Gastrointestinal and liver manifestations of COVID-19

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Abstract

The novel coronavirus 2 (SARS-CoV-2) has spread worldwide. While patients typically present with fever and symptoms of a respiratory illness, patients have also presented with gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain. In addition, some patients were reported to have liver injury. In this article, we review gastrointestinal and liver aspects of COVID-19. In addition, we provide general gastroenterologists with guidance on the management of patients with gastrointestinal and liver disorders from COVID-19.

Keywords: COVID-19, gastrointestinal, liver

BACKGROUND

Coronaviruses are enveloped viruses with positive-sense single-stranded RNA genomes, which infect both humans and animals.[1] There are currently 7 known coronaviruses, which infect humans, including the Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most recently identified human coronavirus, which can cause the coronavirus disease 2019 (COVID-19).[2] SARS-CoV-2 has been known to spread through respiratory droplets and possibly through fecal-oral route.[3] A recent study has observed that the RNA of COVID-19 was positive 11 days after respiratory tract samples were initially reported as negative in patients who were infected with COVID-19, indicating that the virus actively replicates in the patient's digestive system. This also suggests that fecal-oral transmission may occur even after the virus is cleared from the respiratory tract.[4] However, to date, there is not a single reported case of COVID-19 that was transmitted via the fecal-oral route. COVID-19 is likely to be transmitted by asymptomatic as well as symptomatic patients during the incubation period, that is estimated to have an average of 5.1 days but ranges from 2 to 14 days.[2,5,6] The Center for Disease Control identified close contact with laboratory-confirmed COVID-19 patients and history of travel from affected geographic areas within the past 14 days as risk factors.[7]

Fever is the most common presenting symptom of COVID-19, which occurs in 83-98% of patients, followed by cough in 46-82% of patients.[8] Overall, 80% of those infected in Hubei province, China were described as being mild cases, 13.8% were severe cases warranting hospitalization and 6.1% needed intensive care unit (ICU) care.[9] COVID-19 may progress to severe bilateral pneumonia and acute respiratory distress syndrome requiring prolonged mechanical ventilation.[9]

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In the present time, it is important to consider COVID-19 in all patients with fever and lower respiratory illness requiring hospitalization. The priority for testing includes hospitalized patients with signs or symptoms of COVID-19, healthcare personnel with risk of exposure and vulnerable populations, including the elderly, those with chronic lung disease, diabetes, cirrhosis, HIV, and on immunosuppression.[10] Guidance regarding testing or quarantining patients is contingent at this time on the availability of tests and laboratory capacity. To detect SARS-CoV-2, nasopharyngeal oropharyngeal swabs are used to obtain specimens that are then sent for real time reverse transcriptions PCR assay. Routine laboratory testing will oftentimes show leukopenia (9-25% of patients) or lymphopenia.[8]

There is no proven beneficial targeted treatment for COVID-19 as of yet, but multiple potential candidate agents are being evaluated. Antivirals have been explored and include remdesivir, a prodrug of an adenosine analog with activity against RNA viruses, which is currently available for compassionate use by its manufacturer, Gilead.[11] Another antiviral, lopinavir-ritonavir, was used in an open label trial for the treatment of 199 hospitalized patients with severe COVID-19, and was not observed to be of benefit compared to standard of care.[12] The United States Federal Drug Administration announced on March 24, 2020 that convalescent plasma might be collected from patients who have recovered from COVID-19 to use in patients with life threatening severe disease, but reports have yet to become available of its use.[13] Several other therapies have been considered, including chloroquine and hydroxychloroquine. Chloroquine has been demonstrated to block the SARS virus infection by reducing virus and cell fusion. However, the safety and efficacy in COVID-19 is not known.[11] Due to the uncertainty of gastrointestinal and liver-related manifestations of COVID-19, a summary of the recent studies and management in COVID-19 patients with gastrointestinal and liver disorders will be provided.

