RESEARCH ARTICLE

The effectiveness of liver function tests in the prediction of mortality in patients with COVID-19

Erdi Huseyin Erdem, Bahar Aydinli, Serkan Dogru, Harun Ozmen

Abstract

Objective: To evaluate the impact of liver function test abnormalities on mortality in critically ill coronavirus disease-2019 patients.

Method: The single-centre, retrospective study was conducted at the Department of Anaesthesiology and Reanimation, Mersin City Training and Research Hospital, Turkiye, and comprised data from March 2020 to January 2022 of patients with positive real-time reverse transcription polymerase chain reaction test on nasopharyngeal swab sample for coronavirus disease-2019. Comorbidities, demographic data, admission to and discharge from the intensive care unit, Acute Physiology and Chronic Health Evaluation II scores, complete blood count on the first and second day of hospitalisation, coagulation parameters, biochemical analysis, 7-day, 28-day and total mortality of the patients in the intensive care unit were recorded. The patients were then divided into groups, with Group 1 having patients with normal liver enzymes, Group 2 having patients with abnormal liver enzymes, and Group 3 having patients with liver damage. Data was analysed using SPSS 20.

Results: Of the 940 subjects, 587(62.4) were males and 353(37.6) were females. The overall mean age of the patients was 67.11±16.65 years. There were 395(42%) patients in Group 1, 534(56.8%) in Group 2 and 11(1.2%) in Group 3. Gamma-glutamyl transferase-1s, aspartate aminotransferase-2nd and albumin-2nd were significant predictors of mortality (p<0.05).

Conclusion: High gamma-glutamyl transferase, aspartate aminotransferase and low albumin levels in critically ill coronavirus disease-2019 patients could be considered indicators of high mortality rate.

Keywords: Coronavirus, Critical illness, Liver function test, Pandemic. (JPMA 74: 1953; 2024)

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a type of beta-coronavirus with a single-stranded enveloped ribonucleic acid (RNA) virus, was found to be the cause of novel coronavirus disease-2019 (COVID-19).[1] The disease was first detected in Wuhan, China, in December 2019 and was subsequently declared a pandemic by the World Health Organisation (WHO) in March 2020.[2] The clinical aspect of COVID-19 ranges from asymptomatic disease without impairment to viral pneumonia, acute respiratory distress syndrome (ARDS), acute respiratory failure and even death.

It is thought that SARS-CoV-2 penetrates the human body using the angiotensin-converting enzyme receptor-2 (ACE-2) with spike protein in the cell membrane.[3] The widespread presence of ACE-2 receptor in alveolar epithelial cells explains that the lungs are primarily affected organs. However, different levels of liver injury have been reported in a large proportion of patients with COVID-19.[4] A number of possible mechanisms have been suggested for liver damage in COVID-19. The ACE-2 receptor is found in bile duct epithelial cells, and, to a lesser intensity, in hepatocytes.[5] This finding suggests that SARS-CoV-2 may cause damage by direct cytopathic effect on liver tissue. However, there are no reports of viral inclusions detected in liver biopsies or autopsies in patients with COVID-19.[6] Other potential types of liver injury in COVID-19 may include liver damage related to antimalarial drugs, such as hydroxychloroquine that is used in its treatment, antiviral drugs, such as favipiravir, remdesivir, lopinavir, ritonavir and anticytokine, inflammation-mediated liver tissue injury or reperfusion damage caused by hypoxia.

Furthermore, several studies have been published on liver damage during the COVID-19 pandemic, reporting higher levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in severe cases of COVID-19 and mentioning that liver damage was more common in severe cases.[7,8] In contrast, some studies did not find a relationship of COVID-19 severity, length of hospital stay (LOS) or mortality with the severity of liver damage.[9,10] The prognostic value of liver damage for COVID-19 is still unknown.

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The current study was planned to define the impact of liver function test on mortality in critically ill COVID-19 inpatients.

Materials and Methods

The single-centre, retrospective study was conducted at the Department of Anaesthesiology and Reanimation, Mersin City Training and Research Hospital, Turkiye, and comprised data from March 2020 to January 2022 of adult patients with positive real-time reverse transcription polymerase chain reaction (RT-PCR) test on nasopharyngeal swab sample for COVID-19 and subsequent findings related to pneumonia on computerised tomography CT scan or X-ray.

Data was excluded for patients aged <18 years, women with pregnancy, those with a history of chronic liver disease and chronic viral hepatitis, patients without findings in imaging examinations, and patients with incomplete data.

