Gastrointestinal Symptoms Onset in COVID-19 Patients in Wuhan, China

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Received: 16 April 2020 / Accepted: 22 October 2020 / Published online: 12 November 2020
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Abstract

Background Early detection is critical in limiting the spread of 2019 novel coronavirus (COVID-19). Although previous data revealed characteristics of GI symptoms in COVID-19, for patients with only GI symptoms onset, their diagnostic process and potential transmission risk are still unclear.

Methods We retrospectively reviewed 205 COVID-19 cases from January 16 to March 30, 2020, in Renmin Hospital of Wuhan University. All patients were confirmed by virus nuclei acid tests. The clinical features and laboratory and chest tomographic (CT) data were recorded and analyzed.

Results A total of 171 patients with classic symptoms (group A) and 34 patients with only GI symptoms (group B) were included. In patients with classical COVID-19 symptoms, GI symptoms occurred more frequently in severe cases compared to non-severe cases (20/43 vs. 91/128, respectively, p < 0.05). In group B, 91.2% (31/34) patients were non-severe, while 73.5% (25/34) patients had obvious infiltrates in their first CT scans. Compared to group A, group B patients had a prolonged time to clinic services (5.0 days vs. 2.6 days, p < 0.01) and a longer time to a positive viral swab normalized to the time of admission (6.9 days vs. 3.3 days, respectively, p < 0.01). Two patients in group B had family clusters of SARS-CoV-2 infection.

Conclusion Patients with only GI symptoms of COVID-19 may take a longer time to present to healthcare services and receive a confirmed diagnosis. In areas where infection is rampant, physicians must remain vigilant of patients presenting with acute gastrointestinal symptoms and should do appropriate personal protective equipment.

Keywords Novel coronavirus · COVID-19 · SARS-CoV-2 · Gastrointestinal symptoms · Human-to-human transmission

Abbreviations

SARS-CoV-2  Severe acute respiratory syndrome coronavirus 2
COVID-19  2019 Novel coronavirus
GI  Gastrointestine
CT  Computed tomography
RT-PCR  Reverse transcription-polymerase chain reaction
NP  Nucleocapsid protein

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10620-020-06693-6) contains supplementary material, which is available to authorized users.

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Introduction

An outbreak of a novel coronavirus pneumonia has rapidly spread in China and is pandemic worldwide [1–3]. This novel coronavirus was successfully isolated from the human airway epithelial cells and was officially named as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [4]. Chinese researchers shared the virus complete genome sequences and extremely facilitated the studies and confirmation of infected patients [4, 5]. Early detection of infected patients is one of the most important steps to take early isolation and mitigate the spread of the virus [6, 7]. Fever, cough and other respiratory symptoms were reported as common presentations of the novel coronavirus infection (COVID-19), and patients with these classical symptoms warrant further screening for viral infection [3, 5, 8]. Although recent studies have reported gastrointestinal (GI) symptoms in COVID-19 [9–18], we report in detail the disease trajectory of GI symptom-only COVID-19 infection including the onset, duration of symptoms, and time to diagnosis in our population in Wuhan.

Methods

Ethics

The study protocol was approved by the ethics committee of Renmin Hospital of Wuhan University, and waiver of informed consent was obtained.

Patients Selection

We retrospectively reviewed 205 hospitalized COVID-19-confirmed cases from January 16 to March 30, 2020, in Renmin Hospital of Wuhan University (Wuhan, Hubei Province, China) which was the designated hospital for COVID-19 infection. All COVID-19 patients enrolled in this study were diagnosed according to WHO guideline [10]. Severity was defined as follows according to Diagnostic and Treatment Guideline for COVID-19-infected pneumonia (Trial Version 6) by Chinese National Health Committee: (1) non-severe including mild (with mild symptoms but without obvious pneumonia radiological images) and moderate cases (with symptoms and radiological images showing limited pneumonia), and (2) severe cases: with one of the following criteria: (a) respiratory distress with respiratory rate ≥ 30/min, (b) pulse oximeter oxygen saturation ≤ 93% at rest; (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO2/FiO2 ≤ 300 mmHg, and (d) significant progress (> 50%) in radiological changes, and (3) critical severe cases: with one of the following criteria: (a) respiratory failure and required mechanical ventilation; (b) shock; (c) with other organ function failure and required ICU care. The flowchart for patient inclusion is shown in Fig. 1.

