Original Article

Clinical Outcomes of Patients with COVID-19 and Gastrointestinal Manifestations in South-West Iran

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ABSTRACT

Background:
In this research, we examined the association between gastrointestinal (GI) involvement and clinical outcomes in hospitalized patients admitted to hospitals in Khuzestan province.

Materials and Methods:
We analyzed 17892 inpatients (≥18 years old) diagnosed with coronavirus disease 2019 (COVID-19) at 43 hospitals in Khuzestan province from its inception until October 2021. We accumulated demographic information, clinical details, vital signs, laboratory results, kind of therapy, and clinical outcomes from patients' medical records. Patients with gastrointestinal symptoms were compared to those without GI symptoms.

Results:
17892 patients (9690 males) were observed and recruited. The most prevalent GI symptoms reported in 3334 (18.6%) individuals (male = 1806) were anorexia and nausea. Anorexia 1882 (10.5%), followed by nausea 1133 (6.3%), vomiting 895 (5.0%), diarrhea 687 (3.8%), abdominal pain 337 (1.9%), and GI bleeding 11 (0.1%). Cough 10706 (59.8%), fever 7855 (43.9%), myalgia 5687 (31.8%), and headache 1338 (7.5%) were the most common non-GI symptoms. The number of hospitalizations, deaths, intubations, and ICU admissions was substantially different between the GI and non-GI groups, and these outcomes were significantly worse in the non-GI patients ($P<0.001$, $P<0.007$, $P<0.001$, $P<0.001$), respectively.

Conclusion:
COVID-19 can be associated with GI symptoms, but there is no association between the symptoms and the severity of the illness. Moreover, the prevalence of GI symptoms was not associated with an increased risk of mortality. It was correlated with reduced disease severity among COVID-19-positive patients; therefore, the GI group's clinical results were encouraging compared to the non-GI group.

Keywords: SARS-CoV-2, COVID-19, Clinical outcome, Gastrointestinal manifestation, Iran

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multisystem illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has emerged as a worldwide public health emergency with a relatively high fatality rate (3.4%) (1). This extremely contagious virus is primarily transmitted through direct contact; however, it is also believed to be spread by airborne transmission, contaminated items, and possibly fecal-oral transmission (2, 3). It is known that the gastrointestinal (GI) tract and liver are also target organs for SARS-CoV-2. The main receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE-2), is strongly expressed in the GI tract and liver parenchyma, which supports these findings (4-6).

SARS-CoV-2-GI symptoms, such as pneumonia, fever, and cough, have been reported in up to 26% of patients with COVID-19 (7). During an infection, common GI symptoms include diarrhea, nausea, vomiting, abdominal pain, and lack of appetite (8-10). Recent findings, however, imply that the incidence of GI symptoms, such as diarrhea (10.1%) and nausea/vomiting (3.6%), has grown considerably in patients with COVID-19, even though certain studies have reported a reduced frequency of specific GI symptoms, such as diarrhea (1–3.8%) (7, 11). Although we do not know how SARS-CoV-2 affects the GI tract and liver, we do know that digestive symptoms and abnormal liver function tests (LFTs) are useful in predicting the outcome of COVID-19 (12, 13).

As previously stated, SARS-CoV-2-related GI symptoms are fairly typical in individuals with COVID-19, and in some instances, the GI tract may be more affected than the respiratory system (14). It is hypothesized that the identification of SARS-CoV-2-related GI symptoms may play a significant role in detecting individuals and influencing isolation techniques and testing (4).

Although researchers are increasingly interested in investigating whether GI manifestations are associated with COVID-19 severity, morbidity, and mortality, there are insufficient studies to examine this link, and it remains unclear whether GI manifestations are linked to a better prognosis or not (15).

Through a retrospective analysis of patient data, we correlated digestive symptoms with the length of hospital stay, the need for intensive care, the intubation rate, and the mortality of patients with COVID-19 admitted to hospitals in Khuzestan province. We sought to learn more about the origins of GI symptoms and their prevalence in individuals with COVID-19. This is important for developing preventative measures, policies for identifying patients, and treatment options.

MATERIALS AND METHODS

Study design and population

A total of 17892 patients with COVID-19 (≥18 years old, 9690 males) with confirmed pneumonia (by real-time RT-PCR) and any GI manifestations (such as abdominal pain, vomiting, diarrhea, anorexia, and GI bleeding, who had the symptoms at the time of hospital admission or after hospitalization in Khuzestan province, Iran were recruited retrospectively, and patients who had the chronic liver disease were excluded. Only existing information was provided. The data came from the Khuzestan COVID-19 registry. This registry collects information regarding patients with COVID-19 from 43 hospitals, including both teaching and non-teaching institutions. The procedures and methodology for gathering and quality control of this registry's data are described elsewhere. We retrieved data from this registry from its inception until October 2021. There are 17,892 patients with verified COVID-19 in the dataset (positive PCR). This analysis included all patients, regardless of age, sex, color, or ethnicity.

Patient classification

The National Institutes of Health Guidance for COVID-19 (16) allocated patients to one of three categories depending on their disease severity:

- Mild disease: Patients with COVID-19 symptoms but no shortness of breath, abnormal computed tomography (CT) scan or chest radiography findings.
- Moderate disease: Patients with a SpO2 below 94% and abnormal CT scan or chest radiography findings suggesting lower respiratory disease.
- Severe disease: Patients with severe symptoms, such as pulse oxygen saturation values below 93%, a respiratory rate of over 30 times per minute, or rapid pneumonia progression within 24 to 48 hours.

Outcomes

The main objective was to compare the death rate, ICU admission, intubation rate, and length of hospital stay between patients with GI symptoms and those without GI symptoms after a COVID-19 diagnosis.

Statistical analysis

The statistical analysis was conducted to assess the role of various factors in patient outcomes. The frequency of GI symptoms was specified. Only the parameters obtained at the time of hospital admission were used to conduct the statistical analysis. The results of the analysis were presented in terms of the odds ratio (OR) and 95% CI for the OR. Two groups of patients were compared using the t-test or the Mann-Whitney U test (for numerical variables after testing the normal distribution of the data) or the Chi-Square test (for categorical data). In statistical modeling, linear and binary regression analyses were employed

to estimate the relationships between the outcomes of COVID-19 patients and independent variables, including age, sex, disease severity, and comorbidities. A difference of less than 0.05 was considered statistically significant. The data analysis was conducted using the SPSS software, version 18.0.

RESULTS

A total of 17892 patients with COVID-19 were recruited (male = 9690, 54.2%; age mean = 54.38±17.9). Table 1 presents the demographic and clinical information of the patients, including those with and without GI manifestations.

