Research Article *Pamukkale Medical Journal*

Received: 27.10.2024

Accepted: 15.04.2025

Area of Expertise: Infectious Diseases

Title: Evaluation of inflammation-related prognostic scores, CRP/albumin, LDH/albumin and lactate/albumin ratios in patients with sepsis.

Short title: Inflammation-related prognostic scores and sepsis.

Abstract

Purpose: Results regarding the clinical usefulness and predictive accuracy of inflammation-based parameters, including C-reactive protein (CRP), lactate dehydrogenase (LDH), and lactate in septic patients are conflicting. In our study, we aimed to evaluate the relationships of the combination of these inflammatory parameters with albumin, disease severity and prognosis.

Materials and methods: 98 patients diagnosed with sepsis were categorised as survivors (n=68) and nonsurvivors (n=30) according to their intensive care unit (ICU) mortality. Prognostic factors were evaluated with the receiver operating characteristic curve and Cox proportional hazard regression model. Survival was analyzed with the Kaplan-Meier method.

Results: Compared to survivors, nonsurvivors had increased CRP and lactate (13.5 vs 10.0, *p*=0.044; 2.2 vs 1.7, *p*=0.006, respectively), while LDH and albumin levels were not significantly different (246.0 vs 245.0, *p*=0.624; 2.9 vs 3.0, *p*=0.061, respectively). When combined factors were evaluated, CRP/albumin and lactate/albumin were significantly higher in nonsurvivors (4.9 vs 3.0, *p*=0.018; 0.8 vs 0.5, *p*=0.001, respectively), while LDH/albumin was similar in both groups (93.1 vs 78.9, *p*=0.148). Lactate/albumin had the highest AUC of 0.709 (*p*=0.001), while CRP had the lowest AUC of 0.628 (*p*=0.044). In a multivariate analysis of possible predictors of ICU mortality, only lactate could be an independent predictor of poor outcome (HR:1.998; *p*=0.020), while other variables were not independently associated.

Conclusion: Increased CRP, lactate, CRP/albumin and lactate/albumin levels in septic patients were associated with poor outcomes. Lactate level was an independent predictor of mortality.

Keywords: Albumin, C-reactive protein, lactate, prognosis, sepsis.

Makale başlığı: Sepsis hastalarında inflamasyon ilişkili prognostik skorlar CRP/albumin, LDH/albumin ve laktat/albümin oranlarının değerlendirilmesi.

Kısa Başlık: İnflamasyon ilişkili prognostik skorlar ve sepsis.

Öz

Amaç: Septik hastalarda C-reaktif protein (CRP), laktat dehidrogenaz (LDH) ve laktat gibi inflamasyona dayalı parametrelerin klinik yararlılığı ve tahmin doğruluğuna ilişkin sonuçlar çelişkilidir. Çalışmamızda bu inflamatuvar parametrelerin albumin ile kombinasyonunun, hastalık şiddeti ve prognoz ile ilişkilerini değerlendirmeyi amaçladık.

Gereç ve yöntem: Sepsis tanısı konulan 98 hasta, yoğun bakım ünitesi (YBÜ) mortalitelerine göre yaşayanlar (n=68) ve ölenler (n=30) olarak sınıflandırıldı. Prognostik faktörler receiver operating characteristic curve ve Cox proportional hazard regression model ile değerlendirildi. Sağ kalım Kaplan-Meier methodu ile analiz edildi.

Bulgular: Yaşayan hastalarla karşılaştırıldığında, ölen hastalarda CRP ve laktat düzeyleri artmıştı (sırasıyla 13.5'e karşı 10.0, *p*=0.044; 2.2'ye karşı 1.7, *p*=0.006), ancak LDH ve albümin düzeyleri anlamlı derecede farklı değildi (sırasıyla 246.0'ya karşı 245.0, *p*=0.624; 2.9'a karşı 3.0, *p*=0.061). Kombine faktörler değerlendirildiğinde, CRP/albumin ve laktat/albumin ölen hastalarda anlamlı derecede yüksek iken (sırasıyla 4.9'a karşı 3.0, *p*=0.018; 0.8'e karşı 0.5, *p*=0.001), LDH/albumin ise her iki grupta benzerdi (93.1'e karşı 78.9, *p*=0.148). Laktat/albumin 0,709 ile en yüksek AUC'ye sahipken (*p*=0.001), CRP 0,628 ile en düşük AUC'ye sahipti (*p*=0.044). YBÜ mortalitesinin olası belirleyicilerinin çok değişkenli analizinde, yalnızca laktat kötü sonucun bağımsız bir belirleyicisi olabilirken (HR:1.998; *p*=0.020), diğer değişkenler bağımsız olarak ilişkili değildi.

