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Alimentary Tract

Clinical characteristics of coronavirus disease (COVID-19) patients with gastrointestinal symptoms: A report of 164 cases

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ABSTRACT

Objective: To explore the clinical characteristics of Coronavirus Disease (COVID-19) patients with gastrointestinal symptoms.
Methods: The clinical data of 164 COVID-19 patients with gastrointestinal symptoms were extracted and analysed retrospectively.
Results: In total, 505 COVID-19 patients were divided into two groups: those with gastrointestinal symptoms (G group) and those without gastrointestinal symptoms (NG group). Common gastrointestinal symptoms included inappetence, diarrhoea, nausea, abdominal pain, and vomiting. Significantly higher proportions of patients with fever, dizziness, myalgia, and fatigue were noted in group G than in group NG. Compared with patients without fever, there was a significant difference between G group and NG group in moderate fever or above, while there was no significant difference between the two groups in low fever. The laboratory results showed that patients in the G group had significantly higher C-reactive protein, lactate dehydrogenase, and α-hydroxybutyrate dehydrogenase levels than those in the NG group. Moreover, the proportion of patients with severe pneumonia was significantly higher in the G group than in the NG group.
Conclusion: In Wuhan, the proportion of COVID-19 patients who experience gastrointestinal symptoms is relatively high. Patients who experience gastrointestinal symptoms are more likely to suffer from severe pneumonia, which may help clinicians identify patients at high risk of COVID-19 and thus reduce the incidence of this condition.

1. Introduction

Coronavirus disease (COVID-19) is an acute respiratory infection caused by the novel coronavirus (SARS-CoV-2). SARS-CoV-2 has a high transmission rate and is transmitted through respiratory droplets or close contact with an infected individual. The clinical symptoms of gastrointestinal symptoms include fever, cough, fatigue, and diarrhoea [1]. In addition to studies on respiratory symptoms, recent studies have shown that SARS-CoV-2 infection can also cause gastrointestinal symptoms [2,3]. A cohort study of 140 COVID-19 patients showed that gastrointestinal symptoms were observed in 39.6% of the patients, including nausea (17.3%), diarrhoea (12.9%) and vomiting (5.0%) [4]. Recently, atypical cases of SARS-CoV-2 infection characterized by gastrointestinal symptoms have been reported [5]. SARS-CoV-2 infection manifesting as gastrointestinal symptoms may pose diagnostic and treatment difficulties and may result in medical workers being exposed to the virus unknowingly. A recent survey of 2209 gastroenterologists in China showed that only 31–35% provided the correct answers on the clinical characteristics of the digestive system in COVID-19, suggesting that they did not know much about the symptoms that occur after digestive system damage [6]. Therefore, we determined that a retrospective analysis of cases might be useful for clinicians to identify the clinical characteristics of COVID-19 patients with gastrointestinal symptoms.

2. Methods

2.1. Data sources

Clinical data were extracted from the electronic medical records of 504 patients with confirmed COVID-19 patients who were treated at the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology and retrospectively analysed. The patients were divided into two groups according to whether or not they experienced gastrointestinal symptoms: G group, comprising 164 patients who experienced gastrointestinal symptoms, and NG group, comprising 341 patients who did

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not experience gastrointestinal symptoms. All patients enrolled in this study were diagnosed according to the Diagnosis and Treatment Protocol for COVID-19 Patients (Trial Version 5) issued by the National Health Commission of the People's Republic of China and National Administration of Traditional Chinese Medicine [1]. COVID-19 severity was classified as mild, moderate, severe, or critical. Patients in the severe and critical subgroups were deemed to have severe pneumonia, whereas those in the mild and moderate subgroups were deemed to have non-severe pneumonia. This study was approved by the ethics committee of the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology (2020–62).

2.2. Observe indicators

The demographic and clinical data of each patient were retrospectively collected in order to establish an information database of COVID-19 patients. For each COVID-19 patient, the following information was collected: sex, age, comorbidities, highest temperature before admission, C-reactive protein (CRP) levels, procalcitonin levels, D-dimer levels, liver function, renal function, myocardial enzyme levels, and levels of other observe indicators. Comorbidities included chronic lung disease, hypertension, coronary heart disease, diabetes, chronic kidney disease, chronic liver disease (including cirrhosis), cerebrovascular disease, and malignancy. A history of exposure was defined as previous exposure to the Huanan Seafood Wholesale Market or direct contact with a patient with confirmed or suspected COVID-19.

