

Evaluation of Diarrhea in Patients with COVID-19

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Keywords

Coronavirus 2019 · Diarrhea · Symptom assessment

Abstract

Background/Aims: The COVID-19 disease, which was declared epidemic by the WHO, is a global emergency public health problem. Patients with extrapulmonary symptoms are the group of patients who should be considered for person-to-person transmission in the community. In our study, it was aimed to investigate the characteristics of patients with COVID-19-related diarrhea symptoms. **Materials and Methods:** The study was conducted retrospectively in COVID-19 rtRT-PCR-positive patients in 5 medical centers. Three or more loose/liquid stools per day or increased number of defecations compared to normal defecation were defined as diarrhea. The patients were analyzed in 2 groups as those with and without diarrhea. **Results:** One thousand eighty-six patients were included in the study. Seventy-eight (7.2%) of the patients had diarrhea. Diarrhea was watery in 54 (69.2%) patients while with blood and mucus in 18 (23.1%) patients. Diarrhea continued for an average of 5.2 ± 1.6 (2–11) days. The clinical and laboratory findings of patients with diarrhea were more serious than those without diarrhea. Diarrhea is more common in the elderly and people with comorbid dis-

ease, and patients with diarrhea had higher CMI score and CRP and higher complaints of fever, cough, shortness of breath, myalgia, and fatigue. **Conclusions:** The presence of diarrhea should indicate a suspected COVID-19 infection and suggest testing for early diagnosis of the disease. It should be kept in mind that the course of the disease may be more severe in these patients, and precautions should also be taken in terms of fecal transmission during discharge.

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Background

The coronavirus 2019 (COVID-19) pandemic is a global emergency public health problem. Human-to-human transmission can be through droplets and contaminated hands or surfaces. COVID-19, with main symptoms of fever, cough, and dyspnea, manifests itself with severe respiratory clinical findings such as pneumonia, pulmonary edema, and acute respiratory distress syndrome and causes also diarrhea [1]. Although the incidence of diarrhea is not as high as fever and cough, it may be included in the first signs of COVID-19. Although initially found in a small percentage of cases, an increasing number of patients present with the complaint of diarrhea [2, 3]. Cli-

nicians may miss cases initially presenting with extrapulmonary symptoms only if they follow respiratory symptoms to create case definitions for COVID-19. The patient, who could not be diagnosed until respiratory symptoms appear, may also continue his/her life as an infectious in the community. The uncertainty of how long COVID-19 persists in patients' feces leads to the unknown duration of the potential contamination of the stools of the patients discharged. Therefore, it should be kept in mind that COVID-19 patients with diarrhea can cause significant public health problems. We aimed in our study to reveal the epidemiology of COVID-19-related diarrhea, clinical symptoms, and laboratory findings, to determine the management of patients, and to analyze the literature.

Materials and Methods

The study was conducted retrospectively in patients with COVID-19 diagnosed in 5 medical centers in Turkey from 17 March to May 31, 2020. rtRT-PCR-positive patients were included in the study. The demographical data (age and gender) of the patients, their comorbid diseases, Charlson Comorbidity Index (CMI), clinical symptoms (fever, cough, phlegm, dyspnea, sore throat, odor-taste disorder, myalgia, fatigue, nausea, vomiting, diarrhea, and headache), number, amount and duration of diarrhea, any content of blood and mucus, laboratory tests results, and mortality data were reviewed and recorded in the study forms. Three or more loose/liquid stools per day or increased number of defecations compared to normal defecation were defined as diarrhea. The patients were analyzed in 2 groups as those with and without diarrhea.

Statistical Analysis

Descriptive statistical analysis was performed for all variables investigated in the study. The compatibility of the data obtained by the measurement with the normal distribution was ensured by the Kolmogorov-Smirnov test. Student's *t* test was used for data compatible with normal distribution while the Mann-Whitney U test was used for data not compatible with normal distribution. The χ^2 test was used for the analysis of categorical variables. The data obtained by measurement were expressed as mean \pm standard deviation. The data obtained by counting were expressed as number (%). Correlation analysis was performed using Pearson's correlation test or Spearman's correlation test. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the ROC curve, sensitivity, specificity, and negative predictive value and positive predictive value of statistically significant variables. $p < 0.05$ was considered statistically significant.

