Gastrointestinal Symptoms and Liver Damage in Patients with COVID-19

COVID-19'lu Hastalarda Gastrointestinal Semptomlar ve Karaciğer Hasarı

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ABSTRACT

Introduction: Gastrointestinal and hepatic symptoms may be seen before respiratory symptoms in Coronavirus disease 2019 (COVID-19). The purpose of the present study was to evaluate the relationship between liver damage and observed symptoms and laboratory parameters.

Materials and Methods: Patients followed-up with diagnoses of COVID-19 between March and August 2020 were included in the study. Clinical characteristics and laboratory parameters were compared according to liver damage status.

Results: Four hundred and thirteen COVID-19 cases were included. The prevalence of gastrointestinal symptoms was 19.8%, the most common being nausea/vomiting, abdominal pain, and diarrhea (10.4%, 6.1%, and 2.9%, respectively). CT-confirmed pneumonia, intensive care requirement, and mean length of hospitalization differed significantly depending on liver damage status (p< 0.001, p= 0.006, p= 0.002, respectively). Significant differences were determined between the groups with and without liver damage in terms of all the laboratory parameters examined, apart from white blood cell, neutrophil, lymphocyte, neutrophil:lymphocyte ratio (NLR), total bilirubin, and partial thromboplastin time (PTT) (p< 0.05). Significant associations were present between alanine aminotransferase levels and all other laboratory parameters apart from NLR and PTT (p< 0.001). Aspartate aminotransferase (OR: 1.22, CI: 1.16-1.28) and albumin (OR: 2.28, CI: 1.12-4.63) were identified as significant independent risk factors for liver damage in patients with COVID-19.

Conclusion: Gastrointestinal symptoms are not uncommon in COVID-19 patients. Liver damage may be associated with progression to intensive care and systemic inflammation.

Key Words: COVID-19; gastrointestinal symptoms; liver function; systemic inflammation

ÖZ

COVID-19'lu Hastalarda Gastrointestinal Semptomlar ve Karaciğer Hasarı

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Giriş: *Küresel pandemiye neden olan koronavirüs hastalığı 2019 (COVID-19) sıklıkla ateş, öksürük ve nefes darlığı ile kendini göstermektedir. Gastrointestinal şikayetler ve hepatik belirtiler solunum belirtilerinden önce görülebilir. Çalışmamızda karaciğer hasarı ile gözlenen semptom ve laboratuvar parametreleri arasındaki ilişkiyi değerlendirmeyi amaçladık.*

Materyal ve Metod: *Mart-Ağustos 2020 tarihleri arasında COVID-19 tanısıyla takip edilen hastalar çalışmaya dahil edildi. Karaciğer hasar durumuna göre klinik özellikleri ve laboratuvar parametreleri karşılaştırıldı.*

Bulgular: *Çalışmaya toplamda 413 COVID-19 vakası dahil edildi. Gastrointestinal semptom sıklığı %19.8 olup; en sık gastrointestinal semptomlar bulantı/kusma, karın ağrısı ve ishal (sırasıyla %10.4, %6.1 ve %2.9) idi. Karaciğer hasarı olan ve karaciğer hasarı olmayan vakalar arasında karın ağrısı hariç (p= 0.015) diğer semptomların tamamı benzer dağılım gösteriyordu (p> 0.05). CT ile doğrulanmış pnömoni, yoğun bakım gereksinimi ve ortalama hastanede kalış süresi, karaciğer hasar durumuna bağlı olarak anlamlı farklılık gösterdi (sırasıyla p< 0.001, p= 0.006, p= 0.002). Takipleri sırasında karaciğer hasarı olan hastaların %9.6'sında, karaciğer hasarı olmayanların ise %3.1'inde yoğun bakım ihtiyacı doğmuştu (p= 0.006). Hastaların karaciğer hasarına göre hastanede yatış süresi dağılımları arasında anlamlı fark vardı (p= 0.002). Karaciğer hasarı bulunan ve bulunmayan hastalar arasında beyaz kan hücresi, nötrofil, lenfosit, nötrofil-lenfosit oranı (NLR), total bilurubin ve parsiyel tromboplastin zamanı (PTT) hariç değerlendirilen diğer tüm laboratuvar parametreleri açısından anlamlı fark bulunuyordu (p< 0.05). Hastalarda alanin aminotransferaz düzeyleri ile NLR ve PTT hariç diğer laboratuvar parametreleri arasında anlamlı ilişkiler söz konusuydu (p< 0.001). COVID-19'lu hastalarda karaciğer hasarı üzerinde aspartat aminotransferaz (OR: 1.22, CI: 1.16-1.28) ve albumin (OR: 2.28, CI: 1.12-4.63) anlamlı bağımsız risk faktörleri olarak belirlendi.*

