

# Prognostic value of the lactate/albumin ratio for predicting mortality in patients with pneumosepsis in intensive care units

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## Abstract

The lactate/albumin (L/A) ratio correlates with Acute Physiology and Chronic Health Evaluation 2 (APACHE-2) and Sequential Organ Failure Assessment (SOFA) scores. This study examined whether the L/A ratio has prognostic value in a larger group of critically ill (adult) patients admitted to an intensive care unit (ICU) due to pneumosepsis.

This retrospective study analyzed the data of 273 patients with pneumosepsis admitted to the Internal Medicine ICU of Adana City Training and Research Hospital between 2018 and 2020. Patients diagnosed with pneumosepsis were included in the study. The data were obtained from the hospital system. Patients who had cancer, who were pregnant, and patients whose necessary data could not obtain for the study were excluded from the study.

The L/A ratio was superior to lactate or albumin alone as a predictor of mortality. Furthermore, this result was valid for patients with kidney and hepatic dysfunction. A correlation occurred between the L/A ratio and APACHE-2 and SOFA scores in patients with pneumosepsis. The L/A ratio can be an independent predictor of mortality in patients with pneumosepsis and patients with pneumosepsis with renal and hepatic dysfunction. The L/A ratio correlated positively with lactate levels and APACHE-2 and SOFA scores but negatively with albumin levels.

**Abbreviations:** APACHE-2 = Acute Physiology and Chronic Health Evaluation 2, AUC = Area under the curve, CI = Confidence Interval, ICU = Intensive care unit, L/A = Lactate/albumin, L/A ratio = Ratio of lactate to albumin, ROC = Receiver operating characteristic, SOFA = Sequential Organ Failure Assessment.

**Keywords:** albumin, critically ill patients, ICU, lactate, lactate/albumin ratio, pneumosepsis

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The research was performed in accordance with the guidelines stated in the Declaration of Helsinki and was authorized by the Local Ethics Committee of Çukurova University Medicine Faculty (decision no: 56, dated: 05/03/2021).

This study was retrospective, and the hospital resource system was used. Hence, the need of patient consent was waived by Çukurova University Medicine Faculty Local Ethics Committee.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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## 1. Introduction

Sepsis is a syndrome clinically characterized by physiological, biological, and biochemical abnormalities caused by an unregulated inflammatory response to infection. Multiple organ dysfunction and high mortality rates are outcomes of sepsis and inflammatory response.<sup>[1]</sup> Despite advances in intensive care and in managing patients with sepsis, the mortality rate in these patients varies from 20% to 50%. Sepsis is one of the causes, with a high frequency of mortality in noncardiac intensive care units (ICUs).<sup>[2]</sup> Therefore, there exists a need for predictive biomarkers of mortality in patients with sepsis for early detection and treatment and the search for clinically positive outcomes for these patients.

Sepsis is a clinical feature caused by severe inflammation that develops microcirculatory disorders in the patient, including activation of platelets and damage to endothelial cells. Lactic acidosis occurs as a consequence of tissue hypoxia in sepsis and septic shock.<sup>[3]</sup> Elevated lactate levels are associated with poor clinical outcomes and high patient mortality. Consequently, these levels are used for early diagnosis, management, and risk stratification in patients with sepsis/septic shock.<sup>[1,4]</sup>

Scoring systems are widely used to understand the severity of the disease and mortality in ICUs, including patients with sepsis. The Acute Physiology and Chronic Health Evaluation 2 (APACHE-2) scoring system is frequently used in several hospitals. The Sequential Organ Failure Assessment (SOFA) scoring system has been used to diagnose patients with sepsis in the ICU and determine their prognosis.<sup>[5-7]</sup>