Results

One thousand eighty-six rtRT-PCR-positive patients whose diarrhea complaints were questioned in 5 medical centers were included in the study. Seventy-eight (7.2%)

of the patients had diarrhea. Diarrhea was the first symptom in 3 of the patients. They were complaining of defecation with usually high volume 3–12 times per day. Diarrhea was watery in 54 (69.2%) patients while with blood and mucus in 18 (23.1%) patients. Diarrhea continued for an average of 5.2 ± 1.6 (2–11) days. Elderly patients complained of more diarrhea ($p = 0.044$). CMI was higher in patients with diarrhea ($p = 0.033$). The presence of hypertension and cardiac disease was more common in patients with diarrhea ($p = 0.002$; $p = 0.019$). The complaints of fever, cough, dyspnea, myalgia, fatigue, and nausea-vomiting were more common in patients with diarrhea ($p < 0.05$). CRP was also high in patients with diarrhea ($p = 0.037$). There was no significant difference between the 2 groups in terms of discharge time and mortality. Demographic, clinical, and laboratory findings of the patients are shown in Table 1.

In patients, there was positive correlation between the presence of diarrhea and age ($r = 0.061$; $p = 0.044$), CMI ($r = 0.065$; $p = 0.033$), hypertension ($r = 0.094$; $p = 0.002$), cardiac disease ($r = 0.079$; $p = 0.010$), fever ($r = 0.083$; $p = 0.006$), cough ($r = 0.102$; $p = 0.001$), dyspnea ($r = 0.074$; $p = 0.015$), nausea-vomiting ($r = 0.146$; $p < 0.001$), myalgia ($r = 0.070$; $p = 0.021$), fatigue ($r = 0.119$; $p < 0.001$), and CRP ($r = 0.066$; $p = 0.037$). In patients with diarrhea, higher CMI, the presence of hypertension and cardiac disease, complaints of fever, cough, dyspnea, myalgia, fatigue, and nausea-vomiting, CRP level above 50 mg/L, and higher negative predictive value ratio were noted during the ROC analysis (Table 2).

Discussion

Diarrhea is not a common symptom in COVID-19 patients. A diarrhea incidence value is mentioned in clinical studies between 3.8 and 37.1% of cases. The incidence of diarrhea was reported as 37.1% in a retrospective cohort study by Luo et al. [4], in which 183 patients in one medical center were studied. The incidence of diarrhea was reported as 29.3% in a cross-sectional study by Pan et al. [3], in which 204 patients in 3 medical centers were studied. In another study involving 2506 COVID-19 patients, 145 (5.8%) patients were reported to have diarrhea prior to admission [2]. In a retrospective cohort study involving 1,099 patients in 552 hospitals in China, the incidence of diarrhea was reported as 3.8% while the most common symptoms during admission were 43.8% for fever and 67.8% for cough [5]. Seventy-eight (7.2%) of 1,086 patients in 5 medical centers were found to have diarrhea in

Table 1. Demographic, clinical, and laboratory findings of the patients

	Diarrhea (+) (n = 78)	Diarrhea (-) (n = 1,008)	p value
Age	48.0±17.7	43.9±16.9	0.044
Gender (male)	45 (57.6%)	518 (51.3%)	0.535
Charlson Comorbidity Index	1.45±1.8	1.06±1.7	0.033
Hypertension	24 (30.7%)	170 (16.8%)	0.002
Cardiac disease	12 (15.3%)	73 (7.2%)	0.019
Diabetes mellitus	12 (15.3%)	113 (11.2%)	0.358
COPD	8 (10.2%)	91 (9%)	0.847
Duration of symptom, days	4.1±3.0	3.7±2.7	0.215
Fever	41 (52.5%)	373 (37%)	0.009
Cough	61 (78.2%)	593 (58.8%)	0.001
Sore throat	14 (17.9%)	153 (15.1%)	0.618
Myalgia	21 (26.9%)	168 (16.6%)	0.031
Fatigue	31 (39.7%)	208 (20.6%)	<0.001
Headache	10 (12.8%)	106 (10.5%)	0.652
Nausea/vomiting	53 (67.9%)	275 (27.2%)	<0.001
Loss of taste	7 (8.9%)	102 (10.1%)	0.918
Dyspnea	30 (38.4%)	260 (25.7%)	0.021
WBC	6,409±3,192	6,268±2,697	0.812
Lymphocyte count	1,635±784	1,714±764	0.370
Platelet count	183,500±49,784	190,820±66,304	0.873
CRP	28.3±45.2	20.4±35.2	0.037
AST	47.8±28.0	64.6±227.3	0.062
ALT	45.1±36.6	53.0±133.4	0.514
LDH	284.7±94.7	281.0±123.7	0.429
D-dimer	1,009±1,313	1,053±1,431	0.816
Ferritin	466.6±576.5	342.2±498.6	0.242
Day(s) of hospitalization	12.4±4.8	10.9±6.3	0.567
Mortality	2 (2.56%)	36 (3.57%)	0.886