Sonuç: *COVID-19'lu hastalarda gastrointestinal şikayetler nadir değildir. Karaciğer hasarı yoğun bakıma gidişle ve sistemik inflamasyonla ilişkili olabilir.*

Anahtar Kelimeler: *COVID-19; gastrointestinal semptom; karaciğer fonksiyonu; sistemik inflamasyon*

INTRODUCTION

The first cases of Coronavirus disease 2019 (COVID-19) were detected in Wuhan, capital of the Chinese province of Hubei, in December 2019. The first import cases subsequently appeared in Thailand and Japan on 17 January, 2020. The World Health Organization declared a COVID-19 pandemic on 11 March, 2020[1,2]. The first case of COVID-19 in Turkey involved a 44-year-old man presenting to hospital on 9 March, 2020[3]. The clinical signs of the disease are generally fever, cough, fatigue, and airway symptoms[4,5]. Severe COVID-19 cases can result in acute respiratory distress syndrome, acute heart damage, kidney failure, and death. Insufficient information is available concerning non-lung symptoms. The prevalence of gastrointestinal symptoms in COVID-19 patients has been reported as 9% in some meta-analysis studies[6]. Liver damage has been reported in addition to various gastrointestinal symptoms during the course of the disease, such as nausea, vomiting, diarrhea, abdominal pain, anorexia, anosmia, and dysgeusia[7,8].

The purpose of the present study was to evaluate the distribution of symptoms and pneumonic involvement according to alanine transaminase (ALT) level, and the relationship between liver damage and laboratory parameters in patients diagnosed with COVID-19.

MATERIALS and METHODS

Ethical approval for the study was granted by the Turkish Ministry of Health and the Atatürk University Faculty of Medicine Hospital Medical

Faculty ethical committee. The study population consisted of COVID-19 patients treated at the Atatürk University Faculty of Medicine Hospital Health Research Application Center between March and August 2020. Patients meeting the definite case definition based on the Turkish Ministry of Health Public Health General Directorate guideline were included and subjected to clinical classification[3]. Patients with viral hepatitis, alcoholic liver disease, hepatic malignancy, hepatotoxic drug use during admission to the clinic, hepatobiliary disease or other known chronic disease were excluded from the study.

Patients' demographic data, symptoms, accompanying comorbid conditions, smoking status, and hematological and biochemical laboratory parameters (AST: Aspartate aminotransferase, ALT, ALB: albumin, GGT: gamma glutamyl, transaminase, LDH: lactate dehydrogenase, BIL-T: total bilirubin, PTT: partial thromboplastin time), and acute phase reactants (FERR: ferritin, PCT: procalcitonin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, D-Dimer) as well as the presence of pneumonic infiltration at computed tomography (CT) of the lung were retrieved from the hospital records. Since the upper limit for ALT levels was taken as 35 IU/L in our hospital, the patients were divided into two groups based on a laboratory cut-off point. The cases with a higher value were considered as liver damage, and the cases below this value were considered cases without liver damage.

