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Coronavirus Pandemic

Liver damage and hepatomegaly in COVID-19 patients

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Abstract

Introduction: The aim of this study was to evaluate the patients with high liver function test results detected at admission to the hospital diagnosed with COVID-19.

Methodology: Patients diagnosed with COVID-19 by a nasopharyngeal RT-PCR (+) test in the emergency department were included in the study. CRP, liver function tests, and abdominal ultrasonography (US) findings of the patients were recorded.

Results: A total of 367 COVID-19 patients, 254 (69.2%) males and 113 (30.8%) females, with a mean age of 60.39 (16.81) years, were included in the study. It was seen that 236 (68.7%) patients were treated without complications, 131 (35.7%) patients needed intensive care, and 81 (22.1%) patients died. The frequency of hepatomegaly was significantly higher in patients with severe course and mortality ($p < 0.001$). When COVID-19 patients who developed mortality were compared with other patients with a diagnosis of COVID-19, no additional risk factors affecting mortality were detected, except LDH [OR: 1.009, (1.006-1.012); $p < 0.001$] and high CK [OR: 1.001 CI: 95%, (1.000-1.001); $p = 0.032$].

Conclusions: Patients who need to be hospitalized with COVID-19 and who do not have acute and/or chronic liver disease, elevated liver function test results, and an increase in liver sizes at presentation, it was seen that these did not have an effect on the clinical outcome. However, in addition to the presence of advanced age and comorbidity, the presence of hepatomegaly measured by CT at admission, and high LDH and CK levels were associated with poor clinical outcomes.

Key words: COVID-19; LFT; CK; LDH; hepatosteatosis; comorbidity.

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Introduction

The COVID-19 pandemic began in Wuhan in December 2019 and spread around the world [1]. The SARS-CoV-2 virus responsible for the infection is an enveloped RNA betacoronavirus. Although nearly three years have passed since its discovery, the SARS-CoV-2 virus continues to cause a global pandemic today.

The disease is spread by infected droplets inhaled into the respiratory system. Incubation lasts between two and fourteen days. Symptoms are usually fever, loss of taste and smell, cough, and shortness of breath. Considering the data from the period before the rapid vaccination, the case mortality rate is estimated to range between 2 and 3% [2].

Although SARS-CoV-2 infections mainly affect the lungs, approximately 10% of COVID-19 patients also have elevated liver function tests (LFTs) [3]. In the intensive care unit patients with severe COVID-19 increased LFT and associated complications have been reported frequently. Patients with COVID-19 have been linked to various possible liver dysfunction theories. According to widely accepted theories, immune dysfunction results from cytokine storm. The second was identified secondary to direct viral entry and bile duct dysfunction via the known SARS-CoV-2 entry receptor angiotensin-2 converting enzyme (ACE2) found in cholangiocytes in liver tissues [4].

Typically, liver dysfunction associated with various inflammatory markers, as well as high concentrations of LFTs, is one of the most common extrapulmonary manifestations of COVID-19. Compared to baseline values, 35-46% of COVID-19 patients reported elevated LFTs at presentation, with an absolute increase of 14-53% [5–7].

Liver damage can be multifactorial and heterogeneous. Hepatomegaly is an abnormal enlargement of liver size and is defined as a volumetric change [8]. In many studies, the reliability of three-dimensional (3D) CT imaging for hepatomegaly assessment has been demonstrated by 3D volumetric analysis, which is considered the benchmark standard for measuring liver volume. However, very few studies

have evaluated the effect of COVID-19 on liver and hepatomegaly findings in CT [9].

This study aimed at assessing the effect of clinical findings evaluated at admission and the presence of CT-guided hepatomegaly on COVID-19 clinical outcomes in hospitalized patients with a diagnosis of COVID-19.

Methodology

Patients

The study included COVID-19 patients over the age of 18 who were hospitalized for department services and/or intensive care after being diagnosed with the disease via a nasopharyngeal swab in the emergency department or pandemic outpatient clinics. Patients who applied to Van Training and Research Hospital between June 2020 and December 2020 were included in the study.

