Clinical characteristics and outcomes of COVID-19 patients with gastrointestinal symptoms admitted to Jianghan Fangcang Shelter Hospital in Wuhan, China

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Abstract
Coronavirus disease 2019 (COVID-19) is a health emergency worldwide, and gastrointestinal (GI) symptoms are increasingly reported in COVID-19 patients. However, sample size was small and the incidence of GI symptoms in patients was variable across studies, and the correlation between these symptoms and clinical outcomes remains incompletely understood. The objective of this study is to compare clinical characteristics and outcomes between patients with and without GI symptoms admitted to Jianghan Fangcang Shelter Hospital in Wuhan. This retrospective study recruited 1320 COVID-19 patients admitted to hospital from 5 February 2020 to 9 March 2020. On the basis of the presence of GI symptoms, the sample was divided into a GI group (n = 192) and a non-GI group (n = 1128). The three most common GI symptoms were diarrhea (8.1%), anorexia (4.7%), and nausea and vomiting (4.3%). The rate of clinical deterioration was significantly higher in the GI group than in the non-GI group (15.6% vs. 10.1%, \(P = .032\)). GI symptoms (\(P = .045\)), male gender (\(P < .001\)), and increased C-reactive protein (\(P = .008\)) were independent risk factors for clinical worsening. This study demonstrated that the rate of clinical deterioration was significantly higher in the GI group. Furthermore, potential risk factors for developing GI symptoms, male gender, and increased C-reactive protein can help clinicians predict clinical outcomes in COVID-19 patients.

KEYWORDS
clinical progression, COVID-19, Fangcang Shelter Hospital, gastrointestinal symptoms, viral nucleic acid

1 INTRODUCTION

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), has caused a pandemic. As of 13 April 2020, 1 855 587 COVID-19 cases were recorded worldwide, and 114 232 patients died. This respiratory disease quickly attracted attention given its high rate of transmission.¹

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Coronaviruses are single, plus-stranded RNA viruses that infect different animal species, including humans, and cause respiratory, neurological, and hepatic diseases. Previous studies have indicated that the following seven coronaviruses infect humans: 229E, OC43, NL63, HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2. Of these, the latter three viruses cause acute respiratory syndrome.

SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors to enter host cells. ACE2 is highly expressed in alveolar type II cells of the lung and gastrointestinal (GI) epithelial cells. Recent studies have shown that GI symptoms are common in patients with COVID-19, and a small proportion of infected patients have GI symptoms, but not other symptoms, at disease onset. In addition, SARS-CoV-2 nucleic acid was detected not only in nasopharyngeal swabs and saliva samples, but also in stool samples. There was evidence that patients with COVID-19 may transmit the virus through the fecal-oral route. However, few studies evaluated the clinical features and prognosis of COVID-19 patients with GI symptoms. This study analyzed the clinical characteristics and prognosis of these patients and independent risk factors for clinical deterioration.

2 METHODS

2.1 Study design and participants

From 5 February 2020 to 9 March 2020, 1848 patients aged 18 to 65 years old were diagnosed with COVID-19 at the Jianghan Fangcang Shelter Hospital. A total of 1320 COVID-19 patients with mild or common type were enrolled after excluding cases with missing data (Figure 1). Jianghan Fangcang Shelter Hospital is responsible for isolating patients and providing medical care, monitoring disease progression, promote social activities, and cater for basic needs, including food and shelter. Patients whose clinical condition worsened were transferred to tertiary hospitals. Clinical worsening was defined as progression from mild or common to severe type based on one of the following criteria: (a) respiratory rate more than or equal to 30 times per minute; (b) oxygen saturation less than or equal to 93%; (c) arterial partial pressure of oxygen/fraction of inspired oxygen less than or equal to 300 mm Hg. Disease severity was defined according to the Chinese management guidelines for COVID-19.

All study participants were diagnosed based on the Chinese National Diagnosis and Treatment Guidelines for COVID-19. GI symptoms included diarrhea, abdominal pain, nausea and vomiting, and anorexia. Based on the presence of GI symptoms, patients were divided into GI and non-GI groups. Clinical features, laboratory findings, treatment procedures, and clinical outcomes were compared between the two groups. This retrospective study was approved by the Medical Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology ([2020]0038).

