Gastrointestinal and Liver Manifestations of COVID-19

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Abstract

A novel Coronavirus, SARS-CoV-2 illness, has spread throughout the world after the first case was reported from Wuhan, China, in December 2019. This illness typically causes respiratory symptoms like fever, cough, and shortness of breath, although atypical presentation with gastrointestinal symptoms like abdominal pain, nausea, vomiting, or diarrhea are being increasingly reported. The viral RNA has been detected in saliva and stool of such patients, which raises concerns regarding the risk of transmission during gastrointestinal (GI) endoscopy. Many patients also have liver involvement, with the most common manifestation being deranged liver function tests. This review highlights the symptomatology, mechanism, and histopathology findings of SARS-CoV-2 in GI tract and liver. This review also focuses on implications of COVID-19 in patients afflicted with chronic liver disease and in patients undergoing liver transplantation.

Keywords
- COVID-19
- gastrointestinal
- liver
- RNA β-coronavirus
- SARS- CoV-2

Introduction

In December 2019, a novel Coronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported from Wuhan, China.[1] It is a nonenveloped RNA β-coronavirus[2] which has infected 4307287 people with more than 295000 deaths as of May 15, 2020.[3] This outbreak is significantly bigger than the previous pandemics of SARS and Middle East respiratory syndrome (MERS), which were caused by different strains of coronavirus. While lungs are the primary organ of involvement in Coronavirus disease 2019 (COVID-19), liver, and gastrointestinal (GI) involvement is being increasingly reported in the emerging data from various centers across the globe.

Information Source and Literature Search

For this review article, we searched PubMed for articles published from January 1, 2020 using the keywords "COVID-19," "coronavirus," "severe acute respiratory syndrome coronavirus 2," "SARS-CoV-2," and "2019-nCoV." Also, publications on COVID-19 from various journals, including The *Lancet*, *The New England Journal of Medicine*, *JAMA*, *BMJ*, *Gut*, *Gastroenterology*, *Journal of Hepatology*, *Hepatology*, *Liver International*, *Hepatology International* were screened, and relevant articles including preproof publications were included. Further articles were included after screening the reference list of included studies.

GI Symptomatology

The clinical presentation of COVID-19 patients is variable. The most common and typical symptoms reported from a multicenter study from China are fever (88.7%) and cough (67.8%).[4] While GI symptoms are infrequent, nausea/vomiting is seen in around 5% patients and diarrhea in 3.8%.[4] However, in the study by Fang et al,[5] GI involvement was reported in up to 79% of patients with predominant symptoms being anorexia, diarrhea, nausea/vomiting, abdominal pain, and GI bleed. The GI symptoms can also precede fever and dyspnea by 1–2 days in approximately 10% of patients.[6] There is a recent meta-analysis of 57 studies[7] that has reported the prevalence of diarrhea in 7.7%, nausea/vomiting in 7.8%, and abdominal pain in 3.6% of patients. These symptoms of diarrhea, nausea/vomiting, and abdominal pain were reported more commonly from countries other than China.[7] A large number of patients are being recognized in the asymptomatic stage or with atypical symptoms like pain abdomen, with abdominal

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CT scans suggestive of typical findings of COVID-19 in lung bases.[8] Patients can even have GI symptoms in the absence of respiratory symptoms, as seen in 16% of patients in a study by Luo et al.[9] Therefore, accurate history taking and documenting gastrointestinal complaints is essential to prevent missing out on the diagnosis of COVID-19 in patients who lack respiratory symptoms.

GI Symptoms and Severity of COVID-19

The presence of GI symptoms is associated with a more severe form of disease and was first reported by Henry et al.[10] Abdominal pain and nausea/vomiting were associated with increased disease severity, while diarrhea had no such association. A pooled analysis of 10 studies having a total of 1989 confirmed COVID-19 patients revealed severe disease in around 30.1% of patients. In another study by Tian et al,[11] patients with severe disease had more frequent GI symptoms as well (anorexia 66.7% vs. 30.4%; abdominal pain 8.3% vs. 0%). The patients with GI involvement are also more likely to have a longer duration of illness (33% vs. 22%; $p = 0.048$) and test positive for COVID-19 (OR 1.7, 95% CI 1.1–2.5) in one study.[12]

