ORIGINAL ARTICLE

Clinical features and outcomes of gastrointestinal symptoms in patients with COVID-19

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Abstract

COVID-19 infected patients clinically can be asymptomatic or symptomatic. Clinical course in symptomatic patients may be present with mild, moderate, or severe symptoms. The coronavirus can affect multi-organ systems. The respiratory system is the most frequent target for the virus. Besides, gastrointestinal involvement may occur in occasional patients. We aimed to determine the clinical features and outcomes of gastrointestinal symptoms in patients with COVID-19. We retrospectively investigated 188 COVID-19 patients—patients clinical and demographic information obtained from the hospital database. Patients were categorized according to the clinical management guide released by the Republic of Turkey Ministry of Health. The mean age of the patients was 55.95 years (±17.62). 118 (62.8%) of the patients were men, and 70 (37.2%) of women. 118 (62.8%) patients were symptomatic, and 70 (37.2%) patients were asymptomatic. Among symptomatic patients, 56(47.4%) patients have isolated non-gastrointestinal symptoms, 52 (44.06%) patients have both (non-gastrointestinal, and gastrointestinal) symptoms, and 10 (8.4%) patients have isolated gastrointestinal symptoms. The distribution of the symptoms in 118 symptomatic patients was: 61 (32.5 %) patients have a fever, 84 (44.7 %) patients have a cough, 72 (38.3%) patients have dyspnea. The spectrum of gastrointestinal symptoms was as follows: 11 (5.9%) patients have diarrhea, 18 (9.6%) patients have abdominal pain, 24 (12.8%) patients have nausea, 14 (7.5%) patients have vomiting, 38 (18.7%) patients have anorexia, 2 (2.1%) patients have constipation. However, COVID-19 infection present commonly with respiratory and musculoskeletal symptoms; it is important to be aware of the varied clinical presentations in COVID-19, including isolated gastrointestinal symptoms. This will allow increasing the timely detectability of infected patients and more effective contact control measures.

Keywords: COVID-19 pandemic, COVID-19 infection, gastrointestinal symptoms

Introduction

Since the first case detected in China in December 2019, the Novel Coronavirus disease (COVID-19) has caused a pandemic and affected approximately 141 million people; Over three million people died due to this disease around the World [1].

Coronaviruses are a member of the Coronaviridae family. They have an outer envelope and RNA genome. Coronaviruses affect both animals and humans. The most known types that infect humans are HCoV-229E (229E), HCoV-OC43 (OC43), severe acute respiratory syndrome coronavirus (SARS-CoV), HCoV-NL63 (NL63), HCoV-HKU1 (HKU1), and Middle East respiratory syndrome coronavirus (MERS-CoV). All human coronaviruses have similar symptoms. Incubation periods except for only SARS-CoV and MERS-CoV can cause fatality. SARS-CoV-2 (novel coronavirus) virus is accused of the current pandemic [2–4].

The coronavirus can affect multi-organ systems. The respiratory system is the most frequent target for the virus. Patients clinically can be asymptomatic, have mild-moderate symptoms, or severe disease presenting as systemic inflammatory response syndrome [5]. General fatigue, fever, headache, dyspnea, sore throat, cough, myalgia-arthralgia are the most encountered symptoms of the COVID-19 virus [6]. COVID-19 can also cause disease in the entire gastrointestinal tract mucosa, including the esophagus, stomach, pancreas, liver, small and large intestine [7]. Although gastrointestinal symptoms are rare compared to respiratory and musculoskeletal symptoms, diarrhea, vomiting, nausea, abdominal pain are the frequent gastrointestinal symptoms in COVID-19 infected patients [8].

Several mechanisms are accused of gastrointestinal involvement.

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Probable elucidation about the mechanism for the gastrointestinal symptoms and signs is the presence of angiotensin-converting enzyme type 2 receptors in digestive system organs. These receptors provide adherence to the virus and facilitate the occurrence of the disease [9,10]. However, the spike (S) glycoprotein of the virus is accused of the fusion of cell membrane and host membrane during COVID-19 infection [11,12]. COVID-19 leads to gastrointestinal symptoms by directly invading host cells or immune-mediated end-organ damage [13,14]. This virus can cause gastrointestinal symptoms with indirect pathways by making changes in gut microbiota destruction of the epithelium due to hypoxia-related to lung injury and cytokine release [10,15]. Additionally, gastrointestinal symptoms may occur due to adverse drug effects used in COVID 19 treatment. Hickman et al. and Rojo et al. presented cases with bowel perforation after tocilizumab treatment [16,17].

