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Original article

## Liver function as a predictor of mortality in COVID-19: A retrospective study



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## ABSTRACT

**Introduction and Objectives:** In many studies, varying degrees of liver damage have been reported in more than half of the COVID-19 patients. The aim of this study is to determine the effect of liver biochemical parameters abnormality on mortality in critical COVID-19 patients who have been followed in the ICU since the beginning of the pandemic process.

**Materials and Methods:** In this study 533 critical patients who admitted to the ICU due to COVID-19 were included. The patients were divided into three groups according to their ALT, AST, and total bilirubin levels at their admission to the ICU. Group 1 was formed of patients with normal liver biochemical parameters values; Group 2 was formed of patients with liver biochemical parameters abnormality; Group 3 was formed of patients with liver injury.

**Results:** 353 (66.2%) of all patients died. Neutrophil, aPTT, CRP, LDH, CK, ALT, AST, bilirubin, procalcitonin and ferritin values in Group 2 and Group 3 were found to be statistically significantly higher than Group 1. It was detected that the days of stay in ICU of the patients in Group 1 was statistically significantly longer than others group. It was found that the patients in Groups 2 and 3 had higher total, 7-day, and 28-day mortality rates than expected.

**Conclusions:** The study showed that liver disfunction was associated with higher mortality and shorter ICU occupation time.

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## 1. Introduction

In a number of studies, varying degrees of liver damage have been noted in more than half of the patients who diagnosed COVID-19 [1,2]. It has been shown that the SARS-CoV-2 receptor, called ACE 2, is also present highly in bile duct cells except alveolar epithelial cells [3,4]. Some studies support that SARS-CoV-2 can also infect bile duct cells through this receptor and cause

liver biochemical parameters abnormality [5]. In previous studies, it has been noted that 14-78% of COVID-19 patients have an increase in liver biochemical parameters [1,2,6-9]. Additionally, microvesicular steatosis, lobular activity and portal activity were demonstrated in liver biopsy specimens of one patient who died from COVID-19 [10]. This suggests that SARS-CoV-2 may have caused liver damage. Liver dysfunction that develops in these patients can cause to failure of liver and death [11]. For this reason, it is important to investigate liver damage in COVID-19 cases.

Considered the highly contagious and pathogenic nature of SARS-CoV-2 and the high incidence of liver damage, evaluation of liver function in COVID-19 patients is important [5]. Previous studies have reported an association between liver function and duration of hospital stay [5], risk of progression to severe COVID-19 [7-9], and mortality [12].

The aim of this study is to retrospectively determine the effect of liver biochemical parameters abnormalities on mortality in critical patients with COVID-19 who have been followed in the ICU since the beginning of the pandemic process.

**Abbreviations:** COVID-19, Coronavirus disease 2019; ARDS, Acute respiratory distress syndrome; ACE2, angiotensin-converting enzyme 2; ICU, Intensive care unit; ALT, alanine aminotransferase; AST, aspartate aminotransferase; RT-PCR, real-time reverse transcriptase-polymerase chain reaction; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; PT, prothrombin time; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase

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## 2. Materials and methods

### 2.1. Study design

Critical COVID-19 patients who admitted to the ICU of our hospital between April 2020 and October 2020 and who was confirmed with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test were included in this retrospective cohort study. The necessary permits have been taken from The Republic of Turkey Ministry of Health Scientific Research Platform (11/20/2020) and Diyarbakir Gazi Yaşargil of Education and Research Hospital (21/11/2020). The trial was registered with clinicaltrials.gov (NCT04669509). This study was carried out in accordance with the Helsinki Declaration criteria.