Statistical Analysis

The study data were analyzed on SPSS 22 (Statistical Package for the Social Sciences) software. Categorical variables were expressed as number and percentage, and numerical variables as mean ± standard deviation, and as mean and quartiles (Q_1-Q_3) as required. Compatibility with normal distribution of numerical variables was evaluated using z values for skewness and kurtosis, the Kolmogorov Smirnov test, and graphics. The independent sample t test was used to compare normally distributed data between the groups, and the Mann-Whitney U test to compare non-normally distributed data. The χ2 test and Fisher's exact test where necessary were applied in the comparison of categorical data. Spearman's rho correlation analysis was employed to investigate relationships between non-normally distributed continuous variables. Binary logistic regression analysis with the backward LR method was applied to assess independent risk factors affecting liver damage. Independent variables identified as significant at univariate regression were included in the model. p< 0.05 was regarded as significant for all analyses.

RESULTS

Four hundred and thirteen COVID-19 cases confirmed with polymerase chain reaction were included in this study. Patients' mean age was 45.4 ± 18.8 years, and the median age was 44.0 (18.0-95.0). Men constituted 223 (54.0%) cases, with a mean age of 44.6 ± 17.8 years, while women constituted 190 cases, with a mean age of 46.4 ± 19.9. Male and female patients' mean ages were similar (p= 0.349). Fifteen percent of the patients were smokers, and the most common accompanying chronic disease was hypertension (12.1%). Cases with and without liver damage were similar in terms of age, sex, smoking, and accompanying chronic diseases (p> 0.05). The patients' most common symptoms were cough, fever, and lethargy (39.5%, 30.3%, and 28.1%, respectively). The prevalence of gastrointestinal symptoms among patients with COVID-19 was 19.8%. The most frequent gastrointestinal symptoms were nausea/vomiting, abdominal pain, and diarrhea (10.4%, 6.1%, and 2.9%, respectively). With the exception of abdominal pain (p= 0.015), all other symptoms were similarly distributed between the cases with and without liver damage (p> 0.05). CT-confirmed pneumonia was present in 43.8% of the cases, and distributions differed significantly depending on liver damage status (p< 0.001). Intensive care was required during follow-up in 9.6% of patients with liver damage and in 3.1% of those without liver damage, and distributions also differed significantly (p= 0.006). Mean length of hospitalization was 9.1 ± 4.2 days, and distributions again differed depending on liver damage status (p= 0.002) (Table 1).

Laboratory data were also evaluated in COVID-19 patients depending on liver damage status. Significant differences were determined in

Table 1. Demographic and clinical characteristics of patients with COVID-19 depending on liver damage status

Variables	ALT ≤ 35 (n= 288)	ALT > 35 (n= 125)	p
Age	45.7 ± 19.4	44.8 ± 17.2	0.667
Gender, n (%)			0.913
Female	133 (46.2)	57 (45.6)	
Male	155 (53.8)	68 (54.4)	
Clinical classification			0.915
Non-complicated	118 (68.6)	54 (31.4)	
Mild/moderate	120 (70.6)	50 (29.4)	
Severe/critical	50 (70.4)	21 (29.6)	
Smoker, n (%)	43 (14.9)	19 (15.2)	0.944
Accompanying diseases			
HT, n (%)	35 (12.2)	15 (12.0)	0.965
DM, n (%)	21 (7.3)	8 (6.4)	0.745
COPD, n (%)	14 (4.9)	5 (4.0)	0.701
CAD, n (%)	14 (4.9)	8 (6.4)	0.522
Symptoms			
Cough, n (%)	115 (39.9)	48 (38.4)	0.770
Fever, n (%)	79 (27.4)	46 (36.8)	0.057
Lethargy, n (%)	81 (28.1)	35 (28.0)	0.979
Dyspnea, n (%)	55 (19.1)	27 (21.6)	0.558
Nausea/vomiting, n (%)	30 (10.4)	13 (10.4)	0.996
Abdominal pain, n (%)	12 (4.2)	13 (10.4)	**0.015**
Loss of taste/smell, n (%)	13 (4.5)	3 (2.4)	0.411
Diarrhea, n (%)	7 (2.4)	5 (4.0)	0.360
Myalgia, n (%)	8 (2.8)	6 (4.8)	0.374
Lack of appetite, n (%)	6 (2.1)	7 (5.6)	0.071
Pneumonic involvement at thoracic CT, n (%)	108 (37.5)	73 (58.4)	**<0.001**
Intensive care requirement, n (%)	9 (3.1)	12 (9.6)	**0.006**
Length of hospitalization, (days)	8.7 ± 3.2	9.9 ± 3.9	**0.002**

