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Original Article

Clinical Characteristics of COVID-19 Patients with Gastrointestinal Symptoms

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Abstract

Background: We aimed to assess the gastrointestinal (GI) manifestations of patients with severe acute respiratory syndrome coronavirus 2 infection and determine factors predicting disease prognosis and severity among patients with GI symptoms.

Methods: In this retrospective study, we evaluated laboratory confirmed (by real-time polymerase chain reaction) inpatient cases of coronavirus-associated disease 2019 (COVID-19), referred to Sina hospital, a tertiary educational hospital of Tehran University of Medical Sciences, from March 10 to May 20, 2020. Demographic and clinical characteristics, laboratory data, outcomes and treatment data were extracted and analyzed using SPSS version 20.

Results: A total of 611 patients (234 women and 377 men) were included with 155 patients having GI symptoms. The most prevalent reported GI symptom was nausea/vomiting in 115 (18.8%) of patients. A total of 20 patients (3.2%) only had GI symptoms (without respiratory symptoms). There was no statistically significant difference in the clinical outcomes, disease severity, intensive care unit (ICU) admission and mortality between patients with and without GI symptoms. Aspartate Aminotransferase level was associated with 446% increased risk of disease severity (adjusted odds ratio: 5.46, 95% CI: 2.01 to 14.81) ($P=0.040$) among patients with GI symptoms. Additionally, we found that treatment with antibiotics in addition to mechanical ventilation was associated with increased survival among patients with GI symptoms (Pearson Chi square: 6.22; P value: 0.013).

Conclusion: More attention should be paid to patients with only GI symptoms for early patient detection and isolation. Moreover, patients with GI manifestations are not exposed to higher rates of disease severity or mortality.

Keywords: Gastrointestinal diseases, Liver function tests, Mortality, SARS-CoV-2

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Introduction

The coronavirus-associated disease 2019 (COVID-19) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection started from China and rapidly spread worldwide. The World Health Organization (WHO) declared the coronavirus outbreak a pandemic on March 11, 2020.[1,2] Iran was one of the earliest countries attacked by this virus since February 19, 2020.[3] Until April 24, a total of 193,779 and 5574 deaths were reported globally and in Iran, respectively.[2] Up to now, there is no approved cure for COVID-19; therefore, treatment is only supportive.[4]

Due to the dramatic rise in the COVID-19 incidence, clinical and public health management is challenging. The WHO estimated a reproduction number (Ro) of between 1.4 and 2.5 for SARS-CoV-2,[5] while more recent studies have estimated a Ro between 2.24 to 4.00.[6] These findings emphasize the need to characterize the less common clinical presentations of this disease for early detection of affected patients and isolation. Additionally, possible oral-fecal transmission of SARS-CoV-2 has been suggested by multiple studies.[7-10]

COVID-19 is characterized by a febrile disease (recorded in 88.7% of patients), often progressing to cough (57.6%) and dyspnea (45.6%) with 20.3% requiring intensive care unit (ICU) admission according to a recent meta-analysis.[11] Moreover, Hemati et al reported a 20% increased rate of patients referred to gastrointestinal (GI) clinics in Qom, the first city in Iran where COVID-19 was detected, a few weeks before the COVID-19 outbreak in Iran. Surprisingly, SARS-CoV-2 test was positive for all patients with unusual GI symptoms in the referred population, and they showed evidence of lung involvement on chest CT scans through follow-up.[12] Although studies on GI manifestation of COVID-19 disease are limited, recent reports indicate growing evidence of GI symptoms in

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these patients.[8,9,13,14]

In this study, we aim to report clinical presentations, laboratory abnormalities, and different treatment strategies, and their association with disease severity and mortality among COVID-19 patients based on the presence of GI symptoms. We hope this data helps investigators to identify this strange disease behavior.

Patients and Methods

Study Design and Setting

This study is a retrospective, single-center study focusing on inpatient cases of SARS-CoV-2 referred to Sina hospital, a tertiary educational hospital of Tehran University of Medical Sciences, from March 10 to May 20, 2020.

Participants and Data Collection

Since March 2020, Sina hospital was introduced as a COVID-19 center by Iran's ministry of health and medical education. We analyzed laboratory-confirmed as well as highly suspicious cases of COVID-19 based on characteristic chest CT scan findings and supporting clinical presentations who were admitted to the hospital for at least 72 hours.

