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Research Article

Association Between Admission Liver Enzyme Elevation and Mortality in Coronavirus Disease 2019

Koronavirüs hastalığı 2019'da başvuru anındaki transaminazların yüksekliği ile mortalitenin ilişkisi

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Abstract

Aim: Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), predominantly affects the respiratory system but may also involve hepatic dysfunction. This study evaluated liver enzyme abnormalities in hospitalized COVID-19 patients and their association with in-hospital mortality.

Material and Methods: This retrospective study enrolled 1455 adults hospitalized with COVID-19. Admission peripheral oxygen saturation (SpO_2), intensive care unit (ICU) and non-invasive mechanical ventilation (NIMV) requirements, and laboratory parameters were recorded. Patients with admission aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels ≥ 2 times the upper limit of normal (ULN) formed the patient group, while those with values < 2 times the ULN served as the control group. Mortality predictors were analyzed using logistic regression; cut-off values for age, C-reactive protein (CRP), and SpO_2 were determined by ROC analysis, and survival was evaluated using Kaplan-Meier analysis with log-rank comparisons.

Results: The patient group exhibited higher lactate dehydrogenase, total bilirubin, hemoglobin, and CRP levels and lower lymphocyte counts, without differences in in-hospital mortality, ICU admission, or NIMV requirement. Multivariable analysis identified older age, symptom status, lower admission SpO_2, and elevated CRP as independent mortality predictors. ROC analysis yielded cut-offs of 59.5 years, 122.5 mg/L CRP, and 90.5% SpO_2, beyond which survival was shorter (AUC 0.771; $p < 0.001$).

Conclusion: In hospitalized patients with severe COVID-19, admission AST and/or ALT elevations were not associated with mortality or respiratory support, whereas mortality was independently driven by older age, symptom status, elevated CRP, and reduced admission SpO_2, highlighting the prognostic dominance of hypoxia and systemic inflammation over isolated transaminase elevations.

Keywords: COVID-19, SARS-CoV-2, liver enzymes, mortality

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Öz

Amaç: Şiddetli Akut Solunum Yolu Sendromu Koronavirüsü 2 (SARS-CoV-2) tarafından oluşturulan Koronavirüs Hastalığı 2019 (COVID-19) esas olarak solunum sistemini etkilemekle birlikte, hepatik disfonksiyonla da seyredebilir. Bu çalışmada, hastanede yatan COVID-19 hastalarında karaciğer enzim anormalliklerinin değerlendirilmesi ve bunların mortalite ile ilişkisi araştırılmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya COVID-19 tanısıyla hastanede yatan 1455 erişkin hasta dahil edilmiştir. Başvuru anındaki periferik oksijen satürasyonu (SpO_2), yoğun bakım ünitesi (YBÜ) ve non-invaziv mekanik ventilasyon (NIMV) gereksinimi ile laboratuvar parametreleri kaydedilmiştir. Başvuruda aspartat aminotransferaz (AST) ve/veya alanin aminotransferaz (ALT) düzeyleri normal üst sınırın ≥ 2 katı olan hastalar hasta grubunu, < 2 katı olanlar ise kontrol grubunu oluşturmuştur. Mortalitenin belirleyicileri lojistik regresyon analizi ile değerlendirilmiş; yaş, C-reaktif protein (CRP) ve SpO_2 için en uygun eşik değerler ROC analizi ile belirlenmiştir. Sağkalım Kaplan–Meier yöntemi ile analiz edilmiş ve gruplar arası karşılaştırmalar log-rank testi ile yapılmıştır.

Bulgular: Hasta grubunda laktat dehidrogenaz, total bilirubin, hemoglobin ve CRP düzeyleri daha yüksek, lenfosit sayıları ise daha düşük bulunmuştur; ancak mortalite, YBÜ yatışı ve NIMV gereksinimi açısından gruplar arasında anlamlı fark saptanmamıştır. Çok değişkenli analizde ileri yaş, semptom durumu, başvuruda daha düşük SpO_2 ve yüksek CRP düzeyleri mortalitenin bağımsız belirleyicileri olarak tanımlanmıştır. ROC analizinde yaş için 59,5 yıl, CRP için 122,5 mg/L ve SpO_2 için %90,5 eşik değerleri belirlenmiş olup, bu sınırların ötesinde sağkalımın daha kısa olduğu gösterilmiştir (AUC: 0,771; $p < 0,001$).

