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Clinical Manifestations of Gastrointestinal Symptoms in COVID-19 Patients

An Integrative Review

ABSTRACT

After the outbreak of novel coronavirus disease 2019 (COVID-19) in Wuhan, China, its spread to other countries is rapidly increasing. In this integrative review, we report the prevalence of gastrointestinal symptoms in patients with COVID-19. For this purpose, available articles on gastrointestinal manifestations in patients with COVID-19, which were reported from China, were reviewed. All reviewed articles were searched from December 11, 2019, to June 20, 2020, based on specific key words. Related findings in these articles show that the main target of COVID-19 is lung tissue, as after the virus enters the body, it mainly causes respiratory symptoms in affected patients. But in addition to respiratory symptoms, it is possible that, over time, these patients present with other symptoms, the most obvious of which are gastrointestinal symptoms. It is well documented that diarrhea and vomiting are the most common gastrointestinal symptoms in COVID-19 patients. As part of this report, we also look at the incidence and frequency of gastrointestinal symptoms in COVID-19 patients in Iran. The results can be used by providers as a guideline for better management of gastrointestinal symptoms in these patients.

In December 2019, an epidemic of pneumonia cases of unknown origin emerged in Wuhan, Hubei Province, China (Adhikari et al., 2020; Yeo, Kaushal, & Yeo, 2020; Zhu et al., 2020). This acute respiratory syndrome is now known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Gorbalenya et al., 2020). According to a World Health Organization (WHO) report, as of June 27, 2020, it has infected near 10 million individuals globally, with around 500,000 deaths (WHO, 2020a). The WHO has recently declared COVID-19 a global emergency of international concern (Sohrabi et al., 2020). Similar to other coronaviruses, person-to-person transmission of COVID-19 pneumonia occurs primarily through close contact with an infected patient, mainly via respiratory droplets and after touching contaminated objects (Ghinai et al., 2020; WHO, 2020b; Yu, Zhu, Zhang, & Han, 2020). Therefore, effective infection control measures, including patient isolation, are critical for decreasing the infection incidence rate.

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Background

Several studies have reported the clinical characteristics of patients with COVID-19 (Chang et al., 2020; Guan et al., 2020). For better management of the disease, recognition of clinical characteristics of COVID-19 can be helpful for clinicians to make proper decisions. One of the complications of this disease in a large group of patients is gastrointestinal (GI) disorders, although not common (Zarifian et al., 2020). In most studies, it has been reported that patients with COVID-19 have GI symptoms, mainly including diarrhea, nausea, and anorexia, in addition to common respiratory symptoms (An et al., 2020; Chen, Qi, et al., 2020; Meng et al., 2020; Zarifian et al., 2020).

Studies of the COVID-19 pathogenic mechanism have shown that the virus enters the target cell through angiotensin-converting enzyme-2 (ACE-2) (Hoffmann et al., 2020). This enzyme has been shown to play a major role in the cleaving of several peptides interfering in the renin–angiotensin pathway. Because the expression of this enzyme in the epithelial cells of the lung, intestine, kidney, and blood vessels is at its highest level, it is not unreasonable to expect that the main target of this virus is the organs that have a high expression of this enzyme (Harmer, Gilbert, Borman, & Clark, 2002). Lung tissue is one of these organs that have a high overexpression of ACE-2 receptors. Although GI manifestations may be less common in some patients, it may be considered the initial sign of infection with SARS-CoV-2 (Gao, Chen, & Fang, 2020; Gu, Han, & Wang, 2020). However, studies of these complications have reported a different prevalence for some GI symptoms such as diarrhea (Liang et al., 2020).

Methods

Inclusion and Exclusion Criteria

We included available data on COVID-19 patients confirmed in case reports and retrospective clinical studies relating to the GI presentations in hospitalized patients from China that were published in English between December 11, 2019, and June 20, 2020. Studies that did not discuss GI presentations were excluded.

Literature Search

Data for this review article were searched in the published and unpublished preprint articles up to June 20, 2020, in the PubMed, Scopus, and Google Scholar databases. We performed extensive hand searching of reference lists of articles and reports. The search terms used were "SARS-CoV-2" and "COVID-19" combined with "gastrointestinal," "clinical characteristics," or "digestive." We identified 28 articles from the initial search that met inclusion and exclusion criteria based on title and abstract. Of these, 11 were duplicates, resulting in 17 studies included for analysis (Table 1).

Data Extraction

We reviewed the 17 eligible Chinese studies and extracted data for province or city, patient age group range and gender, study size, severity of illness, and symptom categories. When extracting information from the studies, pairs of researchers conferred to compare findings and reach consensus. Where consensus was not reached, an independent researcher was consulted.

