

Evidence of gastrointestinal disturbances in COVID-19: manifestations and theories in pathophysiology

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SARS-CoV-2, a new virus, emerged in December 2019 in Wuhan, China. It belongs to the coronavirus family and has produced an outbreak of acute respiratory infection, the main clinical presentations of which range from mild respiratory symptoms to severe pneumonia and sepsis. Due to its rapid spread around the world, and the fact that it causes thousands of deaths, the World Health Organization (WHO) has classified it as a pandemic. (1)

Studies of SARS-CoV and MERS-CoV, whose infection peaks occurred in 2003 and 2012, have demonstrated that these viruses can potentially invade the human digestive system. (2) MERS-CoV uses dipeptidyl peptidase-4 receptors in the intestinal epithelium for cellular infection which causes inflammation and degradation of this epithelium. (2)

On the other hand, SARS-CoV uses angiotensin converting enzyme II (ACEII) as the receptor for entry into cells and infection of the body. This mechanism has been same proposed for SARS-CoV-2 as well. (2) This hypothesis may be strengthened by the results of Zhang et al. whose genetic analysis has identified the expression of ACE II in various areas of the digestive tract including the esophagus, stomach, ileum and colon. (1, 3).

The ileum and the colon are the places in which greatest expression of ACE II occurs, surpassing even its expression in the lungs. The main effects occur in absorbent enterocytes. When invaded by SARS CoV-2, they produce alterations in absorption and other mechanisms that lead to diarrhea. (1, 3)

In addition, transmembrane protease serine 2, an important enzyme widely expressed at these sites in the gastrointestinal tract, (3, 4) facilitates infection by proteolytic cleavage of ACE2 receptor which promotes viral uptake, and cleavage of coronavirus spike glycoproteins which activates the glycoprotein for host cell entry. Thus, after the virus enters the cell its RNA begins to replicate which produces new virions which are released into the gastrointestinal tract. This theory has been confirmed by detection of SARS-CoV-2 RNA in stool samples up to 5 weeks after the results of respiratory samples are negative. This suggests that the fecal-oral route is a potential transmission mechanism. (5, 6)

It has also been documented that viral infections including with SARS-CoV are related to greater permeability of lipopolysaccharides and migration of intestinal bacteria which alters the lung-intestine axis. This could be immunologically involved in respiratory and digestive effects given the alteration of the microbiota of these systems. This theory may be applicable to SARS-CoV-2 because of its similarities to SARS-CoV. (1, 3, 7).

In general, patients with the 2019 coronavirus disease (Coronavirus Disease 2019, COVID-19) often develop a fever and respiratory tract involvement. (8, 9) However, gastrointestinal symptoms including diarrhea, anorexia, nausea, vomiting, abdominal pain and even gastrointestinal bleeding have been reported in infected patients. (10-12)

A retrospective study by Luo et al. that included 1,141 patients from January 1 to February 20, 2020 found that 16% (183) of these patients had gastrointestinal symptoms including loss of appetite (180), nausea (134), vomiting (119) and diarrhea (68) as their main symptoms. (9)

This is consistent with a retrospective clinical study and case review by Tian et al. which found that loss of appetite was the most common gastrointestinal symptom in adults but that vomiting was the most common in the pediatric population. However, when both groups were analyzed together, diarrhea stood out as the main finding. (8)

Similarly, a study by Guan et al. conducted from December 11, 2019 to January 29, 2020 and including a cohort of 1,099 patients from 552 hospitals in 31 provinces and municipalities in China tried to characterize the first patients diagnosed at the beginning of the COVID-19 outbreak. They documented nausea and vomiting as the main gastrointestinal manifestations. (13)

Another study by Lu et al., conducted between January 28 and February 26, identified 171 pediatric patients under the age of 16 who tested positive for the virus. Fifteen suffered from diarrhea while 11 suffered from vomiting. (14)

Notably, gastrointestinal symptoms have also been reported in pregnant women. A study by Chen et al. found that of 112 patients diagnosed with COVID-19, eight developed diarrhea. (15)

Zhang et al. found that diarrhea and vomiting appeared approximately 5 days after presentation of the first symptoms of COVID-19 in adult patients and persisted for 4 days on average. (16) Other gastrointestinal manifestations also reported by Zhang et al. in another study include abdominal pain in eight of the 139 patients analyzed. (17)

Although each of these symptoms may seem harmless, a retrospective observational study of 52 critically ill patients by Yang et al. has shown that 6% developed digestive tract bleeding raising the question of whether the infection caused the bleeding or if it worsened underlying conditions. (18) This is also related to the observation of another of hemoptysis in 5% of COVID-19 patients. (10)

In addition to gastrointestinal tract disorders, evidence suggests that the liver may also be affected although but this be due to concomitant factors such as antiviral agents and pre-existing conditions. Short term results have been inconclusive and long term evaluations have yet to conclude. (19)

The literature reports growing numbers of unusual and asymptomatic presentations of COVID-19. This provides better information for detection of possible cases. Gastrointestinal symptoms vary among populations, and extrapulmonary manifestations may appear before the characteristic respiratory symptoms associated with this infection.