Sonuç: Hastanede yatan ağır COVID-19 hastalarında, başvuru anındaki AST ve/veya ALT yüksekliği mortalite veya solunum desteği gereksinimi ile ilişkili bulunmamıştır. Buna karşılık mortalite; ileri yaş, semptom durumu, başvuruda düşük SpO_2 ve yüksek CRP düzeyleri ile bağımsız olarak ilişkili bulunmuş olup, bu bulgular COVID-19 prognozunda izole transaminaz yüksekliğinden ziyade hipoksi ve sistemik inflamasyonun belirleyici rol oynadığını ortaya koymaktadır.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, transaminazlar, mortalite

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), most commonly presents with pneumonia and may progress to acute respiratory distress syndrome [1] . Beyond pulmonary involvement, a subset of patients develops severe extrapulmonary and multi-organ manifestations that substantially contribute to morbidity and mortality, including cardiovascular, gastrointestinal, endocrine, and hepatic involvement [2]. Elevations in liver enzyme levels have been frequently reported in COVID-19 and may arise from multiple mechanisms, including direct viral cytopathic effects, systemic hyperinflammation and cytokine storm, a procoagulant state with microvascular injury, disseminated intravascular coagulation, hypoxic–ischemic damage, and drug-induced liver injury related to COVID-19 therapies [3,4].

SARS-CoV-2 gains cellular entry via the angiotensin-converting enzyme 2 (ACE-2) receptor. In the liver, ACE-2 expression is more prominent in cholangiocytes than in hepatocytes, providing a biological basis for the cholestatic and mixed-pattern liver injury observed in COVID-19 [5]. Consistent with this mechanism, several studies have documented elevations in gamma-glutamyl transferase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, and alkaline phosphatase (ALP) among hospitalized COVID-19 patients, with GGT elevation being particularly associated with more severe disease [6]. Nevertheless, despite the high prevalence of hepatic biochemical abnormalities, the prognostic significance of transaminase elevation remains controversial, with conflicting results regarding its independent association with disease severity and mortality [7].

Accordingly, this study aimed to investigate the prognostic impact of admission AST and/or ALT elevation on in-hospital mortality and key clinical outcomes, including intensive care unit (ICU) admission and the requirement for non-invasive mechanical ventilation (NIMV), as well as to identify independent predictors of mortality among hospitalized patients with COVID-19.

Materials and Methods

This single-center, retrospective cross-sectional study included adults hospitalized with COVID-19 in the pandemic wards and intensive care unit of Uşak Training and Research Hospital between 20 March 2020 and 20 March 2021. Ethical approval was obtained from the Uşak University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval ID: 48-48-19; 22 March 2022), and the study was conducted in accordance with the Declaration of Helsinki, with written informed consent obtained from all patients. Electronic medical records of all 1455 polymerase chain reaction (PCR) confirmed adult patients admitted during the study period were retrospectively reviewed via the hospital's electronic medical record system, and no sampling was performed, as the entire eligible population was included.

Patients were eligible for inclusion if they had PCR-confirmed SARS-CoV-2 infection with a diagnosis of COVID-19; were aged ≥18 years; and had admission AST and ALT levels available. Among the included patients, those with a hematological or solid organ malignancy were excluded. Patients with missing key clinical or laboratory data required for the primary analyses were excluded from the final analysis.

The following variables were collected: demographic characteristics (age and sex), presenting symptoms, including cough, fatigue, fever, dyspnea, and myalgia/arthralgia, and SpO_2 at admission. Data on comorbidities, ICU admission, NIMV requirement, and in-hospital mortality were collected. In addition, imaging findings from chest computed tomography (CT) performed at admission, as well as laboratory parameters, including AST, ALT, lactate dehydrogenase (LDH), total bilirubin, creatinine, C-reactive protein (CRP), and complete blood count indices were included in the analysis. Aspartate aminotransferase, ALT, and LDH levels were analyzed using IFCC-traceable spectrophotometric methods, total bilirubin by a photometric diazo-based method, CRP by a particle-enhanced immunoturbidimetric assay, and creatinine by an enzymatic colorimetric method, all analyzed on a Cobas c702 analyzer (Roche Diagnostics, Mannheim, Germany). Complete blood count parameters, including white blood cell, neutrophil, lymphocyte, platelet, and hemoglobin levels, were analyzed using a Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). The reference intervals were defined as follows: AST 0-32 (U/L), ALT 0-33 (U/L), LDH < 223 (U/L), total bilirubin < 1.2 (mg/dL), CRP < 5 (mg/L), creatinine 0.5-0.9 (mg/dL), WBC 4.5-10 ($\times 10^3$/μL), neutrophils 1.8-7.5 ($\times 10^3$/μL), lymphocytes 0.8-3.2 ($\times 10^3$/μL), platelets 150-450 ($\times 10^3$/μL), and hemoglobin 12-16 (g/dL).