Lactic acidosis often occurs in sepsis when lactate production exceeds lactate consumption. The major associations of lactic acidosis are divided into disorders associated with tissue hypoxia (type A) and disorders in which tissue hypoxia is absent (type B). Cardiogenic or hypovolemic shock, severe heart failure, severe trauma, and sepsis are the most common causes of lactic acidosis.<sup>[8]</sup> However, lactic acidosis has been described in patients using metformin and albuterol and patients with hepatic or renal dysfunction, severe hypoxemia, severe anemia, diabetic ketoacidosis, neoplasia, pheochromocytoma, and intoxication.<sup>[8]</sup>

Albumin is a vital protein for our body. Human albumin is the primary oncotic pressure modulator for plasma. Albumin also acts on the transportation of various endogenous and exogenous substances, including hormones and drugs. Albumin also plays a vital role in the maintenance of acid-basic balance.<sup>[9,10]</sup> In addition, albumin is a negative acute-phase protein, and its levels can reflect the magnitude of inflammation. In critically ill patients, the degree of hypoalbuminemia thus represents the severity of the inflammatory response. Consequently, it may be a prognostic biomarker in patients with sepsis. In contrast, nutritional status and chronic inflammatory disorders affect albumin levels. Therefore, an albumin-based prediction could have limitations.<sup>[11–14]</sup>

Although lactate and albumin values independently predict mortality, the ratio of lactate to albumin (L/A ratio) is superior as a predictor to lactate or albumin alone. This result has been recorded in studies conducted in recent years.<sup>[14–19]</sup>

As pneumonia is a frequent cause of sepsis, we conducted the present study to evaluate the prognostic value of serum L/A ratio for predicting mortality in sepsis caused by pneumonia. In this respect, our study is the first to our knowledge in the literature. In contrast to previous studies on the L/A ratio, we evaluated its correlation with clinical parameters, blood biomarkers, and scoring systems.<sup>[20]</sup>

## 2. Materials and methods

This retrospective study included patients with pneumosepsis treated in the medical ICU of Adana City Training and Research Hospital between January 2018 and December 2020. Hospital is a regional tertiary hospital and has forty medical ICU beds. Sepsis was diagnosed according to the Sepsis-3 criteria, and pneumonia was diagnosed according to the American Thoracic Society's guidelines.<sup>[21,22]</sup> Patients over 18 years of age and diagnosed with pneumosepsis at admission to ICU were included in the study. The data were obtained from the hospital system. Patients who had cancer, were pregnant, and patients whose necessary data could not obtain for the study were excluded from the study. A total of 2112 patients were reviewed retrospectively from the hospital information system; 273 patients were included in the study (Fig. 1).

Patient history and laboratory values found in the SOFA score were used to determine patients' organ dysfunction. Laboratory test results at the time of admission were used for this study. Complete blood counts were analyzed using a Sysmex XN-10 Automated Hematology Analyzer (XN series, Sysmex Corporation, Kobe, Japan) according to the manufacturer's instructions. Biochemical parameters, including albumin, were measured using a Becher Coulter AU 5800 (Beckman Coulter GmbH, Krefeld, Germany) with commercial test kits produced or validated by the manufacturer. Blood gas analysis, including lactate, was performed with ABL90 FLEX (Radiometer Medical, København, Denmark).

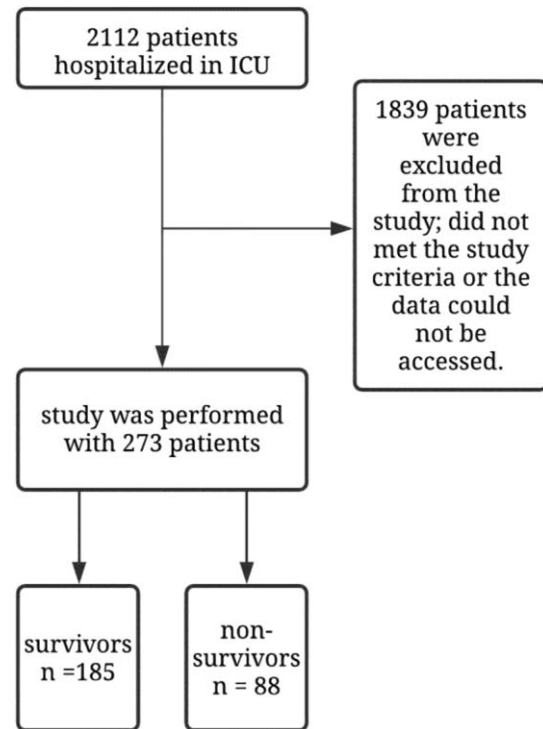


Figure 1. Flow diagram for lactate/albumin ratio studied patients.