Data Collection

The demographic data, clinical characteristics (including exposure history, medical history, comorbidities, signs, and symptoms), laboratory findings, chest-computed tomographic (CT) scans, and clinical outcomes were obtained through data collection tables in electronic medical records. The date of symptoms onset, initial clinic visit, hospital admission, CT scans, and virus nuclei acid tests, as well as the severity of patient condition, were also recorded. Data were reviewed by a trained team of experienced physicians and analyzed by three independent researchers. A questionnaire was sent to all patients with only GI symptoms for collecting the infection history of their family members.

Respiratory Pathogen Detection

To detect the presence of 13 respiratory virus targets and bacteria (including influenza A virus, influenza A virus H1N1 (2009), influenza A virus H3N2, influenza B virus, parainfluenza viruses, orthopneumovirus, metapneumovirus, coronavirus, rhinovirus, adenoviruses, bocaparvovirus, and Mycoplasma pneumoniae, Chlamydia), oropharyngeal swab specimens were tested by using multiple respiratory pathogen multiple detection kit (ResP13) (Haiershi, China) according to the manufacturer’s instructions [11].

Diagnostic Testing for COVID-19

All COVID-19 patients enrolled in this study had a confirmatory oropharyngeal swab which detected the presence of SARS-CoV-2 RNA by real time polymerase chain reaction (RT-PCR). In brief, nasal and oropharyngeal swab specimens were collected and transferred into sterile tube with viral transport media and total RNA was extracted within
Two target genes for SARS-CoV-2 RNA, including nucleocapsid protein (NP) gene and open reading frame (ORF) 1ab gene, were subsequently amplified and tested by using SARS-CoV-2 nucleic acid test kits according to the manufacturer’s protocol (Shanghai bio-germ Medical Technology Co Ltd.). Positive amplification of either NP or ORF 1ab gene or both confirmed SARS-CoV-2 RNA infection.

**Statistical Analysis**

Descriptive data were presented as mean ± SD for normally distributed data and as medians with IQR for non-normally distributed data. Categorical variables were expressed as counts and percentages. When the data were normally distributed, independent t tests were used to compare the mean of continuous variables. Otherwise, the Mann–Whitney test is used. Although Fisher’s exact test was used with limited data (n < 40), the Chi-squared test was used to compare the proportion of categorical variables. The analysis of variance or Kruskal–Wallis rank-sum test was used for comparison between multiple groups. For multiple hypothesis testing, if results indicated significance, post hoc analysis was performed further. All statistical analyses were performed using SPSS version 13.0 software. A p value of less than 0.05 is statistically significant.

**Results**

**Demographic and Clinical Characteristics of COVID-19 Patients**

A total of 205 hospitalized COVID-19 patients were included in this study, with 171 patients presented with classic symptoms including fever, fatigue, and respiratory symptoms (dry cough, sputum) and 34 (16.6%) patients presented with only GI symptoms including anorexia, diarrhea, nausea and/or vomit, and abdominal pain (Table 1). 22% (45/205) patients presented with both classic symptoms and GI symptoms (Table 1, Supplementary Figure 1). Compared to group A1 (with only classic symptoms), group A2 patients (with both classic symptoms and GI symptoms) had a higher proportion of severe cases (40% [18/45] vs. 11.9% [15/126], p < 0.01) including...
Table 1 Baseline clinical characteristics of COVID-19 patients