Ethical approval

This study was approved by the ethics committee of the Van Training and Research Hospital (Decision Number: 2020/10 dated 04.06.2020 (Date and Approval No.). The patient data were anonymized before the analysis. As the study was retrospective, the requirement for consent was waived.

Exclusion criteria

Patients under the age of 18 years, with known liver disease and who had used drugs that could cause LFT elevation defined in the last 3 months were not included in our study. In order to exclude the patients included in the study in terms of chronic and/or acute liver disease, the opinions of the internal medicine and gastroenterology clinics were obtained. In our study, patients diagnosed with viral, hematological diseases, cancer, storage disease, alcoholic, NAFLD, NASH, Wilson's disease, Hemochromatosis, autoimmune hepatitis and patients whose liver parenchyma was not found to be normal in US imaging were excluded from the study.

Demographic information

Symptoms related to COVID-19 have been recorded. In addition, the length of stay in the ICU and the mortality rate were recorded. All patients were followed up until discharge or death. White blood cell count (WBC), platelets, neutrophil count, lymphocyte count, hemoglobin (Hb), HbA1c, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), LFTs were recorded. Liver injury was defined as the presence of elevated ALT and/or elevated AST greater than three times the upper limit of the normal reference range [10].

COVID-19 pneumonia diagnosis

The COVID-19 case was identified based on the Methodological Guide to Coronavirus Pandemic Outbreak published by the National Health Commission of the Ministry of Health Science Board. According to the Ministry of Health-based guideline, RT-PCR positivity in nasopharyngeal swab (NS), sputum, or endotracheal aspirates was accepted as the gold standard for diagnosis. COVID-19 diagnosis date, clinical severity classification, and demographic information were obtained from the clinical records of the patients [11].

Real Time RT-PCR

RT-PCR analysis was performed on the materials obtained from patients with nasal and oral sequential swabs. RT-PCR testing was performed according to the manufacturer's instructions. (2B010271500RD, COVID- 19/Flu- RT- qPCR, Bioeksen R&D, Bio-Speedy, Turkey).

Classification of COVID-19 severity

COVID-19 patients were divided into four groups. Mild symptomatic (1); those without pneumonia and other organ-related damage, (2) moderate; mild pneumonia, (3) severe; and critically ill patients with the presence of dyspnea, respiratory rate > 30/min, blood oxygen saturation < 93%, arterial oxygen partial pressure (PaO_2/FiO_2 < 300 and lung infiltration > 50% in 24 to 48 hours, and (4) respiratory failure, septic shock or multiple organ dysfunction and failure.

Evaluation of hepatomegaly with CT

Hepatomegaly is indicated if the liver size is larger than the average liver size in the healthy population. Unfortunately, there is currently no established guideline nomogram for the volumetric evaluation of hepatomegaly. Some reference ranges can be obtained from the relationship between liver size and the patient's body surface area. In the current study, only cases found to be normal by all radiologists were used to calculate the normograms. The radiologists' performance in diagnosing hepatomegaly was evaluated retrospectively using the H score as the reference standard.

CT works were performed with various imaging protocols for various indications. Non-contrast enhanced CT work was used as long as the technical quality was sufficient to allow volumetric measurements. CT work was performed on Toshiba CT scanners (Alexion/Advance, Toshiba Medical Systems Corporation, Nashua, Japan). CT scans were performed

using advanced image processing analysis software (INFINIT Xelis, v1.0.6.3) to calculate parameters for individual liver sizes by dividing abdominal tissues. Patients whose tomography images of all liver sections were accessed were included in the study [12]. Patients with midclavicular or even liver measurement of 16 cm and above and those with non-variational and non-ectopic livers crossing the lower end of the right kidney were evaluated as hepatomegaly [13]. These criteria are standard and generally accepted criteria in radiology practice. Volume measurement could not be performed for technical reasons.

