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ORIGINAL ARTICLE

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

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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

Disclaimer: The views expressed in the submitted article are our own and not an official position of the institution or funder.

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ORF	Open reading frame
IQR	Interquartile range
Alb	Albumin
TBIL	Total bilirubin
ALP	Alkaline phosphatase
AST	Alanine aminotransferase
AST	Aspartate aminotransferase
LDH	Lactate dehydrogenase
SARS-CoV	Severe acute respiratory syndrome coronavirus
MERS-CoV	Middle East respiratory syndrome coronavirus
ACE2	Angiotensin-converting enzyme II

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-[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 $\leq 93\%$ at rest; (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, $PaO_2/FiO_2 \leq 300$ 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

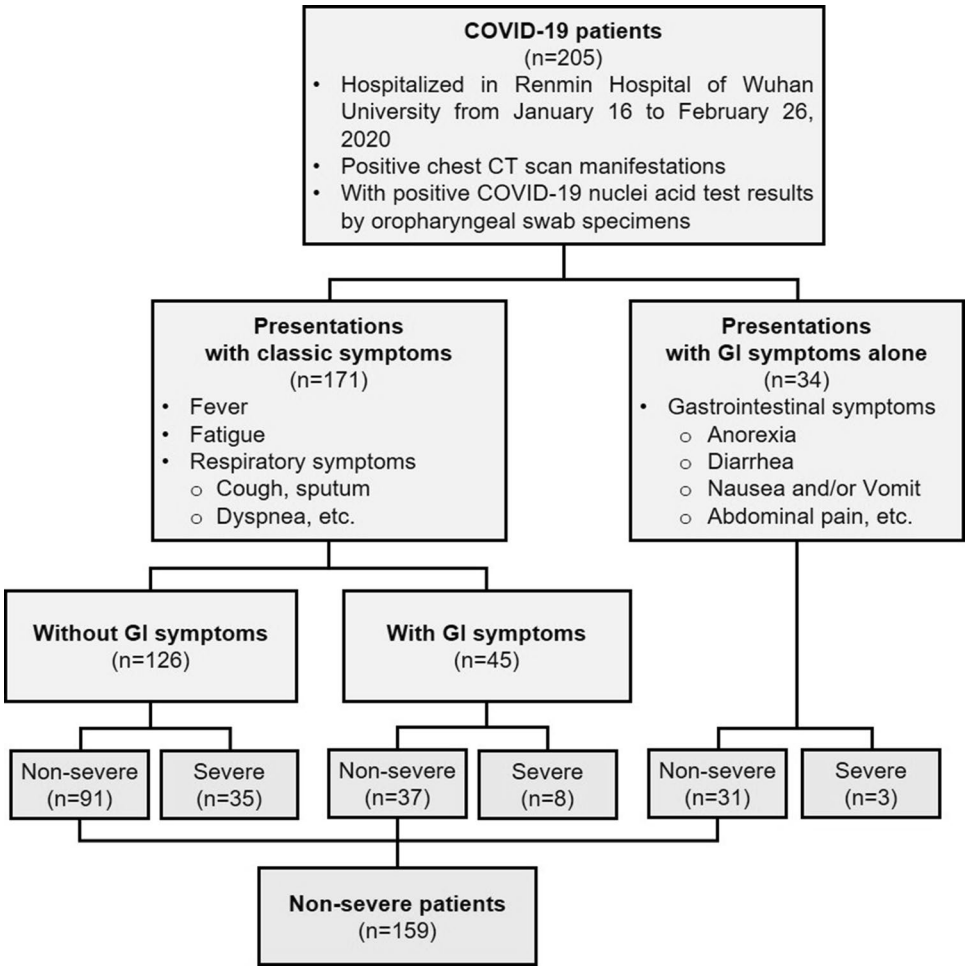

Fig. 1 Flowchart for patient inclusion

2 h. 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, 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 (29.8)	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

Table 1 (continued)

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

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).

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			p value	Group B ($n=31$)	p value
		Total ($n=128$)	Group A1 ($n=91$)	Group A2 ($n=37$)			
Age, median (IQR), y	52 (22–73)	55 (24–73)	56 (25–73)	52 (24–70)		47 (22–67)	
Age, *n* (%)					0.654		< 0.01
> 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		0.132
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) 1ab	82 (51.6)	73 (57.0)	57 (62.6)	16 (43.2)	0.109	9 (29.0)	< 0.05

Table 2 (continued)

	Total ($n=159$)	Group A			p value	Group B ($n=31$)	p value
		Total ($n=128$)	Group A1 ($n=91$)	Group A2 ($n=37$)			
Blood COVID-19 antibody							
COVID-19 IgM	152 (95.6)	123 (96.1)	88 (96.7)	35 (94.6)	0.358	30 (96.8)	0.216
COVID-19 IgG	142 (89.3)	117 (91.4)	87 (95.6)	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