Table 1 shows that 3334 (18.6%) patients (male=1806: 54.2%; age mean = 54.3±18.9) experienced GI symptoms. Age, sex, oxygen saturation, and CT abnormalities were the same for all patients, regardless of whether they had gastrointestinal symptoms or not. However, GI patients often had higher comorbidities and more severe symptoms. Cough was the most common non-GI symptom reported in 60.6% of cases (n=8816). Approximately 0.6% of GI patients (n=21) misused drugs.

The distribution of GI symptoms is shown in Figure 1. It reveals that anorexia and nausea were the most prevalent GI symptoms in GI patients, followed by vomiting, diarrhea, abdominal pain, and GI bleeding. At least one GI symptom was seen in 18.6% of patients with COVID-19.

The rates of ICU admission, intubation, and mortality were compared between the GI and non-GI groups in Figure 2. Of the total patients, 2885 (16.1%) passed away, 2108 (11.8%) required intubation, and 3842 (21.5%) were hospitalized in the intensive care unit. The number of deaths [P = <0.007, OR (CI 95%) = 0.865 (0.778-0.961)], intubations [P = <0.001, OR (CI 95%) = 0.761 (0.672-0.863)], and ICU admissions [P = <0.001, OR (CI 95%) = 0.825 (0.750-0.907)] were different between the GI and non-GI groups, and these outcomes were significantly worse in the non-GI patients.

The lengths of hospitalization (mean and median) for the GI and non-GI groups are compared in Figure 3. This outcome was significantly worse in the non-GI patients (P = <0.001).

According to Table 2, adding GI symptoms to comorbidities generally did not influence the death rate, except for smoking, chronic kidney disease (CKD), and hypertension. Overall, having GI symptoms was related to a decreased mortality rate.

The number of GI and non-GI patients who had mechanical ventilation is shown in Table 3. It demonstrates that, except for drug misuse, rheumatoid arthritis (RA), dialysis, hypertension, and heart disease, adding GI symptoms to comorbidities in those people generally had little effect. Overall, a reduced rate of intubation was associated with experiencing GI symptoms.

The addition of GI symptoms to comorbidity, as indicated in Table 4, often had little impact on ICU admission, except for instances of hypertension, heart disease, and diabetes. In general, reduced ICU admission was associated with experiencing GI symptoms.

Table 5 illustrates the relationship between GI symptoms and comorbidities. Although the majority of cases have resulted in longer hospital admissions, these longer stays are not statistically significant in all cases. The period of hospitalization has been significantly extended in patients who have asthma, Alzheimer's, Parkinson's, cancer, rheumatoid arthritis, HIV, obesity, and drug abuse because of the presence of GI problems.

Overall, according to Table 6, the addition of GI symptoms (in contrast to age, sex, disease severity, comorbidities, and some non-GI symptoms) has no significant effect on the outcomes of patients with COVID-19 and does not increase the rate of mortality, intubation, admission to the ICU, or length of hospital stay.

Table 1. Comparison of demographic and clinical characteristics of patients with gastrointestinal and non-gastrointestinal symptoms with COVID-19

Variables	Non-GI patients (n=14558)	GI patients (n=3334)	Total patients (n=17892)	P value	OR (CI 95%)
Age Mean (± SD), Years Median (Q1, Q3)	 54.4±17.6 55 (41, 67)	 54.3±18.9 56 (41, 68)	 54.38 ±17.9	 0.275	 -
Sex, Male	7884 (54.2%)	1806 (54.2%)	9690 (54.2%)	0.989	1.001(0.928-1.079)
Cough (Yes)	8816 (60.6%)	1890 (56.7%)	10706 (59.8%)	<0.001***	0.852 (0.79-0.92)
Fever (Yes)	6136 (42.1%)	1719 (51.6%)	7855 (43.9%)	<0.001***	1.46 (1.33-1.57)
Myalgia (Yes)	4353 (29.9%)	1334 (40.0%)	5687 (31.8%)	<0.001***	1.56 (1.44-1.69)
Chills (Yes)	170 (1.2%)	87 (2.6%)	257 (1.4%)	<0.001***	2.27 (1.75-2.94)

Table 1.Comparison of demographic and clinical characteristics of patients with gastrointestinal and non-gastrointestinal symptoms with COVID-19