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. For normally distributed continuous variables, the *t*-test was used to analyse differences between groups; otherwise, the Mann–Whitney test was used. For categorical variables, χ^2 test or Fisher's exact test was used to analyse differences between groups. $P<0.05$ was considered to indicate statistical significance. SPSS software, version 25.0 (IBM Corp., Armonk, NY), was used for all statistical analyses.

3. Results

3.1. Demographic and clinical characteristics

A total of 505 patients were enrolled in this study – 228 (45.1%) males and 277 (54.9%) females with an average age of 51.2 ± 17.2 years. Group G comprised 164 patients, 73 males (44.5%) and 91 females (55.5%), with an average age of 53.0 ± 18.3 years. Group NG comprised 341 patients, 155 males (45.5%) and 186 females (54.5%), with an average age of 50.3 ± 16.6 years. Only 6 patients (1.2%) had a history of direct contact with the Huanan Seafood Wholesale Market. The number of patients with a history of exposure in the NG and G groups was 137 and 49, respectively. The duration from symptom onset to admission was 8.7 ± 6.2 days and 8.0 ± 4.9 days in groups NG and G, respectively ($P=0.170$). Overall, 115 patients (33.7%) in the NG group and 63 patients (38.4%) in the G group had comorbidities ($P=0.302$). Moreover, 38 patients in the G group and 54 patients in the NG group had severe pneumonia. The proportion of patients with severe pneumonia significantly differed between the groups ($P=0.046$).

3.2. Clinical manifestations

Gastrointestinal symptoms were observed in 164 (32.5%) COVID-19 patients: 93 (56.7%) had inappetence, 62 (37.8%) had diarrhoea, 27 (16.5%) had nausea, 17 (10.4%) had abdominal pain, and 13 (7.9%) had vomiting. With regard to other clinical manifestations, the proportions of patients with fever, myalgia, fatigue, and dizziness significantly differed between the groups ($P < 0.05$).

Compared with patients without fever, there was a significant difference between G group and NG group in moderate fever or above, while there was no significant difference between the two groups in low fever. Patients' diarrhea frequency was between 3 and 10 times per day. Most of them passed thin pasty yellow or watery stools and did not experience dehydration or haematochezia. Occult blood was detected in stool samples from 28 patients, all of whom passed yellow stools, although obvious red and white blood cells were not detected in routine stool examinations (Table 1).

Table 1
Comparison of clinical data between the two groups.

	NG group	G group	*P* values
Total cases	341	164	–
Fever	252	137	0.016
Low fever	96	50	0.053[a]
Moderate fever	119	64	0.032[a]
High fever or above	37	23	0.036[a]
Dry cough	141	59	0.248
Fatigue	105	103	< 0.001
Chest distress	16	5	0.386
Myalgia	76	50	0.046
Expectoration	91	41	0.686
Dizziness	24	23	0.011
Wheezing	71	31	0.615
Headache	31	13	0.664
Sore throat	15	11	0.271
Runny nose	9	2	0.485[b]
OB	16	12	0.227
Systemic symptom	132	118	< 0.001
Respiratory symptoms	332	158	0.528
Neurological symptoms	46	33	0.055

[a] The control group was non-fever patients.
[b] Continuous correction chi square test used; NG group: COVID-19 patients without gastrointestinal symptoms group; G group: COVID-19 patients with gastrointestinal symptoms; Low fever: 37.3 –38.0 °C; Moderate fever:38.1−−39 °C; High fever or above:>39.1 °C; OB: Faecal occult blood; Systemic symptoms include fatigue and myalgia; Respiratory symptoms include fever, dry cough, expectoration, chest distress, wheezing, sore throat and runny nose; Neurological symptoms include dizziness and headaches.

3.3. Laboratory indicators

In the early stages of COVID-19, patients in the G group exhibited significantly higher CRP, lactate dehydrogenase, and α-hydroxybutyrate dehydrogenase levels than those in the NG group ($P < 0.05$). In contrast, in the early stages of COVID-19, white blood cell count, neutrophil percentage, lymphocyte count, platelet count, and procalcitonin, D-dimer, creatine kinase, total bilirubin, alanine aminotransferase, aspartate transaminase, γ-glutamine transferase, creatinine, and urea levels did not significantly differ between the groups ($P > 0.05$) (Table 2).