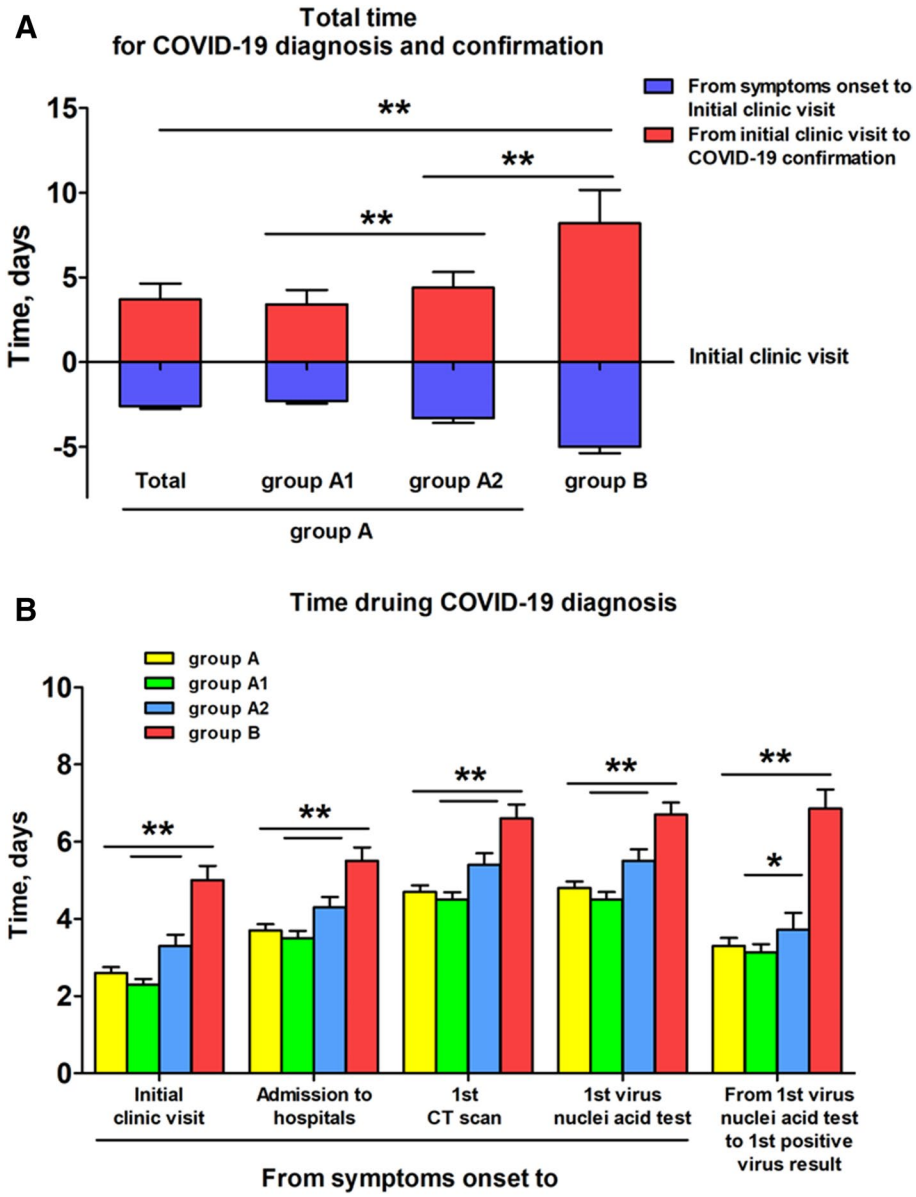

Fig. 2 Time during the clinical diagnosis. Group **a** patients with classic symptoms; group A1: patients with only classic symptoms; group A2: patients with both classic symptoms and GI symptoms; group **b** patients with only GI symptoms. *$p < 0.05$ was considered statistically significant; **$p < 0.01$