Variables	Non-GI patients (n=14558)	GI patients (n=3334)	Total patients (n=17892)	P value	OR (CI 95%)
Headache (Yes)	765 (5.3%)	573 (17.2%)	1338 (7.5%)	<0.001**	3.74 (3.33-4.2)
Sore throat (Yes)	114 (0.8%)	29 (0.9%)	143 (0.8%)	0.612	1.12 (0.79-1.67)
Gustatory dysfunction (Yes)	207 (1.4%)	116 (3.5%)	323 (1.8%)	<0.001***	2.49 (1.99-3.15)
Olfactory dysfunction (Yes)	228 (1.6%)	138 (4.1%)	366 (2.0%)	<0.001**	2.714 (2.19-3.36)
Rhinorrhea (Yes)	24 (0.2%)	11 (0.3%)	35 (0.2%)	0.052	2 (0.98-4.09)
Altered consciousness (Yes)	736 (5.1%)	121 (3.6%)	857 (4.8%)	0.001***	0.707 (0.58-0.86)
Skin lesion/rash (Yes)	15 (0.1%)	8 (0.2%)	23 (0.1%)	0.05*	2.33 (0.99-5.5)
Dizziness (Yes)	235 (1.6%)	305 (9.1%)	540 (3.0%)	<0.001***	6.137 (5.15-7.3)
Lassitude (Yes)	669 (4.6%)	317 (9.5%)	986 (5.5%)	<0.001***	2.18 (1.89-2.5)
Oxygen saturation (mean ± SD)	89.59 ± 13.9	91.28 ±9.86	89.9 ±13.3	0.452	-
Oxygen therapy (Yes)	6186 (42.5%)	1302 (39.1%)	7488 (41.9%)	<0.001***	0.867 (0.803-0.937)
CT abnormalities (Yes)	11755 (97.5%)	2726 (97.8%)	14481 (97.6%)	0.323	0.87 (0.656-1.15)
Any comorbidity (Yes)	5407 (37.1%)	1559 (46.8%)	6966 (38.9%)	<0.001***	1.49 (1.38-1.6)
Hypertension (Yes)	2324 (16.0%)	705 (21.1%)	3029 (16.9%)	<0.001***	1.4 (1.28-1.55)
Heart diseases (Yes)	1675 (11.5%)	479 (14.4%)	2154 (12.0%)	<0.001***	1.29 (1.15-1.44)
Diabetes (Yes)	2702 (18.6%)	821 (24.6%)	3523 (19.7%)	<0.001***	1.43 (1.3-1.57)
Thyroid disease (Yes)	59 (0.4%)	22 (0.7%)	81 (0.5%)	0.048*	1.63 (0.99-2.67)
Immunodeficiency disease (Yes)	36 (0.2%)	11 (0.3%)	47 (0.3%)	0.400	1.33 (0.67-2.67)
Chemotherapy (Yes)	24 (0.2%)	20 (0.6%)	44 (0.2%)	<0.001***	3.65 (2.01-6.62)
Asthma (Yes)	299 (2.1%)	71 (2.1%)	370 (2.1%)	0.782	1.04 (0.799-1.35)
Other lung diseases (Yes)	167 (1.1%)	50 (1.5%)	217 (1.2%)	0.093	1.31 (0.95-1.8)
Neurological disease (Yes)	134 (0.9%)	55 (1.6%)	189 (1.1%)	<0.001***	1.81 (1.32-2.48)
Alzheimer's (Yes)	13 (0.1%)	8 (0.2%)	21 (0.1%)	0.022	2.69 (1.11-6.5)
Parkinson's (Yes)	9 (0.1%)	2 (0.1%)	11 (0.1%)	0.969	0.97 (0.21-4.49)
CVA (Yes)	61 (0.4%)	23 (0.7%)	84 (0.5%)	0.039	1.65 (1.02-2.67)
Chronic kidney disease (Yes)	323 (2.2%)	135 (4.0%)	458 (2.6%)	<0.001***	1.86 (1.52-2.28)
Dialysis/End-stage renal disease (Yes)	135 (0.9%)	54 (1.6%)	189 (1.1%)	<0.001***	1.76 (1.28-2.47)
Hematological disease (Yes)	95 (0.7%)	25 (0.7%)	120 (0.7%)	0.535	1.15 (0.74-1.79)
Cancer (Yes)	189 (1.3%)	68 (2.0%)	257 (1.4%)	0.001***	1.58 (1.19-2.09)
RA (Yes)	34 (0.2%)	24 (0.7%)	58 (0.3%)	<0.001***	3.1 (1.83-5.23)
HIV/AIDS (Yes)	6 (0%)	4 (0.1%)	10 (0.1%)	0.083	2.9 (0.82-10.33)
Obesity (Yes)	12 (0.1%)	2 (0.1%)	14 (0.1%)	0.676	0.728 (0.16-3.25)
Smoking (Yes)	150 (1.0%)	42 (1.3%)	192 (1.1%)	0.246	1.225 (0.896-1.73)
Drug abuse (Yes)	53 (0.4%)	21 (0.6%)	74 (0.4%)	0.031*	1.74 (1.05-2.88)
Pregnancy (Yes)	125 (0.9%)	28 (0.8%)	153 (0.9%)	0.915	0.98 (0.65-1.47)

COVID-19, coronavirus 2019; CVA, Cerebrovascular accident; RA, Rheumatoid arthritis.

Data are presented as median (Q1, Q3), mean±SD, and frequency of individuals (percentage). *: P<0.05; **: P<0.01; ***: P<0.001.

Table 2. Relationship between mortality rate and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	Mortality rate		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
Any comorbidity (Yes)	No	4181 (76.8)	1226 (80.6)	5407 (77.6)	0.799 (0.694-0.921)	0.002 **
	Yes	1263 (23.2)	296 (19.4)	1559 (22.4)		
Hypertension (Yes)	No	1745 (75.7)	579 (80.1)	2324 (76.7)	0.774 (0.63-0.95)	0.014 *
	Yes	561 (24.3)	144 (19.9)	705 (23.3)		
Heart disease (Yes)	No	1215 (76.9)	460 (80.3)	1675 (77.8)	0.815 (0.64-1.033)	0.091
	Yes	366 (23.1)	113 (19.7)	479 (22.2)		
Diabetes (Yes)	No	2094 (76.1)	608 (78.8)	2702 (76.7)	0.815 (0.708-1.043)	0.125
	Yes	657 (23.9)	164 (21.2)	821 (23.3)		
Thyroid disease (Yes)	No	52 (74.3)	7 (63.6)	59 (72.8)	1.651 (0.432-6.306)	0.46
	Yes	18 (25.7)	4 (36.4)	22 (27.2)		
Immunodeficiency disease (Yes)	No	28 (77.8)	8 (72.7)	36 (76.6)	1.313 (0.281-6.135)	0.729
	Yes	8 (22.2)	3 (27.3)	11 (23.4)		
Chemotherapy (Yes)	No	15 (51.7)	9 (60.0)	24 (54.5)	0.714 (0.202-2.528)	0.601
	Yes	14 (48.3)	6 (40.0)	20 (45.5)		
Asthma (Yes)	No	252 (79.7)	47 (87.0)	299 (80.8)	0.586 (0.253-1.359)	0.209
	Yes	64 (20.3)	7 (13.0)	71 (19.2)		
Other lung diseases (Yes)	No	106 (73.6)	61 (83.6)	167 (77.0)	0.549 (0.267-1.129)	0.10
	Yes	38 (26.4)	12 (16.4)	50 (23.0)		
Neurological disease (Yes)	No	99 (71.2)	35 (70.0)	134 (70.9)	1.061 (0.523-2.152)	0.870
	Yes	40 (28.8)	15 (30.0)	55 (29.1)		
Alzheimer's (Yes)	No	8 (61.5)	5 (62.5)	13 (61.9)	0.906 (0.156-5.9)	0.664
	Yes	5 (38.5)	3 (37.5)	8 (38.1)		
Parkinson's (Yes)	No	3 (75.0)	6 (85.7)	9 (81.8)	0.5 (0.023-11.09)	0.618
	Yes	1 (25.0)	1 (14.3)	2 (18.2)		
CVA (Yes)	No	32 (66.7)	29 (80.6)	61 (72.6)	.483 (0.174-1.34)	0.158
	Yes	16 (33.3)	7 (19.4)	23 (27.4)		
CKD (Yes)	No	196 (67.1)	127 (76.5)	323 (70.5)	0.627 (0.406-0.968)	0.034 *
	Yes	96 (32.9)	39 (23.5)	135 (29.5)		
Dialysis/End-stage renal disease (Yes)	No	72 (66.1)	63 (78.8)	135 (71.4)	0.525 (0.270-1.022)	0.056
	Yes	37 (33.9)	17 (21.3)	54 (28.6)		
Hematological disease (Yes)	No	76 (82.6)	19 (67.9)	95 (79.2)	2.250 (0.862-5.87)	0.092
	Yes	16 (17.4)	9 (32.1)	25 (20.8)		
Cancer (Yes)	No	127 (73.0)	62 (74.7)	189 (73.5)	0.915 (0.504-1.66)	0.771
	Yes	47 (27.0)	21 (25.3)	68 (26.5)		
RA (Yes)	No	22 (51.2)	12 (80.0)	34 (58.6)	0.262 (0.65-1.061)	0.051
	Yes	21 (48.8)	3 (20.0)	24 (41.4)		
HIV/AIDS (Yes)	No	2 (40.0)	4 (80.0)	6 (60.0)	0.167 (0.10-2.821)	0.262
	Yes	3 (60.0)	1 (20.0)	4 (40.0)		
Obesity (Yes)	No	8 (88.9)	4 (80.0)	12 (85.7)	2 (0.98-41.003)	0.604
	Yes	1 (11.1)	1 (20.0)	2 (14.3)		
Smoking (Yes)	No	119 (77.3)	31 (81.6)	150 (78.1)	0.768 (0.311-1.893)	0.565
	Yes	35 (22.7)	7 (18.4)	42 (21.9)		