### 2.2. Inclusion and exclusion criteria

Critical patients who had COVID-19 and admitted to the ICU on the dates specified, 18 > age, in serious need of oxygen support according to WHO [13] and the temporary guidelines of The Republic of Turkey Ministry of Health Scientific Committee [14], (respiratory rate > 30 / min. and/or severe respiratory distress and/or oxygen saturation at room air < 90% (the patient receiving oxygen PaO<sub>2</sub> / FiO<sub>2</sub> < 300); bilateral diffuse pneumonia findings detected on chest images; developed or had severe pneumonia, ARDS, sepsis, septic shock and acute renal failure, were included. Patients who 18 < age, pregnant, with a history of liver disease or chronic viral hepatitis infection, whose data are not fully available in the hospital system or the patient file records, with mild-moderate symptoms, no respiratory distress, and no signs of diffuse pneumonia in chest radiography or tomography, and non COVID-19 were excluded.

### 2.3. Demographic and clinical data

The patients' age, gender, comorbidity, and complaints were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, hemogram parameters (white blood cell (WBC), neutrophil, lymphocyte, platelet count), coagulation parameters (prothrombin time (PTZ), Activated Partial Thromboplastin Time (aPTT), and D-dimer), blood biochemistry values (C-reactive protein (CRP), lactate dehydrogenase (LDH), creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and indirect bilirubin; c702-502 autoanalyzer, Roche, Ros-bach, Germany), procalcitonin and ferritin levels were recorded at the time of the ICU admission. In addition, the ICU days, 7-day, 28-day, and total mortality were recorded. Clinical data were collected from the hospital's computer system. Patient data were rechecked for erroneous data before the last data entry and entered into a computerized database.

### 2.4. Liver biochemical parameters

All published literature which analyzed liver biochemical parameters in COVID-19 patients was examined through databases and shown in Table 1 [5,6,11,15–37]. Based on previous studies, liver biochemical parameters abnormalities were defined as the elevation of the following liver enzymes in serum: ALT > 40 U / L, AST > 40 U / L, and total bilirubin > 1.20 mg/d l. As in a previous study, we defined ALT and/or AST over three times upper limits of normal (ULN), and/or total bilirubin over two times ULN as liver injury [7].

### 2.5. COVID-19 severity on mortality

Patients were divided into three groups according to liver biochemical parameters values at their admission to the ICU. Group 1 was formed of patients with normal liver biochemical parameters values; Group 2 was formed of patients with liver biochemical

parameters abnormality; Group 3 was formed of patients with liver injury. All three groups were compared in terms of clinical characteristics, APACHE II and SOFA scores, laboratory values, days of ICU stay, 7-day, 28-day, and total mortality.

### 2.6. Statistical analysis

SPSS 22.0 for Windows program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numerical data were expressed as means with standard deviation. Categorical data as frequencies with percentages. Comparison of categorical data between groups was made using the chi-square test and the results were given as n%. Whether the numerical data fit the normality distribution was evaluated using the Kolmogorov–Smirnov test. The Kruskal Wallis test was used in the comparison of the groups, as the numerical data did not conform to the normal distribution. Student-*t* and Mann–Whitney *U* tests were used to compare groups in pairs. In all comparisons, *p* < 0.05 was considered significant.

## 3. Results

In the study, the data of 567 patients in total were accessed. After exclusion criteria, 34 patients were excluded, and the study was completed with 533 patients. The patients' mean age was 69.2 ± 14.8 years. 283 (53.1%) patients were male and 250 (46.9%) were female. In total, 401 (75.2%) patients had at least one comorbidity and the most common comorbidities were hypertension (218, 40.9%) and diabetes (151, 28.3%). Between the dates of the study, 353 of all patients died. The mortality rate was found to be 66.2%. The average stay in the ICU was 11.3 ± 10.7 days. The patients' demographic and clinical datas are represented in Table 2.

### 3.1. Clinical outcomes

When the groups were compared in terms of demographic and clinical characteristics, it was found that the rates of liver biochemical parameters abnormality and liver injury were higher in the male patients than in the female patients (*p* < 0.001). In addition, those with liver damage were found to have statistically significantly higher SOFA scores (*p* < 0.001) (Table 2).

