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Elevated Liver Aminotransferases Level and COVID-19 Prognosis in Hospitalized Patients: A Prospective Study from Iran

Masood Faghih Dinevari[1], Mohammad Hossein Somi[1], Elham Sadeghi Majd[2], Afshin Fattahzadeh[1], Zeinab Nikniaz[1,*]

[1] Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[*] **Corresponding Author:**
Zeinab Nikniaz, PhD
Liver and Gastrointestinal Diseases Research Center, Tabriz University of Medical Sciences, Imam Reza hospital, Tabriz, Iran

Telefax: +98 4133367473
Email: znikniaz@hotmail.com

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ABSTRACT

BACKGROUND:
Considering the conflicting results and limited studies on the association between elevated liver enzyme levels and COVID-19 outcomes, in the present study, we aimed to investigate the association between hepatic enzyme changes and the prognosis of COVID-19 during hospital admission.

METHODS:
In this prospective study, 1017 consecutive patients with COVID-19 participated and were followed up from admission until they were discharged or deceased. The liver enzyme levels were recorded on admission. The patient/disease-related information was recorded by trained nurses using questionnaires. The primary endpoint was the association between elevated liver enzymes and liver injury and mortality from COVID.

RESULTS:
The mean age of the participants was 62.58±17.45 years; 55.4% of them were male. There was no significant difference between groups regarding the COVID-19 outcomes except for the need for ICU admission ($P=0.02$). Moreover, all COVID-19 outcomes were significantly higher in patients with liver injury compared with other patients except for the quick sequential organ failure assessment (qSOFA) score. After adjusting for covariates, the patients with Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) levels of more than 40 (IU/L) and participants with liver injury on admission had significantly greater odds of death, ICU admission, and mechanical ventilation requirements.

CONCLUSION:
The results of the present study support the hypothesis that poor outcomes of COVID-19 infection were higher in patients with elevated liver enzyme levels and liver injury. Therefore, liver chemicals should be closely monitored during the illness and hospital admission, and patients with COVID-19 and an elevated level of transaminases should be followed up carefully, and necessary interventions should be considered to prevent poor outcomes.

KEYWORDS:
COVID-19; Liver enzymes; Transaminases; Liver injury; Prognosis

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a new public health crisis that was announced as a pandemic by the World Health Organization in March 2020.[1] In February 2020, Iran first reported cases and mortalities; since then, we have had more than 300000 cases.[2] This disease is accompanied by a high morbidity and mortality rate.[3] The mortality rate is higher in patients with older age, male sex, obesity, and other diseases such as diabetes, hypertension, cardiovascular disease, and kidney and liver disease.[4-6]

Initially, it was considered a respiratory tract infection; however, the disease is now known as a multi-organ disease, mostly in moderate to severe cases.[7] The COVID-19 attacks different organs causing long-term damage and mortality. The virus goes into cells through the angiotensin-converting enzyme 2 (ACE2) receptor. These receptors can be found on different cells, including hepatocytes.[8] It has been reported that approximately 14-76.3% of patients with COVID-19 experience liver damage and elevated levels of liver enzymes.[9]

Considering the high rate of liver involvement in patients with COVID-19, different studies have focused on the association between liver enzyme levels and the severity or mortality rate of COVID-19 and have provided mixed results. Some studies showed that patients with an elevated level of liver enzymes were more likely to have severe pneumonia and a higher mortality rate,[10-13] however, others did not show any association between elevated liver enzyme levels and COVID-19 outcomes.[14-16] We found one study from Iran that reported a significant association between elevated levels of Aspartate aminotransferase (AST) but not Alanine aminotransferase (ALT) with a higher risk of transfer to the ICU and mortality rate in 93 patients with COVID-19.[12]

Now that the most concerning health issue worldwide is COVID-19, which has a high mortality rate, and as there are conflicting results and limited studies on the association between elevated liver enzyme levels and COVID-19 outcomes, we aimed to investigate the association between hepatic enzyme levels on admission and the prognosis of COVID-19 during hospital admission.

