Clinical Characteristics of 195 Cases of COVID-19 with Gastrointestinal Symptoms

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ABSTRACT

Background: *Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), have fever, dry cough, dyspnea, and fatigue. The disease has now become a global pandemic. The purpose of this study was to explore the relationship between COVID-19 and gastrointestinal (GI) symptoms.*

Methods: *We collected and analyzed data on patients with laboratory-confirmed COVID-19 by high-throughput sequencing or reverse transcription-polymerase chain reaction. We reviewed electronic medical records of 405 hospitalized COVID-19 patients in the Third Hospital of Wuhan.*

Results: *Among the 405 confirmed patients, 210 had no GI symptoms, 195 had GI symptoms, and the first symptom of 155 patients was GI. The prevalence of vascular and digestive diseases in the group with GI symptoms was significantly higher than in the group without GI symptoms. In patients with GI symptoms, the proportion with fever, cough, dysphoria, chest tightness, poor appetite, chest pain, and pharyngeal pain was significantly higher than in those without GI symptoms. There was no significant difference in imaging between the 2 groups. In patients with GI symptoms, the proportion with increased procalcitonin (PCT) level and decreased lymphocyte count was significantly higher than in those without GI symptoms.*

Conclusion: *COVID-19 patients with GI symptoms had significantly more vascular and digestive system diseases and were more likely to have clinical manifestations of fever, cough, poor appetite, chest tightness, chest pain, insomnia, and pharyngeal pain. There were more patients with diarrhea, nausea, and vomiting. Patients with GI symptoms were more likely to have increased PCT and decreased lymphocyte count.*

Keywords: *COVID-19, gastrointestinal*

INTRODUCTION

In December 2019, a series of unexplained cases of pneumonia were reported in Wuhan, China, which swiftly spread to the rest of China and then the rest of the world within a short period. The virus was subsequently identified as a novel coronavirus (CoV) that belongs to the betacoronavirus lineage B and named severe acute respiratory syndrome CoV (SARS-CoV)-2 by the World Health Organization (WHO).[1]

Patients infected with SARS-CoV-2, which causes coronavirus disease 2019 (COVID-19), have fever, dry cough, dyspnea, and fatigue. In severe cases, it may lead to SARS and even death.[2] There are also many patients with initial extrapulmonary symptoms, especially gastrointestinal (GI) symptoms.[3,4] It is well known that the main route of SARS-CoV-2 transmission is through respiratory droplets and close contact. However, CoV ribonucleic acid (RNA) has also been found in fecal samples from COVID-19 patients.[5-7] Therefore, the possibility of fecal–oral transmission must be taken into account. Respiratory symptoms are usually the most common symptoms of COVID-19, and the main manifestations of GI complications are diarrhea, nausea, and vomiting.[3,8]

In the past 4 months, there have been >2 million confirmed infections worldwide and WHO declared a Public Health Emergency of International Concern on January 30, 2020, and further labeled it as a pandemic on March

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11, 2020. Although the clinical features of patients with COVID-19 have been described in many articles, there are few reports about the GI system. Therefore, the main purpose of this study was to explore the relationship between COVID-19 and GI symptoms and summarize the clinical characteristics of patients with such symptoms.

METHODS

Patient Inclusion and Data Collection

All 405 hospitalized patients (admitted between January 12 and March 8, 2020) in the Third Hospital of Wuhan (one of the designated hospitals for the hospitalization of COVID-19 patients) were diagnosed by high-throughput sequencing or real-time reverse-transcription polymerase chain reaction (RT-PCR) from nasal or pharyngeal swab specimens. Complete data were available for all patients in this study, and all patients lived in Wuhan during the disease outbreak. In order to collect epidemiological and symptomatic data that were not available from electronic medical records, we communicated directly with patients or their families. In view of the urgent need to collect clinical data, the requirement for written informed consent was waived.

