

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 December 14; 27(46): 7866-8039



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Hua-Ge Yin, Production Department Director: Yan-Jie Ma, Editorial Office Director: Ze-Mao Gong.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

December 14, 2021

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Retrospective Cohort Study

# Digestive system involvement and clinical outcomes among COVID-19 patients: A retrospective cohort study from Qatar

Muhammad Umair Khan, Kamran Mushtaq, Deema Hussam Alsoub, Phool Iqbal, Fateen Ata, Hammad Shabir Chaudhry, Fatima Iqbal, Girisha Balaraju, Muna A Al Maslamani, Betsy Varughese, Rajvir Singh, Khalid Al Ejji, Saad Al Kaabi, Yasser Medhat Kamel, Adeel Ajwad Butt

**ORCID number:** Muhammad Umair Khan 0000-0003-3013-4352; Kamran Mushtaq 0000-0002-1787-640X; Deema Hussam Alsoub 0000-0002-8916-4399; Phool Iqbal 0000-0003-3472-9281; Fateen Ata 0000-0001-7121-8574; Hammad Shabir Chaudhry 0000-0002-8358-0287; Fatima Iqbal 0000-0002-6152-6132; Girisha Balaraju 0000-0002-3688-2864; Muna A Al Maslamani 0000-0003-4547-2370; Betsy Varughese 0000-0002-2014-2482; Rajvir Singh 0000-0001-9041-9961; Khalid Al Ejji 0000-0002-7642-7997; Saad Al Kaabi 0000-0003-2084-967X; Yasser Medhat Kamel 0000-0001-5037-2070; Adeel Ajwad Butt 0000-0002-1118-1826.

**Author contributions:** Khan MU and Mushtaq K conceived and designed the study and performed data analysis, literature review, and manuscript writing; Alsoub DH, Iqbal P, Ata F, Chaudhry HS, Iqbal F, Balaraju G, Maslamani MAA, Varughese B, Ejji KA, Kaabi SA, and Kamel YM performed data collection, data analysis, manuscript writing, and literature review; Singh R reviewed the statistical part of the manuscript; Butt AA performed the literature review and revised the final manuscript; all authors verified the final version of the study.

**Muhammad Umair Khan, Kamran Mushtaq, Girisha Balaraju, Betsy Varughese, Khalid Al Ejji, Saad Al Kaabi, Yasser Medhat Kamel,** Department of Gastroenterology and Hepatology, Hamad Medical Corporation, Doha 3050, Qatar

**Muhammad Umair Khan, Kamran Mushtaq, Deema Hussam Alsoub, Fatima Iqbal,** ECPE-Executive and Continuing Professional Education, Harvard T.H. Chan School of Public Health, Boston, MA 02115-5810, United States

**Deema Hussam Alsoub,** Department of Palliative Care, National Center for Cancer Care & Research, Hamad Medical Corporation, Doha 3050, Qatar

**Phool Iqbal, Fateen Ata, Hammad Shabir Chaudhry, Adeel Ajwad Butt,** Department of Medicine, Hamad Medical Corporation, Doha 3050, Qatar

**Fatima Iqbal, Muna A Al Maslamani,** Department of Infectious Disease, Communicable Disease Center, Hamad Medical Corporation, Doha 3050, Qatar

**Rajvir Singh,** Department of Cardiology Research, Heart Hospital, Hamad Medical Corporation, Doha 3050, Qatar

**Adeel Ajwad Butt,** Department of Medicine, Division of Infectious Diseases, Weill Cornell Medical College, New York, NY 10075, United States

**Adeel Ajwad Butt,** Department of Medicine, Weill Cornell Medical College - Qatar, Doha 24144, Qatar

**Corresponding author:** Adeel Ajwad Butt, MBBS, MS, Doctor, Professor, Department of Medicine, Hamad Medical Corporation, PO Box 3050, Hamad Medical Corporation, Doha, Qatar, Doha 3050, Qatar. [aabutt@hamad.qa](mailto:aabutt@hamad.qa)

## Abstract

### BACKGROUND

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 virus most commonly presents with respiratory symptoms. While gastrointestinal (GI) manifestations either at presentation or during hospitalization are also common, their impact on clinical outcomes is

**Institutional review board**

**statement:** The study was approved by the Medical Research Center of Hamad Medical Corporation (MRC-01-20-631).

**Informed consent statement:** Due to the retrospective design of the study, the requirement of informed consent was waived by the Institutional Review Board.

**Conflict-of-interest statement:** All authors and study participants declare no potential conflicting interests related to this paper.

**Data sharing statement:** The authors confirm that the data supporting the findings of this study are available within the article.

**STROBE statement:** The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

**Supported by** Hamad Medical Corporation, No. MRC-01-20-631.

**Country/Territory of origin:** Qatar

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

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controversial. Some studies have described worse outcomes in COVID-19 patients with GI symptoms, while others have shown either no association or a protective effect. There is a need for consistent standards to describe GI symptoms in COVID-19 patients and to assess their effect on clinical outcomes, including mortality and disease severity.

**AIM**

To investigate the prevalence of GI symptoms in hospitalized COVID-19 patients and their correlation with disease severity and clinical outcomes.

**METHODS**

We retrospectively reviewed 601 consecutive adult COVID-19 patients requiring hospitalization between May 1-15, 2020. GI symptoms were recorded at admission and during hospitalization. Demographic, clinical, laboratory, and treatment data were retrieved. Clinical outcomes included all-cause mortality, disease severity at presentation, need for intensive care unit (ICU) admission, development of acute respiratory distress syndrome, and need for mechanical ventilation. Multivariate logistic regression model was used to identify independent predictors of the adverse outcomes.

