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**Digestive system involvement of SARS-CoV-2 and other coronaviruses infection: Clinical manifestations and potential mechanisms**

Zhan GF *et al*. COVID-19 and digestive system

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**Abstract**

Although Coronavirus (CoV) infection is often characterized by its respiratory symptoms, the virus can also affect the extrapulmonary symptoms, especially the symptoms related to the digestive system. The outbreak of coronavirus disease 2019 (COVID-19) is currently the world’s most pressing public health threat and has a significant impact on civil societies and the global economy. The occurrence of digestive system symptoms in COVID-19 patients is closely related to the development and prognosis of the disease. Also, there are no specific antiviral drug and vaccine approved to treat COVID-19 to date. Therefore, we elaborate on the effects of CoVs and the potential underlying mechanisms on the digestive system.

**Key Words:** SARS-CoV-2; Gastrointestinal diseases; Liver dysfunction; COVID-19; Coronavirus; Mechanisms

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**Core Tip:** In this review, it was reported that coronaviruses infection can cause a series of digestive diseases, and may also be accompanied by digestive manifestations and abnormal digestive function. Furthermore, the potential mechanisms of coronavirus disease 2019 on the digestive system, such as angiotensin-converting enzyme 2, immune injury, gut microbiota, hypoxemia and psychological stress, were also exhibited. This review provides a new perspective for the prevention and treatment of severe acute respiratory syndrome coronavirus 2 and other Coronavirus infection.

**INTRODUCTION**

In December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (previously called 2019-nCoV), initially emerged in Wuhan, China, has posed a serious threat to human health worldwide. The World Health Organization has declared that COVID-19 is a public health emergency of pandemic proportions[1]. As of 9 December 2020, a total of 67780361 Laboratory-confirmed cases including 1551214 deaths have been reported in 220 countries, areas and territories[1]. The COVID-19 pandemic is currently the world’s most pressing public health threat and has a significant impact on civil societies and the global economy.

It is well established that most people with COVID-19 infection presented with fever and typical respiratory symptoms, such as cough and dyspnea, similar to that of SARS and Middle East respiratory syndrome (MERS)[2-5]. Therefore, nasopharyngeal and oropharyngeal swabs are the suitable samples for Reverse-transcriptase polymerase chain reaction detection of SARS-CoV-2. However, concurrent extra-pulmonary symptoms, such as gastrointestinal manifestations, mainly includes diarrhea, nausea, vomiting, abdominal pain and anorexia, have also been illustrated in recent studies[6,7]. In addition, it has been reported that rectal swabs and stool specimens of COVID-19 patients has been tested positive for SARS-CoV-2, and the virus remained detectable even after the clearance of the virus in respiratory tract[7-10]. Furthermore, Pan *et al*[11] demonstrated that patients with digestive symptoms have a longer time from onset to admission and a worse prognosis than that of those without digestive symptoms[11]. Together these indicate that SARS-CoV-2 can infect and replicate in the gastrointestinal tract, and it may also have potential to cause the damage of digestive system. With the now ongoing COVID-19 pandemic, those studies are of great guiding significance for disease prevention, control and management. The present review aims to provide insight into the epidemiology, gastrointestinal characteristics, possible mechanisms and the potential therapeutic strategy in patients infected with Coronaviruses (CoVs) from the perspective of digestive system (Figure 1).

**Effects of CoVs on digestive system**

CoVs are a group of enveloped, positive-sense, single-stranded RNA viruses (+ssRNA) with a crown-like appearance, which belongs to the family Coronaviridae of order Nidovirale[12,13]. CoV harbors the largest genome among those known RNA viruses, with a genome length ranging from 26-32 kilobases (kb) and a diameter in the range of 120-160 nm[14-16]. CoVs are genetically classified into four genera: *Alpha-coronavirus*, *Beta-coronavirus*, *Gamma-coronavirus* and *Delta-coronavirus*[12,17]*. Alpha-coronavirus* and *Beta-coronavirus* primarily infect mammals, whereas *Gamma-coronavirus* and *Delta-coronavirus* usually infect birds[16]. To date, seven coronavirus species have been identified to cause diseases in human, which include the following two genera: *Alpha-coronavirus* (HCoV-NL63 and HCoV-229E) and *Beta-coronavirus* (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2)[18].