Sonuç: Septik hastalarda CRP, laktat, CRP/albumin ve laktat/albumin düzeylerindeki artış kötü sonuçlarla ilişkilidir. Laktat düzeyi mortalitenin bağımsız bir belirleyicisidir.

Anahtar kelimeler: Albümin, C-reaktif protein, laktat, prognoz, sepsis.

Introduction

Sepsis, defined as an uncontrolled host response to infection, leads to death as a result of cellular and organ dysfunction caused by dysregulated inflammation [1]. The intensity of the infection and the inflammatory response are the main factors determining the outcome in critically ill patients with sepsis [2]. Various biomarkers have been used for diagnosis, treatment and prognostic evaluation of infections in sepsis patients. The ability to detect the disease with high accuracy using sepsis biomarkers may help to initiate appropriate antibiotic therapy early and evaluate treatment efficacy [3].

Sepsis patients are a heterogeneous population and have different risk factors including age, underlying diseases, infection pattern and organ dysfunction. Due to the wide and complicated structures of immune mediators and the influence of different conditions, it is difficult to find biomarkers with high predictive value based on immune response in critically ill patients. Simultaneous assessment of several sepsis-associated biomarkers may reduce the limitations of any one biomarker. Although some inflammation-based parameters, including C-reactive protein (CRP), lactate dehydrogenase (LDH), lactate and albumin and their combinations have been investigated as potential indicators, mixed results have been obtained regarding their clinical usefulness and predictive accuracy [3-6].

Considering the potential effects of the inflammatory response on the clinical outcome of septic patients, we hypothesised that the combinations of these inflammatory parameters with albumin, a negative acute phase reactant, would be superior in predicting intensive care unit (ICU) mortality. To test this hypothesis, we evaluated the associations of CRP/albumin, LDH/albumin and lactate/albumin ratios with disease severity and their prognostic performance.

Materials and methods

Study design

We conducted a retrospective cohort study involving an analysis of the medical records of patients diagnosed with sepsis within the first 48 hours of admission to the Anesthesiology and Reanimation ICU of Ordu University for a period of 1 year. This study was conducted in accordance with the Declaration of Helsinki between June 2023 and June 2024, with the approval of the Ordu University Non-Interventional Clinical Research Ethics Committee (No.: 108/2024). Informed consent was not obtained due to its retrospective nature.

Inclusion and exclusion criteria

Medical patients aged 18 years and over, diagnosed with clinical sepsis according to the SEPSIS-3 definition and confirmed microbiologically were included in the study [7]. Patients with intoxication, malignancy, preexisting immunodeficiency, steroid use (prednisolone equivalent above 0.3 mg/kg/day), chronic hepatic failure, renal replacement therapy, blood product transfusion and malnutrition were excluded from the study.

Study protocol

Demographic, clinical data and laboratory values were documented. Only the first admission records were used to analyse patients with multiple ICU admissions. In patients diagnosed with sepsis, disease severity determined by the sequential organ failure assessment (SOFA) score, mechanical ventilation requirement and biochemical parameters were measured within the first 48 hours after admission. Microbiological results in samples obtained 48 hours before or after ICU admission were evaluated. Standard microbiological methods were used in the isolation of the samples. Identification and antimicrobial susceptibilities of the growing colonies were determined by Becton Dickinson Phoenix (USA) automated system. Antimicrobial resistance status was defined according to the study of Magiorakos et al. [8]. Minimal inhibitory concentration (MIC) breakpoints, as defined by the European Committee on Antimicrobial Susceptibility Testing, were used to assess MIC results (EUCAST 2023) [9]. Pathogens with intermediate antimicrobial susceptibility were defined as resistant. Empiric antimicrobial therapy with adequate doses of antimicrobial drugs covering likely pathogens was considered appropriate. CRP, LDH, and albumin levels were measured with Cobas 8000 (Roche-Hitachi, Tokyo, Japan), and lactate levels were measured with ABL800 Flex (Radiometer, Copenhagen, Denmark). All the patients received routine sepsis treatment as defined by current sepsis guidelines [7]. The study period was 1 year, and the primary endpoint was 30-day ICU mortality.

Sample size

In our preliminary analysis of 26 patients (18 were survivors and 8 were non-survivors), the areas under the curve (AUC) of lactate/albumin's receiver operating characteristic (ROC) analysis to predict death were 0.68. To determine if a statistically significant difference in lactate/albumin values existed between the groups, with an alpha of 5%, relating to a null value of 0.5 and power of 80%, at least 67 survivors (negative cases) and 29 non-survivors (positive cases) were required.

