Research Article / Araştırma Makalesi

Serum Bilirubin Levels and Mortality Risk: Evaluation of Prognostic Use in a High-Risk Intensive Care Population

Serum Bilirubin Düzeyleri ve Mortalite Riski: Yüksek Riskli Yoğun Bakım Popülasyonunda Prognostik Kullanımının Değerlendirilmesi

Abdullah ŞEN [1], Mahmut YAMAN [1], Tahir Fırat ZADEOĞLU [2], Ercan GÜNDÜZ [3], Murat ORAK [1], Cahfer GÜLOĞLU [1], Şilan GÖGER ÜLGÜT [1], Sema BELEK [1], Berçem TUGAY GÜNEL [1], Mehmet ÜSTÜNDAĞ [1]

[1]Dicle University Faculty of Medicine, Department of Emergency of Medicine, Diyarbakır, TÜRKİYE
[2]Siverek State Hospital, Emergency Department, Şanlıurfa, TÜRKİYE
[3]Dicle University Faculty of Medicine, Department of Emergency Medicine, Internal Medicine, Diyarbakır, TÜRKİYE

Abstract

Background: Serum bilirubin serves as a crucial biomarker for liver function and may reflect the severity of systemic inflammatory responses in critically ill patients. This study aims to assess the prognostic significance of serum bilirubin levels in predicting mortality among high-risk patients admitted to the emergency intensive care unit (EICU).
Materials and Methods: In this retrospective cohort study, an evaluation was conducted on high-risk patients admitted to the EICU between January 2020 and December 2022. The patients were grouped based on 28-day mortality outcomes. Serum bilirubin levels, along with other clinical and laboratory parameters, were recorded and examined using multivariable logistic regression and receiver operating characteristic (ROC) curve analysis.
Results: The most common comorbidities were Chronic Obstructive Pulmonary Disease (COPD) (80.2%) and sepsis (67.2%). Multivariate analyses identified hypertension (OR=4.165, p=0.004), sepsis (OR=8.459, p<0.001), chronic kidney disease (OR=3.910, p=0.009), and total bilirubin levels (OR=1.605, p=0.036) as independent risk factors for mortality. ROC curve analysis demonstrated that a total bilirubin cutoff value of 1.75 mg/dL provided 86.4% sensitivity and 60.0% specificity in predicting mortality. AUC was calculated to be 0.761, indicating that bilirubin levels possess significant power in distinguishing between surviving and died patients.
Conclusions: Elevated serum bilirubin levels have been identified as an independent predictor of mortality in critically ill patients. This finding suggests that bilirubin levels can serve as a reliable indicator in prognostic evaluations within the EICU setting, thereby contributing to more effective management of the patients' treatment process.

Keywords: Bilirubin, Mortality, Emergency intensive care unit, Prognostic marker, Sepsis

Öz

Amaç: Serum bilirubin, karaciğer fonksiyonunun önemli bir biyobelirteci olup, kritik hastalarda sistemik inflamatuar yanıtın şiddetini yansıtabilir. Bu çalışma, yoğun bakım ünitesine (YBÜ) kabul edilen yüksek riskli hastalarda serum bilirubin düzeylerinin mortaliteyi öngörmedeki prognostik önemini değerlendirmeyi amaçlamaktadır.
Materyal ve Metod: Bu retrospektif kohort çalışmasında, Ocak 2020 ile Aralık 2022 tarihleri arasında yoğun bakım ünitesine (YBÜ) kabul edilen yüksek riskli hastalar değerlendirilmiştir. Hastalar, 28 günlük mortalite sonuçlarına göre gruplandırılmıştır. Serum bilirubin düzeyleri ile diğer klinik ve laboratuvar parametreleri kaydedilmiş ve çok değişkenli lojistik regresyon ile alıcı işletim karakteristiği (ROC) eğrisi analizi kullanılarak incelenmiştir.
Bulgular: En sık görülen komorbiditeler Kronik Obstrüktif Akciğer Hastalığı (KOAH) (%80,2) ve sepsis (%67,2) olarak tespit edilmiştir. Çok değişkenli analizlerde hipertansiyon (OR=4,165, p=0,004), sepsis (OR=8,459, p<0.001), kronik böbrek hastalığı (OR=3,910, p=0,009) ve toplam bilirubin düzeyleri (OR=1,605, p=0,036) mortalite için bağımsız risk faktörleri olarak belirlenmiştir. ROC eğrisi analizi, 1,75 mg/dL'lik toplam bilirubin kesim değerinin mortaliteyi öngörmede %86,4 duyarlılık ve %60,0 özgüllük sağladığını göstermiştir. Eğri altında kalan alan (AUC) 0,761 olarak hesaplanmış ve bilirubin düzeylerinin sağ kalan ve ölen hastalar arasında anlamlı bir ayrım gücüne sahip olduğu gösterilmiştir.
Sonuç: Artmış serum bilirubin düzeyleri, kritik hastalarda mortalite için bağımsız bir öngördürücü olarak tanımlanmıştır. Bu bulgu, bilirubin düzeylerinin yoğun bakım ortamında prognostik değerlendirmelerde güvenilir bir gösterge olarak kullanılabileceğini ve hastaların tedavi sürecinin daha etkin yönetilmesine katkı sağlayabileceğini ortaya koymaktadır.

