

# Gastrointestinal manifestations of COVID-19 in a single center in the Eastern Province of Saudi Arabia

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## Abstract

**Background:** Several gastrointestinal (GI) symptoms have been associated with novel coronavirus disease-2019 (COVID-19). Their prevalence and relation to the severity and hospital outcome of COVID-19 have not been well reported in the Middle East and Saudi Arabia. We aimed to examine the GI manifestations of COVID-19 and their association with the severity and hospital outcome of COVID-19 infection.

**Methods:** We conducted a retrospective observational study of hospitalized COVID-19 patients who had a positive SARS-COV2 PCR test and were admitted at a university hospital in Saudi Arabia, from March to September 2020. The primary objective of the study was to describe the GI manifestations of COVID-19. The secondary objective was to investigate the association of GI manifestations with severity and outcome of COVID-19 infection.

**Results:** We included 390 patients, of which 111 (28.5%) presented with GI manifestations. The most common presentation was diarrhea followed by nausea, vomiting, and abdominal pain. Patients without GI manifestations had a higher risk of severe-critical COVID-19 infection evident by the development of lung infiltration in more than 50% of lung fields within 24–48 h, acute respiratory distress syndrome, altered mental status, multiorgan failure, and cytokine storm syndrome ( $P < 0.05$ ). These patients had a higher mortality rate compared to patients with GI manifestations ( $P = 0.01$ ). A lower odds of death was seen among patients with GI symptoms (AOR 0.36; 95% CI, 0.158–0.82;  $P = 0.01$ ).

**Conclusion:** COVID-19 infection presents commonly with GI manifestations. Patients with GI manifestations have less severe COVID-19 disease and lower mortality rates.

**Keywords:** COVID-19 infection, gastrointestinal manifestations, mortality, outcome, severity

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## INTRODUCTION


The novel coronavirus disease 2019 (COVID-19) became a well-recognized disease globally, and the World health organization (WHO) had declared it a pandemic in

March 2020.<sup>[1]</sup> COVID-19 presents most commonly with fever in more than 80% of cases, followed by respiratory symptoms in the form of cough, sputum, and shortness of breath.<sup>[2]</sup> The presentation is variable

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in severity, ranging from asymptomatic status to severe manifestations. Patients with the severe form of the disease present with severe pneumonia, hypoxia, and extensive lung infiltrate.<sup>[3]</sup> They can also present with acute respiratory distress syndrome (ARDS), sepsis, cytokine storm syndrome, and multiorgan failure.<sup>[3]</sup> In addition, COVID-19 infection can present with extra-respiratory manifestations, including gastrointestinal (GI), cardiac, renal, hematological, and others.<sup>[4]</sup>

GI manifestations could be the main presenting symptoms of COVID-19.<sup>[5]</sup> Earlier reports found the prevalence of GI manifestations in individuals with COVID-19 between 2% and 10%<sup>[6,7]</sup>; however, later studies found a higher prevalence of 17%–50%.<sup>[8,9]</sup> Loss of appetite, diarrhea, nausea, vomiting, and abdominal discomfort are the most common GI symptoms associated with COVID-19.<sup>[9,10]</sup>

Given the high morbidity and mortality caused by COVID-19 infection in the Middle East region, studies focusing on the GI manifestations and their association with COVID-19 severity and outcome from the Middle East and Saudi Arabia are scarce. Understanding the effect of GI manifestations on the severity and outcome of COVID-19 would likely improve the management and clinical outcome of such patients. This study retrospectively investigated the association between GI manifestations with the severity and outcome of COVID-19 infection, at a Saudi university hospital.

## METHODS

We conducted a retrospective observational study and reviewed hospitalized patients with COVID-19 who tested positive for the SARS-CoV2 PCR test, between March and September 2020, at King Fahd Hospital of the University, Al-Khobar in the Eastern Province of Saudi Arabia. We included all patients  $\geq 18$  years with positive COVID-19 PCR test. We excluded patients with incomplete medical records, pregnancy, malignancy, and immunodeficiency syndromes, including human immune deficiency infection, to avoid their confounding effects on the results.

