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Remarkable gastrointestinal and liver manifestations of COVID-19: A clinical and radiologic overview

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Abstract

The coronavirus disease 2019 (COVID-19) raging around the world still has not been effectively controlled in most countries and regions. As a severe acute respiratory syndrome coronavirus, in addition to the most common infectious pneumonia, it can also cause digestive system disease such as diarrhea, nausea, vomiting, liver function damage, *etc.* In medical imaging, it manifests as thickening of the intestinal wall, intestinal perforation, pneumoperitoneum, ascites and decreased liver density. Angiotensin-converting enzyme 2 has great significance in COVID-19-related digestive tract diseases. In this review, we summarized the data on the clinical and imaging manifestations of gastrointestinal and liver injury caused by COVID-19 so far and explored its possible pathogenesis.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal; Liver; Radiologic manifestations; Angiotensin-converting enzyme 2; Computed tomography

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Core Tip: There are few reviews on the clinical and radiologic manifestations of gastrointestinal and liver in coronavirus disease 2019 (COVID-19). Here, we review the significant information on the management of patients with COVID-19 and the mechanism of how angiotensin-converting enzyme 2, the key factor of COVID-19 infection, relates to severe acute respiratory syndrome coronavirus 2 with digestive tract symptoms. The potential mechanism of fatty change of the liver is discussed in this review as well.

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INTRODUCTION

As of January 4, 2021, over 80 million people have been infected with coronavirus disease 2019 (COVID-19), and more than 1.8 million people have died from diseases caused by this virus[1]. In December 2020, a novel coronavirus mutant named VU-202012/01 appeared in the United Kingdom, and this strain has higher infectiousness [2]. The coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a positive-strand RNA virus that can result in a severe respiratory syndrome in humans[3]. The most common COVID-19 symptoms are fever and cough, while nausea, vomiting, and diarrhea are less common[4]. A deeper understanding of the disease has shown that, in addition to the respiratory system, some infected patients had clinical manifestations in the digestive system, especially in the gastrointestinal (GI) tract and liver[5]. A study by Zhou *et al*[3] revealed that the COVID-19 virus belongs to the SARS-CoV group. The genome similarity between SARS-CoV-2 and SARS-CoV reached 80%, and the similarity between SARS-CoV-2 and bat coronavirus BatCoV RaTG13 reached 96%. It was also confirmed that SARS-CoV-2 uses the same cell entry receptor, angiotensin converting enzyme 2 (ACE2), as SARS-CoV. A study of 1099 patients with COVID-19 revealed that 5% of these patients had nausea or vomiting, and 3.8% of them had diarrhea[4].

At the early stage of the COVID-19 pandemic, the public was not sensitive to the GI and liver lesions related to coronavirus, and the connection and mechanism were not fully explored. With the emergence of more and more relevant cases, studies on the manifestations and pathophysiological mechanism of GI and liver diseases related to coronavirus have become clearer. Therefore, this article focuses on reviewing the clinical and radiologic manifestations of the GI tract and liver in patients with COVID-19.

CLINICAL MANIFESTATIONS OF GI TRACT INJURY

Although respiratory system symptoms are the most typical and significant manifestation of COVID-19 infection, quite a few patients have presented with digestive symptoms, even as initial symptoms[6].

A fairly comprehensive meta-analysis[7] involving 59254 patients from 11 countries showed that 9% of all included patients had GI symptoms. In addition, a meta-analysis by Cheung *et al*[8] involving 4243 COVID-19 patients concluded that anorexia was present in a large proportion of patients, and other common symptoms included diarrhea, nausea, vomiting, and abdominal pain or discomfort. Another study of 204 patients with COVID-19 performed by Pan *et al*[6] showed that 48.5% of these patients presented with digestive symptoms as their chief complaint. Moreover, 7 cases had digestive symptoms without respiratory symptoms. Compared to patients without digestive symptoms, the patients with digestive symptoms presented with anorexia (83.8%), vomiting (0.8%), diarrhea (29.3%), and abdominal pain (0.4%) and had a longer hospitalization time and a worse prognosis.