**RESULTS**

The prevalence of any GI symptom at admission was 27.1% and during hospitalization was 19.8%. The most common symptoms were nausea (98 patients), diarrhea (76 patients), vomiting (73 patients), and epigastric pain or discomfort (69 patients). There was no difference in the mortality between the two groups (6.21% *vs* 5.5%,  $P = 0.7$ ). Patients with GI symptoms were more likely to have severe disease at presentation (33.13% *vs* 22.5%,  $P < 0.001$ ) and prolonged hospital stay (15 d *vs* 14 d,  $P = 0.04$ ). There was no difference in other clinical outcomes, including ICU admission, development of acute respiratory distress syndrome, or need for mechanical ventilation. Drugs associated with the development of GI symptoms during hospitalization were ribavirin (diarrhea 26.37%  $P < 0.001$ , anorexia 17.58%,  $P = 0.02$ ), hydroxychloroquine (vomiting 28.52%,  $P = 0.009$ ) and lopinavir/ritonavir (nausea 32.65%  $P = 0.049$ , vomiting 31.47%  $P = 0.004$ , and epigastric pain 12.65%  $P = 0.048$ ). In the multivariate regression analysis, age  $> 65$  years was associated with increased mortality risk [odds ratio (OR) 7.53, confidence interval (CI): 3.09-18.29,  $P < 0.001$ ], ICU admission (OR: 1.79, CI: 1.13-2.83,  $P = 0.012$ ), and need for mechanical ventilation (OR: 1.89, CI: 1.94-2.99,  $P = 0.007$ ). Hypertension was an independent risk factor for ICU admission (OR: 1.82, CI: 1.17-2.84,  $P = 0.008$ ) and need for mechanical ventilation (OR: 1.66, CI: 1.05-2.62,  $P = 0.028$ ).

**CONCLUSION**

Patients with GI symptoms are more likely to have severe disease at presentation; however, mortality and disease progression is not different between the two groups.

**Key Words:** COVID-19; Gastrointestinal manifestations; Mortality; Intensive care unit admission; Mechanical ventilation; Disease severity

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**Core Tip:** There is a high prevalence of gastrointestinal symptoms in coronavirus disease 2019 patients both at presentation and during hospitalization. Drugs are associated with the development of gastrointestinal symptoms during hospitalization. The presence of gastrointestinal symptoms in coronavirus disease 2019 patients is associated with disease severity at presentation but is not a predictor of mortality or disease progression.

**Citation:** Khan MU, Mushtaq K, Alsoub DH, Iqbal P, Ata F, Chaudhry HS, Iqbal F, Balaraju G, Maslamani MAA, Varughese B, Singh R, Ejji KA, Kaabi SA, Kamel YM, Butt AA. Digestive

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**Received:** April 28, 2021

**Peer-review started:** April 28, 2021

**First decision:** June 13, 2021

**Revised:** June 29, 2021

**Accepted:** November 28, 2021

**Article in press:** November 28, 2021

**Published online:** December 14, 2021

**P-Reviewer:** Karna ST

**S-Editor:** Liu M

**L-Editor:** Filipodia

**P-Editor:** Liu M



system involvement and clinical outcomes among COVID-19 patients: A retrospective cohort study from Qatar. *World J Gastroenterol* 2021; 27(46): 7995-8009

**URL:** <https://www.wjgnet.com/1007-9327/full/v27/i46/7995.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v27.i46.7995>

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection presents most commonly as a respiratory illness with symptoms including fever, cough, and shortness of breath. Disease severity ranges from mild disease requiring no intervention to severe illness requiring intensive care unit (ICU) admission and mechanical ventilation[1,2]. While most studies have focused on respiratory manifestations of coronavirus disease 2019 (COVID-19), extra-respiratory manifestations have also been described, including gastrointestinal (GI) symptoms and liver enzyme abnormalities[3,4]. The prevalence of GI symptoms in COVID-19 patients ranges from 7% to 15%[5,6]. Fecal shedding of SARS-CoV-2 has been reported in 40.5%-48.1% of the patients[7,8]. The significant variation in the proportion of patients with GI symptoms among different studies might be related to geographical region[5] and whether symptoms were reported on admission or during hospitalization[3,9].

Diarrhea, nausea, vomiting, and abdominal pain are the most frequently reported GI symptoms[5,8]. The association between GI symptoms and adverse outcomes in patients with SARS-CoV-2 infection is controversial[8,10-13]. Some studies have shown an inverse correlation between GI symptoms and adverse outcomes, including mortality[10,11,14], while others have shown a direct correlation of GI symptoms with disease severity and adverse outcomes[8,12]. Still others, including a recent meta-analysis, have shown that GI symptoms bear no association with adverse outcomes or mortality[13,15]. Studies are needed with consistent standards for describing GI symptoms and distinguishing between GI symptoms on admission *vs* symptoms that develop during the hospital stay to determine whether GI symptoms have correlation to disease severity.

The aim of our study was to evaluate the prevalence of GI symptoms in COVID-19 patients at admission and during hospitalization and their association with adverse outcomes, including mortality.

## MATERIALS AND METHODS

### Study design and participants

We conducted a retrospective cohort study investigating the epidemiological and clinical characteristics and outcomes among consecutive adult patients with SARS-CoV-2 infection who were admitted to one of the dedicated COVID-19 hospitals in the state of Qatar between May 1-15, 2020. SARS-CoV-2 infection was diagnosed by real-time polymerase chain reaction assays Cobas SARS-CoV-2 Test (Roche Diagnostics, Rotkreuz, Switzerland) or TaqPath COVID-19 Combo Kit (Thermo Fisher Scientific, Waltham, MA, United States) on nasopharyngeal and throat swabs.

The severity of COVID-19 was defined according to the World Health Organization guidelines and categorized into five groups[16] (see [Supplementary material, Appendix](#)). Demographic, clinical, laboratory, treatment, and outcome data were retrieved from the electronic medical records. These included a complete blood count, renal function, electrolytes, coagulation profile, liver function tests, and other biochemical markers including creatine kinase, lactate dehydrogenase, C-reactive protein, troponin-T, serum lipase, amylase, procalcitonin, and ferritin. Microbiological investigations, including blood, respiratory, fecal, and urine cultures, were reviewed. Radiologic assessments included chest radiography on admission and subsequent chest computed tomography or abdomen ultrasound according to the patient's clinical care needs. X-ray findings were recorded from the medical records and by examining the films.

### Outcomes and definitions

The primary outcome was all-cause mortality during the hospitalization. Secondary outcomes included disease severity at admission, disease progression defined by admission to the ICU, development of acute respiratory distress syndrome, and need

for mechanical ventilation. Other outcomes included the development of septic shock and length of hospital stay. All outcomes were compared between those with and without GI symptoms at admission.

