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COVID-19 and the Digestive System

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The outbreak of novel coronavirus pneumonia in 2019 (Coronavirus disease 2019 [COVID-19]) is now threatening global public health. Although COVID-19 is principally defined by its respiratory symptoms, it is now clear that the virus can also affect the digestive system. In this review, we elaborate on the close relationship between COVID-19 and the digestive system, focusing on both the clinical findings and potential underlying mechanisms of COVID-19 gastrointestinal pathogenesis.

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INTRODUCTION

Novel coronavirus pneumonia (Coronavirus disease 2019 [COVID-19]), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, Hubei province, in early December 2019 (1) and then quickly spread throughout China and subsequently throughout the entire world, evolving into a pandemic and threatening global health. This novel coronavirus, along with the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), belong to β-coronavirus 2b lineage (2). Although SARS-CoV-2 is indeed a distinct entity, the similarities in genetic sequence share 70% and 40% with SARS-CoV and MERS-CoV, respectively (3). This fact may partly explain why SARS-CoV-2 shares some common epidemiologic and clinical features with the 2 other viruses. Previous research has shown that angiotensin-converting enzyme 2 (ACE2) is the functional receptor of SARS-CoV and is critical to the cellular entry of SARS-CoV (4). Several studies also confirm that SARS-CoV-2 also leverages the ACE2 receptor to gain entry into target cells (5–7). In addition, ACE2 is widely distributed in various human organs, including the oral and nasal mucosa, nasopharynx, lung, small intestine, colon, kidney, spleen, liver, and brain. Moreover, it is reported that ACE2 expression is approximately 100-fold higher in the gastrointestinal tract (particularly the colon) than in the respiratory system (8,9). Therefore, it is not surprising that the digestive system, with several ACE2-expressing organs, would present a risk for being invaded by SARS-CoV-2 (10). Although COVID-19 is predominantly characterized by respiratory symptoms, including fever, cough, and dyspnea (11), digestive symptoms are also reported among a clinically important subset of COVID-19 patients, often with concurrently elevated liver enzymes (2,12–14). In some instances, digestive symptoms are reported as the initial presentation of COVID-19 (15). These findings suggest that the virus can impair the digestive system and may explain the range of digestive symptoms seen in COVID-19, including diarrhea, nausea, vomiting, and diminished appetite (16). Exploring the pathogenic mechanisms of COVID-19 in the digestive system holds potential to improve prevention, diagnosis, and treatment for these patients.

CLINICAL AND PATHOLOGIC EVIDENCE FOR COVID-19 INVOLVING THE DIGESTIVE SYSTEM

Digestive symptoms were reported among COVID-19 patients in the initial outbreak in Wuhan, China. In a descriptive, cross-sectional, multicenter study including 204 COVID-19 patients confirmed by laboratory tests, 41.6% of COVID-19 patients suffered nausea or vomiting, and 17.2% of COVID-19 patients presented with diarrhea (17). Importantly, patients with severe disease were found with a higher incidence of diarrhea, nausea, or vomiting than those with nonsevere disease (12). The fact that digestive symptoms are closely associated with COVID-19 condition severity was also proved by another single-center study from 1 hospital in Wuhan (2). Among the overall population, diarrhea, nausea, vomiting, abdominal pain, and anorexia appeared in patients admitted into the intensive care unit (ICU) more prominently than in those not transferred into the ICU, and the occurrence of anorexia between the 2 groups was increased with statistical significance, which may present a good indicator for severe condition (2).

The intestinal damage caused by SARS-CoV-2 infection has been verified by autopsy and biopsy. A recent report described the intestinal autopsy from a COVID-19 patient who developed alternating segmental dilatation and stenosis of the small intestine (18). Xiao et al. (19) also performed gastrointestinal endoscopy for a confirmed COVID-19 patient. Damage to the mucosa was observed in the esophagus, and numerous plasma cells and lymphocytes were found to have infiltrated the lamina propria of the stomach, duodenum, and rectum by histological examination. Furthermore, viral nucleocapsid protein was also detected in the cytoplasm of these sites. It is noteworthy that approximately 3% of COVID-19 cases exhibited only digestive symptoms without respiratory symptoms (17). Acute hemorrhagic colitis could even occur in a COVID-19 patient with digestive discomforts as the primary symptoms (20). Thus, more attention should be given to

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patients who present to the hospital with digestive symptoms, especially those with a history of an epidemiological exposure.