Mechanism of GI-Tropism

The entry of SARS-CoV2 into the host cell happens as a result of the interaction of envelope-anchored spike protein with angiotensin-converting enzyme 2 (ACE2), which is present on host cells.[2] Spike protein of SARS-CoV-2 contains two subunits, S1 and S2.[13] S1 is involved in virus attachment to the cell membrane, and S2 is involved in the fusion of cell membranes by using ACE2.[14] Serine proteases, mainly Transmembrane protease serine 2 (TMPRSS2) is required for priming this process.[15] Binding of SARS-CoV-2 with ACE2 may alter gut microbiota, interfere with innate immunity, and inhibit dietary tryptophan absorption, leading to diarrhea.[16] High-ACE2 receptor staining in the cytoplasm of gastric, duodenal, and rectal epithelial cells of COVID-19 infected patients have been demonstrated,[16] supporting viral entry and GI symptoms of diarrhea, abdominal pain, and nausea/vomiting.

Fecal–Oral Transmission of COVID-19–Is it Possible?

The interest in GI involvement of SARS-CoV-2 was further augmented when viral RNA was detected by real-time reverse transcriptase polymerase chain reaction (rRT-PCR) in the stool sample of the first COVID-19 case in USA.[17] This led to the proposition of the fecal–oral route of transmission (►**Table 1**). Viral RNA can be detected in stool in around 70% of patients even after full resolution of symptoms.[7] However, in spite of high-RNA concentration, viral isolation was not possible from stool samples,[16] thereby questioning the infectivity of COVID-19 through the fecal–oral route. The presence of the live virus has also been detected in saliva by viral culture; however, the clinical significance of this has to be deciphered.[18]

Histopathological Findings in GI Tract in COVID 19 Patients

The histopathological findings in GI tract of COVID-19 patients are variable. The first autopsy report[19] described segmental dilatation and stenosis of the small intestine, while histopathology was suggestive of degeneration, necrosis, and shedding of gastrointestinal mucosa in another patient.[20] Endoscopic biopsies from the esophagus, stomach, duodenum, and rectum suggest that the esophagus shows occasional lymphocytic infiltrate, while lymphoplasmacytic infiltrate and interstitial edema was present in lamina propria of stomach, duodenum and rectum;[16] however, there was no mucosal epithelial damage. Viral nucleocapsid protein was also demonstrated in gastric, duodenal, and rectal glandular epithelial cells in this case. In another autopsy study of two patients,[21] no abnormalities in GI tract were noted except for increased visceral adipose tissue in both patients and gaseous distension of bowel loops in one patient.

Liver Injury with COVID-19

The most common liver injury documented in COVID-19 patients is abnormal liver function tests (LFTs),[1,6,22,23] which is reported in approximately 14 to 53% patients, as shown in ►**Table 2**. According to a recent meta-analysis, elevated AST and ALT are seen in 15% of patients and elevated bilirubin in approximately 16.7% of patients, with a higher proportion of patients with deranged LFTs seen from countries other than China.[7] Most cases are mild and transient, although elevated AST, ALT, ALP, or total bilirubin is associated with increased mortality.[24] The pattern of liver injury is usually hepatocellular type, with AST being elevated more than ALT, and ALP largely remaining normal.[24] Patients with GI symptoms are more likely to have liver dysfunction as well (17.57% vs. 8.84%, $p = 0.035$).[25] The mechanism is unclear, and various factors are implicated like pre-existing chronic liver disease, drug toxicity, ischemic hepatitis secondary to hypotension and, rarely, direct injury by SARS-CoV-2.

Only one case of acute liver failure[26] in a patient of SARS-CoV-2 has been described to date.

The patient was a 65-year-old hypertensive man who presented with typical respiratory signs and symptoms of COVID-19. He had elevated amino transaminases at admission. He required mechanical ventilation on day 2 of admission and was treated with ritonavir/lopinavir and interferon-β. However, therapy had to be stopped, as his aminotransferases started to increase from day 7 and reached a maximum by day 14. The bilirubin went up to a maximum of 22.2 mg/dl by day 20. The etiological workup for viral hepatitis A, B, C, and E and autoimmune hepatitis were negative. At last follow-up (day 20), he was still critically ill, with multiorgan failure, and registered a model for end-stage liver disease (MELD) score of 40.