Anahtar Kelimeler: Bilirubin, Mortalite, Yoğun bakım ünitesi, Prognostik belirteç, Sepsis

Corresponding Author / Sorumlu Yazar

Dr. Abdullah ŞEN
Dicle University Faculty of Medicine, Department of Emergency of Medicine, Diyarbakır, TÜRKİYE

E-mail: drabdullahsen@gmail.com

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Introduction

Bilirubin is a compound metabolized in the liver as a byproduct of heme catabolism and is excreted via bile. This pigment is an important biomarker that reflects the functional status of the liver, and elevated serum levels may indicate liver diseases as well as various systemic inflammatory processes (1,2). However, the prognostic value of bilirubin is not limited to liver diseases alone; it has been demonstrated that bilirubin can also be utilized to predict mortality risk, particularly among critically ill patients (3). A significant portion of patients admitted to intensive care units (ICUs) present with severe comorbidities such as sepsis, chronic kidney disease (CKD), and multiple organ failure, among which mortality rates have been found to be high. (4,5). Bilirubin levels rise as a result of inflammatory processes, oxidative stress, and cellular breakdown, and are therefore closely associated with overall mortality risk (6).

As clinical practice becomes increasingly complex, developing individualized approaches to patient treatment is becoming essential (7). Accurate prognostication in ICU patients is crucial not only for treatment planning but also for providing information to patients' families (8). The role of bilirubin levels in this context has been highlighted in numerous studies, repeatedly demonstrating that elevated levels are associated with poor prognosis (3,9). However, determining the independent impact of bilirubin levels on mortality requires new findings that would facilitate the integration of this biomarker into clinical decision-making processes (10,11).

This study aims to investigate the prognostic value of serum bilirubin levels on mortality among high-risk patients admitted to the ICU. We sought to determine whether bilirubin levels are an independent factor in predicting mortality when adjusted for other clinical and laboratory variables.

Materials and Methods

Patient Population and Study Design

This retrospective cohort study included high-risk patients admitted to the emergency intensive care unit (EICU) between January 2020 and December 2022. Our ICU is a tertiary care unit connected to the emergency department, comprising 23 intensive care beds and dedicated to the management of internal medicine and trauma patients. A total of 1,100 patients admitted to the ICU during the two-year period were reviewed. To ensure the homogeneity of the study, patients with pre-existing liver disease, those receiving hepatotoxic treatment, trauma patients, or those with incomplete medical records were excluded. A total of 116 patients aged 18 years and older, who had elevated bilirubin levels within the first 48 hours of ICU admission, were included in the study. Sepsis was diagnosed according to the Sepsis-3 criteria.

Accordingly, sepsis was defined as patients with a Quick SOFA (qSOFA) score of ≥2 or an increase of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score in response to infection. Septic shock was diagnosed based on the presence of vasopressor requirement and a lactate level exceeding 2 mmol/L (12). Chronic kidney disease (CKD) was defined according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m² or albuminuria of ≥30 mg/g persisting for at least three months (13). Chronic obstructive pulmonary disease (COPD) was diagnosed based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, defined as a forced expiratory volume in one second to forced vital capacity ratio (FEV1/FVC) of <0.70, along with clinical evidence of persistent airflow limitation (14). Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medication (15).