Sultan *et al*[9] found that 7.8% of patients had symptoms of nausea or vomiting in their pooled analysis of 5955 patients with COVID-19. Notably, Fang *et al*[10] found that approximately 22.2% of patients complained of loose stools before the diagnosis of COVID-19, and more than 50% of patients with diarrhea had received or were receiving antiviral treatment. In addition, many patients experienced GI symptoms such as nausea, abdominal pain, and diarrhea during hospitalization or after taking the medication, and these symptoms may also be due to the medication[11]. In addition to the high incidence and most reported GI symptoms, a few rare symptoms such as acute hemorrhagic colitis as well as GI bleeding[6,12] have also been reported.

According to previous studies, it can be concluded that diarrhea is the most common GI manifestation in COVID-19 patients. A study conducted by Xu *et al*[13] showed that diarrhea occurred in 130 of 355 patients, with a prevalence of 36.6% [95% confidence interval (CI): 31.6%-41.9%]. Hajifathalian *et al*[14] found that diarrhea

occurred in 234 of 1059 patients, with a prevalence of 22.1% (95%CI: 19.6%-24.7%). Nausea or vomiting was the second most common symptom. A pooled analysis[9] of 5955 patients with COVID-19 showed a prevalence of nausea or vomiting of 7.8% (95%CI: 7.1%-8.5%) in these patients.

RADIOGRAPHIC MANIFESTATIONS OF GI TRACT INJURY

A large number of studies have indicated the pulmonary radiographic features of COVID-19; however, COVID-19-associated GI injury is also seen on imaging. A number of studies[12,15-21] have demonstrated thickening of different areas of the small and large bowel wall. Thickening of the intestinal wall can also be accompanied by hyperemia and thickening of the mesentery. Several case reports have demonstrated a series of GI imaging findings in patients with COVID-19. Funt *et al*[22] reported a 49-year-old male with COVID-19 infection complaining of left-sided abdominal pain and showed a thick-walled loop of small bowel (arrow) with mild peri-enteric fat stranding in computed tomography (CT) abdominal image; he was finally diagnosed as enteritis (Figure 1A). Another 53-year-old female with COVID-19 infection presented with thick-walled loop of descending colon (arrow) with mild peri-enteric fat stranding in CT image, representing colitis (Figure 1B). One case report[23] involving a COVID-19 infected patient showed extensive pneumoperitoneum caused by perforation of the sigmoid colon on abdominal CT image (Figure 1C). Colonic ileus and intestinal wall pneumatosis were also found on abdominal CT[16,24]. In addition, two separate cases of ileocolic intussusception were detected by ultrasound examination[25,26]. Ascites was also observed by ultrasound in a patient with COVID-19[27]. Bhayana *et al*[21] observed that bowel wall thickening and cholestasis also occurred in SARS-CoV-2 infected patients. Farina *et al*[28] found thrombosis of the superior mesenteric artery in a SARS-CoV-2 infected patient's CT images (Figure 2). Besides the most common radiographic GI manifestations such as bowel wall thickening and colonic ileus, intestinal wall pneumatosis, pneumoperitoneum, and large volume ascites have also been reported.

Research by Bhayana *et al*[21], which included 42 cases with radiographic images, showed that bowel wall thickening involving the colon or small bowel, intestinal ischemia, ischemia with pneumatosis or portal venous gas and bowel perforation, and a fluid-filled colon were seen in SARS-CoV-2 infected patients. According to these cases, the radiologic manifestations of COVID-19-associated GI disease can present as bowel wall thickening, intussusception, colonic ileus, intestinal wall pneumatosis, and intestinal perforation.

PATHOGENESIS OF COVID-19-ASSOCIATED GI INJURY

Although GI symptoms are frequently observed, the mechanism of COVID-19-associated GI disease has not been completely elucidated. Therefore, identification of the mechanism of COVID-19 infection is crucial, not just for the treatment of infected patients but for the identification of infected atypical patients. Notably, several possible explanations have been put forward with more and more studies being carried out.