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CT: Computed tomography.

all laboratory parameters between patients with and without liver damage with the exception of white blood cell (WBC), neutrophil (NE), lymphocyte (LY), neutrophil:lymphocyte ratio (NLR), BIL-T, and PTT values (p< 0.05) (Table 2).

Varying degrees of correlation were observed between ALT and all laboratory parameters apart from NLR and PTT (p< 0.001) (Table 3).

Stepwise binary logistic regression analysis applied in order to evaluate risk factors affecting liver damage in patients with COVID-19 identified AST (OR: 1.22, CI: 1.16-1.28) and ALB (OR: 2.28, CI: 1.12-4.63) as significant independent risk factors (Table 4). Other liver function markers (AST, GGT, and LDH), inflammatory markers (ESR, CRP, D-Dimer, PCT and FERR), presence of pneumonia, and demographic variables such as age and sex exhibited no significant independent association with liver damage in COVID-19 patients.

DISCUSSION

The most common symptoms in patients with COVID-19 are fever, cough, fatigue, dyspnea, sore throat, headache, myalgia, and arthralgia[9]. However, non-pulmonary symptoms like gastrointestinal system and hepatic involvement are becoming increasingly frequently reported[10]. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were more prominent in the first COVID-19 case reported from the USA[11]. One multi-center

Table 2. Laboratory parameters of patients with COVID-19 depending on liver damage status

Variables	ALT ≤ 35 (Q1-Q3)	ALT > 35 (Q1-Q3)	p
WBC (x10^9 cells/L)	6.33 (4.70-8.80)	6.40 (4.95-8.96)	0.679
NE (x10^9 cells/L)	4.10 (2.60-5.97)	3.90 (2.75-5.95)	0.706
LY (x10^9 cells/L)	1.41 (1.00-2.00)	1.46 (0.94-2.10)	0.997
NLR	2.64 (1.54-4.80)	2.68 (1.71-4.93)	0.724
ESR (mm/h)	12.00 (6.00-30.00)	28.00 (8.50-51.50)	**<0.001**
CRP (mg/L)	5.60 (3.00-20.75)	20.30 (4.00-83.00)	**<0.001**
AST (IU/L)	24.00 (19.00-29.00)	42.00 (33.00-70.00)	**<0.001**
ALB (g/dL)	3.70 (3.40-4.00)	3.50 (3.20-3.99)	**0.030**
GGT (IU/L)	24.00 (15.00-40.53)	40.53 (29.00-69.00)	**<0.001**
LDH (IU/L)	267.00 (222.25-322.50)	316.00 (263.50-381.50)	**<0.001**
BIL-T (mg/dL)	0.50 (0.35-0.67)	0.54 (0.40-0.73)	0.151
D-DIMER (µg/mL)	411.00 (272.50-820.50)	698.00 (346.50-1976.00)	**<0.001**
FERR (ng/mL)	81.40 (39.67-221.00)	213.00 (94.70-511.00)	**<0.001**
PCT (ng/mL)	0.04 (0.02-0.15)	0.07 (0.04-0.27)	**0.001**
PTT (sec)	29.04 (27.40-30.50)	29.04 (27.70-30.05)	0.789

WBC: White blood cell, NE: Neutrophil, LY: Lymphocyte, NLR: Neutrophil lymphocyte ratio, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine transaminase, AST: Aspartate transaminase, ALB: Albumin, GGT: Gamma glutamyl transaminase, LDH: Lactate dehydrogenase, BIL-T: Total bilirubin, FERR: Ferritin, PCT: Procalcitonin, PTT: Partial thromboplastin time.