After approval from the institutional ethics review committee, the sample size was calculated using ClinCalc (ClinCalc LLC., Chicago, IL, USA) in line with a study which reported that COVID-19 patients had a mean AST value of 38.87±22.55.[9] Using this data, and estimating a 20% increase in AST value with an alpha value of 0.05 and a beta value of 0.90, a sample size of 425 patients was calculated after inflating it by 20% to account for cases with missing data.

Demographic data, comorbidities, admission to and discharge from intensive care unit (ICU), Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores, white blood cell (WBC), lymphocyte, neutrophil, thrombocyte on the first and second day of hospitalisation, prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), D-dimer, ALT, lactate dehydrogenase (LDH), AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, direct and indirect bilirubin, albumin, ferritin, procalcitonin, 7-day, 28-day and total mortality of the patients in ICU were recorded.

The patients were then separated into three groups. Group 1 had patients with normal liver enzymes, Group 2 had patients with abnormal liver enzymes, and Group 3 had patients with liver damage. Elevated ALT >49U/L, AST >40U/L and total bilirubin >1.20mg/dl were defined as abnormalities of liver biochemical parameters. Liver damage was defined as ALT and/or AST above three-fold increase on the upper limit of normal (ULN) and/or total bilirubin above two-fold elevation on ULN levels. All the groups were analysed for APACHE-II, biochemical analyses, days of ICU stay, 7-days, 28-day and total mortality.

Data was analysed using SPSS 20. Data normality was checked using Kolmogorov-Smirnov test. Categorical data was expressed as frequencies and percentages, while quantitative data was expressed as mean and standard deviation. APACHE-II scores, WBC, neutrophil count, lymphocyte count, platelet count, PT, aPTT, D-dimer, CRP, LDH, ALT, AST, GGT, ALP, total bilirubin, direct bilirubin, indirect bilirubin, albumin, ferritin, and procalcitonin parameters were analysed using paired sample t-test or Wilcoxon test. Intergroup comparisons were one using one-way analysis of variance (ANOVA) test or Kruskal-Wallis test. Tukey's honestly significant difference (HSD_ test was used for intragroup post-hoc analyses. Multivariate regression analysis was used to assess the predictive values of biochemical parameters. P<0.05 was considered statistically significant.

Results

Of the 1,556 patient records assessed initially, 940(60.4%) were included. There were 587(62.4) male and 353(37.6) female patients. The overall mean age was 67.11±16.65 years. There were 395(42%) patients in Group 1, 534(56.8%) in Group 2 and 11(1.2%) in Group 3. The mean APACHE-II score of the patients was 15.75±8.85 and the mean hospital stay was 8.03±7.56 days (Table 1).

Mean values for platelet, albumin, PT, international normalised ratio (INR) and CRP on the first day of hospitalisation were higher than the on the second day, while those for ALT, indirect bilirubin and ferritin on the second day of hospitalisation were higher than the first day (Table 2).

Linear multivariate regression analysis showed that

Table-1: Demographic characteristics.

	Group 1 (n:395)		Group 2 (n:534)		Group 3 (n:11)		*p*-value
	n (%)	Mean±SD	n (%)	Mean±SD	n (%)	Mean±SD	
Mean Age (years)		66.19±16.75		64.96±17.07		76.9±11.98	<0.05*
Gender (Female)	171 (43.3)	-	177 (33.1)	-	5 (45.5)	-	<0.05*
APACHE II score	-	15.27±8.41	-	16.02±9.13		25.36±11.12	<0.05*
Hospital stays (days)	-	8.22±7.1	-	8.44±8.08		4.45±3.83	0.173

APACHE: Acute physiology and chronic health evaluation, SD: Standard deviation; *p<0.05; Chi-square test; Kruskal-Wallis test; Tukey's honestly significant difference (HSD) test; Intragroup comparisons for age; Group 1-Group 2: p=0.518; Group 1-Group 3: p=0.096; Group 2-Group 3: p=0.053; Intragroup comparisons for APACHE II score; Group 1-Group 2: p=0.409; Group 1-Group 3: p<0.05*; Group 2-Group 3: p<0.05*; Intragroup comparisons for hospital stays; Group 1-Group 2: p=0.904; Group 1-Group 3: p=0.241; Group 2-Group 3: p=0.201

Table-2: Haematological and biochemical parameters with respect to mortality.

