

Gastrointestinal manifestations in patients with coronavirus disease-2019 (COVID-19): Impact on clinical outcomes

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Background: In this study, we summarized the data on gastrointestinal (GI) involvement and the potential association with clinical outcomes among the patients admitted to Khorshid Hospital. **Materials and Methods:** We investigated 1113 inpatients (≥ 18 years old) diagnosed with coronavirus disease-2019 (COVID-19) from March to June 2020 in Khorshid Hospital. We collected demographic details, clinical information, vital signs, laboratory data, treatment type, and clinical outcomes from patients' medical records. The data of patients with GI symptoms were compared with those without GI symptoms. **Results:** A total of 1113 patients were recruited (male = 648). GI symptoms were observed in 612 (56.8%) patients (male = 329), the most common of which were nausea 387 (34.7%), followed by diarrhea 286 (25.7%), vomiting 260 (23.4%), and abdominal pain 168 (15.0%). The most prominent non-GI symptoms were cough 796 (71.5%), fever 792 (71.2%), shortness of breath 653 (58.7%), and body pain 591 (53.1%). The number of patients who were discharged, died, and were admitted to intensive care unit was significantly different in groups on the basis of GI and non-GI symptoms ($P = 0.002, 0.009, 0.003$). **Conclusion:** While COVID-19 was predominantly diagnosed in males, GI symptoms were more commonly reported by females. The results indicated that GI symptoms in COVID-19 patients are common, and the symptoms are not correlated with the severity of the disease. Moreover, the presence of GI symptoms was positively related to milder disease. Among COVID-19 positive patients, the clinical outcomes of the GI group were promising, compared to those of non-GI group.

Key words: Coronavirus, coronavirus disease-2019, gastrointestinal manifestations, severe acute respiratory syndrome coronavirus-2

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INTRODUCTION

In December 2019, the first human case of COVID-19 was reported in the seafood market in Wuhan city, China.^[1] On February 11, 2020, the World Health Organization announced the disease by this new virus as coronavirus disease-2019 (COVID-19).^[2,3]

At the time when the current study was underway, over 34 million people across the world have been infected with the severe acute respiratory syndrome coronavirus-2, reporting more than one million deaths as of October 03, 2020.^[4] Widespread distribution, aggressive growth, high rate of mortality, and infectivity of COVID-19 make it an important pathogen and threat.^[1,5]

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COVID-19 can be transmitted through fecal–oral route based on the current studies.^[6-8] The first case of COVID-19 infection confirmed in the United States reported a 2-day persistent history of nausea and vomiting, until finally, COVID-19 RNA was detected in a stool specimen.^[9]

The most common manifestations of COVID-19 include fever, dry cough, dyspnea, weakness, breathing difficulty, fatigue, and myalgia.^[2,7] Some patients also present GI symptoms including nausea, vomiting, diarrhea, and abdominal pain. Gastrointestinal (GI) symptoms could be the initial presenting symptoms in patients suspected of COVID-19.^[10,11] Some patients may present only with GI symptoms during the disease, which can delay diagnosis leading to potential complications for themselves and transmission to others.^[12,13]

The prevalence of GI symptoms varies greatly between patients. Some studies have shown that diarrhea is the most common GI symptom in COVID-19 infection.^[14-18] Therefore, our aim was to report the prevalence of GI manifestation in COVID-19 patients and to investigate their potential association with clinical outcomes.

SUBJECTS AND METHODS

This study involved 1113 patients (≥ 18 years old) suffering from alpha variant of COVID-19 who were hospitalized in Khorshid Hospital from March to June 2020.^[5] The diagnosis was confirmed by positive polymerase chain reaction (PCR) and chest computerized tomography markings suggestive for COVID. A confirmed case of COVID-19 was defined as a positive result on real-time reverse transcriptase–PCR (RT-PCR) assay of nasopharyngeal secretions and throat swab specimens.