First, two linear sections of the right hepatic lobe were obtained in the sagittal image in the midclavicular plane. The maximum oblique size ranged from maximum vertical to maximum horizontal depending on the shape of the liver. Liver volume was then calculated using software-guided manual 3D segmentation. In our study, hepatomegaly was defined as a measured liver volume of 2000 mL or more. Radiologists were unaware of the study during CT liver measurements.

Table 1. Laboratory findings, age distribution, and patient admission characteristics.

	Mean (SD)	Median (Min-Max)
Age (years)	60.4 (16.8)	62 (18-94)
LOS (day)	10.4 (9.6)	8 (0-72)
AST (U/L)	39.4 (49.1)	29.5 (6.7-601.3)
ALT (U/L)	31.3 (31.5)	22.5 (2.4-316.2)
LDH (U/L)	392.3 (200.0)	339.5 (133-1072)
CK (U/L)	228.9 (583.3)	105 (16-6842)
Liver sizes	**n**	**(%)**
Normal	241	65.70%
Hepatomegaly	126	34.30%
Complaint	**n**	**(%)**
Shortness of breath	225	61.30%
Cough	187	51.00%
Weakness	92	25.10%
Myalgia	56	15.30%
Loss of appetite	36	9.80%
Gastrointestinal findings	24	6.50%
Headache	21	5.70%
Changes in consciousness	7	1.90%
Taste-odor reduction	4	1.10%
Absent	42	11.40%
Comorbidity	**n**	**(%)**
Absent	149	40.60%
HT	127	34.60%
DM	84	22.90%
CAD	77	21.00%
COPD	51	13.90%
Neurological	21	5.70%
CKD	15	4.10%
Psychiatric disorders	7	1.90%
Morbid Obesity	6	1.60%
Malignancy	5	1.40%
Other	4	1.10%

SD.: Standard deviation; n: number; LFT: Liver function test; DM: Diabetes Mellitus; HT: Hypertension; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; LOS: Length of stay; AST: Aspartate Aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatinine kinase; U: Unity; L: Liter; SD.: Standard deviation; Min.: Minimum; Max.: Maximum

Liver function tests

All published literature analyzing liver biochemical parameters in COVID-19 patients was reviewed. Based on previous studies, abnormalities in liver biochemistry parameters were defined as elevations in the following LFTs: ALT > 40 U/L, AST > 40 U/L, and total bilirubin > 1.20 mg/dL. As noted in previous studies, liver damage was defined as an ALT and/or AST greater than three times the upper limits of normal (ULN) and/or total bilirubin greater than twice the normal (ULN) [10]. Conditions that may cause an increase in transaminases; HBsAg, anti-HBc-IgM, anti-HCV, anti-CMV-IgM and anti-EBV-IgM and immunoassays, immunoglobulin G levels and antinuclear antibodies were evaluated for autoimmune hepatitis. Patients with elevated liver function tests that could not be explained by infection or the overall clinical picture were not included in the study.

Treatment

Treatment regimens used for the management of COVID-19 treatment included antivirals such as lopinavir-ritonavir and favipiravir, convalescent plasma antibodies, corticosteroid, low molecular weight heparin (LMWH), antifungals, and, in eligible patients, the IL-6 receptor blocker tocilizumab.

Ethical approval

This study was approved by the ethics committee of the Van Training and Research Hospital (Decision Number: 2020/10 Date: 04.06.2020). The patient data were anonymized before the analysis. As the study was retrospective, the requirement for consent was waived.

Statistical analysis

The SPSS 27.0 program was used in the analysis of the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated with the Levene test. The Dunn's Test was used to compare the course of the disease according to quantitative variables such as age, follow-up time, AST, ALT, LDH, and CK. The multinomial logistic regression test was used to determine the cause-effect

relationship between the explanatory variables of the disease course and the binary logistic regression test was used with the Enter method for the disease course reduced to two groups. While quantitative variables were expressed as mean (standard deviation) and median (Min./Max.) and median (IQR25/75) in the tables, categorical variables were shown as n (%). Variables were analyzed at the 95% confidence level and a *p*-value of less than 0.05 was considered significant.

