

ORIGINAL RESEARCH

Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection

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ABSTRACT

Objective To study the GI symptoms in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients.

Design We analysed epidemiological, demographic, clinical and laboratory data of 95 cases with SARS-CoV-2 caused coronavirus disease 2019. Real-time reverse transcriptase PCR was used to detect the presence of SARS-CoV-2 in faeces and GI tissues.

Results Among the 95 patients, 58 cases exhibited GI symptoms of which 11 (11.6%) occurred on admission and 47 (49.5%) developed during hospitalisation. Diarrhoea (24.2%), anorexia (17.9%) and nausea (17.9%) were the main symptoms with five (5.3%), five (5.3%) and three (3.2%) cases occurred on the illness onset, respectively. A substantial proportion of patients developed diarrhoea during hospitalisation, potentially aggravated by various drugs including antibiotics. Faecal samples of 65 hospitalised patients were tested for the presence of SARS-CoV-2, including 42 with and 23 without GI symptoms, of which 22 (52.4%) and 9 (39.1%) were positive, respectively. Six patients with GI symptoms were subjected to endoscopy, revealing oesophageal bleeding with erosions and ulcers in one severe patient. SARS-CoV-2 RNA was detected in oesophagus, stomach, duodenum and rectum specimens for both two severe patients. In contrast, only duodenum was positive in one of the four non-severe patients.

Conclusions GI tract may be a potential transmission route and target organ of SARS-CoV-2.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19) has rapidly spread around China and other countries.^{1–9} The most common symptoms of COVID-19 at the onset of illness are fever, cough, fatigue, myalgia and dyspnoea, whereas the incidence of GI symptoms is low.^{1–5} Evidence indicate that human-to-human transmission has occurred in close contacts, mainly transmitted through respiratory droplets and direct contact.^{7,8} Given that SARS-CoV-2 RNA has been detected in the patient's stool,⁹ it is possible that SARS-CoV-2 could also be transmitted via the faecal–oral route, causing viral GI infection. In this study, to further investigate the impact of SARS-CoV-2 on GI system, we systemically characterised the GI manifestations in patients with COVID-19 in the Zhuhai outbreak.

Significance of this study**What is already known on this subject?**

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of coronavirus disease 2019 (COVID-19) pneumonia globally.
- The most common symptoms in patients infected with SARS-CoV-2 were fever and cough.

What are the new findings?

- Infected patients may have no imaging features of COVID-19 pneumonia but only show GI symptoms.
- There was no significant difference in the clinical outcomes (remained in hospital, discharged or died) between patients with and without GI symptoms.
- The presence of SARS-CoV-2 RNA in faeces does not necessarily indicate more severe GI symptoms.
- SARS-CoV-2 RNA could be detected in the oesophagus, stomach, duodenum and rectum in severe patients.

How might it impact on clinical practice in the foreseeable future?

- The impact of SARS-CoV-2 on GI system warrants further investigation to promote early identification and timely treatment of patients.
- Understanding the varied susceptibility of individual GI system to SARS-CoV-2 will promote the personalised COVID-19 therapy.

MATERIALS AND METHODS**Study design and participants**

In this retrospective, single-centre study, we reviewed the admission data including clinical records, laboratory findings and endoscopy results on 95 laboratory-confirmed cases of SARS-CoV-2 infection from 17 January to 15 February 2020, at the Fifth Affiliated Hospital of Sun Yat-sen University, which is a designated hospital for all SARS-CoV-2 infected patients in Zhuhai, China. The data cut-off for the study was 15 February 2020. The laboratory-confirmed cases included suspected and clinically diagnosed cases with pharyngeal swab

Table 1 Demographics, baseline features and clinical outcomes of 95 patients infected with SARS-CoV-2