Human CoVs of NL63, 229E, OC43 and HKU1 are associated with mild common cold symptoms, whereas the other three highly pathogenic CoVs have caused large-scale pandemic since the beginning of the 21st century: SARS-CoV in 2002 and 2003, MERS-CoV in 2012 and the newly emerged SARS-CoV-2[19]. The three highly contagious pathogens are zoonotic in origin and then cross the species barrier to human, also, these three viruses are known to cause digestive symptoms.

***CoVs and digestive manifestations***

**SARS-CoV:** SARS-CoV have the large RNA genome length of 27.9 kb, emerged in the Guangdong Province of China and then spread to 29 countries and areas with a total of 8098 Laboratory-confirmed cases and causing 774 deaths (case-fatality rate: 9.6%) by the end of the epidemic in July 2003[20]. SARS-CoV was suggested to originate from bats and the intermediate hosts are unequivocally market palm civets and racoon dogs[21].

SARS is characterized by fever and respiratory complications, it may also lead to acute respiratory distress syndrome and multiple organ failure in severe cases, meanwhile, gastrointestinal manifestations are frequently observed in patients with SARS-CoV infection[22]. The tropism of SARS-CoV in digestive system are commonly known, and that a retrospective study demonstrated that 38.4% of patients with SARS had diarrhea, usually within the first week during the course of the disease[23]. It was also demonstrated that up to 60% of patients with SARS suffering from liver impairment, and SARS-CoV was detected in liver tissue although viral inclusions were not observed[24]. In addition, the proportion of SARS-CoV RNA positivity in collected stool specimens increased progressively and peaked at day 11 of the illness, with viral RNA still remained detectable in a stool sample in a patient even after 73 d after symptom onset[23,25]. Furthermore, the presence of SARS-CoV RNA in the gastrointestinal tract may point out a poor prognosis, also, the viral load in stool is correlated with death[26].

**MERS-CoV:** MERS-CoV have the large RNA genome length of 30.1 kb, emerged in the Saudi Arabia and then spread to 27 countries and areas with a total of 2494 confirmed cases and including 858 associated deaths (case-fatality rate: 34.4%) by the end of November 2019[27]. MERS-CoV originated from bats, but the intermediate host is likely dromedary camels[28].

It was reported that the human-to-human transmission of MERS-CoV occurred mainly through nosocomial transmission[29]. Although most patients with MERS-CoV infection present with nonspecific respiratory symptoms, such as fever, cough and shortness of breath. There were approximately a third of patients with MERS have gastrointestinal symptoms, such as diarrhea, vomiting and abdominal pain, which were the most commonly demonstrated extrapulmonary clinical features[30]. In addition, MERS-CoV RNA was detected in 14.6% of stool specimens from those patients with MERS, the positive rate of virus detection was lower than that of SARS[31,32]. Meanwhile, an in-vitro study showed that MERS-CoV could successfully replicate in human primary intestinal epithelial cells[33].

**SARS-CoV-2:** SARS-CoV-2 contains a genome length of 29.9 kb, shares approximately 79% genetic sequence identical to the SARS-CoV and the similarity of the whole-genome to BatCoV RaTG13 (a bat coronavirus detected in *Rhinolophus affinis*) is up to 96.2%[34]. Recent studies showed that bats may probably the natural reservoir of SARS-CoV-2, and there may be multiple potential intermediate hosts, such as pangolins, minks and snakes[35-37]. In terms of the current epidemic situation, the case fatality of COVID-19 may not reach to such a high level as SARS and MERS.