2.2 Procedures

Data on demographic and clinical characteristics, radiological and laboratory findings, treatment procedures, and clinical outcomes were obtained from electronic medical records. The follow-up deadline was 25 March 2020. Normal body temperature was defined as less than 37.3°C without using antipyretic drugs. Nasopharyngeal swab samples were collected, and SARS-CoV-2 nucleic acid was detected by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The re-examination of viral nucleic acid was performed every other day after meeting the following criteria: (a) clinical symptoms were improved; (b) the total course of the disease was longer than 1 week; (c) body temperature was normal for at least 3 days without using antipyretic drugs. Viral clearance was defined as two consecutive negative results on RT-PCR for SARS-CoV-2 RNA amplified at least 24 hours apart, and the date of first negative result was considered as the date of viral clearance. The criteria for hospital discharge were (a) maintenance of normal body temperature for at least 3 days; (b) notable improvement in chest computed tomography (CT) scan and symptoms; (c) two nasopharyngeal swab samples negative for SARS-CoV-2 RNA collected at least 24 hours apart.
2.3 | Statistical analysis

Categorical variables were presented as frequency and percentages, and continuous variables were shown as interquartile range (IQR), median, or mean. Statistical analyses were performed using the χ² test, Mann–Whitney U test, or t-test to evaluate differences between the GI and non-GI groups. Logistic regression analysis was carried out to identify risk factors for clinical deterioration. The time to viral clearance was assessed using the Kaplan–Meier method. Statistical analysis was performed using SPSS software (version 23), and figures were prepared using GraphPad Prism (version 8.0). A two-sided P-value less than .05 indicated a statistically significant difference.

3 | RESULTS

3.1 | Demographic and clinical characteristics

This retrospective study included 1320 patients with confirmed COVID-19 infection admitted to Jianghan Fangcang Shelter Hospital from 5 February 2020 to 9 March 2020. Based on the presence of GI symptoms, the patients were assigned to a GI group (n = 192) or a non-GI group (n = 1128). The median age of the total sample was 50 years (IQR: 40-57 years), and 741 (56.1%) subjects were female. The three most common symptoms were fever (83.0%), cough (42.9%), and fatigue (23.6%) (Table 1). The uncommon symptoms were palpitations (2.2%), sore throat (2.3%), night sweats (2.3%),

| TABLE 1 | Demographic and clinical characteristics of patients with COVID-19 |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Clinical characteristics | All patients | GI group | Non-GI group | P-value |
| Age, median (IQR), y | 50 (40-57) | 50 (38-56) | 51 (41-58) | .134 |
| Gender (n, %) | | | | .387 |
| Male | 579 (43.9%) | 90 (46.9%) | 489 (43.4%) | |
| Female | 741 (56.1%) | 102 (53.1%) | 639 (56.6%) | |
| Symptoms (n, %) | | | | |
| Fever | 1095 (83.0%) | 171 (89.1%) | 924 (81.9%) | .017 |
| Expectoration | 154 (11.7%) | 51 (26.6%) | 103 (9.1%) | <.001 |
| Cough | 566 (42.9%) | 98 (51.0%) | 468 (41.5%) | .014 |
| Palpitations | 29 (2.2%) | 10 (5.2%) | 19 (1.7%) | .005 |
| Chest pain | 44 (3.3%) | 10 (5.2%) | 34 (3.0%) | .127 |
| Nasal congestion | 31 (2.3%) | 8 (4.2%) | 23 (2.0%) | .115 |
| Headache | 53 (4.0%) | 25 (13.0%) | 28 (2.5%) | <.001 |
| Night sweats | 30 (2.3%) | 7 (3.6%) | 23 (2.0%) | .186 |
| Dyspnea | 70 (5.3%) | 13 (6.8%) | 57 (5.1%) | .300 |
| Myalgia | 108 (8.2%) | 38 (19.8%) | 70 (6.2%) | <.001 |
| Fatigue | 311 (23.6%) | 81 (42.2%) | 230 (20.4%) | <.001 |
| Sore throat | 38 (2.9%) | 10 (5.2%) | 28 (2.5%) | .057 |
| Gastrointestinal symptoms (n, %) | | | | |
| Diarrhea | 107 (8.1%) | 107 (55.7%) | 0 | |
| Abdominal pain | 11 (0.8%) | 11 (5.7%) | 0 | |
| Anorexia | 62 (4.7%) | 62 (32.3%) | 0 | |
| Nausea and Vomiting | 57 (4.3%) | 57 (29.7%) | 0 | |
| Treatment (n, %) | | | | |
| Antiviral treatment | 1080 (81.8%) | 162 (84.4%) | 918 (81.4%) | .363 |
| Lianhuaqingwen capsules | 1012 (76.7%) | 154 (80.2%) | 858 (76.1%) | .231 |
| Antibiotic treatment | 342 (25.9%) | 54 (28.1%) | 288 (25.5%) | .476 |
| Corticosteroids | 3 (0.2%) | 1 (0.5%) | 2 (0.2%) | .376 |
| Gamma globulin | 6 (0.5%) | 4 (2.1%) | 2 (0.2%) | .005 |
| Outcome (n, %) | | | | .032 |
| Discharge | 1176 (89.1%) | 162 (84.4%) | 1014 (89.9%) | |
| Transfer | 144 (10.9%) | 30 (15.6%) | 114 (10.1%) | |
| Hospital length of stay, d | 18.5 ± 6.0 | 19.6 ± 5.9 | 18.4 ± 6.0 | .013 |
| Time from symptoms onset to viral clearance, d | 25.0 ± 9.1 | 26.2 ± 9.0 | 24.7 ± 9.1 | .046 |

