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Clinical Significance of Gastrointestinal Symptoms in Hospitalized Patients with COVID-19 Infection

Hastanede Yatan COVID-19 Enfeksiyonlu Hastalarda Gastrointestinal Semptomların Klinik Önemi

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Abstract

Aim: To determine the clinical significance of gastrointestinal (GI) symptoms in mild hospitalized patients with COVID-19 infection.

Material and Method: This study included adult patients who were hospitalized with a confirmed diagnosis of COVID-19 infection. The demographical features, symptoms, clinical presentations, medical history, medications and clinical progress and outcomes were noted using data collection form by the clinicians. The effect of GI symptoms on clinical outcomes in patients with mild COVID-19 infection was statistically evaluated.

Results: 307 patients were included to the study. 159 of patients (51.7%) had an at least one GI symptoms, 18.2% of those presented only GI symptoms while 21.2% only non-GI symptoms. 27% were asymptomatic at admission. The most common GI symptom was loss of appetite that presenting 16.9% patients. The second and third most common GI symptoms were diarrhea in 15% patients, nausea and loss of taste in 14% patients, respectively. There was no significant difference in laboratory parameters between GI and non-GI symptoms groups. When age, gender, smoking status, and comorbidities of patients with GI and non-GI symptoms groups were compared, there was no difference in mean age, gender, smokers, and comorbidities. In addition, the length of hospital stay (p=0.377), complete healing (p=0.372) and mortality (p=0.351) was similar in patients with GI and non-GI symptoms groups respectively.

Conclusion: Early diagnosis of COVID-19 infection presenting with GI symptoms can help prevent infection spread. The majority of these symptoms were mild, and their presence was not associated with worse clinical outcomes.

Keywords: COVID-19, gastrointestinal symptoms, loss of appetite, nausea, diarrhea

Öz

Amaç: Bu çalışmamızda hastanede yatan hafif COVID-19 enfeksiyonu olan hastalarda gastrointestinal (GI) semptomların klinik önemini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, doğrulanmış bir COVID-19 enfeksiyonu teşhisi ile hastaneye yatırılan yetişkin hastaları içermektedir. Demografik özellikler, semptomlar, klinik tablolar, tıbbi öykü, ilaçlar ve klinik ilerleme ve sonuçlar klinisyenler tarafından veri toplama formu kullanılarak not edildi. Hafif COVID-19 enfeksiyonu olan hastalarda GI semptomlarının klinik sonuçlara etkisi istatistiksel olarak değerlendirildi.

Bulgular: 307 hasta çalışmaya dahil edildi. Hastaların 159'unda (%51,7) en az bir GI semptomu vardı. Hastaların %18.2'si sadece GI semptomları, %21,2'si ise sadece GI dışı semptomlar gösterdi. Hastaların %27'si başvuru sırasında asemptomatikti. En sık görülen GI semptom hastaların %16.9'unda görülen iştahsızlıktı. En sık görülen ikinci ve üçüncü GI semptomları sırasıyla %15 hastada ishal, %14 hastada bulantı ve tat kaybıydı. GI ve GI olmayan semptom grupları arasında laboratuvar parametrelerinde anlamlı bir fark yoktu. GI ve GI olmayan semptom grupları olan hastaların yaş, cinsiyet, sigara içme durumu ve komorbiditeleri karşılaştırıldığında, ortalama yaş, cinsiyet, sigara içenler ve komorbiditeler açısından fark yoktu. Ayrıca hastanede kalış süresi (p=0,377), tam iyileşme (p=0,372) ve mortalite (p=0,351) GI ve GI olmayan semptom gruplarında sırasıyla benzerdi.

Sonuç: GI semptomlarıyla kendini gösteren COVID-19 enfeksiyonunun erken teşhisi, enfeksiyonun yayılmasını önlemeye yardımcı olabilir. Hastalarda saptanan GI semptomların çoğu hafif olup bunların varlığı daha kötü klinik sonuçlarla ilişkili saptanmamıştır.