The study population was divided into two groups based on the 28-day mortality outcomes: survivors and non-survivors. Demographic characteristics such as age, gender, and comorbidities were recorded for each patient. In addition to bilirubin levels, other laboratory parameters such as albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and renal function tests were collected.

Statistical Analysis

Statistical analyses were performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) for data with a non-normal distribution. Categorical variables were summarized as frequencies and percentages. Normality of continuous data was assessed using the Shapiro-Wilk test. For comparisons between the survivor and deceased groups, the independent samples t-test was used for normally distributed data, while the Mann-Whitney U test was applied for non-normally distributed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the context.

To identify independent predictors of mortality, multivariable logistic regression analysis was performed, including variables with a p-value < 0.05 in univariable analysis. Results from the logistic regression were reported as odds ratios (OR) with 95% confidence intervals (CI). The ability of serum bilirubin levels to predict mortality was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) calculated to assess discrimination. The Youden Index was applied to determine the optimal bilirubin cutoff value for mortality prediction, balancing sensitivity and specificity. Statistical significance was defined as a p-value < 0.05 for all tests.

Results

A total of 116 patients were included in this study, 71 of whom belonged to the surviving group. The mean age of the overall patient group was 68.3 ± 18.1 years, with an age range of 20 to 100 years. Regarding gender distribution, 61.2% of the patients were male. Among the comorbid conditions, sepsis was the most common, observed in 67.2% of the patients, followed by Chronic Obstructive Pulmonary Disease (COPD), seen in 80.2% of the cases. Diabetes (29.3%), hypertension (48.3%), and malignancy (44.0%) rates were also notable in Table 1.

Table 1. Demographic and Clinical Characteristics of The Study Population

Variables	n = 116
Age	68.3 ± 18.1
Gender (%)	
Male	45 (38.8)
Female	71 (61.2)
Diabetes (%)	34 (29.3)
Hypertension (%)	56 (48.3)
CHF (%)	47 (40.5)
Malignancy (%)	51 (44.0)
COPD (%)	23 (19.8)
CKD (%)	58 (50)
Sepsis (%)	78 (67.2)
Systolic Blood Pressure (mmHg)	119.9 ± 23.6
Diastolic Blood Pressure (mmHg)	70.0 ± 12.5
ALT (U/L)	46.1 (2.8-3418.5)
AST (U/L)	63.0 (6.1-9237.7)
Albumin (g/L)	2.4 (1.2-10.4)
GGT(U/L)	62.2 (6.1-784.0)
Blood Glucose (mg/dL)	124.3 (35.4-478.8)
WBC (10e3/uL)	14.5 ± 8.0
Total Bilirubin (mg/L)	1.9 (1.1-24.3)
HGB (g/dL)	10.1 ± 2.0

BP: Blood Pressure, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, WBC: White Blood Cell.

Table 2 shows the comparative analysis of the surviving and died groups. The died group was significantly older than the surviving group (p=0.005). Hypertension and Chronic Kidney Disease (CKD) (p=0.009) were significantly more prevalent in the died group. Sepsis was also significantly more common in the died group p<0.001. Liver function tests, including AST p<0.001, ALT p<0.001, and total bilirubin p<0.001, were found to be significantly higher in the died group. The albumin level was significantly lower in the died group p<0.001. *Table 3* and *Figure 1* evaluate the impact of variables on mortality between the died and surviving groups. Multivariate analysis demonstrated that hypertension (OR: 4.165, 95%CI: 1.562-11.108, P=0.004), sepsis (OR: 8.459, 95%CI: 2.828-25.305, P<0.001), chronic kidney disease (OR: 3.910, 95%CI: 1.399-10.925, P=0.009), and total bilirubin levels (OR: 1.605, 95%CI: 1.030-2.501, P=0.036) were independent predictors of mortality.

