Original paper

Association between gastrointestinal symptoms and disease severity in patients with COVID-19 in Tehran City, Iran

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Abstract

Introduction: It is important to identify the relationship between COVID-19 and gastrointestinal symptoms for health organizations in different communities.

Aim: To assess the relationship between gastrointestinal symptoms and COVID-19.

Material and methods: It was a cross-sectional descriptive-analytical study that was conducted on 381 patients those where admitted to Imam Hossein Hospital with a confirmed diagnosis of COVID-19 on nasopharyngeal polymerase chain reaction testing for SARS-CoV-2 from first March to end of June in Tehran city; 2020. Data was entered and analyzed by using SPSS version 22 and level of significant was consider less than 0.05.

Results: Out of all the patients with COVID-19, 164 (43%) had gastrointestinal symptoms. The most symptoms of them were nausea (19.2%), vomiting (17.2%), abdominal pain (15.7%), diarrhoea (12.6%), haematomas (1%), melena (1.6%), rectal bleeding (1.6%), and constipation (1.8%), respectively. The mean D-dimer1 value was significantly different between the 2 groups with gastrointestinal symptoms and no gastrointestinal symptoms. In other words, there is a strong relationship between the variable D-dimer1, which is one of the important symptoms showing the severity of COVID-19 disease, and gastrointestinal symptoms ($p < 0.0001$).

Conclusions: Our finding shows a statistical relationship between the level of D-dimer and gastrointestinal symptoms in patients with COVID-19. The mortality rate was higher in patients with gastrointestinal symptoms, which is an important outcome for gastroenterologists.

Introduction

A novel coronavirus has spread throughout China, originating from the city of Wuhan, and has caused many deaths so far [1]. It is a highly contagious virus that has spread rapidly and efficiently. Coronavirus disease 2019 (COVID-19) is caused by a virus (SARS-CoV-2) from the same family as the lethal coronaviruses that caused severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV). COVID-19 is a relatively large virus (120 nm) and is enveloped, containing a positive-sense single-stranded RNA [2]. The virus is transmitted through direct contact with the infected person's respiratory droplets (coughing and sneezing), as well as contact with infected surfaces. The COVID-19 virus can survive for days on surfaces, but a simple disinfectant can eliminate this [3]. COVID-19 signs and symptoms include fever, cough, and

shortness of breath. In more severe cases, infection can lead to pneumonia, serious respiratory problems, and, ultimately, fatalities. Thousands of people have been reported to have been infected with the virus so far [4]. Respiratory symptoms are the main symptoms, but gastrointestinal symptoms such as diarrhoea, nausea, and vomiting are also among the primary symptoms [5, 6].

The virus is excreted in the faeces, which is a sign of gastrointestinal involvement. The most common gastrointestinal symptoms are; anorexia, diarrhoea, nausea, and vomiting. A stool exam may still be positive after the breath sample is negative [7]. Patients with gastrointestinal symptoms may not have typical coronary symptoms [8].

Occurrence of GI symptoms is due to the intestinal tropism of COVID-19 [9]. Moreover, GI symptoms can coexist or even precede respiratory manifestations [10]. Rarely, COVID-19 patients can present with only GI symptoms, without respiratory symptoms [11].

The relationship between many gastrointestinal, clinical, and laboratory parameters and disease severity in different communities is not yet fully known. Examining more parameters can help improve the accuracy of anticipation and prognosis of the disease. On the other hand, patients with critical conditions should be hospitalized in the intensive care unit, while mild patients can be kept and treated separately. Also, due to the widespread outbreak of this virus and the high number of patients, it is necessary to identify the determinant indicators of patients who are the highest risk group for the severity of the disease [12].

After the outbreak of COVID-19 disease in different countries of the world, many studies have been conducted abroad on the subject of the gastrointestinal tract [13–15], but no study has been done on this case inside the country.

Aim

Therefore, the aim of this study was to assess the relationship between gastrointestinal symptoms and disease severity in patients with COVID-19.

Material and methods

This was a cross-sectional descriptive-analytical study that was conducted on 381 patients who were admitted to Imam Hossein Hospital with a confirmed diagnosis of COVID-19 on nasopharyngeal polymerase chain reaction testing for SARS-CoV-2 from 1 March to the end of June 2020 in Tehran city.