The laboratory confirmed cases included clinically diagnosed or clinically suspected patients with positive nasopharyngeal swab test using real-time reverse-transcription polymerase chain reaction (RT-PCR) for COVID-19. We used a viral nucleic acid diagnostic kit (PCR-fluorescence probing) provided by Sansure Biotech (53102E), Changsha, China and real-time detection PCR system (Bio-Rad Laboratories, Inc.) for disease confirmation. Diagnosis of the disease and admission were according to the WHO and Iran's ministry of health and medical education guidelines.[15]

Referred patients were triaged into three groups: mild clinical symptoms without chest CT findings, fever and respiratory symptoms with imaging findings of COVID-19 in young persons without risk factors (mild); clinical symptoms with respiratory distress (respiratory rate ≥30 breaths/min), oxygen saturation ≤93%, clinical symptoms and imaging features of COVID-19 pneumonia with risk factors (moderate); and arterial oxygen tension (or pressure) (PaO_2)/fractional inspired oxygen (FiO_2) ratio ≤300 mm Hg, respiratory failure requiring mechanical ventilation and organ failure (severe). Mild patients were suggested to rest and take medications for symptom relief at home-quarantine (outpatients). Moderate cases were admitted (inpatients) to the general COVID-19 ward. Severe cases were hospitalized in the intensive care unit (ICU). A pharyngeal swab or endotracheal sample was collected from all hospitalized and critical patients.

After recording demographic features, previous medical records (past medical history, previous drug history), and presenting symptoms, the participants were evaluated for vital signs (heart rate, respiratory rate, temperature, and O_2 saturation) upon admission. Data regarding received treatments, disease progression or regression, complications, and laboratory data were extracted from medical records. These data were recorded by physicians and nurses on predesigned report forms and were further entered into an electronic web-based database by trained researchers. We excluded patients who were not able to communicate, unless having reliable family caregivers for basic data gathering. We also excluded patients with GI manifestations with a history of recent (within the previous week) antibiotic or other drug use causing GI symptoms. Additionally, patients with a history of inflammatory bowel disease and gastroesophageal reflux disease were excluded. COVID-19 severity was defined based on Centers for Disease Control and Prevention (CDC) guidelines. Diarrhea was defined based on the seven-item Bristol stool scale types 5 to 7.

Data Analysis

The primary measure of our study was the evaluation of the correlation of GI symptoms with mortality and severity. To calculate sample size, a simple correlation r ($r = 0.4$) of N observations was used. Employing a two-sided test, a 5% significance level test ($\alpha = 0.05$) with 80% power ($\beta = 0.2$), the required sample size is approximately 47 ($n = 47$). Statistical analyses were performed using the SPSS software, version 20.0 (SPSS Inc., Chicago, Ill., USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed variables and median (interquartile range) for non-normal ones, while categorical variables were reported as numbers (percentages). The chi-square test was used to compare the proportions between those with and without GI symptoms. Independent *t* test or Mann-Whitney U test were used for comparing the collected data between the two groups (with and without GI symptom, or severe and non-severe, or expired and surviving) considering normality of distribution and homogeneity of variance. Because the number of variables in a model should be reduced until there are 10 events per variables, we chose *P* values less than 0.05.[16] Therefore, those variables significantly associated with disease severity in the univariate logistic regression analysis were further assessed in a multivariate model. Odds ratios and 95% confidence intervals (CIs) were reported for variables associated with outcomes. We considered a two-tailed *P* value less than 0.05 as statistically significant.

Results

Demographic and Baseline Characteristics

A total of 611 patients (234 women and 377 men) were included in this study with an average age of 56.19 ± 16.15 years. There was a complete set of data including lab data and treatment options for 451 patients. Baseline characteristics and clinical outcomes of patients are shown

based on the presence of GI symptom in Table 1. Most of the patients (62.9%) had a history of previous medical diseases, including hypertension in 230 (37.6%), diabetes mellitus in 189 (30.9%), malignancy in 20 (3.2%), chronic lung disease in 43 (7.0%), cardio-cerebrovascular disease in 125 (20.4%), chronic kidney disease in 39 (6.4%) and cirrhosis in 3 (0.5%) persons. Additionally, 340 (75.4%) patients suffered from the severe form of COVID-19. There was no statistically significant difference in the demographic data or clinical outcomes and disease severity between patients with and without GI symptoms.