Literature Review

Wang, Fang, et al. (2020) aimed to study the clinical characteristics of noncritical COVID-19 patients who were admitted to Dongxihu Fangcang Hospital, China, between February 7 and 12, 2020. Among 1,012 noncritically ill individuals, fever (761 of 1,012; 75.2%) and cough (531 of 1,012; 52.4%) were the most common clinical symptoms. Along with these symptoms, the patients presented some GI symptoms including diarrhea, vomiting, and abdominal pain. Diarrhea was the main GI symptom in 152 patients (15%). Abdominal pain (37 of 1,012; 3.7%) and vomiting (36 of 1,012; 3.6%) were the other GI symptoms occurring in these patients. The high incidence rate for diarrhea compared with similar studies can be considered as one of the main outcomes of the study. In some published studies, the incidence of diarrhea in patients with COVID-19 ranged from 2% to 10% (Guan et al., 2020; Liu et al., 2020; Wang, Fang, et al., 2020; Xu, Wu, et al., 2020). The authors explained that the use of some drugs such as arbidol and moxifloxacin before admission to Fangcang Hospital may be attributed to this high incidence of diarrhea. The research group mentioned that diarrhea, although with a low incidence, should not be ignored in patients with COVID-19, indicating the possibility of fecal–oral transmission. The authors expressed that the severity of the GI symptoms was associated with gender, age, and a history of diabetes and cardiovascular diseases.

Guan et al. (2020) described the results of the clinical characteristics of COVID-19 in a selected cohort of patients throughout China. In 1,099 enrolled patients in their study, fever (43.8% on admission and 88.7% during hospitalization) and cough (48.2%) were the most common presenting symptoms (Table 1). However, diarrhea (3.8%) and nausea or vomiting (5.0%) were the second most common symptoms in these patients. Some patients had high aspartate aminotransferase (AST) levels (>40 U/L; 22.2%), others had high alanine aminotransferase (ALT) levels (>40 U/L; 21.3%), and

TABLE 1. Gastrointestinal Symptoms and Incidence Rate in Initial Studies ($N = 17$) of Chinese COVID-19 Patients

Author (Year)	Study Dates	Subjects	GI Symptoms and Incidence Rates (%)
An et al. (2020)	Jan 17–24, 2020	Nine patients with only digestive symptoms	• Diarrhea (11.1%) • Anorexia (66.7%) • Nausea and vomiting (11.1%)
Chang et al. (2020)	Jan 16–29, 2020, with final follow-up on Feb 4, 2020	13 patients with 2019-nCoV	• Diarrhea (7.7%)
Chen, Qi, et al. (2020)	Jan 20 to Feb 6, 2020, with final follow-up at Feb 25, 2020	249 patients	• Diarrhea ($n = 8$; 3.2%) • Inappetence ($n = 8$; 3.2%) • Elevated levels of ALT and AST
Chen, Zhou, et al. (2020)	From Jan 1 to 20, 2020	99 patients	• Diarrhea (two patients; 2%) • Nausea and vomiting (one patient; 1%)
Guan et al. (2020)	Dec 11, 2019, to Jan 29, 2020; cutoff date for the study was Jan 31, 2020	1,099 patients from 552 hospitals in 30 provinces	• Diarrhea (3.8%) • Nausea or vomiting (5.0%) • High AST level >40 U/L (22.2%), ALT level >40 U/L (21.3%), and high total bilirubin >17.1 μmol/L (10.5%)
He et al. (2020)	Jan 10, 2020, to Feb 13, 2020	204 patients confirmed by nucleic acid testing	• Diarrhea (9.3%) • Anorexia (5.8%) with same severity between patients with severe and nonsevere conditions
Li et al. (2020)	Jan 26, 2020, to Feb 5, 2020, with follow-up until Mar 3, 2020	548 patients • Nonsevere ($n = 279$) • Severe ($n = 269$)	• Vomiting (9% for patients with nonsevere condition and 7.4% for patients with severe condition) • Diarrhea (31.6% for patients with severe condition and 33.7% for patients with nonsevere condition) • Abdominal pain (4.5% for patients with severe condition and 1.4% for patients with nonsevere condition) • Hypoalbuminemia (72.9% for patients with severe condition and 45.8% for patients with nonsevere condition) • High levels of total bilirubin (12.6% for patients with severe condition and 6.3% for patients with nonsevere condition)
Liu et al. (2020)	Jan 7–15, 2020	366 hospitalized children (≤16 years of age)	• Vomiting (57.1%)
Meng et al. (2020)	Jan 1 to Feb 23, 2020	58 asymptomatic cases with COVID-19 pneumonia	• Diarrhea (6.3%)
Song et al. (2020)	Jan 20–27, 2020	51 patients with 2019-nCoV	• Diarrhea (10%) • Loss of appetite (18%) • Nausea and vomiting (6%)

(*continues*)

TABLE 1. Gastrointestinal Symptoms and Incidence Rate in Initial Studies ($N = 17$) of Chinese COVID-19 Patients (*Continued*)

