

# Gastrointestinal and Liver Manifestations of COVID-19



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**The worldwide pandemic of COVID-19, caused by the virus SARS-CoV-2 has continued to progress, and increasing information is becoming available about the incidence of digestive symptoms as well as abnormal liver-associated enzymes in patients who are infected. These are postulated to be related to the virus's use of ACE-2 receptors located on certain intestinal cells, cholangiocytes, and hepatocytes. This brief review summarizes the available limited data on digestive manifestations of COVID-19. A significant proportion of COVID-19 patients can present initially with only digestive complaints. The most common digestive symptoms are anorexia, nausea, vomiting, and diarrhea. Liver-related transaminases are elevated in a substantial proportion of patients, although generally only mildly elevated. Currently there is no firm evidence to suggest that severity of digestive symptoms corresponds to severity of COVID-19 clinical course, however, more severe alterations in liver enzymes may correlate with worse clinical course. Given use of antiviral and antibacterial agents in sicker patients, drug-induced liver injury cannot be ruled out either in these cases. Although viral RNA can be detected in stool, it is unclear whether fecal-oral transmission can be achieved by the virus. As further data becomes available, our understanding of the digestive manifestations of COVID-19 will continue to evolve. (J CLIN EXP HEP-ATOL 2020;10:263–265)**

The virus known as SARS-CoV-2, which causes the disease COVID-19, has caused a global pandemic in a few short months.<sup>1</sup> As of March 29, 2020, there have been over 634,885 confirmed cases globally, and over 29,997 reported deaths worldwide. Although the virus primarily presents as a lower respiratory tract infection and is transmitted via respiratory droplets, there are multiple gastrointestinal and hepatic manifestations of the disease. This brief review summarizes the available limited data on digestive manifestations of COVID-19.

Many parallels in virology can be made between the current SARS-CoV-2 pandemic and prior epidemics related to coronavirus, including the SARS-CoV outbreak of 2002–2003. During that epidemic, up to 73% of patients had diarrhea, generally within the first week of the illness.<sup>2</sup> The pathophysiologic mechanism postulated for this, as well as for the occurrence of digestive symptoms during the current SARS-CoV-2 pandemic, is thought to be related to the virus's strong affinity for angiotensin-converting enzyme 2 receptor which is located in multiple human cell types, including both lung AT2 cells (accounting for the virus's pulmonary toxicity), and certain enterocytes in the ileum and colon.<sup>3–5</sup> ACE2 is partly responsible for mediating inflammation, which could explain

occurrence of diarrhea. In fact, the binding efficiency is thought to be stronger for SARS-CoV-2 than the SARS-CoV-1 outbreak of 2002, which could likely explain its high rate of transmission to others.<sup>3</sup> The binding of virus to primary intestinal epithelial cells also raises the prospect of fecal-oral transmission, which is as of yet unconfirmed for SARS-CoV-2.<sup>4,5</sup>

The largest and most comprehensive study evaluating digestive signs and symptoms in patients with COVID-19 hails from the viral epicenter in Wuhan, where investigators retrospectively reviewed all 1141 cases admitted to a single hospital over an approximately 7 week period.<sup>6</sup> This revealed that 16% of patients presented with gastrointestinal symptoms only. Of these 183 patients, the most common symptoms included loss of appetite. Nausea and vomiting occurred in two-third of the patients, diarrhea in 37%, and abdominal pain in 25% of those who presented with GI symptoms. AST and ALT were both mildly elevated in majority of patients. Notably, the study is retrospective in nature with a relatively small sample size, thus these results may not be generalizable. However, it provides a good starting point from which the managing clinician can put the digestive symptoms of COVID-19 patients in context.

Another study characterizing the digestive symptoms of patients with COVID-19 is a cross-sectional descriptive study of 204 patients from Hubei province, China, who presented to one of 3 hospitals in January and February of 2020.<sup>7</sup> All patients were confirmed to have COVID-19 by real-time polymerase chain reaction (PCR). In this

Received: 31.3.2020; Accepted: 31.3.2020; Available online 1 April 2020

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<https://doi.org/10.1016/j.jceh.2020.03.001>

study, 99 patients (48.5%) had gastrointestinal symptoms. Of these 99 patients, the symptoms included anorexia in 83 (83.8%), diarrhea in 29 (29.3%), vomiting in 8 (8.1%), and abdominal pain in 4 (4.0%), with some patients having multiple symptoms. Most notably, in 7 cases, digestive symptoms were the only complaint with no respiratory symptoms. Unfortunately, patients with digestive symptoms had a longer time from onset of symptoms to admission, likely related to delayed diagnosis as these symptoms are non-specific.