|                          | Total (n = 205) | Group A | p value | Group B (n = 34) | p value |
|--------------------------|----------------|---------|---------|-----------------|---------|
|                          | Total (n = 171) | Group A1 (n = 126) | Group A2 (n = 45) |       |         |
| Age, median (IQR), y     | 54 (22–77)     | 56 (24–77) | 58 (25–77) | 51 (24–70) | –       | 48 (22–70) | –       |
| Age, n (%)               | 0.788          |          |          |                 | <0.05   |          |         |
| >60                      | 68 (33.2)      | 61 (35.7) | 55 (43.7) | 18 (40.0) | –       | 7 (20.6)  | –       |
| <60                      | 137 (66.8)     | 110 (64.3) | 71 (56.3) | 27 (60.0) | –       | 27 (79.4) | –       |
| Sex                      | 0.544          |          |          |                 | 0.081   |          |         |
| Male                     | 122 (59.5)     | 103 (60.2) | 72 (57.1) | 31 (68.9) | –       | 19 (55.9) | –       |
| Female                   | 83 (40.5)      | 68 (39.7) | 44 (34.9) | 24 (31.1) | –       | 15 (44.1) | –       |
| Comorbidities            |               |          |          |                 |         |          |         |
| Hypertension             | 21 (10.2)      | 17 (9.9) | 12 (9.5) | 5 (11.1)     | 0.682   | 4 (11.7)  | 0.173   |
| Diabetes                 | 8 (3.9)        | 6 (3.5) | 4 (3.2)  | 2 (4.4)      | 0.418   | 2 (5.9)   | 0.293   |
| Malignant tumors         | 5 (2.4)        | 4 (2.3) | 3 (2.4)  | 1 (2.2)      | 0.188   | 1 (2.9)   | 0.648   |
| Cardio cerebrovascular disease | 11 (5.4)    | 9 (5.3) | 7 (5.6) | 2 (4.4)  | 0.783 | 2 (5.9)  | 0.465   |
| Chronic renal failure    | 7 (3.4)        | 6 (3.5) | 5 (4.0)  | 1 (2.2)      | 0.945   | 1 (2.9)   | 0.225   |
| Chronic hepatic diseases | 15 (7.3)       | 12 (7.0) | 9 (7.1) | 3 (6.7)  | 0.879   | 3 (8.8)   | 0.781   |
| Smoking                  | 9 (4.4)        | 7 (4.1) | 5 (4.0)  | 2 (4.4)      | 0.576   | 2 (5.9)   | 0.471   |
| Exposure history         |               |          |          |                 |         |          |         |
| Close contacted with confirmed or suspected COVID-19 patients | 89 (43.4) | 73 (42.7) | 55 (60.4) | 18 (48.6) | 0.729 | 16 (47.1) | 0.674 |
| Symptoms                 |               |          |          |                 |         |          |         |
| Typical symptoms         |               |          |          |                 |         |          |         |
| Fever                    | 132 (64.4)     | 141 (35.7) | 108 (42.1) | 33 (17.8) | <0.01 | 0 (0)   | –       |
| Fatigue                  | 61 (29.6)      | 61 (35.7) | 53 (42.1) | 8 (17.8)  | <0.01 | 0 (0)   | –       |
| Sputum                   | 7 (3.3)        | 7 (4.1) | 6 (4.8)  | 1 (2.2)      | 0.956   | 0 (0)    | –       |
| GI symptoms              |               |          |          |                 |         |          |         |
| Anorexia                 | 59 (28.8)      | 34 (19.9) | 0 (0) | 34 (75.6) | –       | 24 (70.6) | <0.01   |
| Diarrhea                 | 20 (9.8)       | 10 (5.8) | 0 (0) | 10 (22.2) | –       | 10 (29.4) | <0.01   |
| Nausea                   | 12 (5.9)       | 6 (3.5) | 0 (0) | 6 (13.3) | –       | 6 (17.6) | <0.01   |
| Vomit                    | 6 (2.9)        | 2 (1.2) | 0 (0) | 2 (4.4) | –       | 4 (11.8) | <0.05   |
| Abdominal pain           | 4 (2.0)        | 2 (1.2) | 0 (0) | 2 (4.4) | –       | 2 (5.9) | 0.096   |
| History of initial clinic visiting or inquiry |           |          |          |                 |         |          |         |
| Pulmonary department     | 35 (17.1)      | 35 (20.5) | 17 (13.5) | 18 (12.6) | 0.113 | 0 (0) | <0.01 |
| Fever clinic             | 114 (55.6)     | 114 (66.7) | 100 (79.5) | 14 (31.1) | <0.01 | 0 (0) | <0.01 |
| Emergency department     | 26 (12.7)      | 26 (15.2) | 24 (19.0) | 2 (4.4) | <0.05 | 0 (0) | <0.01 |
| Gastroenterology department | 38 (18.5) | 11 (6.4) | 0 (0) | 11 (24.4) | <0.01 | 27 (79.2) | <0.01 |
| Cardiological department | 2 (1.0) | 0 (0) | 0 (0) | 0 (0) | – | 2 (5.9) | 0.068 |
| General outpatient clinic | 2 (1.0) | 0 (0) | 0 (0) | 0 (0) | – | 2 (5.9) | 0.057 |
| Assessment of 1st CT scan |           |          |          |                 |         |          |         |
| Mild                     | 62 (30.2)      | 56 (32.7) | 39 (31.0) | 17 (37.8) | 0.086 | 6 (17.7) | <0.05 |
| Moderate                 | 92 (44.9)      | 69 (40.4) | 45 (35.7) | 24 (53.3) | <0.05 | 22 (64.7) | 0.102 |
| Severe                   | 51 (24.8)      | 43 (25.1) | 35 (27.8) | 8 (17.8) | 0.102 | 3 (8.8) | <0.05 |
| Disease severity         |               |          |          |                 |         |          |         |
| Non-severe               | 159 (77.6)     | 128 (74.9) | 91 (72.2) | 37 (82.2) | 0.127 | 31 (91.2) | <0.05 |
| Mild                     | 101 (49.2)     | 87 (50.9) | 65 (51.6) | 22 (48.9) | 0.214 | 14 (41.2) | 0.193 |
| Moderate                 | 58 (28.3)      | 41 (24.0) | 26 (20.6) | 15 (33.3) | 0.132 | 17 (50.0) | <0.05 |
| Severe                   | 46 (22.4)      | 43 (25.1) | 20 (15.8) | 23 (51.1) | <0.05 | 3 (8.8) | <0.05 |
| Severe                   | 36 (17.6)      | 33 (19.3) | 15 (11.9) | 18 (40.0) | <0.05 | 3 (8.8) | <0.05 |
| Critical severe          | 10 (4.9)       | 10 (5.8) | 5 (4.0) | 4 (8.9) | 0.054 | 0 (0) | <0.05 |
| Outcomes                 |               |          |          |                 |         |          |         |
| Discharged               | 199 (97.1)     | 165 (96.5) | 125 (99.2) | 40 (88.9) | 0.634 | 34 (100) | <0.01 |
| Died                     | 6 (2.9)        | 6 (3.5) | 1 (0.8) | 5 (11.1) | <0.01 | 0 (0) | <0.01 |
8.9% [4/45] critical ill cases and 5 deaths. In contrast, patients with only GI symptoms (group B) (31/34, 91.2%) were mainly mild (41.2% [14/34]) or moderate (50% [17/34]). Only 3 cases were severe and with no death. It is also striking that non-severe (mild and moderate) patients in group B had obvious infiltrates on their first chest CT scans but did not have any respiratory symptoms.