Author (Year)	Study Dates	Subjects	GI Symptoms and Incidence Rates (%)
Wang, Hu, et al. (2020)	Jan 1–28, 2020, with final date of follow-up Feb 3, 2020	138 patients	• Anorexia ($n = 55$; 39.9%) • Diarrhea ($n = 14$; 10.1%) • Nausea ($n = 14$; 10.1%) • Abdominal pain ($n = 3$; 2.2%)
Wang, Fang, et al. (2020)	Feb 7–12, 2020, with clinical follow-up until Feb 22, 2020	1,012 noncritically ill individuals	• Diarrhea (15.2%) • Abdominal pain (3.7%) • Vomiting (3.6%)
Wu et al. (2020)	Jan 22 to Feb 14, 2020	80 patients	• No patient with diarrhea symptom ◦ Only three patients (3.75%) presented with the liver function disorder including ALT or AST levels above the normal range
Xia et al. (2020)	Jan 23 to Feb 8, 2020	20 pediatric patients	• Diarrhea (15%) • Vomiting (10%) • Increased ALT levels (>40 IU/L) (25%)
Xu, Wu, et al. (2020)	Jan 10–26, 2020	62 patients with 2019-nCoV	• Diarrhea (8%) • High AST levels (16.1%)
Yang, Cao, et al. (2020)	Jan 17 to Feb 10, 2020	149 patients	• Diarrhea (7.3%), • Nausea and vomiting (1.3%) • Increased ALT levels (12.1%) and decreased ALT levels (1.3%) • Increased AST levels (18.1%) • Increased total bilirubin (2.68%) and decreased total bilirubin levels (4.7%)
Zhang et al. (2020)	Jan 13 to Feb 16, 2020	28 patients with cancer (2.2% of 1,276 patients admitted to three designated hospitals for quarantine and treatment of COVID-19	• Diarrhea (10.7%)

Note. ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal.

some had high total bilirubin levels (>17.1 μmol/L; 10.5%). Findings of this research group demonstrated that patients with more severe conditions showed a higher incidence of diarrhea, as well as higher AST and ALT levels, in comparison with patients with mild conditions (5.8% vs. 3.5% for diarrhea; 28.1% vs. 19.8% for ALT level; 39.4% vs. 18.2% for AST level; and 13.3% vs. 9.9% for total bilirubin).

Chen, Zhou, et al. (2020) investigated 99 patients with confirmed cases of 2019 novel coronavirus (2019-nCoV) in Wuhan Jinyintan Hospital, China, from January 1 to 20, 2020. Their study revealed that fever (83%), cough (82%), and dyspnea (31%) were the main symptoms in these patients. Also, diarrhea (2%) and nausea and vomiting (1%) were the main presenting GI disorders in the patients.

The epidemiology and initial clinical characteristics of confirmed cases of COVID-19 from January 20 to February 6, 2020, were investigated in Shanghai, China, by Chen, Qi, et al. (2020). The majority of COVID-19 cases were mild, and a total of 215 (86.3%) patients were discharged after hospitalization. Fever (n = 235; 94.3%), cough (n = 91; 36.5%), and fatigue (n = 39; 15.7%) were the main symptoms in these patients. Diarrhea (n = 8; 3.2%) and loss of appetite (n = 8; 3.2%) were the only GI disorders in these patients. Elevated levels of ALT and AST were also less common in this sample. The researchers found that gender, age, higher levels of white blood cells, as well as C-reactive protein (CRP) and lactate dehydrogenase (LDH), and low levels of albumin could have a significant effect on the severity of symptoms in hospitalized patients in the intensive care unit (ICU).

Li et al. (2020) evaluated the relationship between risk factors and mortality rate in adult COVID-19 patients admitted to Tongji Hospital, China, from January 26 to February 5, 2020. They retrospectively enrolled 548 patients (279 patients with severe symptoms and 269 with mild symptoms) in the study and analyzed the findings, as well as followed up until March 3, 2020. The main symptoms in patients were fever (95.2%), fatigue (47.1%), cough (75.7%), and dyspnea (56.6%). Patients with both severe and mild symptoms showed an almost equal number of GI disorders including vomiting (9% vs. 7.4%) and diarrhea (33.7% vs. 31.6%). However, the number of patients with severe conditions presented severe abdominal pain (4.5% vs. 1.4%) as well as hypoalbuminemia (72.9% vs. 45.8%) and higher levels of total bilirubin (12.6% vs. 6.3%) than those with mild symptoms. High levels of albumin (<35 g/L), ALT (>40 U/L), and AST (>40 U/L) were seen in both patient groups with nonsevere and severe conditions reported as 45.8% versus 72.9%, 22.3% versus 24.1%, and 23.3% versus 43.4%, respectively.

Meng et al. (2020) aimed to characterize computed tomographic (CT) scan and the clinical course of 58 asymptomatic cases that developed COVID-19 pneumonia retrospectively in patients admitted to the Renmin Hospital, China, between January 1 and February 23, 2020. On admission, patients without any clinical symptoms associated with COVID-19 but who had a history of exposure to SARS-CoV-2 were confirmed by SARS-CoV-2 nucleic acid testing and CT scan. These patients were then followed every 3–7 days. Of these, 16 presented with symptoms of low lymphocyte count and high CRP including fever (n = 8 cases; 50%), cough (n = 9 cases; 56.3%), fatigue (n = 8 cases; 50%), shortness of breath (n = 2 cases; 12.5%), and diarrhea (n = 1 case; 6.3%) (Table 1). The authors emphasized the importance of surveillance for COVID-19 in asymptomatic patients with known exposure (Meng et al., 2020).

Zhang et al. (2020) investigated the clinical characteristics of COVID-19-infected cancer patients (n = 28) admitted to three designated hospitals in Wuhan, China, for quarantine and treatment of COVID-19 from January 13 to February 26, 2020. Among the 28 patients enrolled, lung cancer was the most frequent type of cancer (n = 7; 25.0%). The most common symptoms on admission were fever (n = 23; 82.1%), dry cough (n = 22; 81%), fatigue (n = 18; 64.3%), and dyspnea (n = 14; 50.0%). Diarrhea (n = 3; 10.7%) was the main GI disorder reported.

