

Gastrointestinal and liver manifestations in patients with COVID-19

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Abstract: As the outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread over the world, the World Health Organization has declared the outbreak of COVID-19 an international public health emergency. Besides typical respiratory symptoms and signs of COVID-19, digestive symptoms and liver injury have been frequently reported during the course of the disease. In this review, we summarized the recent studies reporting of gastrointestinal and liver manifestations during the course of COVID-19. Digestive symptoms, including anorexia, nausea, vomiting, and diarrhea, are not uncommon in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. Furthermore, SARS-CoV-2 could be detected in the stool of infected patients, implicating the possibility of fecal–oral transmission. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.

Keywords: COVID-19; Digestive; Gastrointestinal; Liver; Severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in China, in December, 2019, has posed a critical threat to global public health.^{1,2} The World Health Organization (WHO) has recently declared the outbreak of COVID-19 infection an international public health emergency. Lung is considered to be the primary organ of involvement by COVID-19 infection, and most patients with COVID-19 present with typical respiratory symptoms and signs. However, gastrointestinal symptoms and liver injury have also been reported to occur during the course of the disease. In this review, we assess how the digestive system and the liver are affected by COVID-19 using the available evidences to date.

2. GASTROINTESTINAL MANIFESTATIONS OF COVID-19

As SARS-CoV-2 RNA was first detected in stool of the first reported COVID-19 case in the USA, who also presented with

the digestive symptoms of nausea, vomiting, and diarrhea,³ more attentions have been paid to the gastrointestinal manifestations of SARSCoV-2. Digestive symptoms including anorexia, nausea, vomiting, and diarrhea are frequently reported in patients with COVID-19 (Table 1).^{4–13} In the currently largest cohort including 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces in China through January 29, 2020, nausea or vomiting and diarrhea were reported in 55 (5%) and 42 (3.8%) patients, respectively.¹³

In the SARS outbreak of 2002–2003, 16% to 73% of patients with SARS had diarrhea during the course of the disease, usually within the first week of illness.¹⁴ In patients with COVID-19, diarrhea is also a common digestive symptom, with the incidence ranging from 1.3% to 29.3% (Table 1). In addition, SARS-CoV-2–induced diarrhea could be the onset symptom in patient with COVID-19.¹⁵ Nevertheless, the incidence of diarrhea varied widely among different reports, suggesting that the criteria for diagnosing diarrhea may differ in different hospitals. Clinicians might underestimate the value of digestive symptom in clinical practice, and it may affect the preliminary diagnostic accuracy.¹⁶

Pan et al¹⁷ described the clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China. Among the 204 patients with COVID-19 and full laboratory, imaging, and historical data, 99 (48.5%) presented with digestive symptoms as their chief complaint. Patients with digestive symptoms had a variety of manifestations, including anorexia (83.8%), vomiting (0.8%), diarrhea (29.3%), and abdominal pain (0.4%). Compared with patients without digestive symptoms, those presenting with digestive symptoms have a longer time from onset to admission and a worse prognosis. Notably, in 7 (3.4%) cases, there were digestive symptoms but no respiratory symptoms. Based on these findings, clinicians must be aware that digestive symptoms, such as diarrhea, may be a presenting feature of COVID-19 that arise before respiratory symptoms, and on rare occasions may be the only presenting symptom of COVID-19.

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Table 1
Incidence of digestive symptoms and liver injury in patients with SARS-CoV-2 infection

	Patient number	Anorexia, nausea or vomiting	Diarrhea	Liver injury
Huang et al ⁴	41	...	1 (3%)	Abnormal AST: 15 (37%)
Chen et al ⁵	99	Nausea and vomiting: 1 (%)	2 (2%)	Abnormal ALT: 28 (28%) Abnormal AST: 35 (35%)
Xu et al ⁶	62	...	3 (8%)	Abnormal AST: 10 (16.1%)
Wu et al ⁷	80	Nausea and vomiting: 1 (1.25%)	1 (1.3%)	Abnormal ALT: 3 (3.75%) Abnormal AST: 3 (3.75%)
Wang et al ⁸	138	Anorexia: 55 (39.9%) Nausea: 14 (10.1%) Vomiting: 5 (3.6%)	14 (10.1%)	Significantly higher ALT and AST in ICU cases
Shi et al ⁹	81	Anorexia: 1 (1%) Vomiting: 4 (5%)	3 (4%)	Abnormal AST: 43 (53.1%)
Yang et al ¹⁰	52	Vomiting: 2 (4%)	...	Liver dysfunction: 15 (29%)
Mo et al ¹¹	155	Anorexia: 26 (31.7%) Nausea: 3 (3.7%) Vomiting: 3 (3.7%)	7 (4.5)	Significantly higher AST in refractory cases
Zhou et al ¹²	191	Nausea or vomiting: 7 (4%)	9 (5%)	Abnormal ALT: Survivor 24% Non-survivor 48%
Guan et al ¹³	1099	Nausea or vomiting: 55 (5%)	42 (3.8%)	Abnormal ALT: 158 (21.3%) Abnormal AST: 168 (22.2%)
Pan et al ¹⁷ (AJG)	99	Anorexia: 83 (83.8%) Vomiting: 8 (0.8%)	29 (29.3%)	...