Patients with admission AST and/or ALT levels ≥ 2 times the upper reference limit were classified as the liver enzyme elevation (the patient group) (n = 76), whereas those with normal values or values < 2 times the upper reference limit constituted the control group (n = 1379). The primary endpoint was in-hospital mortality, and secondary endpoints included ICU admission, NIMV requirement.

Statistical Analysis

The statistical analyses of the data were carried out with the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS, IBM Corp. Armonk, NY, USA). Descriptive data are presented as median (minimum–maximum) for continuous variables and as counts and percentages for categorical variables. Categorical variables were compared using the chi-square test, and continuous variables using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve analysis, with in-hospital mortality as the endpoint, was used to determine optimal cut-off values for SpO_2, CRP, and age; the area under the curve (AUC) was calculated to assess discriminatory performance. Variables with a p value < 0.10 in univariable analyses were entered into a multivariable binary logistic regression model to identify independent predictors of mortality. Survival was assessed using Kaplan-Meier survival curves, and differences between groups were compared using the log-rank test. Results of logistic regression analyses were reported as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). A two-sided p value < 0.05 was considered statistically significant.

Results

The cohort had a median age of 58 years (range, 18-94), and 52.4% of patients were female (n = 763). Hypertension (28.0%) and diabetes mellitus (23.2%) were the most prevalent comorbidities. The detailed clinical and laboratory characteristics of the 1455 patients are presented in Table 1. At presentation, approximately half of the patients reported cough, followed by fatigue (42.0%), fever (28.9%), dyspnea (24.3%), and myalgia/arthralgia (22.7%), while 10.0% of patients were asymptomatic. Typical radiological features of COVID-19 pneumonia were identified on chest CT in approximately 80% of cases. Median values at admission were 94% for SpO_2, 28 U/L for ALT, 27 U/L for AST, 0.5 mg/dL for total bilirubin, and 45 mg/L for CRP. The overall in-hospital mortality rate was 7.49% (n = 109). Patients who died were significantly older than survivors (p < 0.01).

Table 1. The clinical and laboratory characteristics of the patients included in the study.

	Patients in the study (n = 1455)	
Age (year), median (min-max)	58 (18-94)	
Gender	Female (n, %)	763 (52.4%)
	Male (n, %)	692 (47.6%)
Comorbidity	Diabetes Mellitus (n, %)	338 (23.2%)
	Hypertension (n, %)	407 (28.0%)
	Coronary artery disease (n, %)	163 (11.2%)
	Chronic obstructive pulmonar disease (n, %)	103 (7.1%)
Symptoms at presentation	Fever (n, %)	420 (28.9%)
	Cough (n, %)	706 (48.5%)
	Shortness of breath (n, %)	354 (24.3%)
	Sore throat (n, %)	134 (9.2%)
	Muscle/joint pain (n, %)	331 (22.7%)
	Headache (n, %)	95 (6.5%)
	Nausea (n, %)	102 (7.0%)
	Vomiting (n, %)	50 (3.4%)
	Loss of appetite (n, %)	85 (5.8%)
	Loss of taste/smell (n, %)	59 (4.1%)
	Abdominal pain (n, %)	29 (2.0%)
	Diarrhea (n, %)	51 (3.5%)
	Fatigue (n, %)	611 (42.0%)
	Asymptomatic (n, %)	148 (10.2%)
Chest CT findings at admission	Negative (n, %)	48 (3.3%)
	Typical (n, %)	1174 (80.7%)
	Atypical (n, %)	145 (10.0%)
	Non-COVID-19 (n, %)	55 (3.8%)
	Unknown (n, %)	33 (2.3%)
SpO_2 at admission (%), (min-max)	94 (46-100)	
Creatinin (mg/dL), median (min-max)	0.93 (0.53-10.68)	
AST (U/L), median (min-max)	28 (8-267)	
ALT (U/L), median (min-max)	27 (5-249)	
LDH (U/L), median (min-max)	256 (80-665)	
Total bilirubin (mg/dL), median (min-max)	0.50 (0.10-5.70)	
WBC count (103/dL), median (min-max)	5270 (450-46540)	
Neutrophil count (103/dL), median (min-max)	3420 (90-43140)	
Lymphocyte count (103/dL), median (min-max)	1260 (130-6950)	
Platelet count (103/dL), median (min-max)	199 (13-662)	
Hb (g/dL), median (min-max)	13.60 (5.30-18.80)	
CRP (mg/L), median (min-max)	45.00 (0.10-346)	