GI symptoms were defined by the presence of at least one of the following symptoms: nausea, vomiting, diarrhea, epigastric pain or discomfort, acid reflux, anorexia, or GI bleeding. GI symptoms were recorded on admission and during hospitalization to determine the influence of medical therapy and other external factors. Diarrhea was defined as the passing of loose stools > three times per day with a negative stool culture for routine bacterial pathogens. Diarrhea that developed during hospitalization was recorded only after recording negative stool culture and absence of *Clostridium difficile* infection. Liver enzyme abnormalities were classified into normal, borderline ( $< 2 \times$  upper limit of normal), mild impairment ( $2\text{--}5 \times$  elevation), moderate ( $5\text{--}10 \times$  elevation), and severe ( $> 10 \times$  upper limit of normal).

Travel history in the 3 mo before the presentation and exposure to a confirmed case were recorded. Acute respiratory distress syndrome and shock were defined per the World Health Organization guidelines for COVID-19.

### Study oversight

The study was approved by the Medical Research Center of Hamad Medical Corporation (MRC-01-20-631). Due to the retrospective design of the study, the requirement of informed consent was waived, and Institutional Review Board exemption was granted.

### Statistical analysis

We summarized continuous variables using mean (standard deviation) and median (interquartile range) for normal and non-normally distributed data, respectively. Categorical variables were expressed as number (%) and compared using the Pearson's  $\chi^2$  test or Fisher's exact test, as indicated. Univariate logistic regression analysis was used to identify the risk factors for adverse outcomes. All variables with a *P* value of  $< 0.10$  from univariate analysis were included in a multivariate logistic regression model with the forward method to identify independent predictors of the adverse outcomes. No adjustment for multiple testing was performed. A two-sided *P* value of  $< 0.05$  was considered statistically significant. Statistical analyses were performed using Stata Statistical Software Stata/IC 16.1 (StataCorp LLC, College Station, TX, United States).

## RESULTS

### Demographic and epidemiological characteristics

We identified 601 adult patients hospitalized with confirmed SARS-CoV-2 infection during the study period. The mean age was  $46.20 \pm 13.66$  years, and 85.4% were males. The clinical characteristics at presentation are shown in Table 1. Fever (79.7%), cough (75.7%), and shortness of breath (50.2%) were the most common presenting symptoms. Overall, 163 (27.1%) had at least one GI symptom at presentation. Patients without GI symptoms were more likely to have a cough (77.8% *vs* 68.7%, *P* = 0.02), while patients with GI symptoms had more fatigue (48.0% *vs* 19.0%, *P* < 0.001) and myalgias (38.7% *vs* 27.0%, *P* = 0.007). The patients with GI symptoms had a significantly longer duration of symptoms before the presentation ( $4.81 \pm 2.51$  *vs*  $4.04 \pm 2.51$ , *P* = 0.002) compared to patients without GI symptoms. There was no difference between the two groups regarding exposure to a sick contact, family clustering, and travel outside the country.

Patients with GI symptoms were more likely to have underlying chronic liver disease (1.2% *vs* 0.0%, *P* < 0.001), malignancy (2.5% *vs* 1.8%, *P* < 0.001), and immunosuppression (4.3% *vs* 3.0%, *P* < 0.001) but were less likely to have chronic lung conditions (4.9% *vs* 6.1%, *P* < 0.001). Severe disease at presentation was more frequent in the patients with GI symptoms compared with those without GI symptoms (33.1% *vs* 22.5%, *P* < 0.001). There was no statistically significant difference in the rest of the general demographics or other epidemiological parameters between the two groups. Of those 163 (27.1%) patients reporting at least one GI symptom at admission, the most common symptoms were nausea (98 patients), diarrhea (76 patients), vomiting (73 patients), and epigastric pain or discomfort (69 patients) (Table 2).

### Laboratory and radiological abnormalities

The laboratory parameters of the study participants are presented in Table 3. Alanine

**Table 1 Demographic and epidemiological characteristics and presenting symptoms of coronavirus disease 2019 patients with and without gastrointestinal symptoms, *n* (%)**

Characteristics	Overall ( <i>n</i> = 601)	With GI ( <i>n</i> = 163)	Without GI ( <i>n</i> = 438)	<i>P</i> value
Age (yr)	46.20 13.66	46.45 13.76	46.12 13.64	0.728
Sex, male	513 (85.4)	136 (83.4)	377 (85.9)	0.515
BMI (kg/m <sup>2</sup> )	27.55 (24.90-31.00)	27.49 (24.40-30.60)	27.55 (24.90-31.00)	0.811
Duration of symptoms (d)	4.24 2.53	4.81 2.51	4.04 2.51	0.002 <sup>a</sup>
Nationality				0.765
Qatar	67 (11.1)	17 (25.4)	50 (74.6)	
India	127 (21.1)	27 (21.3)	100 (78.7)	
Nepal	89 (14.8)	23 (25.8)	66 (74.2)	
Bangladesh	105 (17.5)	33 (31.4)	72 (68.6)	
Pakistan	48 (8.0)	14 (29.2)	43 (70.8)	
Philippines	56 (9.3)	18 (32.1)	38 (67.9)	
Arab countries	60 (9.9)	16 (26.7)	44 (73.3)	
Others	49 (8.15)	15 (30.6)	34 (69.4)	
Presenting symptoms				
Fever	478 (79.7)	130 (79.7)	348 (79.1)	0.147
Cough	455 (75.7)	112 (68.7)	343 (77.8)	0.016 <sup>a</sup>
Sputum	75 (12.5)	23 (14.1)	52 (11.8)	0.483
Shortness of breath	303 (50.2)	84 (51.5)	219 (49.7)	0.412
Sore throat	146 (24.3)	37 (22.7)	109 (24.7)	0.747
Nasal obstruction	51 (8.5)	18 (11.0)	33 (7.5)	0.359
Fatigue	163 (27.1)	79 (48.5)	84 (19.1)	< 0.001 <sup>a</sup>
Myalgia	182 (30.3)	63 (38.7)	119 (27.0)	0.007 <sup>a</sup>
Anosmia	303 (50.2)	86 (52.8)	217 (49.5)	0.424
Exposure history				
Smoking	62 (10.1)	24 (14.9)	38 (8.7)	0.199
Ex-smoker	7 (1.2)	3 (1.9)	4 (0.9)	
Alcohol	44 (7.3)	9 (5.6)	35 (8.3)	0.28
Travel history	43 (7.2)	9 (5.6)	34 (7.8)	0.456
Sick contact	142 (23.6)	34 (20.9)	108 (24.6)	0.533
Family cluster	27 (4.6)	10 (6.3)	17 (3.4)	0.477
Pre-existing conditions				
No. of comorbid conditions				0.39
0	261 (43.4)	72 (43.6)	189 (43.0)	
1-2	203 (33.8)	53 (32.1)	150 (32.2)	
> 2	137 (22.8)	38 (24.9)	99 (22.1)	
Diabetes mellitus	242 (40.3)	72 (44.2)	170 (38.6)	0.327
Hypertension	209 (34.6)	52 (31.9)	157 (35.6)	0.536
Coronary artery disease	46 (7.7)	6 (3.7)	40 (9.1)	0.622
Chronic kidney disease	47 (7.8)	12 (7.4)	35 (8.0)	0.882
Chronic liver disease	6 (1.0)	2 (1.2)	4 (0.9)	< 0.001 <sup>a</sup>