### Data collection method

Baseline characteristics were obtained by carefully reviewing the hospital charts and electronic health records of the patients. We collected information on six sections: 1. Demographics such as age, gender, nationality, and comorbid conditions. 2. Presenting GI symptoms such as diarrhea, abdominal pain, nausea, and vomiting. 3. Gastrointestinal complications such as intestinal perforation, intra-abdominal infection, pancreatitis, and

GI bleeding. 4. Laboratory investigations at presentation including complete blood cell count, serum creatinine level, erythrocyte sedimentation rate, C-reactive protein, D-dimer, serum ferritin, liver profile, albumin level, and prothrombin time/international normalized ratio. 5. The severity of COVID-19 was graded based on 2020 Saudi Arabian Ministry of Health (MOH) guidelines<sup>[3]</sup> as a) mild to moderate disease if there is no pneumonia on chest X-ray and no oxygen requirement; b) severe disease if the respiratory rate was  $\geq 30$ /min, oxygen saturation  $\leq 93\%$  on room air, partial pressure of oxygen/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ )  $< 300$ , or lung infiltrates in  $> 50\%$  of the lung field on chest X-ray within 24–48 h; and c) critical disease if the patient presented with any of the following: ARDS, sepsis, altered level of consciousness, multiorgan failure, or with risk factors of cytokine storm syndrome; the latter was defined as the presence of any of the following: serum ferritin  $> 600$   $\mu\text{g/L}$  at presentation and LDH  $> 250$  U/L or an elevated D-Dimer  $> 1$   $\mu\text{g/mL}$ . 6. The outcome of COVID-19 was determined by the length of hospitalization (LOH), the need for intensive care unit (ICU) admission, or mechanical ventilation, and death.

Patients were grouped according to the presence or absence of GI manifestations. GI manifestation group included patients with any of the GI symptoms or complications mentioned above. Finally, the severity and outcome of COVID-19 infection were compared and analyzed between the two groups.

### Ethical approval

King Fahad Hospital of the University is the university hospital affiliated with Imam Abdulrahman Bin Faisal University. Hence, this study's ethical approval was obtained from the ethics committee of the institutional review board (IRB), Imam Abdulrahman Bin Faisal (IRB-2020-01-279).

### Data analysis

Continuous data were summarized as means and standard deviations (SD) or median and inter-quartile ranges (IQR), while categorical data were summarized as numbers or percentages. Comparisons between different groups were performed using the Chi-square test or Fisher's exact test for categorical variables; however, student t-test or Mann–Whitney U test was used for continuous data. A multivariate regression model was used to identify risk factors predictive of developing the study outcomes. Adjusted odds ratio (AOR) for age, gender, and other comorbidities, 95% confidence interval (CI), and the *P* value were reported for the regression analysis. The statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc,

Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at  $P < 0.05$ .

**RESULTS**

**Demographics and comorbidities**

After reviewing 500 patients, 390 patients met our inclusion criteria [Table 1]. Of the 390 patients, 283 (72.6%) were males, and 217 (55.6%) were Saudi. One hundred eleven (28.5%) patients presented with GI manifestations and had a mean age of  $50.44 \pm 15.6$  years, while the mean age for patients without GI manifestations was  $52.87 \pm 15.7$  years ( $P = 0.17$ ). The results showed no statistically significant difference between the two study groups according to gender, nationality, or presence of comorbidities [Table 1].

**Description of GI manifestations and complications**

The most frequent GI symptoms associated with COVID 19 was diarrhea in 57 (14.6%) followed by nausea in 49 (12.6%), vomiting in 46 (11.8%), and abdominal pain in 39 (10%) of patients. Furthermore, the most common GI complication was pancreatitis in 11 (2.8%) patients [Table 2].

**Comparison of laboratory abnormalities between the two study groups**

Serum ferritin and D-dimer levels were significantly elevated in patients without GI manifestations ( $P = 0.01$  and  $P = 0.004$ , respectively). However, no significant variation was found with the remaining laboratory tests [Table 3].

**Association of severity and outcome of COVID-19 with the presence or absence of GI manifestations**

Interestingly, patients without GI manifestations had a higher risk of severe-critical COVID-19 disease. Lung infiltration greater than 50% of lung fields within 24–48 h

of symptom onset was seen in 108 (38.7%) patients without GI symptoms as compared to 29 (26.1%) patients with GI symptoms ( $P = 0.02$ ). PaO<sub>2</sub>/FiO<sub>2</sub> ratio less than 300 was seen in 115 (44.4%) patients without GI symptoms versus 34 (33.3%) patients with GI manifestations with marginal statistical significance ( $P = 0.05$ ). ARDS, altered mental status, multiorgan failure, and cytokine storm syndrome were all higher in the non-GI manifestations group ( $P < 0.05$ ). Mortality was higher in the non-GI manifestations group, and death occurred in 52 (18.6%) patients compared to 9 (8.1%) patients with GI symptoms ( $P = 0.01$ ). Although the need for ICU admission and mechanical ventilation was higher in the non-GI manifestations group, they did not reach statistical significance ( $P > 0.05$ ), and the length of hospital stay was similar between the two groups [Table 4].