The Local Ethics Committee of the Çukurova University Medicine Faculty approved this study (decision no: 56, dated: 05/03/2021).

Statistical analysis was conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL). Mean, standard deviation, and median (interquartile range) were used to describe continuous variables, and number (n) and percentage were used for categorical variables (percent). There were 2 groups of patients: survivors and nonsurvivors.

Depending on the conformity of the data to a normal distribution, comparisons of continuous variables between groups were made using Student *t* test or the Mann–Whitney *U* test. The chi-square test and Fisher's exact test were used to compare the groups in terms of categorical variables.

The Pearson test was used to calculate the correlation coefficients of numerical variables with the homogeneous distribution. The Spearman test was used to calculate the correlation coefficients of numerical variables with a nonhomogeneous distribution.

The sensitivity and specificity of the predictive value of lactate and L/A ratio for patients with different lactate and albumin levels and those for patients with renal or hepatic dysfunction were determined using receiver operating characteristic (ROC) curve analysis. The Youden index was used to determine the best L/A ratio cutoff values. Multivariable logistic regression was used to account for possible confounders in the L/A ratio and mortality relationship.

The variables that would be used in the study were subjected to a linearity test. A correlation was found between the L/R ratio and lactate levels. Lactate variables were excluded from the equation. All other statistically significant and clinically significant variables were considered in this study.

### 3. Results

#### 3.1. Patient characteristics

A total of 273 patients with a median age of 71 years (interquartile range 64–77 years) were included in this study. Of these patients, 134 (49.1%) were men. There were 185 survivors and 88 nonsurvivors in the study population. The mortality rate was calculated as 32.2%. In terms of gender distribution, the groups were highly similar ( $P > .05$ ). When the groups were analyzed in terms of age (64–77 years), it was found that the nonsurvivor group was composed of older people ( $P < .05$ ). According to clinical parameters, the median APACHE-2 ( $P < .001$ ) and SOFA ( $P < .001$ ) scores were higher in the nonsurvivor group. Congestive heart failure, renal disease, and chronic lung disease were more common comorbidities in the nonsurvivor group ( $P < .05$ ), whereas other diseases had a similar L/A ratio distribution ( $P > .05$ ). Invasive mechanical ventilation was administered to 70 (25.6%) patients, and renal replacement therapy was required in 54 (19.8%) patients. Nonsurvivors showed a higher frequency of invasive mechanical ventilation ( $P < .001$ ) and renal replacement therapy ( $P < .05$ ). They also had higher median APACHE-2 ( $P < .001$ ) and SOFA ( $P < .01$ ) scores. Table 1 summarizes the ages and clinical characteristics of all study participants.

#### 3.2. Laboratory tests

The levels of C-reactive protein ( $P < .05$ ), creatinine ( $P < .05$ ), lactate, albumin, and L/A ratio ( $P < .001$ ) were significantly higher in the nonsurvivor group, according to laboratory parameters.

The survivor group showed a higher mean value of thrombocyte levels ( $P < .05$ ). The mean values of the other parameters were identical in both groups. Table 1 lists the laboratory characteristics of all study participants. The Spearman correlation analysis was used to examine the associations between L/A ratio levels, sepsis severity, and inflammation biomarkers, which revealed that L/A ratios correlated positively with APACHE-2 scores ( $r = 0.386$ ,  $P < .001$ ), SOFA scores ( $r = 0.272$ ,  $P < .001$ ), and lactate levels ( $r = 0.922$ ,  $P < .001$ ) but negatively with albumin levels ( $r = -0.380$ ,  $P < .001$ ) (Table 2).