GASTROINTESTINAL SYMPTOMS REPORTED IN PATIENTS WITH COVID-19

For gastroenterologists, it is important to know that the initial presentation of COVID-19 may include diarrhea and nausea in 2-33% of patients.[14] The incidence of these gastrointestinal features varies significantly in different study populations. The first case of SARS-CoV-2 in the United States reported a two-day history of nausea and emesis, then diarrhea on admission day 2.[15]

There have also been reports of isolated diarrhea preceding other symptoms. In a descriptive, cross-sectional

multicenter study, patients were enrolled from 3 hospitals in Hubei province, China from January 18th to February 28th, 2020. In this study, 204 patients with pneumonia of unknown cause were randomly selected from the general wards and the ICU. The study's inclusion criteria were having COVID-19 as confirmed by real-time PCR and having performed a chest computerized tomography and complete routine laboratory tests. A total of 103 patients reported digestive symptoms, including lack of appetite in 81 of these cases, diarrhea in 35 cases, vomiting in 4 cases, and abdominal pain in 2 cases. Patients with digestive symptoms had a significantly longer time from the onset of symptoms to hospital admission (9.0 vs 7.3 days), suggesting that these symptoms may precede other symptoms.[14]

A study of 74 confirmed COVID-19 patients that were admitted from January 17 through February 8, 2020 in the Zhejiang province of China analyzed clinical and virologic characteristics of these patients. The average age of patients with gastrointestinal symptoms was 46 years old. They found that patients with gastrointestinal symptoms tended to develop severe and critical COVID-19, with severe type defined as dyspnea, resting oxygen saturation of ≤93% and artery PaO2/FiO2 ≤300 mm Hg. Critical COVID-19 in this study was defined as requiring ICU admission and mechanical ventilation. Of the patients with severe and critical COVID-19, 22.97% presented with gastrointestinal symptoms.[16] The exact mechanism by which SARS-CoV-2 leads to gastrointestinal symptoms has not yet been elucidated.

It is also important to consider the possibility of a fecal-oral method of transmission for SARS-CoV-2. A retrospective analysis of 14 laboratory confirmed patients with COVID-19 pneumonia, obtained from the Department of Infectious Diseases at the Jinhua Hospital of Zhejiang University in China, hospitalized from January 27, 2020 to February 10, 2020, found that 5 of the 14 patients had a positive stool sample with COVID-19 nucleic acid.[17] This suggests the possibility of transmission through feces, and makes it imperative to identify patients who present early or only with gastrointestinal symptoms.

RECOMMENDATIONS FOR ENDOSCOPY AND CLINICAL PRACTICE

Regarding endoscopy, multiple gastroenterology societies have provided several recommendations.[18,19] They strongly recommend rescheduling elective, and non-urgent endoscopic procedures. Additionally, it has been recommended that all patients should be pre-screened for high-risk exposure or for symptoms of COVID-19,

Table 1: Classification of potential SARS-CoV-2 infection risk in patients undergoing endoscopic examination

Low risk	▪ No symptoms (eg, cough, fever, breathlessness, diarrhea) ▪ No contact with SARS-CoV-2–positive person ▪ Nonstay in high-risk area during the previous 14 days
Intermediate risk	▪ Presence of symptoms with ○ No medical history for contact with SARS-CoV-2–positive person ○ Nonstay in high-risk area during the previous 14 days ▪ No symptoms but ○ Contact with SARS-CoV-2–positive person ○ Stay in high-risk area during the previous 14 days
High risk∗	▪ At least 1 symptom + 1 of the following: ○ Contact with SARS-CoV-2–positive person ○ Stay in high-risk area during the previous 14 days

*In an emergency setting, all the procedures must be considered high risk if adequate patient history cannot be assessed. (Reproduced with permission from Repici A *et al*. Coronavirus outbreak: what the department of endoscopy should know. Gastrointest Endosc. 2020 {ahead of print})[20]

listed in Table 1. Only essential personnel should be present in order to conserve personal protective equipment (PPE). PPE, including gloves, mask, eye shield/goggles, face shields and gown need to available. In addition, for patients considered to be at intermediate risk of SARS-CoV-2 infection, a report out of Italy recommends the use of N95 or FFP 2-3 respirator masks by endoscopists and staff for all upper endoscopies.[20] Lower gastrointestinal endoscopies were considered low-risk procedures in this intermediate risk group, as there was less potential for aerosolized secretions. N95 or FFP 2-3 respirator masks should be utilized for all endoscopic procedures in high-risk patients [Figure 1]. All patients should be at an appropriate distance from one another (6 feet or 2 meters) and should

have their body temperature checked upon arrival. For elective office visits, strong consideration should be made to offer these remotely via telemedicine.