Malignancy	12 (2.0)	4 (2.5)	8 (1.8)	< 0.001 <sup>a</sup>
Lung disease	35 (5.8)	8 (4.9)	27 (6.1)	< 0.001 <sup>a</sup>
Immunosuppression	20 (3.3)	7 (4.3)	13 (3.0)	< 0.001 <sup>a</sup>
Disease severity at admission				0.0024 <sup>a</sup>
Asymptomatic	48 (8.0)	2 (1.2)	46 (10.5)	
Mild	109 (18.1)	32 (19.6)	77 (17.7)	
Moderate	291 (48.4)	75 (46.0)	216 (49.1)	
Severe	70 (11.6)	26 (15.9)	44 (10.0)	
Critical	83 (13.8)	28 (17.2)	55 (12.5)	
Severe–non severe	153(25.5)	54 (33.1)	99 (22.5)	< 0.001 <sup>a</sup>

<sup>a</sup>Statistically significant *P* value.

BMI: Body mass index; GI: Gastrointestinal.

**Table 2 Frequency of gastrointestinal symptoms in coronavirus disease 2019 patients at admission and during hospital stay, *n* (%)**

GI symptoms at admission ( <i>n</i> = 601)	Frequency	During hospital stay ( <i>n</i> = 438)	Frequency
Diarrhea	76 (12.6)	Diarrhea	42 (7.0)
Nausea	98 (16.2)	Nausea	94 (15.6)
Vomiting	73 (12.1)	Vomiting	87 (14.5)
Epigastric pain	69 (11.4)	Epigastric pain	22 (3.6)
GERD	6 (1.0)	GERD	2 (0.3)
Anorexia	66 (10.9)	Anorexia	26 (4.3)
GI bleeding	4 (0.7)	GI bleeding	6 (1.0)
Any GI symptoms	163 (27.1)	Any GI symptoms	119 (19.8)
Any nausea, vomiting, diarrhea	140 (19.0)		

GI: Gastrointestinal; GERD: Gastro-esophageal reflux disease.

aminotransferase levels were significantly higher in patients with GI symptoms ( $P = 0.04$ ). Overall, the proportion of patients with any liver test abnormality was higher in patients with GI symptoms, but the difference did not approach statistical significance.

All but 2 patients had a chest x-ray at presentation. A normal chest x-ray was observed in 23.5% of the patients, and bilateral lung infiltrates (54.6%) were the most common radiological abnormality at presentation.

### Treatment and outcomes

The drug treatment received by the patients is summarized in Table 4. Hydroxychloroquine (HCQ) (90.45%) and azithromycin (90.12%) were the most common drugs administered to the patients followed by broad-spectrum antibiotics other than azithromycin (82.60%). The drug treatment did not differ between the two groups except for broad-spectrum antibiotics, with patients having GI symptoms receiving more antibiotics (92.6% *vs* 78.9%,  $P = 0.000$ ). We also divided the treatment regimen into six groups based on the different combinations of administered drugs. Group 1 containing hydroxychloroquine plus azithromycin was the most frequently administered treatment combination. COVID-19 patients with GI symptoms received significantly more treatment combination 1 HCQ + azithromycin (92.0% *vs* 85.4%,  $P = 0.039$ ) and combination 2 HCQ + azithromycin + oseltamivir + antibiotics (78.5% *vs* 69.2%,  $P = 0.024$ ).

Overall, 34 patients (5.7%) died. Mortality was not different between patients with and without GI symptoms (6.2% *vs* 5.5%,  $P = 0.741$ ). In addition, 260 (43.6%), 185 (30.8%), and 130 (21.6%) patients needed ICU stay, mechanical ventilation, or developed shock, respectively. There was no statistically significant difference

**Table 3 Laboratory and radiological findings of coronavirus disease 2019 patients with and without gastrointestinal symptoms, *n* (%)**