MATERIALS AND METHODS

In the present prospective study, the AzarCoRe (East Azar COVID-19 Registry) study data were used. In the AzarCoRe study, the data were collected during the incidence peak of the COVID-19. In this registry, the patients were registered if COVID-19 was confirmed by reverse transcription-polymerase chain reaction (RT-PCR) or clinically diagnosed based on lung imaging features. For data collection, different questionnaires were designed to include demographic and lifestyle characteristics, vital signs, comorbidities, laboratory parameters (on admission day and for each day of hospitalization), COVID-19-related symptoms, medication, and outcomes. All patients were followed up until they were discharged from the hospital or died. The questionnaires were completed by trained nurses in each COVID-19 related unit.

The Ethics Committee of Tabriz University of Medical Sciences approved the study (Ethics code: IR.TBZMED.REC.1398.1274), and written informed consent was obtained from all patients.

In the AzarCoRe study, we registered data from 1106 consecutive patients; 27 patients had pre-existing liver diseases, and 62 patients had incomplete information on laboratory parameters or disease outcomes. Therefore, the data were analyzed on 1017 patients.

Outcomes

Studying the association between elevated transaminase levels and mortality from COVID-19 in hospitalized patients was our primary endpoint. In addition, our secondary endpoint was assessing the association between elevated liver enzyme levels and disease severity using quick sequential organ failure assessment (qSOFA) score and confusion, uremia, respiratory rate, BP, age≥65 years (CURB-65) score, ICU admission, and mechanical ventilation at any point.

For assessing the transaminase levels, 5 cc of fasting blood was obtained on admission, and the levels of the enzymes were measured using an autoanalyzer with Pars Azmoon kits (Pars Azmoon Inc., Tehran, Iran). ALT and AST levels of more than 40 IU/mL were defined as the levels of serum liver enzyme above the upper level of normal. Liver injury was defined as an ALT level of more than 3 times the upper normal level.

qSOFA was calculated by summing the score of the following criteria: Glasgow Coma Scale<15, respiratory rate (RR)≥22, and systolic blood pressure (SBP)≤100. One point was considered for each criterion. qSOFA

scores were dichotomized at a cutoff of 2 since patients with scores of 2 or greater have a higher risk of mortality.[17]

Curb-65 was calculated as the sum of the following findings, each of which was worth one point: Glasgow Coma Scale < 15, blood urea nitrogen > 19 mg/dL, RR ≥ 30, SBP < 90 mm Hg or diastolic blood pressure ≤ 60 mm Hg, and age ≥ 65 years. CURB-65 scores were dichotomized at a cutoff of 3 since patients with scores of 3 or greater have a higher risk of mortality.[18]

Statistical analysis

For statistical analysis, SPSS software version 25 was used. The normality of the data distribution was analyzed by the Kolmogorov-Smirnov test. The quantitative and qualitative values are reported as the mean (SD) and frequency (%), respectively. Between-group comparisons were performed using the independent test for continuous variables and by the Chi-square test for categorical variables. Logistic regression was used to analyze the association between elevated liver enzyme levels and COVID-19 outcomes in univariate and multivariate models. The covariate candidates for inclusion were those statistically significant in univariate analyses ($P<0.15$): age, sex, smoking, body mass index (BMI), and comorbidities. For all analyses, P value <0.05 was considered significant.

RESULTS

The demographic data and comorbidity prevalence of 1017 patients with COVID-19 are presented in table 1. The mean age of the participants was 62.58 ± 17.45 years, and 55.4% of them were male. Approximately 29.59% of the patients had abnormal hepatocyte function, and 4.1% had a liver injury. There were significant differences between the patients with abnormal hepatocyte function and the patients with normal hepatocyte function regarding sex ($P=0.009$).

Table 2 presents the comparison of the frequency of outcomes in patients with COVID-19 according to their hepatocyte function status. There was no significant difference between the groups regarding the COVID-19 outcomes except for the need for ICU admission and requirement for mechanical ventilation, which were significantly higher in patients with abnormal hepatocyte function. Moreover, all COVID-19 outcomes were significantly higher in patients with liver injury compared with other patients except for the qSOFA score.

