but none of the cases who required oxygen supplementation<sup>[8]</sup>. However, a second report from 138 patients hospitalized with COVID-19 in Wuhan showed a higher prevalence of diarrhea with 10% of patients having diarrhea, and a higher prevalence of diarrhea among ICU patients (17%) compared to non-ICU patients (8%, difference not statistically significant)<sup>[6]</sup>. Authors reported nausea in 10% of cases, vomiting in 4%, and abdominal pain in 2% of cases. Interestingly, ICU patients were significantly more likely to have abdominal pain compared to non-ICU patients (8% *vs* 0%,  $P = 0.02$ ).

### ***Liver test abnormalities***

The same report of 41 patients mentioned above showed elevated levels of aspartate aminotransferase (AST) in 37% of patients, including 62% of ICU patients and 25% of non-ICU patients. The study of 138 patients hospitalized in Wuhan showed that although 3% of cases had pre-existing chronic liver disease, none of these needed ICU care in this cohort<sup>[6]</sup>. Mean AST and alanine aminotransferase (ALT) were both mildly elevated in ICU patients (52 and 35 U/L, respectively), but not in non-ICU patients (29 and 23 U/L), with the AST/ALT ratio of 1.5. A meta-analysis of 10 studies on COVID-19 reported the prevalence of aminotransferase elevation to be between 17% and 37% of patients from different studies<sup>[9]</sup>. A study on 1099 patients with COVID-19 in China reported an 11% prevalence of elevated total bilirubin (> 1 mg/dL) with both elevated aminotransferase levels and total bilirubin being more common among patients who experienced a composite outcome of ICU admission, mechanical ventilation or death<sup>[2]</sup>. Elevation of alkaline phosphatase does not seem to be common in patients with COVID-19 and has been reported to happen in 1%-2% of cases<sup>[10]</sup>. Neither of these studies report acute fulminant liver injury or acute liver failure as a complication of COVID-19. However, given that up to a third of ICU cases can be complicated by shock, it is expected to see varying degrees of ischemic liver injury in these patients. One study has found that an ALT level of > 40 IU/L is associated with inpatient mortality<sup>[11]</sup>, and another study has shown that elevated AST and bilirubin levels can be associated with higher risk of progression to respiratory failure and death<sup>[12]</sup>. Although it is unclear from the available evidence whether elevation of liver enzymes is an "independent" predictor of poor prognosis, these abnormalities (similar to other indicators of end-organ damage) are encountered more frequently in patients with severe disease and need for ICU care and mechanical ventilation.

### ***Summary of GI manifestations***

Considering these findings, it seems that diarrhea is the most common GI manifestation of SARS-CoV-2, with nausea and vomiting, abdominal pain, and mild elevation of AST and ALT as the other presentations (Table 1). Previous studies have shown a higher prevalence of diarrhea (20% to 26%) and other GI symptoms in

patients with SARS-CoV and MERS-CoV<sup>[13,14]</sup>, suggesting a different tropism compared to SARS-CoV-2, although there might be significant variability in the definition used and reporting of GI symptoms for COVID-19 from different hospitals<sup>[2,15]</sup>. The latest available evidence from a paper focusing on digestive system symptoms in 204 COVID-19 cases from Hubei, China, reports diarrhea in up to 29% of cases, but vomiting and abdominal pain in only 0.8% and 0.4%, respectively, again showing some degree of variability in GI presentations of the disease<sup>[16]</sup>. Interestingly, in our experience at our hospital in New York we have observed that mild diarrhea can be present in a much larger proportion of patients, reaching a prevalence of more than 50% in patients admitted with COVID-19, suggesting a possible different clinical manifestation in the North American population. Finally, there is now at least one report of bloody inflammatory diarrhea possibly caused by SARS-CoV-2 virus associated colitis suggesting that this virus can cause a wider variety of luminal presentations as currently reported<sup>[17]</sup>. Importantly, 7 patients in the above-mentioned study (3%) presented only with the digestive complaints mentioned above, and without any respiratory symptoms, in addition to 20% of cases who presented with a combination of respiratory and GI symptoms. Interestingly, patients presenting with GI symptoms had a longer time from the onset of disease to hospital admission compared with patients without digestive symptoms (9.0 d *vs* 7.3 d,  $P = 0.02$ ), and GI symptoms were observed to increase with severity and duration of COVID-19<sup>[16]</sup>. A separate study has also suggested that while COVID-19 shows a male predominance, GI symptoms of the disease are more likely to be present in female patients<sup>[18]</sup>. These findings suggest that while a small group of patients might present initially with only GI symptoms, most of cases develop these symptoms later on during the course of their disease.