Exclusion criteria

Patients were excluded if they were younger than 18 years, were not hospitalized and managed on an ambulatory basis, were pregnant, or for whom results of SARS-CoV-2 nasopharyngeal testing were unavailable.

Study tool

A checklist was made by researchers, which includes 5 sections: demographic information; general symptoms including asthma, cough, fever, chills, fatigue, loss sense of smell, etc.; gastrointestinal symptoms including nausea, vomiting, dark stools, constipation, diarrhoea, etc.; laboratory results; and the final consequences of survival or death. If a particular laboratory test was not performed at the time of admission, the first laboratory values within 24 h of the admission were used.

Ethical considerations

This study was supported by the Deputy of Research in Shahid Beheshti University of Medical Sciences with reference No. IR.SBMU.RETECH.REC.1399.090, and all subjects gave informed consent before participation in this study.

Statistical analysis

Statistical analysis was performed by using SPSS software version 22 (SPSS Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution in 2 groups: with gastrointestinal symptoms and without gastrointestinal symptoms. Descriptive summary statistics are presented as means and SD for continuous variables and frequencies with percentages for categorical variables. Categorical and continuous variables were tested for statistical significance using χ^2 tests and *t*-tests, respectively. For continuous variables that were not normally distributed, we utilized the nonparametric test such as the Mann-Whitney *U* test to compare the groups. The significance level was considered at less than 0.05.

Results

Outbreak rate of gastrointestinal symptoms in COVID-19 patients

A total of 381 patients were hospitalized with confirmed COVID-19 during the study period. Female and male patients comprised 147 (38.6%) and 234 (61.4%), respectively.

The mean age was 62.6 ±17.1 years. Of these, 164 (43%) patients had gastrointestinal symptoms, and 217 (57%) did not.

The most common gastrointestinal symptoms in COVID-19 patients were nausea, vomiting, abdominal pain, and diarrhoea. 19.2% of patients had nausea, and this gastrointestinal symptom was more common in

Table I. Frequency of gastrointestinal symptoms

Gastrointestinal symptoms	Frequency (%)
Hematemesis:	
No	377 (99)
Yes	4 (1)
Melena:	
No	375 (98.4)
Yes	6 (1.6)
Rectorrhagia:	
No	375 (98.4)
Yes	6 (1.6)
Nausea:	
No	308 (80.8)
Yes	73 (19.2)
Vomiting:	
No	315 (82.7)
Yes	66 (17.3)
Constipation:	
No	374 (98.2)
Yes	7 (1.8)
Diarrhoea:	
No	333 (87.4)
Yes	48 (12.6)
Abdominal sonography:	
No	321 (84.3)
Yes	60 (15.7)

women than men (male and female 15.4% and 25.2%, respectively). Also 17.2% of patients had vomiting, and this symptom was observed much more in women than in men. 15.7% of patients had abdominal pain, which was also much more common in women than in men. Diarrhoea occurred in 13.7% of male and 10.9% of females.

Four patients had haematemesis (1%), and melena was found in 6 (1.6%) patients. Other features of the sample under review are listed in Table I.

There was no statistical difference between the 2 groups in values of laboratory data such as mean haemoglobin, white blood cells (WBC), lymphocyte, and platelet counts. The mean ferritin level was lower in the cases than in the controls but did not reach statistical significance (777 vs. 951 ng/ml, $p = 0.61$). Mean C-reactive protein (CRP), creatinine, and lactic acid levels were higher but not statistically significant in both groups, as noted in.

For the whole group of subjects, the mean levels of laboratory data at the time of admission were as follows: WBC 12.1; creatinine (Cr) 2.12; urea 53.7; aspartate aminotransferease (AST) 61.9; alkaline phosphatase (ALP) 216.4; mean lactate dyhydrogenase (LDH) 630.6; mean D-dimer 2247.1; CRP 56.3, and international normalized ratio (INR) 1.31. The means of these variables in the gender groups of men and women as well as in the groups with gastrointestinal symptoms and no symptoms are given in Table II.

Relationship between age, gender, and body mass index (BMI) of people with and without gastrointestinal symptoms

The 2-sample independent *t*-test was used to evaluate the relationship between age of COVID-19 patients and gastrointestinal symptoms.