Anahtar Kelimeler: COVID-19, gastrointestinal semptomlar, iştahsızlık, bulantı, diyare

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INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was firstly reported in Wuhan, China.[1] It swiftly spread over the world and was designated as a pandemic. According to the World Health Organization, there have been over 211 million confirmed cases of COVID-19 and more than 4.4 million deaths worldwide as of August 23, 2021.[2] Fever, cough, and shortness of breath are the most common symptoms, while one-third of patients are asymptomatic.[3] Besides these symptoms nausea, vomiting, diarrhea, lack of appetite, abdominal pain, swelling, loss of taste, and loss of smell are some of the gastrointestinal (GI) symptoms that might occur.[4] Intestinal injury and increased intestinal permeability cause GI symptoms, which trigger immune system activation. In addition, the angiotensin converting enzyme-2 receptor, which is found in the gastrointestinal tract at higher levels than in the respiratory system, was the anchor point for COVID-19 virus. However, its unclear if enteric infection progresses or leads to more serious respiratory and systemic disease.[5,6]

It is estimated in one of five COVID-19 patients have GI symptoms.[7] However, according to other research, GI symptoms occur in 50% of the patients who are impacted. Moreover, some cases have only GI symptoms as presenting symptoms.[4] There was no approved effective treatment of COVID-19 infection in the last 17 months. As a result, it is critical to take steps to avoid the spread of illnesses, such as maintaining a safe social distance, wearing gloves, and being vaccinated. Early detection of COVID-19 infection presenting with GI symptoms can also help to prevent the infection from spreading. Early stages of the disease, also known as the viral phase, are also connected with gastrointestinal illness, whereas the late stages of the illness develop more serious symptoms, such as respiratory issues.[8-11]

Because the studies involved patients with varied degrees of clinical severity (mild, moderate, and severe), it's unclear whether GI symptoms associated with COVID-19 infection are symptoms of the disease or symptoms related to a significant inflammatory response. In our study, only mild individuals with COVID-19 infection were assessed for the incidence of GI symptoms and the prognosis of these patients with GI symptoms.

MATERIAL AND METHOD

Study design

This study was conducted in patients referred to a pandemic hospital in Turkey for follow up and treatment of COVID-19 cases over a 3-month period (between March 23, 2020, and June 30, 2020).

Patients

Adult patients who were hospitalized with a confirmed diagnosis of COVID-19 according to local real-time PCR testing were considered eligible. Throat and nasal swab were taken from all the patients before hospitalization. SARS-CoV-2 PCR test negative patients were excluded, even though they have typical symptoms. Informed consent was obtained from all patients who participated in our study.

Management

All patients have been examined in terms of typical symptoms (fever, chilling, cough, shortness of breath etc.) and GI symptoms (nausea-vomiting, diarrhea, appetite, abdominal pain, swelling, loss of taste and smell) at admission by three gastroenterologists. Fever, blood pressure, pulse, and fingertip oxygen saturation were measured four times a day, or more if necessary. Blood sample was taken for complete blood count (CBC), biochemistry (included kidney functional tests, transaminases, bilirubin, LDH, C-reactive protein), ferritin, d-dimer, coagulation tests as soon as they were hospitalized. Chest X-ray and/or thoracic computerized tomography (CT) was taken. All patients were evaluated with their test results by an infectious diseases specialist, and medical therapy was started based on the recommendations of the COVID-19 Scientific Study Committee of the Turkish Republic Health Ministry. The scientific committee's guideline was first published in march 2020 and then revised in April 2020 and in June 2020. Hydroxychloroquine and azithromycin were given for five days if there were no contraindications (prolonged QRS and QTc). During the patients stay in the hospital, they were also given enoxaparin sodium. When bacterial superinfection was suspected, ceftriaxone, levofloxacin, or piperacillin-tazobactam were added after consulting with an infectious diseases specialist. Every day, all patients were visited and their symptoms, general well-being, and hemodynamic state were assessed. In two weeks, patients who were making good clinical progress were discharged. Before being released, all blood samples and X-ray chest graphy were repeated. Patients whose clinics deteriorated were sent to a higher level of care.