The epidemiological characteristics (including recent exposure history), clinical symptoms and signs, and laboratory findings were extracted from electronic medical records and return visits, bedside consultation, or telephone interviews. Laboratory assessments included leukocyte count (4×10^9-10×10^9/L), lymphocyte count (1.1×10^9-3.2×10^9/L), albumin (40-55 g/L), C-reactive protein (CRP; <5 mg/L), procalcitonin (PCT; <0.05 ng/ml), alanine aminotransferase (ALT; 7-40 U/L), aspartate aminotransferase (AST; 0-45 U/L), lactate dehydrogenase (LDH; 114-240 U/L), creatine kinase (CK; 30-180 U/L), and D-dimer (0-0.5 mg/L). All medical laboratory data were recorded by the laboratory of the Wuhan Third Hospital. GI symptoms included nausea, vomiting, diarrhea, constipation, upper abdominal discomfort, post-sternal discomfort, acid regurgitation, and belching (taking into account that poor appetite can have many causes, and it is not classified as a COVID-19 symptom). The 405 patients were divided into 195 with GI symptoms and 210 without GI symptoms.

Statistical Analysis

All statistical analyses were carried out using the Statistical Packages for the Social Sciences (SPSS) software V.19.0 (IBM Corp.; Armonk, NY, USA). The numerical data were expressed by number of cases and percentage. The chi-square test or Fisher's exact probability method was used for comparison among groups. $P < .05$ was considered statistically significant.

RESULTS

Demographics and Clinical Characteristics

Patients' demographic and clinical characteristics are presented in Table 1. We enrolled 405 patients with confirmed COVID-19, among whom, 195 (48.1%) presented with at least 1 GI symptom. The median age was 56 years (range, 17–95 years); 54.5% of the patients were >60 years old, 54.1% of the patients were female, 11.4% had a history of smoking, and 10.6% had a history of drinking. None of the patients had been directly exposed to Huanan wet markets or wildlife; therefore, we presumed that all cases were community infected. Twenty patients were hospital workers, and family members or friends of 62 patients were infected with SARS-CoV-2. There was no significant difference in sex, smoking history, drinking history, and exposure history between the patients with and without GI symptoms ($P > .05$). Two hundred forty-seven (61%) patients had at least 1 chronic disease, including vascular, digestive, endocrine, respiratory, urinary, motor, or nervous system disease. The most common was vascular diseases (38.5%). Among the patients with no GI symptoms patients, 103 (49.0%) had at least 1 chronic disease, and among those with GI symptoms, 144 (73.8%) had at least 1 chronic disease. This difference was significant ($P < .01$). Fever (76.8%) and cough (53.3%) were the most common symptoms. In addition, 2.9% of the patients were asymptomatic. In the group with GI symptoms, fever accounted for 81.5%, poor appetite 60.0%, cough 59.5%, chest tightness 39.5%, insomnia 37.4%, chest pain 11.8%, and sore throat 10.3%, but the corresponding proportions in the group without GI symptoms were significantly lower ($P < .05$).

The clinical characteristics of 195 patients with COVID-19 and GI symptoms are shown in Table 2. Of 195 patients, GI symptoms were the initial symptom in 155 patients. Sixty-six patients (33.8%) had a history of GI diseases, with chronic gastritis (11.7%) being the most common, followed by peptic ulcers (8.1%). The GI symptoms mainly included poor appetite, diarrhea, nausea, vomiting, epigastric discomfort, acid regurgitation, belching, post-sternal discomfort, heartburn, and constipation, of which diarrhea (57.4%) and nausea/vomiting (39%) were the most common. In terms of medication, most patients (45.1%) used proton pump inhibitors, and

Table 1. Clinical Characteristics of Patients With COVID-19 With and Without GI Symptoms

