

# How is the digestive system affected by coronavirus disease?

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared the sixth public health emergency of international concern by the World Health Organization.<sup>1,2</sup>

Besides the typical symptoms related to respiratory symptoms, gastrointestinal (anorexia, nausea, vomiting, abdominal pain, and/or diarrhea) and hepatic manifestations (abnormal liver enzymes) have been reported in patients with COVID-19,<sup>1</sup> with pooled prevalence rates of 15% and 17%, respectively, based on a recent meta-analysis.<sup>3</sup> These symptoms imply higher disease severity and risk of complications. Furthermore, these non-respiratory symptoms mislead physician assessment and delay diagnosis of COVID-19.<sup>3</sup>

Owing to the low disease incidence of COVID-19 in Taiwan, statistical data regarding gastrointestinal or hepatic symptoms are limited. However, differences in epidemiology between Occidentals and Orientals were reported. Diarrhea, nausea/vomiting, and liver abnormalities were more prevalent in nations other than China.<sup>1</sup>

As it shares similar receptor-binding domain structure with SARS-CoV, SARS-CoV-2 also infects human cells through the binding of the receptor-binding domain to the human angiotensin-converting enzyme 2 (ACE2) receptor.<sup>4</sup> ACE2 receptors are expressed in type II alveolar (AT2) cells of the lung, which leads to the devastating respiratory symptoms after SARS-CoV-2 infection. Besides the respiratory system, ACE2 receptors are highly abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia, which explains the gastrointestinal symptoms in SARS-CoV-2.<sup>1,2</sup>

Diarrhea is the most common gastrointestinal manifestation and can present in the absence of respiratory symptoms or before intervention with medications.<sup>2,3,5</sup> The specific mechanism of COVID-19-related diarrhea remains unclear, but several

hypotheses have been proposed. Viral infection may alter intestinal permeability, which results in enterocyte malabsorption.<sup>6</sup> ACE2 is essential for the expression of the amino acid transporter of the small intestine. Amino acids are important to maintain the homeostasis of the gut microbiome by regulating the secretion of antimicrobial peptides.<sup>6,7</sup>

Other gastrointestinal symptoms may be linked to the nervous system. Although less commonly presented, anosmia (loss of smell) and ageusia (loss of taste) are considered important indicators of COVID-19. Both symptoms have already proven to be particularly predictive as compared with other constitutional symptoms and listed in the diagnostic criteria.<sup>8</sup> Several kinds of viral infections may damage the olfactory epithelium. In addition, the ACE2 expression level in the olfactory epithelium is considered relatively high. Direct viral infection through the olfactory epithelium is a reasonable explanation of the early onset of anosmia among patients with COVID-19. Ageusia may be explained by consequence of olfactory dysfunction. ACE2 receptors are also widely expressed on epithelial cells of the oral mucosa. This may also lead to another explanation of the onset of ageusia.<sup>9</sup>

Abdominal pain, loss of appetite, nausea, and vomiting are all commonly reported symptoms. This phenomenon implies the possible involvement of the autonomic nervous system. The dorsal vagal complex (DVC), located in the medulla, controls several autonomic activities. The nucleus of tractus solitarius (NTS) and area postrema (AP) are components of the DVC. Human NTS is responsible for the regulation of food intake, while AP contains the emetic chemoreceptor trigger zone. These areas also have expressions of the ACE2 receptors, making them potential targets of SARS-CoV-2. One possible route for the invasion of SARS-CoV-2 to the central nervous systems is through the nasopharyngeal epithelium, olfactory nerve, and olfactory bulb. Another hypothesis is via the blood-brain barrier directly.<sup>10</sup>

Abnormal liver biochemistries have also been reported in patients with COVID-19. Most of the cases reported had mildly elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase, and lactic dehydrogenase.<sup>11</sup>

The exact pathogenesis of liver injury is still under investigation. The liver plays a crucial role in maintaining immune tolerance. However, the mechanism is interrupted by psychological stress related to severe COVID-19 infection. Overexpressed immune response and even cytokine storm have been reported among these patients. Poor oxygenation and ventilation resulting from respiratory failure or shock may lead to ischemic liver injury.<sup>2,11</sup>

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In addition, drug-induced liver injury may be a possible explanation. These patients usually receive antipyretic drugs or simultaneous administration of multiple antiviral drugs. People with preexisting hepatic illnesses are also vulnerable to recurrences due to the viral infection.<sup>2,11</sup>

Unlike gastrointestinal symptoms, ACE2 may not be a reasonable explanation of the onset of liver injury. The ACE2 expression level was low in cholangiocytes, but not in hepatocytes, Kupffer cells, and endothelial cells.<sup>2</sup> In an animal model, ACE2 upregulation was considered a compensatory proliferation of hepatocytes. In addition, patients with COVID-19 and liver injury usually present with ALT elevation instead of alkaline phosphatase. The mechanism of liver injury through cholangiocytes is not reasonable on the basis of this finding.<sup>11</sup>

Currently, no gastrointestinal or hepatic specific treatments are available. However, prolonged stool shedding and detection of the virus in the sewage system cause the concern of possible fecal-oral transmission. Proper hand hygiene may be beneficial and must be emphasized.<sup>2</sup> However, definite evidence is still lacking, and in-depth research is still needed for confirmation.<sup>1,3</sup>

In conclusion, gastrointestinal and hepatic manifestations should not be regarded as rare presentations of COVID-19. Moreover, awareness of the connection between these symptoms and poor clinical outcomes and delayed diagnosis is important. Clinicians should be careful to promptly identify a possible contact history and other suspicious symptoms (eg, fever, respiratory symptoms, and loss of taste or smell) while attending to patients with newly developed gastrointestinal symptoms. The interaction between human ACE2 and SARS-CoV-2 is a reasonable but partial explanation of the mechanism of gastrointestinal and hepatic manifestations. Gut hormones<sup>12-14</sup> and hepatokines such as bile acid and fibroblast growth factor,<sup>15</sup> which regulate appetite, nutrient absorption, and immunometabolism, may deserve further exploration. Further investigations are needed for elucidation of the comprehensive pathophysiology and possible treatments of COVID-19.

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