	Exitus		*p*-value	Alive		*p*-value
	1st mea. Mean±SD	2nd mea. Mean±SD		1st mea. Mean±SD	2nd mea. Mean±SD	
WBC (10^3/mm^3)	13.95±20.57	17.48±13.12	<0.05*	11.55±5.93	10.26±5.02	<0.05*
Neutrophile (10^3/mm^3)	10.82±6.36	14.92±9.76	<0.05*	9.34±5.17	8.04±4.13	<0.05*
Lymphocyte (10^3/mm^3)	1.95±12.35	1.38±6.91	<0.05*	1.38±2.32	1.31±2.55	0.683
Platelet (10^3/mm^3)	238.03±128	193.92±131.85	<0.05*	257.56±108.28	269.3±123.29	0.525
AST (U/L)	126.08±386.29	344.9±1107.62	<0.05*	61.72±129.84	43.06±71.36	<0.05*
ALT (U/L)	88.22±263.44	220.27±642.33	<0.05*	61.45±190.03	59.12±137.67	0.145
GGT (U/L)	92.55±227	235±207.11	—	44±54.54	82.26±121.34	0.465
Alb (g/dL)	3.41±0.58	2.67±0.55	<0.05*	3.67±0.55	3.27±0.51	<0.05*
ALP (U/L)	117.04±129.12	144±107.08	>0.05	101.92±167.06	91.76±47.33	0.721
LDH (U/L)	553.96±471.11	986.62±1215.8	<0.05*	410.93±190.09	334.4±172.08	<0.05*
Total Bilirubin (mg/dL)	0.98±2.1	1.09±2.35	0.718	0.82±1.83	0.79±1.77	<0.05*
Direct Bilirubin (mg/dL)	5.29±105.08	0.74±2.08	<0.05*	0.42±1.69	0.38±1.56	<0.05*
Indirect Bilirubin (mg/dL)	23.3±27.83	21.84±37.09	<0.05*	24.77±30.94	28.16±56.67	0.226
Ferritin (ng/mL)	886.96±1370.36	6104.74±40196.31	<0.05*	534.25±1367.06	541.87±1653.05	0.254
Prothrombin (s)	17.52±53.43	18.22±10.3	<0.05*	15.17±44.27	13.29±3.41	0.066
INR	4.93±76.56	1.66±1.08	<0.05*	3.21±45.36	1.15±0.32	<0.05*
aPTT (s)	33.06±33.43	52.51±84.41	<0.05*	33.77±64.36	28.51±26.14	0.221
D-Dimer (mg/L)	6.15±12.37	11.35	<0.05*	4.32±9.07	2.52±4.24	<0.05*
CRP (mg/dL)	12.53±8.99	15.77±10.15	<0.05*	9.25±7.94	5.96±6.68	<0.05*
Procalcitonin (ng/mL)	3.01±8.89	7.09±12.55	<0.05*	6.31±54.46	1.77±6.99	<0.05*

APACHE: Acute physiology and chronic health evaluation, SD: Standard deviation, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, Alb: Albumin, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, INR: International normalised ratio, aPTT: Activated partial thromboplastin time, CRP: C-reactive protien, mm: Milimeter, U: Unit, L: Liter, mg: Milligram, dL: Decilitre, ng: Nanogram, s: Second; *p<0.05; Mann-Whitney U test.

APACHE-II score, albumin-1st, total bilirubin-1st, WBC-2nd, neutrophil-2nd, albumin-2nd, and ALP-2nd measurements were significant predictors of ICU stay (Table 3).

Significant predictors of mortality included APACHE-II score, GGT-1st, CRP-1st, neutrophil-2nd, platelet-2nd, AST-2nd, albumin-2nd and CRP-2nd (Table 4).

Overall and 7-day mortality rates were significantly different among the groups (Table 5).

Discussion

In the present study, abnormal liver biochemical markers and liver damage were detected in 57.9% of critically ill patients with COVID-19 who were treated in the ICU. Liver biochemical marker abnormality was found more in male patients. The average age of the group with liver damage was found to be higher than the other two groups. It was also detected that the mortality rate was higher in the group with abnormal liver biochemical values and liver damage when compared to patients with normal liver biochemical values. An APACHE-II score, elevated GGT-1st measurement, higher 1st and 2nd CRP measurement, raised neutrophil count and AST-2nd measurement, low platelet count and albumin-2nd measurement were found to have predictive value for ICU mortality of COVID-19 patients.