#### 3.3. Indicators of predicting ICU mortality

The predictive performance of several indicators for mortality was investigated using ROC curves (Fig. 2). Table 3 summarizes the area under the curve (AUC), the optimum cutoff value, and the sensitivity and specificity of each indicator.

The table shows the AUC values for lactate levels and the L/A ratio for predicting mortality across different patient subgroups.

The AUC value of the L/A ratio in all patients was 0.73 (95% confidence interval [CI]: 0.67–0.80,  $P < .001$ ), which was higher than that of lactate alone, which was 0.69 (95% CI 0.62–0.76,  $P < .001$ ), and albumin alone, which was 0.66 (95% CI 0.61–0.73,  $P < .001$ ) (Fig. 2).

Irrespective of the lactate level, the AUC value of the L/A ratio was significantly higher than that of lactate alone (lactate  $\leq 2$  mmol/L: 0.64, 95% CI 0.52–0.76 vs 0.61, 95% CI 0.49–0.73 [ $P = .07$ ]; lactate  $> 2$  mmol/L: 0.76, 95% CI 0.68–0.84 vs 0.69, 95% CI 0.60–0.78 [ $P < .001$ ]).

**Table 1**  
Baseline characteristics and laboratory findings of the patients.

Variables	Overall (n = 273)	Survivors (n = 88)	Nonsurvivors (n = 185)	P
Age (years)	71 (64–77)	69 (63–76)	74 (67–80)	.003
Sex (male, %)	134 (49.1)	88 (47.6)	46 (52.3)	.46
Comorbidities				
Hypertension	85 (31.1)	51 (27.6)	34 (38.6)	.065
Diabetes	64 (23.4)	40 (21.6)	24 (27.3)	.303
Renal disease	61 (22.3)	35 (18.9)	26 (29.5)	.049
Coronary artery disease	32 (11.7)	22 (11.9)	10 (11.4)	.899
Chronic lung disease	62 (22.7)	34 (18.4)	28 (31.8)	.013
Cerebrovascular disease	24 (8.8)	11 (4.8)	13 (4)	.136
Hepatic dysfunction	42 (15.4)	27 (14.6)	15 (17)	.600
Congestive heart failure	42 (15.4)	17 (9.2)	25 (28.4)	<.001
During ICU stay				
Invasive mechanical ventilation	70 (25.6)	28 (15.1)	42 (47.7)	<.001
Renal replacement therapy	54 (19.8)	30 (16.2)	24 (27.3)	.032
SOFA score	6 (3–8)	5 (3–8)	7 (4–10)	<.001
APACHE-2 score	23 (17–28)	19 (13–24)	30 (25–36)	<.001
Hemoglobin (g/dL)	10 (8.7–12.2)	10.1 (8.7–12.2)	9.7 (8.7–12.1)	.394
Leukocytes ( $\times 10^3/\mu\text{L}$ )	11.2 (7.7–16.2)	8.1 (11.6–16.2)	12.2 (9.5–17.3)	.143
Thrombocytes ( $\times 10^3/\mu\text{L}$ )	204 (141–300)	216 (141–311)	174 (135–274)	.030
Sodium (mmol/L)	138 (132–141)	139 (133–141)	136 (128–141)	.073
Potassium (mmol/L)	3.9 (3.3–4.4)	3.8 (3.3–4.4)	4 (3.4–4.3)	.092
Creatinine (mg/dL)	1.5 (0.9–2.5)	0.9 (1.6–2.5)	1.7 (1.4–2.4)	.021
C-reactive protein (mg/L)	47 (29–70)	44 (28–67)	57 (39–70)	.017
Procalcitonin (ng/L)	9.3 (3.4–19)	8.9 (2.8–21)	11 (7.3–17)	.237
Lactate (mmol/L)	2.3 (1.4–3)	2 (1.2–2.9)	3 (2–4.5)	<.001
Albumin (g/dL)	2.9 (2.2–3.1)	3 (2.5–3.1)	2.5 (2.1–2.9)	<.001
Lactate-to-albumin ratio	0.85 (0.5–1.33)	0.76 (0.41–0.96)	1.3 (0.87–1.92)	<.001