He et al. (2020) explored the clinical course and dynamic features of immune status in COVID-19 patients at Renmin Hospital of Wuhan, China, between January 10 and February 13, 2020. This research group aimed to find predictors correlated with severity and prognosis of COVID-19. They collected and analyzed the electronic medical records of 204 patients with COVID-19 pneumonia (nonsevere: n = 135; and severe: n = 69) confirmed by nucleic acid testing, retrospectively. Fever (n = 146; 71.5%) and cough (n = 84; 41.1%) were the main presenting symptoms in the patients. Some patients complained of diarrhea (n = 19; 9.31%) and anorexia (n = 12; 5.8%) with the same severity between patients diagnosed with severe and nonsevere COVID-19 conditions (7.2% vs. 10.3% for diarrhea and 7.2% vs. 5.1% for anorexia).

Wu et al. (2020) retrospectively and consecutively investigated the clinical and laboratory characteristics of COVID-19 confirmed cases at hospitals in Jiangsu, China, from January 22 to February 14, 2020. According to their findings, fever (n = 63; 78.7%) and cough (n = 51; 63.7%) were the main symptoms in these patients. No patients had hemoptysis or diarrhea symptoms. Only three patients (3.75%) presented with liver function disorders including elevated ALT or AST levels above the normal range.

Liu et al. (2020) conducted a retrospective analysis involving hospitalized children in Wuhan, China, from January 7 to January 15, 2020. A total of 366 hospitalized children (≤16 years of age) were enrolled in the study. High fever (>102.2 °F) and cough were the common clinical characteristics. Vomiting was the main GI symptom presenting in four cases.

Yang, Cao, et al. (2020) investigated the clinical characteristics and imaging manifestations of hospitalized patients with confirmed COVID-19 infection from January 17 to February 10, 2020, in three tertiary hospitals of Wenzhou City, China. Among 149 real-time reverse transcription–polymerase chain reaction (rRT-PCR)-confirmed positive patients, fever (n = 114; 76.5%) and cough (n = 87; 58.3%) were the main presenting symptoms in these patients. Some patients complained of diarrhea (n = 11; 7.3%) and nausea or vomiting (n = 2; 1.3%). Some patients also showed increased AST levels (n = 27; 18.1%), and others showed both increased (n = 12; 12.08%) and decreased (n = 2; 1.34%) levels of ALT. The other disorders in these patients were both increased (n = 3; 2.01%) and decreased (n = 9; 6.04%) levels of albumin.

An et al. (2020) retrospectively investigated data of admitted patients with 2019-nCoV pneumonia from January 17 to 24, 2019, in Renmin Hospital of Wuhan, China. Of a total of nine patients enrolled in the study, all of them had only digestive symptoms with no fever at the onset. The main GI symptom was anorexia (66.7%), with other symptoms including nausea (11.1%), vomiting (11.1%), and diarrhea (11.1%). No patient reported abdominal pain. The median time for onset of digestive symptoms was 2.1 days. All nine patients were admitted to the hospital under isolation, and none of them was transferred to the ICU. As all of these patients presented with GI symptoms at the onset but without fever or other respiratory symptoms; consideration of these atypical symptoms is very important to avoid missed diagnosis and prevent possible transmission of COVID-19 infection.

Xia et al. (2020) retrospectively analyzed the clinical and CT features of pediatric inpatients with COVID-19 infection from January 23 to February 8, 2020, in Wuhan Children's Hospital, China. They enrolled 20 pediatric patients in the study. Two of them were asymptomatic neonates with positive results from a pharyngeal swab COVID-19 nucleic acid test but negative CT findings. Fever (n = 12; 60%) and cough (n = 13; 65%) were the most common clinical manifestations among these patients. Diarrhea (n = 3; 15%) and vomiting (n = 2; 10%) were the main GI manifestations. Liver dysfunction reflected as increased levels of ALT (>40 IU/L) occurred in five cases (25%).

Chang et al. (2020) investigated the epidemiological and clinical characteristics of COVID-19 infection in 13 patients between January 16 and January 29, 2020, from three hospitals in Beijing, China. Two were children. Twelve patients reported fever (mean = 1.6 days) before hospitalization. Cough (n = 6; 46.2%), upper airway congestion (n = 8; 61.5%), myalgia (n = 3; 23.1%), and headache (n = 3; 23.1%) were the most common symptoms. No patient required respiratory support before being transferred to the specialty hospital after a mean of 2 days. One presented with diarrhea as the main GI disorder (7.7%).

Xu, Wu, et al. (2020) investigated the clinical characteristics of infected patients with SARS-CoV-2 from January 10 to 26, 2020, in Zhejiang Province, China. Among 62 patients in their study, fever (n = 48; 77%), cough (n = 50; 81%), expectoration (n = 35; 56%), and muscle pain (n = 32; 52%) were the most common symptoms. Diarrhea (n = 3; 8%) was the main GI symptom. Some patients presented higher levels of AST (n = 10; 16.1%).