Abbreviations: COVID-19, coronavirus disease 2019; GI, gastrointestinal; IQR, interquartile range.
and nasal congestion (2.3%). Only 14.5% of patients had GI symptoms. In the GI group, the most prevalent GI symptoms were diarrhea (55.7%), and the least common symptom was abdominal pain (5.7%). Compared with the non-GI group, the GI group was more likely to have fever (89.1% vs 81.9%; \( P = .017 \)), cough (51.0% vs 41.5%; \( P = .014 \)), headache (13.0% vs 2.5%; \( P < .001 \)), expectoration (26.6% vs 9.1%; \( P < .001 \)), and fatigue (42.2% vs 20.4%; \( P < .001 \)).

Among the 1320 patients, 1080 patients received antiviral drugs, including Lianhuaxingwen capsules (1012, 76.7%), arbidol (987, 74.8%), or oseltamivir (569, 43.1%). Moreover, the risk of clinical deterioration was significantly higher in the GI group than in the non-GI group (15.6% vs 10.1%; \( P = .032 \)). The length of hospital stay was significantly longer in patients with GI symptoms than in patients without these symptoms (19.6 ± 5.9 vs 18.4 ± 6.0 days; \( P = .013 \)). The average time from symptom onset to viral clearance was 26.2 ± 9.0 days and 24.7 ± 9.1 days in patients with and without GI symptoms, respectively (\( P = .046 \); Table 1).

3.2 Laboratory and radiological findings

The median lymphocyte count was significantly higher in the non-GI group (1.99 vs 1.76; \( P = .038 \)). However, there were no significant intergroup differences in hematological parameters, including leukocyte, neutrophil, and platelet count, hemoglobin, and C-reactive protein (CRP). Of the total patients, the vast majority (66.1%) showed typical ground-glass opacities on chest CT. Bilateral lesions on chest CT were found in 884 patients and were more common in the GI group (78.1% vs 65.1%; \( P < .001 \); Table 2).

3.3 Factors associated with clinical worsening

To identify risk factors related with poor prognosis in our cohort, we compared clinical and laboratory features between patients transferred to tertiary hospitals (n = 144) and those discharged from hospitals (n = 1176). Univariate analysis showed that GI symptoms (\( P = .025 \)), male gender (\( P < .001 \)), and elevated CRP (\( P = .006 \)) were associated with clinical deterioration (Table 3). Multivariable logistic regression analysis showed that GI symptoms (\( P = .045 \)), male gender (\( P < .001 \)), and elevated CRP (\( P = .008 \)) were independent risk factors for patient transfer to a tertiary hospital (Table 3).

3.4 Viral clearance in the upper respiratory route

During the follow-up period, SARS-CoV-2 was detected in nasopharyngeal swab samples from 1320 patients. Viral clearance was defined as two consecutive negative results on RT-PCR. The estimated median time from symptom onset to viral clearance was 24 days in the non-GI group. However, this period was significantly longer in the GI group (27 vs 24 days; \( P < .05 \); Figure 2).