Abbrev.: SpO2: Oxygen saturation, CT: Computed Tomography, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell, Hb: Hemoglobin, CRP: C-reactive protein.

Table 2. Comparison of clinical, imaging, and laboratory variables between the patient group and the control group.

	The Patient Group (n = 76)	The Control Group (n = 1379)	p
Age (year), median (min-max)	60.50 (20-85)	58.00 (18-94)	0.253
Female (n, %)	35 (46.1%)	728 (52.8%)	0.252
Symptomatic at admission (n, %)	69 (90.8%)	1238 (89.8%)	0.928
Typical chest CT findings (n, %)	67 (89.3%)	1107 (82.2%)	0.152
SpO_2 at admission (%), (min-max)	94 (60-98)	94 (46-100)	0.563
Creatinin (mg/dL), median (min-max)	0.98 (0.60-2.10)	0.93 (0.53-10.68)	0.989
LDH (U/L), median (min-max)	**392 (129-665)**	**253 (80-665)**	**< 0.001**
Total bilirubin (mg/dL), median (min-max)	**0.60 (0.18-5.70)**	**0.50 (0.10-3.50)**	**< 0.001**
WBC (103/dL), median (min-max)	5360 (1880-12100)	5270 (450-46540)	0.509
Neutrophil count (103/dL), median (min-max)	3460 (1280-11490)	3420 (90-43140)	0.971
Lymphocyte count (103/dL), median (min-max)	**1130 (290-3000)**	**1270 (130-6950)**	**0.026**
Platelet count (103/dL), median (min-max)	192500 (59000-442000)	199000 (13000-662000)	0.307
Hb (g/dL), median (min-max)	**14.00 (5.30-17.50)**	**13.60 (6.30-18.80)**	**0.045**
CRP (mg/L), median (min-max)	**72.20 (0.10-330.20)**	**43.10 (0.10-346.60)**	**0.023**
ICU requirement (n, %)	13 (17.1%)	162 (11.7%)	0.224
NIMV requirement (n, %)	10 (13.2%)	141 (10.2%)	0.533
Mortality (n, %)	6 (7.9%)	103 (7.5%)	1.000

Abbrev.: CT: Computed tomography, SpO_2: Oxygen saturation, LDH: Lactate dehydrogenase, WBC: White blood count, Hb: Hemoglobin, CRP: C-reactive protein, ICU: Intensive care unit, NIMV: Non-invasive mechanical ventilation.

Table 3. Univariable and multivariable logistic regression analyses of factors associated with mortality.

	Univariable logistic regression			Multivariable logistic regression		
	OR	95% GA	p	OR	95% GA	p
Age (year)	**1.048**	**1.032-1.065**	**< 0.001**	**1.03**	**1.007-1.058**	**0.011**
Gender (female vs male)	1.413	0.960-2.080	0.080			
Symptomatic at admission (present vs absent)	**0.628**	**0.379-1.043**	**0.072**	**0.38**	**0.170-0.876**	**0.023**
Typical chest CT findings (atypical vs typical)	1.011	0.564-1.812	0.971			
SpO_2 at admission (%)	**0.941**	**0.924-0.958**	**< 0.001**	**0.91**	**0.886-0.943**	**< 0.001**
Creatinin (mg/dL)	1.293	1.169-1.429	< 0.001			
AST (U/L)	1.006	0.998-1.013	0.140			
ALT (U/L)	0.995	0.986-1.004	0.259			
LDH (U/L)	**1.005**	**1.003-1.007**	**< 0.001**	**1.00**	**1.000-1.004**	**0.061**
Total bilirubin (mg/dL)	1.463	0.945-2.263	0.088			
WBC count (103/dL)	1.000	1.000-1.000	< 0.001			
Neutrophil count (103/dL)	1.000	1.000-1.000	< 0.001			
Lymphocyte (103/dL)	0.999	0.999-0.999	0.011			
Platelet count (103/dL)	1.000	1.000-1.000	0.112			
Hb (g/dL)	0.851	0.771-0.940	0.001			
CRP (mg/L)	**1.011**	**1.009-1.013**	**< 0.001**	**1.00**	**1.006-1.013**	**< 0.001**

Abbrev.: CT: Computed tomography, SpO2: Oxygen saturation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, WBC: White blood cell, Hb: Hemoglobin, CRP: C-reactive protein.

