Journal of Gastrointestinal & Digestive System

Foroogh Forghani. J Gastrointest Dig Syst 2021, 11:7

Commentary Article Open Access

Effects of COVID-19 on the Digestive System

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Received date: July 09, 2021; **Accepted date:** July 23, 2021; **Published date:** July 30, 2021

Abstract

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.

Keywords Digestive system; COVID-19; Gastro intestinal tract; Abdominal pain

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 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. 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. This fact may partly explain why SARS-CoV-2 shares some common epidemiologic and clinical features with the other viruses. Previous research has shown that angiotensin-converting enzyme is the functional receptor of SARS-CoV and is critical to the cellular entry of SARS-CoV. Several studies also confirm that SARS-CoV-2 also leverages the ACE2 receptor to gain entry into target cells. 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. 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. Although COVID-19 is predominantly characterized by respiratory symptoms, including fever, cough, and dyspnea, digestive symptoms are also reported among a clinically important subset of COVID-19 patients, often with concurrently elevated liver enzymes. In some instances, digestive symptoms are reported as the initial presentation of COVID-19. 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. Exploring the pathogenic mechanisms of COVID-19 in the digestive system holds potential to improve prevention, diagnosis, and treatment for these patients.

The novel coronavirus disease is currently causing a major pandemic. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the *Betacoronavirus* genus that also includes the SARS-CoV and Middle East respiratory syndrome coronavirus. While patients typically present with fever and a respiratory illness, some patients also report gastrointestinal symptoms such as diarrhea, vomiting, and abdominal pain. Studies have identified the SARS-CoV-2 RNA in stool specimens of infected patients, and its viral receptor angiotensin converting enzyme 2 was found to be highly expressed in gastrointestinal epithelial cells. These suggest that SARS-CoV-2 can actively infect and replicate in the gastrointestinal tract. This has important implications to the disease management, transmission, and infection control. In this article, we review the important gastrointestinal aspects of the disease.

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. Importantly, patients with severe disease were found with a higher incidence of diarrhea, nausea, or vomiting than those with nonsevere disease. The fact that digestive symptoms are closely associated with COVID-19 condition severity was also proved by another single-center study from hospital in Wuhan. 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 groups was increased with statistical significance, which may present a good indicator for severe condition.

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 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. Acute hemorrhagic colitis could even occur in a COVID-19 patient with digestive discomforts as the primary symptoms. Thus, more attention should be given to 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. The fact that the digestive system could be infected by SARS-CoV-2 is further illustrated, 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. In another study detecting SARS-CoV-2 RNA of different clinical specimens, 44 of 153 (29%) stool samples were positive. Of particular note, the stool test positivity is higher in those with diarrhea (73%) than those with only respiratory symptoms (14%). 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. 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. Moreover, on average, there are 11 days of SARS-CoV-2 shedding from feces after respiratory symptoms subside. 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 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. 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. 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. 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. 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. 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. 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. 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. 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, and the pathological features of COVID-19 hepatic injury include mild lobular and portal inflammation and moderate microvascular steatosis. 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.

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. 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. 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. The expression of ACE2 messenger RNA and protein in the gut is 100 times than that in the lung.

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.