RECOMMENDATIONS FOR PATIENTS ON IMMUNOSUPPRESSANTS DURING COVID-19 PANDEMIC

Patients with inflammatory bowel disease (IBD) should continue on their immunosuppressive medications. Keeping IBD in remission, and avoiding steroids or hospitalization, outweighs the chance of contracting SARS-CoV-2.[21] Of 1099 patients identified by investigators in China, immunomodulator use was not found to be a risk factor for severe COVID-19.[8] Of note, no patients with IBD were reported to be infected with SARS-CoV-2 from 7 of the largest referral centers with over 20,000 patients or from the three largest tertiary IBD centers in Wuhan, China.[22] However, a multinational initiative to register all IBD patients infected with COVID-19 into a central repository, the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE) registry, has been launched. As of April 1, 2020, a total of 239 cases have been registered into the database.[6]

The International Organization for the Study of Inflammatory Bowel Disease (IOBD) has convened a panel of experts to provide guidance on the treatment of IBD during the pandemic using the RAND/UCLA appropriateness methodology. As a result, this panel released 76 statements that were recently published by IOBD, which summarize the experts' opinions on
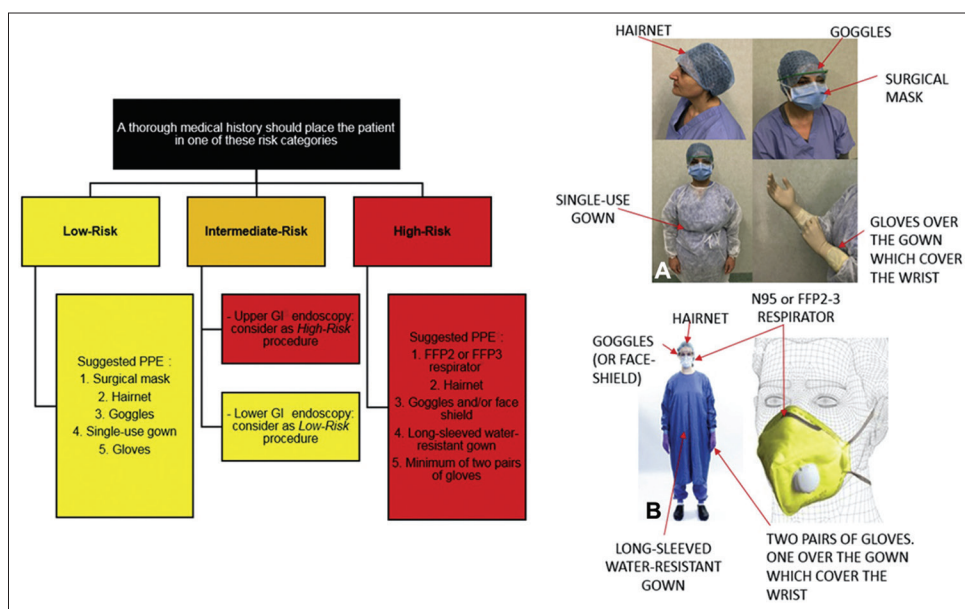
Figure 1: Composition of personal protective equipment (PPE) for personnel during endoscopy on the basis of risk stratification. (A) Low-risk dressing equipment. (B) High-risk dressing equipment. FFP, filtering face-piece (FFP2/3 are equivalent to N95 mask). (Reproduced with permission from Repici A *et al*. Coronavirus outbreak: what the department of endoscopy should know. Gastrointest Endosc. 2020 {ahead of print})[20]

multiple topics. Most significantly, the panel provides guidance for the management of patients on the multiple immunosuppressive agents used for the treatment of IBD. A summary of the recommendations made by the IOIBD can be found in Table 2. These statements are by no means guideline recommendations. However, they do provide much needed advice for clinicians and patients during a time of constant change. The British Society of Gastroenterology released a summary of recommendations as well, and one key difference is that the following immunosuppressives were noted in addition to those identified by IOIBD as without evidence of increasing COVID-19 infection: immunomodulators including azathioprine, anti-TNF and tofacitinib [Table 2]. Recommendations also included early therapeutic drug monitoring when possible of anti-TNF therapy and different degrees of social distancing as determined by the immunosuppression or comorbidities of a patient.[2]

Key points
- SARS-CoV-2 has been known to spread through respiratory droplets and possibly through fecal-oral route
- Fever is the most common presenting symptom, but diarrhea and nausea may precede fever and were reported in 2-33% of patients
- It is strongly recommended to reschedule elective, non-urgent endoscopic procedures
- Endoscopists and staff should ensure proper usage of personal protective equipment (PPE), with the use of N95 or FFP 2-3 respiratory masks during upper endoscopies in intermediate risk patients and during all procedures for high risk patients

- Patients with inflammatory bowel disease and autoimmune hepatitis should continue on their immunosuppressive medications.