The majority of patients with COVID-19 exhibit mild to moderate pulmonary symptoms, and the reach of SARS-CoV-2 can extend to multiple extra-pulmonary organs including heart, brain, kidneys, liver and gut. Based on the data we collected in Table 1, 6.7% of the total patients with SARS-CoV-2 infection suffered from diarrhea and there are such a great number of patients had abnormal liver function with a paucity of concurrent or isolated pre-exiting digestive system comorbidities. It was reported that COVID-19 patients with diarrhea presented severe symptoms of pneumonia compared to that of those without diarrhea, and of those COVID-19 patients with gastrointestinal manifestations or liver injury were far more likely to require mechanical ventilation and hospitalization in intensive care unit (ICU)[7,38-40]. Followed by the positive SARS-CoV-2 RNA detected in stool of the first case of COVID-19 patient in the United States, it was recently reported that viral RNA was detected in 59% of patients with COVID-19 in stool samples and the SARS-CoV-2 lasts significantly longer in stool samples than in respiratory and serum specimens[41,42]. In addition, To and colleagues demonstrated that SARS-CoV-2 could be detected in the self-collected saliva specimens in 91.7% of COVID-19 patients[43]. Furthermore, autopsy studies demonstrated that varying degrees of degeneration, necrosis and shedding were found in the gastrointestinal mucosal of COVID-19 patients and the small intestine presented with segmental dilatation and stenosis[44,45]. Taken together, it is therefore likely that SARS-CoV-2 posing a serious threat to digestive system.

***Digestive diseases related to CoVs infection***

Digestive diseases include a series of disorders that affect the oropharynx and digestive tract, liver and biliary system, and pancreas, affecting human lives commonly. At the beginning of the COVID-19 outbreak, more medical resources were freed up to control the spread of the virus so that more people can be protected, meanwhile, it is safe for most patients with pre-existing diseases. However, it may also increase the relative risk of complications caused by delayed screening, diagnosis and treatment, and afraid of seeking medical attention[46]. Besides, with the now ongoing COVID-19 pandemic, challenges of the most common pre-existing digestive diseases encountered are described below.

***Liver diseases***

Hepatitis refers to inflammation of the liver caused by multiple pathogens (virus, bacteria, drugs and autoimmune factors and so on), which can even progress to fibrosis, cirrhosis and liver cancer, posing a great threat to human health. The most common cause of hepatitis are the five main hepatitis virus (types A, B, C, D, E)[47]. A number of studies have reported that hepatitis occurred in SARS and COVID-19 patients[7,11,48,49]. SARS patients with hepatitis B infection were more likely to develop severe hepatitis, similar to this, it was also been found that severe cases of COVID-19 were more prone to infect HBV than that of non-severe cases[48,50]. Collectively, these findings showed that CoVs might play a significant role in hepatitis, although detailed studies are greatly needed.

Fatty liver disease is a spectrum of disorders characterized by predominantly macrovesicular hepatic steatosis, present a condition of excess fat stored in the liver, including non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (ALD). Patients with hypertension, diabetes, obesity and elder age were more prone to develop severe COVID-19[51], those comorbidities also increase the risk for NAFLD, thus lead to liver injury. The ongoing pandemic of COVID-19 has a huge number of negative effects on individuals, especially those who encountering job loss, financial strain, the death of a loved one and so on. Under these stressors, people’s consumption of alcohol is likely to increase[52]. Therefore, COVID-19 is likely to have a long-lasting impact in ALD.

Given that patients with liver cirrhosis and cancer have a higher risk of infection due to the immunocompromised status[53], hence, preventing infection with SARS-CoV-2 is indeed necessary. Xiao and colleagues designed a subject and showed that none of the participants implemented with precautionary and protective measures had clinical symptoms suggestive of SARS-CoV-2 infection, whereas 17% of the 101 patients with decompensated cirrhosis with no relative precautionary approach carried out were diagnosed with COVID-19[54]. This research suggests that there still much more we can do for preventing patients with liver cirrhosis and cancer during the epidemic of COVID-19, such as online health education and medication guidance.

It was reported that the outbreaks of SARS and MERS might potentially increase the risk of transmission of viral infection from donors to recipients and thus even lead to death[40,55]. Tzedakis *et al*[56] reported that the local liver transplant center decreased transplant activity by 60% since the COVID-19 pandemic and it is crucial and necessary to balance costs and benefits in performing a liver transplant[56]. During the special period, all those donors and recipients for liver transplant must be screened for the presence of SARS-CoV-2 in order to assure the safety and success of the liver transplantation.