The most frequently proposed mechanism for GI tract injury associated with SARS-CoV-2 is related to the ACE2 cell receptor[29,30]. Hoffmann *et al*[29] demonstrated that SARS-CoV-2 uses the receptor ACE2 for entry, similar to SARS-CoV. As a principle factor in novel coronavirus, ACE2 is a type I membrane protein expressed in lungs, heart, kidneys, and intestine, and its main physiological function is to promote the maturation of angiotensin[31,32]. Xiao *et al*[33] found that the ACE2 protein is abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia according to immunofluorescent data, which supports the entry of SARS-CoV-2 into the host cells. As a result, both the small and large intestine are susceptible to SARS-CoV-2 infection due to the high expression of ACE2. ACE2 staining is rarely seen in esophageal mucosa, which may be attributed to esophageal epithelium expressing less ACE2 than glandular epithelial cells. It was found that SARS-CoV-2 was expressed not only in lungs, kidneys, and blood vessels but also in the intestine, especially the terminal ileum and colon, and that ACE2 can connect the virus and its target cells, resulting in digestive symptoms[34]. Another study[35] revealed that the interaction between SARS-CoV-2 and ACE2 can disrupt the function of ACE2 and that diarrhea may occur as a manifestation of this functional impairment of ACE2, which is highly