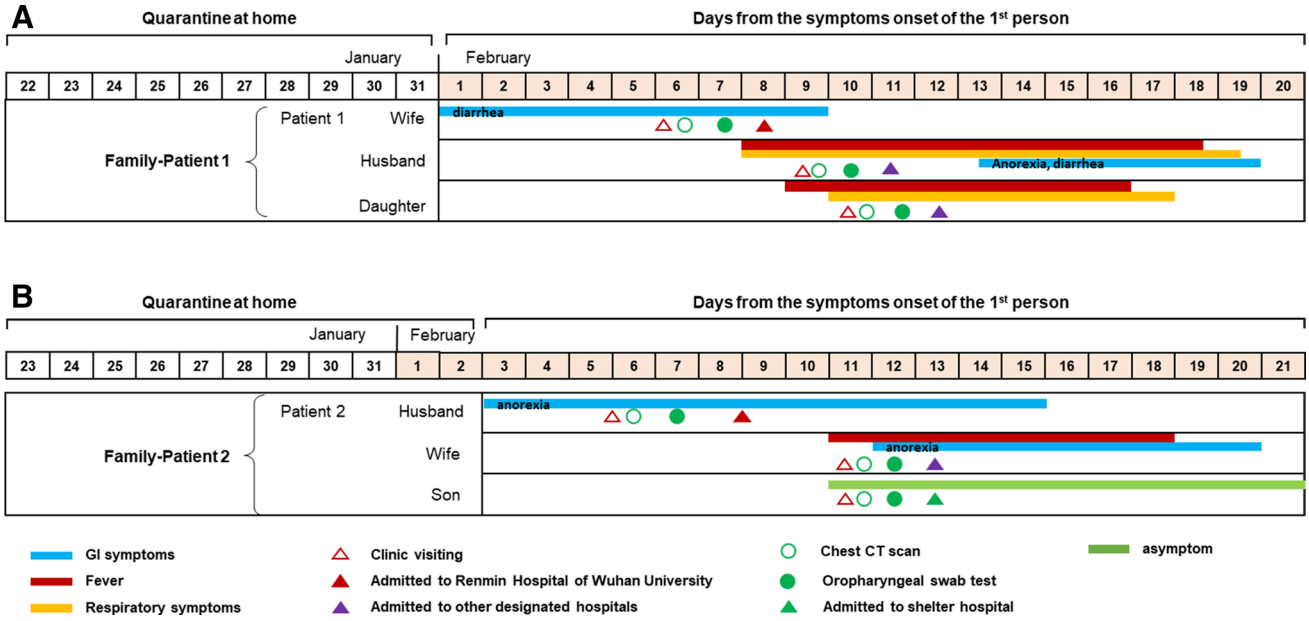

Fig. 3 Chronology of symptoms in family clusters of two patients presented with only GI symptoms. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, 2019 novel coronavirus; GI, gastrointestine; CT, computed tomography; RT-PCR, reverse transcription-polymerase chain reaction; NP, nucleocapsid protein; ORF, open reading frame; IQR, interquartile range; Alb, albumin; TBIL, total bilirubin; ALP, alkaline phosphatase; AST, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; ACE2, angiotensin-converting enzyme II

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 felt 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.

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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.

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Compliance with Ethical Standards

Conflict of interest All authors declared no conflict of interest.

References

1. Hui DS, Madani TA, Ntoumi F, 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 IJID Off Publ Int Soc Infect Dis*. 2020;91:264.
2. European Centre for Disease Prevention and Control. Outbreak of acute respiratory syndrome associated with a novel coronavirus, Wuhan, China; first update.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506.
4. Chen Y, Liu Q, Guo D. Coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol*. 2020;92:418–423.
5. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *New Engl J Med* 2020;382:727–733.

6. Cheng VCC, Wong SC, To KKW, et al. Preparedness and proactive infection control measures against the emerging Wuhan coronavirus pneumonia in China. *J Hosp Infect.* 2020;104:254–258.
7. The Centre for Health Protection closely monitors cluster of pneumonia cases on Mainland. Press release of the Department of Health, Hong Kong Special Administrative Region.
8. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395:514–523.
9. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *Am J Gastroenterol*. 2020;115:766–773.
10. Clinical management of COVID-19. World Health Organization. interim guidance. Accessed May 2020.
11. Zhang D, Feng Z, Zhao M, et al. Clinical evaluation of a single-tube multiple RT-PCR assay for the detection of 13 common virus types/subtypes associated with acute respiratory infection. *PloS ONE*. 2016;11:e0152702.
12. Zhou J, Li C, Zhao G, et al. Human intestinal tract serves as an alternative infection route for Middle East respiratory syndrome coronavirus. *Sci Adv*. 2017;3:eaao4966.
13. Openshaw PJ. Crossing barriers: infections of the lung and the gut. *Mucosal Immunol*. 2009;2:100–102.
14. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;203:631–637.
15. Gui M, Song W, Zhou H, et al. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell Res*. 2017;27:119–129.
16. Zhou P, Wang X, Hu B, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and 1 its potential bat origin. *BioRxiv*. 2020.
17. Xu X, Wang J, Feng J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci. China*. 2020;63:457–460.
18. Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. *BioRxiv*. 2020. https://doi.org/10.1101/2020.01.30.927806.
19. 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;395:565–574.
20. Hoffmann M, Kleine-Weber, H, Kruger, N, et al. The novel coronavirus 2019 (2019-nCoV) uses the SARS-1 coronavirus receptor 2 ACE2 and the cellular protease TMPRSS2 for entry into target cells. *Lancet*. 2020. https://doi.org/10.1101/2020.01.31.929042.