The patients were admitted to the hospital based on their illness severity. Patients with moderate and severe conditions were hospitalized, whereas those with the mild form were managed as outpatients. Therefore, this study included patients only with moderate and severe involvement, based on our country's health protocols for managing COVID-19 infection.

The severe disease is defined as respiratory rate $>30/\text{min}$ or $\text{SpO}_2 \leq 90\%$ and moderate disease is $90\% < \text{SpO}_2 < 93\%$. Patients with moderate symptoms were categorized as nonsevere group in our analysis.^[19] GI symptoms included nausea, vomiting, diarrhea, and abdominal pain. Patient's GI symptoms were recorded at the time of admission to avoid any confusion between the patient's own symptoms and those caused as side effects of the drugs prescribed while being hospitalized.

Written consents were obtained from all of the patients. Patients' medical records were reviewed to acquire demographic information, clinical symptoms, vital signs, laboratory data, treatments, and clinical outcomes (final outcome, i.e., discharged or dead, total hospitalization length, and need for invasive or noninvasive mechanical ventilation). In this study, GI symptoms at the time of admission consisted of nausea, vomiting, diarrhea, or abdominal pain. We considered these symptoms under three categories: symptoms associated with upper GI (nausea and vomiting and abdominal pain), lower GI (diarrhea and abdominal pain), and gastroenteritis (nausea and vomiting and diarrhea and abdominal pain).

Patients were divided into two groups: patients with and without GI symptoms. The two groups were compared in terms of severity of the disease, the kind of treatment, and the obtained clinical outcomes (intensive care unit [ICU] admission, discharge, and death). This study was approved by Research Ethics Committee at Isfahan University of Medical Sciences (Ethical code: IR. MUI. MED. REC.1399.333).

Statistical analysis

To perform descriptive statistical analysis for categorical and quantitative data, the Chi-square and independent *t*-test or the Mann–Whitney test were used, respectively. Results were reported in number with percentage for categorical data and mean with standard deviation for quantitative data. The odds ratio (OR) with 95% confidence interval (CI) were estimated by the binary logistic regression model for categorical outcomes. The linear regression models were proposed to estimate unstandardized confidence for continuous outcomes based on GI groups. The results were considered statistically significant with $P < 0.05$. STATA (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). software was used to carry out all the statistical analyses.

RESULTS

A total of 1113 patients were recruited (male = 648: %58; age mean = 59.0 ± 15.6). The patients' demographic and clinical characteristics are presented in Table 1.

According to Table 1, GI symptoms were observed in 612 (56.8%) patients (male = 329: 53.7%; age mean = 56.8 ± 16). The most prominent non-GI symptom reported was cough in 71.5%.

Each patient had at least one comorbidity. About 10% of patients ($n = 110$) were smokers and addicts. Table 2 depicts a detailed list of GI symptoms.

Table 1: COVID-19 patients' demographic and clinical characteristics

Social demographic variables	Total cases (n=1113), n (%)	GI symptoms (n=612), n (%)	Non-GI symptoms (n=501), n (%)	P
Age	59.0 (±15.6)	56.8 (±16.0)	61.6 (±14.7)	<0.001
Sex				
Male	648 (58.2)	329 (53.7)	319 (63.7)	0.001
Smoker/addiction				
Smoker/addiction	110 (9.8)	55 (8.9)	55 (10.9)	0.166
Non-GI symptoms				
Cough	796 (71.5)	466 (76.1)	330 (65.8)	0.035
Fever	792 (71.2)	468 (76.4)	324 (64.6)	0.001
Shortness of breath	653 (58.7)	352 (57.5)	301 (60.1)	0.114
Body pain	591 (53.1)	367 (59.9)	224 (44.7)	0.001
Decreased appetite	468 (42.0)	296 (48.4)	172 (34.3)	0.008
Headache	362 (32.5)	253 (41.3)	109 (21.7)	<0.001
Chest pain	269 (24.2)	186 (30.3)	83 (16.5)	<0.001
Sore throat	186 (16.7)	131 (21.4)	55 (10.9)	0.002
Weight loss	161 (14.5)	119 (19.4)	42 (8.3)	<0.001
Loss of smell	124 (11.14)	81 (13.2)	43 (8.6)	0.624
Runny nose	109 (9.7)	70 (11.4)	39 (7.7)	0.431
Sneeze	79 (7.1)	55 (8.9)	24 (4.7)	0.099
Symptom duration	8.0 (±6.5)	7.9 (±5.3)	8.1 (±7.6)	0.721
Comorbidities				
Hypertension	436 (39.2)	244 (39.9)	192 (38.3)	0.678
Diabetes	333 (29.9)	177 (28.9)	156 (31.1)	0.417
Ischemic heart diseases	185 (16.6)	94 (15.3)	91 (18.1)	0.196
Chronic kidney disease	65 (5.8)	27 (4.4)	38 (7.6)	0.024
Cancers	35 (3.1)	18 (2.9)	17 (3.3)	0.662
Pulmonary disease	31 (2.7)	16 (2.6)	15 (2.9)	0.667
Other comorbidity	256 (23.0)	139 (22.7)	117 (23.3)	0.742