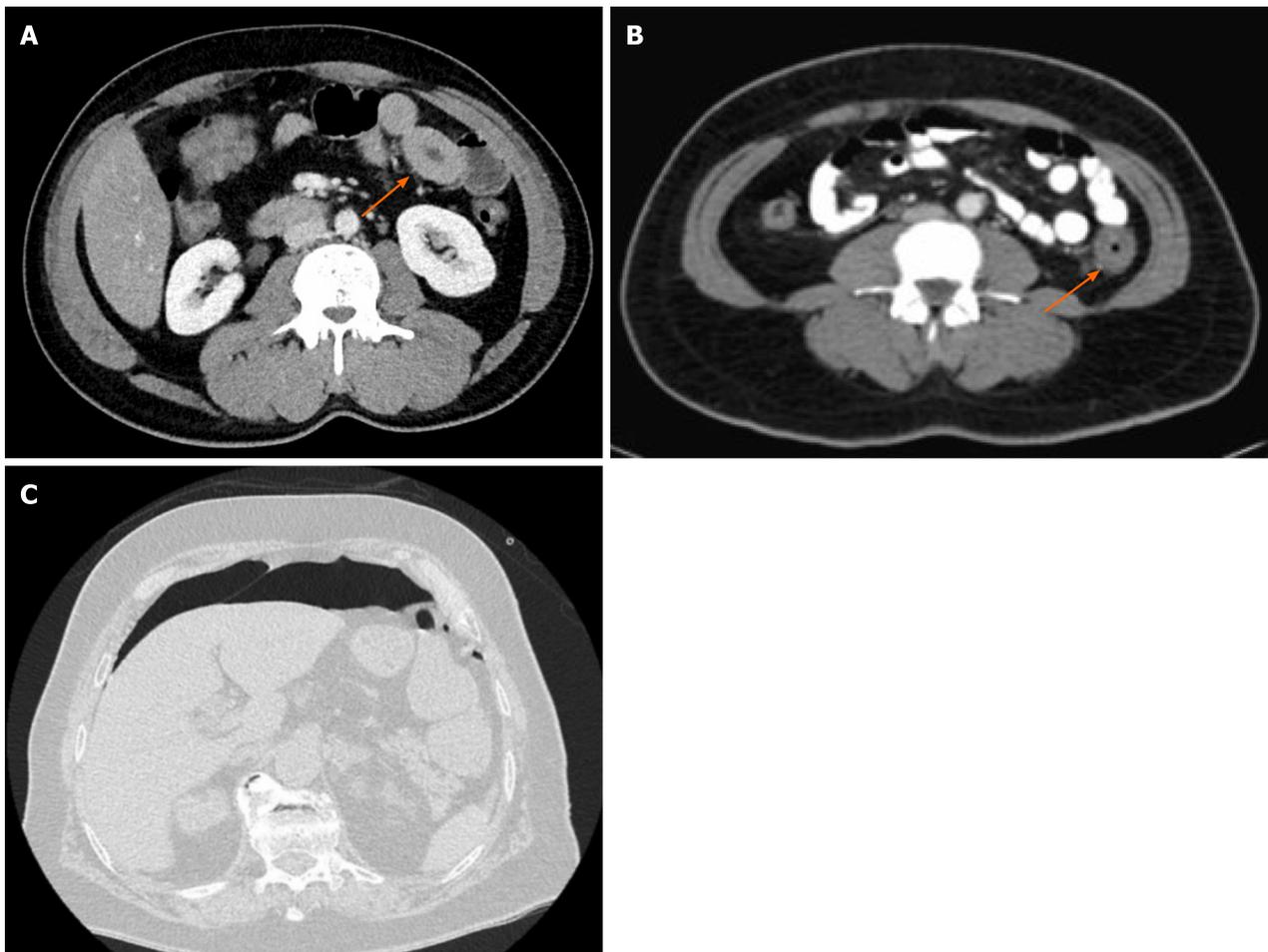


Figure 1 Computed tomography images[22,23]. A: Thick-walled loop of small bowel (arrow) with mild perienteric fat stranding in computed tomography (CT) abdominal image; B: Thick-walled loop of descending colon (arrow) with mild perienteric fat stranding in CT image; C: Extensive pneumoperitoneum caused by perforation of the sigmoid colon on abdominal CT image.

expressed in the small intestine, especially in proximal and distal enterocytes.

ACE2 is known to be a cell receptor for SARS-CoV[36]. It is also known that ACE2 controls intestinal inflammation and diarrhea. In the case of SARS-CoV, the spike glycoprotein (S protein) subunit on the virion surface can directly bind to the peptidase domain of ACE2[37] and results in membrane fusion. The S protein of SARS-CoV-2 might infect the host in the same way[3,29,36,38]. As the receptor for SARS-CoV, ACE2 is essential for the expression of neutral amino acid transporters in the gut, and ACE2 can regulate innate immunity and affect the composition of gut microbiota, which may explain why diarrhea and intestinal inflammation occur[39]. Oliveira *et al*[40] revealed that the ACE2/Ang 1-7 axis can affect the composition of the microbiota by regulating the immune response and is one of the physiological causes of diseases, such as diarrhea and intestinal inflammation. It was found that ACE2 is the key regulator in intestinal inflammation and diarrhea[41]. Furthermore, SARS-CoV-2 may trigger the large-scale release of pro-inflammatory cytokines, such as interleukin-2 and interleukin-7, granulocyte monocyte colony stimulating factor, and tumor necrosis factor alpha, which cause changes in intestinal motility and affect the GI flora, increasing the incidence of diarrhea[42]. The immune response activates the coagulation pathway and leads to the excessive production of pro-inflammatory cytokines, which further leads to multiorgan damage. Thrombin can also increase inflammation through protease-activated receptors[43]. During the course of inflammation, this procoagulant-anticoagulant imbalance easily develops into microthrombosis, diffuse intravascular coagulation, and multiple organ failure[42].

In addition, another possible mechanism is the “lung-intestine” axis[6,44,45]. Abdominal symptoms can be caused by microbial metabolites and endotoxins that are produced during pneumonia due to the alteration in the gut microbiome. In addition, the adverse effects of antivirals and antibiotics can also induce diarrhea[46].

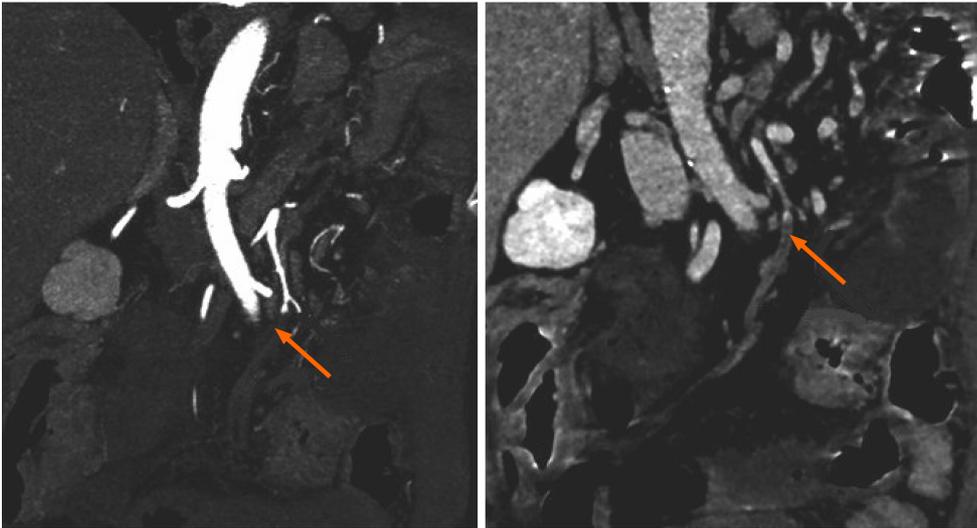


Figure 2 Thrombosis of the superior mesenteric artery in a severe acute respiratory syndrome coronavirus 2 infected patient's computed tomography images[28]. Arrows: Thrombosis of the superior mesenteric artery.