Table II. Mean laboratory data levels at the time of admission

Variable	Male	Female	*P*-value	COVID-19 patient with gastrointestinal symptoms (mean)	COVID-19 patient without gastrointestinal symptoms (mean)	*P*-value
White blood cell	14.81	8.0095	0.36	9.0659	14.544	0.46
Creatinine	2.1762	2.0317	0.754	2.7337	1.657	0.03
Urea	56.756	49.037	0.142	62.596	45.543	0.001
Aspartate transaminase	72.108	45.087	0.074	80.94	47.025	0.102
Alkalosis	211.76	224.41	0.553	240.98	197.18	0.047
Lactic dehydrogenase	662.48	575.99	0.401	669.58	594.47	0.46
D-dimer	2405.8	1991.9	0.560	3651.4	933.46	< 0.0001
Cyclic receptor protein	60.81	49.25	0.053	50.932	60.422	0.103
International normalized ratio	1.2476	1.4084	0.466	1.275	1.3398	0.765

The mean age of patients in the 2 groups was not statistically significant (p = 0.317). The χ^2 test was used to examine the relationship between gender and gastrointestinal symptoms in patients with COVID-19, showing that there was statistically significant between gender and gastrointestinal symptoms (p < 0.0001). Also, there was no statistically significant difference between the BMI of patients and gastrointestinal symptoms (p =0.35) (Table III).

Relationship between age and BMI and length of hospital stay with outcome (death or improved)

In the group of improved patients, the mean age was 60.2 years, with a standard deviation of 16.8 years and with an age range of 20 to 94 years.

In the death group, the mean age was 72.9 years with a standard deviation of 14.7 years with an age range of 41 to 100 years. There was a statistically significant difference between the 2 groups in terms of age (p < 0.001).

The mean body mass index was 28.4 ±12.2 in the improved group and 26.84 ±8.7 in the deceased group, which was not statistically significant between the 2 groups (p > 0.05). The mean number of hospitalization days in the hospital in the recovered patient group was 6.76 days and in the deceased group it was 7.06 days. In other words, the length of stay of the deceased patients was 0.3 days longer than the improved patients, but this difference was not statistically significant (p = 0.493 > 0.05) (Table IV).

Relationship between gastrointestinal symptoms and severity of COVID-19 disease

The 2-sample independent t-test was used to investigate the relationship between the variables of severity of COVID-19 disease and gastrointestinal symptoms. The severity of COVID-19 disease was assessed in 2 groups: patients with gastrointestinal symptoms and patients without gastrointestinal symptoms. The results are shown in Table V.

According to the 2-sample independent t-test, only the mean D-dimer1 level was significantly different between the 2 groups (with gastrointestinal symptoms and without gastrointestinal symptoms). In other words, there is a strong relationship between the D-dimer1 variable, which is one of the important symptoms showing the severity of COVID-19 disease, and gastrointestinal symptoms (p < 0.0001). As can be observed in Table V, the mean D-dimer1 value is 3651 in the group with no gastrointestinal symptoms and 933 in the group without gastrointestinal symptoms, which indicates a significant difference between the 2 groups, but other severity of COVID-19 disease.

According to the above table, among LDH, erythrocyte sedimentation rate (ESR), D-dimer and O_2PulseOximeter variables, D-Dimer variable had a significant difference between the two groups of patients with gastrointestinal symptoms and without gastrointestinal symptoms. The means of ESR, CRP, dimer, LDH, and O_2PulseOximeter are also seen in the 2 groups in Table V.

Table III. Relationship between age, gender, and BMI of people with and without gastrointestinal symptoms

Characteristics	COVID-19 patients with gastrointestinal symptoms	COVID-19 patients without gastrointestinal symptoms	*P*-value
Age, mean (SD)	63.66 (17.195)	61.88 (17.123)	0.31
BMI, mean (SD)	29.98 (16.47)	27.5 (6.39)	0.35
Female gender, *n* (%)	78 (47.6)	69 (31.8)	< 0.0001

Table IV. Relationship between age, BMI, and length of hospital stay with outcome

Variable	Outcome	Frequency	Mean	Standard deviation	*P*-value
Age	Improved	307	60.19	16.8	< 0.001
	Death	74	72.86	14.74	
BMI	Improved	239	28.35	12.21	0.207
	Death	43	26.84	8.7	
Duration of hospital stay	improved	307	6.76	5.32	0.493
	death	74	7.06	6.89	