Table 3. Spearman correlation analysis results between ALT levels and various laboratory parameters

Variables		NLR	ESR	CRP	GGT	LDH	ALB	BIL-T	D-DIMER	FERR	PCT	PTT
ALT	r	0.018	0.179	0.217	0.472	0.334	-0.167	0.163	0.220	0.385	0.164	-0.015
	p	0.710	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.755
AST	r	0.096	0.320	0.357	0.423	0.563	-0.281	0.188	0.413	0.449	0.220	0.017
	p	0.052	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.734

Table 4. Logistic regression analysis results

Variable	Wald	p value	OR	95% CI
Pneumonia	3.20	0.074	1.78	0.946-3.368
AST	70.21	**<0.001**	1.22	1.164-1.278
GGT	3.06	0.080	1.01	0.999-1.023
LDH	19.36	0.089	1.01	0.989-1.019
ALB	5.16	**0.023**	2.27	1.120-4.635

R^2= 0.61 (Nagelkerke), χ^2 (8)= 9.35 (Hosmer & Lemeshow).

cross-sectional study has reported that approximately 50% of patients experience symptoms such as diarrhea, nausea, vomiting, and abdominal pain[12]. Although viral RNA was not detected in the patient's stool specimen, one case reported identified hematochezia among the symptoms observed[13].

Consistent with the previous literature, the most frequent symptoms in COVID-19 cases in the present study were cough, weakness, fever, and dyspnea. The most frequent gastrointestinal symptoms were nausea/vomiting, abdominal pain, and diarrhea, and the prevalence of gastrointestinal

symptoms was 19.8%. With the exception of abdominal pain, no diference was observed in gastrointestinal symptoms between patients with and without liver damage. The reported prevalence of gastrointestinal symptoms in patients with COVID-19 ranges between 11.3% and 79.1%[12,14-16].

With the exception of abdominal pain, the presence of gastrointestinal symptoms in the group with high ALT levels was not affected by the severity of the disease. One previous study has reported a significantly higher rate of fever, fatigue, dyspnea, and headache in COVID-19 patients with gastrointestinal symptoms[14]. A study from Hubei in China reported has that 99 (48.5%) out of 204 patients diagnosed with COVID-19 presented with digestive problems, and that prognosis was poorer among patients with such problems than those without digestive difficulties[12]. According to one systematic meta-analysis, gastrointestinal symptoms such as vomiting and diarrhea are statistically higher among severe patients than non-severe patients[17].

Gastrointestinal symptoms in COVID-19 emerge through different mechanisms. Angiotensin-converting enzyme 2 (ACE2) receptors used by the virus for cellular entry are found in both the respiratory tract and the gastrointestinal tract. The virus entering the cell produces viral replication in the gastrointestinal tract and causes direct damage to the gastrointestinal system in association with the inflammatory response[12]. Enterocytes can also be infected with COVID-19 and damaged. Symptoms that activate the enteric symptom, such as diarrhea, resulting from malabsorption or impaired balance in intestinal secretions can be seen[18]. On the basis of these findings, clinicians should consider COVID-19 in patients with gastrointestinal symptoms, either alone or accompanied by respiratory symptoms.

Hepatic damage of varying severity has been reported in COVID-19 patients, and can be revealed using specific laboratory parameters[19]. According to the American College of Gastroenterology, abnormal hepatic enzyme levels have been seen in 20-30% of confirmed COVID-19 cases (20). Another study has reported that 50.7% of 148 patients had abnormal liver functions on hospita-

lization[19]. Additionally, total bilirubin, ALP and GGT elevation may also be present[4,19,21]. In the present study, ALT elevation was present in 125 (30.3%) of the 413 confirmed cases of COVID-19.

The mechanism involved in liver damage in COVID-19 patients is still unclear. Theories such as the virus infecting hepatocytes via ACE2 receptors, immune deficiency, or drug hepatotoxicity have been proposed[22]. Due to the presence in the gastrointestinal system of high levels of ACE2 receptors used by SARS-CoV-2 for cellular entry, the posibility has been reported of the virus causing liver damage by infecting cholangiocytes via these receptors[22,23]. Viral inclusion was not detected in a liver biopsy specimen from a postmortem COVID-19 case, although microvesicular steatosis and mild lobular activity were observed[24].