	All Patients (*n* = 405)	No GI Symptoms (*n* = 210)	GI Symptoms (*n* = 195)	*P*
Age—median (range)	61 (17-95)	62.5 (27-92)	59 (17-95)	
Age-groups—No. (%)				
<30	12 (3.0)	2 (1.0)	10 (5.0)	.02
30-44	63 (15.6)	26 (12.4)	37 (19.0)	
45-59	109 (26.9)	58 (27.6)	51 (26.2)	
60-74	182 (44.9)	99 (47.1)	83 (42.6)	
≥75	39 (9.6)	25 (11.9)	14 (7.2)	
Sex—No. (%)				
Male	186 (45.9)	106 (50.5)	80 (41.0)	.057
Female	219 (54.1)	104 (49.5)	115 (59.0)	
Exposure history—No. (%)				
Hospital staff	20 (5)	12 (5.7)	8 (4.1)	.451
Familiar/cluster infections	62 (15.8)	36 (17.1)	26 (13.3)	.443
Smoking history—No. (%)				
Yes	46 (11.4)	26 (12.4)	20 (10.3)	.501
No	359 (88.6)	184 (87.6)	175 (89.7)	
Drinking history—No. (%)				
Yes	43 (10.6)	22 (10.5)	21 (10.8)	.924
No	362 (89.4)	188 (89.5)	174 (89.2)	
Chronic medical disease—No. (%)	247 (61)	103 (49.0)	144 (73.8)	<.001
Circulatory system disease	156 (38.5)	83 (39.5)	123 (63.1)	<.001
Digestive system disease	102 (25.2)	37 (17.6)	65 (33.3)	<.001
Blood endocrine system disease	88 (21.7)	44 (21.0)	44 (22.6)	.694
Respiratory system disease	31 (7.7)	13 (6.2)	18 (9.2)	.25
Urinary system disease	28 (6.9)	11 (5.2)	17 (8.7)	.168
Motor system disease	18 (4.4)	5 (2.4)	13 (6.7)	.037
Nervous system disease	5 (1.2)	4 (1.9)	1 (0.5)	.21
Other disease	9 (2.2)	3 (1.4)	6 (3.1)	.216
Signs and symptoms—No. (%)				
Fever	311 (76.8)	152 (72.4)	159 (81.5)	.029
Cough	216 (53.3)	100 (47.6)	116 (59.5)	.017
Poor appetite	170 (42.0)	53 (25.2)	117 (60.0)	<.001
Fatigue	155 (38.3)	75 (35.7)	80 (41.0)	.272
Chest tightness	124 (30.6)	47 (22.4)	77 (39.5)	<.001
Insomnia	103 (25.4)	30 (14.3)	73 (37.4)	<.001
Sore throat	29 (7.2)	9 (4.3)	20 (10.3)	.02
Chest pain	23 (5.7)	0	23 (11.8)	<.001
Gasp/dyspnea	9 (2.2)	7 (3.3)	2 (1.0)	.107
Headache/dizziness	5 (1.2)	4 (1.9)	1 (0.5)	.21
Asymptomatic	12 (3.0)	12 (5.7)	0 (0)	.001

GI, gastrointestinal.

Table 2. Clinical Characteristics of 195 Patients with COVID-19 and GI Symptoms

Digestive system disease—No. (%)	66 (33.8)
Chronic gastritis	22 (11.3)
Peptic ulcer	15 (7.7)
Holelithiasis/cholecystitis	15 (7.7)
Chronic liver disease	13 (6.7)
Gastroesophageal reflux disease	3 (1.5)
Digestive system tumor	2 (1)
Hepatic cyst	2 (1)
Enteritis	2 (1)
Gastrointestinal polyps	1 (0.5)
Gastrointestinal symptoms as the first symptom-No. (%)	155 (79.4%)
Signs and symptoms—No. (%)	
Diarrhea	112 (57.4)
Nausea/vomiting	76 (39.0)
Upper abdominal discomfort	41 (21.0)
Sour regurgitation/belching	37 (19)
Constipation	15 (7.7)
Post sternal discomfort/heartburn	26 (13.3)
Digestive system medication—No. (%)	
Proton pump inhibitors	88 (45.1)
Probiotics	56 (28.7)
Hepatoprotective agent	42 (21.5)
Other	20 (12.8)
Nothing	18 (0.9)

GI, gastrointestinal.

some hepatoprotective drugs and probiotics to improve GI symptoms. After treatment, the symptoms of the vast majority of patients improved significantly.