Statistical analysis

Data analysis was conducted using SPSS software (version 26.0). Continuous variables were summarised using mean values ± SD or medians (interquartile ranges), and categorical variables were expressed using percentages. To compare potential predictors between survivors and non-survivors, the Mann-Whitney U test were employed. Spearman's rank correlation test was utilised to examine the association between inflammatory markers and SOFA scores. The predictive performance in mortality discrimination of the variables found significant in the univariate analysis was evaluated by ROC analysis, and the AUC values were calculated. The optimal cut-off values were established using Youden's index with maximisation of sensitivity and specificity. Differences between ROC curves were analysed using the DeLong et al. [10] method. The independent predictors of mortality in critically ill patients were defined by the Cox proportional hazard regression model. Covariates, including age, sex, and SOFA score, were used for adjustment. Lactate-related variables that reached the highest AUC values in the ROC analysis were further examined. Kaplan-Meier survival curves were created using the prognostic cut-off values of these parameters and analysed with the log-rank test. Statistical significance was defined as two-sided *p*-values lower than 0.05.

Results

Out of 118 patients admitted to the ICU, 98 medical patients met the study criteria and were included in the statistical analysis. The median age of these participants was 76.5 years, 45.9% male and 54.1% female. Clinical data and some laboratory parameters are shown in Table 1. In this cohort, a median stay of 15 days was spent in the ICU; hypertension was the most common comorbidity with 44.9%; the median SOFA score was 8 and 41.8% of patients received mechanical ventilation.

When the sources of infection were evaluated, the most common infection site responsible for the development of sepsis was pneumonia, with 31.6%. Of the 113 microorganisms identified in septic patients, 67 were gram-negative, 37 were gram-positive, and 9 were fungal agents. When the responsible bacteria were evaluated according to their antimicrobial resistance status, the incidence of multi-drug resistant (MDR) agents was highest in gram-negative pathogens with 54, while it was found to be 27 in gram-positive pathogens (Table 1).

CRP, LDH, lactate and albumin determined in the blood withdrawn within the first 24 hours of admission to the ICU are shown in Table 2. Compared to survivors, non-survivors presented increased CRP and lactate (13.5 vs 10.0, p=0.044; 2.2 vs 1.7, p=0.006, respectively), while LDH and albumin levels were not significantly different

(246.0 vs 245.0, *p*=0.624; 2.9 vs 3.0, *p*=0.061, respectively) When combined factors were evaluated, CRP/albumin and lactate/albumin were significantly higher in non-survivors (4.9 vs 3.0, *p*=0.018; 0.8 vs 0.5, *p*=0.001, respectively), while LDH/albumin was similar in both groups (93.1 vs 78.9, *p*=0.148).

Correlation coefficients of SOFA score and inflammatory parameters were evaluated by bivariate analysis. SOFA score determined in the initial stage of sepsis was positively correlated with CRP, lactate, CRP/albumin and lactate/albumin ratio (r=0.314, *p*=0.002; r=0.278, *p*=0.006; r=0.300, *p*=0.003; r=0.320, *p*=0.001, respectively). Compared to other parameters, the relationship between lactate/albumin ratio and SOFA score was more pronounced. Nonetheless, no statistically significant association between SOFA score and LDH, albumin, and LDH/albumin ratio was observed (r=0.180, *p*=0.076; r=-0.117, *p*=0.252; r=0.191, *p*=0.060, respectively) (Table 3). Additionally, a significant positive association was observed among the lactate/albumin ratio and other important predictors of mortality, namely CRP, lactate, and CRP/albumin ratio (r=0.259, *p*=0.004; r=0.225, *p*=0.010; r=0.279, *p*=0.002) (data not shown).

The usefulness of each indicator in predicting critically ill patient mortality was evaluated by ROC analysis (Table 4, Figure 1). Lactate/albumin had the highest AUC of 0.709 (*p*=0.001), while CRP had the lowest AUC of 0.628. CRP/albumin had the best sensitivity (63.4%) in predicting death with a cut-off value of 4.5, and lactate had the best specificity (95.6%) with a cut-off value of 3.4. When ROC curves were compared pairwise with lactate/albumin, which had the highest performance for mortality prediction, no significant difference between AUC values was observed. Therefore, the predictive ability of all variables in the mortality of critically ill patients was similar.

In a multivariate analysis of possible predictors of critically ill ICU mortality, in addition to demographic factors, including age and sex, we checked the SOFA score, which included disease severity. When adjusted for these parameters, only lactate could be an independent predictor of poor outcome (HR:1.998; *p*=0.020), while the other variables were not independently associated (Table 5).