When the groups were compared in terms of laboratory values at the time of first admission to the ICU, the neutrophil, aPTT, CRP, LDH, CK, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, procalcitonin, and ferritin values were statistically significantly higher in Group 2 and Group 3 than Group 1 (*p* = 0.047 for neutrophil; *p* = 0.025 for aPTT; *p* = 0.033 for CRP; *p* 0.001 for other values). Although most laboratory values were found to be higher in Group 3 than Group 2, mean CRP and indirect bilirubin values were higher in Group 2 than Group 3, but this difference was not statistically significant in the dual analysis performed (*p* = for CRP. 0.36; *p* = 0.87 for indirect bilirubin) (Table 2).

### 3.2. Association of liver biochemical parameters abnormality with death and COVID-19

It was found that the length of ICU stay of the patients were statistically significantly longer in Group 1 than in Groups 2 and 3 (*p* = 0.033). When Group 2 and Group 3 were compared, it was found that the duration of stay in the ICU of the patients were statistically significantly shorter in Group 3 than in Group 2 (*p* = 0.042) (Table 2).

It was found that the patients in Groups 2 and 3 had higher total, 7-day, and 28-day mortality rates than expected (*p*-values: 0.004; 0.001; 0.003, respectively) (Table 3).

**Table 1**  
Characteristics of eligible studies in world literature.

Author	Year	Country	Groups	Cases	Age	Liver biochemical parameters	Outcomes
Fan [5]	2020	China	Normal LB	93	50 (36–63)	ALT, AST, ALP, GGT, LDH, bilirubin	Mortality 0%
Huang [6]	2020	China	Abnormal LB	55	52 (37–65)	ALT, AST, ALP, GGT, bilirubin	Mortality 1.8%
			Normal LB	370	53.5 (37–64)		Severe 1.35%
Jiang [11]	2020	China	Abnormal LB	253	58.0 (47.0–67.0)	ALT, AST, ALP, bilirubin	Severe 12.65%
			Liver Injury	52	51.5 (35.7–60.2)		Severe 30.77%
Zhang [15]	2020	China	Non-critically ill	104	47.2 ± 13.3	ALT, AST, ALP, GGT, LDH, bilirubin	Liver injury 51.9%
			Critically ill	27	67.0 ± 16.2		Liver injury 81.5%
Medetalibeyoglu [16]	2020	Turkey	Mild COVID-19	84	43.9 ± 14.8	ALT, AST, ALP, GGT, LDH, bilirubin	Mortality 0%
			Severe COVID-19	31	64.5 ± 13.2		Mortality 1%
Chen [17]	2021	China	AST–ALT ≤ 40	401	57.0 ± 15.5	ALT, AST, ALP, GGT, LDH, bilirubin	Mortality 4.7%
			AST–ALT > 40	153	56.4 ± 16.4		Mortality 13.7%
Ding [18]	2020	China	Non-LBA	603	49.0 (32.0)	ALT, AST, GGT, bilirubin	Mortality 10.0%
			Mild LBA	195	56.0 (26.0)		Mortality 17.0%
Yeoman [19]	2020	Wales	Liver injury	32	54.5 (31.25)	ALT, ALP, bilirubin	Mortality 15.2%
			Deceased	200	70.0 (63.7–78.0)		Liver abnormalities 73.0%
Guo [20]	2020	China	Discharged	1873	61.0 (48.0–69.0)	ALT, ALP, bilirubin	Liver abnormalities 43.4%
			Cholestatic injury	72	69		Mortality 41.8%
Yip [21]	2020	China	Mixed injury	21	60	ALT, AST, ALP, GGT, LDH, bilirubin	Mortality 23.8%
			Hepatocellular injury	2	61		Mortality 50%
Chu [22]	2020	China	Normal LB	234	48 (34.8–63.3)	ALT, AST, ALP, GGT, bilirubin	Severe 3.4%
			Abnormal LB	98	54 (39–64.3)		Severity 18.4%
Xie [23]	2020	China	SARS- CoV	1507	44 ± 20	ALT, AST, ALP, LDH, GGT, bilirubin	Mortality 17.1%
			SARS- CoV-2	816	38 ± 18		Mortality 0.4%