Considering the literature on COVID-19, the incidence of liver damage has been reported between 16% and 53%.[11] However, the mechanism of liver injury in COVID-19 patients remains unclear. Active replication and direct cytopathic impact of SARS-CoV-2 in hepatic cells, complications due to COVID-19 infection or mechanical ventilator therapy, changes due to severe inflammation caused by the virus, sepsis, septic shock, hypoxic damage or drugs used in the treatment are considered possible mechanisms. SARS-CoV-2 uses the ACE-2 receptor to enter the cell. The ACE-2 receptor is widely found in heart, kidney, small intestine and lung. The glycoprotein (S protein) of SARS-CoV-2 associates with the ACE-2 cellular membrane and enables SARS-CoV-2 to bind to the target cells. Studies have shown that ACE-2 expression is found in 2.6% of hepatocytes and 59.7% of cholangiocytes.[12] ACE-2 expression of cholangiocytes is much higher compared to hepatocytes.

Hepatocyte damage may be caused by virus-induced immune interactions involving cytotoxic T and Kupffer cells in which biopsy samples were used to determine the mechanism of hepatic damage. In this context, Xu et al. showed that microvesicular steatosis as well as mild lobular and portal inflammation were detected during COVID-19, while Zhang et al. reported mild sinusoidal dilatation and minimal lymphocytic infiltration.[6,9] Since no intranuclear or

Table-3: Predictors affecting intensive care unit (ICU) stay.

	Beta	T	*p*-value
Age (years)	0.004	0.149	0.882
Gender	-0.004	-0.159	0.873
APACHE-II score	-0.118	-4.503	<0.05*
WBC-1st	0.169	1.195	0.232
Neutrophil-1st	-0.067	-1.036	0.300
Lymphocyte-1st	-0.187	-1.435	0.151
Platelet-1st	-0.011	-0.371	0.710
AST-1st	-0.032	-0.792	0.429
ALT-1st	-0.018	-0.516	0.606
GGT-1st	-0.029	-1.107	0.269
Albumin-1st	0.087	3.298	<0.05*
ALP-1st	-0.015	-0.598	0.550
LDH-1st	-0.041	-1.595	0.111
Total bilirubin-1st	0.091	2.079	<0.05*
Direct bilirubin-1st	-0.030	-1.032	0.302
Indirect bilirubin-1st	-0.046	-1.643	0.101
Ferritin-1st	-0.011	-0.415	0.678
Prothrombintime-1st	-0.201	-1.530	0.126
INR-1st	0.188	1.456	0.146
aPTT-1st	-0.017	-0.708	0.479
D-Dimer-1st	0.024	1.005	0.315
c-RP-1st	-0.003	-0.128	0.898
Procalcitonin-1st	-0.016	-0.676	0.499
WBC-2nd	0.698	2.138	<0.05*
Neutrophile-2nd	-0.636	-2.362	<0.05*
Lymphocyte-2nd	-0.322	-1.738	0.082
Platelet-2nd	0.049	1.703	0.089
AST-2nd	-0.024	-0.635	0.526
ALT-2nd	0.041	1.146	0.252
GGT-2nd	0.028	1.102	0.271
Albumin-2nd	-0.449	-15.508	<0.05*
ALP-2nd	0.060	2.345	<0.05*
LDH-2nd	-0.052	-1.751	0.080
Totalbilirubin-2nd	-0.081	-0.944	0.345
Directbilirubin-2nd	0.022	0.261	0.794
Indirectbilirubin-2nd	0.025	0.783	0.434
Ferritin-2nd	-0.013	-0.534	0.593
Prothrombintime-2nd	-0.005	-0.018	0.986
INR-2nd	0.037	0.139	0.889
aPTT-2nd	-0.038	-1.411	0.158
D-Dimer-2nd	-0.010	-0.363	0.717
CRP-2nd	-0.050	-1.948	0.052
Procalcitonin-2nd	-0.010	-0.385	0.701

APACHE: Acute physiology and chronic health evaluation, SD: Standard deviation, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, Alb: Albumin, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, INR: International normalised ratio, aPTT: Activated partial thromboplastin time, CRP: C-reactive protein; *$p<0.05$; Linear regression analysis ($F=10.01$, $p<0.05$); This model explains the 17.8% of the variance.

Table-4: Predictors of intensive care unit (ICU) mortality.