In contrast to the above study, another study of 1099 patients from China showed that the most common symptoms on admission were fever (43.8%) and cough (67.8%).<sup>8</sup> Less common were gastrointestinal symptoms with 5% (55/1099) of patients presenting with nausea or vomiting and 3.8% (42/1099) of patients presenting with diarrhea. Similarly, in a single-center case series of 138 hospitalized patients with COVID-19 in China, 10.1% (14/138) of patients had diarrhea and/or nausea, but the proportion of patients with only digestive symptoms was not outlined.<sup>9</sup>

To date, there has not been a study of COVID-19 patients in the United States that reports on gastrointestinal symptoms. In a case series of 21 critically ill patients with COVID-19 in Washington State, the initial symptoms were shortness of breath (76%), fever (52%), and cough (48%) but the authors do not report on other symptoms.<sup>10</sup> In one of the most recent studies from China, the authors reported gastrointestinal symptoms in 74 of 651 (11.4%) patients.<sup>11</sup> Nausea, vomiting and diarrhea were the common symptoms; GI symptoms were more common with more severe Covid-19 disease (23% vs. 8.1%) and family clustering (31.1% vs. 20.5%) was also more common in those with GI symptoms. As such, more data will be necessary to gain a clearer understanding of the gastrointestinal manifestations of COVID-19. More importantly it is not known whether there is any correlation between those with gastrointestinal symptoms and worse outcomes.

Another question that is increasingly being asked in the medical community is whether SARS-CoV-2 is transmissible by the fecal-oral route.<sup>4,5</sup> The above studies did not test for RNA of the virus in the stool, so correlation cannot be made between digestive symptoms and active viral RNA replication in the digestive tract. However, a case report of a 25-year-old female who presented with respiratory symptoms and fever suggested that the virus could be excreted in feces.<sup>12</sup> Ten days after the initial presentation, she underwent real-time PCR of a pharyngeal sample that was negative for SARS-CoV-2, but a separate fecal sample was positive. Over the following 7 days she had 4 additional samples from the respiratory tract, all of which were negative for SARS-CoV-2. This suggests that her only documented source of virus was in the gastrointestinal tract, and thus may have been transmitted via the fecal-oral route, although this is not proven. In addition, the first case of COVID-19 in the United States pre-

sented with a 2-day history of nausea and vomiting along with a dry cough and passed a loose bowel movement on hospital day 2.<sup>13</sup> The stool and respiratory specimens later tested positive for SARS-CoV-2 again highlighting the possibility for viral shedding and potentially transmission in the stool. Interestingly, in a recent Singaporean study, 50% of patients with COVID-19 had SARS-CoV-2 detected in their stool samples, but detection of this did not correlate with digestive symptoms.<sup>14</sup> The duration of viral RNA after recovery was examined in a recent study.<sup>15</sup> In this study, the median time from the onset of symptoms to first negative RT-PCR test from oropharyngeal swab was 9.5 (6.0–11.0) days, but 16.7% (11/67) patients tested positive for viral RNA from stool specimens for a median of 11.0 (9.0–16.0) days after symptom onset. In addition, the duration of viral RNA in the stool was longer (20 days vs. 11 days,  $p < 0.0001$ ) in those who received glucocorticoid treatment compared non-glucocorticoid group. These observations merit further examination since there is a potential, although unproven, for fecal-oral transmission risk for many days after clinical recovery.

With regard to liver-related complications of COVID-19, a varying degree of liver test abnormalities has been described in affected patients. In one study, total bilirubin, AST and ALT was elevated in 10%, 21% and 22% of patients respectively.<sup>8</sup> Other small series have reported ALT abnormalities in 16%–53%.<sup>16–21</sup> Hitherto, no cases of acute liver failure have been reported. Liver dysfunction is seen more in patients with more severe disease upon presentation. It is difficult to separate the independent effect of viral infection from various treatment modalities, including antibiotics and experimental antiviral drugs that were utilized in these patients. In addition these changes could be nonspecific abnormalities related to the infection, sepsis or hypoxia. Other laboratory abnormalities such as leukopenia, thrombocytopenia, and creatinine kinase were more common in patients who were sicker on presentation or who died. There is no information on liver pathology except one patient who had an autopsy and this showed micro vesicular steatosis, and mild lobular and portal inflammation on liver histology.<sup>22</sup>

Since ACE2 receptors are seen in the hepatocytes and cholangiocytes, it is not surprising that the liver is also involved with COVID-19 infection, as there may be an up-regulation of ACE2 receptors in the presence of this viral infection.<sup>23</sup> Interestingly, cholestatic pattern is rarely seen with this infection and most reports suggest that alkaline phosphatase is normal. The cytokine storm and ischemic hypoxic reperfusion also may play a role in those with severe hepatocellular damage. Underlying liver diseases such as chronic hepatitis B could have contributed to elevated liver enzyme abnormalities as most of these studies are reported from China, which has a high prevalence of hepatitis B. Further characterization of liver injury and its independent role in mortality will be defined in future

studies. Until then, physicians need to be cautious when using experimental drugs in these patients as many of these drugs are likely to be eliminated by the liver.

As can be seen with this brief review of limited available data, the gastrointestinal and hepatic manifestations of COVID-19 are protean, and as data continue to be published on this pandemic, clinicians will gain a better understanding of this disease. However, it is clear with the current data that digestive symptoms and abnormal liver-associated enzymes play a prominent role in a significant number of patients, and in some small number of cases, may in fact be the only presenting feature. Thus we must be vigilant in considering COVID-19 even in the atypical patients, as confirmation of more patients at time of presentation will prove critically in stemming the growth of this pandemic.

## CONFLICTS OF INTEREST

The authors have none to declare.

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