Mortality at 30 days from ICU admission was analysed using the Kaplan-Meier method, using the cut-off values for lactate and lactate/albumin variables obtained from our data. Using a lactate cut-off value of 3.4, the survival probability of critically ill patients with <3.4 was significantly higher than those with ≥3.4 (*p*=0.040, log-rank test). However, when the cut-off value of 0.75 for lactate/albumin was used, the mortality rates of critically ill patients did not differ significantly (*p*=0.107, log-rank test) (Figure 2).

Discussion

In this study, lactate levels were independently associated with time to death censored right at day 30 in critically ill patients experiencing sepsis, and the risk of mortality increased approximately twofold after adjusting for confounding factors. At the same time, lactate/albumin presented similar predictive values to other prognostic parameters, namely CRP, lactate and CRP/albumin, in distinguishing mortality in septic patients.

CRP is an acute-phase reactant synthesised in the liver by the significant stimulation of interleukin-6 in response to infection and inflammation [11]. CRP levels, which start to increase in the first 2 hours in acute conditions, can reach peak levels within 48 hours. The relatively short half-life of CRP, 19 hours, is important in the follow-up of infectious diseases and inflammatory conditions [12]. In the study by Ye et al. [13] examining the relationships of different markers with infection and sepsis, CRP performed superiorly to procalcitonin. In the study by Zhang et al. [14], CRP elevation was independently linked with a poorer prognosis in patients with sepsis. In our study, CRP levels, although reaching higher values in the Non-survivors group, were not independent predictors of mortality.

Serum albumin levels, a nutritional parameter, are an indirect indicator of the inflammatory response and vary according to the severity of inflammation [15]. In a study conducted by Artero et al. [16] in community-acquired sepsis patients, hypoalbuminemia was identified as the most important risk factor associated with mortality. In another prospective study, Yin et al. [15] examined the prognostic significance of serum albumin levels in sepsis patients who did not receive exogenous albumin supplementation. They revealed that the risk of mortality was increased in patients with serum albumin below 29.2 g/L. Similarly, in our study, where we excluded patients receiving replacement therapy and prevented the potential confounding effect, although albumin levels were lower among non-survivors, the difference between the groups was at the limit of statistical significance. This difference may also be related to the fact that albumin levels are affected by other variables, such as chronic inflammation and nutritional status [17].

The study sought to enhance predictive capacity by combining single parameters that have been shown to be independent predictors of mortality. The CRP/albumin ratio is being examined as a prognostic score in patients with systemic inflammation, sepsis and cancer. In the study conducted by Filho et al. [18] in critically ill surgery patients, the CRP/albumin ratio, although it reached higher AUC values than CRP and albumin in predicting mortality, was not a prognostic indicator for the mortality of septic patients. Ranzani et al. [19], in their study conducted on medical ICU patients, investigated the

association between the CRP/albumin ratio and the likelihood of death within 90 days of patients with sepsis. They showed that residual inflammation assessed by the CRP/albumin ratio at the discharge from the ICU was an independent predictor of long-term mortality after a sepsis episode and that the results had higher prognostic accuracy than single CRP measurements. In our study, CRP/albumin ratio had prognostic significance for 30-day ICU mortality in septic patients; its poor predictive value was similar to CRP but was not independently associated with mortality. These findings align with the results of earlier research, which suggest that residual effects may persist for up to 90 days post-ICU in septic patients and that inflammatory parameters could offer superior insight into long-term prognosis [20, 21].

Results regarding the prognostic significance of serum LDH levels in sepsis patients considered an indicator of anaerobic glycolysis, are contradictory. In the study conducted by Erez et al. [22] in medical patients, isolated LDH elevation, in addition to being associated with the severity of the underlying disease and infection, was an independent predictor of mortality. On the contrary, Miglietta et al. [23] showed that despite a higher incidence of mortality, LDH levels were lower in patients with systemic candidiasis than in patients with bacterial sepsis. The fact that LDH levels were not correlated with mortality in septic patients in our study was consistent with the second-mentioned study.

Low peripheral oxygenation, which leads to increased anaerobic glycolysis due to inadequate oxygen delivery in sepsis, increases lactate production [24]. However, lactate levels, generally considered an indicator of tissue hypoxia, also increase in conditions other than tissue oxygenation [25]. Hyperlactatemia observed in septic patients with normal oxygen delivery and tissue perfusion is associated with increased aerobic glycolysis due to overstimulation of the Na^+-K^+-ATPase pump in the skeletal muscle [26]. In addition, hepatic or renal dysfunction may increase lactate levels by decreasing lactate elimination [27]. Previous studies have shown that in patients with sepsis, along with the diagnostic value, increased lactate levels are linked to disease severity and mortality [28].