Seventy-six patients constituted the patient group, while 1379 patients served as controls. Comparative analyses between the groups are summarized in Table 2. Patients in the liver enzyme elevation group (the patient group) exhibited significantly higher levels of LDH and total bilirubin compared with controls (both $p < 0.001$), while lymphocyte counts were significantly lower ($p = 0.026$). Additionally, hemoglobin (Hb) levels were modestly but significantly higher in the liver enzyme elevation group ($p = 0.045$), as were CRP levels ($p = 0.023$). No significant differences were observed between groups in other clinical, laboratory, or imaging variables. Consistent with the primary study objective, admission tranaminase elevation was not associated with an increased risk of in-hospital mortality, ICU admission, or NIMV requirement compared with the control group (Table 2). Kaplan-Meier survival curves were comparable between the patient group and the controls (log-rank $p = 0.708$) (Figure 1).

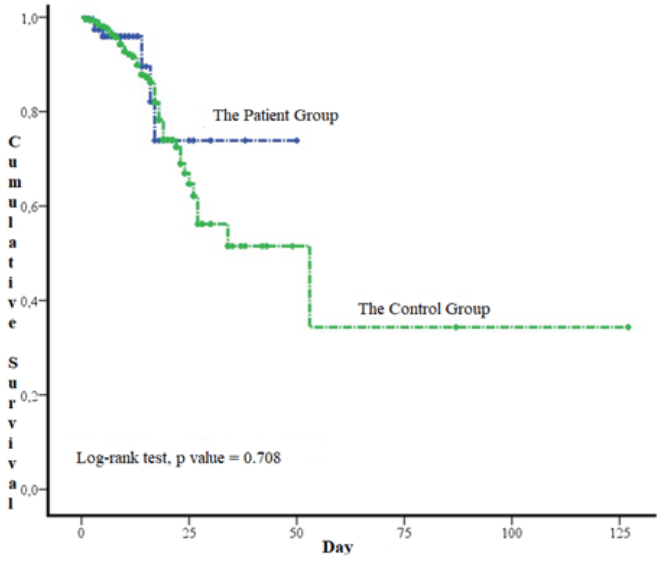

Figure 1. Kaplan-Meier survival curves were comparable between the patient group and the controls.

The results of univariable and multivariable logistic regression analyses are detailed in Table 3. In the multivariable model, increasing age was independently associated with in-hospital mortality (OR = 1.032; 95% CI: 1.007-1.058; $p = 0.011$). Symptom status at admission (OR = 0.386; 95% CI: 0.170-0.876; $p = 0.023$), lower SpO_2 at admission (OR = 0.914; 95% CI: 0.886-0.943; $p < 0.001$), and higher CRP levels (OR = 1.009; 95% CI: 1.006-1.013; $p < 0.001$) were also identified as independent predictors of mortality, whereas admission AST and/or ALT elevation was not associated with mortality in the multivariable model ($p > 0.05$). Receiver operating characteristic analysis determined optimal cut-off values for mortality of 59.5 years for age, 122.5 mg/L for CRP, and 90.5% for SpO_2 at admission (Figure 2). For these parameters, sensitivity was 87.2%, specificity was 56.1%, and the AUC was 0.771 ($p < 0.001$). Kaplan-Meier survival analyses using these cut-off values demonstrated significantly shorter survival among patients older than 59.5 years and those with admission $SpO_2 < 90.5\%$ (both $p < 0.001$). Detailed results for the remaining variables are provided in the Table 3, and Figure 2.