	Beta	T	*p*-value
Age (years)	-0.021	-0.946	0.344
Gender	-0.005	-0.261	0.794
APACHE-II score	0.215	9.488	<0.05*
Intensive care stay (days)	0.004	0.159	0.874
WBC-1st	-0.025	-0.209	0.835
Neutrophil-1st	-0.018	-0.319	0.750
Lymphocyte-1st	0.055	0.495	0.620
Platelet-1st	-0.002	-0.086	0.931
AST-1st	0.020	0.594	0.553
ALT-1st	-0.027	-0.883	0.378
GGT-1st	0.071	3.198	<0.05*
Albumin-1st	0.006	0.267	0.790
ALP-1st	-0.015	-0.695	0.487
LDH-1st	0.020	0.924	0.355
Total bilirubin-1st	-0.065	-1.746	0.081
Direct bilirubin-1st	0.040	1.596	0.111
Indirect bilirubin-1st	—	-0.020	0.984
Ferritin-1st	0.010	0.460	0.645
Prothrombintime-1st	0.046	0.405	0.685
INR-1st	-0.014	-0.127	0.899
aPTT-1st	-0.017	-0.845	0.398
D-Dimer-1st	-0.013	-0.602	0.547
c-RP-1st	0.075	3.506	<0.05*
Procalcitonin-1st	-0.024	-1.219	0.223
WBC-2nd	-0.364	-1.299	0.194
Neutrophile-2nd	0.595	2.575	<0.05*
Lymphocyte-2nd	0.205	1.286	0.199
Platelet-2nd	-0.148	-5.998	<0.05*
AST-2nd	0.065	2.030	<0.05*
ALT-2nd	0.013	0.415	0.678
GGT-2nd	—	-0.020	0.984
Albumin-2nd	-0.217	-8.119	<0.05*
ALP-2nd	0.006	0.286	0.775
LDH-2nd	0.019	0.737	0.461
Totalbilirubin-2nd	0.016	0.212	0.832
Directbilirubin-2nd	-0.012	-0.163	0.871
Indirectbilirubin-2nd	0.005	0.176	0.860
Ferritin-2nd	-0.019	-0.900	0.368
Prothrombintime-2nd	-0.234	-1.026	0.305
INR-2nd	0.260	1.156	0.248
aPTT-2nd	0.015	0.640	0.522
D-Dimer-2nd	0.034	1.453	0.147
c-RP-2nd	0.123	5.638	<0.05*
Procalcitonin-2nd	0.019	0.877	0.380

*$p<0.05$; Linear regression analysis ($F=23.04$, $p<0.05$); This model explains the 40.2% of the variance; APACHE: Acute physiology and chronic health evaluation, SD: Standard deviation, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, Alb: Albumin, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, INR: International normalised ratio, aPTT: Activated partial thromboplastin time, CRP: C-reactive protein.

intracytoplasmic viral inclusion bodies were detected in the histopathological examination of any biopsy specimen, it was suggested that these kinds of changes were not specific to SARS-CoV-2 infection and may also result in hypoxemia or drug-induced liver damage.[7] The fact that the ACE-2 receptor is much less expressed in hepatocytes and that no viral inclusion bodies can be detected in biopsy samples indicates that a direct cytopathic effect of SARS-CoV-2 is highly unlikely. Chai et al. defined cholangiocytes-specific ACE-2 expression in liver samples

Table-5: Mortality rate across the study groups.

	Group 1 (n=395) n (%)	Group 2 (n=534) n (%)	Group 3 (n=11) n (%)	*p*-value
Mortality rate	160 (40.5)	286 (53.5)	9 (81.8)	<0.05*
7-days mortality rate	66 (16.7)	166 (31)	8 (72)	<0.05*
28-days mortality rate	159 (40.2)	282 (52.8)	9 (81.8)	0.716

*p<0.05; Chi-square

of healthy people and of colorectal cancer patients.[12] They suggested that cholangiocytes were multifunctional, and played a key role in liver regeneration amid immune response, and, hence, liver involvement in the disease is mostly drug-related and dependent on cytotoxicity.

Cai et al. stated that a total of 20.75% of liver function disorders were hepatocellular, 29.25% were cholestatic, and 43.4% were of mixed type.[8] Another study showed that there was mostly hepatocellular type injury, and merely 2.6% of cholestatic type damage.[13] This situation could not be explained by the binding of the virus to ACE-2 receptors on cholangiocytes alone. Another possibility is that systemic viral infections may temporarily lead to liver biochemical disturbance. In relation, liver biochemical enzyme levels may increase as a result of general immune activation or inflammation due to circulating cytokines. In addition, severe COVID-19-related hypoxia due to ARDS may also lead to liver damage.