Definitions

Clinic deterioration was considered by the following criteria: Respiratory rate per minute >30/min, $SatO_2$<90% in room air and Lymphocyte count <800/ microliter or C-reactive protein >40 mg/L or ferritin >500 ng/ml or D-dimer >1000 ng/ml in the peripheral blood samples. Diffuse and bilateral pneumatic infiltration on chest X-ray and/or CT.

Mild disease was defined by the following criteria: Respiratory rate per minute < 12/min, $SatO_2$ >93% in room air and non diffuse or bilateral pneumatic infiltration on chest X-ray and/or CT.

For males, the upper limit of normal ALT (alanine aminotransferase) was set at 33 units/L, and for females, it was set at 25 units/L.[12] Loss of appetite was formerly thought to be a GI symptom, although it is a non-specific symptom of viral infection.

Data collection

The demographical features, clinical presentations, symptoms, medical history, medications and clinical progress and outcomes were noted using data collection form (supplement). Laboratory tests and radiologic imaging were collected using electronic medical records. All records were analyzed by the clinicians. Data collection form was manually filled to make certain of high accuracy by only three gastroenterologists.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.23 (SPSS, IBM, Chicago, IL, USA). Normality of distribution of the continuous variables was tested using Kolmogorov-Smirnov test. For regularly distributed variables, the results are provided as mean standard deviation, and for abnormally distributed variables, the median (interquartile range 25-75). For parametric continuous variables, the Student t test was employed, and for nonparametric continuous variables, the Mann-Whitney U test was utilized. Categorical variables were compared using the Chi-square test, the results of which are presented as percentages. A two tailed p value<0.05 was considered statistically significant.

Ethics

This study was complied with the ethical guidelines of the 1975 Helsinki Declaration that was then modified in 2008. The study protocol was approved by ethics committee.

RESULTS

307 patients were included in the study, 190 (61.8%) were men, mean age of whole study group was 42.3± 15.9. 124 (40%) patients were active smokers and 68 (22%) had at least one comorbidity. Three percent of patients had a preexisting gastrointestinal luminal disease. The most prevalent non-GI symptom was dry cough, which was reported by 92 (30%) patients. The second and third most common symptoms were fever in 83 (27%) patients and fatigue in 67 (21.8%) patients, respectively. 159 of patients (51.7%) had an at least one GI symptoms, 111 of those (36.1%) at admission and 48 (15.6%) of those during hospitalization. 56 (18.2%) presented only GI symptoms while 65 (21.2%) only non-GI symptoms. 83 (27%) were asymptomatic at admission. The most common GI symptom was loss of appetite that presenting 52 (16.9%) patients. The second and third most common GI symptoms were diarrhea in 46 (15%) patients, nausea and loss of taste in 43 (14%) patients, respectively. The median day between symptom onset to admission was 2.3 day±1.2-day. GI symptoms improved during hospitalization in 119 (74.8%) patients and persisted at discharge in 40 (25.2%) patients. 89 (29%) patients had elevated liver enzymes at admission. Mean length of hospital stay was 12.6±4.2 day. 20 (6.5%) patients were referred to a tertiary center or intensive care unit during hospitalization. 64 of those (%20.8) had a travel abroad history. Patients' demographics, symptoms, comorbidities and clinical outcomes were listed in **Table 1**.

Table 1. Demographic characteristics, comorbidities and clinical outcomes of patients with COVID-19 disease.