Yang et al. reported the case of a 62-year-old male patient with a history of hypertension, diabetes, and hyperlipidemia who was admitted to the hospital with a clinical picture of diarrhea and fever before respiratory symptoms developed. This patient's presentation was atypical presentation for this disease. (20)

Similarly, the only respiratory symptom of a 53-year-old male patient with a history of epilepsy and a clinical picture

Table 1. Studies of gastrointestinal manifestations in COVID-19 patients

Authors	Time Interval Analyzed	Country	Number of Patients	Diarrhea	Nausea or Vomiting	Abdominal Pain	Total Patients with Gastrointestinal Symptoms
Guan et al. (13)	December 11, 2019 to January 29, 2020	China	1099	42	55	0	97
Liu et al. (24)	December 30, 2019 to January 24, 2020	China	137	11	0	0	11
Lu et al. (14)	January 28 to February 26, 2020	China	171	15	11	0	26
Wang et al. (25)	January 1 to January 28, 2020	China	138	14	19	3	36
Zhang et al. (17)	January 16 to February 3, 2020	China	139	18	31	8	57
Zhou et al. (26)	December 29, 2019 to February 1, 2020	China	191	9	7	0	16
Nobel et al. (27)	March 10 to March 21, 2020	United States	278	56	63	0	119
Yao et al. (28)	January 30 to February 11, 2020	China	108	8	0	0	8
Total			2261	173	186	11	370

of fever, malaise, and swelling was a dry cough despite the presence of a ground glass pattern in the lower part of the lobe of the left lung. (21)

Nevertheless, gastrointestinal symptoms can appear throughout the course of this disease, even after respiratory symptoms appear. An example is the case of a patient who consulted for unquantified fever and four days of coughing who later developed nausea, vomiting, diarrhea, and abdominal discomfort. (22)

Patients may also develop alterations of both the respiratory and gastrointestinal systems, as reported by Azwar et al. They documented the case of a patient who consulted for chest and epigastric pain as well as respiratory distress, nau-

sea and vomiting. (23) This may cast doubt about which factors specifically influence the effects on each system.

In summary, it is speculated that the gastrointestinal system is another that is organ directly affected by SARS-CoV-2. Health care professionals should consider a diagnosis atypical presentation of COVID-19 when extrapulmonary symptoms occur. Furthermore, evidence of viral RNA in the feces of apparently recovered patients can guide the creation of protocols for managing biological residues of these patients in order to avoid possible fecal-oral contagion.

Table 1 and **Figure 1** provide details regarding studies of gastrointestinal manifestations in patients with COVID-19. (13, 14, 24-28)

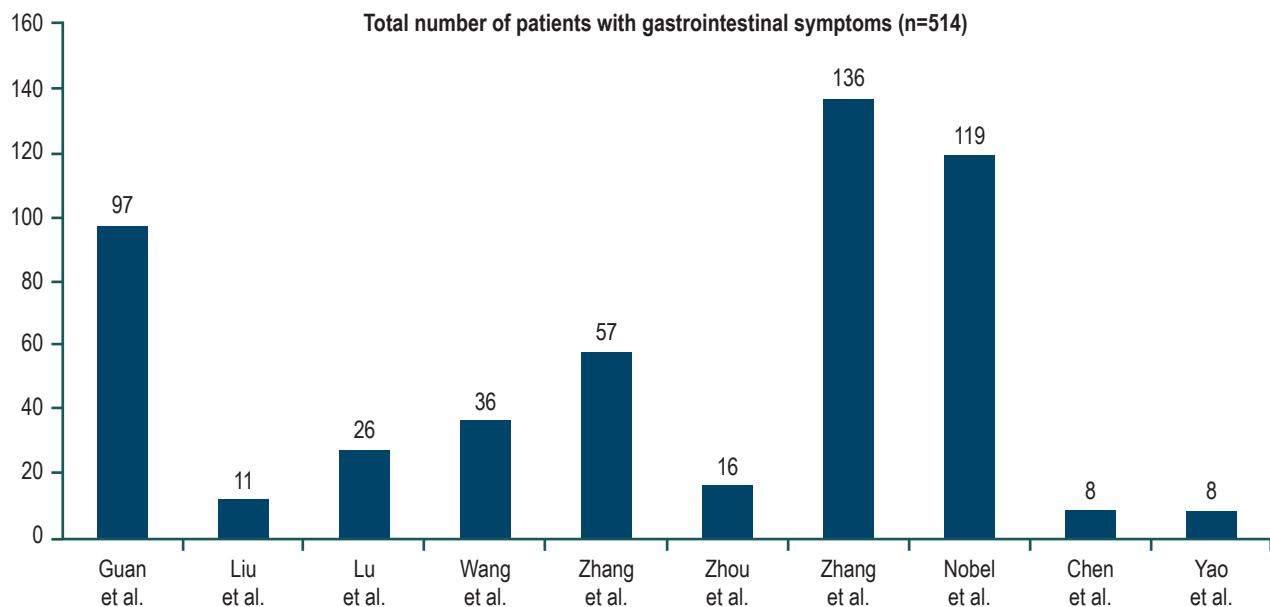


Figure 1. Total patients with gastrointestinal symptoms reported in studies.

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