***Gastrointestinal diseases***

Ulcerative colitis and Crohn's disease are two major idiopathic inflammatory bowel disorders (IBD), which could cause prolonged inflammation of the gastrointestinal tract[57]. Patients with IBD using immunosuppressive and biologics agents are more susceptible to opportunistic and severe infections[58,59]. Therefore, it was reasonable to be concerned that COVID-19 patients comorbid with IBD may be more severe, although there were no direct clinical evidence to prove it. An and colleagues showed that none of the 318 IBD patients (204 with ulcerative colitis and 114 with Crohn‘s disease) have been reported to be infected with SARS-CoV-2 followed by early effective warning and protective measures[60]. In addition, patients with cancer are also more prone to infection[61]. Furthermore, it was demonstrated that individuals with cancer might have a high risk of severe events when suffering COVID-19 and encountered a poorer prognosis[62]. Although whether patients with gastrointestinal cancer are more susceptible to SARS-CoV-2 infection remains unknown, effective precautionary approaches is necessary in order to better protect patients.

**Possible mechanisms of COVID-19 on the digestive system**

It has been commonly known that respiratory droplets and direct contact are the two major transmission pathways of SARS-CoV-2, while a recent study performed by Liu and colleagues showed the potential for aerosol transmission[63]. A large number of studies have reported gastrointestinal symptoms and liver dysfunction in patients with SARS-CoV-2 infection. At the same time, SARS-CoV-2 could be detected in rectal swabs and stool specimens in patients with COVID-19[7,10]. Also, biopsy and autopsy reports have revealed that COVID-19 will cause pathological changes in the digestive system. In addition, highly concentration of airborne SARS-CoV-2 were observed in toilet room where gathering with COVID-19 patients in Fangcang Hospital[63]. Taken together, these research evidence provide a theoretical basis for the spread of COVID-19 through the faecal-oral route, although there is no direct evidence for the transmission pathway so far.

The digestive tract communicates with the outside world directly, similar to the respiratory tract. Therefore, SARS-CoV-2 have the opportunity to enter the gastrointestinal tract and lead to direct cytopathic effect by local replication. In addition, systemic responses to excessive immune inflammation induced by SARS-CoV-2 infection may also cause indirectly lesion to digestive system. However, the mechanisms of how COVID-19 affect digestive system remains poorly known. Furthermore, there are also no specific antiviral drug and vaccine approved to treat COVID-19 to date, it is particularly urgent to find the potential therapeutic strategies for the treatment of COVID-19.

***Angiotensin-converting enzyme 2 and transmembrane serine protease 2***

Angiotensin-converting enzyme 2 (ACE2) is a well-known receptor located in various organs for regulating cardiovascular disease through the renin-angiotensin system, eliciting a major role in regulating hypertension and anti-atherosclerosis mechanisms[64,65]. In recent two decades, the role of ACE2 in SARS-CoV and influenza virus infection as a target functional receptor attract widespread attention[66-68]. It has been reported that the entry of SARS-CoV-2 into the host cell depends on the binding of viral Spike (S) proteins to the SARS-CoV receptor ACE2 followed by the Transmembrane Serine Protease 2 (TMPRSS2) for the S Protein priming[69]. Therefore, human cells co-expressing of ACE2 and TMPRSS2 are susceptible to SARS-CoV-2 infection[70]. Recent study performed by Zhang and colleagues demonstrated that higher expression of ACE2 and TMPRSS2 exists in type II alveolar cells than that of type I alveolar cells in the lung, besides, co-expression of ACE2 and TMPRSS2 was also found in the glandular cells of upper oesophageal and absorptive enterocytes of ileum and colon[70,71]. Intestinal epithelial cells can act as a barrier and help to coordinate immune responses when suffering microbial infections[72]. A number of studies reported that absorptive enterocytes can be damaged or developed malabsorption and intestinal secretion abnormalities due to coronavirus, rotavirus infection, and thus resulting in diarrhea and vomiting[73,74]. Therefore, gastrointestinal manifestations of COVID-19 patients might be associated with the infected enterocytes co-expressing ACE2 and TMPRSS2. Moreover, co-expression of ACE2 and TMPRSS2 was observed in cholangiocytes while absent in hepatocytes[75]. Cholangiocytes play a pivotal role in liver regeneration and immune responses, and lesion of cholangiocytes may cause a variety of diseases and even lead to liver failure[76]. Therefore, we can preliminarily conclude that the abnormal liver function in patients with COVID-19 may not be caused by the virus infection of hepatocytes directly, but may be caused by damage to cholangiocytes. Of course, liver damages may also be caused by other factors, such as drug used in the treatment or systemic inflammatory response.

