Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1588255

J Health Sci Med. 2024;8(1):85-90

Efficacy of serum lactate/albumin ratio as a prognostic biomarker in patients with ventilator-associated pneumonia

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Cite this article as: Kırıcı Berber N, Korkmaz Dişli Z, Acun Delen L, Şahin Gür L, Yetişgen A, Berber İ. Efficacy of serum lactate/albumin ratio as a prognostic biomarker in patients with ventilator-associated pneumonia. *J Health Sci Med.* 2025;8(1):85-90.

Received: 19.11.2024 ◆ **Accepted**: 11.12.2024 ◆ **Published**: 12.01.2025

ABSTRACT

Aims: This study aims to evaluate the efficacy of the serum lactate/albumin ratio (LAR) as a prognostic marker in patients with ventilator-associated pneumonia (VAP) who are hospitalized in the intensive care unit (ICU).

Methods: This single-center retrospective observational clinical study was conducted between January 1, 2022, and October 1, 2024. The study group comprised 58 patients admitted to the ICUs of Malatya Training and Research Hospital, Turkiye, with intubation but without a diagnosis of pneumonia at the time of admission. These patients were diagnosed with VAP 48 hours after intubation. The serum LAR was calculated within the first 24 hours after admission to the ICU and correlated with mortality and morbidity.

Results: The mean age of the patients was 68 years, with the majority being over 65 years of age. Of the 58 patients included in the study, 43 (74.1%) ultimately succumbed to their illness. The LAR of those who died in the study was significantly higher than that of those who survived. The LAR was identified as a reliable predictor, exhibiting a sensitivity of 83.7% and a specificity of 60% when a cutoff value of 1.13 was applied. The survival time of patients with a LAR of ≤1.13 was significantly longer than that of patients with a ratio of >1.13.

Conclusion: In our study, the mortality prediction performance of the LAR in patients with VAP was superior to that of the serum lactate level or serum albumin level alone. Therefore, the LAR may be a useful and readily available prognostic factor for early risk stratification of VAP patients.

Keywords: Ventilator-associated pneumonia, biomarker, lactate/albumin ratio, prognostic factor

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as the occurrence of new pneumonia in the lung parenchyma in patients who require invasive mechanical ventilation for a minimum of 48 hours in the intensive care unit (ICU).[1] VAP represents a significant complication in patients who are mechanically ventilated. In patients on mechanical ventilators in intensive care, the incidence of VAP was found to be between 15% and 60%, with a mortality rate between 25% and 76%.[2] Additionally, the prevalence of underlying disease states, including sepsis, trauma, central nervous system, and respiratory diseases, was demonstrated to elevate the incidence of VAP.[3] Patients with VAP have longer hospital stays and higher hospitalization costs.[4] Serum albumin is a major plasma protein that is produced in the liver and is a negative acute-phase reactant.[5] In a study by Kendall et al.,[6] low serum albumin levels were found to be associated with mortality in patients admitted to the ICU with sepsis. In numerous clinical studies conducted in medical settings, including those examining sepsis, traumatic brain injury, decompensated heart failure, and Coronavirus disease 2019 (COVID-19), hypoalbuminemia was linked to unfavorable outcomes and a shorter survival period.[7,8] As a consequence of cellular dysfunction, tissue hypoxia, mitochondrial defect in oxygen utilization, impaired pyruvate dehydrogenase function, and increased aerobic glycolysis activity, high serum lactate levels (>10 mmol/L) and lactic acidosis (pH <7.35) occur, which is associated with significant morbidity and mortality.[9,10] In clinical studies conducted on patients with septic shock, heart failure, cardiac arrest, and those with COVID-19, the lactate/albumin ratio (LAR) was identified as a crucial prognostic indicator for mortality prediction.[11-14] The prognostic role of the LAR in patients with VAP remains to be

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elucidated. With this in mind, the present study was designed to investigate whether the serum LAR at admission can serve as an early prognostic biomarker of mortality in ICU patients diagnosed with VAP. We hope that the findings of this study will contribute to the existing literature on this topic (deleted).

METHODS

Ethics

The study was conducted following the Declaration of Helsinki and received approval from the Malatya Turgut Özal University Ethics Committee (Date: 11/07/2024, Decision No: E-30785963-020-262686).