Table 1 Summary of studies documenting viral RNA detection in feces

S. No.	Authors	Type of Study	No. of patients	GI symptoms	Sample	Results
1.	Jiang X et al[54]	Case Report	1	Asymptomatic	Anal swab	Detected up to 42 days
2.	Siew C Ng et al[55]	Case series	21 cases and 114 healthy individuals	NA	Feces	Detected in all 81 stool samples from 21 patients
3.	Wu et al[56]	Observational study	132	NA	Anal swabs & feces	RNA detected in 9.8% of stool samples and 10% of anal swabs
4.	Wu et al[57]	Observational study	98	31%	Feces	55% patients had positive fecal RNA. Fecal samples remained positive for 27.9 ± 10.7 days While respiratory swabs were positive for 16.7 ± 6.7 days
5.	Chen et al[58]	Retrospective study	42	19%	Feces	66.67% patients had detectable RNA in feces 64.29% patients remained positive for RNA in feces for 6–10 days after pharyngeal swabs were negative
6.	Chen et al[59]	Case report	1	NA	Pharyngeal swab, sputum and feces	Pharyngeal swab and sputum negative and fecal RT-PCR Positive
7.	Zhang et al[60]	Observational study	39 in 1st investigation and 139 in 2nd investigation	NA	Pharyngeal, oral swab, anal swab and serum	15 patients had PCR positive after treatment out of which 4 were anal swab positive. On day 5, anal swabs were more positive than oral swabs (75% vs. 50%)
8.	Yun et al[61]	Retrospective study	2510 patients screened in fever clinic	NA	Pharyngeal swab, feces, serum	32 (1.3%) positive for RNA by pharyngeal swab and eight patients had positive RNA in feces
9.	Cheung et al[62]	Retrospective data from Hong-Kong cohort & Systematic review and meta-analysis	59 patients Meta-analysis of 60 studies (n = 4243)	25.4% 17.6%	Feces	15.3% tested positive for RNA in feces. 38.5% with diarrhea and 8.7% without diarrhea had stool RNA In meta-analysis, 48.1% stool samples were positive for RNA. Of these, 70.3% samples were collected after respiratory samples were negative
10.	Zhang et al[63]	Retrospective study	14	None	Oropharyngeal swabs, feces	Four out of 62 stool samples (6.5%) positive for viral RNA
11.	Xiao et al[16]	Observational study	73	NA	Serum, naso-pharyngeal and oropharyngeal swabs, urine, stool, endoscopic biopsy	53.42% had positive viral RNA in feces 23.29% continued to have positive fecal RNA after negative respiratory swab
12.	Wei et al[64]	Retrospective study	84	31% patients had diarrhea	Feces	Patients with diarrhea had longer duration of fever/dyspnea ($p < 0.05$) Viral RNA in stool detected in 69% with diarrhea and 17% without diarrhea ($p < 0.001$)

Abbreviation: NA, Not available.

Two cases of acute on chronic liver failure (ACLF) related to SARS-CoV-2 have been recently described. The first report[27] of ACLF is by EASL-CLIF definition due to insult by SARS-CoV-2. The patient was a 56-year-old woman with alcohol-related decompensated cirrhosis and a history of upper GI bleed due to gastric varices.

The second case[28] describes a patient with nonalcoholic steatohepatitis (NASH) cirrhosis and ascites who was also admitted with complaints of nausea, vomiting, diarrhea, and anorexia without any respiratory symptoms that progressed to grade 2 ACLF for which liver transplantation was done at day 28 of admission.

Postulated Mechanisms of Liver Injury

ACE2 in Liver Injury

ACE2 receptors and TMPRSS2 are expressed in cholangiocytes and hepatocytes, and viral binding to these receptors may result in entry of SARS-CoV-2 in liver cells.[29,30] However, only a small percentage of hepatocytes express ACE2 receptors (~2.6%).[29]