Table 2. Relationship between mortality rate and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	Mortality rate		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
Drug abuse (Yes)	No	29 (61.7)	24 (88.9)	53 (71.6)	0.201 (0.053-0.766)	0.013 *
	Yes	18 (38.3)	3 (11.1)	21 (28.4)		
Pregnancy (Yes)	No	121 (81.8)	4 (80.0)	125 (81.7)	1.120 (0.12-10.426)	0.641
	Yes	27 (18.2)	1 (20.0)	28 (18.3)		

CVA, Cerebrovascular accident; CKD, Chronic kidney disease; RA, Rheumatoid arthritis.
Data are presented as the frequency of individuals (percentage). *: P<0.05; **: P<0.01.

Table 3. Relationship between intubation rate and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	Intubation		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
Any comorbidity (Yes)	No	4525 (76.8)	882 (82.0)	5407 (77.6)	0.725 (0.613-0.857)	<0.0001 * * *
	Yes	1366 (23.2)	193 (18.0)	1559 (22.4)		
Hypertension (Yes)	No	1936 (76.0)	388 (80.7)	2324 (76.7)	0.758 (0.594-0.968)	0.026 *
	Yes	612 (24.0)	93 (19.3)	705 (23.3)		
Heart disease (Yes)	No	1360 (76.8)	315 (82.0)	1675 (77.8)	0.727 (0.548-0.964)	0.026 *
	Yes	410 (23.2)	69 (18.0)	479 (22.2)		
Diabetes (Yes)	No	2270 (76.4)	432 (78.5)	2702 (76.7)	0.882 (0.707-1.1)	0.264
	Yes	703 (23.6)	118 (21.5)	821 (23.3)		
Thyroid disease (Yes)	No	56 (75.7)	3 (42.9)	59 (72.8)	4.148 (0.874-20.31)	0.062
	Yes	18 (24.3)	4 (57.1)	22 (27.2)		
Immunodeficiency disease (Yes)	No	28 (73.7)	8 (88.9)	36 (76.6)	0.35 (0.039-3.16)	0.333
	Yes	10 (26.3)	1 (11.13)	11 (23.4)		
Chemotherapy (Yes)	No	18 (58.1)	6 (46.2)	24 (54.5)	1.615 (0.439-5.945)	0.469
	Yes	13 (41.9)	7 (53.8)	20 (45.5)		
Asthma (Yes)	No	257 (79.3)	42 (91.3)	299 (80.8)	0.365 (0.127-1.055)	0.0503
	Yes	67 (20.7)	4 (8.7)	71 (19.2)		
Other lung diseases (Yes)	No	117 (74.5)	50 (83.3)	167 (77.0)	0.585 (0.271-1.261)	0.168
	Yes	40 (25.5)	10 (16.7)	50 (23.0)		
Neurological disease (Yes)	No	100 (68.0)	34 (81.0)	134 (70.9)	0.501 (0.215-1.165)	0.104
	Yes	47 (32.0)	8 (19.0)	55 (29.1)		
Alzheimer's (Yes)	No	9 (60.0)	4 (66.7)	13 (61.9)	0.750 (0.103-5.47)	0.59
	Yes	6 (40.0)	2 (33.3)	8 (38.1)		
Parkinson's (Yes)	No	5 (71.4)	4 (100)	9 (81.8)	0.556 (0.31-0.997)	0.382
	Yes	2 (28.6)	0 (0)	2 (18.2)		
CVA (Yes)	No	43 (68.3)	18 (85.7)	61 (72.6)	0.358 (0.095-1.358)	0.120
	Yes	20 (31.7)	3 (14.3)	23 (27.4)		
CKD (Yes)	No	231 (68.1)	92 (77.3)	323 (70.5)	0.628 (0.386-1.021)	0.059
	Yes	108 (31.9)	27 (22.7)	135 (29.5)		
Dialysis/End-stage renal disease (Yes)	No	81 (64.8)	54 (84.4)	135 (71.4)	0.341 (0.158-0.735)	0.005 *
	Yes	44 (35.2)	10 (15.6)	54 (28.6)		
Hematological disease (Yes)	No	83 (80.6)	12 (70.6)	95 (79.2)	1.729 (0.547-5.471)	0.347
	Yes	20 (19.4)	5 (29.4)	25 (20.8)		

Table 3. Relationship between intubation rate and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	Intubation		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
Cancer (Yes)	No	146 (74.1)	43 (71.7)	189 (73.5)	1.132 (0.593-2.159)	0.707
	Yes	51 (25.9)	17 (28.3)	68 (26.5)		
RA (Yes)	No	26 (53.1)	8 (88.9)	34 (58.6)	0.141 (0.016-1.217)	0.045 *
	Yes	23 (46.9)	1 (11.1)	24 (41.4)		
HIV/AIDS(Yes)	No	4 (57.1)	2 (66.7)	6 (60.0)	0.667 (0.039-11.285)	0.778
	Yes	3 (42.9)	1 (33.3)	4 (40.0)		
Obesity (Yes)	No	10 (90.9)	2 (66.7)	12 (85.7)	5 (0.212-117.894)	0.287
	Yes	1 (9.1)	1 (33.3)	2 (14.3)		
Smoking (Yes)	No	125 (77.6)	25 (80.6)	150 (78.1)	0.833 (0.317-2.187)	0.711
	Yes	36 (22.4)	6 (19.4)	42 (21.9)		
Drug abuse (Yes)	No	34 (64.2)	19 (90.5)	53 (71.6)	0.188 (0.04-0.898)	0.024 *
	Yes	19 (35.8)	2 (9.5)	21 (28.4)		
Pregnancy (Yes)	No	119 (81.0)	6 (100.0)	125 (81.7)	0.952 (0.915-0.990)	0.237
	Yes	28 (19.0)	0 (0)	28 (18.3)		

CVA, Cerebrovascular accident; CKD, Chronic kidney disease; RA, Rheumatoid arthritis.