Design of the Study and the Subjects

This single-center retrospective observational clinical study was conducted between January 1, 2022, and October 1, 2024. The data of 1436 patients who were hospitalized, followed up, and treated in the ICUs were obtained. The study population consisted of patients from Malatya Training and Research Hospital, Turkiye, who were diagnosed with VAP according to the National Healthcare Safety Network (NHSN) criteria 48 hours after intubation between January 1, 2022, and October 1, 2024. The study included patients aged 18 to 85 years. Patients under the age of 18 or over the age of 85, patients with a diagnosis of pneumonia at the time of hospitalization, patients diagnosed with sepsis, trauma patients, patients who died within 30 days of hospitalization, patients with multiple consecutive diagnoses of VAP during long hospitalizations, patients who had reached the point of brain death and multi-organ failure were excluded from the study. A total of 120 patients who were intubated at the time of hospitalization and subsequently admitted to the ICUs were identified through a retrospective review of the hospital's data processing system. The data of 58 patients who met the criteria for VAP were subjected to analysis.

Data Collection and Definitions

The following demographic and clinic variables were collected from all patients: age, gender, comorbidities, microorganisms, C-reactive protein (CRP), procalcitonin (PCT), ferritin, lactate, albumin, LAR, leukocyte (Leu), neutrophil percentage (Neu %), platelet (Plt), platelet distribution width (PDW), length of ICU stay, and survival status. The clinical and laboratory variables were evaluated within the first 24 hours following admission to the ICU. Additionally, data were collected from 58 patients with a diagnosis of VAP according to the NHSN criteria. All patients were monitored in the ICU throughout their stay or until death. Patients were classified as either survivors (i.e., those who survived the observation period) or non-survivors (i.e., those who died during the observation period). The term "30-day mortality" was defined as the mortality rate occurring on or after the 30th day of hospitalization. All patients' mortality data were retrieved from the hospital's medical record system.

The most recent studies have established a standardized diagnostic algorithm for VAP according to the National Healthcare Safety Network (NHSN) criteria.[15] This definition was utilized in the diagnosis of VAP.

The diagnostic criteria for VAP according to the National Healthcare Safety Network (NHSN) are as follows:

- Minimum positive end-expiratory pressure (PEEP) ≥3 cm H_2O or minimum fraction of inspired oxygen (FIO_2) >20 cm H_2O for at least two consecutive days.
- A fever of less than or equal to 36.0°C or greater than 38.0°C, a leukocyte count of less than or equal to 4000 or greater than 12000 cells/mm^3, and the continuation of one or more new antibiotics for four days.
- A gram stain, endotracheal aspirate, or bronchoalveolar lavage (BAL) with a neutrophil count of ≥25 and an epithelial cell area of ≤10, or a positive sputum culture, endotracheal aspirate, BAL, or lung tissue sample, is indicative of the presence of the disease.
- A positive endotracheal aspirate culture of at least 105 colony-forming units (CFU) per milliliter, or a positive BAL culture of at least 104 CFU/ml, is indicative of the presence of the pathogen. A positive culture of a sterile specimen of at least 103 CFU/ml is also diagnostic.

Alternatively, one of the following criteria may be met in the absence of purulent secretion:

- A positive pleural fluid culture (thoracentesis or chest tube),
- A positive lung histopathology,
- A positive diagnostic test for *Legionella*,
- *Influenza* virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human positive diagnostic test in respiratory secretion for metapneumovirus, coronavirus.

Statistical Analysis

The statistical analysis was conducted using the SPSS (statistical package for social sciences) 22 package program. Descriptive data were presented as absolute and relative frequencies for categorical variables and as mean±standard deviation (M±SD) and median interquartile range (25th-75th percentile) for continuous variables. A Chi-square analysis (Pearson Chi-square) was employed to ascertain the significance of the observed differences between the categorical variables within the various groups. The compliance of continuous variables with a normal distribution was evaluated using the Kolmogorov-Smirnov test. The student t-test was employed for variables exhibiting a normal distribution, whereas the Mann-Whitney U test was utilized for variables lacking a normal distribution. Overall survival was assessed with Kaplan-Meier for univariate analysis. Log-rank (Mantel-Cox) analysis was employed to compare survival time between categorical variables. The optimal cut-off value of the LAR was determined with the use of a receiver operating characteristic (ROC) curve. The statistical significance level was set at $p<0.05$ for all analyses.

RESULTS

Key Features of the Study

The study included a total of 58 patients aged 18 years and older, of whom 26 (44.8%) were female and 32 (55.2%) were male. The mean age of the patients was 68 years. Of the patients 36.2% had COPD, 39.7% had CVD, 41.4% had HT,

15.5% had DM and 12.1% had trauma. The most prevalent microorganisms isolated from patients with VAP were *Acinetobacter baumannii* (21 patients, 36.2%), *Klebsiella pneumonia* (12 patients, 20.7%), and *Pseudomonas aeruginosa* (6 patients,10.3%) (Table 1).