Zhou [24]	2020	China	Normal liver function	409	56 (43–66)	ALT, AST, ALP, GGT, bilirubin	Mortality 6.1%
			Liver injury	429	61 (49–69)		Mortality 24.9%
Phipps [25]	2020	USA	Without liver injury	50	56 (45.5–65.0)	ALT, AST, bilirubin	Length of stay (days) 11.4
			With liver injury	29	62.0 (46.0–67.0)		Length of stay (days) 15.4
Weber [26]	2020	Germany	Survivors	137	52 (45–58)	ALT, LDH	Mortality 16.2%
			Non-survivors	54	69 (63–76)		
Mendizabal [27]	2021	Argentina	ALT <2 × ULN	1784	66 (53–78)	ALT, AST, ALP, bilirubin	Mortality 21%
			ALT 2-5 × ULN	344	61 (50–73)		Mortality 23%
Qi [28]	2020	China	ALT >5 × ULN	145	63 (50–71)	ALT, AST, ALP, GGT, bilirubin	Mortality 42%
			Severe COVID-19	217	63 (18–97)		Liver abnormalities 57.6%
Chen [29]	2020	China	Normal LB	882	50.7 ± 18.2	ALT, ALP, bilirubin	Mortality 12.2%
			Abnormal LB	729	54.2 ± 16.1		Mortality 18.7%
Desai [30]	2020	USA	Without liver injury	38	38.5 (26.0–47.2)	ALT, AST, bilirubin	Length of stay (days) 15
			With liver injury	32	41.0 (27.5–50.0)		Length of stay (days) 16
Shen [31]	2021	China	Recovered patients	161	51.0 (37.0–66.0)	ALT, AST, ALP, GGT, LDH, bilirubin	Liver injury 9%
			Deaths	113	68.0 (62.0–77.0)		Liver injury 2%
Kumar [32]	2020	India	Without liver injury	163	61.9 ± 17.3	ALT, AST, ALP	Mortality 22.7%
			With liver injury	476	58.8 ± 15.6		Mortality 35.5%
Meszaros [33]	2020	France	No liver injury	179	53.5 (43.5–66.5)	ALT, AST, bilirubin	Length of stay (days) 20.5
			Liver injury	177	59 (45–68.5)		Length of stay (days) 30
Piano [34]	2020	Italy	Normal LB	24	42 (20–77)	ALT, AST, ALP, bilirubin	Mortality 0%
			Abnormal LB	67	45 (15–82)		Mortality 3%
Roedl [35]	2021	Germany	Normal LB	78	69 ± 14	ALT, AST, ALP, GGT, bilirubin	Mortality 7.7%
			Abnormal LB	156	66.5 ± 14		Mortality 19.9%
Wang [36]	2020	China	Normal LB	236	65 (15)	ALT, AST, ALP, GGT, bilirubin	Mortality 11%
			Abnormal LB	329	66 (15)		Mortality 21%
Zhang [37]	2021	China	No liver dysfunction	50	64 (55–73)	ALT, AST, bilirubin	Mortality 16%
			Severe liver dysfunction	22	62 (51–73)		Mortality 68%
Zhang [37]	2021	China	Non-liver injury	354	64 (51.0–71.0)	ALT, Bilirubin	Severe/critical 30.8%
			Liver injury	303	62 (47.0–70.0)		Severe/critical 48.8%
Zhang [37]	2021	China	Normal LB	186	61 (18)	ALT, AST, bilirubin	Mortality 11.2%
			Abnormal LB	185	63 (23)		Mortality 45.9%
			Liver injury	69	65 (17)		Mortality 42.9%

LB; liver biochemistry; LBA; liver biochemistry abnormality; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactic dehydrogenase;

#### 4. Discussion

In this study, liver biochemical parameters abnormality and liver injury were detected in 52% of critical COVID-19 patients during the stay in the ICU. Neutrophil, CRP, LDH, CK, procalcitonin, and ferritin values were found to be higher in patients with liver biochemical parameters abnormality and liver injury compared to patients with normal liver biochemical parameters. In addition, it was determined that patients with liver biochemical parameters abnormality and liver injury had a shorter stay in the ICU than expected, and higher total, 7-day, and 28-day mortality rates compared to patients with normal liver biochemical parameters.