We aimed to determine the gastrointestinal symptoms and involvement patterns in clinically non-severe patients. Thereby this might be useful for clinicians to identify the clinical characteristics of COVID-19 patients with gastrointestinal symptoms.

Materials and Methods

Patients'clinical and demographic information was retrospectively obtained and analyzed by scanning both record files and electronic medical records of 188 patients with confirmed COVID-19 patients who were treated at the Sivas Numune Hospital between January and March 2021. Diagnosis of COVID-19 was done by nucleic acid amplification tests and/or radiologically computed thorax tomography findings.

Patients were categorized according to the criteria released by the Republic of Turkey Ministry of Health. That guide classifies the patients as mild-moderate and severe. Proposed severe disease indexes were; Dyspnea and respiratory distress (Respiratory rate of ≥ 30 / min, PaO2 / FiO2 <300, SpO2 <90% or PaO2 <70 mmHg despite 5 L / min oxygen therapy), hypotension (systolic blood pressure<90 mmHg and 40 mmHg decrement from usual SBP and mean arterial pressure<65 mmHg, tachycardia>100/min, acute kidney damage, acute liver function test disturbances, confusion, unidentified acute bleeding diathesis, development of acute organ dysfunction, patients with immunosuppression, increased troponin levels, arrhythmia, and lactate> 2 mmol. More than one criteria are accepted as a severe disease [18].

Inclusion criteria: Patients over 18 years of age who were treated with COVID-19 and whose symptoms were not severe were included in this study.

Exclusion criteria: Patients who have missing data were excluded from the study. Besides, due to patients with high severity indexes being treated in the intensive care unit, those patients couldn't be included in this study.

Patients had been received treatment during the follow-up under the guidelines of the COVID-19 published by the Republic of Turkey Ministry of Health for COVID-19 pandemic services. The Sivas Cumhuriyet University Faculty approved this study of the Medicine Ethics Committee (Number: 2021-01/26, date: 13.01.2021).

Statistical analysis

All analyses were performed with SPSS 24.0 statistics software for windows. The compliance of the data to normal distribution was evaluated by the histogram, q-q graphs, and Shapiro-Wilk test. Variance homogeneity was tested with the Levene test. The dependent sample t-test and the Wilcoxon test were used to compare the variables measured at admission and discharge. Thesignificancelevelwasaccepted is p <0.05.

Results

We enrolled a total of 188 COVID-19 positive patients in this study. The mean age of the patients was 55.95 years (±17.62). 118 (62.8%) of the patients were men, and 70 (37.2%) of women. Among the patients' comorbidities, hypertension must be lowercase 65 (34.6%), diabetes mellitus 50 (26.6%), and ischemic heart disease 24 (12.8%) were the most frequent [Table 1]. 118 (62.8%) patients were symptomatic, and 70 (37.2%) patients were asymptomatic. Among symptomatic patients, 56 (47.4%) patients have isolated non-gastrointestinal symptoms, 52 (44.06%) patients have both (non-gastrointestinal, and gastrointestinal) symptoms, and 10 (8.4%) patients have isolated gastrointestinal symptoms. The distribution of the symptoms in 118 symptomatic patients was: 61 (32.5 %) patients have a fever, 84 (44.7 %) patients have a cough, 72 (38.3%) patients have dyspnea, 26 (13.9%) patients have musculoskeletal ache, 26 (13.9 %) patients have a headache, 38 (30.3%) patients have a sore throat,78 (41.5%) patients have fatigue, 7 (3.8%) patients have ageusia-anosmia [Table-2].

The spectrum of gastrointestinal symptoms was as follows: 11 (5.9%) patients have diarrhea, 18 (9.6 %) patients have abdominal pain, 24 (12.8%) patients have nausea, 14 (7.5%) patients have vomiting, 38 (18.7%) patients have anorexia, 2 (2.1%) patients have constipation [Table-3].

Vital signs of patients were: Fever: 36.73°±0.81°, systolic blood pressure: 126.64±36.34 mm Hg, diastolic blood pressure 76.08±19.37 mm Hg, pulse 103.57±21.34 per/min, respiratory rate: 30.38±7.46 per/min. Laboratory results on admission and discharge were shown in Table-4.

Discussion

COVID19 infection usually presents with respiratory and musculoskeletal symptoms. Besides, gastrointestinal symptoms may occur alone or in combination with respiratory and musculoskeletal symptoms in infected patients. Common gastrointestinal symptoms in COVID19 infection are nausea, abdominal pain, and diarrhea [10]; less frequently, other signs and manifestations are liver function test abnormalities [19], gastrointestinal bleeding [20], bowel perforation [21], ischemic colitis [22], Pneumatosis intestinalis [23].