GI=Gastrointestinal

Table 2: Clinical features of COVID-19 patients with gastrointestinal symptoms

Variable	All patients, n (%)	Severe patients (n=512), n (%)	Nonsevere patients (n=601), n (%)	P	OR (95% CI)
Nausea	387 (34.7)	183 (35.7)	204 (33.9)	0.530	
Diarrhea	286 (25.7)	111 (21.7)	175 (29.1)	0.005	0.67 (0.51-0.88)
Vomiting	260 (23.4)	133 (25.9)	127 (21.1)	0.057	
Abdominal pain	168 (15.0)	59 (11.5)	109 (18.1)	0.002	0.58 (0.41-0.82)
Nausea and vomiting	202 (18.1)	101 (20.7)	61 (15.9)	0.401	1.37 (1.01-1.86)
Diarrhea and vomiting	69 (8.4)	38 (7.4)	61 (9.3)	0.260	
Diarrhea and abdominal pain (lower GI)	86 (7.9)	20 (5.2)	12 (10.3)	0.4000	0.48 (0.30-0.77)
Nausea and vomiting and Diarrhea	9 (6.6)	39 (6.6)	90 (6.6)	0.662	
Nausea and vomiting and Abdominal pain (upper GI)	62 (4.6)	28 (5.4)	29 (3.9)	0.296	
Nausea and vomiting and diarrhea and abdominal pain (gastroenteritis)	26 (2.6)	19 (2.7)	16 (2.4)	0.803	

GI=Gastrointestinal; OR=Odds ratio; CI=Confidence interval

Table 2 shows that the most common GI symptoms were nausea, followed by diarrhea, vomiting, and abdominal pain. To evaluate whether the difference of GI symptoms between severe and nonsevere patients was statistically significant, a Chi-square test was conducted. According to the results, diarrhea and abdominal pain were significantly higher in the nonsevere patients ($P = 0.005$, 0.002 , respectively).

Lower GI symptoms were higher in the nonsevere COVID-19 patients ($P = 0.002$). While nausea and vomiting

considered as separate symptoms were not statistically significant across the severe and nonsevere patients, they portrayed an overall statistical significance ($P = 0.091$) across the severe and nonsevere patients (nonsevere > severe).

In Table 3, patients were categorized into four groups based on their age. The distribution of the GI symptoms was investigated across these groups.

According to the above table, all GI symptoms were observed in a larger number of females than males.

However, only the differences for nausea and abdominal pain were significant ($P < 0.001$) [Table 3].

Table 4 presents the number of patients who underwent treatment with corticosteroid and mechanical ventilation. In addition, the clinical outcomes of the GI and non-GI groups are presented.