Data are presented as the frequency of individuals (percentage). *: P<0.05; **: P<0.01; ***: P<0.001.

Table 4. Relationship between ICU admission and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	ICU		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
Any comorbidity (Yes)	No	3833 (76.3)	1574 (81.0)	5407 (77.6)	0.758 (0.665-0.864)	<0.0001 * * *
	Yes	1189 (23.7)	370 (19.0)	1559 (22.4)		
Hypertension (Yes)	No	1628 (75.2)	696 (80.6)	2324 (76.7)	0.726 (0.597-0.882)	<0.001 * * *
	Yes	538 (24.8)	167 (19.4)	705 (23.3)		
Heart disease (Yes)	No	1085 (76.0)	590 (81.2)	1675 (77.8)	0.737 (0.590-0.920)	0.007 * *
	Yes	342 (24.0)	137 (18.8)	479 (22.2)		
Diabetes (Yes)	No	1907 (75.2)	795 (80.6)	2702 (76.7)	0.727 (0.606-0.872)	<0.001 * * *
	Yes	630 (24.8)	191 (19.4)	821 (23.3)		
Thyroid disease (Yes)	No	40 (69.0)	19 (82.6)	59 (72.8)	0.468 (0.139-1.547)	0.213
	Yes	18 (31.0)	4 (17.4)	22 (27.2)		
Immunodeficiency disease (Yes)	No	23 (79.3)	13 (72.2)	36 (76.6)	1.474 (0.375-5.790)	0.577
	Yes	6 (20.7)	5 (27.8)	11 (23.4)		
Chemotherapy (Yes)	No	14 (53.8)	10 (55.6)	24 (54.5)	0.933 (0.279-3.123)	0.911
	Yes	12 (46.2)	8 (44.4)	20 (45.5)		
Asthma (Yes)	No	239 (79.9)	60 (84.5)	299 (80.8)	0.730 (0.362-1.474)	0.379
	Yes	60 (20.1)	11 (15.5)	71 (19.2)		
Other lung diseases (Yes)	No	98 (72.6)	69 (84.1)	167 (77.0)	0.499 (0.247-1.008)	0.050
	Yes	37 (27.4)	13 (15.9)	50 (23.0)		
Neurological disease (Yes)	No	81 (68.6)	53 (74.6)	134 (70.9)	0.743 (0.384-1.44)	0.379
	Yes	37 (31.4)	18 (25.4)	55 (29.1)		
Alzheimer's (Yes)	No	10 (62.5)	3 (60.0)	13 (61.9)	1.11 (0.142-8.68)	0.656
	Yes	6 (37.5)	2 (40.0)	8 (38.1)		
Parkinson's (Yes)	No	5 (83.3)	4 (80.0)	9 (81.8)	1.250 (0.058-26.869)	0.727
	Yes	1 (16.7)	1 (20.0)	2 (18.2)		

Table 4. Relationship between ICU admission and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms	ICU		Total (n,%)	OR (CI 95%)	P value
		No (n,%)	Yes (n,%)			
CVA (Yes)	No	35 (72.9)	26 (72.2)	61 (72.6)	1.036 (0.393-2.726)	0.944
	Yes	13 (27.1)	10 (27.8)	23 (27.4)		
Chronic kidney disease (Yes)	No	202 (68.0)	121 (75.2)	323 (70.5)	0.703 (0.456-1.083)	0.109
	Yes	95 (32.0)	40 (24.8)	135 (29.5)		
Dialysis/End-stage renal disease (Yes)	No	78 (69.0)	57 (75.0)	135 (71.4)	0.743 (0.386-1.43)	0.373
	Yes	35 (31.0)	19 (25.0)	54 (28.6)		
Hematological disease (Yes)	No	67 (79.8)	28 (77.8)	95 (79.2)	1.126 (0.436-2.909)	0.806
	Yes	17 (20.2)	8 (22.2)	25 (20.8)		
Cancer (Yes)	No	124 (75.2)	65 (70.7)	189 (73.5)	1.256 (0.71-2.22)	0.433
	Yes	41 (24.8)	27 (29.3)	68 (26.5)		
RA (Yes)	No	23 (54.8)	11 (68.8)	34 (58.6)	0.55 (0.163-1.862)	0.334
	Yes	19 (45.2)	5 (31.3)	24 (41.4)		
HIV/AIDS(Yes)	No	4 (66.7)	2 (50.0)	6 (60.0)	2.0 (0.150-26.734)	0.548
	Yes	2 (33.3)	2 (50.0)	4 (40.0)		
Obesity (Yes)	No	8 (88.9)	4 (80.0)	12 (85.7)	2.0 (0.098-41.003)	0.604
	Yes	1 (11.1)	1 (20.0)	2 (14.3)		
Smoking (Yes)	No	101 (78.9)	49 (76.6)	150 (78.1)	1.145 (0.559-2.347)	0.711
	Yes	27 (21.1)	15 (23.4)	42 (21.9)		
Drug abuse (Yes)	No	26 (66.7)	27 (77.1)	53 (71.6)	0.593 (0.211-1.664)	0.318
	Yes	13 (33.3)	8 (22.9)	21 (28.4)		
Pregnancy (Yes)	No	106 (79.7)	19 (95.0)	125 (81.7)	0.207 (0.026-1.613)	0.081
	Yes	27 (20.3)	1 (5.0)	28 (18.3)		

CVA, Cerebrovascular accident; CKD, Chronic kidney disease; RA, Rheumatoid arthritis.

Data are presented as the frequency of individuals (percentage). *: P<0.05; **: P<0.01; ***: P<0.001.

Table 5. Relationship between hospitalization and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms		P value
	No Median (IQR)	Yes Median (IQR)	
Any comorbidity (Yes)	5 (4)	4.5 (4)	<0.0001***
Hypertension (Yes)	5 (4)	4.5 (4)	<0.0001***
Heart diseases (Yes)	4.5 (4)	4.5 (3.84)	<0.0001***
Diabetes (Yes)	5 (4)	4.5 (4)	<0.0001***
Thyroid disease (Yes)	5 (4.5)	4.5 (4.3)	<0.0001***
Immunodeficiency disease (Yes)	5.27 (6)	5.33 (5)	0.513
Chemotherapy (Yes)	4.7 (4.8)	4.7 (4.8)	0.491
Asthma (Yes)	4 (4.4)	5 (3.8)	<0.0001***
Other lung diseases (Yes)	4.8 (5)	4.8 (5.1)	0.112
Neurological disease (Yes)	5 (3.2)	5 (5.6)	0.727
Alzheimer's (Yes)	4 (4.25)	5 (5.4)	0.044*
Parkinson's (Yes)	4 (4.75)	5 (-)	0.018 *
CVA (Yes)	5 (5.8)	4.67 (2)	<0.0001***

