Review Article

Gastrointestinal and Liver Manifestations of COVID-19

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Abstract

Almost every country in the world has been affected by the pandemic of Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in Wuhan, China, in December 2019. The clinical manifestation is diverse, ranging from asymptomatic to severe pneumonia requiring mechanical ventilation. In addition, gastrointestinal symptoms have also been reported to occur during the course of the disease. In some patients, gastrointestinal symptoms may precede respiratory tract symptoms. Interestingly, the SARS-CoV-2 RNA could be detected in the stool of COVID-19 patients, implying that SARS-CoV-2 may be transmitted by fecal-oral route. Moreover, mild transient abnormal liver biochemical tests have been reported in these patients. This review aims to provide a summary of existing evidence to date on how the digestive system is affected by COVID-19.

Keywords: COVID-19, SARS-CoV-2

Received: 20 January 2021 **Revised: 12 July 2021** **Accepted: 23 August 2021**

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has rapidly spread across the world. It is an enveloped, single-stranded, positive-sense RNA virus with high transmissibility.[1-3] To date, on January 8, 2021, there have been 86,436,449 confirmed cases and 1,884,341 deaths globally.[4] COVID-19 patients typically present with various respiratory tract symptoms ranging from mild flu-like symptoms (e.g., cough, sore throat, and fever) to severe pneumonia. In addition, a significant number of COVID-19 patients report concomitant gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain. Less commonly, gastrointestinal manifestations have been reported as a sole presentation in these patients. In this review article, we aim to provide a concise review of the gastrointestinal and liver involvement of COVID-19 patients.

Gastrointestinal symptoms of COVID-19

Previous multicenter and cross-sectional studies have demonstrated that COVID-19 patients frequently have gastrointestinal symptoms such as anorexia, nausea, vomiting, diarrhea, and abdominal pain (Table 1). Aumpan et al. reported the clinical characteristics of COVID-19 patients at Thammasat University Hospital between 1 January 2020 and 30 April 2020. Among the 40 patients with laboratory-confirmed COVID-19, 12 (30%) had gastrointestinal symptoms. The most common gastrointestinal symptoms were anorexia (17.5%), followed by diarrhea (15%).[5] Patients with gastrointestinal symptoms had a longer duration from clinical onset to admission (9 *vs.* 7.3 days), and a worse prognosis.[6] Interestingly, diarrhea, which has a reported incidence ranging from 3.8% to 75%, can be the first symptom leading to the diagnosis of COVID-19.[7] Of note, previous study has shown that 49.5% of COVID-19 patients had diarrhea, of which almost half had diarrhea before the diagnosis of COVID-19.[7] However, diarrhea can also appear after the confirmation of SARS-CoV-2 infection with a median time after diagnosis of 3.3 days.[8]

There have been few reports showing that a small number of COVID-19 patients can present with diarrhea or vomiting only without fever or cough.[8-10] Ping *et al.* reported a series of 9 patients with laboratory-confirmed COVID-19 who presented with gastrointestinal symptoms without other manifestations at the clinical onset.[9] The main symptoms in this series were anorexia, nausea, vomiting, and diarrhea. During hospitalization, 4 patients had no fever nor respiratory symptoms, while the others 5 had fever and/or respiratory symptoms 2 - 5 days after the onset.[9] Another study reported that 3/31 (9.68%) children with COVID-19 had diarrhea at the first presentation, and one of them had omiting without fever or cough.[10] Base on these findings, clinicians must be aware that gastrointestinal symptoms may be the first presentation, arising before respiratory manifestations, of COVID-19 patients. A recently published meta-analysis including 60 studies reported a prevalence of gastrointestinal symptoms of 17.6% in COVID-19 patients. Interestingly, the proportion of patients with severe COVID-19 was documented with gastrointestinal symptoms compared with those with non-severe disease (17.1% vs. 11.8%).[11]

The mechanism of gastrointestinal manifestations of SARS-CoV-2 infection is proposed to link with the angiotensin-converting enzyme 2 (ACE2) cell receptor. This virus uses the ACE2 receptor for host cells entry. In addition, host cell proteases such as transmembrane protease serine 2 (TMPRSS2) are essential for viral S protein priming.[12] Apart from type 2 alveolar cells in lung, previous study has shown that ACE2 was abundantly distributed in the cilia of glandular epithelial cell of gastric, duodenum and rectum.[13] Nevertheless, this receptor rarely expresses in the esophageal epithelium because esophageal lining is mainly squamous epithelial cells, which express less ACE2 than glandular epithelial cells.[13, 14] Another study showed that ACE2 was highly expressed in the small intestine, especially in proximal and distal enterocytes.[15] Therefore, diarrhea is probably a consequence of ACE2 dysfunction, caused by mutual interaction between SARS-CoV-2 and ACE2 receptor.