Radiological and Laboratory Findings

Table 3 shows the chest computed tomography (CT) scan and laboratory assay results on admission. Abnormal CT scans were obtained in 378 patients (93.3%), and 349 (86.2%) had changes in both lungs. Most patients (n = 294, 72.6%) showed typical ground-glass opacity and 125 (30.9%) showed consolidation. In addition, 5.4% of the patients had pleural effusion. In patients with GI symptoms, 67.2% had ground-glass opacity and only 7.2% had pleural effusion. In patients without GI symptoms, 73.3% had ground-glass opacity, and only 3.8% had pleural effusion. In conclusion, there was no significant difference between the two groups for unilateral and bilateral lesions, pleural effusion, and pathological changes (P > .05).

Laboratory data showed that >70% of patients had lymphopenia, hypoproteinemia, and elevated CRP. Leukopenia was observed in 17.8% of patients. Most patients had an elevated level of D-dimer, but elevated levels of PCT, LDH, and CK were less common. In addition, AST and ALT levels increased in about 20% of the patients. In the patients with GI symptoms, 79% and 33.8% showed an increase in CRP and PCT, and 62.6% showed a decrease in lymphocyte count. In patients without GI symptoms, 66.2% and 19.5% showed elevated CRP and PCT, respectively, and 48.6% showed a decrease in lymphocyte count. The difference between the two groups was significant (P < .05).

DISCUSSION

Most of the 405 patients with community-acquired COVID-19 were middle-aged or elderly; the median age was 61 years, which is consistent with that reported by Wang et al.[9] but older than that reported by Zhang et al. (57 years)[10] and Chen et al. (55 years).[11] Among the 405 patients, 54.1% were female, 11.4% had a history of smoking, and 10.6% had a history of drinking. There was no significant difference in the above data between the two groups. Therefore, we speculated that sex, smoking history, and drinking history had no effect on the GI symptoms. In our study, 61% of patients had at least 1 chronic disease, with vascular (38.5%), digestive (25.2%), and endocrine (21.7%) diseases being the most common chronic comorbidities, consistent with other recent reports.[12] Additionally, our results showed that patients with vascular and digestive diseases were more likely to have GI symptoms.

Consistent with previous reports,[2,12,13] fever (76.8%) and cough (53.3%) were the most common symptoms in patients with COVID-19. However, the proportion of patients with fever and cough was lower than previously reported. About 2.7% of patients in our study were asymptomatic. These patients had a history of close contact with COVID-19 patients, and therefore they were examined. When they turned out to be positive, they were hospitalized, but they did not develop COVID-19 symptoms. In our statistical analysis of patients with confirmed COVID-19, nearly half had GI symptoms, and 155 had GI symptoms as the first manifestation. In many previous studies, GI symptoms were uncommon[2,10,11,13] but

Table 3. CT and Laboratory Findings of Patients with COVID-19 With and Without GI Symptoms

	All Patients (*n* = 405)	No GI Symptoms (*n* = 210)	GI Symptoms (*n* = 195)	*P*
Chest CT images—No. (%)				
Abnormal	27 (6.7)	11 (5.2)	16 (8.2)	.28
Single lung	29 (7.2)	18 (8.6)	11 (5.6)	-
Bilateral lung	349 (86.2)	181 (86.2)	168 (86.2)	-
Ground-glass opacity	285 (70.4)	154 (73.3)	131 (67.2)	.175
Lung consolidation	120 (29.6)	58 (27.6)	62 (31.8)	.358
Pleural effusion	22 (5.4)	8 (3.8)	14 (7.2)	.135
Laboratory findings—No. (%)				
Leukocytes				
Increased	31 (7.7)	13 (6.2)	18 (9.2)	.384
Decreased	72 (17.8)	35 (16.7)	37 (19.0)	
Lymphocytes				
Decreased	293 (72.3)	133 (63.3)	160 (82.1)	<.001
CRP				
Increased	293 (72.3)	139 (66.2)	154 (79.0)	.004
PCT				
Increased	107 (26.4)	41 (19.5)	66 (33.8)	.001
ALT				
Increased	82 (20.2)	44 (21.0)	38 (19.5)	.714
AST				
Increased	84 (20.7)	47 (22.4)	37 (19.0)	.398
LDH				
Increased	140 (34.6)	70 (33.3)	70 (35.9)	.588
CK				
Increased	37 (9.1)	19 (9.0)	18 (9.2)	.949
D-dimer				
Increased	257 (63.5)	135 (64.3)	122 (62.6)	.719
Albumin				
Decreased	290 (71.6)	150 (71.4)	140 (71.8)	.935