4 DISCUSSION

COVID-19 has attracted attention worldwide in light of its high infectivity. Research on this disease has accelerated because of its significant health and economic burden, and studies have investigated the epidemiology, clinical characteristics, and viral genome sequences of this entity. Studies conducted at the early stage of the COVID-19 outbreak indicated that respiratory symptoms such as fever and cough, but not GI symptoms, were common at disease onset. However, later studies showed that the first clinical manifestations in some patients were diarrhea, abdominal discomfort, and nausea. These patients contribute to the potential risk of infection for front-line clinicians and pose a greater challenge for early diagnosis of patients with COVID-19. Therefore, patients with GI symptoms deserve special attention, and understanding

### TABLE 2 Laboratory and radiological findings in patients with COVID-19

| Laboratory examination | All patients | GI group | Non-GI group | \( P \)-value |
|------------------------|-------------|----------|--------------|--------------|
| Hematologic, median (IQR) |             |          |              |              |
| C-reactive protein, mg/L | 0.86 (0.43-2.18) | 0.89 (0.30-2.18) | .285 |
| Leukocytes, \( \times 10^9 \)/L | 6.39 (5.33-7.49) | 6.48 (5.40-7.49) | .688 |
| Lymphocytes, \( \times 10^9 \)/L | 1.76 (1.58-2.21) | 1.99 (1.60-2.34) | .038 |
| Neutrophils, \( \times 10^9 \)/L | 3.83 (2.99-4.66) | 3.80 (2.99-4.58) | .557 |
| Eosinophils, \( \times 10^9 \)/L | 0.12 (0.08-0.20) | 0.13 (0.08-0.20) | .805 |
| Hemoglobin, g/L | 137 (129-146) | 137 (129-147) | .658 |
| Platelets, \( \times 10^9 \)/L | 240 (203-294) | 241 (200-286) | .255 |
| Chest CT (n, %) |             |          |              |              |
| Bilateral lungs | 150 (78.1%) | 734 (65.1%) | <.001 |
| Ground-glass opacities | 134 (69.8%) | 739 (65.5%) | .284 |
| Pleural effusion | 2 (1.0%) | 5 (0.4%) | .271 |

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; GI, gastrointestinal; IQR, interquartile range.
differences in clinical characteristics and prognosis between patients with and without these symptoms is crucial.

Our results indicated that the most common manifestations of SARS-CoV-2 infection were fever (83.0%), cough (42.9%), and fatigue (23.6%), which was consistent with a previous study. Moreover, middle-aged and elderly people were more susceptible to SARS-CoV-2 infections, which may be the result of lower immunity in these populations. The most common GI symptoms in our sample were diarrhea (8.1%). COVID-19 patients with GI symptoms were more likely to have symptoms of fatigue, myalgia, and headache, which may be due to electrolyte disturbances. Moreover, GI disturbances may lead to intestinal flora imbalance, potentially affecting the central nervous system through the gut-brain axis and causing symptoms such as headache and fatigue. GI disorders caused by SARS-CoV-2 infection may damage the intestinal barrier, which triggered bacterial translocation from the GI tract to internal compartments, aggravating infection and inflammation. In our cohort, the proportion of patients transferred to tertiary hospitals was 10.9%, and there was a significant difference in the rate of clinical deterioration between the GI and non-GI group (15.6% vs 10.1%). Among discharged patients, the length of hospital stay was significantly longer in patients with GI symptoms than those without these symptoms (19.6 ± 5.9 vs 18.4 ± 6.0 days; \( P = .013 \)). Furthermore, a previous study showed that the need for mechanical ventilation and ICU care was significantly higher in