Parameters	Total	With GI symptoms ( <i>n</i> = 163)	Without GI symptoms ( <i>n</i> = 438)	<i>P</i> value
Hematological parameters				
Hemoglobin gm/dL	14.0 (12.7-15.0)	13.9 (12.7-15.0)	14.0 (12.7-15.1)	0.590
Hematocrit	42.1 (39.0-45.2)	42.0 (38.7-45.0)	42.3 (39.1-45.3)	0.010
WBC (10 <sup>3</sup> /L)	6.3 (4.9-8.6)	6.2 (4.6-8.6)	6.4 (5.0-8.5)	0.595
Neutrophils (10 <sup>3</sup> /L)	4.3 (3.1-6.6)	4.4 (2.9-6.5)	4.3 (3.1-6.6)	0.617
Lymphocytes (10 <sup>3</sup> /L)	1.2 (0.8-1.6)	1.1 (0.8-1.6)	1.2 (0.8-1.6)	0.987
Eosinophils (10 <sup>3</sup> /L)	0 (0-0.02)	0 (0-0)	0 (0-0.05)	0.643
Monocytes (10 <sup>3</sup> /L)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.919
Platelets (10 <sup>3</sup> /L)	211 (169-261)	202 (155-257)	215 (170-261)	0.961
Coagulation function				
INR	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.486
Blood biochemistry				
BUN (mmol/L)	4.0 (3.0-5.3)	3.8 (2.4-5.2)	4.1 (3.1-5.3)	0.758
Creatinine (mol/L)	85 (70-102)	86 (69-101)	84 (70-103)	0.407
Sodium (mmol/L)	136 (133-138)	135 (132-137)	136 (133-138)	0.225
ALT (U/L)	32 (22-51)	34 (22-56)	32 (22-49)	0.043 <sup>a</sup>
AST (U/L)	37 (25-59)	42 (28-69)	36 (24-55)	0.116
ALK-P (U/L)	70 (57-88)	71 (58-88)	70 (57-89)	0.199
Bilirubin (mol/L)	9 (6-12)	8 (7-12)	9 (6-12)	0.438
Albumin (gm/L)	36 (31-39)	35 (30-38)	36 (32-39)	0.058
Glucose (mmol/L)	6.6 (5.4-9.0)	6.7 (5.5-9.0)	6.6 (5.4-9.0)	0.708
Lactate (mmol/L)	1.3 (1.0-1.8)	1.4 (1.1-1.9)	1.2 (1.1-1.8)	0.297
CK (U/L)	218 (72-481)	147 (84-518)	237 (68-477)	0.455
Amylase (U/L)	48 (25-124)	47 (23-119)	47 (28-109)	0.604
Lipase (U/L)	55 (35-129)	56 (35-152)	54 (36-103)	0.648
Troponin-T (ng/L)	10 (6-26)	10 (6-17)	11 (6-26)	0.296
LDH (U/L)	436 (305-559)	446 (337-578)	435 (302-547)	0.167
Infection-related biomarkers				
CRP (mg/L)	55.3 (16.0-113.7)	55.5 (24.9-113.7)	55.3 (13.2-113.7)	0.614
Procalcitonin (ng/ml)	0.21 (0.10-0.68)	0.21 (0.10-0.50)	0.21 (0.10-0.70)	0.789
Ferritin (g/L)	659 (327-1229)	805 (450-1475)	618 (289-1154)	0.561
Liver injury at admission				0.059
None	272 (45.87)	65 (40.37)	207 (47.92)	
Abnormality < 2 × ULN	218 (36.76)	61 (37.89)	157 (36.34)	
Mild	85 (14.33)	30 (18.63)	55 (12.73)	
Moderate	15 (2.53)	5 (3.11)	10 (2.31)	
Severe	2 (0.34)	0 (0.00)	2 (0.46)	
Liver injury during hospitalization				0.302
None	107 (19.60)	26 (16.56)	81 (20.88)	
Abnormality < 2 × ULN	163 (29.91)	51 (32.48)	112 (28.87)	

Mild 2-5 ×	171 (31.40)	44 (28.03)	127 (32.73)
Moderate 5-10 ×	63 (11.56)	21 (13.38)	42 (10.82)
Severe > 10 ×	41 (7.52)	15 (9.55)	26 (6.70)
Radiological findings			
X-ray chest			0.286
Not done	2 (0.3)	0 (0.0)	2 (0.5)
Normal	141 (23.5)	35 (21.6)	107 (24.3)
Unilateral PNA	100 (16.6)	24 (14.8)	76 (17.2)
Bilateral PNA	328 (54.6)	96 (59.3)	232 (52.6)
Ground glass	29 (4.8)	7 (4.3)	22 (5.0)

WBC: White blood cells; BUN: Blood urea nitrogen; INR: International normalized ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase, ALK-P: Alkaline phosphatase; CK: Creatine Kinase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ULN: Upper limit of normal; PNA: Pneumonia; GI: Gastrointestinal.

between the two groups. Seven (1.2%), 29 (4.8%), and 48 (8.0%) patients developed acute liver failure, renal failure requiring renal replacement therapy, and multiorgan failure, respectively, with no significant difference between the two groups. Patients with GI symptoms had a longer total hospital length of stay compared with patients without GI symptoms (15 d *vs* 14 d,  $P = 0.036$ ).

### GI symptoms during hospitalization

An additional 119 patients (19.8%) developed GI symptoms during hospitalization. Nausea (15.64%) and vomiting (14.48%) were the most commonly reported GI symptoms, followed by diarrhea (6.99%) and anorexia (4.32%) (Table 2). Regarding the treatment administered, use of HCQ was associated with vomiting (28.52%,  $P = 0.009$ ), ribavirin use was associated with diarrhea (26.37%,  $P < 0.001$ ) and anorexia (17.58%,  $P = 0.02$ ), while the use of lopinavir/ritonavir was independently related to the development of nausea (32.65%,  $P = 0.05$ ), vomiting (31.47%,  $P = 0.004$ ), and epigastric pain (12.65%,  $P = 0.05$ ) (Table 5).

The frequency of GI symptoms in different treatment combinations is shown in the Supplementary Table 1, along with significant  $P$  values. Specifically, treatment group 3 had more chances of developing nausea and vomiting, while treatment groups 5 and 6 had a significant association with anorexia.