Comparison of Key Clinical Characteristics between Survivors and Non-survivors

A comparison of key clinical characteristics between survivors and non-survivors of the total 58 patients who participated in the study revealed that 43 (74.1%) had mortality, while 15 (25.9%) did not. The mortality rate was 80.8% among women and 68.8% among men, with no statistically significant difference between the two groups (p=0.299). The mean age of those who died was significantly higher than the mean age of those who did not (p=0.038). The mortality rate for individuals aged 65 years and above (83.3%) was significantly higher than that observed in individuals under 65 years of age (59.1%) (p=0.041). The lactate dehydrogenase (LDH) rate of patients who died was found to be significantly higher than the LDH rate of patients who survived (p=0.008) (Table 1).

The capacity of the LAR to predict 30-day mortality was examined through the use of ROC analysis, resulting in the determination of optimal cut-off values. Upon establishing a cut-off value of 1.13 for LAR, a sensitivity of 83.7% and a specificity of 60% were observed, indicating that this metric possesses satisfactory predictive efficacy (Figure 1).

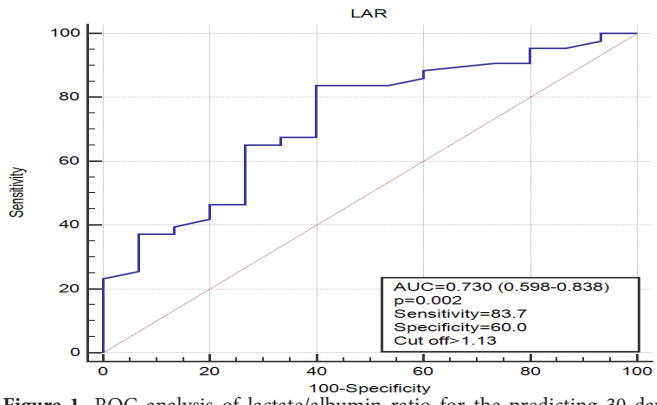

Figure 1. ROC analysis of lactate/albumin ratio for the predicting 30-day mortality

LAR: Lactate/albumin ratio, ROC: Receiver operating characteristic

Table 1. Comparison of mortality according to all data

		Total (n=58)	Non-survivors (n=43)	Survivors (n=15)	
		n (%)	n (%)	n (%)	p*
Gender	Female	26 (44.8)	21 (80.8)	5 (19.2)	0.299
	Male	32 (55.2)	22 (68.8)	10 (31.2)	
Age		68.00 (60.00-80.00)	69.00 (64.00-83.00)	63.00 (45.00-73.00)	0.038**
Age group	≥65	36 (62.1)	30 (83.3)	6 (16.7)	0.041
	<65	22 (37.9)	13 (59.1)	9 (40.9)	
COPD	Present	21 (36.2)	16 (76.2)	5 (23.8)	0.788
	Absent	37 (63.8)	27 (73.9)	10 (27.0)	
CVH	Present	23 (39.7)	18 (78.3)	5 (21.7)	0.561
	Absent	35 (60.3)	25 (71.4)	10 (28.6)	
HT	Present	24 (41.4)	19 (79.2)	5 (20.8)	0.462
	Absent	34 (58.6)	24 (70.6)	10 (29.4)	
DM	Present	9 (15.5)	7 (77.8)	2 (22.2)	0.786
	Absent	49 (84.5)	36 (73.5)	13 (26.5)	
Microorganism	*Acinetobacter baumannii*	21 (36.2)	17 (81.0)	4 (19.0)	0.528
	Klebsiella pneumoniae	12 (20.7)	9 (75.0)	3 (25.0)	
	Pseudomonas aeruginosa	19 (32.8)	14 (73.7)	5 (26.3)	
	Other	6 (10.3)	3 (50.0)	3 (50.0)	
CRP, mg/dl		15.63±9.21	15.75±9.73	15.29±7.82	0.870***
PCT, µg/l		1.18 (32-6.30)	1.08 (0.29-6.30)	1.27 (0.39-6.55)	0.770**
Ferritin, ng/ml		320.50 (132.00-775.00)	365.00 (155.00-765.00)	158.00 (77.60-905.00)	0.311**
Lactate, mmol/L		3.01±1.16	3.18±1.11	2.55±1.23	0.074***
Albumin, g/dl		2.01±0.51	1.93±0.53	2.21±0.41	0.066***
LAR		1.59±0.73	1.74±0.73	1.17±0.55	0.008***
Leu, 10^3 /µl		13.23 (10.42-17.50)	13.40 (10.18-17.50)	12.64 (11.20-17.78)	0.929**
Percent neutrophils, %		84.02±7.90	84.24±8.46	83.40±6.20	0.726***
Plt, 10^3 /µl		211.00 (164.00-328.00)	225.00 (146.00-325.00)	211.00 (165.00-362.00)	0.873**
PDW, %		13.98±3.44	14.01±3.56	13.86±3.16	0.891***