On multivariate logistic regression analysis, severe or critical disease development due to COVID-19 was higher in older patients and non-Saudis with an AOR of 1.06 and 1.94, respectively ( $P < 0.001$  and  $P = 0.01$ , respectively) [Table 5].

Age and non-Saudi nationality were significant predictors of prolonged hospitalization, ICU admission, mechanical ventilation, and death. In addition, being a male increased the odds of requiring mechanical ventilation and death ( $P < 0.05$ ). Interestingly, the presence of GI symptoms was associated with lower odds of death with an AOR of 0.36 ( $P = 0.01$ ) [Table 6].

**DISCUSSION**

This retrospective study evaluated the GI manifestations of COVID-19. Understanding the association of GI manifestations of COVID-19 with the severity and outcome would likely improve the management and clinical course of such patients. There are three key findings in the present

**Table 1: Demographic data and comorbid conditions**

	GI Manifestations (N=111)	No GI Manifestations (N=279)	P
Age (Mean±SD)	50.44±15.58	52.87±15.66	0.17
Gender			0.91
Female	30 (27.03%)	77 (27.60%)	
Male	81 (72.97%)	202 (72.40%)	
Nationality			0.237
Saudi	67 (60.36%)	150 (53.76%)	
Non-Saudi	44 (39.64%)	129 (46.24%)	
Comorbidities			
Diabetes mellitus	54 (48.65%)	131 (46.95%)	0.762
Hypertension	43 (38.74%)	105 (37.63%)	0.839
Chronic respiratory diseases	3 (2.70%)	19 (6.81%)	0.113
Chronic kidney diseases	5 (4.50%)	13 (4.66%)	0.948
Pre-existing GI diseases	12 (8.11%)	14 (3.58%)	0.07

GI: Gastrointestinal

**Table 2: Gastrointestinal manifestations of COVID-19 disease**

Gastrointestinal Manifestations	Frequency/Percentage
Symptoms	
Nausea	49 (12.56%)
Vomiting	46 (11.79%)
Diarrhea	57 (14.62%)
Abdominal pain	39 (10.00%)
Complications	
Intestinal perforation	3 (0.77%)
Intra-abdominal infection	4 (1.03%)
GI bleeding	6 (1.54%)
Pancreatitis	11 (2.84%)
Other GI complications	
Intra-abdominal hematoma	3 (0.77%)
Acute cholecystitis	2 (0.51%)
Acute appendicitis	2 (0.51%)
Splenic laceration	1 (0.25%)
Acute diverticulitis	1 (0.25%)

GI: Gastrointestinal

**Table 3: Comparison of laboratory abnormalities between groups of GI and non-GI Manifestations**

Test	Normal Range	GI Manifestations Median (IQR)	No GI Manifestations Median (IQR)	P
White Blood Cells	(4-11) k/ $\mu$ L	5.278 (4.1)	6.10 (5.4)	0.12
Neutrophils	(2-7.5) k/ $\mu$ L	3.88 (0.8)	4.05 (4.1)	0.27
Lymphocytes	(1-5) k/ $\mu$ L	1.17 (0.8)	1.20 (0.82)	0.65
Hemoglobin	(12-16) g/dL	12.37 (2.3)	12.42 (2.8)	0.33
Platelets	(140-450) k/ $\mu$ L	222.0 (100)	227 (110)	0.85
Creatinine	(0.6-1.3) mg/dL	0.91 (0.4)	0.93 (0.42)	0.24
ESR	(0-20) mm/h	40.00 (32.0)	44.00 (39)	0.76
CRP	(0.1-0.5) mg/dL	5.45 (32.1)	5.47 (39.0)	0.13
D-dimer	$\leq$ 0.5 $\mu$ g/mL	0.73 (0.89)	0.93 (1.55)	0.004*
Ferritin	(21.81-274.66) ng/mL	407.7 (565.8)	565.6 (1105)	0.01*
ALT	(7-55) U/L	36.78 (4.15)	34.61 (3.56)	0.61
AST	(5-34) U/L	43.95 (7.26)	42.57 (5.3)	0.43
ALP	(40-150) U/L	43.95 (7.26)	42.57 (5.3)	0.43
GGT	(12-64) U/L	82.77 (11.24)	80.72 (11.84)	0.56
LDH	(81-234) U/L	61.24 (14.44)	62.54 (12.08)	0.54
Albumin	(3.2-5.2) g/dL	3.91 (0.90)	3.84 (0.97)	0.66
PT/INR	$\leq$ 1.1	2.45 (0.42)	2.41 (0.54)	0.74

