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**COVID-19 and gastroenteric manifestations**

Chen ZR *et al*. COVID-19 and gastroenteric manifestations

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**Abstract**

Coronavirus disease 2019 (COVID-19), caused by the infection of a novel coronavirus (severe acute respiratory syndrome coronavirus 2), has become a pandemic. The infection has resulted in about one hundred million COVID-19 cases and millions of deaths. Although severe acute respiratory syndrome coronavirus 2 mainly spreads through the air and impairs the function of the respiratory system, it also attacks the gastrointestinal epithelial cells through the same receptor, angiotensin converting enzyme 2 receptor, which results in gastroenteric symptoms and potential fecal-oral transmission. Besides the infection of severe acute respiratory syndrome coronavirus 2, the treatments of COVID-19 also contribute to the gastroenteric manifestations due to the adverse drug reactions of anti-COVID-19 drugs. In this review, we update the clinical features, basic studies, and clinical practices of COVID-19-associated gastroenteric manifestations.

**Key Words:** COVID-19; SARS-CoV-2; Gastroenteric manifestations; Adverse drug reaction; Management

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**Core Tip:** Gastroenteric manifestations, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding, can worsen the situation of patients with coronavirus disease 2019 (COVID-19). More efforts should be spared to understand its pathology and mechanism. Besides the infection of severe acute respiratory syndrome coronavirus 2 virus, the treatments of COVID-19 also contribute to the gastroenteric manifestations due to the adverse drug reactions of anti-COVID-19 drugs. Timely supportive or symptomatic treatment and withdrawal of adverse drug reaction-inducing drugs can help to manage COVID-19-associated gastroenteric manifestations.

**INTRODUCTION**

The Coronaviridae family can infect both humans and animals, of which seven types of coronaviruses (CoVs) can infect humans[1]. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-CoV emerged in the 21st century and were endemic locally[2,3]. Since late 2019 through January 2021, SARS-CoV-2 has accounted for over one hundred million confirmed cases and over two million deaths in all countries and all seven continents (https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6). SARS-CoV-2 is a beta coronavirus that originated in bats[4]. It is still poorly understood how those zoonotic coronaviruses were transmitted from bats to humans despite some clues[5,6].

The RNA of SARS-CoV-2 can be detected in the blood, kidneys, liver, heart, brain, and other organs of infected patients[7]. The infection of SARS-CoV-2 mainly occurs in the respiratory tract. The clinical manifestations of the SARS-CoV-2 infection range from asymptomatic infection, mild influenza-like symptoms (mainly fever, cough, and fatigue), severe pneumonia, multiorgan failure, and even death[8]. Some of the COVID-19 patients who suffer from the disease induced by the infection of SARS-CoV-2 have gastroenteric manifestations, mainly manifested as anorexia, nausea, vomiting, diarrhea, and abdominal pain[9,10]. The mechanism of COVID-19-associated gastroenteric manifestations has not been fully demonstrated. Also, the anti-COVID-19 treatments can induce gastroenteric side effects that may confuse with or superimpose with the COVID-19-associated gastroenteric manifestations. This review introduces the clinical features, mechanism, and management of COVID-19-associated gastroenteric manifestations.

**Gastroenteric manifestations of COVID-19 patients**

Respiratory symptoms, including fever, fatigue, and dry cough, are the most common manifestations among COVID-19 patients. In addition, some patients suffered gastrointestinal tract disorders, including anorexia, nausea, vomiting, diarrhea, and abdominal pain[8]. The incidence of gastroenteric manifestations among COVID-19 patients varied between initial reports and subsequent studies[11]. Guan *et al*[12] andWang *et al*[13] reported that gastroenteric manifestations can be found among 2% to 10% of COVID-19 patients. However, some meta-analyses found that the prevalence can be 9.8%, 33.4%, and 50.5%[14-16]. This divergence can be explained partly by the difference of included patients, which consist of outpatients and hospitalized patients. The RNA of SARS-CoV-2 can be detected in the stools of infected people, and the fecal viral shedding duration and positive viral rectal swabs can last for a long time after the respiratory specimens or nasopharyngeal swabs turned negative in both adults and children[17]. Those findings proposed the potential fecal-oral transmission. But the viral RNA detected in stools does not fully equate to live viruses, and further studies need to be done.

Typical gastrointestinal symptoms of COVID-19 patients consist of anorexia, nausea and vomiting, diarrhea, and abdominal pain[18]. In addition to the above-mentioned typical symptoms, some specific symptoms can be observed, such as gastrointestinal bleeding[18,19]. Noteworthily, the above-mentioned gastroenteric manifestations were observed before fever in 14 (10.1%) patients in a study[13]. Most typical gastrointestinal symptoms are mild and common[20]. The diagnosis of gastrointestinal manifestations related to COVID-19 is essential but difficult due to the atypical features in the clinic[21]. Some COVID‐19 patients may not exhibit respiratory symptoms but gastrointestinal or other such atypical symptoms[21].