Table 2 Summary of studies highlighting liver injury in patients with COVID-19

Authors	Type of study	No. of Patients	Total bilirubin (μmol/L)	Abnormal bilirubin (%)	AST (IU/L)	Abnormal AST (%)	ALT (IU/L)	Abnormal ALT (%)	Pre- existing liver disease (%)	Remarks
Guan et al[4]	Retrospective study	1099	NA	10.5	NA	22.3%	NA	21.3	2.1	18.2% patients with nonsevere disease and 39.4% patients with severe disease had elevated AST. 19.8% patients with nonsevere disease and 28.1% patients with severe disease had elevated AST.
Bhatraju et al[65]	Retrospective study	24	NA	NA	NA	41	NA	32	NA	–
Wei et al[64]	Retrospective study	84	9.2 ± 3.0	NA	29 ± 13.1	NA	28.3 ± 19.3	NA	NA	–
Chen et al[58]	Retrospective study	42	9.4 (8.18–13.2)	NA	26 (18.75–39)	NA	22 (16.75–33)	NA	NA	43.4% had elevated AST, ALT, LDH
Holshue et al[17]	Case report	1	NA	NA	89	NA	203	NA	None	–
Qi et al23	Prospective multicenter study	70	18.0–148.0	35.71	42.9–61	7.14	42–72	21.43	NA	45.71% had liver injury at admission
Chen et al[23]	Retrospective study	99	15.1 ± 7.3	18	34 (26–48)	35	39 (22–53)	28	11.1	–
Huang et al[1]	Retrospective study	41	11.7(9.5–13.9)	NA	34 (26–48)	37	32 (21–50)	NA	2.4	–
Wang et al[6]	Retrospective study	138	9.8 (8.4–14.1)	NA	31 (24–51)	NA	24 (16–40)	NA	2.9	–
Singh et al[42]	Retrospective study	2780	1.2 ± 2.9 in PLD group and 0.8 ± 1.2 in non-PLD group	25% in PLD group and 9.1% in non- PLD group	221 ± 1799 in PLD group 133 ± 678 in non-PLD group	61.5% in PLD group and 67.5% in non-PLD group	100 ± 444 in PLD group and 80 ± 227 in non-PLD group	46.1% in PLD group and 50.6% in non-PLD group	9%	–
Xu et al[66]	Retrospective study	62	NA	NA	26 (20–32)	16.1	22 (14–34)	NA	11.3	–
Cai et al[37]	Retrospective study	417	10.9 (8.3–16.3)	23.19	26.5 (21–35)	18.23	21 (15–31)	12.95	5.04	76.3% had abnormal liver tests. 21.5% had liver injury[a]
Chen et al[40]	Retrospective study	123	9.6 (7.8–12.8)	NA	25 (19–38)	NA	22 (15–34.5)	NA	2.4%–cirrhosis 12%–HBV	10 out of 13 HBV-infected patients had detectable DNA levels (> 20 IU/L)
Fan et al[67]	Retrospective	148	21–46.6	6.1	37–107	21.6	41–115	18.2	6.1	37.2% had abnormal LFT

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; LFT, liver function test; NA, not available; PLD, pre-existing liver disease.
[a]Liver injury defined as AST and/or ALT > 3xULN, ALP, GGT and/or total bilirubin > 2xUL.

Table 3 Drugs used for treatment in COVID-19, their mechanism of action, and GI side effects

Treatment	Dose	Route	Class of drug	GI/Liver side effects
Remdesivir	200 mg stat followed by 100 mg OD for 10 days	Intravenous	Antiviral	Nausea, vomiting, elevated transaminases
Lopinavir/Ritonavir	400 mg/100 mg BD	Oral	Antiviral	Deranged liver enzymes (not shown to be clinically significant in a RCT[68])
Hydroxychloroquine	800 mg stat followed by 400 mg daily	Oral	Antimalarial	Nausea, vomiting, weight loss, abdominal pain
Chloroquine	500 mg BD	Oral	Antimalarial	Elevated transaminases, anorexia, nausea, vomiting, diarrhea, abdominal cramps
Azithromycin	500 mg OD	Oral	Antibacterial	Diarrhea, nausea, vomiting, pain abdomen
Tocilizumab	8 mg/kg IV single dose	Intravenous	IL-6 receptor antagonist	Elevated transaminases, bowel perforation, pancreatitis, abdominal pain, reactivation of chronic hepatitis B
Favipiravir	1000–1600 mg on first day followed by 400–800 mg BD for 4–13 days	Oral	Antiviral	Not reported
Ivermectin	200 µg/kg body weight single dose	Oral	Antiparasitic	Nausea, vomiting, diarrhea

Abbreviations: GI, gastrointestinal; RCT, randomized controlled trial.