In conclusion, the main infection mechanism in GI lesions caused by SARS-CoV-2 may be the fusion of SARS-CoV-2 and organs with high expression of ACE2, such as the gastroduodenum, terminal ileum, and rectum, which will destroy the function of ACE2 receptors in the corresponding areas and lead to diarrhea. In addition, the release of a large number of inflammatory factors due to viral infection can lead to corresponding digestive symptoms, including gastroenteritis changes, such as intestinal wall edema and exudation, and intestinal necrosis due to intestinal embolism caused by fibrin clot formation. The “lung-intestine” axis may also be involved in the pathogenesis of COVID-19-associated GI symptoms.

As reported previously, nausea, vomiting, diarrhea, and loss of appetite were the main GI symptoms of patients with COVID-19 infection. More severely, there were previous reports of esophageal bleeding, mesenteric artery embolism, intestinal perforation, and hemorrhagic colitis of patients with COVID-19 infection[12,47]. If not promptly treated, these lesions can eventually lead to shock. Coronavirus-infected patients presenting with GI symptoms had longer duration from illness onset to hospital admission[48].

CLINICAL MANIFESTATIONS OF LIVER INJURY

Almost all the studies on COVID-19-associated liver injuries have revealed abnormal liver function tests such as elevated bilirubin or liver transaminases including alanine transaminase (ALT) and aspartate transaminase (AST). A study by Wang *et al*[49], which included 69 patients, showed that 23 of these patients had elevated ALT (33%) and 19 had elevated AST (28%) levels. The study by Zhang *et al*[50] revealed that the incidence of liver injury can reach 78% among patients with confirmed SARS-CoV-2 infection. In addition, Cai *et al*[51] found that 44 of 298 patients (14.8%) had liver injury, and patients with severe liver injury (36.2%) were more likely to have elevated liver transaminases than those with mild liver injury (9.6%). A retrospective cohort study[52] of 1827 patients with confirmed COVID-19 found that abnormal liver tests were commonly observed (AST 66.9%, ALT 41.6%, alkaline phosphatase 13.5%, total bilirubin 4.3%, albumin 56.7%) on hospital admission. Furthermore, patients with abnormal liver tests were more likely to develop severe COVID-19. Most patients with abnormal liver function tests had minimal elevations pre-hospitalization or at admission, but it was also revealed that patients who received drug treatment (lopinavir/ritonavir, hydroxychloroquine, remdesivir, tocilizumab) experienced more extreme elevations in liver transaminases ($> 5 \times$ upper limit of normal) during hospitalization[53]. Of all the COVID-19 patients included in a systematic review[9], the pooled prevalence of abnormally-elevated AST and ALT was 15%, and the combined prevalence of elevated bilirubin was 16.7%.

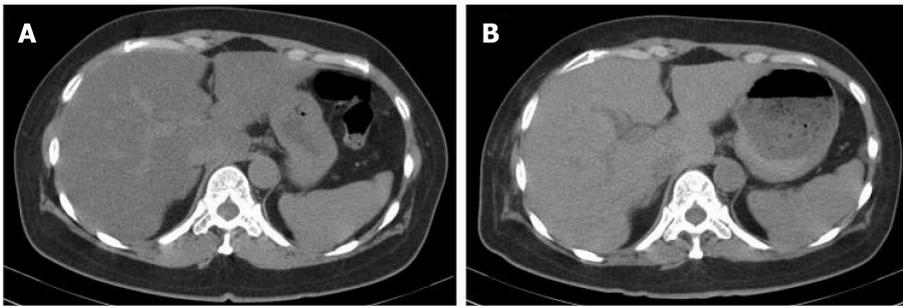


Figure 3 An inpatient coronavirus disease 2019 patient's abdominal computed tomography image[55]. A: Decreased hepatic computed tomography (CT) attenuation value and liver-to-spleen attenuation (L/S) ratio; B The hepatic CT attenuation value and L/S ratio returned to normal level after intensive therapies.