Song et al. (2020) investigated noncontrast chest CT findings in patients with laboratory-confirmed 2019-nCoV infection performed from January 20 to January 27, 2020, at the Center for Disease Control, Shanghai, China. Of 51 patients enrolled in the study, fever (96%), cough (47%), and muscle pain (31%) were the most common symptoms. Diarrhea (n = 5; 10%), loss of appetite (n = 9; 18%), and nausea and vomiting (n = 3, 6%) were the main GI symptoms presenting in these patients.

Wang, Hu, et al. (2020) reported a case series of 138 consecutive hospitalized patients with confirmed 2019-nCoV-infected pneumonia at Zhongnan Hospital of Wuhan University, China, from January 1 to 28, 2020. Of these, 26% of patients required admission to the ICU and 4.3% died. Fever (n = 136; 98.6%), dry cough (n = 82; 59.4%), and muscle pain (n = 96; 69.6%) were the most common symptoms. The other common symptoms included lymphopenia (n = 97; 70.3%), prolonged prothrombin time (n = 80; 58%), and elevated LDH (n = 55; 39.9%). Anorexia (n = 55; 39.9%), diarrhea (n = 14; 10.1%), nausea (n = 14; 10.1%), and abdominal pain (n = 3; 2.2%) were the main GI symptoms among the patients. High levels of ALT, AST, and total bilirubin were observed in this population. Findings demonstrated that the patients with severe COVID-19 conditions (n = 36) showed a higher incidence of GI disorders than patients with mild conditions (n = 102).

Discussion

Disastrous consequences of COVID-19, as a new infectious disease in humans, are rising sharply all over the world (Liu et al., 2020; Zhu et al., 2020). COVID-19 presents extraordinary challenges for healthcare workers (Carnero Contentti & Correa, 2020; Han et al.,

2020; Zahidie, Iqbal, & Hussain, 2020). Respiratory symptoms are the most important manifestations of the disease, and human-to-human transmission is the main way for spread of the virus in the community setting (Liu et al., 2020; Smargiassi et al., 2020). From February 21 to June 20, 2020, more than 89,000 cases have been diagnosed with COVID-19 in the authors' country of Iran, with 6,150 deaths reported (Jahangiri, Jahangiri, & Najafgholipour, 2020; Nikpouraghdam et al., 2020; Shojaee et al., 2020). Staying at home or quarantining in an isolated center and minimizing going out are effective ways to battle the spread of COVID-19 (Aminnejad & Hormati, 2020; Hormati, Ghadir, Foroghi Ghomi, et al., 2020; Hormati, Ghadir, Zamani, et al., 2020; Hormati, Niya, et al., 2020).

With the outbreak of COVID-19 infection starting in Wuhan, Hubei Province, China, patients were noted to exhibit various clinical symptoms. On the basis of these findings, we hypothesized that COVID-19 has a spectrum of symptoms, with GI symptoms among them. This review focuses on GI symptoms of COVID-19 in China beginning after the first report of this infection there.

After infection with COVID-19, patients may present various spectrum of symptoms (Baj et al., 2020; Xu, Li, Tian, Li, & Kong, 2020). It is well documented that respiratory symptoms are the main characteristic features of COVID-19, occurring in the majority of patients with cough and fever (Xu, Wu, et al., 2020). Although not the primary symptom, it is well documented that GI symptoms are also consistently manifested with the disease (Redd et al., 2020; Tian, Rong, Nian, & He, 2020). The main GI complaints include anorexia, diarrhea, vomiting, nausea, abdominal pain, hepatic involvement, and GI bleeding (Hormati et al., 2021; Hormati, Shahhamzeh, Afifian, Khodadust, & Ahmadpour, 2020; Musa, 2020; Redd et al., 2020).

Diarrhea is the most common GI symptom reported and may be considered as an initial symptom in some infected patients (D'Amico, Baumgart, Danese, & Peyrin-Biroulet, 2020; Yang, Zhao, et al., 2020). In comparison with adults in whom decreased appetite is prominent, vomiting is more prominent in children. Huang et al. (2020) first reported the clinical GI symptoms of COVID-19, noting that only 3% of their patients had diarrhea (Huang et al., 2020). We previously reported that patients with SARS-CoV-2 infection can present unusual or pure GI symptoms in the absence of respiratory symptoms (Hormati, Shahhamzeh, Afifian, et al., 2020; Hormati, Shahhamzeh, Aminnejad, Afifian, & Ahmadpou, 2020). In some patients, GI symptoms (e.g., diarrhea) did not occur due to infection with COVID-19, and other reasons such as the side effects of medications are the likely cause for this symptom (Hu et al., 2020).