\*Significant at  $P < 0.05$  level. GI, Gastrointestinal; ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; ALT, Alanine Aminotransferase; +AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; GGT, Gamma Glutamyl Transferase; LDH, Lactate Dehydrogenase; PT, Prothrombin Time; INR, International Normalized Ratio

**Table 4: Association of severity and outcome of COVID-19 with the presence and absence of GI manifestations**

	GI Manifestations	No GI Manifestations	P
MOH Severity Criteria			
Mild-Moderate	52 (46.85%)	105 (37.63%)	0.14
Severe	34 (30.63%)	86 (30.82%)	
Critical	25 (22.52%)	88 (31.54%)	
Severe			
Pneumonia on chest X-ray	82 (73.87%)	215 (77.34%)	0.47
Respiratory rate $>30$ /min	34 (30.63%)	114 (40.86%)	0.06
SpO <sub>2</sub> $<93\%$ on room air	60 (54.05%)	175 (62.72%)	0.11
PaO <sub>2</sub> and FiO <sub>2</sub> ratio $<300$	34 (33.33%)	115 (44.40%)	0.05
Lung infiltration $>50\%$ of lung fields within 24-48 h	29 (26.13%)	108 (38.71%)	0.02*
Critical			
ARDS	23 (20.72%)	86 (30.82%)	0.04*
Sepsis	15 (13.51%)	52 (18.64%)	0.23
Altered mental status	11 (9.91%)	51 (18.28%)	0.04*
Multiorgan failure	8 (7.21%)	44 (15.77%)	0.02*
Cytokine storm syndrome	23 (21.50%)	89 (33.21%)	0.02*
Outcome			
Length of hospitalization	13.56 $\pm$ 18.88	13.54 $\pm$ 13.58	0.99
Need for ICU admission	33 (29.73%)	106 (37.99%)	0.12
Need for mechanical ventilation	22 (19.82%)	80 (28.67%)	0.07
Death	9 (8.11%)	52 (18.64%)	0.01*

\*Significant at  $P < 0.05$  level. GI, Gastrointestinal; MOH, Ministry of Health; SpO<sub>2</sub>, Oxygen Saturation; PaO<sub>2</sub>, Partial Pressure of Oxygen; FiO<sub>2</sub>, Fraction of Inspired Oxygen; ARDS, Adult Respiratory Distress Syndrome; ICU, Intensive Care Unit

**Table 5: Multivariate logistic regression analysis of association of severity of COVID-19 with comorbidities and the presence of GI manifestations**

Covariate	Severe or critical AOR (95%CI)	P
Age	1.06 (1.037-1.08)	$<0.001$ *
Gender (Male)	1.55 (0.893-2.68)	0.12
Nationality (Non-Saudi)	1.94 (1.17-3.22)	0.01*
Diabetes Mellitus	1.56 (0.929-2.63)	0.09
Hypertension	1.10 (0.605-1.98)	0.76
Respiratory diseases	0.69 (0.245-1.94)	0.48
Chronic kidney diseases	1.55 (0.488-4.91)	0.45
Preexisting GI diseases	1.75 (0.569-5.40)	0.32
GI manifestations	0.71 (0.43-1.18)	0.18

\*Significant at  $P < 0.05$  level. AOR, Adjusted Odds Ratio; CI, confidence interval, GI: Gastrointestinal

study. First, 28.5% of our patients with COVID-19 presented with GI symptoms, most commonly diarrhea and nausea/vomiting. Second, patients without GI manifestations had more severe COVID-19 infection and worse outcome. In addition, patients with GI manifestations had lower odds of death. Moreover, patients without GI symptoms had significantly higher D-dimer and ferritin on presentation compared to those with GI symptoms. Third, age and non-Saudi nationality were predictive of severe-critical COVID-19 disease, LOH, ICU admission, mechanical ventilation, and death. At the same time, the male gender was predictive of need for mechanical ventilation and death only.