The major expression is seen in cholangiocytes (~59.7%)[29]; however, injury to bile duct cells is not clinically evident, as ALP remains largely normal in patients infected with COVID-19. A recent study, however, showed elevated GGT in 54% of patients, suggesting injury to bile duct cells.[31] Along with cholangiocytes, TMPRSS2 is also expressed in periportal liver sinusoidal endothelial cells and erythroid cells in liver, suggesting a pathologic basis for infection of liver by SARS-CoV-2.[30] In an autopsy series of 22 patients,[32] low-levels of viral RNA were detectable in liver tissues. Viral particles have also been shown to be abundant in the cytoplasm of infected hepatocytes.[33]

Inflammatory Cytokines

Another contributor to liver injury is an inflammatory cytokine storm. Lymphopenia, commonly seen in these patients, leads to decreased inhibition of the innate immune response. As a result, Interleukin-6 (IL-6), IL-10, IL-12, and IFN-γ are increased in circulation, which causes multiorgan dysfunction, including involvement of liver.[34] The presence of lymphopenia and elevated CRP is independently associated with liver injury,[35] which highlights the plausible role of cytokine storm in inciting liver dysfunction. Another interesting finding seen on immunohistochemistry of post-mortem liver biopsies was the presence of increase CD68+ cells in hepatic sinusoid which is suggestive of Kupffer cell activation.[33]

Ischemic Hepatitis and Drug Toxicity

Ischemic hepatitis does not seem to be a major contributory factor in the elevation of transaminases as AST and ALT are only rarely elevated to > 5 x ULN in patients with COVID-19.[36] Also, features of ischemic hepatitis are not seen on liver biopsy.[33] Various drugs used to treat COVID-19 can also lead to drug-induced liver injury (►**Table 3**). However, no concrete data are available regarding a plausible cause and effect relationship.

Histopathological Findings in the Liver

The available liver biopsy findings from patients with COVID-19 are limited. One patient showed mild vesicular steatosis with watery degeneration of hepatocytes and sinusoidal inflammation,[37] while another patient showed moderate vesicular steatosis with mild lobular and portal activity.[38] A case series of four patients described mild sinusoidal dilatation and lobular lymphocytic inflammation with no evidence of steatosis, and one of the patients showing patchy hepatocyte necrosis.[39] A recent study[33] also demonstrated mitochondrial swelling, endoplasmic reticulum dilatation, and a decrease in glycogen granule reserve of hepatocytes with massive hepatic apoptosis.

COVID-19 and Chronic Liver Disease

The prevalence of chronic liver disease among patients infected with COVID-19 is 2 to 11%, as shown in ►**Table 2**. The prevalence of hepatitis B virus (HBV) infection in patients with COVID-19 is approximately 12%.[40] The patients with HBV infection had a higher prevalence of cirrhosis, elevated bilirubin (p = 0.039 and 0.0178, respectively), more severe disease (46.7% vs. 2.8%), and high mortality (13.3% vs. 2.8%). The burden of alcohol-related liver disease was estimated to be around 30% in hospitalized patients with COVID-19 in one series.[41]

In another series,[42] 2,780 COVID-19 patients were analyzed, out of which 9% had pre-existing chronic liver disease. The most common chronic liver disease coexisting with COVID-19 was NASH, seen in 42% of patients with pre-existing liver disease.[42] Cirrhosis was seen in 1.8% cases, and

patients with pre-existing liver disease and cirrhosis had a high-risk of mortality. Increased disease progression, higher likelihood of abnormal LFT, and longer viral shedding time of approximately 5 days in patients with nonalcoholic fatty liver disease NAFLD have also been reported.[43]

In another study describing the clinical course of COVID-19 in patients with autoimmune hepatitis (AIH) on immunosuppression, it was found that 70% of patients with AIH were asymptomatic.[44] Respiratory symptoms were present in 26% cases, and they were classified as suspected cases since testing was not conducted. Only 3% of patients were confirmed COVID-19 cases. This suggests that the incidence of COVID-19 in patients with AIH is similar to that seen in the general population.