In a total of 159 non-severe patients, 128 (80.5%) presented with classic symptoms. Of these, 91 had classic symptoms without GI symptoms (group A1) and 37 had classic symptoms with GI symptoms (group A2). 31 patients (19.5%) presented with GI symptoms only (group B). (Table 2). There were similar comorbidities regarding hypertension, diabetes, malignant tumors, cardiovascular, cerebrovascular disease and chronic renal failure, history of smoking, and exposure to confirmed or suspected COVID-19 patients between each group. The common clinics for group A patients to visit were fever clinic (53.5%, 85/159), pulmonary department (12.6%, 12/159), and emergency department (10.1%, 16/159), while 83.9% (26/31) group B patients with only GI symptoms selected or were designated to gastroenterology department. It is worth noting that the GI symptoms onset in group B patients were not chronic which occurred 1–8 days before their clinic visits (Fig. 2b).

**Laboratory Findings in Non-severe COVID-19 Patients**

There was no significant difference in systolic pressure, oximetry saturation, respiratory rate, complete blood counting, C-creative protein, liver function (albumin [Alb], total bilirubin [TBIL], alkaline phosphatase [ALP], alanine aminotransferase [AST], aspartate aminotransferase [AST]), kidney function (urea, creatinine), electrolyte, and lactate dehydrogenase (LDH) between group A and group B or between group A1 and group A2 (Supplementary Table 1). However, for the first virus swabs, only 38.7% (12/31) patients with only GI symptoms in group B were positive, while significant higher positivity (61.7% [79/128]) was for patients with both GI and classic symptoms (group A) (p < 0.01) (Table 2). However, most of these non-severe patients had positive virus antibodies (96.1% [123/128] in group A and 96.8% [30/31] in group B for IgM; 91.4% [117/128] in group A and 80.6% [25/31] in group B for IgG).