Compared with control mice, ACE2 knock-out mice are more susceptible to induced colitis while treatment with chemical irritants[77]. The expression of ACE2 protein is downregulated after virus entry, which may worsen the digestive symptoms. Recently, studies demonstrated that the fusion protein of human recombinant ACE2 (hrACE2) with the Fc fragment of the human immunoglobulin IgG1 shows high affinity binding to the receptor-binding domain (RBD) of SARS-CoV-2 and potently neutralized SARS-CoV-2 *in vitro*[78,79]. A newly online published report in *Nature* demonstrated that CB6, a neutralizing monoclonal antibody (MAb) isolated from a convalescent COVID-19 patient, was able to block the binding of soluble SARS-CoV-2 RBD with ACE2 receptor, showed inhibitory effect to SARS-CoV-2 infection *in vitro* and rhesus monkeys[80]. Additionally, a recent *in vivo* study reported that hrACE2 could block the early stages of SARS-CoV-2 infection in the organoid level of engineered human blood vessels, kidneys and small intestinal enterocytes[78,81]. Moreover, a serine protease TMPRSS2 inhibitor has been approved for clinical use to block the entry of CoVs[69]. Taken together, it is therefore likely that ACE2 and TMPRSS2 may be the potential targets for prevention and treatment of the COVID-19 patients with digestive symptoms.

***Immune injury***

Immune injury plays an important role in the occurrence, development and prognosis of digestive system diseases[82-84]. A growing body of studies suggest that patients with severe COVID-19 can activate innate and adaptive immune responses, increase serum levels of pro-inflammatory cytokines and chemokines including interleukin (IL)-6, IL-1β, IL-2, IL-10, tumour necrosis factor α, interferon-gamma-inducible protein-10 (CXCL10), monocyte chemoattractant protein-1, and granulocyte-macrophage colony stimulating factor, and even induce systemic inflammatory response syndrome and cytokine storm, thus leading to local and systemic tissue damage[40,85,86]. Concentrations of IL-6 was significantly different between patients with mild and severe COVID-19, and elevated IL-6 was found to be a stable indicator of adverse outcomes for severe COVID-19 patients. A clinical trial (ChiCTR2000029765) which explore the potential therapeutic effect of IL-6 receptor-targeted mAb in patients with severe COVID-19, showed that effectiveness of controlling fever and improving respiratory function quickly[87]. It has been reported that vagus nerve stimulation (VNS) can exert anti-inflammatory effects *via* activation of the cholinergic anti-inflammatory pathway[88,89]. Based on preliminary observations and a scientific and clinical foundation, it was speculated that VNS may play a vital role in improving the prognosis of COVID-19 patients[90]. Additionally, patients with severe COVID-19 are more frequently had lymphopenia, as well as drastically decreased numbers of CD4+ and CD8+ T cells than that of moderate cases. Furthermore, support for inflammation-mediated gastrointestinal tissue damage in patients with COVID-19 is provided by the histopathological evidence of diffuse endothelial inflammation in the small intestine submucosa[91]. It was also been confirmed by the presence of numerous infiltrating plasma cells and lymphocytes with interstitial edema in the lamina propria of the stomach, duodenum, and rectum of patients with COVID-19[10].