Several studies have shown that the SARS-CoV-2 RNA could be detected in the stool of COVID-19 patients, implying that SARS-CoV-2 may be transmitted by fecal-oral route.[14, 16-18] Xiao *et al.* reported that 53.4% of COVID-19 patients were tested positive for SARS-CoV-2 RNA in stool, with a duration ranging from 1 to 12 days.[13] Notably, stool sample remained positive for SARS-CoV-2 RNA

after negative test in respiratory samples in 23.3% of patients. Moreover, they performed endoscopic sampling from different parts of the gastrointestinal tract, and detected the viral nucleocapsid protein by intracellular staining method in gastric, duodenal, and rectal epithelium. This study provides the direct evidence that the infectious virions may be secreted from the virus-infected gastrointestinal cells.[13, 14] In a previously mentioned meta-analysis, the pooled prevalence of stool samples that were positive for virus RNA was 48.1%, more interestingly, 70.3% of them were positive despite negative respiratory samples.[11]

The possibility of fecal-oral transmission of SARS-CoV-2 emphasizes an importance of request and proper hand hygiene, especially in areas with poor sanitation. A recent study has shown that the maximum duration of viral shedding detected in stools of COVID-19 patients was 46 days after being discharged from hospital.[19] Therefore, strict precautions must be taken when handling the stool sample of patients with COVID-19, and sewage from hospitals should also be properly disinfected.[14]

Finally, the gastrointestinal endoscopy departments face significant risk for transmissions of SARS-CoV-2 during the procedures. Possible routes of transmission during endoscopic procedures are person-to-person, respiratory droplets, aerosols generated during endoscopy, and contact with contaminated surroundings (e.g. body fluids, and fecal material). The World Endoscopy Organization, the American Society for Gastrointestinal Endoscopy, and the European Society of Gastrointestinal Endoscopy have provided recommendations on the performance of endoscopy during the COVID-19 pandemic.

Liver injury in COVID-19

Liver injury is commonly found in COVID-19 patients. The clinical spectrum ranges from mild to severe liver injury, and its degree is associated with the severity of diseases. The common abnormal findings were elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). According to the previous study, abnormal liver function was observed in 20 - 30% of patients with laboratory-confirmed COVID-19.[20] One of the initial report of COVID-19 cases revealed that elevated AST was documented in 8/13 (62%) of patients in the intensive care unit compared with 7/28 (25%) patients who did not require the ICU.[3] Another study including 1,099 patients with laboratory-confirmed COVID-19 from China found that patients with more severe disease had more abnormal liver aminotransferase levels than non-severe patients.[21] Ratana-Amornpin et al. reported that, among 41 Thai patients with laboratory-confirmed COVID-19, 7/19 (36.8%) patients who were tested for liver function test within 24 hours after admission had elevated hepatic transaminases.[22] The incidence of elevated transaminases was significantly higher in COVID-19 patients with severe symptom compared with those with mild symptom (71.4% *vs.* 16.7%, $P = 0.045$).[22] Additional studies have demonstrated similar findings regarding the abnormalities of liver function tests (Table 2). Most studies have found that the majority of COVID-19-related liver injury are mild and transient, however severe damage can occur in severe COVID-19 cases.[14, 20, 23]