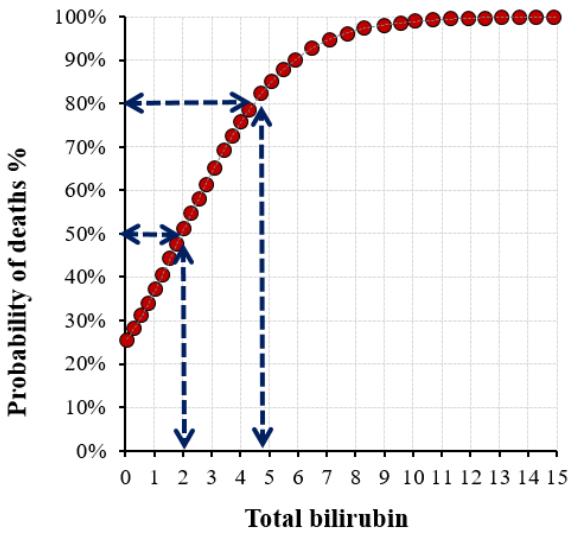

Figure 1. Probability of death based on total bilirubin levels

Table 4 and Figure 2 assess the effectiveness of total bilirubin levels in distinguishing between died and surviving patients using the area under the ROC curve. The effectiveness of total bilirubin in distinguishing between died and surviving patients was significant [Area under the curve 0.761 (0.674-0.849)]. A significant [Area under the curve 0.732 (0.635-0.828)] effectiveness was observed for a total bilirubin cutoff value of 1.75 in distinguishing between died and surviving patients. At a total bilirubin cutoff value of 1.75, the sensitivity in distinguishing between died and surviving patients was 86.4%, positive predictive value 74.0%, specificity 60.0%, and negative predictive value 76.9%.

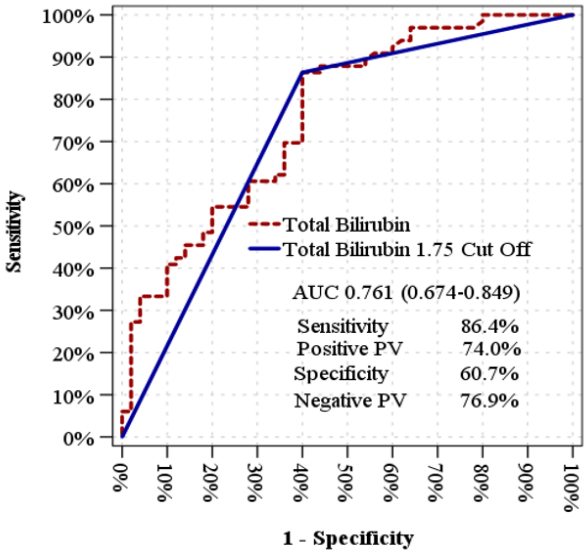

Figure 2. ROC curve analysis of total bilirubin and its 1.75 cut-off for predicting mortality

Table 2. Comparison of Demographic and Clinical Characteristics Between Surviving and Died Patients

		Surviving	Died		
Variables		**n=50**	**n=66**	p	
Age		62.1 ± 20.5	73.1 ± 14.5	***0.005***	m
Gender (%)	Female	22 (44.0)	23 (34.8)	0.316	X^2
	Male	28 (56.0)	43 (65.2)		
Diabetes (%)		18 (36.0)	16 (24.2)	0.168	X^2
Hypertension (%)		14 (28.0)	42 (63.6)	***0.001***	X^2
CHF (%)		15 (30.0)	32 (48.5)	***0.045***	X^2
Malignancy (%)		25 (50.0)	26 (39.4)	0.254	X^2
COPD(%)		8 (16.0)	15(22.7)	0.368	X^2
CKD (%)		18 (36.0)	40 (60.6)	***0.009***	X^2
Sepsis (%)		19 (38.0)	59 (89.4)	***0.001***	X^2
Systolic Blood Pressure (mmHg)		121.8±18.1	118.4±27.1	0.489	m
Diastolic Blood Pressure (mmHg)		70.0±10.1	69.9±14.1	0.686	m
ALT (U/L)		28.3	66.3	***0.001***	m
AST (U/L)		38.1	135.4	***0.001***	m
Albumin (g/L)		2.7	2.3	***0.001***	m
GGT (U/L)		62.2	61.8	0.971	m
Blood Glucose (mg/dL)		126.4	122.3	0.304	m
WBC (10e3/uL)		12.9	14.0	0.110	m
Total Bilirubin (mg/L)		1.7	2.4	***0.001***	m
HGB (g/dL)		10.2	9.1	0.092	m

m Mann-Whitney U Test , X^2 Chi-Square Test, SD: Standard Deviation.
BP: Blood Pressure, CHF: Congestive Heart Failure, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, WBC: White Blood Cell.