***Gut microbiota***

The human intestine harbors nearly 100 trillion (1014) microorganisms and is composed of more than 1000 different bacterial species, including but not limited to bacteria, fungi and virus[92,93]. It is known that gut microbiota plays a vital role in a variety of diseases, including digestive, metabolic system, respiratory diseases, and even neuropsychiatric diseases[94-96]. Additionally, many studies have reported that chronic respiratory diseases and pneumonia can not only change the airway microbiota, but also alter the gut microbiota indirectly through circulatory and lymphatic systems[97-100]. SARS-CoV-2 may cause the down-regulation of the expression of ACE2 in the intestine, which affects the absorption of tryptophan, resulting the disturbance of the gut microbiota and possibly influence intestinal inflammation[101,102]. Xu *et al*[103] indicated that some patients with COVID-19 showed gut microbial dysbiosis with decreased abundance of *Lactobacillus* and *Bifidobacterium*[103]. Zuo *et al*[104] showed that the increased levels of *Coprobacillus*, *Clostridium hathewayi* and *Clostridium ramosum* were positively correlated with the susceptibility and severity of COVID-19[104]. Furthermore, studies have shown that short-chain fatty acids, the most critical metabolites of the gut microbiota, play an important role in reducing the intestinal pH and maintaining the integrity of intestinal epithelium, as well as enhancing the host systemic immunity[105-107]. The use of antibiotics is a common treatment for COVID-19, however, it can also perturb the composition of the human gut microbiota profoundly[108]. Guidance from China’s National Health Commission and National Administration of Traditional Chinese Medicine demonstrated that the use of probiotics has a good curative effect in patients with severe SARS-CoV-2 infection. Taken together, improvement of the composition of the gut microbiota and its metabolites may be a potential strategy for the treatment of COVID-19.

***Hypoxemia***

After SARS-CoV-2 infects the lungs, it will cause inflammation and edema of the pulmonary parenchyma and interstitium, which in turn affects alveolar gas exchange, thereby leads to hypoxemia[109]. Hypoxemia can cause metabolism and normal physiological dysfunctions in various tissues and organs including the digestive system. Long-term hypoxemia can cause cell necrosis, which in turn leads to damage to the gastrointestinal mucosal cells, leading to ulceration and bleeding.

***Psychological stress***

Psychological stress has a profound influence on digestive system, such as altering the intestinal motility, increasing the gastrointestinal permeability, and changing the composition of intestinal microbiota[110]. A study on active Weibo users showed that people were more concerned about their health and showed more negative emotions, such as anxiety and depression after the outbreak of the COVID-19[111]. Quarantine is an effective measure to protect people from contagious patients and those who are at risk of infection, however, it may also increase negative psychological stress[112]. Taken together, digestive diseases and symptoms of COVID-19 patients may be partially caused by psychological stress.

***Others***

Multiple lines of evidence have shown that some patients with COVID-19 have digestive system symptoms, such as nausea, vomiting and anorexia, which indirectly reflect the impairment of the dorsal vagal complex[6,113,114]. One of the possible mechanisms is that the neurotropic virus retrogrades along the vagus nerve once the virus enters the vagal nerve endings, thus damaging the brainstem[115]. Also, with or without crossing the Blood-brain barrier, the virus may reach the brainstem through the circulatory system[113].

**CONCLUSION**

CoVs infection can cause a series of digestive diseases, and may also be accompanied by digestive manifestations and abnormal digestive function. Although it is still unknown whether the SARS-CoV-2, which causes abnormalities in the digestive system, enters the digestive system directly or indirectly affects the digestive system, it is necessary to take early measures to prevent the spread of the virus through the fecal-oral transmission. In addition to ACE2 and immune injury, gut microbiota, hypoxemia, psychological stress, etc*.* may also targets for future intervention and treatment of digestive system damage caused by COVID-19. Further research is warranted to elucidate the relationship between the COVID-19 and the digestive system.

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**Figure Legends**



**Figure 1 Possible mechanisms of coronavirus disease 2019 on the digestive system.** ACE2: Angiotensin-converting enzyme 2; CXCL10: Interferon-gamma-inducible protein-10; GM-CSF: Granulocyte-macrophage colony stimulating factor; IL: Interleukin; MCP: Monocyte chemoattractant protein; SIRS: Systemic inflammatory response syndrome; TMPRSS2: Transmembrane serine protease 2; TNF: Tumour necrosis factor.