Gastrointestinal Signs and Symptoms

GI symptoms on admission were defined as diarrhea, nausea/vomiting, abdominal pain or GI bleeding. The most prevalent GI symptom reported was nausea/vomiting in 115 (18.8%) of total patients. Twenty patients (3.2%) only had GI symptoms (without respiratory symptoms). Although the prevalence of GI symptoms was not different based on the severity of COVID-19 disease, in terms of hepatic function impairment, Alanine transaminase (ALT) and aspartate transaminase (AST) levels were detected to be significantly different between patients with severe and non-severe disease (both $P = 0.033$) (Table 2).

We did not find any relationship between respiratory symptoms and GI symptoms in the present study ($P = 0.952$). In terms of the duration of symptom from onset to admission, there was no significant difference between patients with only GI symptoms and those with respiratory symptoms ($P = 0.126$).

Laboratory Data Comparisons

In terms of inflammatory markers such as procalcitonin, C-reactive protein, and white blood cell count as well as electrolytes and kidney, liver, and cardiac injury markers (creatinine, urea, ALT, AST, bilirubin, and troponin), there was no significant difference between COVID-19 patients with and without GI symptoms (Table 3).

Complications and Treatment

We found that treatment with antibiotics in addition to mechanical ventilation were associated with increased survival among patients with GI symptoms (P value: 0.013). In patients with GI symptoms compared to those

Table 1. Demographic and Clinical Characteristics of Patients with and Without GI Symptoms

Characteristics	All patients (n = 611) No. (%)	Patients with GI manifestations (n = 155) No. (%)	Patients without GI manifestations (n = 456) No. (%)	*P* Value*
Age (y)	56.19 ± 16.15	54.35 ± 15.84	56.78 ± 16.22	0.154
Gender				
Female	234 (38.3)	67 (43.2)	167 (36.6)	0.152
Male	377 (61.7)	88 (56.8)	289 (63.4)	
Current smoking	23 (4.7)	5 (3.2)	18 (3.9)	0.742
Comorbidities				
Hypertension	230 (37.6)	66 (42.6)	164 (36.0)	0.151
Diabetes Mellitus	189 (30.9)	75 (48.3)	114 (25.0)	0.341
Cardio-cerebrovascular disease	220 (36.0)	62 (40.0)	158 (34.6)	0.357
Malignancy	20 (3.3)	7 (4.5)	13 (2.9)	0.305
Chronic lung disease	43 (7.0)	15 (9.7)	28 (6.1)	0.147
Chronic kidney disease	39 (6.3)	16 (10.3)	28 (6.1)	0.411
Cirrhosis	3 (0.5)	2 (1.3)	1 (0.2)	0.160
Disease classification				
Non-severe	111 (24.6)	31 (25.2)	80 (24.4)	0.302
Severe	340 (75.4)	92 (74.8)	248 (75.6)	0.463
Clinical outcome				
Intensive care unit admitted	100 (22.2)	26 (21.1)	74 (22.6)	0.308
Discharged from ward	407 (66.6)	97 (62.5)	310 (67.9)	0.456
Died	104 (23.1)	32 (26.0)	72 (22.0)	0.351
Hospitalization (day)	6.03 (5.12)	5.76 (4.09)	6.13 (5.32)	0.486
Duration from illness onset to first admission (day)	6.98 (5.02)	6.74 (4.53)	7.15 (5.56)	0.434
Acute respiratory distress syndrome	98 (21.7)	28 (22.8)	70 (21.3)	0.798
Acute kidney injury	69 (15.8)	21 (17.5)	48 (15.2)	0.559
Multi-organ damage	91 (20.2)	26 (21.1)	65 (19.8)	0.793
Acute cardiac injury	112 (33.1)	29 (33.0)	83 (33.2)	0.538
Mechanical ventilation	83 (18.4)	23 (18.7)	60 (18.3)	0.892

* Independent *t* test was used to compare means between two groups.