There might be a potential explanation for relatively high prevalence of diarrhea and risk of small bowel involvement with SARS-CoV-2 compared with other GI symptoms, as both SARS-CoV and SARS-CoV-2 are thought to have a high affinity for angiotensin-converting enzyme 2 (ACE2) receptor potentially permitting virus entry into cells, and ileal epithelial cells have a significantly high ACE2 expression, while cholangiocytes and esophageal epithelial cells also express this receptor as a potential target for the virus<sup>[3,19,20]</sup>. An available report of elevated gamma-glutamyl transferase, a diagnostic biomarker for cholangiocyte injury, in patients with COVID-19 (up to half of cases in a cohort from China) provides further evidence regarding cholangiocyte injury<sup>[10]</sup>. Although ACE2 expression in hepatocytes is relatively lower than cholangiocytes, it is worth noting that previous autopsy and liver biopsy studies from SARS-CoV patients have found viral particles in hepatic parenchyma as well as eosinophilic bodies and ballooning, suggesting hepatocyte injury<sup>[21,22]</sup>. It should be noted that the observed GI manifestations including elevated liver enzymes can be confounded by adverse reactions due to different pharmacotherapy agents in COVID-19 patients (discussed below), as well as associated ischemia and hypoxia in severe cases.

### Pharmacotherapy

Thus far there is no proven specific treatment for COVID-19, and the mainstay of management remains to be supportive care. However, the available pre-clinical evidence shows *in-vitro* efficacy of both chloroquine and hydroxychloroquine against SARS-CoV-2 infection potentially through increasing endosomal pH and interfering with the glycosylation of cellular receptor of SARS-CoV<sup>[23,24]</sup>. This has led to clinical use of these drugs in COVID-19, while the results of ongoing clinical trials are pending. It is important to note that although chloroquine and hydroxychloroquine rarely result in clinically significant acute liver injury (except in patients with porphyria cutanea tarda), they should be used with caution in patients with hepatic impairment, or those taking concurrent hepatotoxic medications<sup>[25]</sup>. Other experimental agents include Lopinavir-Ritonavir, Remdesivir, Favipiravir, Tocilizumab, Sarilumab, and Siltuximab, all with unproven efficacy. Use of Lopinavir-Ritonavir can be associated with GI adverse reactions such as diarrhea, nausea and vomiting, abdominal pain, and increased serum aminotransferase, amylase and lipase levels, as well as risk of hepatitis and exacerbating underlying chronic liver disease, for example in patients with chronic viral hepatitis. For example, Four out of five patients treated with Lopinavir-Ritonavir in an abovementioned study from Singapore developed Nausea, vomiting, and/or diarrhea, and three developed abnormal liver tests<sup>[8]</sup>. However, after publication of a trial failing to show a significant benefit for Lopinavir-Ritonavir, its use has declined for the treatment of COVID-19<sup>[26]</sup>. Similarly, Tocilizumab and similar medications such as Sarilumab can be associated with increased aminotransferase levels as well as risk of acute liver injury and failure. The full extent of GI adverse events of the antiviral treatments for COVID-19, such as Remdesivir and Favipiravir, is not yet clear; however, the existing

**Table 1** Gastrointestinal manifestations of coronavirus disease 2019

Manifestation	Reported prevalence	
Luminal		
Diarrhea	Very common	10%-29%, potentially 50% in North America
Abdominal pain	Common	1%-29%
Nausea and vomiting	Common	1%-29%
Hemorrhagic enterocolitis	Rare	Case report
Liver		
Acute liver failure	So far not reported	
Mild to moderately elevated AST and ALT	Very Common	17%-62%
Elevated bilirubin	Uncommon	Up to 11%
Elevated alkaline phosphatase	Uncommon	< 5%
Elevated GGT	Common	Up to 54%

GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

reports suggest nausea and vomiting and varying degrees of liver test abnormalities as potential side effects. It is reasonable to obtain baseline liver function tests before using the abovementioned pharmacologic agents for management of COVID-19 and continue to monitor them during treatment. Regarding immunosuppressive medication used in patients with inflammatory bowel disease and autoimmune hepatitis, the current guidance from a multi-society task force recommends continuation of medication given that risk of disease flare and associated complications currently outweighs the risk of contracting COVID-19<sup>[27]</sup>. These patients, as well as patients with chronic liver disease and cirrhosis, should be counseled to remain cautious and follow guidelines for at-risk group with optimal hand hygiene and social isolation to minimize their risk during the pandemic. As an example, a report from China has suggested that a simple intervention by sending messages to patients with cirrhosis regarding precautions to take against COVID-19 can significantly decrease the risk of contracting the disease<sup>[28]</sup>.

### Testing and fecal shedding

Current guidelines from the WHO and Center for Disease Control and Prevention recommend nasopharyngeal swabs for testing for SARS-CoV-2, with additional oropharyngeal swabs as an option<sup>[29]</sup>. The presence of SARS-Cov-2 is then verified using reverse-transcription polymerase chain reaction. A positive result confirms the presence of SARS-CoV-2, but due to the potential for false negative results, the WHO recommends re-sampling and repeat testing in case of negative results with clinical suspicion for COVID-19<sup>[30]</sup>. As mentioned earlier, SARS-CoV-2 RNA is present in patients' stool. A study of 292 cases from China reported the presence of viral RNA in stool to be persistent in 17% of convalescent cases, with 78% of cases having longer duration for stool specimens staying positive for viral RNA compared to viral RNA from throat swabs, with a median delay of 2.0 d<sup>[4]</sup>. A separate study on 74 patients with confirmed COVID-19 and both fecal and respiratory sample testing reported that while viral RNA is not positive in all cases (it was negative in 45% of cases), the fecal RNA remains positive during convalescence and for a longer period compared to respiratory samples (mean 28 d *vs* 17 d after first symptoms) and can stay positive for up to 5 wk after the initial presentation<sup>[31]</sup>. Although stool samples are not currently used for diagnosis of COVID-19, these findings suggest a potential role for stool samples to be used both for diagnosis and for evaluation of risk of transmission and need for isolation during convalescence, as well as a potential risk for fecal-oral transmission of this disease. Interestingly, there is now a report of a patient with COVID-19 and positive fecal viral test but with several negative pharyngeal and sputum polymerase chain reaction tests over time, suggesting that fecal testing can potentially play a role in the diagnosis of COVID-19<sup>[32]</sup>. Fecal microbiota transplant donors are a special group with potential for widespread transmission of the disease, and testing for viral RNA in their stool samples should be seriously considered, especially if they have a history of typical COVID-19 symptoms over the past 4 to 6 wk<sup>[33]</sup>. Finally, it is reasonable to consider the donors and recipients of liver transplantation as a special population and recommend universal testing for SARS-CoV-2 before liver transplantation<sup>[34]</sup>. As mentioned above, given reports of a small minority of patients initially presenting exclusively with GI symptoms, it is important

for GI consultants to remain vigilant and include COVID-19 in their differential diagnosis even in the absence of respiratory symptoms, especially in febrile patients.