Table V. Relationship between gastrointestinal symptoms and severity of COVID-19 disease

Variable	Groups	Frequency	Mean	SD	*P*-value
Cyclic receptor protein	Gastrointestinal symptoms	157	50.93	52.80	0.107
	No gastrointestinal symptoms	204	60.42	57.17	
ESR	Gastrointestinal symptoms	126	45.45	26.74	0.551
	No gastrointestinal symptoms	145	47.35	25.46	
Lactic dehydrogenase	Gastrointestinal symptoms	93	669.58	950.16	0.45
	No gastrointestinal symptoms	100	594.47	275.80	
D-dimer	Gastrointestinal symptoms	29	3651.44	3030.50	< 0.0001
	No gastrointestinal symptoms	31	933.46	1219.79	
O_2 pulse oximeter	Gastrointestinal symptoms	114	89.82	2.46	0.559
	No gastrointestinal symptoms	168	89.24	2.32	

Table VI. Relationship between severity of COVID-19 disease and gastrointestinal symptoms according to qualitative variables

Variable	With gastrointestinal symptoms *n* (%)	Without gastrointestinal symptoms *n* (%)	Total	*P*-value
Outcome:				0.41
Improved	307 (80.6)	178 (82)	129 (78.7)	
Death	74 (19.4)	39 (18)	35 (21.3)	
Unilateral lung involvement:				0.526
Yes	42 (11)	22 (10.1)	20 (12.2)	
No	339 (89)	195 (89.9)	144 (87.8)	
Bilateral lung involvement:				0.589
Yes	294 (87.5)	167 (88.4)	127 (86.4)	
No	42 (12.5)	22 (11.6)	20 (13.6)	

The χ^2 test was used to evaluate the relationship between mortality frequency and pulmonary involvement rate with or without gastrointestinal symptoms. One of the most important symptoms in diagnosing the severity of COVID-19 disease is the frequency of death in the groups.

In the study of pulmonary involvement rate in patients, no statistically significant relationship was observed between the severity of COVID-19 disease and the rate of pulmonary involvement in these patients (p = 0.589) (Table VI).

Discussion

In this study, we found that 164 (43%) of the patients hospitalized with COVID-19 presented with at least one gastrointestinal (GI) symptom such as diarrhoea, nausea, vomiting, or abdominal pain. Nausea was the most common GI symptom, followed by vomiting, abdominal pain, and diarrhoea. There were no significant differences in terms of patient demographics between patients with and without GI symptoms, but there were significant differences between some laboratory data such as creatinine, urea and D-dimer between patients with and without GI symptoms. Furthermore, there was no association between severity of COVID-19 disease and gastrointestinal symptoms.

Our study shows that the prevalence of GI symptoms in COVID-19 patients is 43%, which is lower than the prevalence of GI symptoms reported by other studies in the USA and China in the range of 50.5–61.3% [9, 16]. The higher reported rate of GI symptoms in those studies could probably be due to the inclusion of