Liver Transplantation and COVID-19

The number of liver transplants performed in the past 2 to 3 months has declined drastically in various transplant centers across the globe. The available data from Italy and the USA have shown that organ procurement for transplant had decreased by approximately 25% in the first month of the outbreak[45,46]; however, the incidence of infection was low in liver transplant recipients.[47] High mortality (23%) has been reported in liver transplant recipients due to COVID-19[41]; hence, liver transplantation should only be done for emergency indications. Since there are concerns regarding donor and recipient safety, the Liver Transplant Society of India (LTSI) and National Organ and Tissue Transplant Organization (NOTTO) have recommended that elective transplants be deferred.[48] They recommend that only transplants for acute liver failure and ACLF should be performed after donor and recipient testing and proceed only if COVID testing is negative.[49]

The management of COVID-19 in the posttransplant patient is also a challenge due to the interplay of immunosuppression, drug-induced liver injury, and direct cytopathic effects of SARS-CoV-2. A recent case report[50] describes COVID-19 infection in a liver transplant recipient on postoperative day 19, which was successfully managed while continuing tacrolimus and glucocorticoids. However, another report describes a 59-year-old patient,[51] who underwent a liver transplant in 2017 for decompensated HBV cirrhosis with hepatocellular carcinoma and succumbed to COVID-19 with nosocomial sepsis and multiorgan failure on day 45 of hospital admission. However, more data are required to identify the risk factors for COVID-related mortality in liver transplant recipients and guide immunosuppressive regimens and management after liver transplant.

Gastrointestinal Endoscopy in the COVID-19 Era

Gastrointestinal endoscopy is an aerosol-generating procedure, and given the high prevalence of SARS-CoV-2 viral RNA in feces of COVID-19 infected patients, it appears necessary to consider GI secretions as infective and capable of transmitting the virus during endoscopic procedures. Hence, it is necessary to take all necessary preventive measures to prevent the spread of disease to healthcare workers (HCWs).

Endoscopic procedures should be divided into emergency, urgent, and routine-based on their urgency. The current joint guidelines from Society of Gastrointestinal Endoscopy of India (SGEI), Indian Society of Gastroenterology (ISG), and Indian National Association for the Study of the Liver (INASL) state that only emergency and urgent endoscopy procedures be performed and elective endoscopy be postponed till the current threat of COVID-19 persists.[52] All patients scheduled for endoscopy should be screened for fever, cough, shortness of breath, diarrhea, abdominal pain, nausea/vomiting, history of travel to or residence in a high-transmission zone of COVID-19, or contact with confirmed COVID-19 case. They should be assessed regarding the urgency of endoscopy, and elective procedures should be postponed. Based on the presence of symptoms or history of travel to or contact with a COVID-19 positive case, patients can be divided into a low-risk group, intermediate-risk group, and high-risk group. The low-risk patients do not have any symptoms of COVID-19 or history of travel to an area of high-transmission zone or history of contact with a confirmed COVID-19 patient. The high-risk patients have at least one symptom, and either have a history of contact with COVID-19 case or history of travel to or stay in high-transmission zone. All those not fitting into either of these categories are classified as an intermediate-risk group. All high-risk patients should be tested for COVID-19 by RT-PCR. The endoscopy room should be a negative pressure room, have minimum and experienced staff, and all team members should wear personal protective equipment (PPE) including gloves, gown/plastic apron, N-95 mask and face shield. In all high-risk procedures, donning and doffing of PPE should follow standard protocol.

Although viral RNA has been documented in saliva and feces, whether it is infective is a question of debate, as data from Italy suggest that only one patient out of 851 who underwent endoscopy developed COVID-19[53] and no HCW who came in contact with this patient developed respiratory symptoms. Although this was a retrospective study, it might suggest that endoscopy may be a low-risk procedure for transmission if proper precautions are followed.

Conclusion

COVID-19 is caused by a novel coronavirus, and data regarding the epidemiology, symptomatology, and transmission are rapidly evolving. As the outbreak is progressing, more and more cases with nonrespiratory symptoms and signs are being recognized, with liver and GI involvement being common. As viral RNA shedding has been documented in saliva and feces of infected patients, it becomes prudent for gastroenterologists and hepatologists to identify these symptoms early and take necessary precautions in performing diagnostic and therapeutic procedures in these patients. Although the quality of evidence is low, various gastrointestinal and hepatology associations have issued guidelines for management, which should be followed strictly until further data are available.

Conflict of Interest
None declared.

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