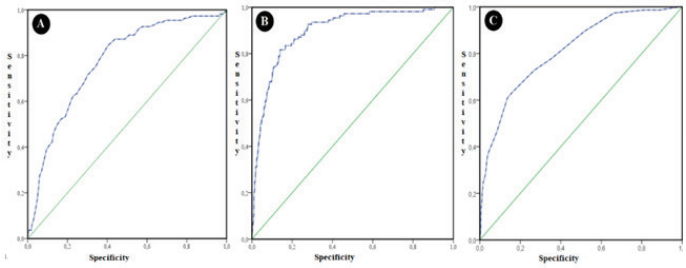

Figure 2. Receiver operating characteristic (ROC) curves demonstrating the predictive performance of (A) age, (B) C-reactive protein (CRP), and (C) admission peripheral oxygen saturation (SpO_2) for in-hospital mortality.

Discussion

In this single-center retrospective cohort of 1455 hospitalized patients with COVID-19, admission elevation of AST and/or ALT to at least two times the ULN was not associated with in-hospital mortality, ICU admission, or NIMV requirement were comparable to those of the control group. These findings suggest that isolated transaminase abnormalities at presentation do not independently confer adverse prognostic significance. By contrast, multivariable analysis identified advanced age, symptom status, reduced SpO_2 at admission, and elevated CRP levels as independent drivers of mortality, underscoring the predominant roles of hypoxia and systemic inflammation in determining clinical outcomes.

Liver enzyme abnormalities are common in COVID-19 and reflect a multifactorial pathogenesis involving direct viral tropism for hepatic and biliary cells mediated by host entry factors such as ACE2 and transmembrane serine protease 2 (TMPRSS2), as well as downstream intracellular signaling, mitochondrial injury, systemic inflammation, hypoxic–ischemic damage, and coagulopathy-related vascular alterations in severe disease [8]. Drug-induced liver injury also represents a clinically relevant contributor, particularly in the context of the widespread use of antivirals, corticosteroids, and antibiotics in COVID-19 management. Indeed, a systematic review and meta-analysis reported a pooled incidence of drug-induced liver injury of approximately 25% among patients with COVID-19 [3]. Despite the strong biological plausibility of these mechanisms, our findings suggest that transaminase elevations primarily reflect overall disease severity rather than acting as independent predictors of mortality.

Consistent with this framework, several studies have demonstrated that the unadjusted association between transaminase elevation and adverse outcomes diminishes after adjustment for overall disease severity in multivariable analyses. Notably, in large cohorts of hospitalized patients, significant liver injury during admission was not independently associated with mortality, supporting the interpretation that hepatic biochemical abnormalities predominantly reflect the severity of systemic illness rather than directly contributing to fatal outcomes [7]. Similar findings have also been reported in Turkish clinical data, in which transaminase levels did not predict ICU admission or mortality [9]. In this context, the comprehensive multivariable design of our study, integrating multiple clinical and laboratory parameters, provides a more robust estimation of the independent prognostic contribution of admission transaminase elevations.

However, these findings are not universal. Some studies indicate that liver enzyme abnormalities may be associated with adverse outcomes when considered alongside other clinical risk factors. In this context, Krishnasamy et al. reported that admission transaminase elevations, when combined with comorbidities, were independently associated with an approximately fivefold increased risk of mortality in hospitalized COVID-19 patients [10]. This observation suggests a potential synergistic interaction between transaminase elevations and underlying comorbidities in determining patient prognosis. Collectively, these divergent findings highlight the marked heterogeneity across studies and underscore the importance of interpreting hepatic biochemical abnormalities within the broader clinical, metabolic, and inflammatory context, rather than considering them as isolated predictors of outcome.

In the present study, patients with admission transaminase elevation exhibited significantly higher levels of LDH and total bilirubin, along with lower lymphocyte counts, compared with controls. These findings suggest that liver enzyme elevation in COVID-19 is more closely associated with systemic inflammation and cellular injury rather than isolated hepatic involvement or direct liver-related prognostic impact, a pattern consistently reported in prior studies [11,12] .

Elevated LDH has been widely linked to widespread tissue damage, hypoxia, and disease severity in COVID-19, serving as a nonspecific marker of cellular injury rather than organ-specific dysfunction. Accordingly, the higher LDH levels observed in the liver enzyme elevation group likely reflect a greater inflammatory and metabolic burden rather than a causal pathway leading to adverse clinical outcomes [13].

Similarly, lymphopenia, an established marker of COVID-19 severity, was more pronounced in patients with elevated transaminases, suggesting that hepatic enzyme abnormalities reflect underlying immune dysregulation and inflammatory activity rather than independently determining prognosis. Consistent with prior evidence linking lymphocyte depletion to cytokine-mediated immune exhaustion and disease severity, these findings indicate that transaminase elevation may serve as a surrogate marker of overall disease burden [14].