	n: 307 (%)
Mean Age (mean year±SD)	42.3 ±15.9
Gender (male)	190 (61.8%)
Smokers	124 (40%)
Comorbidities (at least one)	68 (22%)
Hypertension	24 (8%)
Diabetes	17 (6%)
Coronary artery disease	11 (4%)
Gastrointestinal luminal disease	10 (3%)
Chronic pulmonary disease	4 (1%)
Cerebrovascular disease	1 (0.3%)
Chronic kidney disease	1 (0.3%)
Symptoms (Non GI)	
Cough	92 (30%)
Fever	83 (27%)
Fatigue	67 (21.8%)
Myalgia	41 (13.4%)
Pharyngalgia	34 (11.1%)
Headache	33 (10.7%)
Dizziness	21 (6.8%)
Dyspnea	11 (3.6%)
Symptoms (GI)	
Anorexia(loss of appetite)	52 (16.9%)
Diarrhea	46 (15%)
Nausea	43 (14%)
Loss of taste	43 (14%)
Loss of smell	26 (8.5%)
Abdominal pain	13 (4.2%)
swelling	10 (3.3%)
Vomiting	9 (2.9%)
Heartburn/regurgitation	2 (0.7%)
Asymptomatics	83 (27%)
Patients with only GI symptoms	56 (18.2%)
Patients both GI and non-GI symptoms	103 (33.6%)
Patients with only non-GI symptoms	65 (21.2%)
Patients with GI symptoms	159 (51.7%)
At admission	111 (36.1%)
During hospitalisation	48 (15.6%)
Symptom onset to admission (median days ±SD)	2.3±1.2
Course of GI symptoms	
Improved during hospitalisation	119 (74.8%)
Persisted at discharged	40 (25.2%)
Liver Enzyme Abnormalities at admission	89 (29%)
Length of stay (mean day)	12.6±4.2
Referral to tertier center or ICU	20 (%6.5)

The physical examination, laboratory data, and CT results of individuals with GI and non-GI symptoms were compared. Patients presenting with non- GI symptoms had higher fever values at admission (36.7±0.4 vs. 37.0±0.7, p=0.002) than GI symptoms. While the fingertip oxygen saturations of both groups were similar at admission, there was no significant difference in laboratory parameters (white blood cell, lymphocyte, hemoglobin, platelet, urea, creatinine, AST, ALT, LDH, CRP, ferritin, d-dimer, procalcitonin) between GI and non-

GI symptoms groups (for all parameters p>0.05). Pulmonary involvement on computed tomography was similar between two groups (23 versus 36, p=0.286) (**Table 2**).

Table 2. Physical examination, Laboratory parameters and CT findings based on patients with GI symptoms or Gon-GI syptoms.

	GI Sympytoms n: 56	Non-GI Symptoms n: 65	P value
Fever (°C)	36.7±0.4	37.0±0.7	0.002
Fingertip oxygen saturation, SO_2, (%)	96.8±1.2	96.5±1.5	0.149
Wbc, count x103/mm³	6.6±2.0	6.2±2.4	0.342
Lymphocyte, count x103/mm³	1.9±0.6	1.7±0.6	0.101
Hemoglobin, gr/dl	14.2±1.6	14.2±1.8	0.807
Platelet count, x103/mm³	234.0±49.8	235.0±79.0	0.930
Urea, mg/dL	26.2±7.5	26.9±9.7	0.672
Creatinin, mg/dL	0.8±0.2	0.8±0.2	0.932
ALT, IU/L	20.0 (14.2-34.7)	25.0 (17.5-40.0)	0.051
AST, IU/L	22.0 (18.2-27.7)	23.0 (19.5-33.0)	0.099
LDH, IU	217.3±64.6	223.7±60.4	0.592
CRP, mg/dL	0.5 (0.1-1.1)	0.8 (0.3-1.8)	0.089
Ferritin, ng/ml	152.0 (94.7-259.7)	152.0 (79.0-219.0)	0.257
D-dimer, ng/ml	0.3 (0.1-0.6)	0.3 (0.1-0.5)	0.849
Procalcitonin, ng/ml	0.03 (0.02-0.07)	0.04 (0.02-0.06)	0.659
Lung involvement in CT (pneumonia), n (%)	23 (41)	36 (54)	0.286

Results are expressed as mean±SD or median (IQR) or frequency (%). GIS: Gastrointestinal system, WBC: White blood cell , AST: Aspartate aminotransferase, ALT: Alanin aminotransferase, LDH: , CRP: C-reactive protein., CT: computed tomography

When age, gender, smoking status, and comorbidities of patients with GI and non-GI symptoms groups were compared, there was no difference in mean age (38.3 15.3 vs. 41.0 16.3, p=0.540), gender (39 vs. 45, p=0.961), smokers (24 vs. 22, p=0.309), and comorbidities (9 vs. 11, p=0.900). In addition, the length of hospital stays (12.0 vs. 13.0, p=0.377), complete healing (55 vs. 61, p=0.372) and mortality (0 versus 1, p=0.351) was similar in patients with GI and non-GI symptoms groups respectively (**Table 3**).