In our study, 118 (62.4%) patients were symptomatic. Among the symptomatic patients, 56 (47.4%) patients have isolated non-gastrointestinal symptoms,52 (44.06%) patients have both (non-gastrointestinal, and gastrointestinal) symptoms, and 10 (8.4%) patients have isolated gastrointestinal symptoms. The frequency of the isolated gastrointestinal symptoms in our study was compatible with the review conducted by Abbas et al. According

Table 1. Demographic features of patients at presentation

Variables		Descriptive Statistics
Patient characteristic		
Age(y)		55.95±17.62
Female sex		70 (37.2)
Male sex		118 (62.8)
Diabetes mellitus	No	138 (73.4)
	Yes	50 (26.6)
Hypertension	No	123 (65.4)
	Yes	65 (34.6)
Ischemic heart disease	No	164 (87.2)
	Yes	24 (12.8)
Cirrhosis	No	186 (98.9)
	Yes	2 (1.1)
Non-alcoholic fatty liver disease	No	187 (99.4)
	Yes	1 (0.6)
Viral hepatitis	No	186 (98.9)
	Yes	2 (1.1)
Chronic kidney failure	No	175 (93)
	Yes	13 (17)
Chronic obstructive pulmonary disease	No	180 (95.7)
	Yes	8 (4.3)
Malignancy	No	166 (88.2)
	Yes	12 (11.8)
Other diseases	No	150 (79.7)
	Yes	38 (20.3)
Smoking status	No	171 (90.9)
	Yes	17 (9.1)
Alcohol use	No	188 (100)
	Yes	0 (0)

Table 2. Clinical features of symptomatic patients

Variables		n(%)
Clinic Symptoms	No	70 (37.2)
	Yes	118 (62.8)
Fever	No	127 (67.5)
	Yes	61 (32.5)
Cough	No	104 (55.3)
	Yes	84 (44.7)
Shortness of breath	No	116 (61.7)
	Yes	72 (38.3)
Joint or muscle pain	No	162 (86.1)
	Yes	26 (13.9)
Headache	No	162 (86.1)
	Yes	26 (13.9)
Sore throat	No	150 (79,7)
	Yes	38 (30.3)
Fatigue	No	110 (58.5)
	Yes	78 (41.5)
Loss of taste and smell	No	181 (96.2)
	Yes	7 (3.8)

Table 3. Clinical features of patients with gastrointestinal symptoms

Variables		n(%)
Diarrhea	No	177 (94.1)
	Yes	11 (5.9)
Abdominal pain	No	170 (90.4)
	Yes	18 (9.6)
Nausea	No	164 (87.2)
	Yes	24 (12.8)
Vomiting	No	174 (92.5)
	Yes	14 (7.5)
Anorexia	No	153 (81.3)
	Yes	38 (18.7)
Constipation	No	186 (98.9)
	Yes	2 (2.1)