### Prediction of risk factors for severe/critical COVID-19 and adverse outcomes

In the multivariate regression analysis, age > 65 years was the only significant factor associated with increased mortality risk [adjusted odds ratio (aOR) 7.53, confidence interval (CI): 3.09-18.29,  $P < 0.001$ ]. For disease severity at presentation, presence of GI symptoms (aOR: 1.66, CI: 1.09-2.52,  $P = 0.02$ ), diabetes (aOR: 1.92, CI: 1.28-2.87,  $P = 0.002$ ), hypertension (aOR: 1.68, CI: 1.08-2.60,  $P = 0.02$ ), and smoking (aOR: 1.62, CI: 1.01-2.63,  $P = 0.05$ ) were independent predictors in multivariate regression. Risk factors for ICU admission included age > 65 years (aOR: 1.79, CI: 1.13-2.83,  $P = 0.012$ ), male sex (aOR: 1.82, CI: 1.05-3.15,  $P = 0.033$ ) fever at admission (aOR: 2.14, CI: 1.24-3.69,  $P = 0.006$ ), shortness of breath (aOR: 2.90, CI: 1.99-4.24,  $P < 0.001$ ), and hypertension (aOR: 1.82, CI: 1.17-2.84,  $P = 0.008$ ). Risk factors for mechanical ventilation included age > 65 (aOR: 1.89, CI: 1.94-2.99,  $P = 0.007$ ), male sex (aOR: 1.88, CI: 1.02-3.45,  $P = 0.043$ ), vomiting (aOR: 2.03, CI: 1.10-3.75,  $P = 0.023$ ), fever (aOR: 3.16, CI: 1.63-6.09,  $P < 0.001$ ), shortness of breath (aOR: 2.36, CI: 1.57-3.55,  $P < 0.001$ ), and hypertension (aOR: 1.66, CI: 1.05-2.62,  $P = 0.028$ ) (Table 6). The univariate analysis of risk factors for severe coronavirus disease 2019 at presentation and clinical outcomes is shown in Supplementary Table 2.

## DISCUSSION

COVID-19 disease caused by the novel coronavirus SARS-CoV-2 started in China in December 2019 and soon became pandemic, causing unprecedented global public health challenges. COVID-19 mainly presents with respiratory symptoms; however, GI

**Table 4 Clinical outcomes and treatment in coronavirus disease 2019 patients with and without gastrointestinal symptoms, *n* (%)**

	Total	With GI symptoms <i>n</i> = 163	Without GI symptoms <i>n</i> = 438	<i>P</i> value
<b>Outcomes</b>				
ICU admission	260 (43.55)	78 (48.45)	182 (41.74)	0.143
ARDS	206 (34.30)	61 (38.12)	145 (33.30)	0.268
Shock	130 (21.60)	40 (25.00)	90 (20.64)	0.254
MOF	48 (8.00)	15 (9.32)	33 (7.59)	0.491
ALF	7 (1.20)	1 (0.62)	6 (1.38)	0.447
MV	185 (30.80)	55 (34.80)	130 (29.90)	0.252
ECMO	4 (0.70)	1 (0.62)	3 (0.69)	0.929
CRRT	29 (4.80)	6 (3.73)	23 (5.28)	0.610
Death	34 (5.70)	10 (6.21)	24 (5.50)	0.741
LOS (d)	15 (8-21)	15 (10-22)	14 (7-21)	0.036 <sup>a</sup>
<b>Treatment</b>				
Azithromycin	538 (90.12)	151 (93.80)	387 (88.80)	0.068
HCQ	540 (90.45)	150 (93.20)	390 (89.40)	0.170
Chloroquine	38 (6.30)	7 (4.35)	31 (7.11)	0.388
Antibiotics	493 (82.6)	149 (92.6)	344 (78.9)	< 0.001 <sup>a</sup>
Steroids	248 (41.61)	67 (41.60)	181 (41.60)	0.831
IFN	62 (10.30)	21 (13.04)	41 (9.43)	0.368
RBV	91 (15.10)	31 (19.25)	60 (13.80)	0.097
Tocilizumab	236 (39.50)	66 (40.99)	170 (38.99)	0.657
Lopinavir/ritonavir	340 (56.6)	96 (59.6)	244 (56.0)	0.422
Oseltamivir	510 (85.43)	139 (86.30)	371 (85.09)	0.702
Darunavir	48 (8.0)	14 (8.7)	34 (7.8)	0.782
<b>Treatment groups</b>				
Group 1	524 (87.2)	150 (92.0)	374 (85.4)	0.039 <sup>a</sup>
Group 2	431 (71.7)	128 (78.5)	303 (69.2)	0.025 <sup>a</sup>
Group 3	307 (51.1)	88 (54.0)	219 (50.0)	0.409
Group 4	181 (30.1)	50 (30.7)	131 (29.9)	0.920
Group 5	61 (10.1)	22 (13.5)	39 (8.9)	0.128
Group 6	56 (9.3)	20 (12.3)	36 (8.2)	0.155

<sup>a</sup>Statistically significant *P* value.

Group 1: Hydroxychloroquine + Azithromycin; Group 2: Hydroxychloroquine + Azithromycin + Oseltamivir + Antibiotics; Group 3: Hydroxychloroquine + Azithromycin + Oseltamivir + Antibiotics + Lopinavir/ritonavir; Group 4: Hydroxychloroquine + Azithromycin + Oseltamivir + Antibiotics + Lopinavir/ritonavir + Steroids; Group 5: Hydroxychloroquine + Azithromycin + Oseltamivir + Antibiotics + Lopinavir/ritonavir + Steroids + Interferon/ribavirin; Group 6: Hydroxychloroquine + Azithromycin + Oseltamivir + Antibiotics + Lopinavir/ritonavir + Steroids + Interferon/ribavirin + Tocilizumab.

ARDS: Acute respiratory distress syndrome; MOF: Multiorgan failure; ALF: Acute liver failure; MV: Mechanical ventilation; ECMO: Extra-corporal membrane oxygenation; CRRT: Continuous renal replacement therapy; LOS: Length of stay; HCQ: Hydroxychloroquine; IFN: Interferon; RBV: Ribavirin; GI: Gastrointestinal; ICU: Intensive care unit.

manifestations were quickly recognized as frequent presenting symptoms. While numerous studies have reported GI symptoms in COVID-19 patients, the criteria of GI symptoms have been variable and inconsistent[3,4,11,17,18]. Furthermore, some studies reported symptoms at presentation only while others described anytime during illness.