HEPATIC MANIFESTATION IN COVID-19 INFECTION

Liver injury has been reported in patients with COVID-19.[23] Liver injury mainly presents as mild elevation of aspartate transaminase (AST) and/or alanine transaminase (ALT) with a rare incidence of cholestasis. Current data is limited and it is difficult to ascertain whether the liver injury is due to direct viral infection, drug-induced, or from complications such as ischemic hepatitis.

PATHOPHYSIOLOGY

There is sufficient evidence supporting that the coronavirus (CoV) family can cause direct hepatic damage, although little is known specifically for SARS-CoV-2.[23] Liver injury was found in 60% of patients with SARS-CoV-1 infection, which was identified as the cause of the SARS outbreak in 2003.[23] The liver biopsy from patients infected with SARS showed increased mitosis and apoptosis along with positive reverse transcription polymerase chain reaction (RT-PCR), consistent with SARS-associated coronavirus infection.[23] The SARS-COV-2 shares 82% genome sequence similar to the SARS-CoV-1, thus it is possible that patients with COVID-19 infection may have direct hepatic injury from the viral infection. However, SARS-CoV-2 viral inclusions were not found in liver tissue from a patient who died from COVID-19 infection.[24]

Table 2: Summary of recommendations regarding immunosuppressive therapy

| International Organization for the study of Inflammatory Bowel Disease	British Society of Gastroenterology

Does not increase risk of COVID-19
  5-ASA
  Budesonide
  Vedolizumab
  Ustekinumab
	Does not increase risk of COVID-19
	  5-ASA
	  Budesonide
	  Vedolizumab
	  Ustekinumab
	  Anti-TNF
	  Immunomodulators
	  Tofacitinib

Uncertain whether the risk of COVID-19 is increased
  Azathioprine or 6-MP
  Anti-TNF
  Tofacitinib
  Combination therapy with an anti-TNF and thiopurine/methotrexate
	Uncertain whether the risk of COVID-19 is increased
	  No medications included

Stop therapy if positive for COVID-19
  Prednisone if ≥20 mg/d
  Azathioprine or 6-MP
  Anti-TNF
  Ustekinumab
  Tofacitinib
  Combination therapy with an anti-TNF and thiopurine/methotrexate
	Stop therapy if positive for COVID-19
	  Thiopurines in patients >65 years old or those with significant respiratory, cardiac or other comorbidities
	  Steroids after a rapid taper of steroids of 10 mg/week

Both SARS-CoV-1 and SARS-CoV-2 use the angiotensin-converting enzyme 2 (ACE2) receptor to enter target cells.[25] Interestingly, a study using ribonucleic acid (RNA) sequencing technique found more ACE2 expression in cholangiocytes compared to hepatocytes, suggesting that SARS-CoV-2 may lead to direct damage of intrahepatic bile ducts.[23] However, the finding does not explain why the majority of patients with COVID-19-related liver injury tend to present with abnormal AST and/or ALT but not a cholestasis picture.

INCIDENCE OF LIVER INJURY

Several case series reported abnormal liver biochemical tests at the time of admission, listed in Table 3.[8,26-28,30,31] The number of patients included in the studies ranged from 21 to 1,099; one case series was from the United States.[26] Data regarding AST and ALT elevations were available in all studies. However, data regarding total bilirubin (TB) elevation were available in 3 studies[8,27,28] and only one study reported whether there was alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) elevation.[28]

Incidence data are summarized in Figure 2. Elevated AST found in 22% (14-53%), elevated ALT 21% (15-30%) and elevated TB 11% (6-18%). Data on ALP and GGT elevation were available in only one report, and was 4% and 18%, respectively.[28] In this report, only 5% of patients had pre-existing liver disease, suggesting that the elevated liver biochemical test was associated with COVID-19 infection.[28]

Liver injury was more prevalent in COVID-19 patients with severe pneumonia. Guan *et al.* reported AST, ALT and TB elevation in 39%, 28% and 13%, respectively
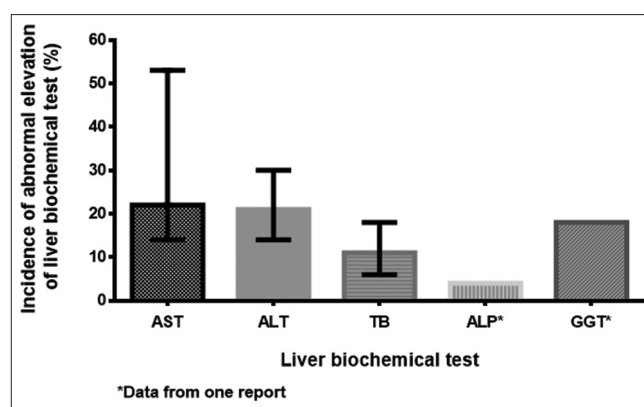
Figure 2: Incidence of abnormal elevation of liver biochemical tests at the time of admission in patients with COVID-19 infection. (Line shows range among different case series)

in severe cases, compared to 22%, 21% and 11%, respectively, in non-severe cases.[8] In this study, severe pneumonia was defined using the American Thoracic Society guidelines for community-acquired pneumonia.[32] Similarly, Huang *et al.* reported AST elevation in 62% of patients admitted to the intensive care unit, compared to 37% in patients admitted to the general floor.[29] Decrease in albumin level was also observed in severe COVID-19 infection.[27]