The association between liver enzymes and COVID-19 outcomes is shown in table 3. The results of logistic regression analysis showed that after adjusting for covariates (age, sex, smoking, BMI, comorbidities, and drug use), patients with ALT and AST levels of more than 40 IU/L and liver injury on admission had significantly

Table 1: The demographic characteristics of diabetic patients with COVID-19

Variables	Total (n = 1017)	Normal hepatocyte function (n = 693)	Abnormal hepatocyte function (n = 301)	Liver injury (n = 23)	*P* value*	*P* value**
Age (years) mean ± SD	62.58 ± 17.45	62.97 ± 17.51	61.57 ± 17.40	63.37 ± 17.40	0.27	0.83
BMI (kg/m^2) mean ± SD	27.33 ± 4.98	27.33 ± 4.80	27.45 ± 4.90	25.46 ± 2.36	0.73	0.11
Male sex n (%)	562 (55.2)	359 (51.8)	190 (62.6)	13 (56.52)	0.009	0.78
Comorbidities						
CVD	236 (23.2)	164 (23.6)	65 (22.2)	7 (30.4)	0.37	0.40
Respiratory diseases	135 (13.2)	92 (13.2)	40 (13.2)	3 (13.04)	0.89	0.71
HTN	415 (42.2)	288 (41.5)	119 (39.1)	8 (34.7)	0.41	0.68
Kidney diseases	86 (8.4)	65 (9.3)	21 (6.4)	0 (0.00)	0.19	0.20
Carcinoma	50 (4.9)	30 (4.3)	18 (6.1)	2 (8.69)	0.28	0.23
Autoimmune diseases	10 (0.9)	8 (1.1)	1 (0.6)	1 (4.34)	0.20	0.67
Diabetes	238 (23.4)	171 (24.6)	62 (20.6)	5 (21.73)	0.13	0.79

CVD: cardiovascular disease; HTN: Hypertension
*P value of comparison between the groups with normal vs. abnormal hepatocyte function
** P value of comparison between liver injury group and patients without liver injury

Table 2: The frequency of outcomes of COVID-19 in patients

Outcomes	Total (n=1017)	Normal hepatocyte function (n=693)	Abnormal hepatocyte function (n=301)	Liver injury (n=23)	*P* value*	*P* value**
Death n (%)	170 (16.7)	105 (16.8)	54 (17.9)	11 (47.82)	0.35	<0.001
Requirement for mechanical ventilation n (%)	41 (4)	21 (3)	13 (4.3)	7 (30.43)	0.32	<0.001
ICU admission n (%)	273 (26.8)	163 (23.52)	94 (31.2)	16 (66.56)	0.005	<0.001
CURB-65					0.33	0.03
0-1	493 (48.4)	320 (46.1)	162 (53.8)	9 (39.13)		
2	316 (31.0)	213 (30.7)	98 (32.55)	6 (26.08)		
3-5	208 (20.3)	160 (23.0)	41 (13.6)	8 (34.78)		
qSOFA score n (%)						0.21
0	619 (60.8)	429 (61.9)	179 (59.4)	11 (47.82)	0.99	
1	359 (35.2)	241 (34.7)	108 (35.8)	10 (43.47)		
2	37 (3.6)	21 (3.0)	14 (4.6)	2 (8.69)		

Curb-65: confusion, uremia, respiratory rate, BP, age≥65 years; qSOFA: quick sequential organ failure assessment
* *P* value of comparison between the groups with normal vs. abnormal hepatocyte function
** *P* value of comparison between liver injury group and patients without liver injury

greater odds of death, ICU admission, and mechanical ventilation requirements. However, there was no significant association between ALT and AST levels and COVID-19 severity scores after adjusting for covariates.

DISCUSSION

COVID-19 is a new infectious disease with high morbidity and mortality rates. Different factors are proposed as important causes of death and poor outcomes in such patients. Various studies have assessed the association between chronic liver diseases and COVID-19 outcomes. The results of a meta-analysis summarizing these studies indicated that the presence of chronic liver disease was significantly associated with more severe COVID-19 infections and mortality.[19] However, in the present study, we excluded patients with chronic and pre-existing liver diseases and analyzed the association between elevated liver enzymes on admission and the risk of poor outcomes in patients with COVID-19. The results showed that the patients with COVID-19 who had elevated levels of ALT and AST on admission were more vulnerable to poor outcomes of COVID-19. These findings are in line with the findings reported by Hundt and colleagues on the US population that reported poorer clinical outcomes in patients with COVID-19 and abnormal liver test.[11] In another study, Omrani-Nava and colleagues reported that an elevated level of AST but not ALT was associated with a higher risk of transfer to the ICU and mortality rate.[12] Moreover, the results of a study on patients with COVID-19 in Wuhan, China, showed a significantly higher level of ALT and AST in non-survivors compared with survivors.[14] In another study, Cai and others showed that the presence of abnormal liver tests on admission was associated with the progression to severe pneumonia.[10] However, some studies did not report any association between elevated liver enzymes and disease severity.[13,15,16] The differences between the results of various studies may be partly related to the differences in the participants' age, presence of comorbidities, and sample size.