The positive detection of SARS-CoV-2 in the stool was a breakthrough, which suggested that the virus can replicate and exist in the digestive tract (21). The fact that the digestive system could be infected by SARS-CoV-2 is further illustrated by Guan et al. (22), who reported that SARS-CoV-2 RNA was detected in 4 of 62 (6.5%) stool specimens, and 4 rectal swabs were positive for SARS-CoV-2 RNA. In addition, the percentage of positive stool samples has been reported up to 53.42% among hospitalized patients confirmed with COVID-19 (19). In another study detecting SARS-CoV-2 RNA of different clinical specimens, 44 of 153 (29%) stool samples were positive (23). Of particular note, the stool test positivity is higher in those with diarrhea (73%) than those with only respiratory symptoms (14%) (16). The situation is further complicated by the findings that some COVID-19 patients still present with nucleic acid–positive stool after the virus in pharyngeal swab turns negative (24,25). Consistent with this, SARS-CoV-2 RNA was detected in stool specimens in the first American COVID-19 patients, although serum specimens were repeatedly negative (21). Moreover, on average, there are 11 days of SARS-CoV-2 shedding from feces after respiratory symptoms subside (26). Thus, it is reasonable that a standard of care for COVID-19 patients leaving the hospital include fecal viral examination because of its delayed elimination. At present, whether the live SARS-CoV-2 virus could be detected in the stool is the focus of researches for its clinical value for fecal–oral spread and infectivity. Wolfel et al. (27) analyzed the virology of 9 COVID-19 patients with mild symptoms, although failed to isolate the live SARS-CoV-2 from the stool. This negative result may be related to the subjects with mild symptoms, the limited number of stool specimens, and the tests only for the live virus on 6–12 days and in 4 patients. In addition, the absence of data on early time points in this study may cause the missing of a critical window of stool infectivity in the early stages. However, the study from the research teams of Prof Zhong at the State Key Laboratory of Respiratory Disease in China demonstrated that the live SARS-CoV-2 dose exist in the stool (28). Thus, the existence of live SARS-CoV-2 virus in the stool is vital to define the fecal–oral spread of COVID-19, and this finding is helpful to the development of public health strategies during fighting against COVID-19.

It has also been reported that SARS-CoV-2 infection can lead to liver injury, and abnormal liver function and liver enzymes are positively associated with COVID-19 severity. Compared with nonsevere COVID-19 patients, severe COVID-19 patients have higher levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin (TBL) (12). Elevated hepatic enzymes are also more likely to be found in COVID-19 patients treated in the ICU than those not treated in the ICU (2). In the first COVID-19 confirmed case in the United States, there was an overall upward trend of hepatic enzymes during his treatment, which suggested that SARS-CoV-2 infection can directly affect the liver (21). The acute hepatitis caused by COVID-19 infection has been reported recently, and the severe liver damage could be presented before the typical symptoms of COVID-19, which resulted in misdiagnosis in the early stage (29). It is worth noting that the elevated prothrombin time among the COVID-19 patients with digestive symptoms is more common than that in those only with respiratory symptoms (17). Hence, close monitoring of liver function and liver enzymes should be early implemented in COVID-19 patients with digestive symptoms. Furthermore, 23 of 1,099 COVID-19 patients (2.1%) have been diagnosed with hepatitis B coinfection, although the proportions of patients with coincident abnormal liver enzymes and increased TBL reach to more than 20% and 10%, respectively (12). In another study, digestive system disease was present in 11% of COVID-19 patients , but 43% of patients suffered with varying degrees of liver enzyme abnormality, and 18% of patients suffered with increased TBL (30). Such drastic differences cannot only be ascribed to the coexisting illness and conversely, to some extent, suggest that the pathogenic mechanism of SARS-CoV-2 may result in liver injury. Liver injury associated with COVID-19 infection has also been revealed through autopsy and biopsy. Gross examination of the liver reveals it to be gray (18), and the pathological features of COVID-19 hepatic injury include mild lobular and portal inflammation and moderate microvascular steatosis (31). Thus, the liver is indeed damaged during COVID-19 infection, so it is vital to closely and actively monitor liver function in COVID-19 patients.