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**Diagnostic Process During COVID-19 Confirmation in Non-severe Patients**

We further analyzed the durations for patient presentation to healthcare services and clinical diagnosis of COVID-19. Compared to group A, from detectable symptoms onset, patients in group B (with only GI symptoms) took a longer time to present to healthcare services (5.0 days vs. 2.6 days, \( p < 0.01 \)), obtained chest CT scans (6.6 days vs. 3.8 days, \( p < 0.01 \)) and viral swabs (7.6 days vs. 4.2 days, \( p < 0.01 \)) (Fig. 2). Furthermore, group B patients had longer durations to hospital admission after initial clinic presentations (8.2 days vs. 3.7 days, \( p < 0.01 \)) and to virus RNA confirmation (6.9 days vs. 3.3 days, \( p < 0.01 \)) in contrast to group A. As for hospitalization days, there was no difference between these two groups (17.4 days in group B vs. 18.2 days in group A, \( p > 0.05 \)) (Table 2). In total, patients with only GI symptoms spent a longer time from their detectable symptoms to hospital admissions (13.2 days in group B vs. 6.3 days in group A, \( p < 0.01 \)) (Fig. 2b).

**Potential Risk of Human-to-Human Transmission for Patients with Only GI Symptoms**

It is important to evaluate the transmission risk of patients with only GI symptoms, especially for their potential misdiagnosis or delayed diagnosis. The infection history of patient families in group B was collected. On January 23, 2020, Wuhan was locked down and all citizens were in quarantine. After 10 to 11 days, 2 patients in group B occurred GI symptoms including diarrhea and anorexia (Fig. 3). Seven and eight days later, their family members (2 persons in Patient 1 family and 1 person in Patient 2 family) started to present symptoms such as fever, respiratory symptoms, anorexia, and diarrhea. Three members were later diagnosed as COVID-19. One member of Patient 2 was entirely asymptomatic and was diagnosed as a virus carrier.

**Discussion**

Recent published studies indicated that the most common onset symptoms of COVID-19 pneumonia were fever, cough, and myalgia or fatigue. Most infected patients had fever, while cough (76%) and fatigue (44%) were also usually presented onset [3]. Less common illness presentations included sputum production, headache, hemoptysis, and
Table 2  Baseline clinical characteristics of non-severe COVID-19 patients