The reported incidence of GI symptoms in COVID-19 patients is a matter of debate. Similar to our study, Ramachandran *et al.*<sup>[11]</sup> reported 20.6% of COVID-19 patients had at least one GI symptom, with diarrhea being the most common in 14.7%, followed by nausea or vomiting (10.7%) and abdominal pain (2%). In contrast, Pan *et al.*<sup>[9]</sup> reported a higher prevalence of GI manifestations of 50%. In addition, the evidence is highly variable regarding individual GI symptoms prevalence. For example, diarrhea was reported in 2%–50% of cases,<sup>[12]</sup> nausea in 3.7%–73%,<sup>[13,14]</sup> vomiting in 3.9%–65%, and abdominal pain in 1.9%–25% of cases.<sup>[9,14]</sup> Anorexia was the most common in several reports when it was included as one of the GI symptoms.<sup>[9,14]</sup> However, our study did not include anorexia because it is not a specific GI symptom and could be attributed to infection and inflammation. In addition, we were not able to assess the real incidence of GI manifestations because most of them are managed outside medical facilities. Other GI manifestations occurred rarely in our cohort, most commonly acute pancreatitis (2.8%). There were no studies examining the exact incidence of pancreatitis in the setting of COVID-19. However, it was only reported in several case reports.<sup>[15,16]</sup> One of the extremely rare GI manifestations that has been reported in case reports is abdominal vessel thrombosis.<sup>[17]</sup> However, there were no such cases identified in our cohort.

Our study shows that patients without GI manifestations were more likely to develop severe-critical COVID-19 infection and worse outcome. Moreover, patients with GI manifestations had a lower mortality rate. Although it did not reach statistical significance, patients with GI symptoms had lower ICU admissions and mechanical ventilation rates. Similarly, in a retrospective study by Laszkowska *et al.*,<sup>[18]</sup> they concluded that the presence of GI symptoms was associated with lower rates of intubation and mortality. Additionally,

Nobel *et al.*<sup>[19]</sup> reported a lower mortality rate in patients with GI symptoms. However, evidence is heterogenous in this regard. For example, a meta-analysis conducted by Liu *et al.*<sup>[20]</sup> found no statistical significance between COVID-19 severity and the presence or absence of GI symptoms. Ramachandran *et al.*<sup>[11]</sup> reported no difference in the length of hospital stay or mechanical ventilation between patients of GI and non-GI manifestations. In addition, a study from Saudi Arabia by Aleanizy *et al.*<sup>[21]</sup> investigated the clinical characteristics of 1026 COVID-19 cases and found that the presence of nausea, vomiting, or diarrhea did not differ between mild, severe, or critical infection. On the contrary, Menon *et al.*<sup>[22]</sup> showed an increased risk of severe COVID-19 infection in the presence of GI symptoms. A meta-analysis of seven studies found that patients with GI symptoms had a higher risk of ARDS.<sup>[23]</sup> The differences observed in the present study compared to the previously reported findings in other studies can be explained by distinct patients' populations and different viral strains. In addition, GI manifestations were observed to occur early in the disease course even in the absence of typical respiratory symptoms,<sup>[24]</sup> which might have played a role in the better outcome noticed in the current study.

Significantly higher ferritin and D-dimer levels were observed in patients without GI symptoms compared to patients with GI symptoms. Ferritin is an acute-phase reactant that could be an early predictor of severe COVID-19 disease<sup>[25]</sup> and a higher mortality rate.<sup>[26]</sup> Severe COVID-19 infection could lead to extensive activation of cytokine secreting cells, progressing to cytokine storm syndrome, ARDS, and multiorgan failure.<sup>[25]</sup> Moreover, high D-dimer reflects severe COVID-19 disease and worse outcomes.<sup>[27]</sup> Both findings could explain the worse outcome observed in the non-GI manifestations group in our cohort.

**Table 6: Regression analysis of the association of GI manifestations and demographics with the outcome of COVID-19 disease**