	All patients (n=95)	Patients with GI symptoms (n=58)	Patients without GI symptoms (n=37)	P value
Age, years	45.3±18.3	48.0±17.1	41.1±19.5	0.073
Age groups				0.30
<15	5 (5.3)	1 (1.7)	4 (10.8)	
15–39	37 (38.9)	23 (39.7)	14 (37.9)	
40–49	9 (9.5)	5 (8.6)	4 (10.8)	
50–64	31 (32.6)	19 (32.8)	12 (32.4)	
≥65	13 (13.7)	10 (17.2)	3 (8.1)	
Sex				0.84
Female	50 (52.6)	31 (53.4)	19 (51.4)	
Male	45 (47.4)	27 (46.6)	18 (48.6)	
Epidemiological history				0.46
Recently been to Wuhan or surrounding cities	76 (80.0)	45 (77.6)	31 (83.8)	
Contacted with people from Wuhan	19 (20.0)	13 (22.4)	6 (16.2)	
Smoking history				0.40
Current smoking	6 (6.3)	5 (8.6)	1 (2.7)	
Drinking history				1.00
Current drinking	9 (9.5)	6 (10.3)	3 (8.1)	
Disease classification				0.36
Non-severe	75 (78.9)	44 (75.9)	31 (83.8)	
Severe	20 (21.1)	14 (24.1)	6 (16.2)	
Coexisting illness				
Hypertension	16 (16.8)	10 (17.2)	6 (16.2)	0.90
Diabetes mellitus	6 (6.3)	3 (5.2)	3 (8.1)	0.67
Cardio-cerebrovascular disease	4 (4.2)	3 (5.2)	1 (2.7)	1.00
Malignant tumour	5 (5.3)	4 (6.9)	1 (2.7)	0.65
Chronic lung disease	5 (5.3)	1 (1.7)	4 (10.8)	0.074
Chronic kidney disease	1 (1.1)	1 (1.7)	0	1.00
Viral RNA detection				0.31
Positive faeces	31/65 (47.7)	22/42 (52.4)	9/23 (39.1)	
Clinical outcome				0.86
Remained in hospital	58 (61.1)	35 (60.3)	23 (62.2)	
Discharged	37 (38.9)	23 (39.7)	14 (37.8)	
Died	0	0	0	

Data are presented as n (%), n/N (%) and N is the total number of patients with available data.

P value refers to the comparison between patients with GI symptoms and those without.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

specimens tested positive using real-time reverse transcription PCR (RT-PCR) for SARS-CoV-2.

The diagnose of COVID-19 was according to the WHO interim guidance and new coronavirus pneumonia prevention and control programme (in Chinese).^{3 10} Briefly, a suspected case was defined by the epidemiological history and clinical manifestations. The epidemiological history includes travel history to Wuhan or contact with patients with COVID-19 or other person with fever or respiratory symptoms from Wuhan, within 14 days before illness onset. The clinical manifestations include fever with or without respiratory symptoms and normal or reduced white blood cell count or reduced lymphocyte count in early onset. Suspected cases were classified as clinically diagnosed cases if they have CT imaging characteristics of COVID-19 pneumonia. Symptoms of COVID-19 were classified into four grades: mild clinical symptoms without CT imaging features of pneumonia (mild); fever, respiratory symptoms and imaging features of COVID-19 pneumonia (ordinary); respiratory distress (respiratory rate ≥30 breaths/min), oxygen saturation ≤93% and arterial oxygen tension (or pressure) (PaO₂)/fractional inspired oxygen (FiO₂) ratio

≤300 mm Hg (serious), respiratory failure *requiring mechanical ventilation* and organ failure (critically). The patients were divided into non-severe (mild and ordinary) and severe (serious and critically) groups.

Gastroscopy and rectoscopy

Six patients with GI symptoms (two severe and four non-severe cases) were subjected to gastroscopy and two severe of them were subjected to proctoscopy in a negative pressure room, preventing virus from drifting to other areas. Routine stool tests for other pathogens were negative. Endoscopy staff were equipped with protective suits, goggles, N95 mask and surgical gloves to protect themselves from exposure. Endoscopic images were recorded by mobile phones, and the GI specimens were taken from the oesophagus, stomach, duodenum and rectum for viral RNA detection. One severe patient (case 1) exhibited symptoms of GI bleeding. Therefore, gastroscopy was used to localise the bleeding, and the diagnosis revealed the bleeding in the oesophagus. The other five patients (cases 2–6) exhibiting worsening digestive symptoms also underwent

Table 2 GI manifestations of 58 patients with SARS-CoV-2 infection

	All patients (n=58)	On initial presentation (n=11)	During hospitalisation (n=47)
Symptoms			
Diarrhoea	23 (24.2)	5 (5.3)	18 (18.9)
Anorexia	17 (17.9)	5 (5.3)	12 (12.6)
Nausea	17 (17.9)	3 (3.2)	14 (14.7)
Vomiting	4 (4.2)	0	4 (4.2)
Acid reflux	2 (2.1)	1 (1.1)	1 (1.1)
Epigastric discomfort	2 (2.1)	0	2 (2.1)
Upper GI haemorrhage	2 (2.1)	0	2 (2.1)
Hepatic function impairment	31 (32.6)	1 (1.1)	30 (31.6)
Total bilirubin ($\mu\text{mol/L}$; normal range 3.0–24.0)			11.4 \pm 3.6 (37.7 \pm 18.2)
Increased	22 (23.2)	0	22 (23.2)
ALT (U/L; normal range 7–40 in female, 9–50 in male)			22.5 \pm 19.2 (91.8 \pm 31.5)
Increased	5 (5.3)	1 (1.1)	4 (4.2)
AST (U/L; normal range 13–35 in female, 15–40 in male)			17.6 \pm 5.6 (73.2 \pm 19.0)
Increased	4 (4.2)	0	4 (4.2)

Data are presented as n (%) and mean \pm SD on initial presentation (maximum value during hospitalisation). % is the percentage in 95 patients. ALT, alanine aminotransferase; AST, aspartate transaminase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

endoscopy as we tried to exclude the possibility of erosions, ulcers and bleeding.