Table 5. Relationship between hospitalization and having gastrointestinal symptoms and comorbidities

Comorbidities	Any gastrointestinal symptoms		P value
	No Median (IQR)	Yes Median (IQR)	
CKD (Yes)	5 (4)	4.5 (4)	<0.0001***
Dialysis/End-stage renal disease (Yes)	4.1 (2.7)	4.8 (3.5)	0.413
Hematological disease (Yes)	5 (4.25)	4 (2)	<0.0001***
Cancer (Yes)	4.5 (4)	5.2 (3.75)	0.002**
RA (Yes)	5.5 (4)	6 (3.5)	<0.0001***
HIV/AIDS (Yes)	2.75 (9)	7.5 (9.75)	0.005**
Obesity (Yes)	4.67 (3.6)	7.5 (-)	0.011*
Smoking (Yes)	3.75 (4)	3.25 (3.5)	<0.0001***
Drug abuse (Yes)	4 (3.27)	4.33 (3.5)	0.045*
Pregnancy (Yes)	3 (3.5)	2 (4.3)	<0.0001***

CVA, Cerebrovascular accident; CKD, Chronic kidney disease; RA, Rheumatoid arthritis.

Data are presented as median (IQR). *: P<0.05; **: P<0.01; ***: P<0.001.

Table 6. Regression analysis for factors associated with the outcome of the studied patients with COVID-19

Variables	Mortality rate		ICU		Intubation		Length of hospital stay	
	Beta	P value	Beta	P value	Beta	P value	Beta	P value
Age	0.041	<0.0001***	0.017	<0.0001***	0.022	<0.0001***	0.020	<0.0001***
Sex	0.206	<0.0001***	0.071	0.097	0.128	0.029*	0.006	0.942
Moderately ill group (n=10928, 61.1%)	0.513	0.433	0.323	0.57	0.762	0.241	0.530	0.642
Severely ill group (n=6964, 38.9%)	0.205	<0.0001***	0.648	<0.0001***	1.02	<0.0001***	-0.216	0.006**
Abdominal pain	-0.033	0.876	0.09	0.602	0.352	0.128	-0.644	0.054
Nausea	0.191	0.194	-0.039	0.751	0.209	0.216	-0.072	0.732
Vomiting	0.064	0.675	0.116	0.36	-0.019	0.915	-0.028	0.897
Diarrhea	0.007	0.968	-0.037	0.796	-0.245	0.242	-0.001	0.996
Anorexia	-0.043	0.769	0.025	0.838	-0.165	0.331	0	0.999
Any gastrointestinal symptoms	-0.068	0.659	-0.226	0.077	-0.142	0.427	-0.259	0.239
Gastrointestinal bleeding	1	0.218	0.222	0.783	0.215	0.828	0.441	0.792
Cough	-0.164	0.002***	-0.167	<0.0001***	-0.118	0.049*	-0.199	0.013*
Fever	0.117	0.027*	0.002	0.964	0.071	0.23	-0.052	0.516
Myalgia	-0.226	<0.0001***	-0.086	0.067	-0.142	0.028*	-0.422	<0.0001***
Chills	-0.624	0.01*	-0.221	0.223	-0.31	0.236	-0.452	0.166
Headache	-0.166	0.143	-0.077	0.388	-0.129	0.309	-0.359	0.021*
Sore throat	0.066	0.872	0.408	0.17	-0.038	0.934	0.352	0.546
Olfactory dysfunction	-0.017	0.945	-0.24	0.239	0.11	0.675	-0.251	0.437
Gustatory dysfunction	-0.606	0.019*	-0.462	0.024*	-0.321	0.217	-0.221	0.508
Rhinorrhea	-1.092	0.371	-1.384	0.207	-0.386	0.732	-1.837	0.179
Altered consciousness	2.384	<0.0001***	1.1	<0.0001***	2.444	<0.0001***	-0.129	0.477
Skin lesion/rush	0.513	0.433	0.323	0.57	0.762	0.241	0.530	0.642

Table 6. Regression analysis for factors associated with the outcome of the studied patients with COVID-19

Variables	Mortality rate		ICU		Intubation		Length of hospital stay	
	Beta	P value	Beta	P value	Beta	P value	Beta	P value
Dizziness	-0.395	0.023*	0.02	0.881	0.107	0.547	-0.407	0.082
Lassitude	-0.156	0.139	-0.077	0.383	-0.13	0.281	-0.384	0.021*
Oxygen saturation	1.64	<0.0001***	0.96	<0.0001***	1.575	<0.0001***	1.156	<0.0001***
Oxygen therapy	0.205	<0.0001***	0.648	<0.0001***	1.02	<0.0001***	-0.216	0.006**
CT abnormal	-0.096	0.683	-0.329	0.083	0.244	0.341	-1.705	<0.0001***
Any comorbidity	0.09	0.323	0.251	0.001***	0.135	0.181	-0.161	0.277
Hypertension	-0.024	0.755	-0.03	0.64	-0.04	0.637	-0.062	0.622
Heart diseases	0.195	0.012*	0.317	<0.0001***	0.065	0.462	-0.360	0.007**
Diabetes	0.106	0.167	0.049	0.446	0.087	0.314	-0.020	0.880
Thyroid disease	-0.16	0.679	0.331	0.237	-0.29	0.529	0.881	0.126
Immunodeficiency disease	1.225	0.006**	0.862	0.021*	1.101	0.03*	2.139	0.007**
Chemotherapy (Yes)	-0.137	0.772	0.042	0.919	0.117	0.814	-1.176	0.177
Asthma	-0.178	0.346	-0.264	0.086	0.159	0.421	0.240	0.388
Other lung diseases	0.415	0.039	0.362	0.034	0.741	<0.0001***	-0.118	0.741
Neurological disease	-0.307	0.169	0.208	0.249	0.034	0.886	0.015	0.967
Alzheimer's	-0.593	0.338	-1.372	0.025*	-0.3	0.644	-0.523	0.620
Parkinson's	2.002	0.008**	0.566	0.429	0.986	0.299	-0.833	0.559
CVA	0.362	0.187	0.353	0.158	0.017	0.958	0.577	0.288
Chronic kidney disease	0.825	<0.0001***	0.237	0.123	0.717	<0.0001***	0.621	0.048*
Dialysis/End-stage renal disease	0.14	0.585	0.048*	0.836	0.192	0.486	-0.618	0.193
Hematological disease	0.349	0.225	0.337	0.16	0.024	0.944	0.143	0.770
Cancer	1.105	<0.0001***	0.565	0.002**	0.853	<0.0001***	0.587	0.114
RA	0.631	0.097	0.313	0.346	0.238	0.616	0.446	0.502
HIV/AIDS	0.745	0.409	0.054	0.941	-0.287	0.744	2.228	0.155
Obesity	1.407	0.071	0.498	0.463	0.071	0.941	-0.697	0.610
Smoking	-0.352	0.139	0.25	0.181	-0.239	0.352	-0.450	0.248
Drug abuse	0.886	0.008**	0.509	0.08	0.599	0.094	-1.414	0.023*
Pregnancy	0.193	0.71	-0.043	0.882	-0.064	0.893	-1.332	0.004*

CVA, Cerebrovascular accident; CKD, Chronic kidney disease; RA, Rheumatoid arthritis.