4. Discussion

Coronaviruses are a group of viruses whose host species include birds and mammals. Coronaviruses exhibit broad tissue tropism, which can cause acute or chronic damage to the respiratory system, digestive system, and nervous system of the host. During the past two decades, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and 2019-nCoV, three cross-species coronaviruses, have infected human beings and seriously affected global public health.

Table 2
Comparison of laboratory parameters between the two groups.

Test	Normal ranges	NG group	G group	P values
WBC (10^9/L)	3.5–9.5	5.4 ± 2.4	5.4 ± 3.2	1
Neutrophils (%)	40–75	65.9 ± 13.9	66.3 ± 13.8	0.761
Leukomonocytes (10^9/L)	1.1–3.2	1.2 ± 0.6	1.1 ± 0.6	0.08
Platelets (10^9/L)	125–350	198.0 ± 78.2	188.4 ± 75.8	0.188
CRP (mg/dL)	0–0.6	2.5 ± 3.3	3.2 ± 3.8	0.044
Procalcitonin (ng/ml)	<0.1	0.2 ± 0.8	0.7 ± 4.5	0.16
D-dimer (μg/ml)	0–1	2.0 ± 8.7	1.5 ± 3.1	0.346
CK (U/L)	26–140	112.9 ± 132.2	152.9 ± 344.2	0.152
LDH (U/L)	103–227	195.4 ± 85.6	231.0 ± 146.0	< 0.001
α-HBDH (U/L)	72–182	152.0 ± 64.7	176.4 ± 98.3	0.004
TBIL (μmol/L)	2–20.4	9.9 ± 5.6	11.3 ± 12.4	0.169
ALT (U/L)	7–40 u /L	27.4 ± 38.4	42.1 ± 120.3	0.128
AST (U/L)	13–35	26.4 ± 22.0	48.1 ± 188.9	0.144
GGT (U/L)	7–45	42.3 ± 72.3	45.8 ± 106.4	0.703
Creatinine (μmol/L)	41–73	79.6 ± 131.9	66.0 ± 24.0	0.066
Urea (mmol/L)	1.7–8.3	4.7 ± 3.6	4.6 ± 3.2	0.753

NG group: COVID-19 patients without gastrointestinal symptoms group; G Group: COVID-19patients with gastrointestinal symptoms; WBC: white blood cells count; CRP: C-reactive protein; CK: creatine kinase; LDH: lactate dehydrogenase; α-HBDH: α-butyrate dehydrogenase; TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartic acid transferase; GGT: γ-glutamyl transferase.

In 2003, there was an outbreak of 320 SARS cases in Amoy Gardens, Hong Kong, and 66% of patients experienced diarrhoea. This outbreak was found to be related to the pollution of water sources by SARS-CoV [7]. Gastrointestinal symptoms are a relatively common clinical manifestation of MERS [8]. In addition, viral nucleic acid was detected in the faeces of 14.6% of 823 specimens from 37 MERS patients [9]. SARS-CoV-2 is similar to the aforementioned coronaviruses and is known to also cause gastrointestinal symptoms. Zhong et al. [10] studied 1099 COVID-19 patients and showed that only 3.7% had diarrhoea and 5% had vomiting. However, Fang et al. [3] showed that 79.1% of patients in the Wuhan area experienced gastrointestinal symptoms. In our study, 32.5% of COVID-19 patients had gastrointestinal symptoms, primarily inappetence (56.7%), diarrhoea (37.8%), and nausea (16.5%). Notably, abdominal pain and vomiting were rare. The incidence of gastrointestinal symptoms in COVID-19 patients in the Wuhan area was significantly higher than the overall incidence of gastrointestinal symptoms in COVID-19 patients across China, which may be related to the virulence of SARS-CoV-2. Wuhan is the epicentre of the outbreak, so COVID-19 patients in Wuhan were more critically ill than in other areas across China. SARS-CoV-2 evolved into two major types: L type with more aggressive and spread more quickly, and S type with evolutionarily older and less aggressive. Tang et al. showed that S type of the virus was observed in 3.7% of viral isolates in Wuhan and 38.4% of viral isolates outside of Wuhan, while L type of the virus was observed in 96.3% of viral isolates in Wuhan and 61.3% of viral isolates outside of Wuhan [11] Furthermore, our study analysed gastrointestinal symptoms occurring before admission, and gastrointestinal symptoms occurring during hospitalisation were not considered. Therefore, the incidence of gastrointestinal symptoms in our cohort was lower than that reported by Fang et al.