Table 2. ROC analysis data obtained to determine the diagnostic efficacy of diarrhea

Parameters	Cutoff	AUC	AUC, 95% CI	Sensitivity	Specificity	PPV	NPV	p value
Age	>42	0.568	0.538–0.598	62.8	50.6	9.0	94.6	0.043
Charlson Comorbidity Index	>1	0.566	0.536–0.595	39.7	73.1	10.3	94.0	0.041
Hypertension	1	0.570	0.540–0.600	31.1	82.9	12.4	94.0	0.010
Cardiac disease	1	0.541	0.511–0.571	15.5	92.6	14.1	93.4	0.052
Fever	1	0.578	0.548–0.608	52.5	63.0	9.9	94.5	0.008
Cough	1	0.597	0.567–0.626	78.2	41.2	9.3	96.1	<0.001
Dyspnea	1	0.563	0.533–0.593	38.4	74.2	10.3	94.0	0.026
Myalgia	1	0.551	0.521–0.581	26.9	83.3	11.1	93.7	0.048
Fatigue	1	0.596	0.566–0.625	39.7	79.4	13.0	94.5	0.001
Nausea/vomiting	1	0.524	0.497–0.542	75.4	14.2	11.8	83.8	0.003
CRP	>50	0.571	0.539–0.602	61.0	49.6	9.2	93.8	0.037

ROC, receiver operating characteristic; AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

our study. Diarrhea was the first symptom in only 3 of these patients. In a study where Tian et al. [6] studied the incidence of specific symptoms in both children and adults, they stated that diarrhea was the one of the most

common symptoms that persisted about 4 days in both children and adults. Complaint of diarrhea lasted for an average of 5 days in all patients disappeared during follow-up.

In the presence of diarrhea, COVID-19 should be considered to affect the intestines. Theoretically, the intestines are the target organ for COVID-19 infection. COVID-19 infects human cells through angiotensin converting enzyme 2, and angiotensin converting enzyme 2 expression in the small intestines is significantly higher than the expression in the lungs [7, 8]. Probably for this reason, digestive symptoms may become more prominent as the severity of the disease increases [3]. The results of our study confirm this information. The clinical and laboratory findings of patients with diarrhea were more serious than those without diarrhea. Compared to patients without diarrhea, CMI score and CRP values of patients with diarrhea were higher, and the presence of fever, cough, shortness of breath, myalgia, and fatigue was higher ($p < 0.05$).

Studies reveal that viral nucleic acid is detected in stool samples even after being cleared from patients' airways [9–11]. However, it is not clear how long COVID-19 persists in the stools of patients. Scientific studies are needed to determine this. This deficiency must be eliminated to prevent potential contamination of discharged patients. This situation should be stated in terms of isolation measures during the discharge of patients diagnosed with COVID-19, especially who have diarrhea.

As a result, the presence of diarrhea should indicate a suspected COVID-19 infection and suggest testing for early diagnosis of the disease. It should be kept in mind that the course of the disease may be more severe in these patients, and precautions should also be taken in terms of fecal transmission during discharge.

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Statement of Ethics

The study protocol was approved by the local ethics committee (Umraniye Training and Research Hospital Ethics Committee; Protocol No. 25.06.2020/B.10.1.TKH.4.34.H.GP.0.01/260). The study was conducted in accordance with the Helsinki Declaration. Written informed consent was not required as it was a retrospective study conducted in the form of file scanning. This situation has been accepted by the ethics committee. The feasibility of the study has also been approved by the Ministry of Health.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.C. participated in study design and coordination, prepared the methodology, and worked on drafting and finalizing the manuscript. S.Ö., A.K., M.A., and H.N.K. participated in saving patient data and methodology and worked on drafting. G.Y. participated in study design and coordination, methodology, and statistical analysis and worked on drafting and finalizing the manuscript. All authors read and approved the final manuscript.