The observed association between elevated liver enzyme levels and poor outcomes in patients with COVID-19 may be partly related to the increased level of inflammatory factors. Numerous studies have reported higher C-reactive protein (CRP) and Tumor Necrosis Factor-alpha (TNF-α) levels in patients with higher liver enzyme level.[20] The critical role of pro-inflammatory cytokines in the COVID-19 mortality rate has been documented.[21]

The results of the present study should be interpreted considering the study limitations. In the present study, we only analyzed the ALT and AST levels. However,

Table 3: The logistic regression analysis of liver enzymes and COVID-19 outcomes

	ALT>40 IU/L				AST>40 IU/L				Liver injury			
Outcomes	**OR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**aOR (95% CI)**	***P* value**
Death	3.02 (1.81, 5.03)	<0.001	4.28 (2.35-7.97)	<0.001	2.62 (1.64, 4.21)	<0.001	3.02 (1.70, 5.35)	<0.001	8.08 (3.21, 23.45)	<0.001	11.24 (3.51, 35.99)	<0.001
Requirement for mechanical ventilation	3.55 (1.59, 7.92)	0.002	8.86 (3.01-26.57)	<0.001	1.85 (0.85, 4.04)	0.12	3.26 (1.15, 9.23)	<0.001	12.09 (4.45, 32.83)	<0.001	55.13 (13.74, 222.34)	<0.001
ICU admission	3.08 (1.97, 4.80)	<0.001	3.47 (2.10-5.72)	<0.001	2.56 (1.73, 3.77)	<0.001	2.62 (1.69, 4.07)	<0.001	8.51 (3.05, 23.68)	<0.001	14.5 (3.89, 54.10)	<0.001
CURB-65	1.62 (0.88, 2.97)	0.11	1.88 (0.60, 5.68)	0.25	1.72 (1.01, 2.90)	0.04	1.65 (0.91, 2.96)	0.09	3.59 (1.29, 9.36)	0.01	9.02 (2.26, 35.56)	0.002
qSOFA	2.15 (0.84, 5.54)	0.11	1.72 (0.87, 3.39)	0.11	2.25 (0.90, 5.59)	0.08	1.83 (0.64, 5.20)	0.25	2.75 (0.59, 12.63)	0.19	3.66 (0.67, 19.9)	0.12

Curb-65: confusion, uremia, respiratory rate, BP, age≥65 years; qSOFA: quick sequential organ failure assessment
Dependent variables: Death, the requirement for mechanical ventilation, ICU admission, CURB-65, qSOFA
Independent variable: an elevated level of liver enzymes and liver injury
aOR: adjusted OR for age, sex, smoking status, BMI, comorbidities, and drug use

earlier studies indicated that transaminase levels were good indicators of liver injury.[22] Another limitation of our study that could influence the conclusion was the wider confidence intervals in the liver injury group, which reflects a low sample size in this group. The strengths of this study include the prospective nature of the study, including the large sample of patients with COVID-19, excluding the patients with pre-existing liver diseases, and considering a large number of confounding factors that may affect the association between liver enzymes and COVID-19 outcomes.

CONCLUSION

The results of the present study support the hypothesis that poor outcomes of COVID-19 infection were higher in patients with elevated liver enzyme levels. Therefore, from the clinical point of view, liver chemicals should be closely monitored during the illness and hospital admissions, and patients with COVID-19 with an elevated level of transaminases should be followed up carefully, and necessary interventions should be considered to prevent poor outcomes. From the research point of view, more studies measuring the levels of pro-inflammatory factors should be conducted to illustrate the mechanisms underlying this association.

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ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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