However, the fact that lactate levels are affected by different diseases may limit their diagnostic and prognostic use. The fact that lactate and albumin are associated with different mechanisms in the septic process suggests that a ratio in which inflammatory and nutritional parameters with prognostic importance are evaluated together may reach a higher predictive value. Wang et al. [29] assessed in a prospective study the clinical use of the lactate/albumin ratio in predicting the development of organ failure and mortality in patients with sepsis. Although lactate levels were higher in patients with multiple organ dysfunction syndrome (MODS), the risk of mortality was not increased. An increase in the lactate/albumin ratio was shown to be associated with MODS and

mortality. In another study, Lichtenauer et al. [30] examined the importance of the lactate/albumin ratio in risk stratification of septic patients. Lactate levels were higher in non-survivors, and its predictive value in the short-term analysis, including in-hospital mortality, was comparable to that of the lactate/albumin ratio. However, in the long-term study, including post-discharge mortality, the lactate/albumin ratio had a higher prognostic value. Therefore, it was suggested that the combination of lactate, which indicates the severity of acute disease, and albumin, a long-term indicator such as nutritional status, may increase the prognostic capacity. In our study, admission lactate levels assessed by time-to-event analysis were linked to an elevated risk of 30-day ICU mortality in septic patients. Although the lactate/albumin ratio reached the highest predictive value, its prognostic capacity was similar to serum lactate.

The increase in inflammation parameters observed in septic patients due to the acute phase response generated by the innate immune system is related to the severity of the clinical condition [1]. Since disease severity is an indicator of organ dysfunction caused by increased inflammation in sepsis patients, the significant correlation found in our study between the SOFA score and the highest predictive marker, the lactate/albumin ratio, suggests that our results are consistent with the relationship between increased inflammatory responses and the lactate/albumin ratio [31]. Hypothetically, disease severity assessed by the SOFA score, similar to other inflammatory conditions, is an important indicator of changes in inflammatory mediators observed in the acute phase of sepsis patients. Therefore, in accordance with the positive relationships between the well-known inflammatory markers CRP, lactate and CRP/albumin ratio and the lactate/albumin ratio, a significant relationship can be expected between the lactate/albumin ratio and the SOFA score.

There were some limitations in this study. The fact that our study was a single centre restricts the generalisation of our results to other institutions. Although we tried to measure the severity of disease in critically ill patients with sepsis using the SOFA score, unmeasured confounding variables and other causes of inflammation may prevent more reliable measurements of prognostic markers. Due to the lack of nutritional data such as body mass index or total protein, it was not possible to evaluate to what extent the parameters used for mortality risk estimation are related to nutritional status or sepsis-induced inflammation. In our results, only the relationship of inflammatory indicators with short-term mortality was evaluated. Therefore, multicenter prospective studies are needed to assess better the prognostic scores examined in our study as mortality predictors in septic patients.

In conclusion, increased CRP, lactate, CRP/albumin and lactate/albumin levels in sepsis patients were associated with a poor outcome and had similar prognostic values. However, only lactate was an independent predictor of mortality. Using these parameters in the early stages of sepsis may help identify high-risk patients and determine specific treatments.

Funding: None.

Ethics committee approval: The approval of the study was given by Ordu University Non-Interventional Clinical Research Ethics Committee (date: July 26, 2024 and no: 108/2024).

Authors' contributions: A.I. constructed the main idea and hypothesis of the study. O.I. collected the data. A.I. and O.I. developed the theory and arranged the material and method section. O.I. has done the evaluation of the data in the results section. Discussion section of the article was written, reviewed, corrected and approved by A.I. and O.I. In addition, all authors discussed the entire study and approved the final version.

Conflict of interest: No conflict of interest was declared by the authors.

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Table 1. Characteristics of study cohort