Table 2. GI Signs and Symptoms Based on COVID-19 Disease Severity

	All Patients (n = 451) No. (%)	Severe (n = 340) No. (%)	Non-severe (n = 111) No. (%)	*P* Value*
GI symptoms				
Diarrhea	42 (9.3)	35 (10.3)	7 (6.3)	0.260
Nausea/Vomiting	92 (20.4)	67 (19.7)	25 (22.5)	0.567
Abdominal discomfort/pain	22 (4.9)	15 (4.4)	7 (6.3)	0.448
Upper GI bleeding	2 (0.3)	2 (0.5)	0 (0.0)	0.308
Hepatic function impairment				
Total bilirubin (μmol/L; normal range 3.0–24.0)	1.09 ± 0.82	1.12 ± 0.88	0.94 ± 0.45	0.087
Increased total bilirubin	14 (3.1)	12 (10.8)	2 (8.7)	0.863
ALT (U/L; normal range 7–40 in female, 9–50 in male)	48.10 ± 5.82	50.61 ± 6.40	38.58 ± 2.36	0.033
Increased ALT	149 (33.0)	127 (45.8)	22 (30.1)	0.017
AST (U/L; normal rage 13–35 in female, 15–40 in male)	66.06 ± 10.23	70.55 ± 11.29	49.02 ± 3.79	0.033
Increased AST	243 (53.9)	212 (76.5)	31 (42.5)	<0.001

ALT, alanine transaminase; AST, aspartate transaminase.
*Independent *t* test was used to compare means between tow groups.

without symptoms, there was no significant difference in ICU admission rate (21.1% with GI symptoms versus 22.6% without, $P = 0.802$) and the rate of in-hospital death (26.0% with GI symptoms versus 22.0% without, $P = 0.358$).

Prediction of COVID-19 Severity in Patients with GI Symptoms

Initial univariate logistic regression analysis of clinical and demographic variables in addition to laboratory data, identified seven significant predictive factors for COVID-19 severity. In the multivariable model including all variables associated with severity among COVID-19 patients with GI symptoms, AST level was associated with 446% increased risk of disease severity (adjusted odds ratio 5.46, 95% confidence interval, 2.01 to 14.81) ($P = 0.040$) (Table 4). We did not find any factors predicting mortality among patients with GI symptoms independently.

Table 5 shows the odds ratios of COVID-19 clinical outcomes predicting mortality in patients with GI symptoms.

Discussion

Recent reports on increased prevalence of GI manifestations among COVID-19 patients referred to hospitals in Iran compelled us to evaluate GI symptoms among coronavirus-infected patients.

To the best of our knowledge, this study represents the largest group of cases outside China, with GI manifestations among COVID-19 patients.

Our findings suggest a higher rate GI symptoms (25.4%) compared to previous studies from China which range from 3% to 18.6%.[13,17,18] The most common symptoms included loss of appetite and nausea/vomiting in most studies, consistent with our findings,[17,19] while some studies have reported diarrhea as the most common

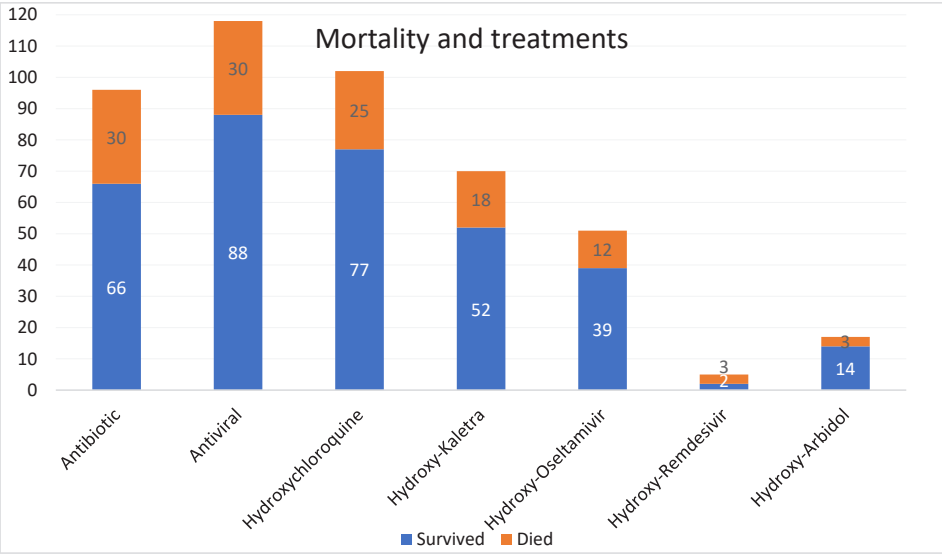

Figure 1. Mortality by Received Treatment in COVID-19 Patients with GI Symptoms.