*Chi-square analysis, **Mann-Whitney U test, ***Student T test were applied, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular diseases, HT: Hypertension, DM: Diabetes Mellitus, CRP: C-reactive protein, PCT: Procalcitonin, LAR: Lactate/albumin ratio, Leu: Leukocyte, Neu %: Neutrophil percentage, Plt: Platelet, PDW: Platelet distribution range

Of the 58 patients included in the study, 43 died, yielding an overall survival rate of 25.9%. When all patients were evaluated together, the mean survival time was 65.3 days. Patients with LAR level ≤1.13 exhibited a significantly higher survival time than patients with LAR level >1.13 (p=0.016) (Table 2, Figure 2).

Table 2. Comparison of overall survival and LAR level

		Survival rate	Mean	SE	95% CI	p*
LAR	≤1.13	56.3	115.2	18.7	78.5-151.8	0.016
	>1.13	14.3	51.9	3.9	44.1-59.7	
Total		25.9	65.3	7.3	50.9-79.6	

*A log rank (Mantel-Cox) analysis was performed, LAR: Lactate/albumin ratio, SE: Standard error, CI: Confidence interval

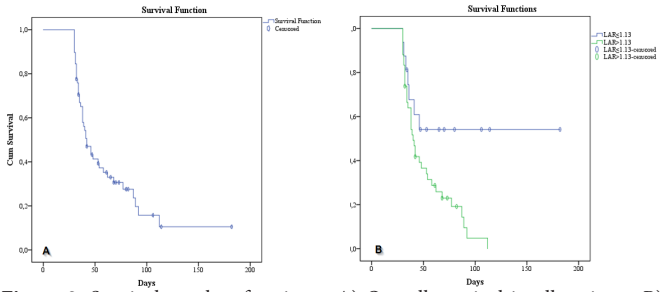

Figure 2. Survival graphs of patients, A) Overall survival in all patients, B) Overall survival curve according to LAR group

LAR: Lactate/albumin ratio

A comparison of the LAR group according to all data revealed a significantly higher rate of LAR values above 1.13 in those with CVH (87%) compared to those without CVH (62.9%) (p=0.045) (Table 3).

DISCUSSION

In our study, which analyzed the prognostic factor of LAR in patients with VAP who were followed up in the ICU, we found that the survival time of those with serum LAR levels ≤1.13 was significantly higher than the survival time of those with LAR levels >1.13. Furthermore, the LAR cut-off value of 1.13 exhibited 83.7% sensitivity and 60% specificity in predicting mortality beyond the 30th day. These findings indicate that LAR is a reliable biomarker for predicting mortality.

Patients hospitalized and critically ill with VAP have a high mortality and morbidity rate. In light of these considerations, several studies have recently been conducted to predict the severity and prognosis of the disease employing various factors, including laboratory and clinical variables. For example (deleted) In a study of patients with sepsis, it was demonstrated that the predictive value of LAR was superior to that of lactate and albumin alone in predicting mortality and length of hospital stay (discharge). The sensitivity and specificity of LAR were 100% and 88%, respectively.[16] In a study conducted by Jia Liang Zhu et al.,[17] LAR was found to have predictive value in predicting 30-day mortality in patients with severe acute myocardial infarction.

Table 3. Comparison of the LAR group according to all data

		LAR ≤1.13 (n=16)	LAR >1.13 (n=42)	p*
		n (%)	n (%)	
Gender	Female	8 (30.8)	18 (69.2)	0.625
	Male	8 (25.0)	24 (75.0)	
Age		68.00 (55.00-76.00)	68.00 (60.00-81.00)	0.761**
Age group	≥65	10 (27.8)	26 (72.2)	0.967
	<65	6 (27.3)	16 (72.7)	
COPD	Present	6 (28.6)	15 (71.4)	0.899
	Absent	10 (27.0)	27 (73.0)	
CVH	Present	3 (13.0)	20 (87.0)	0.045
	Absent	13 (37.1)	22 (62.9)	
HT	Present	6 (25.0)	18 (75.0)	0.711
	Absent	10 (29.4)	24 (70.6)	
DM	Present	3 (33.3)	6 (66.7)	0.696
	Absent	13 (26.5)	36 (73.5)	
Trauma	Present	3 (42.9)	4 (57.1)	0.381
	Absent	13 (25.5)	38 (74.5)	
Microorganism	*Acinetobacter baumannii*	5 (23.8)	16 (76.2)	0.229
	Klebsiella pneumoniae	5 (41.7)	7 (58.3)	
	Pseudomonas aeruginosa	3 (15.8)	16 (84.2)	
	Other	3 (50.0)	3 (50.0)	
CRP		12.46±6.72	16.84±9.80	0.106***
PCT		2.74 (0.34-7.74)	1.12 (0.32-4.32)	0.476**
Ferritin		217.00 (134.00-624.00)	352,00 (128.00-785.00)	0.476**
Leu		13.17 (11.68-17.14)	13.31 (10.20-17.50)	0.670**
Neu		84.70±7.18	83.76±8.22	0.690***
Plt		218.00 (166.50-347.50)	200.00 (146.00-318.00)	0.439**
PDW		12.69±4.53	14.48±2.82	0.079***