SEVERITY OF LIVER INJURY

Liver damage is often mild and transient and rarely requires special treatment.[10,28,33] However, there were rare cases of severe liver damage with AST more than 7000 U/L and AST more than 1000 U/L.[12,27,34] In those cases, baseline chronic liver disease or ischemic hepatitis could not be ruled out. To the best of our knowledge, there was no report of acute liver failure caused by COVID-19 infection.

Table 3: Incidence of abnormal elevation of liver biochemical test among different case series

	Guan[8]	Fan[27]	Chen[26]	Shi[29]	Xu[30]	Huang[28]	Arentz[25]
Center, no	552	1	1	2	7	1	1
Location	China	Shanghai	Wuhan	Wuhan	Zhejiang	Wuhan	WA, USA
Patients, no	1,099	148	99	81	62	41	21
Age, years	47	51	56	50	41	49	70
Male, %	58%	51%	68%	52%	56%	73%	52%
Fever, %	44%	70%	83%	73%	77%	98%	52%
Cough, %	68%	45%	82%	59%	81%	76%	48%
Diarrhea, %	4%	4%	2%	4%	8%	3%	-*
Elevation of liver biochemical tests							
AST	22%**	22%	35%	53%	16%	37%***	14%****
ALT	21%**	18%	28%	30%	-	-	14%****
TB	11%**	6%	18%	-	-	-	-
ALP	-	4%	-	-	-	-	-
GGT	-	18%	-	-	-	-	-
Chronic liver disease	2% HBV	-	-	-	-	-	5% Cirrhosis

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TB: Total bilirubin; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; HBV: Hepatitis B virus. *Data not reported, ** In severe cases, AST, ALT and TB were elevated in 39%, 28% and 13%, respectively. ***AST elevated in 62% in patients admitted in the intensive care unit. ****Reported as acute liver injury, defined as AST or ALT more than 3 times the upper limit of normal

It is currently unknown whether patients with chronic liver disease are more susceptible to direct liver injury from SARS-CoV-2. In this context, the Saudi Association for the Study of Liver diseases and Transplantation (SASLT) released a statement that can be utilized by gastroenterologists and hepatologists as a guidance in the management of patients with chronic liver disease during the COVID-19 pandemic.[35]

INVESTIGATIONS OF ABNORMAL LIVER BIOCHEMICAL TEST DURING COVID-19 PANDEMIC

During the pandemic, COVID-19 infection should be in the differential diagnosis when evaluating patients with abnormal liver biochemical test, patients with acute flare, and patients with acute decompensation of chronic liver disease. However, it is important to limit investigations to only those with clinical necessity. This approach is aimed to reduce the viral exposure to other health care workers. Imaging such as computed tomography, magnetic resonance imaging or magnetic resonance cholangiopancreatography, should be restricted for cases with high suspicion of biliary obstruction, cholangitis or venous thrombosis. Liver biopsy should be performed only when the result will impact the management plan.

Key points

- Abnormal liver biochemical test can be found in up to 53% of patients with COVID-19 infection
- Mildly elevated AST or ALT is the most common presentation
- Although not proven in SARS-CoV-2, SARS-CoV-1 directly caused liver damage
- Outcome data is needed for patients with underlying chronic liver disease or patients who have a received liver transplantation.

CONCLUSION

The COVID-19 pandemic has upended the long-standing norms in societies across the entire world. In medicine, its effects are even more profound. Individuals in all disciplines are now tasked with changing their practice habits, while also combating a novel disease. Gastroenterologists and hepatologists specifically have a unique role in supporting high-risk patients with severe systemic disease or on iatrogenic immunosuppression through this crisis. In addition, routine endoscopic practice has been forced to be largely placed on hold, with emergencies now requiring aggressive use of PPE. Through this unprecedented time, we must continue to be nimble and adapt, and continue to learn the ways in which this disease may impact our patient populations.

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