In conclusion, the digestive tract may serve as an infection route for COVID-19 based on clinical and pathological evidence. We should place more value on the reported digestive symptoms in infected patients, monitor liver enzymes among those infected with the virus, and consider screening for SARS-CoV-2 in fecal samples both to establish the diagnosis and to monitor for viral clearance.

MECHANISMS OF INTESTINAL DAMAGE DURING COVID-19 INFECTION

The high expression of ACE2 in the intestinal tract makes the small bowel and colon highly susceptible to SARS-CoV-2 infection (10). Currently, this hypothesis was supported in a COVID-19 patient via a bioinformatic analysis based on single-cell transcriptomes to identify the distribution of ACE2-expressing cells. A recent study demonstrated that ACE2 expression was more frequently observed in the ileum and colon than in the lung and was mainly expressed in the absorptive enterocytes of the ileum and colon, which offers a potential explanation for diarrhea observed in many COVID-19 patients (9). Moreover, this study also revealed that ACE2 is found in the stratified epithelial cells of the esophagus, which may be helpful to explain the esophagitis caused by COVID-19 (9). The expression of ACE2 messenger RNA and protein in the gut is 100 times than that in the lung shown by the Human Protein Atlas database (32). This database is a large transcriptome and proteome database based on RNA sequencing analysis and immunohistochemical analysis and is used to analyze the differential expression of proteins in normal tissues and tumor tissues (33). The mechanisms of esophageal damage in COVID-19 warrant further study, and the reported differences for ACE2 distribution may be related to the various detection techniques.

Another proposed molecular explanation of COVID-19 intestinal pathogenesis is that SARS-CoV-2 may interfere with the absorption of tryptophan because this process requires intestinal ACE2 to regulate the expression of neutral amino acid transporters. In ACE2-deficient mice, the colon was highly susceptible to develop inflammation and colitis after treatment with chemical irritants. Strikingly, such experimentally induced colitis could be reversed by administering glycine tryptophan dipeptide, a unique amino acid that can be taken up by another amino acid transporter, proton-coupled peptide transporter PepT1. However, this same effect did not occur when treated jointly with an mTOR inhibitor. Moreover, the mTOR inhibitor significantly downregulated antimicrobial peptide expression, markedly altered the ileocecal gut microbiome, and resulted in intestinal inflammation. A similar

intestinal inflammatory phenotype was observed in wild-type mice after transplantation with the ileocecal gut microbiota from ACE2 mutant mice (34). Thus, intestinal SARS-CoV-2 may influence tryptophan absorption via ACE2, resulting in decreased antimicrobial peptide and consequently altering gut microbiota to confer intestinal inflammation. Although this mechanism has not yet been demonstrated in humans, intestinal microbial dysbiosis has indeed been identified in some COVID-19 patients, such as decreased *Lactobacillus* and *Bifidobacterium* (35), and the importance of treatment with probiotics for COVID-19 has also been emphasized in the guidance given from China's National Health Commission (Version 6). More basic and clinical researches should be focused on the relationships between intestinal microbiota and COVID-19 in future studies.