*: P<0.05; **: P<0.01; ***: P<0.001.

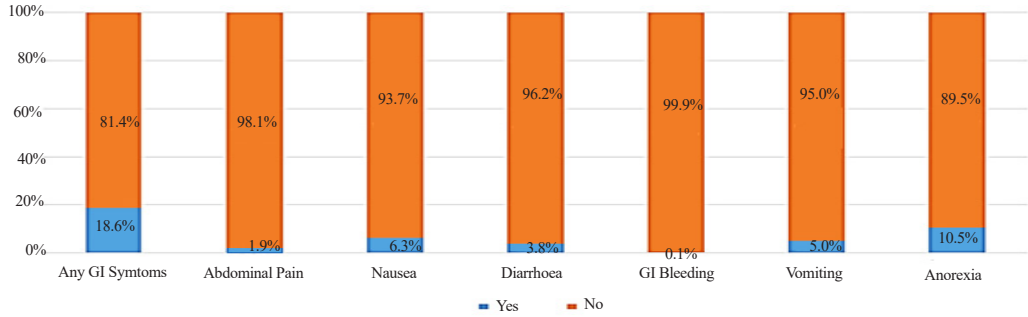

Figure1. Distribution of gastrointestinal symptoms among patients with COVID-19.
Data are presented as the frequency of individuals (percentage).

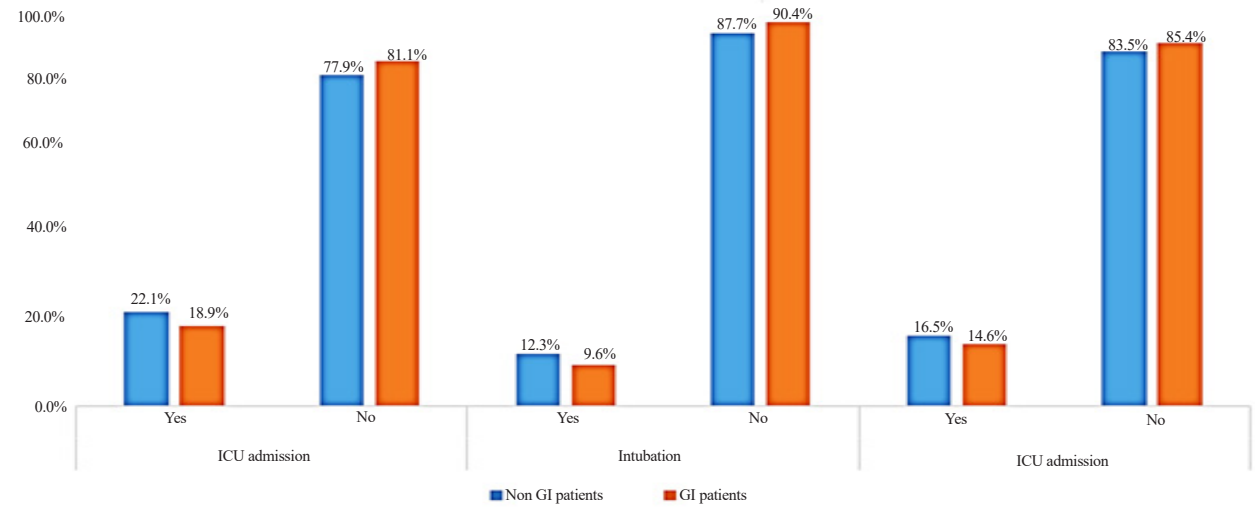

Figure 2. Comparison of ICU admission, intubation, and mortality between patients with COVID-19 with or without gastrointestinal symptoms. Data are presented as the frequency of individuals (percentage).

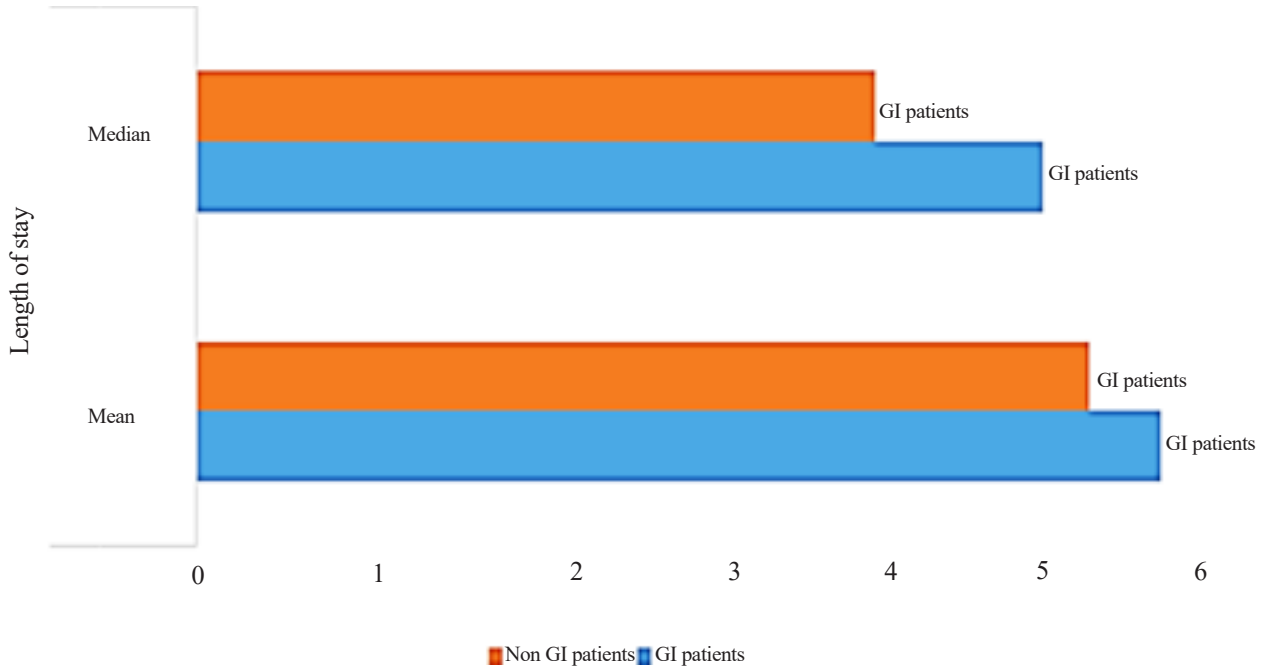

Figure 3. Comparison of hospitalization between patients with COVID-19 with or without gastrointestinal symptoms. Data are presented as median (IQR), mean±SD,