**Table 5 Association of gastrointestinal symptoms with individual drugs, *n* (%)**

	Azithromycin ( <i>n</i> = 538)	HCQ ( <i>n</i> = 540)	Antibiotics ( <i>n</i> = 493)	Steroids ( <i>n</i> = 248)	RBV ( <i>n</i> = 91)	Tocilizumab ( <i>n</i> = 236)	L/r ( <i>n</i> = 340)	Oseltamivir ( <i>n</i> = 510)
Diarrhea	78 (14.50)	79 (14.63)	70 (14.20)	37 (14.92)	24 (26.37) <sup>P</sup> < 0.001 <sup>a</sup>	35 (14.83)	44 (12.94)	75 (14.71)
Nausea	160 (29.74)	165 (30.60)	147 (29.82)	74 (29.84)	26 (8.57)	66 (27.97)	111 (32.65) <sup>P</sup> = 0.049 <sup>a</sup>	153 (30.00)
Vomiting	148 (27.51)	154 (28.52) <sup>P</sup> = 0.009 <sup>a</sup>	135 (27.38)	68 (27.42)	22 (24.18)	64 (27.12)	107 (31.47) <sup>P</sup> = 0.004 <sup>a</sup>	140 (27.45)
Epigastric pain	57 (10.59)	60 (11.11)	54 (10.95)	29 (11.69)	13 (14.29)	24 (10.17)	43 (12.65) <sup>P</sup> = 0.048 <sup>a</sup>	55 (10.78)
Anorexia	55 (10.22)	58 (10.74)	50 (10.14)	30 (12.10)	16 (17.58) <sup>P</sup> = 0.022 <sup>a</sup>	28 (11.86)	41 (12.06)	56 (10.98)
Any GI symptoms	208 (38.66)	209 (38.70)	191 (38.74)	95 (38.31)	41 (45.05)	92 (38.98)	138 (40.59)	194 (38.04)

<sup>a</sup>Statistically significant *P* value.

HCQ: Hydroxychloroquine; RBV: Ribavirin; L/r: Lopinavir/ritonavir; GI: Gastrointestinal

In our cohort, 27% of the patients had at least one GI symptom at presentation. Our cohort has a similar prevalence of symptoms as reported in the different meta-analyses [5,6,12,15], and slight variation can be attributed to different geographic locations and varied ethnic backgrounds and patients' perceptions of the importance of symptoms. However, our study differentiated clearly between GI symptoms at presentation and those developing during hospitalization. GI symptoms at the time of presentation are more likely attributable to COVID-19 as most patients were not taking any medications before the hospitalization. In contrast, GI symptoms developing during hospitalization may be multifactorial, including nosocomial infection, drug-related side effects, or progression of COVID-19.

Numerous mechanisms have been proposed for the development of GI symptoms in COVID-19 patients. The entry of the SARS-CoV-2 virus into host cells depends on the interaction of the virus spike protein with the receptor angiotensin-converting enzyme 2 and priming of the spike protein by host cell transmembrane serine protease 2 [19,20]. Angiotensin-converting enzyme 2 and transmembrane serine protease 2 have been reported to be coexpressed in the GI tract, including esophageal upper epithelial and gland cells and absorptive enterocytes from the ileum and colon [19,20]. These enterocytes can be damaged, resulting in malabsorption and intestinal secretion abnormalities due to coronavirus or rotavirus infection [21,22]. It is, therefore, possible that GI manifestations in patients with COVID-19 might be associated with direct infection of enterocytes with the SARS-CoV-2 virus [19]. Elevated levels of fecal calprotectin, an inflammatory marker secreted by infiltrated neutrophils, in the fecal samples of COVID-19 patients with diarrhea also support this hypothesis [20].

Gut dysbiosis has been proposed as another mechanism to explain GI symptoms in COVID-19 patients. It is characterized by an increase in the opportunistic pathogens and reduction of beneficial commensals and correlates with COVID-19 severity and fecal levels of SARS-CoV-2 [23]. It has been shown that the gut microbial signature of COVID-19 patients is different from healthy controls [24]. Although the clinical significance of these findings is still uncertain, it is possible that gut microbiota composition plays a role in modulating the systemic immune response.

The two primary modes of transmission for SARS-CoV-2 are respiratory droplets and direct contact [25], while the possibility of aerosol transmission has been suggested as well [25]. The GI tract has recently been proposed as an alternative transmission route for SARS-CoV-2 infection in a non-human primate model [26], raising the possibility of potential fecal-oral spread of the disease in humans as well. However, our study did not show any significant correlation of GI symptoms in family clusters, thus arguing against the potential fecal-oral transmission of the virus. Studies have reported the SARS-CoV-2 RNA in fecal samples or rectal swabs and fecal shedding of the virus continues even after clearance of respiratory samples [8,27-29]. The risk of transmission secondary to this prolonged shedding is unknown and warrants further studies.

**Table 6 Multivariate analysis of risk factors for severe coronavirus disease 2019 at presentation and clinical outcomes, *n* (%)**

Risk factors	Multivariate analysis	
	Adjusted odds ratio	<i>P</i> value
	Death	
Age > 65 yr	7.53 (3.09-18.29)	< 0.001
	Disease severity at presentation	
Hypertension	1.68 (1.08-2.60)	0.021
Diabetes mellitus	1.92 (1.28-2.87)	0.002
GI symptoms	1.66 (1.09-2.52)	0.017
Smoking	1.62 (1.01-2.63)	0.049
	ICU admission	
Age > 65 yr	1.79 (1.13-2.83)	0.012
Sex	1.82 (1.05-3.15)	0.033
Fever	2.14 (1.24-3.69)	0.006
Shortness of breath	2.90 (1.99-4.24)	< 0.001
Hypertension	1.82 (1.17-2.84)	0.008
	Mechanical ventilation	
Age > 65 yr	1.89 (1.94-2.99)	0.007
Sex	1.88 (1.02-3.45)	0.043
Fever	3.16 (1.63-6.09)	0.001
Shortness of breath	2.36 (1.57-3.55)	< 0.001
Hypertension	1.66 (1.05-2.62)	0.028
Vomiting	2.03 (1.10-3.75)	0.023

GI: Gastrointestinal; ICU: Intensive care unit.

COVID-19 patients with GI symptoms were more likely to have a longer duration of symptoms before diagnosis, more likely to have fatigue and myalgias, and less likely to have a cough. Lack of typical COVID symptoms (cough) and presence of atypical symptoms (GI symptoms) may result in delayed recognition and diagnosis of COVID-19 patients. Our findings are in keeping with those reported earlier[6,14]. The increased prevalence of myalgias and fatigue has been previously reported as well[9] and may be a reflection of the increased inflammatory burden in these patients. Patients with GI symptoms were more likely to have underlying malignancy and chronic liver disease. This finding has also been reported in the literature[30] and warrants careful evaluation of GI symptoms in cancer patients.