Real-time RT-PCR assay for screening of SARS-CoV-2

Pharyngeal swab specimens were collected from all suspected cases at admission. Specimens of confirmed cases, including oesophagus, stomach, duodenum, rectum and faeces, were collected during hospitalisation. RNA was extracted from different specimens using the QIAamp Viral RNA Mini Kit (Qiagen), according to the manufacturer's instructions. RT-PCR

assays were performed using the novel coronavirus real-time RT-PCR Kit (Shanghai ZJ Bio-Tech Co, Ltd, Shanghai, China), targeting the open reading frame lab (ORF1ab) and nucleoprotein (N) gene regions.^{4 10 11} If two targets tested positive, the case was considered to be laboratory confirmed. A cycle threshold value (Ct-value) less than 37 was treated as a positive test, while a Ct-value of 40 or more was defined as a negative test. A Ct-value of 37–40 required sample retesting. If the repeated Ct-value was less than 40 and an obvious peak was observed, the retest was considered as positive.

Statistical analysis

All statistical analyses were processed with SPSS software (V.19.0). Continuous variables expressed as mean \pm SD were compared by unpaired ttest and categorical data presented as number (%) were compared by χ^2 test or Fisher's exact test between GI symptoms group and non-GI symptoms group. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 95 patients (50 women and 45 men) were included in this study with an average age of 45.3 \pm 18.3 years (table 1). Among them, 76 (80.0%) patients recently had been to Wuhan or surrounding cities, and the remaining 19 (20.0%) patients were in close contact with people from Wuhan. Most of the patients (78.9%) were non-severe. Additionally, 35 (36.8%) patients had coexisting illnesses, including hypertension in 16, diabetes mellitus in 6, malignant tumour in 5, chronic lung disease in 5, cardiocerebrovascular disease in 4 and chronic kidney disease in 1 patient. There was no statistically significant difference in the general demographics or clinical outcomes between patients with and without GI symptoms (table 1). For the 58 (61.1%) patients showing GI symptoms, only 11 patients (11.6%) occurred on admission, while the remaining 47 (49.5%) developed symptoms during hospitalisation (table 2). Moreover, 32.6% of the patients developed hepatic function impairment during hospitalisation with elevated bilirubin, aspartate transaminase or alanine aminotransferase (table 2). Diarrhoea (2–10 loose or watery stools a day, 24.2%), anorexia (17.9%) and

Table 3 Drug treatment involvement in GI symptoms developed during hospitalisation

	Antibiotic treatment	Non-antibiotic treatment	P value
Diarrhoea	17/90 (18.9)	1/90 (1.1)	0.034
Non-diarrhoea	49/90 (54.4)	23/90 (25.6)	
Anorexia	11/90 (12.2)	1/90 (1.1)	0.17
Non-anorexia	54/90 (60.0)	24/90 (26.7)	
Nausea	12/92 (13.0)	2/92 (2.2)	0.33
Non-nausea	54/92 (58.7)	24/92 (26.1)	
Vomiting	3/95 (3.2)	1/95 (1.1)	1.00
Non-vomiting	66/95 (69.5)	25/95 (26.3)	
Increased bilirubin	20/95 (21.1)	2/95 (2.1)	0.028
Normal bilirubin	49/95 (51.6)	24/95 (25.3)	
	Antiviral treatment	Non-antiviral treatment	P value
Diarrhoea	18/90 (20.0)	0	0.34
Non-diarrhoea	66/90 (73.3)	6/90 (6.7)	
Anorexia	12/90 (13.3)	0	1.00
Non-anorexia	72/90 (80.0)	6/90 (6.7)	
Nausea	14/92 (15.2)	0	0.59
Non-nausea	72/92 (78.3)	6/92 (6.5)	
Vomiting	4/95 (4.2)	0	1.00
Non-vomiting	85/95 (89.5)	6/95 (6.3)	
Increased bilirubin	22/95 (23.2)	0	0.33
Normal bilirubin	67/95 (70.5)	6/95 (6.3)	

Data are presented as n/N (%). N is the total number of patients except for those who have related GI symptoms on initial presentation.