According to the incidence of some GI symptoms in patients with COVID-19 globally, the authors' country is no exception. After the first outbreak of COVID-19 in Qom City, Iran, the number of patients referred to our GI clinics increased by 20% (Hormati, Ghadir, Zamani, et al., 2020; Hormati, Shahhamzeh, Afifian, 2020; Hormati, Shahhamzeh, Aminnejad, et al., 2020). The incidence of GI complications during COVID-19 is unexpected, and most of these GI symptoms are resistant to medications. Diarrhea and anorexia were the most common GI symptoms in patients who visited our GI clinic. The incidence of other GI symptoms is less common and includes nausea, vomiting, and hemorrhage. GI bleeding and abdominal pain were more frequent in severely ill patients. We also noticed the incidence of some rare GI symptoms such as hyperbilirubinemia, upper GI bleeding, and dysentery (Hormati et al., 2021). We noticed that the incidence of GI manifestations was higher in the later stage than in the early stage of the COVID-19 pandemic, and the proportion of GI symptoms in severely affected patients was higher than that in nonsevere patients. Most patients had no respiratory symptoms at the time of referral to our GI clinic and some had GI symptoms (Hormati, Shahhamzeh, Afifian, et al., 2020). Because these patients were unaware of their COVID-19 infection, these patients were carriers of the disease during the onset of their GI symptoms.

During COVID-19, awareness and diagnosis of the incidence of GI symptoms have an inestimable importance, as timely diagnosis can play a significant role in controlling the spread of the virus. Because COVID-19 is still new and its complications are increasing day by day, in some cases, we find no suitable justification for some GI symptoms. On the basis of this, we relied on other diagnostic methods, such as endoscopy and colonoscopy, to ensure and distinguish the symptoms of the disease from other diseases such as inflammatory bowel diseases or cancer. Because performing these procedures requires a close proximity between the endoscopist, the nurse(s), and the infected patient, the possibility of infection in our clinic personnel is increased (Almadi et al., 2020). As a result, we have attentively used recommended infection control approaches to protect the health of our GI team during risky procedures (Hormati, Ghadir, Zamani, et al., 2020; Hormati, Niya, et al., 2020).

Conclusion

We have previously reported that reducing close contact is the only effective way to fight the COVID-19 virus (Hormati, Ghadir, Foroghi Ghomi, et al., 2020). As a result, we have attempted to conduct most of our clinical visits virtually and reserve high-risk diagnostic methods only for emergencies. Over time, another new range of symptoms may emerge with COVID-19, some of which may be related to the GI tract. Based on our analysis of the initial

studies emerging from China, particularly related to the manifestation of GI complaints, careful examination and recording of these symptoms can be a way to identify the disease and the pathogenic infectious mechanism of this mysterious disease. ✪

REFERENCES

Adhikari, S. P., Meng, S., Wu, Y. J., Mao, Y. P., Ye, R. X., Wang, Q. Z., … Zhou, H. (2020). Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. *Infectious Diseases of Poverty*, *9*(1), 29.

Almadi, M. A., Aljebreen, A. M., Azzam, N., Alammar, N., Aljahdli, E. S., Alsohaibani, F. I., … Batwa, F. (2020). COVID-19 and endoscopy services in intermediately affected countries: A position statement from the Saudi Gastroenterology Association. *Saudi Journal of Gastroenterology*, *26*(5), 240–248.

Aminnejad, R., & Hormati, A. (2020). The equal danger of improper use of face mask and use of improper mask. *Archives of Clinical Infectious Diseases*, *15*(3), e103100.

An, P., Chen, H., Ren, H., Su, J., Ji, M., Kang, J., … Yu, H. (2020). Gastrointestinal symptoms onset in COVID-19 patients in Wuhan, China. *Digestive Diseases and Sciences*. Advance online publication. doi: 10.1007/s10620-020-06693-6.

Baj, J., Karakuła-Juchnowicz, H., Teresiński, G., Buszewicz, G., Ciesielka, M., Sitarz, E., … Maciejewski, R. (2020). COVID-19: specific and non-specific clinical manifestations and symptoms: The current state of knowledge. *Journal of Clinical Medicine*, *9*(6), 1753.

Carnero Contentti, E., & Correa, J. (2020). Immunosuppression during the COVID-19 pandemic in neuromyelitis optica spectrum disorders patients: A new challenge. *Multiple Sclerosis and Related Disorders*, *41*, 102097.

Chang, D., Lin, M., Wei, L., Xie, L., Zhu, G., Dela Cruz, C. S., … Sharma, L. (2020). Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*, *323*(11), 1092–1093.

Chen, J., Qi, T., Liu, L., Ling, Y., Qian, Z., Li, T., … Lu, H. (2020). Clinical progression of patients with COVID-19 in Shanghai, China. *Journal of Infection*, *80*(5), e1–e6.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., … Zhang, L. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *The Lancet*, *395*(10223), 507–513.

D'Amico, F., Baumgart, D. C., Danese, S., & Peyrin-Biroulet, L. (2020). Diarrhea during COVID-19 infection: Pathogenesis, epidemiology, prevention and management. *Clinical Gastroenterology and Hepatology*, *18*(8), 1663–1672.

Fang, D., Ma, J., Guan, J., Wang, M., Song, Y., Tian, D., & Li, P. (2020). Manifestations of digestive system in hospitalized patients with novel coronavirus pneumonia in Wuhan, China: A single-center, descriptive study. *Chinese Journal of Digestive Diseases*, (12), E005–E005.

Gao, Q. Y., Chen, Y. X., & Fang, J. Y. (2020). 2019 Novel coronavirus infection and gastrointestinal tract. *Journal of Digestive Diseases*, *21*(3), 125–126.