The severity of disease at presentation seen in COVID-19 patients with GI symptoms could be related to increased inflammatory activity in the intestines contributing to the systemic inflammatory response and cytokine syndrome[22]. Cytokine release syndrome is considered a leading cause of severe pneumonia and even death during COVID-19 disease[31]. Higher plasma levels of both proinflammatory and anti-inflammatory cytokines interleukin (IL)-2, IL-6, IL-7, IL-10, IL-18, granulocyte-macrophage colony-stimulating factor, C-C motif chemokine ligand 2 (also known as MCP1), tumor necrosis factor, and macrophage inflammatory protein 1  $\alpha$  have been detected in patients with severe disease compared to those with moderate disease[31,32]. The intestine produces high levels of IL-6 normally involved in crypt homeostasis[33] and can potentially contribute to the increased systemic IL-6 concentrations seen in COVID-19 patients with severe disease[32]. Similarly, the intestinal release of another proinflammatory cytokine, IL-18, can also contribute to disease severity and GI manifestations[34,35]. One recent study has shown downregulation of essential inflammatory genes in the small intestine and relative absence of inflammatory response in COVID-19 patients with GI symptoms[36]. These patients also had reduced levels of inflammatory proteins in circulation and reduced disease severity

and mortality, suggesting that gut inflammatory response has a potential role in modulating systemic immune reaction[36].

The new-onset GI symptoms during the hospitalization were most likely related to the use of several repurposed drugs, including hydroxychloroquine, ribavirin, and lopinavir/ritonavir. The GI side effects of these drugs have been reported in the literature and among COVID-19 patients in different clinical studies[37-39]. It must be noted that most of these therapies were administered during the first wave due to the lack of robust clinical evidence. Ribavirin, lopinavir/ritonavir, and hydroxychloroquine have not shown significant efficacy over standard care/placebo in COVID-19 patients[40,41]. This, coupled with potential adverse effects, warrant against the routine use of these medicines for COVID-19 treatment.

Our study has several limitations. It was a retrospective design, and reporting bias might affect the accurate estimates. We did not evaluate the mechanism and pathogenesis of GI symptoms in our patients. We also did not report the fecal viral load as there was no validated test available during the study period.

The strengths of our study include large sample size, a multi-ethnic population representing a real-world cohort, well-defined inclusion criteria, clear definition of GI symptoms, and distinction of GI symptoms at admission from those developing during the hospitalization. We had clearly defined outcomes and estimated the severity of the disease at presentation and later disease progression. We used multivariate regression to identify the independent risk factors.

## CONCLUSION

In this current retrospective cohort study conducted in Qatar on a population with diverse ethnic backgrounds, we found a high prevalence (27.1%) of at least one GI symptom at presentation among COVID-19 patients requiring hospitalization. The mortality and disease progression was not different in patients with or without GI symptoms at presentation. However, patients with GI symptoms were more likely to have the severe disease at presentation and longer length of stay in the hospital. Additionally, one-quarter of the patients developed new GI symptoms during hospital admission. The most common culprit drugs associated with new GI symptoms development were lopinavir/ritonavir, ribavirin, and hydroxychloroquine. The lack of efficacy of several repurposed drugs for COVID-19 coupled with side effect profile warrants against their routine use in clinical practice. Further studies are needed to elucidate the mechanism and importance of GI manifestations in COVID-19 patients. Long-term sequelae of GI manifestations in COVID-19 patients remains unknown and needs to be studied.

## ARTICLE HIGHLIGHTS

### Research background

Gastrointestinal (GI) manifestations are present in 7%-15% of the patients with coronavirus disease 2019 (COVID-19). The association of GI manifestations with adverse clinical outcomes remains controversial, with some studies suggesting protective effects while others have reported adverse outcomes.

### Research motivation

Previous studies reporting the association of GI symptoms with clinical outcomes in COVID-19 patients varied in determining the timing of symptoms development. We planned this study to clearly define GI symptoms in COVID-19 patients and distinguish between GI symptoms on admission and symptoms that develop during the hospital stay. We wanted to determine if there is any correlation of GI symptoms with disease severity and adverse clinical outcomes.

### Research objectives

We aimed to determine the prevalence of GI symptoms in COVID-19 patients at admission and during hospitalization. We also aimed to study the correlation of GI symptoms with all-cause mortality, and disease severity at admission and disease progression during hospitalization defined by admission to the intensive care unit, development of acute respiratory distress syndrome, and need for mechanical ventilation.

### Research methods

We conducted a retrospective cohort study investigating the epidemiological and clinical characteristics and outcomes among 601 consecutive adult patients with SARS-CoV-2 infection who were admitted to one of the dedicated COVID-19 hospitals in the state of Qatar between May 1-15, 2020. Clinical characteristics, laboratory parameters, treatment data, and disease outcome, including mortality, were compared between patients with and without GI symptoms. A multivariate logistic regression model with the forward method to identify independent predictors of the adverse outcomes.

### Research results

The prevalence of any GI symptom at admission was 27.1% and during hospitalization was 19.8%. Nausea, vomiting, and diarrhea were the most common GI symptoms on presentation. There was no difference in mortality between the two groups (6.21% *vs* 5.50%,  $P = 0.7$ ). However, patients with GI symptoms were more likely to have severe disease at presentation (33.13% *vs* 22.50%,  $P < 0.001$ ) and prolonged hospital stay (15 d *vs* 14 d,  $P = 0.04$ ). Age  $> 65$  years was the single risk factor associated with increased mortality on multivariate regression analysis.

### Research conclusions

Patients with GI symptoms are more likely to have severe disease at presentation. However, there is no difference in mortality between patients with and without GI symptoms.

### Research perspectives

Future studies are needed to elucidate the mechanism of GI symptoms development in COVID-19 patients. Long-term effects and follow-up of COVID-19 patients with GI symptoms are needed.

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