Table 3. Clinical findings and outcomes of SARS-CoV-2 infection with GI and without GI symptoms.

	GI symptoms n: 56	Non GI symptoms n: 65	P value
Age, years	38.3 ± 15.3	41.0 ± 16.3	0.540
Gender (Male), n (%)	39 (70)	45 (69)	0.961
Smoking, n (%)	24 (43)	22 (34)	0.309
Comorbidity, n (%)	9 (16)	11 (17)	0.900
Outcomes			
Length of stay, days	12.0 (11.0-14.0)	13.0 (12.0-14.0)	0.377
Complete healing	55 (98)	61 (94)	0.372
Referral to tertier center or ICU	1 (2)	4 (6)	0.372
Mortality, n (%)	0 (0)	1 (2)	0.351

Results are expressed as mean ± SD or median (IQR) or frequency (%). SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, GI: Gastrointestinal.

DISCUSSION

In this prospective study, 44.6% of patients with COVID-19 had at least one gastrointestinal symptom. While this rate was as low as 15% in the first studies on COVID-19, however, our results were consisted with more recent studies.[13,14] 30.3% of patients had GI symptoms at admission and 14.3% of patients developed GI symptoms during hospitalization. GI symptoms developing during hospitalization may be associated with GI side effects of medications such as hydroxychloroquine and azithromycin.[15] The majority of gastrointestinal symptoms were mild level.

In this study, most common GI symptom was loss of appetite (16.9%) and was similar to recent studies (16). Also, diarrhea (15%), nausea (14%), and loss of taste (14%), respectively, were the most prevalent second and third GI symptoms, with a higher incidence than some previous research.[14-17] While 27.4% of the patients were asymptomatic in our study, it was found as high as 51% in some studies.[18] GI symptoms are frequently underreported, and patients are mistakenly labeled as asymptomatic. According to certain studies, the prevalence of GI symptoms is reduced in this scenario.[19] At the beginning of the COVID-19 pandemic in our country, all patients with COVID-19 were hospitalized and followed up. In this study, consideration of GI symptoms (by using collecting data form) and prospective study design may have provided more consistent estimation rates of GI symptoms. Additionally, the symptoms of the patients were observed daily and thus the presence of symptoms was revealed with high accuracy.

GI symptoms may occur in the course of infectious diseases. This is more prominent in severe disease. One of the advantages of our study is that we detected the presence of GI symptoms in patients with non-severe COVID-19. The presence of GI symptoms in mild disease may increase the likelihood of being a characteristic symptom of COVID-19 infection rather than symptoms secondary to a severe inflammatory response.

The presence of GI symptoms at admission or during hospitalization was not associated with disease progression or transfer to the internal care unit, similar to previous studies.[13,14]

The limitations of our study are that we cannot distinguish whether patients with elevated transaminase levels are associated with underlying liver disease or, medication, or COVID-19 disease. Another limitation of the study was the low mortality rate since the majority of the patients had a mild course, and we could not evaluate the relationship between GI symptoms and mortality.

CONCLUSION

Gastrointestinal symptoms and liver test abnormalities are common among patients with COVID-19 disease, and early diagnosis of SARS-CoV-2 infection presenting with GI symptoms can help prevent infection spread. However, the majority of these symptoms were mild, and their presence was not associated with worse clinical outcomes.

Main Points

- Gastrointestinal symptoms and liver test abnormalities are common among patients with COVID-19 disease.
- Early diagnosis of SARS-CoV-2 infection presenting with GI symptoms can help prevent infection spread.
- The presence of GI symptoms at admission or during hospitalization was not associated with disease progression or transfer to the internal care unit.
- The presence of GI symptoms in mild disease may increase the likelihood of being a characteristic symptom of COVID-19 infection rather than symptoms secondary to a severe inflammatory response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by Ankara City Hospital ethics committee (Approval No: E1/785/2020).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: The author declare that he has all participated in the design, execution, and analysis of the paper, and that he has approved the final version.

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