anorexia as one of the GI symptoms. Anorexia is a non-specific symptom that could be related to an overall infectious or inflammatory process and hence was not included as a specific GI symptom in our study. In a US study by Redd *et al.* [17], the prevalence of GI symptoms in COVID-19 patients was reported to be as high as 61.3%. In that study, anorexia was reported in 34.8% of cases, diarrhoea in 33.7%, and nausea in 26.4%. In a study by Guan *et al.* [9] from Wuhan, China, even though about 50% reported having GI symptoms, the majority of these patients had anorexia (78.6%). When anorexia was excluded from the analysis, only 18.6% had specific GI symptoms. A trend of increasing recognition of GI manifestations among COVID-19 patients has been noted since its outbreak in Wuhan, China. During the original outbreak in Wuhan, diarrhoea was reported in only 3% of the cases [18]. This number increased to 10% in a subsequent study from Wuhan and 25% in a study from Singapore [3, 19]. As awareness is increasing among health-care workers about the GI manifestations in COVID-19 patients, the reports of the presence of GI symptoms are increasing in the studies. In our study, there was no association between the GI symptoms and outcomes in COVID-19 patients. Previous studies have reported conflicting findings concerning the presence of GI symptoms and poor outcomes. In the study by Guan *et al.* [9] from Wuhan, China, patients with digestive symptoms had longer LOS (9 vs. 7.3 days, $p = 0.013$). Furthermore, this study noted that as the severity and duration of COVID-19 increase, GI symptoms increase as well. In a multicentre study of 191 patients by Zhou *et al.* [20], the presence of GI symptoms was associated with elevated CRP (7.3 vs. 3.8 mg/l, $p = 0.021$), elevated alanine aminotransferase (64.1 vs. 46.6 U/l, $p = 0.049$), and lower haemoglobin levels, when compared to patients without GI symptoms. However, in the study by Redd *et al.* [17] there were no differences in clinical outcomes in patients with or without GI symptoms. Also, they reported no significant differences in the leukocyte count, haemoglobin, platelets, coagulation, or liver tests in groups with or without GI symptoms. Although the specific mechanisms causing GI manifestations in COVID-19 are not entirely known, there are several proposed theories. Intestinal tropism has been noted with SARS-CoV-2, which could be due to its strong affinity to angiotensin-converting enzyme-2 receptors, and angiotensin-converting enzyme-2 receptors are highly expressed in the oesophagus and intestinal epithelial cells [21]. Hence, there is a strong possibility of direct small bowel involvement, resulting in direct cytopathic effects causing GI symptoms. Furthermore, Redd *et al.* [17] noted that loss of smell (anosmia) and loss of taste (ageusia) were commonly associated with nausea (adjusted OR = 2.71, 95% CI: 1.21–6.20; $p = 0.015$) and anorexia (adjusted OR = 3.70, 95% CI: 1.49–9.16; $p = 0.0048$) after controlling for potential confounders. While the exact cause of this association is unclear, it could be due to damage to olfactory and gustatory receptors during viral entry through nasal and oral routes [22]. Additionally, in a study from Hong Kong, patients with diarrhoea on presentation had higher rates of stool RNA positivity when compared to those without diarrhoea (38.5 vs. 8.7%, $p = 0.02$). This is suggestive of the direct effects of the SARS-CoV-2 on the GI tract [19]. Also, the viral infection can cause altered intestinal permeability, resulting in malabsorption [23]. Finally, the inflammatory response from a cytokine storm in severe COVID-19 patients can cause hypoxia-induced bowel ischaemia and contribute to diarrhoea. Gastrointestinal symptoms were associated with D-dimer1 rate in patients, but other variables such as CRP, ESR, LDH, pulse oximeter, and pulmonary involvement rate did not have a statistically significant relationship with having gastrointestinal symptoms. Despite the lack of a significant relationship between mortality due to COVID-19 disease and gastrointestinal symptoms, a significant difference in the frequency of mortality was observed between the 2 groups (with gastrointestinal symptoms and without symptoms).

Specific limitations to this study include the cross-sectional design, relatively single-centre hospital-based nature, and lack of validated symptom instruments. This could introduce selection bias and limit the reliability and generalizability of the results. We could not correlate the presence of SARS-CoV-2 RNA with GI symptoms because this test was not routinely performed in our institution.

The second limitation was related to the selection of patients who were hospitalized in the hospital and hence a high frequency of pulmonary involvement in the group of patients who did not have gastrointestinal symptoms. Therefore, the lack of a significant of relationship between pulmonary involvement and gastrointestinal symptoms with the severity of COVID-19 disease may be due to the fact that only patients with moderate to severe disease were referred to hospital. Therefore, it cannot be said with certainty that the rate of pulmonary involvement has no relationship with gastrointestinal symptoms.

Conclusions

GI symptoms are commonly encountered in hospitalized COVID-19 patients. In our study the most common gastrointestinal symptom was nausea. Gastrointestinal symptoms of nausea, vomiting, and abdominal pain were more common in women, and diarrhoea was

more common in men. Gastrointestinal symptoms had a statistically significant relationship with the rate of D-dimer1, and the mean value of D-dimer1 in patients with gastrointestinal symptoms was more than in patients without gastrointestinal symptoms. Also, the incidence of death in patients with gastrointestinal symptoms was more than in patients without gastrointestinal symptoms. Other variables indicating the severity of COVID-19 disease, such as pulmonary involvement rate, did not have significant relationship with gastrointestinal symptoms. The reason for this might be the acute diseases among people who are hospitalized.

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Conflict of interest

The authors declare no conflict of interest.

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