An additional possible cause of liver damage in patients with COVID-19 may be the drugs used in the treatment, including antimalarial drugs, such as hydroxychloroquine, which are thought to be effective in the treatment of COVID-19, antiviral drugs, such as favipiravir, remdesivir and lopinavir/ritonavir, anti-cytokine agents, such as tocilizumab and corticosteroid, antibiotics and anticoagulants. There are limited studies on liver damage caused by hydroxychloroquine, in which hydroxychloroquine is primarily metabolised in the liver. Hence, care should be taken in terms of hepatotoxicity in patients with chronic liver disease and when used together with hepatotoxic drugs.[14] Antiviral drugs, such as lopinavir/ritonavir, have been reported to cause hepatotoxicity at a rate of 2-10%.[15] Favipiravir, one of the antiviral drugs that was actively used during the COVID-19 pandemic, is considered a hepatotoxic drug.[16] Information on the administration of remdesivir in patients diagnosed with COVID-19 is limited, and in a case series of 53 patients, 22% patients reported elevated liver enzymes.[17] Although tocilizumab, which is among the anti-cytokine treatment regimes, does not cause clinically significant liver damage, and elevated ALT in patients can be observed.[14] In relation, hepatitis B reactivation and cytomegalovirus reactivation have been reported because it is an immunosuppressive agent.[14] Low-molecular-weight heparin increases serum liver biochemical enzyme values in 4% to 13% patients.[14] Antimicrobial treatments, such as azithromycin, may also cause hepatotoxicity.[18] In the present study, treatment of critical patients with COVID-19 using azithromycin, favipiravir, hydroxychloroquine, corticosteroid, low-molecular-weight heparin, and toculizumab were deemed appropriate based on the COVID-19 Guidelines of the Turkish Ministry of Health.[19]

Several studies in patients with COVID-19 reported that the group with abnormal liver biochemical values had longer hospital stay than the group with normal liver biochemical values.[20] Jiang et al. suggested that liver damage causes impairments in the immune system, and, hence, recovery takes longer.[21] However, Salik et al. revealed that patients with abnormal liver function tests and liver damage had lesser ICU stay than patients with normal liver biochemical parameters.[22] While the duration of ICU stay was found to be similar in patients with and without liver damage, it was observed that the duration of ICU stay was shorter in the group with liver damage compared to the other groups in the present study. This finding suggested that patients with liver damage had a higher mortality rate compared to the others.

A systematic search of the literature revealed that there are various studies indicating that abnormal liver function tests are closely related to raised mortality in patients with COVID-19.[20,23] A retrospective study on 1,512 cases showed that abnormal liver biochemical values and the presence of comorbidity increases the mortality of COVID-19.[23] Another study on 1,003 cases evaluated liver biochemical values at admission and during hospitalisation, and that abnormal values were associated with disease severity and mortality.[24] In a meta-analysis comprising 25 studies and 5,971 patients, it was determined that higher levels of AST, ALT, total bilirubin, LDH, GGT, globulin, and low albumin levels were related to mortality.[25] In addition, Salik et al. showed that liver dysfunction was associated with higher mortality and shorter ICU stay.[22]

The current study showed that those with liver damage had higher liver biochemical values than those with abnormal liver biochemical values, and those with abnormal liver biochemical values had higher 7-day and total mortality rates than those with normal liver biochemical values. This finding showed the importance of liver enzyme follow-up in terms of mortality, and suggested that the monitoring of enzyme levels could have a predictive value for the patient's follow-up in the ICU and during the clinical course.

The current study has limitations because only ICU patients were included, while those treated at home and in the

wards were excluded, which could have limited the generalisability of the findings in terms of determining mortality and predictive values. However, the study's objective was to calculate predictive values and to determine mortality predictors in critically ill patients. Further comprehensive studies are required to validate the current findings.

Conclusion

High GGT and AST levels and low albumin level in critically ill COVID-19 patients could be considered indicators of high mortality rate. Clinicians responsible for the treatment of such patients should closely monitor abnormal liver function tests and adjust treatment strategies accordingly.

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Author Contribution:

EHE: Data collection, analysis, reviewed the literature and writing.
BA: Drafting and revision.
SD: Performed statistical analysis and data interpretation.
HO: Evaluated the final version and final approval.