Table 3. Laboratory Data Comparison between Patients with and Without GI Symptoms.

Blood Test	Patients with GI Symptoms (n = 123)	Patients without GI Symptoms (n = 328)	*P* Value	Blood Test	Patients with GI Symptoms (n = 123)	Patients without GI Symptoms (n = 328)	*P* Value
Hemoglobin Mean g/dL (SD)	13.40 (2.21)	13.46 (2.21)	0.884	Sodium Mean, mmol/L (SD)	134.65 (4.88)	135.67 (5.46)	0.078
Hemoglobin, Median g/dL (IQR)	13.30 (2.60)	13.55 (3.00)	0.792	Sodium Median, mmol/L (IQR)	134.10 (5.90)	135.50 (6.40)	0.055
Hematocrit, Mean % (SD)	39.38 (4.87)	39.54 (4.97)	0.757	Potassium Mean, mmol/L (SD)	4.36 (0.61)	4.27 (0.53)	0.152
Hematocrit, Median % (IQR)	39.20 (7.20)	39.10 (7.10)	0.639	Potassium Median, mmol/L (IQR)	4.20 (0.70)	4.30 (0.60)	0.311
Platelet, Mean × 10^9/L (SD)	195.86 (84.34)	211.78 (85.78)	0.387	Magnesium Mean, mmol/L (SD)	2.32 (0.47)	2.21 (0.40)	0.087
Platelet, Median × 10^9/L (IQR)	191.00 (98.00)	180.00 (107.00)	0.063	Magnesium Median, mmol/L (IQR)	2.10 (0.37)	2.30 (0.50)	**0.027**
White blood cell count, Mean × 10^3/L (SD)	8.46 (5.56)	7.95 (3.44)	0.324	Calcium Mean mmol/L (SD)	8.55 (0.63)	8.55 (0.74)	0.963
White blood cell count, Median × 10^3/L (IQR)	6.50 (4.80)	6.60 (4.30)	0.949	Calcium, Median, mmol/L (IQR)	8.60 (0.90)	8.60 (0.90)	0.906
Lymphocyte count, Mean × 10^3/L (SD)	1.76 (1.33)	1.42 (0.76)	0.160	Vit D3 level Mean, IU/L (SD)	24.78 (4.87)	24.87 (4.34)	0.135
Lymphocyte count Median × 10^3/L (IQR)	1.23 (0.76)	1.16 (0.75)	0.765	Vit D3 level Mean, IU/L (SD)	22.40 (22.00)	25.30 (25.70)	0.489
Neutrophil count, Mean × 10^3/L (SD)	5.90 (1.07)	5.13 (0.83)	0.075	Amylase Mean, U/mL (SD)	72.32 (8.98)	54.43 (4.67)	0.152
Neutrophil count, Median × 10^3/L (IQR)	4.89 (3.89)	4.85 (3.93)	0.966	Amylase Median, U/mL (IOR)	46.00 (37.00)	45.00 (44.00)	0.481
Creatinine, Mean µmol/L (SD)	1.26 (0.76)	1.33 (0.70)	0.720	C-reactive protein Mean IU/L (SD)	70.33 (5.46)	72.83 (5.23)	0.727
Creatinine, Median µmol/L (IQR)	1.04 (0.43)	1.09 (0.45)	0.455	C-reactive protein Median IU/L (IQR)	55.10 (97.92)	62.30 (87.10)	0.465
Albumin, Mean mmol/L (SD)	3.11 (0.76)	3.12 (0.90)	0.184	Erythrocyte sedimentation rate Mean IU/L (SD)	48.44 (29.23)	53.11 (31.93)	0.814
Albumin, Median mmol/L (IQR)	3.35 (1.21)	3.20 (1.18)	0.731	Erythrocyte sedimentation rate Median, IU/L (IQR)	44.00 (47.25)	46.50 (54.25)	0.257
ALT, Mean IU/L (SD)	46.80 (3.97)	63.73 (3.97)	0.700	Lactate dehydrogenase Mean, IU/L (SD)	639.72 (27.27)	629.34 (34.61)	0.814
ALT, Median IU/L (IQR)	36.00 (23.00)	37.00 (26.00)	0.852	Lactate dehydrogenase Median, IU/L (IQR)	574.00 (296.00)	537.50 (292.00)	0.333
AST, Mean IU/L (SD)	64.00 (4.35)	66.90 (11.81)	0.810	CPK IU/L Mean (SD)	273.52 (52.87)	292.53 (54.41)	0.754
AST, Median IU/L (IQR)	50.00 (37.00)	52.00 (30.00)	0.331	CPK IU/L Median (IQR)	142.00 (188.25)	139.50 (217.75)	0.634
ALP, Mean IU/L (SD)	192.51 (13.38)	204.27 (13.77)	0.473	Ferritin Mean IU/L (SD)	635.97 (64.38)	631.77 (60.69)	0.970
ALP, Median IU/L (IQR)	167.00 (79.00)	171.00 (95.00)	0.370	Ferritin Median IU/L (IQR)	376.17 (578.17)	408.40 (616.65)	0.899
Bilirubin Total (µmol/L), Mean (SD)	1.10 (0.80)	1.08 (0.83)	0.893	Prothrombin time Mean, s (SD)	16.14 (7.65)	15.10 (3.38)	0.236
Bilirubin total (µmol/L), Median (IQR)	0.83 (0.50)	0.86 (0.57)	0.903	Prothrombin time Median, s (IQR)	14.30 (2.70)	14.40 (2.50)	0.972
Bilirubin Direct (µmol/L), Mean (SD)	0.51 (0.50)	0.46 (0.43)	0.525	Procalcitonin ng/mL, Mean (SD)	1.07 (2.27)	5.07 (1.88)	0.257
Bilirubin Direct (µmol/L), Median (IQR)	0.30 (0.42)	0.32 (0.32)	0.888	Procalcitonin ng/mL, Median (IQR)	0.20 (0.29)	0.34 (0.58)	0.135
D-dimer Mean, µg/Ml (SD)	2824.36 (310.01)	2323.84 (282.43)	0.189	Troponin, ng/mL, Mean (SD)	388.72 (33.70)	118.57 (10.58)	0.096
D-dimer Median, µg/mL (IQR)	1436.50 (187.39)	1154.00 (159.32)	0.828	Troponin, ng/mL, Median (IQR)	6.40 (14.14)	6.60 (24.42)	0.188