Of the total patients, 1018 (91.4%) were discharged, 95 (8.5%) died, and 164 (14.7%) were admitted to ICU. The number of patients who were discharged, died, and were admitted to ICU was significantly different across

the GI and non-GI groups ($P = 0.002, 0.009, 0.003$). During hospitalization, the majority of patients (79.6%) were treated with corticosteroids. The use of invasive and noninvasive mechanical ventilation was higher in the non-GI symptom group ($P \leq 0.001, 0.007$, respectively). Hospital duration was $6.8 (\pm 6.1)$ days, which was not statistically significant across the two groups ($P = 0.660$) [Table 4]. In Table 5, we used logistic regression for removing the effect of confounding factors.

As shown in Table 5, the discharge rate in model 1 (without considering confounding factors) was approximately

Table 3: Clinical features of patients with gastrointestinal symptoms based on sex and age

	Age				P	Gender		P
	18-29 (n=29), n (%)	30-49 (n=276), n (%)	50-64 (n=391), n (%)	+65 (n=417), n (%)		Male (n=648), n (%)	Female (n=465), n (%)	
Nausea	17 (58.6)	115 (41.4)	143 (36.6)	112 (26.8)	0.002	193 (29.8)	194 (41.7)	<0.001
Vomiting	9 (31.0)	75 (26.9)	88 (22.5)	88 (21.1)	0.522	144 (22.2)	116 (24.9)	0.262
Diarrhea	13 (44.8)	101 (36.3)	102 (26.1)	70 (16.8)	<0.001	161 (24.8)	125 (26.8)	0.257
Abdominal pain	6 (20.7)	63 (22.7)	47 (12.0)	52 (12.4)	0.004	77 (11.9)	91 (19.6)	<0.001

Table 4: Treatments and clinical outcomes

	Total cases (n=1113), n (%)	GI symptoms (n=612), n (%)	Non-GI symptoms (n=501), n (%)	P
Treatment				
Corticosteroid	880 (79.6)	966 (81.5)	388 (77.4)	0.061
Invasive mechanical ventilation	59 (5.3)	18 (2.9)	41 (8.1)	<0.001
Noninvasive mechanical ventilation	27 (2.4)	8 (1.3)	19 (3.7)	0.007
Clinical outcomes				
Hospitalization duration (days)	6.8 (± 6.1)	6.7 (± 6.4)	6.9 (± 5.8)	0.660
Discharge	1018 (91.4)	573 (93.6)	444 (88.6)	0.002
Death	95 (8.5)	40 (6.5)	55 (10.9)	0.009
ICU admission	164 (14.7)	73 (11.9)	91 (18.7)	0.003

GI=Gastrointestinal; ICU=Intensive care unit

Table 5: The estimated correlation between different outcomes and gastrointestinal group

Outcome	Logistic regression		P	Linear regression		P
	Model 1	OR (95% CI)		Model 1	B coefficient (95% CI)	
Discharge	2.03	(1.20-3.19)	0.002	Hospitalization duration (days)	-0.11 (-0.8-0.62)	0.768
Death	0.56	(0.37-0.87)	0.009			
ICU admission	0.60	(0.43-0.84)	0.003			
	Model 2			Model 2		
Discharge	1.72	(1.07-2.7)	0.023	Hospitalization duration (days)	0.20 (-0.5-0.94)	0.596
Death	0.67	(0.43-1.05)	0.087			
ICU admission	0.69	(0.49-0.97)	0.036			
	Model 3			Model 3		
Discharge	1.80	(1.08-3.02)	0.024	Hospitalization duration (days)	0.21 (-0.50-0.92)	0.559
Death	0.66	(0.40-1.07)	0.095			
ICU admission	0.63	(0.42-0.92)	0.020			
	Model 4			Model 4		
Discharge	1.7	(1.0-2.87)	0.046	Hospitalization duration (days)	0.19 (-0.52-0.90)	0.601
Death	0.69	(0.42-1.14)	0.153			
ICU admission	0.63	(0.42-0.93)	0.021			