Table 3. Univariate and Multivariate Logistic Regression Analysis of Factors Associated with Mortality

	Univariate Model						**Multivariate Model**				
	OR	**%95 CI**			**p**		**OR**	**%95 CI**			**p**
Age	1.037	1.013	-	1.061	*0.002*						
Hypertension	4.500	2.031	-	9.969	*0.001*		4.165	1.562	-	11.108	*0.004*
CHF	2.196	1.013	-	4.761	*0.046*						
CKD	2.735	1.279	-	5.847	*0.009*		3.910	1.399	-	10.925	*0.009*
Sepsis	13.752	5.216	-	36.260	*0.001*		8.459	2.828	-	25.305	*0.001*
ALT	1.001	1.000	-	1.002	0.132						
AST	1.003	1.000	-	1.006	*0.035*						
Albumin	0.995	0.965	-	1.026	0.734						
Total Bilirubin	1.752	1.164	-	2.637	*0.007*		1.605	1.030	-	2.501	*0.036*
Logistic Regression (Forward LR), OR: Odds Ratio, CI: Confidence Interval, SD: Standard Deviation											

BP: Blood Pressure, CHF: Congestive Heart Failure, CKD: Chronic Kidney Disease, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, HGB: Hemoglobin, WBC: White Blood Cell.

Table 4. Receiver Operating Characteristic (ROC) Curve Analysis for Total Bilirubin and Its Predictive Value for Mortality

		Area Under the Curve			% 95 Confidence Interval			p
Total Bilirubin		0.761			0.674	-	0.849	***0.001***
Total Bilirubin 1.75 Cut Off		0.732			0.635	-	0.828	***0.001***
		Surviving	Died					%
Total Bilirubin	≤ 1.75	30	9		Sensitivity			86.4%
	> 1.75	20	57		Pozitive Predictive Value			74.0%
					Specificity			60.0%
					Negative Predictive Value			76.9%

ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval.

Discussion

This study demonstrated that elevated serum bilirubin levels are independently associated with mortality in critically ill patients admitted to the emergency intensive care unit. Additionally, hypertension, sepsis, and chronic kidney disease were identified as significant predictors of mortality. These findings suggest that bilirubin levels could be integrated into clinical prognostic models to enhance risk stratification. Age was found to be significantly associated with mortality, with older age strongly correlated with higher mortality rates, consistent with previous research conducted in intensive care settings. Elderly patients are more susceptible to the systemic effects of critical illnesses, and their physiological reserves are often inadequate to counteract the stress of severe conditions (16). This vulnerability is further exacerbated by the presence of comorbidities, which are more prevalent in older populations. Conversely, gender did not emerge as a significant predictor of mortality in our study, aligning with several studies suggesting that gender differences in ICU outcomes are generally negligible when other variables are controlled (17,18).

The significant association between high bilirubin levels and mortality observed in this study is consistent with previous research. Bilirubin, an indicator of oxidative stress and inflammation, has been linked to adverse outcomes in various patient populations, including those with sepsis and liver dysfunction (19). The mechanisms underlying this relationship are multifaceted, involving the role of bilirubin in modulating inflammatory responses and its potential as a surrogate marker of hepatic and extrahepatic injury (20). Prior studies have demonstrated that hyperbilirubinemia is associated with increased mortality in septic patients, supporting the notion that elevated bilirubin levels may reflect the severity of systemic inflammation and multiple organ failure (21). The role of total bilirubin levels in predicting mortality is particularly noteworthy when compared with comorbidities such as sepsis, chronic kidney disease (CKD), and hypertension. Our study demonstrated that elevated bilirubin levels remained significantly associated with mortality even after adjusting for these comorbidities (22). This finding suggests that bilirubin levels not only reflect liver function but also serve as an indicator of systemic inflammation and organ dysfunction (1,23).