ALT, alanine transaminase; AST, aspartate transaminase; IQR, interquartile range; SD, standard deviation; GI, gastrointestinal.
*Independent *t* test and Mann-Whitney U test were employed for analysis.

Table 4. Factors Associated with Severity and Mortality among Patients with GI Symptoms

Variables	Factors Associated with Severity				Factors Associated with Mortality			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age (y)	0.998 (0.973–1.024)	0.904	0.975 (0.941–1.010)	0.162	1.059 (1.027–1.091)	<0.001	1.039 (0.990–1.090)	0.122
Absolute neutrophil count	2.374 (0.924–6.095)	0.072	—	—	1.121 (1.022–1.230)	0.016	1.006 (860–1.117)	0.939
ALT, U/L	4.071 (1.268–13.072)	0.018	1.010 (0.967–1.056)	0.646	1.012 (1.000–1.025)	0.055	—	—
AST, U/L	5.460 (2.012–14.817)	0.001	1.039 (1.002–1.078)	**0.040**	1.030 (1.012–1.049)	0.001	1.031 (0.996–1.068)	0.087
Blood sugar mmol/L	1.008 (0.999–1.016)	0.083	—	—	1.012 (1.005–1.019)	<0.001	1.007 (0.997–1.018)	0.154
Lactate dehydrogenase, U/L	1.002 (1.000–1.005)	0.069	—	—	1.002 (1.000–1.004)	0.026	1.000 (0.997–1.004)	0.811
C-reactive protein mg/L	1.009 (1.001–1.018)	0.036	1.003 (0.993–1.013)	0.517	1.008 (1.000–1.015)	0.053	—	—

ALT, alanine transaminase; AST, aspartate transaminase; OR, odds ratio; GI, gastrointestinal.