### **Endoscopy during SARS-CoV-2 pandemic**

A multi-society guideline published on March 15, 2020 by the AASLD, ACG, AGA and ASGE has recommended postponing non-urgent endoscopic procedures during the pandemic<sup>[27]</sup>. Examples of these procedures include screening and surveillance endoscopic procedures in asymptomatic patients (such as colon cancer screening or Barrett's esophagus surveillance), esophageal pH testing, motility studies (such as esophageal and anorectal manometry), and diagnostic procedures where results are not urgently needed (such as endoscopic ultrasound exam for pancreatic cyst with intermediate risk of malignancy). Naturally, endoscopists will have to continue to perform procedures for urgent cases such as food impactions or severe dysphagia, GI bleeding, cholangitis or acute biliary obstruction, or time-sensitive endoscopic examinations such as evaluation of malignancies and endoscopic or echoendoscopic staging. Multiple guidelines published by different GI and endoscopic societies provides further details regarding endoscopy during the COVID-19 pandemic<sup>[35-37]</sup>. Patients should be screened for presence of fever and clinical symptoms compatible with COVID-19 according to institutional protocols prior to admission to endoscopy suite, and the number of people present in the endoscopy suite should be minimized to decrease the risk of exposure and transmission and usage of personal protective equipment (PPE). Given the presence of viral DNA in pharyngeal and GI secretion, risk of aerosolization should be minimized by efficient intubation (when needed) with experienced anesthesiology providers, and minimizing the length of the endoscopic procedures and use of CO<sub>2</sub><sup>[38]</sup>. In addition to standard PPE including disposable hairnet, gowns, gloves, surgical mask and face shield, providers should consider using N95 respirators (or equivalent, such as FFP2 or FFP3) while providing care for all patients during the COVID-19 pandemic. While some authors have suggested using N95 respirators only for confirmed or high risk cases and during upper endoscopy in intermediate risk patients, it should be noted that near universal spread of the virus across communities will qualify almost all patients as "high-risk" according to the current guidelines with a need for using N95 respirators for all endoscopic procedures<sup>[37,39]</sup>. Finally, it is reasonable to change gastroenterology and hepatology clinic visits to telehealth care using phone calls and video visits (according to availability and institutional protocols) in patients who do not have an absolute need for physical examination.

## **DISCUSSION**

The current pandemic due to SARS-CoV-2 virus has caused an extreme burden for health care systems globally, and the number of cases is expected to continue to increase, at least in the immediate future. Familiarity of health care providers with this virus and its clinical manifestations can significantly help with efficient and timely management of patients with COVID-19. The review of the available literature with a focus on GI manifestations of COVID-19 is presented here. The available reports suggest that GI involvement in COVID-19 is less common compared with previous Coronavirus outbreaks, namely SARS-CoV, and MERS-CoV. Nonetheless, a significant proportion of patients present with GI symptoms and signs in addition to the cardinal manifestations of lower respiratory tract involvement and pneumonia. In some cases the GI symptoms may precede any respiratory symptoms<sup>[16]</sup>. The most common luminal manifestation of the disease is diarrhea reported in up to 17% of the cases, but the available literature is limited regarding the severity of diarrhea.

The high expression of ACE2 in the ileum suggests it as a potential target of the virus in the GI tract. Additionally, mild to moderate elevation of aminotransferases has been reported in 20% to 50% of the cases. Although acute liver failure has not been reported as a direct consequence of severe COVID-19, the extent of abnormal liver tests seems to be associated with disease severity and worse outcomes. It is important to note that medications used for management of COVID-19, such as chloroquine or Lopinavir-Ritonavir can be associated with varying degrees of liver test abnormalities and GI adverse reactions. It is important to obtain a baseline evaluation of patients' liver function before initiation of treatment and continue to monitor liver function tests during the treatment. It is also important to check patients for presence of chronic viral hepatitis (HBV, and HCV), as well as risk factors for chronic liver disease especially alcohol use before starting the treatment with these agents. In addition to direct effects of SARS-CoV-2 and similar to any other patients with severe illness, these patients remain at risk for the complications commonly

managed by gastroenterology and hepatology consultants such as *C. difficile* infection in context of frequent antibiotic use, and ischemic liver injury or cholestasis of critical illness. As detailed above, delaying endoscopic procedures in non-urgent cases, and strict adherence to hand hygiene, contact precautions, and correct use of PPE will help minimize the risk of exposure and transmission during COVID-19 pandemic and conserve health-care resources.

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