Results

Demographic information

During this period, 745 patients were admitted to our hospital. 144 patients without CT imaging and 228 patients whose liver sizes could not be detected in abdominal CT scans were not included in the study. After the exclusion of a total of 7 patients with chronic liver disease, diagnosis of malignancy, and unspecified LFT elevation history, 367 patients who were eligible for the study were evaluated. A total of 367 COVID-19 patients, 254 (69.2%) males and 113 (30.8%) females, with a mean age of 60.4 (16.8) years, were included in the study. 218 of the patients (59.4%) had at least one comorbid disease. The distribution of other comorbidities is summarized in Table 1.

Symptoms

The most common complaints of patients presenting to the emergency department were found to be shortness of breath (61.3%), cough (51%), fatigue (25.1%) and myalgia (15.3%), in order of frequency. However, 42 (11.4%) patients were found to be mildly symptomatic. Other application complaints are summarized in Table 1.

Table 2. Demographic findings.

	n (%)
Gender, Male	254 (69.2)
Comorbidity (≥ 1)	218 (59.4)
Symptom (≥ 1)	325 (88.6)
Intensive care (+)	131 (35.7)
Complication (≥ 1)	115 (31.3)
High LFT (≥ 5 × UNL)	78 (21.3)
Treatment	
Antiviral	367 (100)
Antibiotic	216 (58.9)
Corticosteroid	45 (12.3)
Convalescent immune plasma	33 (9)

SD.: Standard deviation; n: number; LFT: Liver function test; DM: Diabetes Mellitus; HT: Hypertension; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; UNL: upper normal limit.

COVID-19 treatment

All patients (n = 367) had received antiviral treatment (favipiravir) due to RT-PCR positivity. In addition, 216 (58.9%) of the patients were given additional antibiotic therapy, while 45 (12.3%) were given varying doses of systemic steroids, and 33 (9.0%) patients were given convalescent immune plasma therapy (Table 2).

Laboratory findings

The laboratory tests taken during the emergency service admissions of the patients are summarized in Table 1. The Median AST value was 29.5 (6.7-601.3) IU/L, median ALT value was 22.5 (2.4-316.2) IU/L, median LDH levels were 339.5 (133-1072) IU/L, and median CK levels were 105 (16-6842) IU/ L (Table 1).

Table 3. Grouping by the course of disease.

	Disease Severity				
	Uncomplicated (A) (n = 123)	**Mild-Medium (B) (n = 132)**	**Severe (C) (n = 31)**	**Mortality (D) (n = 81)**	***p***
Age, median (q1/q3)	56 (36/67) **BCD**	61 (49.5/69.5) **CD**	67 (57/75)	72 (63/81)	**< 0.001** [j]
Gender, Male n (%)	80 (65.0)	97 (73.5)	21 (67.7)	56 (69.1)	0.548 [c]
Hepatomegaly	26 (21.1)	45 (34.1) **A**	15 (48.4) **AB**	40 (49.4) **AB**	**< 0.001** [c]
Comorbidity (≥ 1)	77 (62.6) **BCD**	51 (38.6) **CD**	4 (12.9)	17 (21.0)	**< 0.001** [c]
Symptom (≥ 1)	81 (65.9)	132 (100.0) **A**	31 (100.0) **A**	81 (100.0) **A**	**< 0.001** [f]
Intensive care	123 (100.0) **CD**	104 (78.8) **CD**	3 (9.7)	6 (7.4)	**< 0.001** [c]
Complication (≥ 1)	14 (11.4)	40 (30.3) **A**	18 (58.1) **AB**	43 (53.1) **AB**	**< 0.001** [c]
High LFT (≥ 5*UNL)	13 (10.6)	33 (25.0) **A**	7 (22.6)	25 (30.9) **A**	**0.003** [c]
LOS, median (q1/q3)	5 (3/8) **BCD**	8 (5/13)	20 (11/25) **BD**	10 (4/18)	**< 0.001** [j]
AST (U/L)	25.3 (18.2/34.9) **D**	29.7 (19.3/44)	26.4 (20/48.1)	35.55 (24.35/48.4)	**< 0.001** [j]
ALT (U/L)	19.3 (14.3/31.75)	24.05 (15.55/39.15)	26 (16.2/41.6)	22.5 (15.2/34.1)	0.367 [j]
LDH (U/L)	217 (185/267) **BCD**	304 (231/391) **CD**	373 (337/527) **D**	557 (463/700)	**< 0.001** [j]
CK (U/L)	87 (57/146) **CD**	94 (48/180) **CD**	170 (83/387)	162 (75/227)	**0.001** [j]