Characteristic	Value
Age	76.5 (67-87)
Gender, male, n (%)	45 (45.9)
Comorbidity, n (%)	
Diabetes mellitus	25 (25.5)
Hypertension	44 (44.9)
Renal failure	12 (12.2)
Heart disease	21 (21.4)
Pulmonary disease	19 (19.4)
Neurological disease	15 (15.3)
Vasopressor use	42 (42.9)
SOFA	8 (5-10)
Mechanical ventilation, n (%)	41 (41.8)
Hemoglobin (g/dL)	11.4 (9.5-12.7)
White Blood Cells (10^9/L)	13.3±5.1
Procalcitonin (ng/mL)	7.9 (5-12)
Serum creatinine (mg/dL)	0.9±0.3
Alanine aminotransferase, (IU/L)	38 (19-51)
Primary infection site, n (%)	
Pneumonia	31 (31.6)
Urinary tract	20 (20.4)
Skin/soft tissues	13 (13.3)
Abdominopelvic	10 (10.2)
Other	24 (24.5)
Identified microorganisms, n (%)	
Gram negative bacilli / MDRO	67 (68.4) / 54 (80.6)
Gram positive cocci / MDRO	37 (37.8) / 27 (73.0)
Fungi	9 (9.2)
Appropriate antimicrobial treatment, n (%)	64 (65.3)
Length of ICU stay (days)	15 (8-24)

n=98 patients. Data shown as mean ± standard deviation, median (interquartile ranges) or n (%)
SOFA: sequential organ failure assessment, MDRO: multi-drug resistant organism
ICU: Intensive care unit

Table 2. Comparison of selected possible predictors of mortality

Predictor	Total (n=98)	Survivors (n=68)	Nonsurvivors (n=30)	*p* value	z
CRP (mg/dL)	11.4 (4-18)	10 (3-16)	13.5 (7-81)	0.044*	-2.012
LDH (U/L)	245.5 (200-343)	245 (193-321)	246 (207-403)	0.624	-0.489
Lactate (mmol/L)	1.8 (1-3)	1.7 (1-2)	2.2 (2-4)	0.006*	-2.763
Albumin (g/dL)	3 (2-3)	3 (3-4)	2.9 (2-3)	0.061	-1.873
CRP/albumin	3.7 (2-7)	3 (1-6)	4.9 (2-29)	0.018*	-2.366
LDH/albumin	82.6 (67-122)	78.9 (64-113)	93.1 (67-151)	0.148	-1.445
Lactate/albumin	0.6 (0.4-0.9)	0.5 (0.3-0.7)	0.8 (0.4-1.4)	0.001*	-3.303

Data shown as median (interquartile ranges). * Survivors vs Nonsurvivors group (p<0.050)
CRP: C-reactive protein, LDH: lactate dehydrogenase, z was the test value of the Mann-Whitney U test

Table 3. Correlation between SOFA scores and inflammatory biomarkers

Variable	SOFA	
	rs#	*p* value
CRP	0.314	0.002*
LDH	0.180	0.076
Lactate	0.278	0.006*
Albumin	-0.117	0.252
CRP/albumin	0.300	0.003*
LDH/albumin	0.191	0.060
Lactate/albumin	0.320	0.001*

SOFA: sequential organ failure assessment, CRP: C-reactive protein
LDH: lactate dehydrogenase, #Spearman correlation, *p<0.05

Table 4. Performance of significant variables in predicting ICU mortality

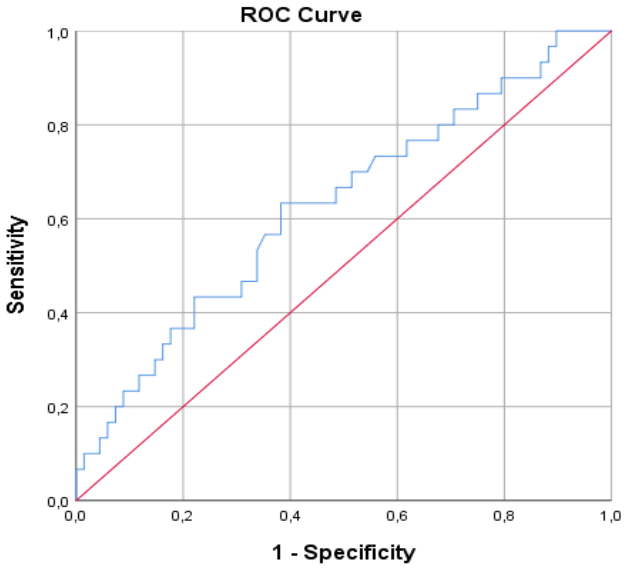
Variables	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	*p* value
CRP	12.3	0.628 (0.524-0.723)	63.3	61.8	0.308
Lactate	3.4	0.675 (0.573-0.767)	33.3	95.6	0.168
CRP/albumin	4.5	0.650 (0.548-0.744)	63.4	69.1	0.453
Lactate/albumin	0.75	0.709 (0.608-0.796)	56.7	76.5	

DeLong et al. Receiver operating characteristic plot analysis of significant variables with respect to prediction of ICU mortality. The *p* values correspond to the difference between the AUC of the parameters and the AUC of Lactate/albumin ratio. AUC: Area under the receiver operating characteristic curve, CI: Confidence interval, CRP: C-reactive protein