Model 1=No adjusted variables; Model 2=Model adjusted by sex and age; Model 3=Model adjusted by sex, age, and SaO₂; Model 4=Model adjusted by sex, age, SaO₂, and significant comorbidities; OR=Odds ratio; CI=Confidence interval; ICU=Intensive care unit; SaO₂=Oxygen saturation

twice as much in the GI group compared to the non-GI group (OR = 2.03; 95% CI: 1.20–3.19). Moreover, death and ICU admission in model 1 were significantly different from those of non-GI group (OR = 0.56 and 0.60, respectively). Having adjusted for the confounding factors (model 2: sex and age; model 3: sex, age, and Sao2; and model 4: sex, age, Sao2, and significant comorbidities) while the death rate did not alter significantly, discharge rates and ICU admission decreased significantly in the GI group, compared to the non-GI group. Besides, after adjusting for the confounding factors (model 2: sex and age; model 3: sex, age, and Sao2; and model 4: sex, age, Sao2, and significant comorbidities), no significant difference was observed between GI and non-GI groups in terms of hospital duration.

DISCUSSION

In this study, among the 1113 patients hospitalized with COVID-19, 56.8% manifested at least one GI symptom, the most common of which were nausea followed by diarrhea and abdominal pain. The prevalence of GI symptoms in our study was similar to those reported by Pan *et al.* and Han *et al.*, ranging from 50.5% to 61.3%.^[2,13] While anorexia was included as a GI symptom in those studies, it was considered a nonspecific symptom (not a GI symptom) in the present study. Lin *et al.* and Mao *et al.* indicated that nausea, diarrhea, and vomiting were the main GI symptoms. There were no significant differences between severe and nonsevere groups in terms of nausea and vomiting.^[7,20] In a US study by Ramachandran *et al.*,^[21] the prevalence of GI symptoms in COVID-19 patients was reported to be 20.6%. In their study, diarrhea was reported as the most common GI symptoms in 48.4% of the patients. Moreover, the most prevalent comorbidity in our study was hypertension, followed by diabetes. Overall, these results were confirmed by those of other studies.^[7,8,13,22,23]

While COVID-19 was predominantly diagnosed in males, GI symptoms were more commonly reported by females. Although acute respiratory symptoms including cough, fever, and shortness of breath are the most common manifestations of COVID-19, GI symptoms can also occur in COVID-19 patients presenting as an early manifestation of the disease. Failure to identify these patients early enough may often lead to further spread of the disease.

In our study, abdominal pain and diarrhea were prominent in the nonsevere group when the symptoms were evaluated individually; meanwhile, lower GI symptoms and gastroenteritis were more prevalent in the nonsevere group when lower GI, upper GI, and gastroenteritis were considered collectively. In addition, results indicated that

GI symptoms in COVID-19 patients were common, and the symptoms did not correlate with the severity of the disease. Moreover, the presence of GI symptoms positively correlated with the milder form of the disease. Among COVID-19-positive patients, the clinical outcomes of the GI group were promising, compared to those of the non-GI group.

Nobel *et al.* and Ferm *et al.* reported that GI symptoms were not significantly correlated along with increased rates of ICU admission, intubation, and mortality.^[18,24] In contrast, Tian *et al.* showed patients with digestive symptoms tended to have a worse prognosis than those without digestive symptoms (34.3% discharged vs. 60% discharged).^[16] Moreover, Zheng *et al.* indicated that the rate of clinical deterioration was significantly higher in GI group than that of non-GI group.^[25]

The present study faced two limitations, i.e., limited patient sample and the inability to test stool RNA in a large sample.

CONCLUSION

Previous studies have indicated that COVID-19 enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor. ACE2 is expressed within the human respiratory and GI (esophagus, ileum, and colon) tracts. Furthermore, diagnosis of COVID-19 viral RNA in patients' stool and the transmission of the disease through fecal–oral have increased.^[8,20,26] Thus, early detection of COVID-19 in patients with GI symptoms is warranted.

Follow-up studies can be conducted to investigate the presence of GI symptoms in COVID-19 patients during the posttreatment period. To evaluate the validity of the present results, further studies on diverse populations and in other centers are deemed essential.

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Conflicts of interest

There are no conflicts of interest.

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