Liver damage in COVID-19 patients can be attributed to a number of secondary effects of the disease as well as the primary infection. Alternative etiologies such as systemic inflammatory response and cytokine storm associated with COVID-19, drug-induced liver damage, hypoxia, hepatic ischemia, and shock can be counted among these secondary effects [15,38]. Compared to the normal liver biochemical parameters group, we found that patients with liver biochemical parameters abnormality and liver injury had higher levels of neutrophils, CRP, procalcitonin, and ferritin, which may be associated with an immune response after virus infection. This suggests that the inflammatory response also contributes to the occurrence of COVID-19 associated liver damage.

**Table 2**  
Demographic, clinical and laboratory characteristics (Mean±SD).

	Total (n = 533)	Group 1 (n = 256)	Group 2 (n = 231)	Group 3 (n = 46)	p value
Age	69,2 ± 14,8	69,1 ± 15,6	69,7 ± 13,9	67,0 ± 15,0	0,48
Gender					<.001*
Female (%)	250 (46,9)	145 (56,6)	89 (38,5)	16 (34,8)	
Male (%)	283 (53,1)	111 (43,4)	142 (61,5)	30 (65,2)	
Comorbidity (Yes)	401 (75,2)	199 (77,8)	170 (73,6)	32 (69,6)	0,37
APACHE II	16,9 ± 7,4	16,3 ± 6,7	16,6 ± 7	21 ± 11,2	0,14
SOFA	4,3 ± 2,5	4,1 ± 2,2	4,2 ± 2,2	6,5 ± 3,9	<.001*
<b>Laboratory values</b>					
White blood cells (× 10 <sup>3</sup> /uL)	11,4 ± 6,8	11,2 ± 7,7	11,4 ± 5,8	12 ± 6,1	0,14
Neutrophil (× 10 <sup>3</sup> /uL)	9,5 ± 5,1	9,2 ± 5,5	9,6 ± 4,5	10,5 ± 5,4	0,047*
Lymphocyte (× 10 <sup>3</sup> /uL)	1,4 ± 4,5	1,6 ± 6,0	1,2 ± 2,6	1,0 ± 0,77	0,43
Platelet (× 10 <sup>3</sup> /uL)	247 ± 104	243 ± 101	246 ± 101	272 ± 137	0,61
Prothrombin time (s)	14,0 ± 5,1	13,9 ± 5,1	13,7 ± 2,6	16,6 ± 11,0	0,08
aPTT (s)	31,4 ± 14,8	31,3 ± 19,3	31,1 ± 9,0	32,9 ± 6,6	0,025*
D-dimer (ng/ml)	1942 ± 4776	2065 ± 5581	1657 ± 3512	2686 ± 5391	0,09
C-reactive protein (mg/L)	139 ± 88	129 ± 87	150 ± 88	135 ± 82	0,031*
Lactate dehydrogenase (U/L)	524 ± 433	395 ± 171	535 ± 207	1188 ± 1135	<.001*
Creatine kinase (U/L)	326 ± 803	147 ± 227	410 ± 595	896 ± 2230	<.001*
Alanine aminotransferase (U/L)	47 ± 112	18 ± 7	39 ± 20	256 ± 313	<.001*
Aspartate aminotransferase (U/L)	76 ± 247	26 ± 8	57 ± 22	457 ± 747	<.001*
Total bilirubin (mg/dl)	0,73 ± 0,52	0,58 ± 0,25	0,8 ± 0,42	1,26 ± 1,23	<.001*
Direct bilirubin (mg/dl)	0,42 ± 0,72	0,36 ± 0,92	0,4 ± 0,23	0,82 ± 0,9	<.001*
Indirect bilirubin (mg/dl)	0,36 ± 0,67	0,27 ± 0,16	0,45 ± 0,99	0,43 ± 0,37	<.001*
Procalcitonin (ng/ml)	3,8 ± 15,9	3,1 ± 16,7	3,3 ± 11,4	10,0 ± 26,5	0,001*
Ferritin (μg/L)	874 ± 639	723 ± 579	985 ± 636	1160 ± 766	<.001*
Intensive care unit days	11,3 ± 10,7	12,1 ± 11	10,6 ± 9,5	10,3 ± 13,9	0,033*