|                              | Total (n = 159) | Group A (n = 128) | Group A1 (n = 91) | Group A2 (n = 37) | p value | Group B (n = 31) | p value |
|------------------------------|-----------------|-------------------|-------------------|-------------------|---------|-----------------|---------|
| Age, median (IQR), y         | 52 (22–73)      | 55 (24–73)        | 56 (25–73)        | 52 (24–70)        | 47 (22–67) | 0.654           | <0.01   |
| Age, n (%)                   |                 |                   |                   |                   |         |                 |         |
| > 60                         | 59 (37.1)       | 54 (42.2)         | 39 (42.9)         | 14 (37.8)         | –       | 5 (16.1)        | –       |
| < 60                         | 100 (62.9)      | 74 (57.8)         | 51 (56.0)         | 23 (63.3)         | –       | 26 (83.9)       | –       |
| Sex                          |                 |                   |                   |                   |         |                 | 0.760   |
| Male                         | 87 (54.7)       | 70 (55.6)         | 49 (53.8)         | 21 (56.8)         | –       | 17 (54.8)       | –       |
| Female                       | 72 (45.3)       | 58 (44.4)         | 42 (46.2)         | 16 (43.2)         | –       | 14 (45.2)       | –       |
| Comorbidities                |                 |                   |                   |                   |         |                 |         |
| Hypertension                 | 12 (7.5)        | 10 (7.8)          | 7 (7.7)           | 3 (8.1)           | 0.768   | 2 (6.57)        | 0.231   |
| Diabetes                     | 4 (2.5)         | 3 (2.3)           | 2 (2.2)           | 1 (2.7)           | 0.867   | 1 (3.2)         | 0.186   |
| Malignant tumors             | 2 (1.3)         | 1 (0.8)           | 1 (1.14)          | 1 (2.7)           | 0.143   | 1 (3.2)         | 0.106   |
| Cardio cerebrovascular disease | 4 (2.5)     | 3 (2.3)           | 2 (2.2)           | 1 (2.7)           | 0.175   | 1 (3.2)         | 0.089   |
| Chronic renal failure        | 1 (0.6)         | 0 (0)             | 0 (0)             | 1 (2.7)           | 0.121   | 1 (3.2)         | 0.051   |
| Chronic hepatic diseases     | 11 (6.9)        | 8 (6.2)           | 6 (6.6)           | 2 (5.4)           | 0.793   | 3 (9.6)         | 0.143   |
| Smoking                      | 4 (2.5)         | 3 (2.3)           | 2 (2.2)           | 1 (2.7)           | 0.453   | 1 (3.2)         | 0.355   |
| Exposure history             |                 |                   |                   |                   |         |                 |         |
| Close contacted with confirmed or suspected COVID-19 patients | 89 (56.0) | 73 (42.7)         | 55 (60.4)         | 18 (48.6)         | –       | 16 (47.1)       | –       |
| Unclear exposure             | 70 (44.0)       | 55 (57.3)         | 36 (39.6)         | 19 (51.4)         | –       | 15 (52.9)       | –       |
| Symptoms                     |                 |                   |                   |                   |         |                 |         |
| Typical symptoms             |                 |                   |                   |                   |         |                 |         |
| Fever                        | 105 (66.0)      | 105 (82.0)        | 82 (90.1)         | 23 (62.2)         | <0.05   | 0 (0)           | –       |
| Dry cough                    | 58 (36.5)       | 58 (45.3)         | 45 (49.4)         | 13 (35.1)         | <0.05   | 0 (0)           | –       |
| Fatigue                      | 46 (11.9)       | 46 (35.9)         | 42 (46.2)         | 4 (10.8)          | <0.01   | 0 (0)           | –       |
| Sputum                       | 4 (2.5)         | 4 (3.1)           | 3 (3.3)           | 1 (2.7)           | 0.571   | 0 (0)           | –       |
| GI symptoms                  |                 |                   |                   |                   |         |                 |         |
| Anorexia                     | 48 (30.2)       | 28 (21.9)         | 0 (0)             | 28 (75.7)         | –       | 20 (64.5)       | <0.01   |
| Diarrhea                     | 14 (8.8)        | 6 (4.7)           | 0 (0)             | 6 (16.2)          | –       | 8 (25.8)        | <0.01   |
| Nausea                       | 5 (3.1)         | 3 (2.3)           | 0 (0)             | 3 (8.1)           | –       | 2 (6.5)         | <0.01   |
| Vomit                        | 2 (1.3)         | 0 (0)             | 0 (0)             | 0 (0)             | –       | 2 (6.5)         | <0.01   |
| Abdominal pain               | 2 (1.3)         | 1 (0.8)           | 0 (0)             | 1 (2.7)           | –       | 1 (3.2)         | 0.211   |
| History of Initial clinic visiting or inquiry | | | | | | |
| Pulmonary department         | 20 (12.6)       | 20 (15.6)         | 6 (6.6)           | 14 (37.8)         | <0.01   | 0 (0)           | –       |
| Fever clinic                 | 85 (53.5)       | 85 (66.4)         | 71 (78.0)         | 14 (37.8)         | <0.01   | 0 (0)           | –       |
| Emergency department        | 16 (10.1)       | 16 (12.5)         | 14 (15.4)         | 2 (5.4)           | <0.01   | 0 (0)           | –       |
| Gastroenterology department | 33 (20.8)       | 7 (5.5)           | 0 (0)             | 7 (18.9)          | <0.01   | 26 (83.9)       | <0.01   |
| Cardiological department    | 2 (1.3)         | 0 (0)             | 0 (0)             | 0 (0)             | –       | 2 (6.5)         | –       |
| General outpatient clinic    | 2 (1.3)         | 0 (0)             | 0 (0)             | 0 (0)             | –       | 2 (6.6)         | –       |
| Assessment from 1st CT scan  |                 |                   |                   |                   |         |                 |         |
| Mild                         | 60 (37.7)       | 54 (42.2)         | 41 (45.1)         | 13 (35.1)         | <0.01   | 6 (19.4)        | <0.05   |
| Obvious                      | 90 (56.6)       | 68 (53.1)         | 45 (49.5)         | 23 (62.2)         | <0.01   | 22 (71.0)       | <0.01   |
| severe                       | 9 (5.7)         | 6 (4.7)           | 5 (5.5)           | 1 (2.7)           | <0.01   | 3 (9.7)         | <0.01   |
| Virological tests            |                 |                   |                   |                   |         |                 |         |
| Positive results at 1st test (Oropharyngeal swab specimens) | 91 (57.2) | 79 (61.7)         | 61 (67.0)         | 18 (48.6)         | 0.109   | 12 (38.7)       | <0.01   |
| Nucleocapsid protein (NP) gene | 90 (56.6) | 79 (61.7)         | 61 (67.0)         | 18 (48.6)         | 0.083   | 11 (35.5)       | <0.01   |
| Open reading frame (ORF) lab | 82 (51.6)       | 73 (57.0)         | 57 (62.6)         | 16 (43.2)         | 0.109   | 9 (29.0)        | <0.05   |
Table 2 (continued)