[j] Jonckheere-Terpstra Test (Monte Carlo); Post Hoc Test: Dunn's Test; [f] Fisher Freeman Halton (Monte Carlo); [c] Pearson Chi Square Test(Monte Carlo; Exact); Post Hoc Test: Benjamini-Hochberg correction; Q1: percentile 25; Q3: percentile 75; LOS: Length of stay; AST: Aspartate Aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; CK: Creatinine kinase; U: Unity; L: Liter; SD.: Standard deviation; UNL: upper normal limit; Min.: Minimum; Max.: Maximum; The letters A; B; C and D indicate intergroup significance.

Liver size measurements

Liver sizes were found to be normal in 241 (65.7%) of 367 patients included in the thorax tomography scans, and hepatomegaly was present in 126 (35.3%) patients. The frequency of hepatomegaly was significantly higher in patients with a severe course and mortality compared to other patients ($p < 0.001$). However, there was no significant finding that predicted the poor course of COVID-19-related disease in hepatomegaly ($p > 0.05$) (Table 1).

Clinical outcome

The median hospital stay of the patients was 8 (0-72) days. While it was determined that 236 (68.7%) patients were treated without complications, it was observed that 131 (35.7%) patients developed a need for intensive care. A total of 112 (30.5%) patients were diagnosed with severe COVID-19 and mortality developed in 81 (22.1%) patients (Table 3).

In the study, it was found that patients who had developed severe COVID-19 were older, had higher comorbidity rates, and had higher AST, CK, and LDH levels. It was determined that the patients with no complications and those with mild to moderate severity with a diagnosis of COVID-19 were younger than the patients who had complications and/or died ($p < 0.001$) (Table 3).

The longest hospitalization period was found in the severe COVID-19 group (Median: 20 days [Q1-Q3:11-25]), while the shortest hospitalization was in the mild COVID-19 group (Median: 5 days [Q1-Q3:3-8]). Although AST levels of COVID-19 patients, who had mortality, were higher than those of patients with a mild COVID-19 diagnosis, they were found to be similar to those in patients with moderate and severe COVID-19 (Table 3). In addition, LDH levels increased in line with the increase in COVID-19 severity. CK levels were found to be higher in patients where the course was severe or mortality resulted compared to those in other patients ($p < 0.001$) (Table 3).

Logistic regression analysis results

The patients were grouped and evaluated in the multiple logistic regression model to determine mortality, severe prognosis, and poor clinical course in all groups (Table 4). It was determined that high LDH (OR: 1.021, CI: 95%, [1.014-1.028]; $p < 0.001$) and CK (OR: 1.001, CI: 95%, [1.0003-1.002]; $p = 0.015$) and

Table 4. Predictor factors of severe COVID-19 course.