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase; GI, gastrointestinal; PCT, procalcitonin; CK, creatine kinase.

there are also reports of some cases with GI symptoms as the first manifestation.[14-16] Therefore, clinicians must pay attention to GI symptoms, recognize and prevent the early spread of COVID-19, and avoid missed cases. The GI symptoms mainly included diarrhea, nausea, vomiting, epigastric discomfort, acid regurgitation, belching, poststernal discomfort, heartburn, and constipation; 33.8% of the patients had a history of digestive system diseases, with chronic gastritis (11.3%) being the most common, followed by peptic ulcers (7.7%) and cholelithiasis/cholecystitis (7.7%). Based on these data, we can infer that COVID-19 may cause acute gastritis or enteritis consistent with Chen's reports,[11] but it still needs further study. In 195 patients with GI symptoms, the most common were fever (81.5%), poor appetite (60.0%), and cough (59.5%), which was consistent with the characteristics of COVID-19. However, patients with GI symptoms are more likely to suffer from poor appetite. On the one hand, this is related to fever. The increase in body temperature leads to the deactivation of some enzymes in

the body that affect appetite. On the other hand, poor appetite is caused by GI discomfort. Additionally, most patients with GI symptoms gradually improved after using GI drugs, indicating that the impact of the virus on the digestive system is not serious.

Radiologically, the most common sign in CT scans is ground-glass opacity in both lungs,[2,10,13] and our results were consistent with these findings. In our study, 93.3% of the patients had abnormal CT scans, and 86.2% had lesions involving both lungs, mainly ground-glass opacity. However, 30.9% of patients had pulmonary consolidation and 5.4% had pleural effusion. Consistent with two recent reports,[12,17] lymphopenia and hypoproteinemia were the most common laboratory abnormalities, followed by elevated D-dimer levels. In some patients, leukocyte count, CRP, PCT, D-dimer, and CK levels were increased, indicating that COVID-19 may lead to inflammatory and coagulation disorders. CRP, PCT, and lymphocyte count are related to infection and immunity, while the proportion of patients with GI symptoms who have increased CRP, PCT, and decreased lymphocyte count is significantly higher than that of patients without GI symptoms. This means that patients with GI symptoms had a more severe infection and disorders of the immune system. This might be related to reduced food intake and disorder of digestive tract flora, which leads to dysregulation of immune systems, aggravation of infection, and then the decrease of appetite, thus forming a vicious circle.[18,19] Therefore, in patients with GI symptoms, we should include symptomatic treatment, if necessary, to increase immunity and regulate intestinal flora, so as to avoid further aggravation of COVID-19 patients and more effectively control the development of COVID-19. In addition, 20% of patients had abnormal liver function, which indicated that SARS-CoV-2 not only affects the GI tract but also the liver.

The first confirmed case in the United States was by RT-PCR detection of viral nucleic acid in stool and respiratory tract samples, indicating that SARS-CoV-2 may be located in the GI tract. Next-generation sequencing technology and molecular modeling have revealed that SARS-CoV-2 shares about 79% sequence identity with SARS-CoV-1 (another lineage B betacoronavirus), indicating that these two viruses are homologous.[20] Angiotensin-converting enzyme (ACE) 2 is known to be an entry receptor for SARS-CoV-1. Lu et al. reported that the receptor binding domains of SARS-CoV-1 and SARS-CoV-2 are structurally similar, as indicated by molecular modeling. Therefore, SARS-CoV-2 might also use ACE2 as an entry receptor, despite the presence of amino acid mutations in the SARS-CoV-2 ACE2 receptor binding domain.[20] ACE2 is abundant in human lung and intestinal epithelium, in agreement with the notion that the pulmonary and GI tracts are possible routes of SARS-CoV-2 infection.[12] Hashimoto et al. showed that ACE2 is mainly expressed on the luminal surface of differentiated small intestinal epithelial cells, and mutations in ACE2 can reduce the expression of antimicrobial peptides and alter the gut microbial composition.[21] Therefore, we speculate that acute gastroenteritis caused by SARS-CoV-2 infection may be related to intestinal flora imbalance. Previous studies have shown that most patients infected with SARS-CoV-2 have respiratory symptoms, but few have GI symptoms. However, recent studies have found that the proportion of patients with GI symptoms is increasing.[10,11,22] Additionally, in our study, the proportion of patients with GI symptoms was nearly 50%, while the proportions of patients with fever and cough were significantly lower than previously reported. We speculate that this difference is due to the mutation of the virus that has increased its infectivity and organ susceptibility but decreased its virulence. However, the mechanisms by which SARS-CoV-2 causes GI symptoms remain to be explored.