Covariate	Outcome							
	†Length of hospitalization AOR (95% CI)	P	ICU admission AOR (95%CI)	P	Mechanical ventilation AOR (95%CI)	P	Death AOR (95%CI)	P
Age	1.03 (1.01-1.04)	0.002*	1.04 (1.025-1.06)	<0.001*	1.05 (1.026-1.07)	<0.001*	1.08 (1.045-1.11)	<.001*
Gender	1.45 (0.869-2.41)	0.15	1.71 (0.955-3.05)	0.07	2.32 (1.171-4.58)	0.016*	2.66 (1.09-6.47)	0.03*
Male								
Nationality	1.67 (1.037-2.68)	0.03*	2.21 (1.336-3.65)	0.002*	2.77 (1.581-4.85)	<.001*	3.59 (1.73-7.44)	<.001*
Non-Saudi								
Diabetes mellitus	1.26 (0.772-2.06)	0.35	1.29 (0.78-2.13)	0.32	1.52 (0.876-2.62)	0.13	1.49 (0.753-2.93)	0.25
Hypertension	1.27 (0.724-2.22)	0.40	1.25 (0.714-2.17)	0.42	1.15 (0.629-2.09)	0.65	1.11 (0.542-2.29)	0.76
Chronic respiratory diseases	0.65 (0.246-1.71)	0.38	1.16 (0.422-3.20)	0.77	1.18 (0.395-3.50)	0.77	1.57 (0.454-5.44)	0.47
Chronic kidney diseases	2.27 (0.694-7.43)	0.17	1.77 (0.631-4.98)	0.27	1.18 (0.385-3.60)	0.7	1.80 (0.507-6.38)	0.36
Preexisting GI diseases	2.10 (0.704-6.27)	0.18	1.85 (0.62-5.55)	0.26	2.11 (0.651-6.86)	0.21	3.74 (0.926-15.12)	0.06
GI manifestations	0.82 (0.508-1.31)	0.40	0.73 (0.433-1.22)	0.22	0.63 (0.353-1.14)	0.12	0.36 (0.158-0.82)	0.01*

\*Significant at P<0.05 level. AOR, Adjusted Odds Ratio; CI, Confidence Interval; ICU, Intensive Care Unit; GI, Gastrointestinal. †Length of hospitalization (we used cut-off of more than 7 days) which is correlated with a reported median duration of hospital stay in Saudi Arabia.<sup>[36]</sup>

Our findings highlight that being older and non-Saudi were significantly associated with an increased risk of severe-critical COVID-19 infection, LOH, ICU admission, mechanical ventilation, and death. In addition, the male gender was associated with an increased risk of mechanical ventilation and death. These results are consistent with previous reports, which showed that age and male gender are associated with severe-critical COVID-19 disease and mortality.<sup>[28,29]</sup> Martos-Benítez *et al.*<sup>[30]</sup> found that old age is associated with an increased odds of ICU admissions, intubation, and mortality. Moreover, non-Saudi patients had a higher risk of severe to critical disease in the same study by Aleanizy *et al.*<sup>[21]</sup> One explanation for the poor outcome associated with age and male sex is that impaired T cell response due to advanced age is associated with worse outcomes, especially in male patients.<sup>[31]</sup> Genetic factors might be implicated in the increased risk of severe COVID-19 infection among non-Saudi patients. In addition, low income can be a contributor as people with poor economic status likely seek medical advice only late in the course of the disease when severe manifestations occur.

The pathogenesis of the GI involvement in SARS-CoV-2 is not fully understood and is likely to be multifactorial. Once in the GI tract, the virus gains entry into the cells via binding to angiotensin-converting enzyme-2 (ACE-2) receptors, which were proven to be abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia, supporting the entry of SARS-CoV-2 into the GI cells.<sup>[32]</sup> Histopathology of affected patients showed abundant infiltrating plasma cells and lymphocytes with interstitial edema in the stomach, duodenum, and rectum lamina propria, suggesting that GI symptoms of COVID-19 infection might be caused by the direct cellular toxicity as well as tissue and organ damage due to the immune response.<sup>[32]</sup> In addition, it can induce cytokine-mediated inflammatory response leading to intestinal inflammation evident by high fecal calprotectin in the stool.<sup>[33,34]</sup> Moreover, multiple reports have shown the possibility of fecal-oral spread by persistently positive SARS-CoV-2 PCR in stool samples, even after clearance of respiratory samples.<sup>[32,35]</sup>

To our knowledge, this is the first report from the Middle East and Saudi Arabia, focusing on the relationship between GI symptoms with the severity and outcome of COVID-19. Second, the collected variables were extracted rigorously using a predetermined protocol to minimize extraction errors and missing values. However, being a retrospective study from a single center limits the generalizability of our results.

In conclusion, the current study shows that COVID-19 infection presents commonly with GI manifestations. Patients with GI symptoms have a better hospital course with lower mortality rates and less severe COVID-19 infection. Future large-scale randomized-controlled studies are warranted to confirm the current study's findings and better understand the mechanisms underlying the differences, as this can lead to an improved clinical outcome in patients infected with COVID-19.

#### Data availability statement

The analyzed datasets used in this study and all analysis output reports are available upon reasonable request from the corresponding author. The data does not contain any identifiable data, and the confidentiality of the included patients is fully maintained.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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