\* Statistically significant; APACHE II=Acute Physiology and Chronic Health Evaluation II score; SOFA=Sequential Organ Failure Assessment score; aPTT=Activated partial thromboplastin time;

**Table 3**  
Comparison of 7-day, 28-day and total mortality rates between groups.

	Total (n = 533)	Group 1 (n = 256)	Group 2 (n = 231)	Group 3 (n = 46)	p value
<b>7-days mortality</b>					
Yes	167 (31,3)	66 (25,8)	77 (33,3)	24 (52,2)	0,001*
No	366 (68,7)	190 (74,2)	154 (66,7)	22 (47,8)	
<b>28-days mortality</b>					
Yes	345 (64,7)	147 (57,4)	165 (71,4)	33 (71,7)	0,003*
No	188 (35,3)	109 (42,6)	66 (28,6)	13 (28,3)	
<b>Total mortality</b>					
Yes	353 (66,2)	152 (59,4)	165 (71,4)	36 (78,3)	0,004*
No	180 (33,8)	104 (40,6)	66 (28,6)	10 (21,7)	

\* Statistically significant

In a systematic review of 107 studies from various countries, Kul-karni et al. reported that 19.2% of COVID-19 survivor patients and 43.3% of COVID-19 non-survivor patients had elevated liver biochemical parameters (elevated was defined AST or ALT levels above 40 U/L and severe liver injury was defined as any elevation of enzymes over three times ULN and bilirubin over 2 ULN) at the first admission) [39]. In another review, Xu et al. reported that the incidence of liver damage in COVID-19 patients ranged from 14.8% to 53%; and serum ALT and AST levels increased up to 7590 U/L and 1445 U/L, respectively, in a severe COVID-19 patient [40]. Recent studies conducted in the United States reveal abnormal liver biochemical parameters (abnormalities were defined as AST >33 U/L, ALT >34 U/L and TBIL >1.2 mg/dL) association with severity, ICU stay, mechanical ventilation, and death. And they found that abnormal liver biochemical parameters are usually minimally elevated (1–2 × ULN), although more-severe hepatitis (2–5 × or >5 ×) may be observed. [41]. Parohan et al. noted that the incidence of liver damage ranged from 58% to 78% in patients with severe COVID-19, and the higher serum levels of AST (weighted mean difference, 8.84 U/L), ALT (weighted mean difference, 7.35 U/L) and total bilirubin (weighted mean difference, 2.30 mmol/L) were associated with severe outcome from COVID-19 infection [42]. In a retrospective study Zhang et al. reported that the mean level of ALT, AST or total bilirubin in severe COVID-19 patients were higher than that in mild (37.87 ± 32.17 vs 21.22 ± 12.67;

38.87 ± 22.55 vs 24.39 ± 9.79; 14.12 ± 6.37 vs 10.27 ± 4.26) [9]. Similarly, Huang et al. found that the rate of high AST value was higher in ICU patients (62%) than non-ICU patients (25%) (mean values respectively 44.0 U/L vs 34.0 U/L) [6]. In this study, 43.3% of critical COVID-19 patients were found to have liver biochemical parameters abnormality and 8.6% were found to have liver injury during the stay in the ICU. The results of our study are in line with previous studies.