The concept of the "cytokine storm" has been emphasized since the COVID-19 outbreak, which is associated with a systemic inflammatory reaction and multiple organ dysfunction, including the digestive damage. Cytokine dysregulation and abnormal immune responses will lead to more severe disease and death. Higher expression of T-helper-1-related cytokines was noticed in the serum of COVID-19 patients, including interferon-γ (IFN-γ), T-helper-1 chemokine IFN-γ-inducible protein-10, monocyte chemoattractant protein-1, interleukin (IL) IL-6, and human granulocyte-macrophage colony stimulating factor. Concentrations of these cytokines were also significantly different between patients in the ICU and those in non-ICU. However, increased levels of T-helper-2-related anti-inflammatory cytokines, IL-4 and IL-10, were also found, whose mechanistic roles remain to be elucidated (1). Activated T cells in the peripheral blood obtained from a patient with COVID-19 manifested high cytotoxicity with more cytotoxic granules, granulysin and perforin, suggesting that pathogenic T cells are associated with accelerating the systemic inflammation in this disease (31). Moreover, deteriorating intestinal inflammation was observed in mice during intragastric gavage with MERS-CoV. Importantly, lung infection was then verified in these mice at day 5 after intragastric MERS-CoV inoculation, and histological examination of the lung revealed inflammatory cell infiltration and viral antigen-positive cells, indicating the possibility that pulmonary infection can be secondary to a primary MERS-CoV infection in the intestine through hematogenous viral trafficking (36). However, whether intestinal lesions of COVID-19 are the result of a secondary response after systemic inflammation, are the result of a primary intestinal infection, or are the combined results of both mechanisms remains uncertain. Further investigations of intestinal specimens from biopsy and autopsy are required to explore this mechanism. Dynamic monitoring of lymphocytes and cytokines can help achieve early detection, early diagnosis, and early treatment for COVID-19. Monoclonal antibodies targeting the excessive release of inflammatory cytokines may be promising for COVID-19 treatment.

MECHANISMS OF LIVER INJURY DURING COVID-19 INFECTION

ACE2 presumably plays a vital role in the pathogenesis of liver damage in COVID-19. ACE2 is an ACE homologue that has the ability to counteract the vasoconstricting effect of angiotensin (Ang) II through degrading Ang II into Ang 1–7, thereby decreasing damage to the liver caused by the renin–angiotensin system (37). ACE2 was identified with moderate expression in healthy livers in the previous study (38), but a recent single-cell RNA sequencing study of healthy liver tissues found that ACE2 was highly expressed in both cholangiocytes and hepatocytes, particularly in more than half of cholangiocytes, providing a new theoretical basis for liver injury in COVID-19 infection (39). Moreover, the pathologic examination from a COVID-19 death case found moderate microvascular fatty degeneration and mild hepatic lobular portal region active inflammation in the liver (31), suggesting that liver damage in COVID-19 tends to be due to a secondary injury from hypoxia. An *in vitro* experiment also showed that the expression and activity of ACE2 were sharply increased in hepatocytes and bile duct cells under hypoxia (37). In general, the condition of patients with coexisting liver disease may be potentially worsened during COVID-19 infection from the increased expression of ACE2 caused by hypoxia during the cytokine storm. Thus, more attention should be given to these patients in clinical practice. Choosing appropriate liver medications to protect liver function for COVID-19 patients is necessary.

Drug toxicity has served as 1 mechanism for COVID-19-associated liver injury, which also indicates that liver damage is secondary. Some drugs used in COVID-19 patients have different degrees of liver function damage, including traditional Chinese medicine, antipyretics, and antiviral drugs. In a severe acute respiratory syndrome–associated report, 7 of 41 patients with severe acute respiratory syndrome treated with Kaletra experienced liver dysfunction, and 1 patient had severe liver dysfunction and therefore had to discontinue antiviral treatment (40). In a Singapore study, 3 of 5 COVID-19 patients treated with lopinavir–ritonavir developed liver function disturbance (41). However, little is known about the incidence of hepatotoxicity of various drugs used in COVID-19. More efforts should be made toward future studies regarding this concern, which will be important for developing a reasonable intervention and reducing the harmful effects of drug-induced hepatotoxicity for patients.

CONCLUSION

Digestive symptoms should be treated with caution in the early stage of COVID-19, and dynamic monitoring of liver function and cytokines is imperative during clinical practice to reduce the complications and mortality of COVID-19. ACE2 and abnormal immune reactions could be targets in future studies to treat COVID-19. Moreover, the detection of SARS-CoV-2 in fecal samples is essential for clinical practice, particularly for patients with atypical symptoms, and should be performed when COVID-19 patients are leaving the hospital as well to confirm viral clearance. The relationship between the digestive system and COVID-19 deserves to be further explored in future related studies.

CONFLICTS OF INTEREST

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