RADIOGRAPHIC MANIFESTATIONS OF LIVER INJURY

Unfortunately, few studies have investigated the radiographic manifestations of the GI tract and liver of COVID-19 patients. Only a few studies observed cholestasis and hepatocyte steatosis on CT images. Palomar *et al*[52] found that hepatic steatosis was independently associated with severe COVID-19 pneumonia. A retrospective study [54] of 316 patients revealed that COVID-19 infected individuals had a significantly higher prevalence of steatosis. Uchida *et al*[55] reported an inpatient 52-year-old woman with COVID-19 infection showing a decreased hepatic CT attenuation value and liver-to-spleen attenuation (L/S) ratio in CT images. The hepatic CT attenuation value and L/S ratio returned to normal level after intensive therapies (Figure 3). It was also found that the results of liver CT images on admission were related to the severity of COVID-19 during hospitalization. Fatty liver and cholestasis were noted on sonographic images in a retrospective cross-sectional study[21] of 412 patients. Pathological studies in COVID-19 showed hepatocellular degeneration with focal necrosis and moderate steatosis in the liver, inflammatory infiltration in the hepatic lobules and portal area, and sinus congestion[56]. CT scans of the upper abdomen usually reveal decreased liver density and fat adhesion around the gallbladder. Homogeneous or heterogeneous low density in the liver is the most common CT manifestation[57]. In addition, the L/S attenuation ratio quantified by CT was measured to indicate the severity of liver damage and indicated a reduced L/S attenuation ratio. Further studies showed that the L/S attenuation ratio and pulmonary lesions were positively correlated with the severity of the disease. Therefore, low liver density and decreased L/S attenuation ratio may be attributable to hepatic steatosis[57]. Furthermore, postmortem liver biopsies in these patients have shown microvesicular steatosis[58].

PATHOGENESIS OF COVID-19-ASSOCIATED LIVER INJURY

At present, the mechanism by which SARS-CoV-2 causes liver damage is not fully understood. It is known that the primary viral entry receptor, ACE2, is highly expressed in the liver[9,59]. The pattern of liver injury is primarily hepatocyte injury rather than cholestasis. Expression of the ACE2 receptor in biliary epithelium is 20 times higher than that in hepatocytes[60]. SARS-CoV-2 can directly lead to viral cytopathic lesions with microvesicular steatosis and invasion of hepatic lobules or portal veins through the cytopathic effects of direct immune damage to hepatocytes [56,61]. SARS-CoV-2 can access the biliary system *via* the portal vein; thus Hundt *et al* [53] insisted that a direct cytopathic effect by SARS-CoV-2 is probably not the main mechanism of liver damage. This injury may be related to overactivation of Kupffer cells, virus-induced cytotoxic T cell response, and innate immune response that induces regulatory dysregulation[62]. In addition to this, SARS-CoV-2 can also trigger the massive release of pro-inflammatory cytokines, which can exacerbate underlying liver injury[63]. So far, the mechanism of fatty change of the liver has not been certainly discussed.

Potential association between novel coronavirus infection and hepatocyte steatosis may due to the following factors. Firstly, disorganized intestinal flora can increase the absorption of monosaccharides, which in turn promote the synthesis of fatty acids and triglycerides in the liver by increasing the activity of acetyl-CoA carboxylase and fatty

Table 1 Clinical and radiologic findings in the gastrointestinal tract and liver of patients with coronavirus disease 2019