It has been stated in some publications that the rate of male patients is higher in severe COVID-19 compared to female patients [12,21,23,41,43]. In addition, it has been reported that patients with abnormal liver biochemical parameters and liver injury in COVID-19 patients are mostly male patients, but the underlying mechanism is not clear [5,7]. In our study, 53.1% of our total number of patients were male, and in accordance with previous studies, it was determined that the groups with abnormal liver biochemical parameters and liver injury were mostly male patients.

In studies conducted on COVID-19 patients, the length of hospital stay was longer in patients with abnormal liver biochemical parameters at the time of admission than in patients with normal liver biochemical parameters [5,11]. Jiang et al. concluded that liver damage would lead to problems in the immune system and thus delay the clearance of the virus. This can be explained by the prolonged hospital stay, the more time needed for liver function to recover, or the failure to eradicate the virus. In the same study, the duration of

hospitalization in patients with liver damage in the critically patient group was numerically higher than in patients without liver damage, but this was not statistically significant [11]. In our study, it was found that the time of stay at the ICU in patients with liver biochemical parameters abnormality and liver injury were shorter than patients with normal liver biochemical parameters. We think that hospitalization periods in critically patients who had COVID-19 are affected by many factors, and the high mortality rates in the liver biochemical parameters abnormality and liver injury groups may cause a short stay in the ICU.

Many studies have reported that abnormal liver biochemical parameters, especially elevated AST and ALT, are associated with increased disease severity and mortality in COVID-19 patients [7,12,24,25,27,44]. Yip et al. stated that ALT / AST elevation and acute liver damage in patients with COVID-19 were independently associated with mortality and that such biochemical changes had important consequences [21]. Huang et al. stated that dynamic changes of ALT and AST levels in COVID-19 patients were more pronounced in patients with liver function damage and in patients who died; The patients with AST > three times the upper limit of normal (ULN) have the highest risk of death and mechanical ventilation [45]. Lei et al. reported that elevated ALT, AST, ALP, and total bilirubin levels in COVID-19 patients are associated with an increased risk of death and that elevated AST among these liver enzymes is associated with the highest risk of death [12]. In their study, Chen et al. noted that ALT, AST, GGT, ALP, and total bilirubin concentrations were significantly higher in patients who died than in healed patients; and that approximately 52% of patients who died and 16% of those who recovered had high AST levels [29]. Again Kulkarni et al., in their meta-analysis, found a higher rate of abnormal liver biochemical parameters results in the non-survive group at the first admission compared to the survive group in COVID-19 patients [39]. In our study, in line with previous studies, it was found that in patients with liver biochemical parameters abnormality and liver injury had higher total, 7-day, and 28-day mortality rates compared to patients with normal liver biochemical parameters.

This study has some limitations. Our data were not capable of evaluating the causality of liver damage and poor clinical outcomes associated with COVID-19.

## 5. Conclusions

As a result, liver dysfunction evaluated by biochemical blood analysis (AST, ALT, and total bilirubin levels) is common in critical COVID-19 patients followed in the ICU. Abnormal liver biochemical parameters are closely related to an increased risk of mortality in critically ill COVID-19 patients. Therefore, these indicators should be closely monitored during the stay in the ICU and special attention should be paid to liver damage.

## Authors' contributions

FS is the first author. Each author either made substantial contributions to the conception or design of the work. FS, CKK, and OU wrote the paper. Each author involved in the acquisition, analysis, or interpretation of data for the work. FS, MB and OU were involved in data cleaning, mortality follow-up, and verification. Each author drafted the manuscript or revised it critically for important intellectual content; and provided final approval of the version to be published. All authors have read and approved the final manuscript. FS and CKK are the study guarantors.

## Clinical trials

The trial was registered with clinicaltrials.gov (NCT04669509)

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## Conflicts of interest

The authors declare that they have no conflict of interest.

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