Table 4. Biochemical parameters of patients

Variables	(n=183)		p
	Admission measurement value	Measurement value at discharge	
AST(U/L)	22.1(17.0-35.0)	24.2(17.0-35.5)	0.280
ALT(U/L)	19.5(13.0-34.0)	25.7(15.0-44.0)	<0.001
ALP (U/L)	79.3(60.0-100.0)	76.6(60.0-105.0)	0.636
GGT(U/L)	30.1(18.0-65.0)	43.6(17.0-82.0)	0.012
TOTAL BILIRUBIN(mg/dL)	0.52(0.4-0.7)	0.41(0.3-0.6)	0.058
DİRECT BILIRUBIN(mg/dL)	0.24(0.1-0.3)	0.25(0.1-0.3)	0.816
AMILASE(U/L)	55.4(40.5-80.5)	57.0(44.0-79.0)	0.049
LIPASE(U/L)	29.2(18.0-41.0)	34.6(25.0-65.0)	<0.001
LDH(U/L)	254.6(201.0-335.0)	258.8(193.0-345.0)	0.398
GLU(mg/dL)	121.9(99.0-174.0)	117.7(92.0-159.8)	0.065
WBC(10^9/L)	6475(4800-9910)	6487(5000-9520)	0.775
PLT (10^9/L)	273.6(191.5-187500.0)	291.3(197.5-209500.0)	0.002
NEUTROPHIL(%)	4247.2(2895.0-7295.0)	3981.7(2790.0-7580.0)	0.733
LYMPHOCYTE(%)	1430.0(955.0-1880.0)	1445.0(870.0-1980.0)	0.848
BUN(mg/dL)	17.8(11.7-26.8)	18.1(12.7-34.0)	0.063
CREATINE (mg/dL)	0.92(0.8-1.2)	0.81(0.7-1.2)	0.022
SODIUM(mmol/L)	137.0(135.0-141.0)	141.0(136.0-142.0)	0.001
SEDIMENTATION(mm/h)	31.9(18.0-60.0)	28.6(14.0-59.0)	0.875
C-reactive protein(mg/dL)	22.3(6.0-84.0)	16.1(3.3-61.0)	0.026
TROPONIN(pg/mL)	0.008(0.004-0.042)	0.007(0.004-0.034)	0.100
FERRITIN(ng/mL)	233.3(102.0-500.0)	235.7(113.0-495.0)	0.073
PH	7.4(7.3-7.4)	7.4(7.2-7.4)	0.120
LACTATE(mmol/L)	1.7(1.2-2.9)	1.7(1.2-2.6)	0.914
TOTAL PROTEIN(g/L)	6.79±0.98	6.11±1.12	<0.001
ALBUMIN(g/d)	4.01±0.78	3.52±0.94	<0.001
HEMOGLOBIN(g/dL)	13.29±2.34	12.04±2.70	<0.001
POTASSIUM(mmol/L)	4.52±0.80	4.35±0.70	0.009

AST: aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT; γ-glutamyltransferase, LDH; Lactate dehydrogenase, PTT; Partial prothrombin time, GLU; Glucose. WBC; White blood cell, PLT, Thrombocyte, BUN; Blood urine nitrogen, INR; International normalized ratio, MPV; Mean platelet volume SD standard deviation, *P values indicate differences between patients admission and at discharge measurement value. P < 0.05 was defined as statistically significant

to our findings, the most common gastrointestinal symptoms in COVID -19 patients were anorexia (%18.7) and nausea (%12.8). Distribution of gastroenterological symptoms was: 11 (5.9%) patients have diarrhea, 18 (9.6%) patients have abdominal pain, 24

(12.8%) patients have nausea, 14 (7.5%) patients have vomiting, 38 (18.7%) patients have anorexia, 2 (2.1%) patients have constipation.

Several studies have been conducted about the gastrointestinal involvement of COVID -19 infection. In a systemic review including 43 studies, Silva et al.reported that the gastrointestinal symptoms are frequent and be aware of liver function tests in COVID -19 infected patients. Also, they concluded the most common gastrointestinal symptom was diarrhea (11.5%) [7]. Nevertheless, Chao Cao et al. showed that the most frequent symptom is anorexia (74.6%) [24]. In our study, the most frequent gastrointestinal symptom was anorexia (18.7%).

In another study that evaluated the spectrum of the gastrointestinal symptoms and the relation between the severity of the disease, Ghoshal et al. found gastrointestinal symptoms are not uncommon, and vomiting was the common symptom in COVID -19 infected patients. In addition, they concluded that gastrointestinal symptoms were related to severe COVID -19 disease. In the same study, the percentage of gastrointestinal symptoms were (10.3%) [25]. In parallel with this study, our results have shown that gastrointestinal symptoms are as common as non-gastrointestinal symptoms (55.9% vs. 54.1%). Sun et al. also showed gastrointestinal damage incidence is high in severe and critically ill patients (86.7%) [26]. However, they concluded gastrointestinal symptoms were related to severe COVID -19 disease. We think that gastrointestinal symptoms are related to severe and non –severe patients because our study population included non-severe patients.

Although our study does not contain data about mortality or length of hospital stay, there are controversial studies that exist about the association between gastrointestinal symptoms and high mortality or length of hospital stay. Cholankeril et al. found that digestive system symptoms are related to the long hospitalization require [27]. Contrary to this research, Ramachandran and colleagues did not found any relation between gastrointestinal symptoms with high mortality or length of hospital stay [28]. A. PAPA et al. concluded that gastrointestinal symptoms are linked with better clinical outcomes [29].

Conclusion

Although fever, myalgia, and respiratory tract complaints are usually seen in the clinic of patients with COVID-19 infection, gastrointestinal system symptoms can be seen to a considerable extent.This sentence should be rewritten It is important to be aware of the varied clinical presentations in COVID-19, including isolated gastrointestinal symptoms. This will allow increasing the timely detectability of infected patients and more effective contact control measures.

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