Ghinai, I., McPherson, T. D., Hunter, J. C., Kirking, H. L., Christiansen, D., Joshi, K., … Layden, J. E.; Illinois COVID-19 Investigation Team. (2020). First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. *Lancet*. *395*(10230), 1137–1144.

Gorbalenya, A. E., Baker, S. C., Baric, R. S., de Groot, R. J., Drosten, C., Gulyaeva, A. A., … Ziebuhr, J. (2020). Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. *Nature Microbiology*. Retrieved from https://doi.org/10.1101/2020.02.07.937862

Gu, J., Han, B., & Wang, J. (2020). COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology*, *158*(6), 1518–1519.

Guan, W. J., Ni, Z. Y., Hu, Y, Liang, W. H, Ou, C. Q., He, J. X., … China Medical Treatment Expert Group for Covid-19. (2020). Clinical characteristics of coronavirus disease 2019 in China. *The New England Journal of Medicine*, *382*(18), 1708–1720.

Han, Y.-J., Ren, Z.-G., Li, X.-X., Yan, J.-L., Ma, C.-Y., Wu, D.-D., & Ji, X.-Y. (2020). Advances and challenges in the prevention and treatment of COVID-19. *International Journal of Medical Sciences*, *17*(12), 1803–1810.

Harmer, D., Gilbert, M., Borman, R., & Clark, K. L. (2002). Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Letters*, *532*(1-2), 107–110.

He, R., Lu, Z, Zhang, L., Fan, T., Xiong, R., Shen, X., … Geng, Q. (2020). The clinical course and its correlated immune status in COVID-19 pneumonia. *Journal of Clinical Virology*, *127*, 104361.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., ... Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, *181*(2), 271–280.e8.

Hormati, A., Ghadir, M. R., Foroghi Ghomi, S. Y., Afifian, M., Khodadust, F., & Ahmadpour, S. (2020). Can increasing the number of close contact lead to more mortality in COVID-19 infected patients?*Iranian Journal of Public Health*, *49*, 117–118.

Hormati, A., Ghadir, M. R., Saeidi, M., Aminnejad, R., Khodadust, F., Afifian, M., & Ahmadpour, S. (2021). Dysentery as a rare GI symptom found in COVID-19 patients. *Gastroenterology and Hepatology*, *44*(1), 31–34.

Hormati, A., Ghadir, M. R., Zamani, F., Khodadadi, J., Afifian, M., & Ahmadpour, S. (2020). Preventive strategies used by GI physicians during the COVID-19 pandemic. *New Microbes and New Infections*, *35*, 100676.

Hormati, A., Niya, M. H. K., Ghadir, M., Lankarani, K. B., Ajdarkosh, H., Tameshkel, F. S., & Zamani, F. (2020). COVID-19 in the endoscopy ward: A potential risk for gastroenterologists. Infection *Control & Hospital Epidemiology*, *41*(10), 1242–1243.

Hormati, A., Shahhamzeh, A., Aminnejad, R., Afifian, M., & Ahmadpour, S. (2020). Gastrointestinal presentation in a patient with COVID-19 without respiratory tract symptoms: A case report from Qom, Iran. *Jundishapur Journal of Microbiology*, *13*(5), e102844.

Hormati, A., Shahhamzeh, A., Afifian, M., Khodadust, F., & Ahmadpour, S. (2020). Can COVID-19 present unusual GI symptoms? *Journal of Microbiology, Immunology and Infection*, *53*(3), 384–385.

Hu, Z., Song, C., Xu, C., Jin, G., Chen, Y., Xu, X., … Shen, H. (2020). Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China Life Sciences*, *63*(5), 706–711.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., … Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, *395*(10223), 497–506.

Jahangiri, M., Jahangiri, M., & Najafgholipour, M. (2020). The sensitivity and specificity analyses of ambient temperature and population size on the transmission rate of the novel coronavirus (COVID-19) in different provinces of Iran. *The Science of the Total Environment*, *728*, 138872.

Liang, W., Feng, Z., Rao, S., Xiao, C., Xue, X., Lin, Z. … Qi, W. (2020). Diarrhoea may be underestimated: A missing link in 2019 novel coronavirus. *Gut*, *69*(6), 1141–1143.

Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., … Zhao, J. (2020). Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. *Journal of Allergy and Clinical Immunology*, *146*(1), 110–118.

Liu, W., Zhang, Q., Chen, J., Xiang, R., Song, H., Shu, S., … Liu, Y. (2020). Detection of COVID-19 in children in early January 2020 in Wuhan, China. *The New England Journal of Medicine*, *382*(14), 1370–1371.

Meng, H., Xiong, R., He, R., Lin, W., Hao, B, Zhang, L., … Geng, Q. (2020). CT imaging and clinical course of asymptomatic cases with COVID19 pneumonia at admission in Wuhan, China. *Journal of Infection*, *81*(1), e33–e39.

Musa, S. (2020). Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? *Arab Journal of Gastroenterology*, *21*(1), 3–8.

Nikpouraghdam, M., Jalali Farahani, A., Alishiri, G., Heydari, S., Ebrahimnia, M., Samadinia, H., … Bagheri, M. (2020). Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. *Journal of Clinical Virology, 127,* 104378.