| Blood COVID-19 antibody | Total (n = 159) | Group A | p value | Group B (n = 31) | p value |
|-------------------------|-----------------|---------|---------|-----------------|---------|
| COVID-19 IgM            | 152 (95.6)      | 123 (96.1) | 35 (94.6) | 0.358 | 30 (96.8) | 0.216 |
| COVID-19 IgG            | 142 (89.3)      | 117 (91.4) | 30 (81.1) | 0.265 | 25 (80.6) | 0.128 |
| Total days in hospital  | 17.9 ± 10.2     | 18.2 ± 11.3 | 18.0 ± 11.8 | 19.2 ± 10.9 | 0.211 | 17.4 ± 12.0 | 0.062 |
| Days from symptom onset to diagnosis | 4.8 ± 3.2 | 3.3 ± 2.1 | 3.1 ± 2.5 | 4.3 ± 1.9 | 0.094 | 6.9 ± 2.4 | <0.05 |

Data are presented as means (IQR) and n/N (%) or means ± std. Group A: patients with classic symptoms; group A1: patients with only classic symptoms; group A2: patients with both classic symptoms and GI symptoms; group B: patients with only GI symptoms. Abbreviations: GI, gastrointestinal. p values indicate differences between group A1 and group A2 or between group A and group B. p < 0.05 was considered statistically significant.

Fig. 2 Time during the clinical diagnosis. Group a patients with classic symptoms; group A1: patients with only classic symptoms; group A2: patients with both classic symptoms and GI symptoms; group B: patients with only GI symptoms. *p < 0.05 was considered statistically significant; **p < 0.01
diarrhea. These classic symptoms alerted clinicians of possible COVID-19 infection when screening patients.

Although previous studies reported GI symptoms in COVID-19 patients, the clinical characteristics, diagnostic duration, and transmission risk for patients with only GI symptoms were still unclear. Here, demographic and clinical characteristics analysis revealed that GI symptoms were presented in 38.5% (79/205) patients (Table 1) which were not less common as previously reported [3]. Additionally, patients with both classic and GI symptoms were more severe which resulted in higher morbidity and mortality than those with only classic symptoms. For patients in group B, GI symptoms were not chronic and always not severe. Awareness and recognition of these acute and mild GI presentations might benefit early screening and clinical diagnosis of COVID-19. Although GI symptoms in patients with classic symptoms (group A2) were related to more severe cases which could be because of viral infection in the digestive tract, multi-organ failure, or preexisting comorbidities (Table 1), most patients [91.2% (31/34)] with only GI symptoms (group B) were non-severe. Importantly, 73.5% patients with only GI symptoms already had obvious infiltrates in their first chest CT scans. Mild GI symptoms with sub-clinical COVID-19 pneumonia possibly led to patient misdiagnosis and facilitated the spread of disease. Three severe cases in group B also needed close monitoring. It is also critical for clinicians to follow-up patients with GI symptoms suspicious of COVID-19 because classic symptoms can have a later onset. Early identification and management of these patients can benefit pandemic COVID-19 control (Supplementary Figure 1).

Data extracted from clinical process indicated that the common clinics for patients with only GI symptoms were gastroenterology department but not fever clinic, pulmonary department and emergency department which were mostly visited by patients in group A (Table 2). Furthermore, only 38.7% group B patients were positive for the first virus swabs, while most of them had positive serum antibodies. Therefore, we strongly suggest virus nuclei acid testing and antibody testing are done simultaneously. If patients test positive for IgM antibodies, repeat viral swabs are advised. It is also imperative that gastroenterology and endoscopy staff do the appropriate PPE to reduce the risk of nosocomial transmission.