### TABLE 3 Risk factors associated with clinical deterioration

|                      | Univariate logistic regression |                      |                      |
|----------------------|-------------------------------|----------------------|----------------------|
|                      | OR    | 95% CI | P-value | OR    | 95% CI | P-value |
| Age, y               |       |        |         |       |        |         |
| <60                  | 1 (ref) |        |         | 1 (ref) |        |         |
| ≥60                  | 1.106 | 0.721-1.696 | .644 | 2.342 | 1.639-3.345 | <.001 |
| Male (vs female)     | 2.342 | 1.639-3.345 | <.001 | 2.347 | 1.639-3.360 | <.001 |
| Fever                | 1.397 | 0.843-2.316 | 1.095 | 1.397 | 0.843-2.316 | 1.095 |
| Gastrointestinal symptoms | 1.647 | 1.066-2.545 | .025 | 1.547 | 1.011-2.450 | .045 |
| Leukocytes, ×10⁹/L   |       |        |         |       |        |         |
| <4                   | 1.039 | 0.362-2.983 | .943 | 1.039 | 0.362-2.983 | .943 |
| 4-10                 | 1 (ref) |        |         | 1 (ref) |        |         |
| >10                  | 1.889 | 0.704-5.070 | .207 | 1.889 | 0.704-5.070 | .207 |
| Neutrophils, ×10⁹/L  |       |        |         |       |        |         |
| <1.8                 | 1.254 | 0.368-4.277 | .718 | 1.254 | 0.368-4.277 | .718 |
| 1.8-6.3              | 1 (ref) |        |         | 1 (ref) |        |         |
| >6.3                 | 1.520 | 0.701-3.298 | .289 | 1.520 | 0.701-3.298 | .289 |
| Lymphocytes, ×10⁹/L  |       |        |         |       |        |         |
| >1.1                 | 0.764 | 0.091-6.411 | .804 | 0.764 | 0.091-6.411 | .804 |
| ≤1.1                 | 1 (ref) |        |         | 1 (ref) |        |         |
| C-reactive protein, mg/L |       |        |         |       |        |         |
| <10                  | 1 (ref) |        |         | 1 (ref) |        |         |
| ≥10                  | 3.483 | 1.419-8.549 | .006 | 3.483 | 1.419-8.549 | .006 |
| Size of lung lesions on CT |       |        |         |       |        |         |
| Normal               | 1 (ref) |        |         | 1 (ref) |        |         |
| Unilateral pulmonary | 1.131 | 0.330-3.883 | .844 | 1.131 | 0.330-3.883 | .844 |
| Bilateral pulmonary   | 2.343 | 0.717-7.651 | .159 | 2.343 | 0.717-7.651 | .159 |

Abbreviations: CI, confidence interval; CT, computed tomography; OR, odds ratio.

### FIGURE 2 Time to viral clearance by polymerase chain reaction analysis of nasopharyngeal swab samples. The median time from symptom onset to viral clearance was significantly longer in the gastrointestinal (GI) group than in the non-GI group (3 days; \( P < .05 \)).
patients with GI symptoms (P = 0.034), indicating that prognosis was worse in this group. The average time from symptom onset to viral clearance was 26.2 ± 9.0 days and 24.7 ± 9.1 days in patients with and without GI symptoms, respectively (P = 0.046). Patients in the GI group were more likely to have bilateral lesions on chest CT, which might indicate higher viral load in the respiratory system. A large number of viruses present in the respiratory tract may have reached the GI tract through the blood, leading to GI infection, and higher viral load may prolong the time to viral clearance in the GI group.

Findings on the relationship between GI symptoms and illness progression are inconsistent across studies. In our cohort, GI symptoms, male gender, and elevated CRP were independent risk factors for clinical deterioration. SARS-CoV-2 may infect GI epithelial cells in COVID-19 patients with GI symptoms, leading to inflammation. Therefore, GI symptoms may be associated with higher viral load. In addition, the time from symptom onset to admission was significantly longer in patients with GI symptoms, which might cause diagnostic delay and clinical worsening. The smoking rate is higher among men in China. Studies have proved that smoking can upregulate ACE2 receptors, which may explain why male patients are at higher risk of clinical deterioration than female patients. The increase in CRP is an independent risk factor for clinical deterioration, which is consistent with current research. High CRP levels reflect a persistent inflammatory state.

In summary, our study demonstrated that a higher proportion of COVID-19 patients with GI symptoms were transferred to tertiary hospitals than those without these symptoms. Potential risk factors for developing GI symptoms, male gender, and increased CRP may help clinicians predict clinical worsening in patients with COVID-19.

This study has limitations. First, the study was single-center and retrospective; therefore, larger sample sizes are necessary to confirm our conclusions. Second, viral nucleic acid tests were not performed daily for each patient; there was a delay in the recorded time of viral clearance compared to actual time of viral clearance. Last but not least, since our hospital was designated for to enroll the mild and common type patients with COVID-19, there was shortage of information about severe and critical type patients with COVID-19.

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AUTHOR CONTRIBUTIONS
All authors made significant contributions to this study and approved the final manuscript. Ting Zheng and Chao Yang contributed equally to this work. Concept and design: TZ and CY; data acquisition, analysis, or interpretation: HW, XC, ZW, and LY; manuscript writing: TZ and CY; manuscript review and editing: HS; supervision: HS.

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