In this study, red and white blood cells were not identified in the faeces of patients who experienced gastrointestinal symptoms, a finding characteristic of viral infections. Compared to patients without gastrointestinal symptoms, patients with gastrointestinal symptoms are more likely to have severe COVID-19. A recent meta-analysis also showed that gastrointestinal symptoms were found to be associated with severe COVID-19 [12]. We speculate that gastrointestinal symptoms may be related to the degree of viral replication, with increased severity of disease associated with a high viral load. In addition, this result suggests that the correlation between gastrointestinal symptoms and systemic symptoms such as dizziness, myalgia, and fatigue observed in this study increases the difficulty of clinical diagnosis. One possibility is that the medical staff was trained to focus mainly on obvious respiratory symptoms, and extrapulmonary symptoms may be initially overlooked during the widespread outbreak.

The mechanism by which SARS-CoV-2 causes gastrointestinal symptoms is unclear. There are several possible explanations for the gastrointestinal symptoms in COVID-19 patients. Firstly, it has been shown that angiotensin-converting enzyme 2 (ACE2) is a host cell receptor of SARS-CoV-2. ACE2 is highly expressed not only in alveolar epithelial cells but also in the epithelium of the oesophagus, small intestine, and colon [13–15]. Previous studies revealed that SARS-CoV and MERS-CoV RNAs could be detected in the SARS and MERS patients' stool sample, respectively [16,17], suggesting that coronavirus has a tropism to the gastrointestinal tract. Similarly, gastrointestinal shedding of SARS-CoV-2 RNA detected in faeces has been reported [18]. Electron microscopy on autopsy specimens of COVID-19 patients also showed damage to the oesophagus, stomach, and intestines [19]. The tropism of SARS-CoV-2 to the gastrointestinal tract is associated to gastrointestinal symptoms. Therefore, it is possible that SARS-CoV-2 attacks the gastrointestinal tract, which would explain the presence of gastrointestinal symptoms in COVID-19 patients. These evidences have provided basis for its possible transmission route in faeces. Secondly, gastrointestinal symptoms may be a manifestation of an indirect or direct SARS-CoV-2 effects through the cytokine storm syndrome. Over-activated lymphocytes secrete a large number of cytokines, resulting in systemic inflammatory response syndrome, which causes inflammation and damage of the gastrointestinal tract [20]. Patients who experienced gastrointestinal symptoms exhibited higher CRP, lactate dehydrogenase, and α-hydroxybutyrate dehydrogenase levels. These data suggest a possible correlation between gastrointestinal injury and the inflammatory responses induced by SARS-CoV-2 infection. Thirdly, gastrointestinal symptoms may be drug-induced. The side effect of drug treatment, such as antibiotic and antiviral, may be related to the gastrointestinal symptoms, yet whether it damages the digestive system in patients remains to be investigated.

The present study has several limitations. First, the diagnosis of COVID-19 was based on the 5th version guidance according to National Health Commission of China. However, some enrolled patients in this cohort were diagnosed based on clinical diagnostic criteria, not the gold standard. During the early stage of COVID-19

outbreak, suspected cases with characteristic manifestations in CT scans were treated as confirmed cases even when the nucleic acid test was negative or unavailable [1]. Second, this study was the lack of the result of SARS-CoV-2 RNA in the stool of COVID-19 patients, so we did not determine the hypothesis that the severity of gastrointestinal symptoms may be related to the presence of viral replication in stool. Third, our analysis was based on a retrospective study with a relatively small sample, which might cause bias and limit the reliability or generalizability of our results.

In summary, the proportion of COVID-19 patients who experience gastrointestinal symptoms in the Wuhan area is relatively high. The most common gastrointestinal symptoms are inappetence and diarrhoea, and these are typically accompanied by moderate or high fever. Patients who experience gastrointestinal symptoms are more likely to suffer from severe pneumonia, which may help clinicians identify patients at high risk of COVID-19 and thus reduce the incidence of this condition.

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Declaration of Competing Interest

None.

Author contributions

Zhang Heng designed this study and critically revised the manuscript; Zhang Hu, Gong Jing, and Liu Jing were responsible for data acquisition and extraction; Zhang Hu and Zhang Heng drafted the manuscript, analysed the data, and interpreted the results; Xia Xi and Liao Yu-Sheng were involved in editing the manuscript; all authors read and approved the final manuscript.

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