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ICU = intensive care unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Several reports showed that the SARS-CoV-2 RNA could be detected in the stool of patients with COVID-19, implying that SARS-CoV-2 may be transmitted by the fecal–oral route.^{3,18,19} COVID-19 disease in a patient with positive fecal but negative pharyngeal and sputum viral tests has been reported.²⁰ Wang et al¹⁹ showed that 44 of 153 (29%) patients with COVID-19 were tested positive for the virus in stool. Xiao et al showed that among the 73 hospitalized COVID-19 patients in China, 39 (53.42%) were tested positive for SARS-CoV-2 RNA in stool.²¹ The duration of positive stool ranged from 1 to 12 days, and 17 (23.29%) patients remained positive in stool after showing negative in respiratory samples. They performed endoscopic sampling of different parts of the gastrointestinal tract from a patient, and the viral RNA could be detected in esophagus, stomach, duodenum, and rectum. This study provide the direct evidence that gastrointestinal infection of SARS-CoV-2, and the infectious virions may be secreted from the virus-infected gastrointestinal cells.²¹

The mechanism for gastrointestinal tract infection of SARS-CoV is proposed to be the angiotensin-converting enzyme 2 (ACE2) cell receptor.^{22,23} SARS-CoV-2, which has the genome sequence of 82% similar to SARS-CoV, may use the same cell entry receptor ACE2, but more efficiently than the 2003 strain of SARS-CoV.²⁴ By analyzing endoscopic biopsy samples, Xiao et al²¹ showed that ACE2 was rarely expressed in esophageal epithelium, but abundantly distributed in cilia of glandular epithelia, while staining of viral nucleocapsid protein was visualized in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell, but not in esophageal epithelium. Another study also displayed that ACE2 was highly expressed in the small intestine, especially in proximal and distal enterocytes.¹⁶ The mutual interaction between SARS-CoV-2 and ACE2 might disrupt the function of ACE2 and results in diarrhea.

The possibility of fecal–oral transmission of SARS-CoV-2 emphasized the importance of frequent and proper hand hygiene, especially in areas with poor sanitation. Strict precautions must be observed when handling the stools of patients with COVID-19, and sewage from hospitals should also be

properly disinfected. The presence of SARS-CoV-2 in the gastrointestinal tract also raises the concerns of COVID-19 infection in patients with preexisting digestive diseases as well as potential fecal microbiota transplant donors. Nevertheless, the comorbidity spectrum of digestive conditions and its impact on treatment and outcome of COVID-19 remains largely unknown.²⁵ To prevent SARS-CoV-2 transmission by fecal microbiota transplantation, additional screening methodologies to the current donor screening measures should be performed.²⁶

Finally, the gastrointestinal endoscopy departments face significant risk for transmissions of SARS-CoV-2 during endoscopy.²⁷ In one of the earliest report of COVID-19 in Wuhan, 29% of patients (40 out of 138) were healthcare workers and suggest that the risk of infection to healthcare providers is significant.⁸ Possible routes of SARS-CoV-2 transmission during endoscopy examination include person-to-person, respiratory droplets, aerosols generated during endoscopy, and contact with contaminated surroundings, body fluids, and fecal material. The World Endoscopy Organization,²⁸ the American Society for Gastrointestinal Endoscopy,²⁹ and the European Society of Gastrointestinal Endoscopy³⁰ have provided recommendations on the performance of endoscopy during the COVID-19 pandemic.

3. LIVER INJURY IN COVID-19

Liver injury was common in the patients infected by the other two highly pathogenic coronavirus—SARS-CoV and the Middle East respiratory syndrome coronavirus—and associated with the severity of diseases.³¹ In patients with COVID-19, several studies have reported the incidence of liver injury (Table 1), indicating that 2% to 11% of patients with COVID-19 had liver comorbidities and 16% to 53% cases reported abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST).³² Guan et al¹³ showed that elevated AST levels were observed in 18.2% of patients with nonsevere disease and 39.4% of patients with severe disease, whereas elevated ALT levels were observed in 19.8% of patients with nonsevere disease

and 28.1% of patients with severe disease. Huang et al⁴ showed that elevation of AST was observed in 8 (62%) of 13 patients in the intensive care unit (ICU) compared with 7 (25%) of 28 patients who did not require care in the ICU. Wang et al⁸ also showed that patients admitted to ICU had significantly higher ALT (35 vs 23, $p = 0.007$) and AST (52 vs 29, $p < 0.001$) levels. These data suggest that liver injury is more prevalent in severe cases than in mild cases of COVID-19.

Liver injury in patients with COVID-19 might be due to viral infection in liver cells or due to other causes such as drug-induced liver injury and systemic inflammation induced by cytokine storm or pneumonia-associated hypoxia.³² SARS virus has been shown to be present in the liver tissue, although the viral titer was relatively low because viral inclusions were not observed.³³ Nevertheless, a case report of pathological analysis of a patient who died from COVID-19 did not identify viral inclusions in the liver tissue.³⁴

The impact of COVID-19 in patients with preexisting chronic liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease, and alcohol-related liver disease, remains to be evaluated. The study from China showed that patients with underlying chronic hepatitis B infection did not have higher disease severity compared with the overall population.¹³ Currently there is no report of liver failure in COVID-19 patients with chronic liver diseases, such as chronic hepatitis B or C.

In conclusion, in this review, we summarized the recent reports of digestive symptoms and liver injury caused by COVID-19. Digestive symptoms are not uncommon in patients with COVID-19, and in some cases digestive symptoms may occur in the absence of any respiratory symptoms. COVID-19 patients with digestive symptoms have worse clinical outcomes and higher risk of mortality compared with those without digestive symptoms. Attention should also be paid to monitor liver function during the course of COVID-19, especially in patients with higher disease severity.

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