	Odds Ratio	95% Confidence Interval for Odds Ratio		*p*
		Lower Bound	Upper Bound	
[a] Mortal vs Uncomplicated				
AST	1.005	0.968	1.044	0.781
ALT	1.019	0.978	1.061	0.367
LDH (↑)	1.021	1.014	1.027	**< 0.001**
CK (↑)	1.001	1	1.002	**0.018**
Liver size (↑)	1.592	0.343	7.394	0.553
Comorbidity	3.453	0.782	15.256	0.102
[a] Mortal vs Mild-Medium course				
AST	1.017	0.984	1.051	0.31
ALT	1.022	0.987	1.059	0.212
LDH (↑)	1.009	1.006	1.013	**< 0.001**
CK	1	0.999	1.001	0.619
Liver size (↑)	1.168	0.36	3.79	0.796
Comorbidity	1.551	0.433	5.558	0.505
[a] Mortal vs Severe course				
AST	1.027	0.993	1.062	0.127
ALT	1.031	0.995	1.068	0.094
LDH (↑)	0.995	0.992	0.999	**0.011**
CK	1.001	1	1.001	0.060
Liver size (↑)	1.299	0.389	4.341	0.671
Comorbidity	2.342	0.532	10.309	0.260
[b] Mortal vs All				
Age	1.067	1.027	1.109	**0.001**
LDH (↑)	1.009	1.006	1.012	**< 0.001**
CK (↑)	1.001	1	1.001	**0.042**
[b] (Mortal + Heavy Course) vs (Uncomplicated + Mild-Medium course)				
Age (↑)	1.048	1.015	1.082	**0.005**
Comorbidity	0.448	0.174	1.156	0.097
LDH (↑)	1.009	1.006	1.012	**< 0.001**

[a] Multiple Nominal Logistic Regression; [b] Multiple Logistic Regression (Method = Enter); C.I.: Confidence interval.

the presence of at least one comorbid disease (OR: 4.393, CI: 95%, [1.255-15.384]; $p = 0.021$) were more common in COVID-19 patients who developed mortality compared to mild COVID-19 cases.

It was determined that only LDH levels were higher in patients with COVID-19 where mortality resulted compared to patients with moderate course of follow-up (OR: 1.010, CI: 95%, [1.006-1.013]; $p < 0.001$). It was seen that high LDH (OR: 1.010, CI: 95%, [1.007-1.013]; $p < 0.001$) and the presence of comorbidity (OR: 3.203, CI: 95%, [1.301-7.887]; $p = 0.011$) were more common in COVID-19 patients with severe course and mortality compared to mild and moderate COVID-19 patients. When COVID-19 patients who developed mortality were compared with other patients with a diagnosis of COVID-19, there was no additional risk factor affecting mortality except high LDH (OR: 1.009, CI: 95%, [1.006-1.012]; $p < 0.001$) and CK (OR: 1.001 CI: 95%, [1.000-1.001]; $p = 0.032$) (Table 4).

Discussion

Although the pulmonary system is primarily affected, several studies have reported that COVID-19 infection affects other organs and systems, including the kidneys, cardiovascular, gastrointestinal, and hepatic systems. Elevated LFT at presentation is significantly associated with clinical severity. In this study, new retrospectively collected data on the association of LFT at admission with clinical outcomes in 367 well-characterized COVID-19 patients are presented.

Gastrointestinal symptoms are common in COVID-19 patients and have been reported to correlate with disease severity. Furthermore, the identification of virus particles in the contents of the gastrointestinal lumen suggested a relationship between the virus and the gastrointestinal tract. In a study conducted in the early stages of the epidemic, SARS-CoV-2 RNA was detected in stool samples of COVID-19 patients with diarrhea. In Wuhan, Chen *et al.* [14] first reported that LFTs were elevated in 43.9% of patients. According to consecutive reports published subsequently, the incidence of COVID-19-related liver injury ranges from 14.8% to 78%. The most common changes detected are mild elevations of AST and/or ALT (usually 3 times the upper normal limit) [5–7].

Jin *et al.* [15] showed that liver dysfunction is common in patients diagnosed with COVID-19 with gastrointestinal findings. Ponziani *et al.* [16] found that baseline liver enzyme abnormality was associated with a 2.19-fold increased risk of ICU admission. Yip *et al.* [17] reported elevated ALT/AST levels and liver damage in patients diagnosed with COVID-19 who developed adverse clinical outcomes (including ICU admission, use of invasive mechanical ventilation, and death).