Ref.	Gastrointestinal clinical manifestations	Gastrointestinal radiologic manifestations	Liver clinical manifestations	Liver radiologic manifestations
Pan <i>et al</i> [6]	Anorexia, Vomiting, Diarrhea, Abdominal pain			
Cheung <i>et al</i> [8]	Anorexia, Diarrhea, Nausea, Vomiting, Abdominal pain or discomfort			
Sultan <i>et al</i> [9]	Nausea, Vomiting		Elevated AST and ALT	
Fang <i>et al</i> [10]	Loose stool, Diarrhea			
Pan <i>et al</i> [6], Carvalho <i>et al</i> [12]	Hemorrhagic colitis/GI bleeding			
Xu <i>et al</i> [13]	Diarrhea			
Hajifathalian <i>et al</i> [14]	Diarrhea			
Carvalho <i>et al</i> [12], Guo <i>et al</i> [19], Kim <i>et al</i> [17], Bhayana <i>et al</i> [21], Jaijakul <i>et al</i> [18], Calinescu <i>et al</i> [20], Tang <i>et al</i> [15], Sattar <i>et al</i> [16]		Bowel wall thickening, Hyperemia, Mesenteric thickening		
Corrêa Neto <i>et al</i> [23]		Perforation		
Sattar <i>et al</i> [16], Behzad <i>et al</i> [24]		Colonic ileus, Intestinal wall pneumatosis		
Martínez-Castaño <i>et al</i> [25], Moazzam <i>et al</i> [26]		Ileocolic intussusception		
Culver <i>et al</i> [27]		Ascites		
Bhayana <i>et al</i> [21]		Bowel wall thickening, Cholestasis		Fatty liver, Cholestasis
Farina <i>et al</i> [28]		Ischemic changes in loops of the small bowel		
Wang <i>et al</i> [49]			Elevated ALT and AST	
Zhang <i>et al</i> [50]			Abnormal ALT and AST	
Cai <i>et al</i> [51]			Abnormal ALT and AST	
Hundt <i>et al</i> [53]			Abnormal liver tests	
Palomar <i>et al</i> [52], Uchida <i>et al</i> [55]				Hepatic steatosis
Medeiros <i>et al</i> [54]				Steatosis
Lei <i>et al</i> [57]				Pericholecystic fat stranding, Homogeneous/heterogeneous liver hypodensity

ALT: Alanine transaminase; AST: Aspartate transaminase; GI: Gastrointestinal.

acid synthase[64]. Secondly, drugs received by patients with COVID-19 may induce an acute energy crisis by interrupting adenosine triphosphate synthesis by mitochondria, resulting in microvesicular steatosis[65]. Thirdly, ACE2 plays an important role in releasing cytokines produced through the c-Jun N-terminal kinase and inhibitor of nuclear factor κ B kinase- β pathways in COVID-19 patients, which induce insulin resistance and lead to ectopic accumulation of fat in various organs, including the liver [42,66,67].

COVID-19 may do harm to liver and can ultimately result in severe body damage. On one side, it is known that non-alcoholic fatty liver disease is a major cause of liver cirrhosis and hepatocellular carcinoma. On the other side, coronavirus-infected

patients with metabolic syndrome and liver steatosis are more likely to develop drug-induced liver injury[68]. In addition, it was revealed that coronavirus-infected patients with chronic liver disease were at a higher risk of prolonged hospitalization and death [69]. Besides, patients complicated with chronic liver disease, decompensated cirrhosis, and hepatocellular carcinoma may be predictors of higher overall mortality during the course of infection[70].

CONCLUSION

With further knowledge on COVID-19, SARS-CoV-2 has been found to affect the function of the ACE2 cell receptor and the function of the respiratory system and cause digestive system diseases (Table 1). Clinical manifestations of COVID-19 in the GI tract include diarrhea, nausea, vomiting, *etc.* Radiologic manifestations include intestinal wall thickening, intestinal obstruction, intestinal perforation, pneumoperitoneum, ascites, *etc.* With regard to liver damage, liver function is impaired, liver enzymes and bilirubin are elevated, and fatty liver changes and cholestasis are observed on CT images. The distribution and high expression of ACE2 receptors in gastric, duodenal, jejunal terminal, colon, and bile duct cells are possibly involved in the pathogenesis of COVID-19. In addition, the inflammatory storm caused by SARS-CoV-2 also increases the risk of diarrhea and causes direct cell damage.

However, the pathogenesis and radiologic features of COVID-19-associated digestive changes have not been fully determined, impeding diagnostic sensitivity and appropriate treatment. More in-depth and comprehensive studies are necessary to help us understand SARS-CoV-2 infection-related digestive symptoms. Under the circumstance of novel coronavirus mutation, more information is essential to deal with the emergency response more comprehensively and timely.

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