Anorexia, which manifests as loss of appetite, is the most common gastroenteric manifestations, and the prevalence ranged from 1.0% to 79%[22,23]. The mechanism of COVID-19 associated anorexia is still poorly understood. Gustatory dysfunction of COVID-19 patients may explain it partly[23]. Gustatory dysfunction was markedly associated with olfactory dysfunction, which is a specific feature of early SARS-CoV-2 infection[24].

Nausea and vomiting, as a symptom of COVID-19, may result from the SARS-CoV-2 impact on the digestive system and/or central nervous system[22]. The prevalence of nausea and vomiting ranged from 7.8% to 22.7%[22]. Some anti-COVID-19 treatments can also induce nausea and vomiting, which is independent of the viral infection. In addition, treatment-induced nausea and vomiting may be merged with disease-induced nausea and vomiting and worsen the clinical status of COVID-19 patients.

Diarrhea, a common disorder of COVID-19 patients, can be induced by the intestinal SARS-CoV-2 infection itself, the disturbance of gut microbiota, and some anti-COVID-19 treatments (such as oseltamivir and abidol hydrochloride). The prevalence has been reported as 5%-10%, 2%-50%, and 22.1% in three independent reports[14,15,25]. Twenty-two percent of COVID-19-associated diarrhea were not treatment-induced[22]. Considering the potential fecal-oral transmission of SARS-CoV-2, more attention should be paid to COVID-19-associated diarrhea as a public health issue that could lead to the community transmission of COVID-19.

Abdominal pain was less common among COVID-19 patients compared with the above-mentioned gastrointestinal symptoms[22]. The mechanism of COVID-19 associated abdominal pain has also not been well elucidated yet. The SARS-CoV-2 infection-induced visceral pain and/or the involvement of the peritoneum may contribute to COVID-19 associated abdominal pain[22].

Gastrointestinal bleeding is a rare specific manifestation of COVID-19 patients and causes hematemesis or melena. Several gastrointestinal bleeding cases of COVID-19 patients have been reported, and it is more fatal than general gastrointestinal manifestations[18,19,26]. Cavaliere *et al*[19] reported 6 COVID-19 patients with upper gastrointestinal bleeding and concluded that COVID-19 patients with upper gastrointestinal bleeding should be treated without endoscopy. But there are still some controversies because some disorders (pulmonary embolism, myocardial infarction, and renal failure) and the intake of substances (iron supplements, bismuth subsalicylate, and foods such as blood soup) can lead to coffee-ground hematemesis episodes or black stools similar to melena[27]. Thus, despite those patients’ responses to conservative treatment in 24 h[19], Duan *et al*[27] states that endoscopy is still essential to find the cause of hematemesis or melena.

**pathology and mechanism of SARS-CoV-2 infecting the gastroenteric tract**

Pathological research confirmed that SARS-CoV-2 mainly targets the respiratory system and causes the impairment of pulmonary function. COVID-19 has similar pathological features of SARS and Middle East respiratory syndrome[20]. In addition, autopsy and endoscopy studies demonstrated that the infection of SARS-CoV-2 also causes lesions in the gastroenteric tract. Some researchers analyzed 28 autopsy studies that include 341 COVID-19 cases, and concluded that most studies focused on pulmonary alterations, and only a few pieces of information are given about the features of other organs and systemic findings[28-30]. Elsoukkary *et al*[29] found that the color of the stomach mucosa turned crimson, and some bleeding points can be seen on the stomach mucosa *via* the gross examination of a COVID-19 death autopsy, while the color of the intestine has not changed[31]. In the intestine autopsy of an 85-year-old man with COVID-19, segmental dilatation and stenosis alternating was found. However, it is still not clear whether it is induced by the infection of SARS-CoV-2[31]. Furthermore, viral particles were found in enterocytes in the large intestine after COVID-19 death autopsy through electron microscope[32]. Those findings provide further evidence of the possibility of the fecal-oral transmission of SARS-CoV-2.

Efforts to discover the mechanism of SARS-CoV-2 infecting gastroenteric tract cells led to studies involving cell lines, animals, and organoids[33,34]. Four human intestinal epithelial cell lines are permissive to SARS-CoV-2 infection, including T84, C2BBe1, Caco-2, and CL14[8]. Human organoids and bat intestinal organoids also support the infection of SARS-CoV-2[35,36]. Organoids are self-assembled, differentiated, nontransformed, and three-dimensional microphysiologically culture systems that contain multiple cell types similar to the cells in a specific tissue[37]. Organoids can model niche-mimicking and form similar architectures of original organs[37]. There are unique advantages for the utilization of organoids in medical research, especially infectious diseases, cancer, genetic diseases, and novel drug discovery. Human intestinal organoids are the most advanced accessible tool for the simulation of SARS-CoV-2 infection of gastroenteric tract cells[37]. Multiple intestinal epithelial cell types, such as enterocytes, goblet cells, tuft cells, enteroendocrine cells, and Paneth cells, can be found in human intestinal organoids.