DISCUSSION

Contrary to what was previously assumed, it has been shown that SARS-CoV-2 may infect several organ systems. Although the association remains unclear due to contradictory research, GI problems have been associated with inferior outcomes in patients with COVID-19 (17-19). In this study, 18.6% of hospitalized patients with COVID-19 reported experiencing at least one GI symptom. Men were also more likely to be diagnosed with COVID-19 and to report GI issues. Anorexia (10.5%), nausea (6.3%), vomiting (5.0%), diarrhea (3.8%), abdominal pain (1.9%), and GI bleeding (0.1%) were the most prominent GI symptoms in that order. The prevalence of GI symptoms in our study was similar to that seen in previous studies (10,

20). Despite being excluded as a GI symptom in several previous reports, anorexia was considered the most relevant GI symptom in the present investigation (21). According to Lin and others and Mao and colleagues, nausea, diarrhea, and vomiting were also the most common GI symptoms (22, 23). In rare situations, GI symptoms, such as diarrhea, may be the sole presenting indication of COVID-19 (20, 24, 25). If these individuals are not promptly identified, the disease has the potential to rapidly spread.

In our research, diabetes and hypertension were the most prevalent comorbidities. In addition, some symptoms, such as cough, fever, myalgia, and headaches, may persist in both GI and non-GI patients. Overall, the results of some other studies corroborated similar conclusions (9, 20, 22, 26, 27).

In a U.S. study conducted by Ramachandran and others, the incidence of GI symptoms in patients with COVID-19 was 20.6%. (28). In their research, 48.4% of patients reported that diarrhea was their most frequent GI symptom. According to Cheung and others, 17.6% of the 4,243 infected people developed GI symptoms (5). According to other research, the incidence of GI complaints ranged from 2% to 50%. Abdominal pain and GI bleeding were evident in some patients, including patients with vomiting and those who were severely ill(29). Contradictory information exists about the incidence of GI symptoms in people with severe COVID-19. According to Fang and others, high GI symptoms are seen in both stable and severe patients, with prevalence rates of 85% and 79%, respectively (30). Consistent with this trend, a comprehensive analysis of 1,099 patients revealed no difference in the prevalence of GI symptoms between severe and non-severe COVID-19 cases (31). In contrast, recent research suggests that severely ill and hospitalized patients experience a significantly higher incidence of GI problems (11). According to a separate study by Dorrel et al., patients with severe COVID-19 had a high prevalence of GI symptoms (32). In our analysis, a distinct pattern emerged, with patients with non-severe COVID-19 exhibiting a higher prevalence of GI symptoms. However, no research has shown GI symptoms to be a predictor of mortality (30).

Our study found that individuals with GI symptoms, compared with those without GI manifestations, had a decreased rate of mortality. Our investigation showed that the overall death rate and GI mortality rate were 16.5 and 14.6, respectively. In addition, the GI symptoms of patients with COVID-19 did not significantly influence their likelihood of ICU admission, intubation, prolonged hospitalization, or death, except for comorbidities, such as CKD, hypertension, drug addiction, rheumatoid arthritis, dialysis, heart disease, or cancer. In keeping with the findings of numerous previous studies (21, 28, 30), our analysis revealed that patients with mild COVID-19 had a higher frequency of GI symptoms than those with severe disease. In contrast, according to studies by Tian and others, patients with GI problems often have a worse outcome than those without GI symptoms (34.3% discharged vs. 60% released) (6). In addition, Zheng and colleagues found that the rate of clinical deterioration was much higher in the GI group than in the non-GI group (33).

On the other hand, Nobel and others, as well as Ferm and colleagues, showed a greater incidence of GI symptoms in individuals with mild COVID-19 compared with those with severe illness. They observed no correlation between GI symptoms and higher rates of ICU admission, intubation, prolonged hospitalization, and death. Our research aligns with these studies (34, 35). According to our research, the GI symptoms of patients with COVID-19 were not associated with adverse outcomes, such as increased mortality, longer hospital stays, more mechanical intubations, or ICU admission. It seems that GI symptoms may be a bystander in patients with COVID-19.

Limitations

The lack of a validated symptom questionnaire survey is one of the study's limitations. Regrettably, due to the substantial number of patients with COVID-19 during the study period and the incomplete nature of the information provided in the patients' questionnaire survey data, it was not feasible to thoroughly examine the potential side effects of drugs in relation to the occurrence of symptoms. One additional limitation was the difference between the studied groups at the time of admission to the hospital, which may have interfered with the GI manifestations of the different studied groups.

CONCLUSION

In Southern Iran, 18.6% of hospitalized patients who tested positive for COVID-19 had stomach pain, loss of appetite, nausea, vomiting, GI bleeding, or diarrhea. Having GI symptoms at the time of presentation seemed to be associated with a reduced mortality rate, a shorter hospital stay, a lower requirement for mechanical ventilation, and a lower risk of ICU admissions. However, it also appeared to be a strong predictor of prognosis. Regarding GI issues, both local and large-scale prior research has shown substantial variation in terms of findings. Our thorough retrospective study, which included a multivariable analysis with full covariate adjustments, makes a significant contribution to the existing body of research on COVID-19.

Footnotes

ACKNOWLEDGMENTS

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AUTHORS' CONTRIBUTIONS

Abbas Sheikh Taheri and Zahra Shokati Eshkiki conceived and designed the study. Ebtesam Savari, Farid Yousefi, Fatemeh Ahmadi, Arman Shahriari, Atefeh Roumi, Seyed Mohammad Alavi, and Zia Azizi participated in clinical follow-ups of the patients. Javad Zarei, Niloofar Neisi, Seyyed Saeed Azandeh, Zahra Shokati Eshkiki, and Seyed Ali Mard analyzed and interpreted the data. Ali Akbar Shayesteh, as the corresponding author, managed the study. All authors approved the final version.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare related to this work.

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ETHICAL STATEMENTS

All methods were conducted in accordance with relevant guidelines and regulations. The study was reviewed and approved by Ahvaz-Jundishapur University of Medical Sciences (IR.AJUMS.REC.1399.324). Since the current investigation was a retrospective study, written informed consent to participate was waived by the Ahvaz Jundishapur University of Medical Sciences ethics committee.

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