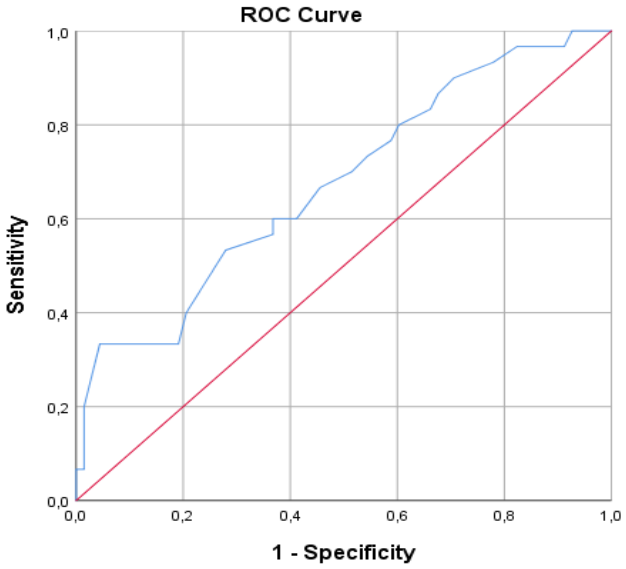
Table 5. Independent variables for predicting ICU mortality by multivariate Cox regression analysis

Predictor	B-value	HR	95% CI	*p* value
CRP	0.007	1.008	0.985-1.031	0.523
Lactate	0.692	1.998	1.114-3.581	0.020*
CRP/albumin	-0.004	0.996	0.943-1.051	0.878
Lactate/albumin	-0.972	0.378	0.107-1.341	0.132

Hazard ratio (HR) was calculated using a Cox proportional-hazards model adjusted by age, sex and SOFA score. The HR indicates the risk of ICU mortality, *p<0.05, CI: Confidence interval, CRP: C-reactive protein



Diagonal segments are produced by ties.



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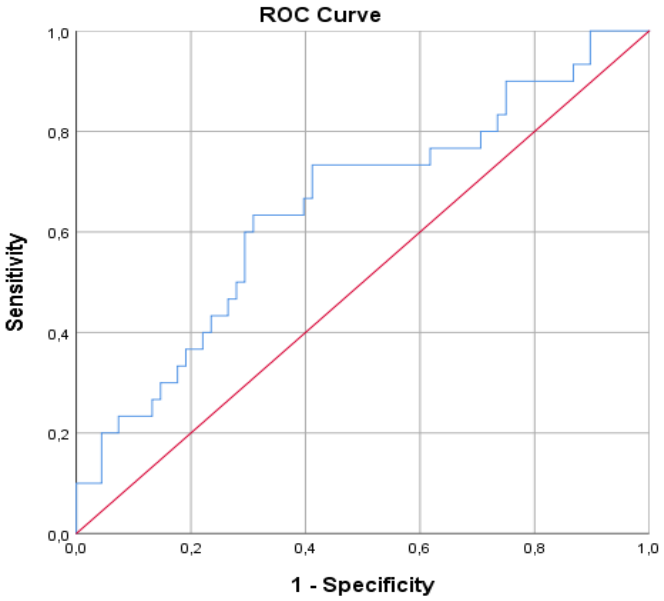

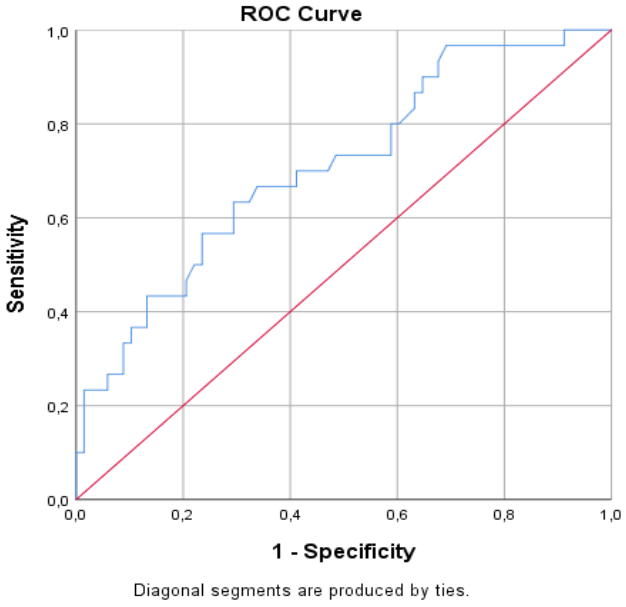

Figure 1. Receiver operating characteristics curves for a) C-reactive protein, b) Lactate, c) CRP/albumin and d) Lactate/albumin in predicting ICU mortality