**Table 1 Presentation of gastrointestinal symptoms, abnormal liver function and pre-existing digestive diseases in patients with severe acute respiratory syndrome coronavirus 2 infection**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patients with COVID-19** | **Gastrointestinal symptoms** | **Patients with abnormal biochemical indicators of liver function** | **Patients with pre-existing digestive diseases** | **Patients tested positive for SARS-CoV2 in stool or rectal swab specimens** |
| **Diarrhoea** | **Nausea and vomiting** | **Abdominal pain** |
| Guan *et al*[7] | 1099 | 42 (3.8%) | 55 (5.0%) | NA | Abnormal AST: 168/757 (22.2%). Abnormal ALT: 158/741 (21.3%). Abnormal TBIL: 76/722 (10.5%) | CHB: 23 (2.1%) | Stool specimens: 4/NA. Rectal swab: 4/NA |
| Wang *et al*[6] | 138 | 14 (10.1%) | 19 (13.7%) | 3 (2.2%) | Mild elevation of AST and ALT | 4 (2.9%) | NA |
| Huang *et al*[40] | 41 | 1/38 (2.6%) | NA | NA | Abnormal AST: 15 (31.0%) | Chronic liver disease: 1 (2%) | NA |
| Fan *et al*[116] | 148 | 6 (4.1%) | 3 (2.0%) | NA | Abnormal AST: 32 (21.6%). Abnormal ALT: 27 (18.2%). Abnormal TBIL: 9 (6.1%) | 9 (6.1%) | NA |
| Cai *et al*[49] | 298 | 9 (3.0%) | NA | NA | Abnormal AST: 25 (8.4%). Abnormal ALT: 39 (13.1%). Abnormal TBIL: 24 (8.1%) | CHB: 5 (1.7%). NAFLD: 14 (4.7%). ALD: 9 (3.0%) | NA |
| Chen *et al*[3] | 99 | 2 (2.0%) | 1 (1.0%) | NA | Abnormal AST: 35 (35.0%). Abnormal ALT: 28 (28.0%). Abnormal TBIL: 18 (18.0%). Abnormal albumin: 97 (98.0%) | NA | NA |
| Holshue *et al*[41] | 1 | 1 | 1 | NA | Abnormal AST: 1. Abnormal ALT: 1. Abnormal TBIL: 1. Abnormal albumin: 1 | NA | Stool specimens: 1/1  |
| Zhang *et al*[117] | 140 | 18/139 (12.9%) | 31/139 (22.3%) | 8/139 (5.8%) | NA | FLD and abnormal liver function: 8 (5.7%). Chronic gastritis and gastric ulcer: 7 (5.0%). Cholelithiasis: 6 (4.3%) | NA |
| Xiao *et al*[10] | 73 | 26 (35.6%) | NA | NA | NA | NA | Stool specimens: 39/73 (53.4%) |
| Zhou *et al*[118] | 191 | 9 (4.7%) | 7 (3.7%) | NA | Abnormal ALT: 59/189 (31.2%) | NA | NA |
| Zhang *et al*[119] | 82 (Deaths) | 10 (12.2%) | 2 (2.3%) | NA | Abnormal AST: 44/72 (61.1%). Abnormal ALT: 22/72 (30.6%). Abnormal TBIL: 22/72 (30.6%). Abnormal albumin: 56/72 (77.8%) | Liver disease: 2/82 (2.4%) | NA |
| Xu *et al*[120] | 62 | 3 (4.8%) | NA | NA | Abnormal AST: 10 (16.1%) | Liver disease: 7 (11.3%) | NA |
| Chen *et al*[121] | 21 | 4/20 (20.0%) | NA | NA | Abnormal AST: 6 (28.6%). Abnormal albumin: 8 (38.1%) | NA | NA |
| Pan *et al*[11] | 204 | 29 (14.2%) | 8 (3.9%) | 4 (2.0%) | Abnormal AST: NA. Abnormal albumin: NA | CHB: 1 (0.5%). FLD: 1 (0.5%). Gastritis: 1 (0.5%) | NA |
| Luo *et al*[122] | 1141 | 68 (5.9%) | Nausea: 134 (11.7%). Vomiting: 119 (10.4%) | 45 (3.9%) | Mild elevation of AST and ALT | NA | NA |
| Total | 3738 | 174/2592 (6.7%) |  |  |  |  |  |

ALD: Alcoholic fatty liver disease; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; COVID-19: coronavirus disease 2019; FLD: Fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; TBIL: Total bilirubin.