When evaluated through ROC analysis, bilirubin levels were found to provide high sensitivity and acceptable specificity in predicting mortality, with a cutoff value of 1.75 mg/dL. This result supports the use of bilirubin levels as a prognostic marker in critically ill patients in the ICU (8,11). However, the predictive capability of bilirubin levels in forecasting mortality should be assessed in conjunction with other clinical markers. For instance, low albumin levels have also been associated with poor prognosis, and in our study, this was found to be an independent risk factor for mortality alongside bilirubin (9,24). The prognostic value of bilirubin may vary depending on the underlying cause of its elevation. For example, patients with pre-existing liver disease may have chronically elevated bilirubin levels, complicating its use as a mortality predictor (25,26). In contrast, acute elevations in bilirubin in the context of sepsis or multiple organ failure are more likely to reflect the severity of critical illness and may presage a poorer prognosis (1). Therefore, while bilirubin is a useful marker, its interpretation should be contextualized within the broader clinical picture.

When comparing our findings with similar studies, the prognostic utility of bilirubin in critically ill patients appears robust. For instance, the study by Shah et al. found that elevated bilirubin levels were associated with increased mortality in septic ICU patients, reinforcing our findings (27). Additionally, the results of our study are consistent with the research by Han et al., which suggested that bilirubin, when used alongside a broader panel of liver function tests, can effectively predict mortality in the ICU setting (11). These studies and our findings suggest that bilirubin should be routinely considered in prognostic assessments, particularly in critically ill patients with complex comorbidities.

Our study has important implications for clinical practice. Integrating bilirubin levels into the prognostic assessments of ICU patients may improve risk stratification and guide therapeutic decision-making. For instance, patients with elevated bilirubin levels may benefit from more aggressive monitoring and early interventions to prevent adverse out-

comes (28). Furthermore, our findings suggest that bilirubin could serve as a therapeutic target for interventions aimed at reducing oxidative stress and improving patient outcomes in the ICU (29). The use of bilirubin levels as a prognostic marker is also important for treatment planning. In patients with elevated bilirubin levels, closer monitoring and the implementation of aggressive treatment strategies may improve prognosis. However, an aggressive treatment approach is feasible only with a detailed assessment of the clinical condition in the intensive care unit and the creation of an individualized plan. For instance, elevated bilirubin levels in patients with sepsis may indicate liver dysfunction or multiple organ failure, necessitating early initiation of hemodynamic support or organ support therapies. In this context, bilirubin levels can serve not only as a prognostic marker but also as a guide in determining therapeutic strategies (30).

Limitations

This study has several limitations. Its retrospective design may introduce selection bias and limit the generalizability of the findings. Additionally, liver function was not assessed using advanced imaging or histopathological evaluation, which could have provided more detailed insights into bilirubin dynamics and its prognostic value.

Conclusion

This study highlights the independent association of bilirubin with mortality, emphasizing its importance as an indicator of disease severity, alongside factors such as age, sepsis, and chronic kidney disease (CKD). The findings suggest that bilirubin levels can serve as a reliable prognostic marker in critically ill patients, thereby contributing to improved risk stratification and guiding therapeutic decisions.

Ethical Approval: *The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (Approval Date: March 15, 2023; Approval Number: 86). The study was conducted in accordance with the principles of the Helsinki Declaration*

Author Contributions:
Concept: A.Ş., M.Y., T.F.Z., E.G., M.O.
Literature Review: A.Ş., C.G., Ş.G.Ü., S.B., B.T.G.
Design : M.O., C.G., Ş.G.Ü., S.B.
Data acquisition: C.G., Ş.G.Ü., S.B., B.T.G., M.Ü.
Analysis and interpretation: A.Ş., M.Y., M.O., C.G.
Writing manuscript: A.Ş., M.Y., M.O., C.G.
Critical revision of manuscript: A.Ş., E.G., M.O., C.G., M.Ü.
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