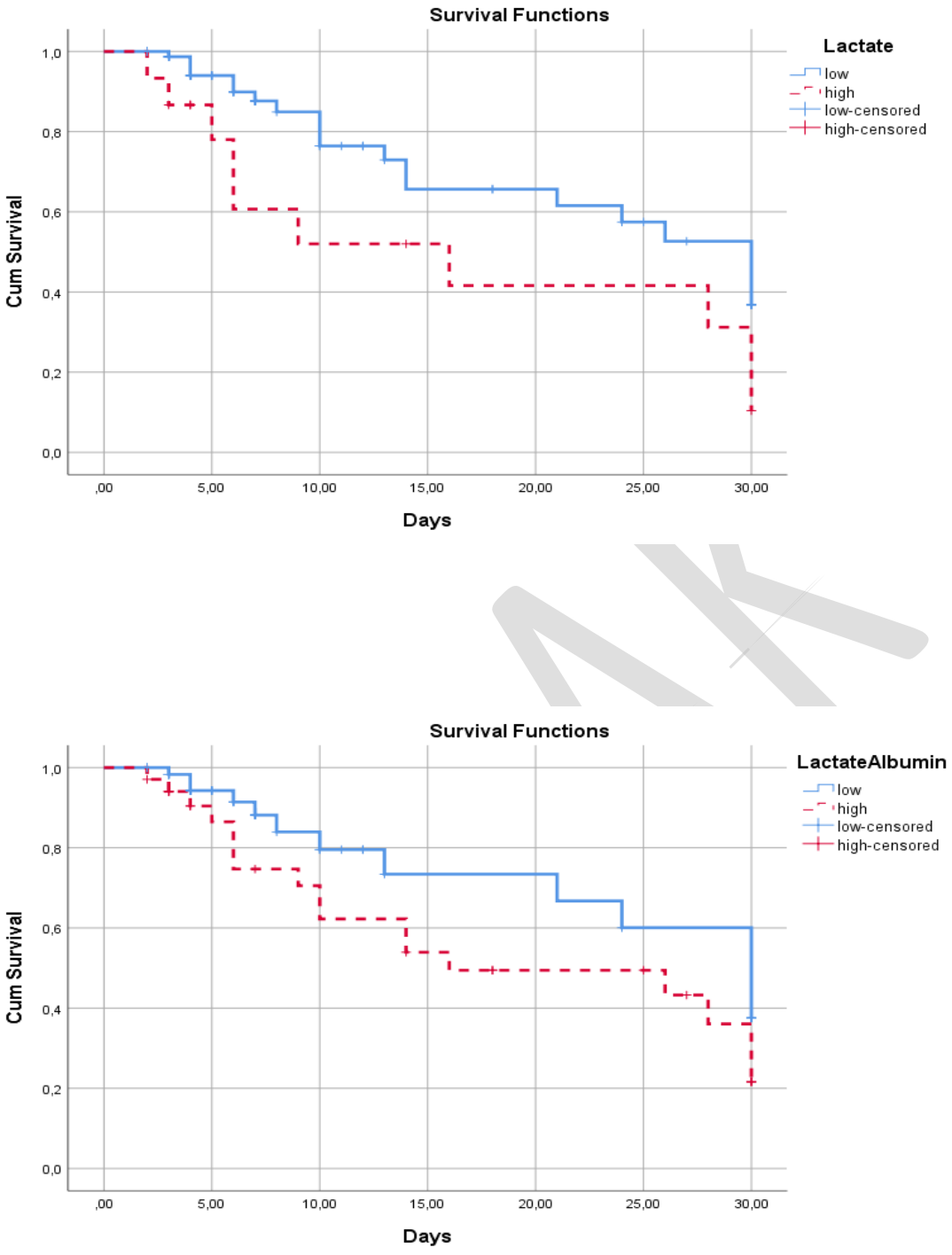

Figure 2. Kaplan-Meier survival curves of the critically ill patients stratified by a) Lactate and b) Lactate/albumin ratio

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Ayşegül İlban, PhD. Ordu University, Training and Research Hospital, Department of Microbiology, Ordu, Türkiye, e-mail: ayseguli688@gmail.com (https://orcid.org/0000-0001-7450-551X) (Corresponding Author)

Ömür İlban, Assoc. Prof. Ordu University, Training and Research Hospital, Department of Intensive Care, Ordu, Türkiye, e -mail: droilban@gmail.com (https://orcid.org/0000-0001-8320-3150)