The definite pathophysiology of liver injury of SARS-CoV-2 infection is still unclear. There are many proposed pathogenic mechanisms: (1) ACE2-mediated direct viral infection of hepatocyte; (2) critically-ill status and immune-mediated liver injury or; (3) drug-related hepatotoxicity.[20] It is known that ACE2 receptors are highly expressed in the gastrointestinal epithelial cells. Therefore, the virus are capable of infecting cholangiocyte due to its highly expression of this receptor, which consequently results in hepatic dysfunction.[20, 23] Notably, histological examination of the liver biopsy from a deceased COVID-19 patient showed micro-vesicular steatosis and mild lobular activity, but no viral inclusion was observed in the liver.[23, 24] Thus, in critically-ill COVID-19 patients, hepatocellular injury or even liver failure may be secondary to hypotension, immune-mediated inflammation, pneumonia-associated hypoxia, and drug-induced hepatotoxicity.[20]

The reported prevalence of chronic liver disease (CLD) in COVID-19 patients was approximately 3%, including chronic viral hepatitis, nonalcoholic fatty liver disease, autoimmune hepatitis, hepatocellular carcinoma, and alcohol-related liver disease.[25] A recent meta-analysis has shown that CLD patients were more likely to have severe COVID-19 manifestations when compared to those without underlying CLD. Of note, a high

mortality rate has been reported in these patients.[25] Therefore, they should be carefully monitored and treated properly.

Discussion

Although SARS-CoV-2 virus primarily affects the respiratory system, it can also cause gastrointestinal symptom and liver injury. The definite mechanism of gastrointestinal involvement is still unclear. To date, recent evidences have shown that the pathogenesis is related to ACE2 receptor on the host cells. Gastrointestinal symptom is commonly found during the clinical course of COVID-19 infection, and it can even precede respiratory symptoms. Notably, recent evidence has shown that a presence of concomitant gastrointestinal symptom is associated with a worse prognosis in COVID-19 patients. Regarding COVID-19 related liver injury, elevated transaminases have been reported in a significant number of patients. Even though most liver injuries are mild and transient, severe damage can occur in severe COVID-19 patients. Finally, current evidence has demonstrated that SARS-CoV-2 RNA can remain in stool longer than respiratory specimen, therefore strict precautions should be taken when handling the stool sample of patients, and sewage from hospitals.

For the reasons addressed above, clinicians must be aware that gastrointestinal symptoms may be the first presentation of COVID-19 patients. In addition, liver function should be closely monitored during the course of disease, especially in patients with severe clinical manifestation.

Table 1 Incidence of specific gastrointestinal symptoms in COVID-19 patients

Study	Number of patients, N	Anorexia, N (%)	Nausea, N (%)	Vomiting, N (%)	Diarrhea, N (%)	Abdominal pain, N (%)
Aumpan N, et al.[5]	40	7 (17.5)	2 (5)	2 (5)	6 (15)	2 (5)
Guan W, et al.[21]	1099	NA	55 (5)	55 (5)	42 (3.8)	NA
Wang D, et al.[18]	138	55 (40)	14 (16)	5 (3.6)	14 (10)	3 (2.2)
Jin X, et al.[26]	74	NA	13 (17.5)	14 (18.6)	56 (75)	NA
Zhang JJ, et al.[27]	139	17 (12.2)	24 (17.3)	7 (5)	18 (13)	8 (13)
Pan L, et al.[6]	204	81 (39.7)	NA	4 (2)	35 (17.2)	2 (1)
Mo P, et al.[28]	155	26 (31.7)	3 (3.7)	3 (3.7)	7 (4.5)	3 (2)

NA: not applicable, Adapted from reference[20]

Table 2 Incidence of liver injury in COVID-19 patients

Study	Number of patients, N	Elevated AST, N (%)	Elevated ALT, N (%)	Elevated total bilirubin, N (%)
Ratana-Amornpin S, et al.[22]	41	5 (26.3)	4 (21.1)	0
Guan W, et al.[21]	1099	168 (22.2)	158 (21.3)	76 (10.5)
Fang D, et al.[7]	304	24 (8)	19 (6)	6 (2)
Chen N, et al.[30]	99	35 (35)	28 (28)	18 (18)
Pan L, et al.[6]	204	22 (10.8)	27 (13.2)	NA
Mo P, et al.[28]	155	26 (31.7)	3 (3.7)	3 (3.7)
Shi H, et al.[29]	81	43 (53)	NA	NA

NA: not applicable, Adapted from reference[20]

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