The definition of liver damage from COVID-19 has not yet been established. Therefore, many investigators interpret it as any clinical or laboratory abnormality of the liver that occurs during disease and treatment in patients with or without pre-existing liver disease. Kaneko *et al.* [18] stated that C-reactive protein (CRP), oxygenation, intubation and loss of appetite, diarrhea and nausea measured at admission are predictors of liver disorder that occur with elevated transaminase. Many antiviral drugs and steroids are used to treat the disease where the level of severity is moderate or severe, which can cause liver toxicity in COVID-19 patients. Abnormal liver tests and the presence of liver damage are associated with progression to severe pneumonia, and it has been reported that the use of lopinavir/ritonavir increases the probability of liver damage by 4 times [19]. The systemic immune response can worsen the progression of the infection and result in liver damage. Large amounts of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) in serum were found in the most severe infections, indicating cytokine storm disturbance depending on the severity of the infection. It has been shown that drugs used in the treatment of COVID-19 can also cause liver dysfunction. Since the patients in our study did not start to use medication at the time of their admission, the evaluation was made independently of the medication.

About one-third of hospitalized patients had baseline AST, ALT, or GGT levels that increased, although the elevations were usually mild. Consistent with previous studies, the most frequently elevated enzyme was AST [20–22]. Abnormal LFTs are common in COVID-19 patients. Elevated bilirubin, alkaline phosphatase (ALP), and GGT levels have been reported in addition to elevations of AST or ALT in 13–58% of patients [23–25].The pattern of liver damage is usually hepatocellular rather than cholestatic and is usually mild. Liver test abnormalities are more common in patients with more severe COVID-19, and these higher levels are closely related to COVID-19 outcome [26]. AST rises more frequently than ALT and is associated with COVID-19 severity and mortality, which may reflect immune-mediated inflammation or other extrahepatic causes [20,27].

Elevated LFTs have previously been associated with NASH and obesity. In the current study, it was observed that patients who developed severe COVID-19 were older, had a higher frequency of comorbidities,

and had higher AST, CK, and LDH levels. It was determined that patients with no complications and those where the COVID-19 infection was of mild to moderate severity were younger than those patients who had developed complications and/or had died ($p < 0.001$). In a meta-analysis evaluating the impact of comorbidity on the course of COVID-19 and including 46,248 patients, hypertension (14-22%) was reported as the most common comorbidity, followed by diabetes mellitus (6-11%) and cardiac Cardiovascular disease (4-7%) and respiratory disease (1-3%) in COVID-19 patients [20,27]. In the current study, 218 (59.4%) of the patients had at least one comorbid disease. The distribution of the most common comorbidities was found to be HT, T2DM, CVD, and COPD, in order of frequency, similar to that reported in the literature. Since these rates were evaluated in patients requiring hospitalization, they were determined to be higher than the comorbidities found in the general population.

In a study of critically ill COVID-19 patients, US findings consistent with hepatomegaly were reported in 56% (23/41) of patients [29]. Biliary problems such as cholecystitis, gallbladder wall thickness, and prominent common bile duct were observed in 41.4% (17/41) of patients. Findings associated with acute liver injury, including signs of acute hepatitis (e.g., gallbladder wall thickening, hepatomegaly, and decreased hepatic parenchymal echogenicity) and vascular complications, were noted in 48.7% of COVID-19 patients hospitalized in the ICU [30].

Abdominal CT scan findings are rarely mentioned in the evaluation of hepatomegaly. In a retrospective cohort study of 115 patients with COVID-19, hepatic hypodensity (26.09%) and streaking in pericholecystic adipose tissue (21.27%) were detected on upper abdominal CT. Liver hypodensity, on the other hand, was noted with an increased frequency (58.82%) in critical cases [31]. The current study found that the incidence of hepatomegaly is higher in patients with severe and/or fatal COVID-19. However, logistic regression analysis failed to show the increased risk of a severe or fatal COVID-19 outcome with an increase in liver size. This can be explained by the fact that severe COVID-19 patients are older, and have a higher rate of comorbidities that require multiple drug use (chronic polypharmacy-associated hepatosteatosis).