**Table 2**  
Correlation of serum lactate-to-albumin (L/A) ratios with clinical parameters and blood markers.

Parameter	Spearman correlation <i>r</i> value	<i>P</i>
Age, yr	0.022	.716
APACHE-2 score	0.386	<.001
SOFA score	0.272	<.001
Leukocytes ( $\times 10^3/\mu\text{L}$ )	0.075	.220
Thrombocytes ( $\times 10^3/\mu\text{L}$ )	-0.058	.341
C-reactive protein (mg/L)	0.078	.201
Procalcitonin (ng/L)	0.084	.166
Lactate (mmol/L)	0.922	<.001
Albumin (g/dL)	-0.387	<.001

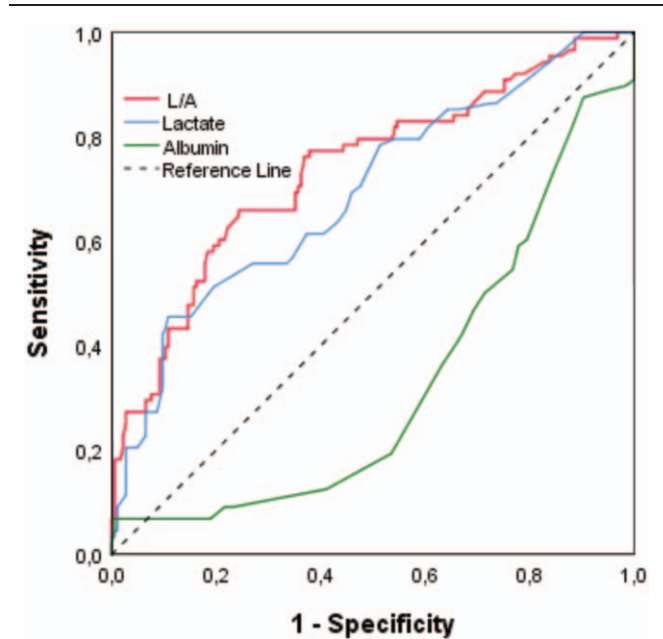
The L/A ratio exhibited a slightly higher prognostic value in the renal (0.70, 95% CI 0.56–0.84 vs 0.68, 95% CI 0.53–0.83, *P* = .016) and hepatic (0.82, 95% CI 0.69–0.94 vs 0.71, 95% CI 0.55–0.86, *P* = .026) dysfunction subgroups.

We conducted univariate and multivariate logistic regression analyses to validate the relationship between variables and mortality (Table 4.). The L/A ratio was related to mortality in the multivariate logistic regression [95% CI 1.672–6.423, odds ratio (OR) = 3.277, *P* < .01].

**4. Discussion**

The prognosis of patients with sepsis has been determined using a variety of biochemical markers. Our study findings indicate that the L/A ratio at the time of ICU admission can be used as an independent indicator of mortality in patients with sepsis or septic shock due to pneumonia. Moreover, the L/A ratio correlated with APACHE-2 and SOFA scores in patients with pneumosepsis.