Redd, W. D., Zhou, J. C, Hathorn, K. E., McCarty, T. R., Bazarbashi, A. N., Thompson, C. C., … Chan, W. W. (2020). Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the United States: A multicenter cohort study. *Gastroenterology*, *159*(2), 765–767.e2.

Shojaee, S., Pourhoseingholi, M. A., Ashtari, S., Vahedian-Azimi, A., Asadzadeh-Aghdaei, H., & Zali, M. R. (2020). Predicting the mortality due to COVID-19 by the next month for Italy, Iran and South Korea; A simulation study. *Gastroenterology and Hepatology from Bed to Bench*, *13*(2), 177–179.

Smargiassi, A., Soldati, G., Borghetti, A., Scoppettuolo, G., Tamburrini, E., Testa, A.C., Moro, F., Natale, L., Larici, A.R., Buonsenso, D. and Valentini, P., 2020. Lung ultrasonography for early management of patients with respiratory symptoms during COVID-19 pandemic. Journal of Ultrasound, 07 Jul 2020, *23*(4):449-456. DOI: 10.1007/s40477-020-00501-7 PMID: 32638333 PMCID: PMC7338342.

Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., … Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*, *76*, 71–76.

Song, F., Shi, N., Shan, F., Zhang, Z., Shen, J., Lu, H., … Shi, Y. (2020). Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*, *295*(1), 210–217.

Tian, Y., Rong, L., Nian, W, & He, Y. (2020). Review article: Gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Alimentary Pharmacology & Therapeutics*, *51*(9), 843–851.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., … Peng, Z. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA, 323*(11), 1061–1069.

Wang, X., Fang, J., Zhu, Y., Chen, L., Ding, F., Zhou, R., … Zhao, Q. (2020). Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. *Clinical Microbiology and Infection*, *26*(8), 1063–1068.

World Health Organization. (2020a). *Coronavirus disease (COVID-2019) situation reports*. Retrieved from https://www.WHO.Int/docs/defaultsource/coronaviruse/situationreports/20200221-sitrep-32-covid19

World Health Organization. (2020b). *Modes of transmission of virus causing COVID-19: Implications for IPC precaution recommendations: Scientific brief, 27 March 2020*. Geneva, Switzerland: Author.

Wu, J., Liu, J., Zhao, X., Liu, C., Wang, W., Wang, D., … Li, L. (2020). Clinical characteristics of imported cases of coronavirus disease 2019 (COVID-19) in Jiangsu Province: A multicenter descriptive study. *Clinical Infectious Diseases*, *71*(15), 706–712.

Xia, W., Shao, J., Guo, Y., Peng, X., Li, Z., & Hu, D. (2020). Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatric Pulmonology*,*55*(5), 1169–1174.

Xu, X. W., Wu, X. X., Jiang, X. G., Xu, K. J., Ying, L. J., Ma, C. L., … Li, L. J. (2020). Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. *BMJ (Clinical Research Ed.)*, *368*, m606.

Xu, Z., Li, S., Tian, S., Li, H., & Kong, L. Q. (2020). Full spectrum of COVID-19 severity still being depicted. *The Lancet*, *395*(10228), 947–948.

Yang, W., Cao, Q., Qin, L., Wang, X., Cheng, Z., Pan, A., … Yan, F. (2020). Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): A multi-center study in Wenzhou city, Zhejiang, China. *Journal of Infection*, *80*(4), 388–393.

Yang, X., Zhao, J., Yan, Q., Zhang, S., Wang, Y., & Li, Y. (2020). A case of COVID-19 patient with the diarrhea as initial symptom and literature review. *Clinics and Research in Hepatology and Gastroenterology, 44*(5), e109–e112.

Yeo, C., Kaushal, S., & Yeo, D. (2020). Enteric involvement of coronaviruses: Is faecal-oral transmission of SARS-CoV-2 possible? *The Lancet Gastroenterology & Hepatology*, *5*(4), 335–337.

Ye, J., Zhang, B., Xu, J., Chang, Q., McNutt, M. A., Korteweg, C., … Gu, J. (2007). Molecular pathology in the lungs of severe acute respiratory syndrome patients. *American Journal of Pathology*, *170*(2), 538–545.

Yu, P., Zhu, J., Zhang, Z., & Han, Y. (2020). A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. *Journal of Infectious Diseases*, *221*(11), 1757–1761.

Zahidie, A., Iqbal, M., & Hussain, S. W. (2020). Worsening of the COVID-19 Pandemic in New York City: Analysis of response gaps and challenges at the public policy and community levels. *Journal of the College of Physicians and Surgeons Pakistan*, *30*(6), 32–36.

Zarifian, A., Bidary, Z. M., Arekhi, S., Rafiee, M., Gholamalizadeh, H., Amiriani, A., ... Ganji A. (2020). Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis. *Journal of Medical Virology*. Advance online publication. doi: 10.1002/jmv.26314

Zhang, L., Zhu, F., Xie, L., Wang, C., Wang, J., Chen, R., … Zhou, M. (2020). Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. *Annals of Oncology*, *31*(7), 894–901.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., ... Tan, W.; China Novel Coronavirus Investigating and Research Team. (2020). A novel coronavirus from patients with pneumonia in China, 2019. *The New England Journal of Medicine*, *382*(8):727–733.