Table 5. Odds Ratio of COVID-19 Clinical Outcomes Predicting Mortality in Patients with GI Symptoms

Clinical outcomes	Odds Ratio	95% CI (Lower, Upper)	*P* value
Acute respiratory distress syndrome	65.25	18.09, 235.26	<0.001
Acute kidney injury	23.80	7.02, 80.60	<0.001
Multi-organ damage	47.85	13.70, 167.06	<0.001
Acute cardiac injury	9.09	3.23, 25.53	<0.001
Mechanical ventilation	67.00	24.05, 162.59	<0.001

manifestation.[20]

Concerning liver function impairments of COVID-19 patients, the studies are controversial. Although most studies have reported total bilirubin, AST, and ALT elevations, even mild, and have reported that liver dysfunction is associated with more severe disease upon presentation,[21,22] others have failed to observe these changes.[23,24] These heterogeneous findings could be explained by different timing in obtaining laboratory tests or not excluding patients with previous liver injury, including fatty liver disease as the most prevalent liver disease. Fortunately, our data indicate that patients with GI symptoms in our study rarely had underlying digestive diseases (five patients) but we should highlight that fatty liver is prevalent in Iran and is not diagnosed in most cases.[25]

Considering the high affinity of SARS-CoV-2 for ACE2 receptors, not only in the respiratory system but also in hepatocytes and cholangiocytes, hepatic involvement in COVID-19 infection is not surprising.[26] Moreover, we cannot exactly distinguish the sources of liver abnormalities (infection, immune system reaction or hypoxia) due to the nonspecific changes. Cholestasis has been rarely reported with this infection and most reports, in the same vein as our study, suggest normal alkaline phosphatase levels.[8,9,14]

In a study of 74 patients in China, a significantly increased rate of acute respiratory distress syndrome, increased disease severity, need for mechanical ventilation, and ICU admission were reported in patients with GI symptoms compared to those without GI symptoms.[27] This difference was explained in the mentioned study by increased prevalence of electrolyte abnormality seen in patients with GI symptoms.[13] In contrast with the findings of the mentioned study, we did not find any difference between patients with and without GI manifestations in terms of acute respiratory distress syndrome or disease severity.

We reported 20 patients with GI symptom without respiratory manifestations. Identifying these cases are important because routinely, most clinicians search for respiratory symptoms to define suspected COVID-19 cases. Therefore, patients with extra-pulmonary presentations would be missed and delayed in diagnosis. This not only influences the mortality rate of such patients due to delayed diagnosis or admission, but also increases the risk of infection in family or healthcare members.

The "Gut-lung axis" is a theory defining the digestive tract flora and respiratory tract interactions through intermediary of the mucosal immune system,[28] which may explain the relationship between digestive and respiratory symptoms. We did not find such a relationship in the present study.

We found a lower mortality rate among patients with GI symptoms receiving antibiotics in comparison with those not taking antibiotics. Patients with GI symptoms such as diarrhea who lose immunoglobulins or those with anorexia and nausea/vomiting with restricted fluid intake

showed impaired defensive mechanism for discharge of shed viruses through respiratory or intestinal secretion,[29] resulting in more bacterial super-infection and so may have better outcome using antibiotics. It must be noted that confounding factors are not evaluated in this relationship analysis; so, interpretation should be cautious.

As comparison of our findings with limited available data shows controversial results, reporting larger number of standardized cases could possibly lead to a better understanding of this disease. However, out study sheds light on digestive symptoms and abnormal liver function enzymes in a significant number of COVID-19 patients, which in a small number of cases, importantly, was the only presenting symptom. Thus, we must be conscious when considering COVID-19 disease even in patients with non-pulmonary symptoms, for faster detection of more patients at the time of presentation.

This study has several limitations. First, our analysis was based on a retrospective, single-center study with limited reliability or generalizability. Second, we did not search for SARS-CoV-2 viral RNA in the stool samples of patients to confirm fecal transmission probability. Third, blood biochemical examinations are based on a comparison of means and medians in our study and they are not individualized for abnormality detection. Fourth, considering huge ORs in some analyses, sparse-data bias is possible due to lack of an adequate number of observations for some combination of outcomes.[30]

In conclusion, we reported, for the first time, the largest cases of patients with COVID-19 with GI symptoms outside China. Earlier attention should be paid to patients with only GI symptoms for early patient detection and isolation. Moreover, patients with GI manifestations are not exposed to higher rates of disease severity or mortality.

Authors' Contribution

All authors participated in idea formation, data gathering, data analysis and interpretation, manuscript drafting and revising. All contributors approved the manuscript and agreed with study publication.

Conflict of Interest Disclosures

Authors declare no conflict of interest.

Ethical Statement

We adhered Helsinki protocol designing and implementing this study and the Tehran University of Medical Sciences ethics committee approved this study (IR.TUMS. VCR.REC.1300.005).

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