Previous studies have shown that the L/A ratio has a prognostic value in patients with sepsis.<sup>[14–19]</sup> Although pneumonia is the most common cause of sepsis, no previous study has explicitly examined the L/A ratio in patients with pneumosepsis.<sup>[20]</sup> They found that respiratory infections were the most common source of sepsis and that mortality was significantly higher in this population. When they examined sepsis due to respiratory infections, they found that the L/A ratio was superior to lactate alone.<sup>[15]</sup> Moreover, according to Shin et al, the L/A ratio outperformed a single lactate measurement in predicting 28-day mortality in critically ill patients with sepsis. Patients with sepsis



**Figure 2.** Receiver operating characteristic (ROC) curves for in-hospital mortality in all patients with sepsis concerning pneumonia.

with respiratory infections had a substantially higher mortality rate.<sup>[18]</sup>

However, no further research was conducted in those trials on patients with pneumosepsis. Therefore, to our knowledge, the present study is the first in the literature to examine the L/A ratio in patients with pneumosepsis. The importance of our study is that only patients with pneumosepsis were examined in great detail. Serum lactate concentrations of >2mmol/L are a well-known prognostic factor for patients with sepsis and a requirement in sepsis/septic shock guidelines.<sup>[21]</sup> Because an elevated lactate level is related to poor prognosis, it is a vital component of the initial assessment.<sup>[21]</sup> In the present study, the nonsurvivor group showed significantly higher serum lactate levels. In the case of pneumosepsis, the L/A ratio was also superior to lactate alone (AUC 0.73 vs 0.69). Lactate levels (lactate > 2mmol/L and lactate ≤ 2mmol/L) were found to improve the prognostic accuracy in both subgroups.

As albumin is a negative acute-phase protein, the degree of hypoalbuminemia in critically ill patients reflects the severity of

**Table 3**  
Cutoff limits for in-hospital mortality among different patient subgroups based on the area under the curve (AUC) and lactate/albumin ratio.

	AUC for mortality (95% CI)		<i>P</i>	L/A cutoff threshold		
	Lactate	L/A		Cutoff	Sensitivity	Specificity
Overall patients	0.69 (0.62–0.76)	0.73 (0.67–0.80)	<.001	0.97	0.66	0.75
Lactate levels (mmol/L)						
≤2	0.61 (0.26–0.50)	0.64 (0.52–0.76)	.036	0.49	0.61	0.57
>2	0.69 (0.60–0.78)	0.76 (0.68–0.84)	<.001	1.30	0.67	0.68
Albumin levels (mmol/L)						
≤3.0	0.71 (0.63–0.79)	0.73 (0.65–0.80)	<.001	0.98	0.68	0.70
>3.0	0.70 (0.52–0.88)	0.64 (0.45–0.83)	.113	0.73	0.51	0.48
Decreased lactate elimination						
Renal dysfunction	0.68 (0.53–0.83)	0.70 (0.56–0.84)	.007	0.91	0.65	0.68
Hepatic dysfunction	0.71 (0.55–0.86)	0.82 (0.69–0.94)	.001	1.01	0.80	0.81

**Table 4**

**Univariate and multivariate logistic regression analyses to examine the relationship between mortality and the statistically significant variables of the study.**

	Univariate analysis			Multivariate analysis		
	Odds ratio (OR)	95% CI	P	OR	95% CI	P
Sex (male)	1.646	0.987–2.744	.056			
Age, yr	1.032	1.008–1.057	.008	1.046	1.010–1.083	.011
APACHE-II score	1.217	1.159–1.278	<.001	1.219	1.151–1.291	<.001
SOFA score	1.178	1.089–1.273	<.001			
Congestive heart failure	3.922	1.985–7.747	<.001	3.653	1.298–10.280	.014
Renal disease	1.797	0.999–3.234	.050			
Chronic lung disease	2.073	1.157–3.712	.014			
Hepatic dysfunction	1.202	0.603–2.396	.60			
Invasive mechanical ventilation	5.120	2.866–9.146	<.001	7.456	3.058–18.179	<.001
Renal replacement therapy	1.937	1.052–3.568	.034	4.342	1.587–11.880	.004
Thrombocytes ( $\times 10^3/\mu\text{L}$ )	.998	0.995–1.000	.029			
Creatinine (mg/dL)	1.007	0.999–1.016	.083			
C-reactive protein (mg/L)	1.009	1.001–1.018	.027			
Albumin	0.429	0.270–0.681	<.001	0.497	0.255–0.968	.040
L/A	5.110	3.039–8.591	<.001	2.460	1.178–5.137	.017