Table 4 Viral RNA detection of GI system specimens in six patients underwent endoscopy examination or biopsy

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	77	60	34	62	29	23
Sex	Male	Male	Female	Male	Male	Female
Disease severity	Severe	Severe	Non-severe	Non-severe	Non-severe	Non-severe
Viral detection						
Oesophagus	+	+	–	–	–	–
Stomach	+	+	–	–	–	–
Duodenum	+	+	+	–	–	–
Rectum	+	+	NA	NA	NA	NA
Syndromes of other organ systems	Acute respiratory distress syndrome, septic shock, multiple organ dysfunction syndrome (lung, heart and kidney).	Acute respiratory distress syndrome, respiratory failure and septic shock.	None	None	None	None
Clinical outcome	Hospitalisation	Hospitalisation	Hospitalisation	Hospitalisation	Discharged	Discharged

+, means positive; –, means negative; NA, not available.

nausea (17.9%) were the most frequently observed manifestations. We found that antibiotic treatment was associated with diarrhoea ($p=0.034$) and elevated bilirubin levels ($p=0.028$) during hospitalisation (table 3). However, antiviral treatment did not exert such effects. Importantly, 11 (11.6%) patients did not have any imaging features of COVID-19 pneumonia but only show GI symptoms (see online supplementary table S1). Among them, 3 (27.3%) occurred at diagnosis and 8 (72.7%) during hospitalisation.

We explored the associations between GI symptoms and the presence of SARS-CoV-2 in faeces for 65 hospitalised patients including 42 with and 23 without GI symptoms, of which 22 (52.4%) and 9 (39.1%) had SARS-CoV-2 positive faeces, respectively (table 1). The proportion of positive faecal cases did not show significant difference between two groups, suggesting the presence of SARS-CoV-2 RNA in faeces does not necessarily indicate more severe GI symptoms.

To further determine the causes of GI symptoms, six cases of this cohort were subjected to gastroscopy examination (table 4, online supplementary figure S1). One severe patient (case 1) exhibited symptoms of GI bleeding and the source of bleeding was localised in the oesophagus by endoscopy. There were multiple round herpetic erosions and ulcers with a diameter of 4–6 mm at a distance of 26 cm from incisors. The surface of ulcers was covered with white moss and blood clots, and some of them were fused into pieces with a small amount of bleeding (figure 1). SARS-CoV-2 RNA was detected in the oesophageal erosion and bleeding site, as well as in the stomach, duodenum and rectum tissues of case 1. Further follow-up of this patient

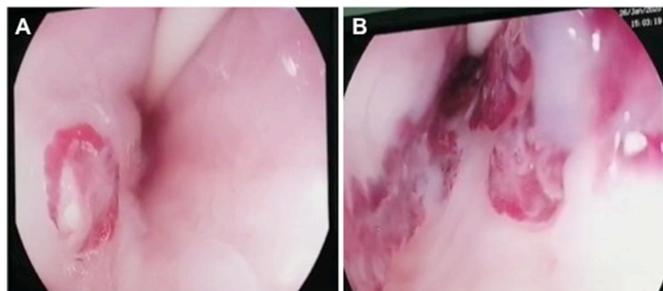


Figure 1 Gastroscopy of the oesophagus in a severe patient with SARS-CoV-2 infection. A and B were different parts of the oesophagus under the endoscopy. (A) A round ulcer (4–6 mm in size) was covered with white moss. (B) Some ulcers were fused into pieces with a small amount of bleeding.

revealed increased bilirubin and organ failure in the heart and kidney (online supplementary figure S1). The other five patients (cases 2–6) exhibiting worsening digestive symptoms also underwent endoscopy, and we did not observe any erosions, ulcers or bleeding (table 4). SARS-CoV-2 RNA could also be detected in the oesophagus, stomach, duodenum and rectum of another severe patient (case 2). In contrast, it was only detected in the duodenum of the non-severe case 3 and could not be detected in any GI specimens of the non-severe cases 4–6.

DISCUSSION

In early reports, 2%–10% of patients with COVID-19 had GI symptoms such as diarrhoea and vomiting.^{1–5} In our study, 11 (11.6%) cases presented with GI symptoms *at the onset of illness*. In contrast, 47 (49.5%) cases exhibited GI symptoms during hospitalisation, which could be aggravated by various drugs including antibiotics. Nevertheless, there was no significant difference in the clinical outcomes between patients with and without GI symptoms.

A recent study reported a patient initially presented with only GI symptoms.¹² In our study, 11 (11.6%) patients did not have any CT imaging features of COVID-19 pneumonia but only show GI symptoms with 3 (27.3%) occurred at diagnosis, indicating their higher susceptibility of GI system to SARS-CoV-2. While the presence of SARS-CoV-2 in faeces does not necessarily indicate more GI symptoms, the presence of SARS-CoV-2 in GI tissue generally indicates severe symptoms based on the fact that two severe patients have SARS-CoV-2 positive oesophagus, stomach, duodenum and rectum specimens but not the four non-severe patients. In summary, the significance of GI symptoms in clinical practice should not be underestimated. Understanding the varied susceptibility of individual GI system to SARS-CoV-2 will promote the personalised COVID-19 therapy.

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