The majority of studies have reported that liver damage is mild and transient, although severe damage can also occur. More severe liver damage has been detected in individuals with severe disease[22,23]. A higher probability of fever has been reported in patients with high liver function tests, and such elevation is greater in male patients[19]. Gender distributions by ALT levels were similar in the present study. Liver damage is more common in patients with pneumonia. Guan et al. have reported AST, ALT and total bilirubin elevation at 39%, 28%, and 13%, respectively, in cases with severe disease, compared to 22%, 21%, and 11% in non-severe cases[21]. Distribution of pneumonic infiltration in the present study differed significantly according to ALT levels. Liver damage in COVID-19 patients may be associated with viral infection in liver cells, cytokine storm, or drugs, or may derive from systemic inflamation caused by pneumonia-related hypoxia[25].

Significant differences were observed between intensive care requirements during follow-up in patients with high ALT levels (9.6%) compared to the group with normal ALT levels. Wang et al. have reported higher AST and ALT levels among patients admitted to the intensive care unit[26]. Huang et al. have reported AST elevation in 62% of patients admitted to the intensive care unit[27]. A significant difference was determined in the present study in terms of length of hospital stay between patients with high and normal ALT

levels. However, there was no significant difference between liver damage and clinical classification distributions showing disease severity in COVID-19 cases (Table 1).

Patients with liver damage have longer hospitalizations than patients without liver damage. Pan et al. have described the clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China. Patients presenting with digestive symptoms have shown longer hospital stays and worse prognosis compared to those without digestive symptoms[12]. Prolonged hospital stay may be associated with the severity of COVID-19 disease and the need for care in the intensive care unit.

Higher WBC and neutrophil counts, NLR, D-Dimer, fibrinogen, and CRP levels and lower lymphocyte counts have been shown in cases of severe COVID-19 compared to non-severe cases[28]. One meta-analysis has reported that lymphocytopenia, thrombocytopenia, and high CRP and D-Dimer were associated with severe pneumonia[28]. Another meta-analysis has reported higher procalcitonin, creatinine, and lymphocyte counts in the severe patient group compared to non-severe patients[17]. ALT levels were positively correlated with the acute phase reactants ESR, CRP, D-Dimer, ferritin, PCT and AST, GGT, and LDH used to evaluate severity of disease in the present study (Table 3).

CONCLUSION

Although respiratory symptoms predominate among COVID-19 patients, gastrointestinal symptoms may also be seen, either alone or together with respiratory symptoms. According to the results of this study, nausea, vomiting, abdominal pain, loss of taste and smell are among the most common gastrointestinal symptoms. Gatrointestinal symptoms and liver damage in COVID-19 may develop due to the presence of the viral receptor ACE2 in the gastrointestinal system. In the study, there was a significant difference between patients with and without liver damage in terms of ESR, CRP, AST, ALB, GGT, LDH, D-Dimer, FERR, and PCT. Additionally, AST (OR: 1.22, CI: 1.16-1.28) and ALB (OR: 2.28, CI: 1.12-4.63) were significant independent risk factors for liver damage in patients with COVID-19. Hepatic

damage may be more in the presence of pneumonia. The need for care in the intensive care unit of COVID-19 patients with hepatic damage is increasing and the duration of hospitalization is prolonged. Evaluation of parameters determining severity of disease in COVID-19 patients with liver function test abnormalities may contribute to the success of follow-up.

ETHICS COMMITTEE APPROVAL

The approval for this study was obtained from Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Date: 07.05.2020, Decision No: 02).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: HA, ZÖ, AA, KÖ, EP

Data Collection or Processing: HA, FKC, AA, ZÖ, EP, KÖ, ET, AOK

Analysis/Interpretation: HA, SY

Literature Search: HA, FKC, SY

Writing: HA

Final Approval: HA, SY, ZÖ

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