Interestingly, hemoglobin levels were modestly but significantly higher in patients with elevated liver enzymes; however, this difference is unlikely to be clinically meaningful and may reflect relative hemoconcentration, hypoxia-related erythropoietic responses, or baseline physiological variation rather than a pathophysiologically relevant contributor to liver injury or mortality. In contrast to markers of disease severity, hemoglobin levels have not been consistently associated with adverse outcomes in COVID-19 across clinical series [15].

Despite these laboratory differences, ICU admission, NIMV requirement, and in-hospital mortality did not differ significantly between groups, indicating that admission transaminase elevation alone does not imply a more severe clinical course or poorer prognosis. In line with prior studies, mild-to-moderate liver enzyme elevations appear common in COVID-19 but do not independently predict critical illness or mortality after adjustment for age, hypoxemia, and systemic inflammation [11,15].

Overall, our findings align with growing evidence that liver enzyme elevation in COVID-19 primarily reflects systemic inflammation, immune dysregulation, and hypoxic injury as epiphenomena, rather than direct hepatic dysfunction driving adverse outcomes [5]. The absence of an independent association with ICU admission, ventilatory support, or mortality in multivariable analyses further supports interpreting admission transaminase elevation as a biochemical marker of disease burden rather than a standalone prognostic indicator.

The most clinically relevant findings of this study pertain to advanced age, hypoxia at presentation, and systemic inflammation. Advanced age remains one of the most robust and consistently reported predictors of COVID-19–related mortality worldwide, and in our cohort, ROC analysis identified a marked reduction in survival among patients older than the threshold of 59.5 years [1]. Elevated CRP, reflecting systemic inflammatory burden, independently predicted mortality,

with values above 122.5 mg/L associated with worse survival, in line with previous cohorts and meta-analyses [16]. Admission SpO_2 emerged as a particularly powerful prognostic marker; values below 90.5 percent independently predicted mortality and were associated with shorter survival duration [17]. This finding is clinically intuitive, as SpO_2 is a direct indicator of pneumonia severity and respiratory failure and is incorporated into established risk stratification tools such as the National Early Warning Score 2 (NEWS2) [18]. Furthermore, the higher mortality observed among symptomatic patients reinforces the association between greater clinical severity at presentation and adverse outcomes [19].

Limitations of the Study

Several limitations warrant consideration. The retrospective, single-center design limits generalizability, and the lack of pre-infection liver enzyme measurements prevents definitive attribution of transaminase elevation to COVID-19 rather than underlying liver disease, although no chronic liver disease was reported at admission. Symptom heterogeneity required analyses based on symptomatic status, precluding assessment of individual symptom patterns, while the imbalance in group sizes may have affected statistical power. Additionally, stratification of transaminase levels and subgroup analyses might have yielded more granular insights into dose-response relationships. Despite these limitations, the large sample size and the integrated analysis of clinical, laboratory, and survival data represent key strengths of the study.

Overall, our findings indicate that admission transaminase elevation should not be overemphasized in the prognostic stratification of hospitalized patients with COVID-19. Instead, greater clinical weight should be assigned to well-established determinants of outcome, particularly advanced age, hypoxia at presentation, and markers of systemic inflammation. Larger, multicenter prospective studies are warranted to validate these observations and to further refine evidence-based risk stratification strategies in this patient population.

In conclusion, in this cohort of 1455 hospitalized adults with COVID-19, admission AST and/or ALT elevation ≥2× the ULN was not associated with in-hospital mortality, ICU admission, or NIMV requirement. Instead, adverse outcomes were independently driven by advanced age, symptom status, reduced admission SpO_2, and elevated CRP levels. These findings underscore that transaminase elevation at presentation should not be considered in isolation for risk stratification, and that greater prognostic emphasis should be placed on markers of hypoxia, systemic inflammation, and patient age. Further large-scale, multicenter prospective studies are warranted to validate and extend these observations.

Declaration of conflicting interests

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Ethics approval

Ethical approval was obtained from the Uşak University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (approval ID: 48-48-19; 22 March 2022)

Authors' contributions

M.K.: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing - original draft. C.A.: Methodology, formal analysis, investigation, data curation, writing - review & editing, visualization, supervision, project administration. C.D.: Conceptualization, methodology, resources, writing - review & editing, supervision.All authors declare that they have participated in the study to an extent sufficient to take public responsibility for its content.

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