*Chi-square analysis, **Mann-Whitney U test, ***Student T test were conducted, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular diseases, HT: Hypertension, DM: Diabetes mellitus, CRP: C-reactive protein, PCT: Procalcitonin, LAR: Lactate/albumin ratio, Leu: Leukocyte, Neu %: Neutrophil percentage, Plt: Platelet, PDW: Platelet distribution range

The correlation between age and risk appears to be inconclusive, particularly in the context of VAP. In a multicenter cohort study, the incidence of VAP was 13.7% in middle-aged patients (45-64 years), 16.6% in elderly patients (65-74 years), and 13.0% in very elderly patients (≥75 years). The logistic regression analysis did not identify a heightened risk of VAP among older patients. However, elevated mortality rates were observed in the very old (aged 85 and above).[18] Our study revealed a higher mortality rate among elderly patients (aged 65 and above), with a death rate of 83.3% compared to 59.1% in patients below the age of 65.

In recent studies, the prognostic value of LAR has been subjected to analysis. In a study by Shin et al.,[11] it was demonstrated that LAR was a predictor of 28-day mortality in patients with critical sepsis. In a separate study by Kong et al.,[12] it was indicated that LAR serves as a prognostic marker for neurogenic outcome and survival in patients whose spontaneous circulation was restored following out-of-hospital cardiac arrest. In a study, LAR was identified as an indicator of short- and long-term mortality in critically ill patients with heart failure.[13] Additionally, LAR was reported as a prognostic marker for predicting 30-day mortality in critically ill patients diagnosed with COVID-19.[12] The available evidence indicates that LAR is a novel clinical biomarker with prognostic significance in a range of diseases. A review of the literature revealed no studies indicating that LAR is a prognostic biomarker in patients with VAP. Accordingly, the present clinical retrospective study was designed to examine patients with VAP. As with the aforementioned studies, our findings revealed that serum LAR levels were markedly elevated in patients who succumbed to their illnesses compared to those who survived. A study conducted on patients with acute ischemic stroke and low-attenuation signals on brain imaging (LAR) revealed a linear correlation between LAR and mortality risk. It was identified as a predictor of all-cause mortality within 28 days of the onset of acute ischemic stroke.[19] In a separate clinical investigation conducted on patients with spontaneous subarachnoid hemorrhage, LAR was identified as a significant predictor of in-hospital mortality.[20] In our study, a comparison of LAR levels between patients with and without cerebrovascular disease (CVD) revealed a significantly higher prevalence of LAR in patients with CVD (87%) compared to those without CVD (62.9%). These findings suggest that LAR level may serve as a potential biomarker for mortality in patients with VAP and CVD, given the high prevalence of CVD among other comorbidities.

Limitations

However, this study is not without limitations. The current study was retrospective and had a relatively small sample size, which precluded the ability to correlate clinical data with disease prognosis. To confirm these results, larger sample sizes are needed, ideally from multicenter prospective studies.

CONCLUSION

The primary outcome of this study was that a LAR result greater than 1.13 was associated with survival. As the LAR level increases, the survival time decreases. The LAR was identified as an independent and significant predictor of mortality, exhibiting a sensitivity of 83.7% and a specificity of 60% when the cut-off value for predicting mortality was 1.13. Furthermore, in patients with VAP, the LAR proved to be a more effective predictor of mortality than either the serum lactate level or the serum albumin level alone. Consequently, the LAR may serve as a valuable and readily accessible prognostic biomarker for early risk stratification of VAP patients, facilitating mortality prediction and more optimal management of VAP patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Malatya Turgut Özal University Faculty of Medicine Clinical Researches Ethics Committee (Date: /06/2024, Decision No: 2024/5038).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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