the inflammatory response. Our findings revealed that the nonsurvivor group had significantly lower serum albumin levels. However, in pneumosepsis, the L/A ratio outperformed albumin alone (AUC 0.73 vs 0.66). The improved prognostic accuracy was observed in all albumin subgroups (albumin 3 g/dL). As discussed earlier, lactate and/or albumin levels may be prognostic markers for the outcomes in various clinical environments. However, combining these markers could also have a more substantial prognostic value for both inflammation and nutritional status.

According to Bou et al, the L/A ratio has better prognostic output than the initial serum lactate level for in-hospital mortality in adult patients with sepsis ( $n=1381$ , AUC=0.67).<sup>[15]</sup> Lichtenauer et al reported that an increased lactate/albumin ratio was significantly associated with poor outcomes in critically ill patients admitted to the ICU ( $n=348$ , AUC=0.814).<sup>[16]</sup> Gharipour et al showed that the L/A ratio correlated with both ICU and in-hospital mortality, suggesting that it is a safer risk parameter for stratifying critically ill patients ( $n=414$ , AUC=0.69).<sup>[14]</sup> Furthermore, Shin et al reported that the L/A ratio outperformed a single lactate measurement in predicting 28-day mortality in critically ill patients with sepsis ( $n=946$ , AUC=0.69).<sup>[18]</sup> Wang et al found that in patients with extreme sepsis and septic shock, a higher L/A ratio correlated with the production of multiple organ dysfunction syndrome (MODS) and mortality ( $n=54$ , AUC=0.8458 and 0.8449 for MODS and mortality, respectively).<sup>[19]</sup> Our study found that the L/A ratio was more accurate than lactate alone in predicting mortality in patients with pneumosepsis (AUC 0.73 vs 0.69).

Lactate is primarily metabolized by the liver, with the kidney performing a minor role. Our analysis explored the prognostic value of the L/A ratio in particular subpopulations, such as patients with hepatic or renal dysfunction, both of which affect lactate and albumin levels. In this group, we found that the L/A ratio has a higher predictive value than lactate alone. On the basis of the findings of the current and previous studies, the L/A ratio can be used as a prognostic factor in patients with hepatic and kidney dysfunction, in addition to patients with sepsis and pneumosepsis.<sup>[14–19]</sup>

In the ICU, the APACHE-2 and SOFA scoring systems are used to evaluate the prognosis of patients with sepsis. In this study, we

found that the L/A ratio was consistent with these strong prognostic scoring systems. Moreover, as predicted, the L/A ratio correlated positively with lactate levels and negatively with albumin levels.

The major limitation of our study is the retrospective design and this study was conducted in a single center. Furthermore, we have no data on albumin replacement or the total amount of fluids administered. Our results should be strengthened by prospective multicenter studies.

## 5. Conclusion

In patients with pneumosepsis, the L/A ratio is an independent indicator of mortality. Moreover, in patients with pneumosepsis with hepatic and kidney dysfunction, the L/A ratio can be used as an indicator. The L/A ratio shows a positive correlation with lactate levels and APACHE-2 and SOFA scores, whereas it shows a negative correlation with albumin levels. Prospective studies should be performed to learn more about the role of the L/A ratio in pneumosepsis and pneumosepsis-related mortality.

## Author contributions

Murat Erdogan: Conceptualization, Investigation, Methodology, Project administration, Resources, Visualization, Roles/Writing - original draft, Writing - review & editing

Hüseyin Avni Fındıklı: Conceptualization, Data curation, Formal analysis, Software, Supervision, Validation, Methodology.

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**Writing – original draft:** Murat Erdogan.

**Writing – review & editing:** Murat Erdogan.

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