The duration of clinical visits and clinical diagnosis was further investigated. It was evident that group B patients presented later to healthcare services (5.0 days in group B vs. 2.6 days in group A, \( p < 0.01 \)). Mild symptoms possibly contributed to the clinic visit delay. Patients in group B also needed more time to obtain CT scans (6.6 days vs. 3.8 days, \( p < 0.01 \)), virus nuclei acid tests (7.6 days vs. 4.2 days, \( p < 0.01 \)), and finally hospitalizations (8.2 days vs. 3.7 days, \( p < 0.01 \)) when compared to group A (Fig. 2a). Patients in Wuhan were screened for COVID-19 by RT-PCR testing.
from nasal and oropharynx swabs, complete blood tests, virus antibody tests (IgM and IgG), and chest CT scans. Patients had characteristic lung infiltrates with or without classic symptoms but negative for viral RNA which were identified as suspected patients and needed further nuclei acid testing; especially, positive virus IgM was detected. Limited experiences of clinicians, awareness of these patients with only GI symptoms, and variability of virus tests were the possible reasons for delayed diagnosis and treatment. In this study, patients with only GI symptoms took an obviously longer time from their symptoms onset to hospital admissions (13.2 days in group B vs. 6.3 days in group A, $p < 0.01$) (Fig. 2b). These results indicated that GI symptoms were easily neglected or underestimated and might be misdiagnosed. Although anorexia sometimes was not considered as a GI symptom, it was one of the commonest symptoms for patients in China to search GI clinic services. Here, we strongly recommended healthcare workers to pay more attention to extra-pulmonary symptoms of COVID-19.

Previous studies demonstrated that GI symptoms also occurred in severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infection [12–14]. A metallopeptidase, angiotensin-converting enzyme II (ACE2) is proved to be the host cell receptor for COVID-19 recognition, the same as SARS-CoV infection [15–17]. Researchers postulated that besides the most recognized mode of transmission through aerosol droplets, feco-oral transmission was also a potential route of COVID-19 transmission. [18] Just recently, studies revealed that in digestive system, ACE2 expressed in esophagus upper and stratified epithelial cells and absorptive enterocytes from ileum and colon [18, 19]. More importantly, Hoffmann et al. demonstrated SARS-CoV-2-S used ACE2 for entry into target cells and offered important implications for SARS-CoV-2 transmissibility and pathogenesis [20]. These results provided evidence of digestive tract as a potential invasive target for SARS-CoV-2 which possibly contributed to gastrointestinal symptoms.

Finally, two family clusters of SARS-CoV-2 infection in patients group B were reported (Fig. 3). All these two family members were quarantined at home 10 to 11 days before the detectable GI symptoms of the first patients. In Family 1 (Fig. 3a), the husband of the patients occurred typical symptoms in the followed 7 days, while their daughter fell ill 1 day later. In Family 2 (Fig. 3b), on the 8th day of the GI symptoms onset occurred in the husband, the wife had a fever. Their son was later diagnosed as asymptomatic carrier by the positive virus RNA but normal chest CT scans. Although these familiar clusters did not provide evidence of fecal–oral transmission in COVID-19, they indicated the possibility of transmission risk for patients with only GI symptoms.

This study has limitations. First, small scale in current retrospective study was studied, which could cause biases in clinical observation. It would be better to include more patients. Second, further progression and prognosis were not assessed yet for all patients’ current hospitalization. Third, elevation of serum COVID-19 IgM and IgG levels was observed in most patients and its role in diagnosis and disease progress was a very interesting topic and needed further in-depth exploration. Fourth, stool testing for virus nuclei acid needed further investigation including the lasting time and positive rates.

In conclusion, we recommend physicians remain vigilant of COVID-19 infection in patients who present with acute GI illness, and screen patients accordingly if suspicious for COVID-19. We also recommend that appropriate PPE be worn by all staff working in gastroenterology.

Acknowledgments This work was partly supported by the grant from the National Natural Science Foundation of China [Grant Nos. 81672387 to Yu Honggang], the National Natural Science Foundation of China [Grant Nos. 81302131 to Ping An], and the Wuhan COVID-19 Emergency Scientific Research Project [Grant Nos. EX20B04 to Ping An].

Author’s contribution YH and DY conceived and supervised the overall study. AP, CH, and RH contributed to writing of the report. YH, CH, RH, and AP contributed to critical revision of the report. JM, KJ, JX, RH, LX, SJ, CW, CM, LJ, DC, and YA contributed to recording and collecting the data of patients. YY, DW, and ZZ contributed to the statistical analysis. YH guaranteed the article. All authors reviewed and approved the final version of the manuscript.

Funding This work was partly supported by the grant from the National Natural Science Foundation of China [Grant Nos. 81672387 to Yu Honggang] and the National Natural Science Foundation of China [Grant Nos. 81302131 to Ping An].

Compliance with Ethical Standards

Conflict of interest All authors declared no conflict of interest.

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