In conclusion, when we consider the typical symptoms of COVID-19, we should not ignore its accompanying symptoms. GI symptoms are the most common extrapulmonary symptoms found in COVID-19. Therefore, clinicians should be more vigilant for GI symptoms in clinical diagnosis and should not ignore atypical clinical features while treating patients. Only by paying full attention can we be more effective in preventing the spread of COVID-19.

Ethics Committee Approval: This study was approved by the Ethics and Science Committee of Wuhan University Tongren Hospital (KY2020-021).

Informed Consent: In view of the urgent need to collect clinical data, the requirement for written informed consent was waived.

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REFERENCES

1. Ramphul K, Mejias SG. Coronavirus disease: a review of a new threat to public health. Cureus. 2020 Mar 15;12(3):e7276. [CrossRef]
2. Henry BM, Vikse J. Clinical characteristics of Covid-19 in China. N Engl J Med. 2020 May 7;382(19):1860–1861. [CrossRef]
3. Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020 May;158(6):1518–1519. [CrossRef]
4. Kotfis K, Skonieczna-Żydecka K. COVID-19: gastrointestinal symptoms and potential sources of 2019-nCoV transmission. Anaesthesiol Intensive Ther. 2020;52(2):171–172. [CrossRef]
5. Silva AAMD. On the possibility of interrupting the coronavirus (COVID-19) epidemic based on the best available scientific evidence. Rev Bras Epidemiol. 2020 Mar 16;23:e200021. [CrossRef]
6. Lee IC, Huo TI, Huang YH. Gastrointestinal and liver manifestations in patients with COVID-19. J Chin Med Assoc. 2020 Jun;83(6):521–523. [CrossRef]
7. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): what do we know till now? Arab J Gastroenterol. 2020 Mar;21(1):3–8. [CrossRef]
8. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health – the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020 Feb;91:264–266. [CrossRef]
9. Guan GW, Gao L, Wang JW, et al. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. Zhonghua Gan Zang Bing Za Zhi. 2020 Feb 20;28(2):100–106. [CrossRef]
10. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Jul;75(7):1730–1741. [CrossRef]
11. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15 ;395(10223):507–513. [CrossRef]
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497–506. [CrossRef]
13. Guan WJ, Zhong NS. Clinical characteristics of Covid-19 in China (reply). N Engl J Med. 2020 Feb 15;395(10223):497–506.[CrossRef]
14. Nobel YR, Phipps M, Zucker J, et al. Gastrointestinal symptoms and COVID-19: case-control study from the United States. Gastroenterology. 2020 Jul;159(1):373–375.e2. [CrossRef]
15. Henry BM, de Oliveira MHS, Benoit J, Lippi G. Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (COVID-19): a pooled analysis. Intern Emerg Med. 2020 Aug;15(5):857–859. [CrossRef]
16. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020 Jun;69(6):997–1001. [CrossRef]
17. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 Mar 17;323(11):1061–1069. [CrossRef]
18. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020 May;51(9):843–851. [CrossRef]
19. Zuo T, Zhang F, Lui GCY, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology. 2020 Sep;159(3):944–955.e8. [CrossRef].
20. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Feb 22;395(10224):565–574. [CrossRef]
21. Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature. 2012 Jul 25;487(7408):477–81. [CrossRef]
22. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020 Jun;69(6):1002–1009. [CrossRef]