A systematic review and meta-analysis from China (35 studies, 6,686 COVID-19 patients) that included increased ALT (OR = 1.89) and increased AST (OR = 3.08) in severe cases showed significantly higher rates of hepatic dysfunction have been reported compared to patients with a non-serious COVID-19 diagnosis [32]. Similarly, liver enzyme abnormality was found to be an independent predictor of ICU admission or death. For this reason, it is recommended to regularly monitor the liver functions of patients with a diagnosis of COVID-19 [3]. COVID-19-related mortality rates can increase exponentially due to significant differences such as the presence of comorbidity, age, geographical situation, and access to treatment. Severe cases may lead to the development of ARDS, in which case assisted respiratory support (NIMV or MV) is required. It was emphasized that four out of 5 patients with severe COVID-19 had at least one additional comorbidity [33].

Because our hospital is a tertiary centre due to its location, the study sample in the current study consisted of inpatients, patients admitted with complex symptoms, and patients with multiple comorbidities and longer hospital stays after symptom onset. The resulting sample composition could have explained the significantly higher mortality rate (22.7%) compared to studies in the literature.

In one of the largest studies evaluating the outcome of COVID-19 related to liver dysfunction, 12,882 hospitalized confirmed COVID-19 patients were reviewed. In this study, the overall prevalence of hepatic comorbidities ranged from 2% to 11%, and they were not associated with poorer outcomes [34]. However, another study focused on patients with pre-existing liver disease (9% of 2780), with a higher risk of death (12% vs. 4%) and an increased risk of prolonged hospital stay [35,36]. In the current study, because patients with previously known chronic liver disease were not included, it was determined that an elevated liver function test was not associated with severe disease course and mortality.

There was no significant relationship between gender distribution, the presence of hepatomegaly, and ALT levels at presentation and during the clinical course. However, in patients with severe COVID-19 and COVID-related mortality, the presence of at least one comorbid disease, the frequency of intensive care unit admission, the frequency of additional complications, and the detection of elevated LFTs were found to be significantly higher compared to figures recorded in the mild and moderate groups.

The current study aimed to assess the relationship between LFT elevation and COVID-19-related mortality. While AST levels of COVID-19 patients who developed mortality were higher than those of patients with mild COVID-19, similar levels were observed in moderate and severe COVID-19 patients. In COVID-19 patients who develop mortality, high LDH (OR = 1.021) and CK (OR = 1.001), as well as the presence of

at least one comorbidity (OR: 4.393), were found to be more common when compared to levels in patients with a mild course of COVID-19. It was concluded that the factors that affected COVID-19-related mortality most were the presence of comorbidity and LDH. In addition, LDH levels increased in line with the increase in COVID-19 severity. On the other hand, CK levels were higher in COVID-19 patients, which resulted in mortality, compared to those in other patients ($p < 0.001$). When comparing COVID-19 with other patients who developed mortality, no additional risk factors were found to predict mortality except high LDH (OR = 1.009) and CK (OR = 1.001).

There are some limitations of the current study, which uses a retrospective method of file scanning. The study's shortcomings include the contact status of the patients, information on the incubation period, and the inability to obtain detailed medical treatment and examination histories before admission to the emergency department. In addition, in this study, bias may have occurred in situations that directly affected LFT levels, for example, in relation to the information about chronic liver disease in some patients, and the use of drugs, alcohol, and herbal products. However, the fact that the distribution regarding the administration of the COVID-19 vaccine was not clearly known during the process of our study created an inevitable limitation in the evaluation of patients.

In conclusion, in patients who needed to be hospitalized with a diagnosis of COVID-19 and who did not have acute and/or chronic liver disease, elevated liver function test results and an increase in liver size at presentation were seen not to have an effect on the clinical outcome. However, in addition to the presence of advanced age and comorbidity, the effects of which were clearly defined before, the presence of hepatomegaly measured by CT at admission, and high LDH and CK levels were associated with poor clinical outcomes. In this regard, there is a need for more comprehensive studies in which the liver sizes and measurements of the normal population are re-evaluated.

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