Studies with the above-mentioned models have demonstrated the process that SARS-CoV-2 infects gastroenteric tract cells. There are four structural proteins in SARS-CoV-2: spike, envelope, membrane, and nucleocapsid. The spike protein binds to the adhesion receptor of hosts first, then binds to the entry receptor and activates a fusion of the viral and cellular membranes. Angiotensin converting enzyme 2 (ACE2) is the entry receptor for SARS-CoV-2, and transmembrane protease serine 2 is a spike priming protease[8,20]. There is a higher expression of ACE2 in the gastroenteric tract than in the respiratory tract[38]. Generally, the higher expression of ACE2 in a tissue, the more likely it was infected by SARS-CoV-2. The human colon expressed ACE2 much lower than stomach epithelial cells and enterocytes from the small intestine[39]. Consequently, human colon organoids are affected to a lesser extent than small intestine organoids, and SARS-CoV-2 infects only enterocytes, not goblet cells, enteroendocrine cells, tuft cells, or Paneth cells[36].

The infection of SARS-CoV-2 can induce alterations in gut microbiota[40]. The alterations in gut microbiota, the increase of opportunistic pathogens, and the loss of salutary bacteria contribute to the gastroenteric manifestations[41]. Bacterial species *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii* are enriched in the stools of COVID-19 patients with higher SARS-CoV-2 infectivity[41]. In another study, the reduction of an anti-inflammatory bacterium, *Faecalibacterium prausnitzii*, and the increase of *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* were found to be correlated with the severity of COVID-19[42]. Management to alter the gut microbiota, such as the utilization of intestinal microecological preparations, may help to relieve disease symptoms[42,43].

**COVID-19 treatment-associated gastroenteric manifestations**

Gastroenteric disorders were the most frequent adverse drug reactions (ADRs) for the patients with COVID-19[44]. There is still a lack of specific treatment for COVID-19. Most anti-COVID-19 therapies are supportive and symptomatic treatments. Numerous drugs and chemical or biological entities have been reported as inhibitors of SARS-CoV-2 or the cures of COVID-19. Those drugs, including interferon, ribavirin, arbidol (umifenovir), lopinavir/ritonavir, hydroxychloroquine/chloroquine, azithromycin, remdesivir, *etc*. are controversial for their unproven and contradictory anti-COVID-19 effects[45]. Nevertheless, those drugs have been associated with many ADRs, of which gastrointestinal reaction are the most common[46]. Some researchers analyzed 1452 ADRs caused by antiviral agents named ribavirin, chloroquine phosphate, arbidol, and lopinavir/ritonavir and revealed that all four drugs can induce gastroenteric manifestations[47]. Gastroenteric ADRs are very common among lopinavir/ritonavir or arbidol treated patients (46.50% and 45.71%, respectively)[47,48] and less common among ribavirin or chloroquine phosphate treated patients (17.63% and 2.99%, respectively)[47]. Remdesivir can induce diarrhea, nausea, and vomiting in 3% to 9% and 3% to 5% of patients with COVID-19[49,50]. The pathology and mechanism of COVID-19 treatment-associated gastroenteric manifestations are still not revealed. Hydroxychloroquine can alter gut microbiota[51], but its correlation with gastroenteric symptoms is still not clear.

**Management of COVID-19-associated gastroenteric manifestations**

There is still no report or guideline on the treatment of COVID-19-associated gastroenteric manifestations[20]. Supportive and symptomatic therapies are suggested for the management of COVID-19-associated gastroenteric manifestations. Supportive care includes the intake of nutrients, calories, fluid, and salt to maintain balance. For patients with mild dehydration, oral rehydration is enough. But for patients with severe dehydration, intravenous rehydration should be considered. For symptomatic treatments, antiemetic drugs, such as metoclopramide and ondansetron, are suggested for patients with nausea and vomiting. Antidiarrheal medicines, like loperamide, are suggested for patients with diarrhea[20]. Intestinal microecological agents may help to mitigate the symptoms induced by the disorder of intestinal bacteria[52-54].

**CONCLUSION**

Gastroenteric manifestations, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding, can be found in most COVID-19 patients, which appears to be associated with worse clinical outcomes. More patients with gastrointestinal symptoms were hospitalized compared with patients without gastrointestinal symptoms[55]. Because most gastroenteric symptoms are milder than respiratory symptoms, physicians may underestimate the risk of it. In addition, anti-COVID-19 treatments can induce gastroenteric disorders independently. The merging of SARS-CoV-2 infection-induced manifestations and COVID-19 treatment-induced manifestations may worsen the situation of patients with COVID-19. Timely supportive or symptomatic treatment and withdrawal of ADR-inducing drugs should be considered (Figure 1).

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**Figure Legends**



**Figure 1 The causes, symptoms, and management of coronavirus disease 2019 patients with gastroenteric manifestations.** Both the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the treatments of coronavirus disease 2019 (COVID-19) can induce gastroenteric manifestations. Those symptoms include anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding. Supportive or symptomatic treatments should be considered for patients with the above-mentioned disorders. The administration of drugs, which may cause those adverse drug reactions, should be discontinued.



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