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The Role of the Lactate-to-Albumin Ratio in Predicting In-Hospital Mortality in Patients with Heart Failure with Preserved Ejection Fraction Presenting to the Emergency Department

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Abstract

Background

Heart failure with preserved ejection fraction (HFpEF) is an important form of heart failure associated with high mortality rates. Identifying risk factors is crucial for improving hospital mortality rates. The lactate/albumin ratio (LAR) has been found to be associated with adverse clinical outcomes in conditions such as sepsis and myocardial infarction. In this study, we aim to evaluate the potential of LAR as a prognostic marker for mortality in patients with HFpEF.

Methods

In this retrospective study, patients diagnosed with HFpEF were included. Data from patients who were admitted to the emergency department or cardiology clinic between January 1, 2023, and June 1, 2024, were used from the hospital information system database.

Results

A total of 503 patients were included in the study, of whom 74 died during hospitalization. Univariate and multivariate Cox regression analyses were performed to determine the relationship between LAR at admission and hospital mortality. The LAR value was significantly higher in the group of patients who died during hospitalization compared to survivors (0.07 vs 0.05, $p < 0.05$). The area under the ROC curve was 0.636 (95% CI: 0.520–0.752), and the optimal cut-off value for LAR was 0.48.

Conclusion

An elevated LAR is significantly associated with mortality in HFpEF and can be used as an early prognostic marker for mortality in these patients.

Background

Heart failure is not a pathological diagnosis per se, but rather a clinical syndrome characterized by signs and symptoms of central and/or peripheral congestion arising from structural and/or functional abnormalities of the heart [1]. Although heart failure may arise from conditions such as valvular, pericardial, or endocardial diseases, it most commonly develops as a consequence of myocardial dysfunction. Additionally, arrhythmias and conduction system disorders can also precipitate heart failure. Identifying the underlying etiology is essential for the implementation of targeted, etiology-specific therapies.

The classification most widely accepted in recent years is based on left ventricular ejection fraction. This categorization provides a clinically practical approach for guiding medical therapy. According to this system, patients who exhibit signs and/or symptoms of heart failure are classified as having reduced ejection fraction heart failure (HFrEF) if the left ventricular EF is ≤ 40%, mildly reduced ejection fraction heart failure (HFmrEF) if the EF ranges between 41–49%, and preserved ejection fraction heart failure (HFpEF) if the EF is ≥ 50%. [1].

The concepts of acute heart failure and chronic heart failure are also frequently used in clinical practice, reflecting the onset and progression of heart failure symptoms. Chronic HF refers to patients with an established diagnosis of heart failure or those with a more slowly progressive clinical course, whereas acute heart failure is used for rapidly developing clinical presentations (over minutes, hours, or days). For functional classification of heart failure, systems based solely on symptom severity—such as the NYHA classification—may be employed [2].

Despite advances in the prevention and treatment of cardiovascular diseases, the incidence of heart failure continues to increase in parallel with rising life expectancy [2, 3]. The prevalence of heart failure in adults is estimated to range between 1% and 2% [4–6]. In addition, the age-related increase in prevalence is noteworthy [4, 7, 8]. Among the various types of heart failure, HFpEF is the most frequently encountered in people over 65 years old, reflecting its growing clinical importance in the aging population [9]. It is estimated that patients with reduced ejection fraction heart failure account for approximately 50% of all heart failure cases [7, 8, 10]. According to long-term follow-up data from the European Society of Cardiology, 60% of ambulatory heart failure patients were found to have HFrEF, whereas 16% had HFpEF [11].

HFpEF patients show notable differences when compared with those having reduced ejection fraction. HFpEF patients are generally older, predominantly female, and more likely to suffer from a range of non-cardiac health issues. Women constitute more than 50% of patients with heart failure [5, 12]. This population exhibits a lower frequency of coronary artery disease [13]. Although the exact pathophysiology remains uncertain, numerous studies indicate that patients with HFpEF exhibit elevated levels of pro-inflammatory markers both in the heart and peripheral circulation. These studies also highlight the significant link between chronic, recurring immune-inflammatory activation and the worsening of ventricular diastolic dysfunction, as well as the progression of HFpEF [14, 15]. The development of preserved ejection fraction heart failure is influenced by various factors, including advanced age, systemic hypertension (HT), obesity, physical inactivity, myocardial ischemia, and diabetes mellitus (DM), all of which complicate treatment strategies. Effectively identifying and managing underlying risk factors, causes, and coexisting health conditions can improve patient outcomes [16]. In patients hospitalized with HFpEF, the estimated annual mortality is approximately 15%, and long-term prognosis remains poor, with only about 35% surviving beyond five years (Borlaug BA). This prognosis is notably worse than many types of cancer [17].

Several scoring systems have been proposed for the diagnosis of heart failure with preserved ejection fraction, although none has demonstrated clear superiority over the others. In establishing the diagnosis of heart failure with preserved ejection fraction, evidence of elevated left ventricular filling pressures, diastolic dysfunction, or increased levels of natriuretic peptides may be used as indicators of underlying structural and/or functional cardiac abnormalities. An increasing number of these abnormalities proportionally raises the likelihood of a diagnosis of HFpEF [1].

Certain biochemical markers are crucial in optimizing the treatment of critically ill those suffering from cardiac insufficiency. A significant relationship has been observed between elevated lactate levels and mortality, which is commonly seen in critical patients [18, 19]. Additionally, in cases of liver or kidney dysfunction, a series of complex changes can occur in the body (such as reduced lactate clearance and accelerated glycolysis), which may initially result in lower lactate levels. Lactate serves as a valuable tool in the early identification and therapeutic decision-making for patients with or at risk of infectious shock [20, 21]. In the context of sepsis, serum albumin functions not only as a negative acute phase protein but also as an important indicator of disease severity and prognosis [22]. Various pathological factors, including nutritional insufficiencies and inflammatory responses, can influence the levels of both lactate and serum albumin in the body [23]. Research has shown that the lactate-to-albumin ratio (LAR) serves as a reliable biomarker used to assess survival chances in sepsis or septic shock patients [24, 25]. Another study revealed that LAR performed better than lactate in severe sepsis [24]. According to one study, the lactate/albumin ratio was found to be a better predictor of both survival and favorable neurological recovery compared to lactate levels alone [26].

It is still unclear whether the lactate/albumin ratio is an effective predictor of clinical outcomes in patients with HFpEF. This study intends to investigate how well the LAR can predict mortality in HFpEF patients admitted to the emergency department or cardiology unit.

Methods

A retrospective investigation was carried out on individuals who sought care at the emergency department or cardiology clinic during the period from January 1, 2023, to June 1, 2024. According to the 2021 ESC Heart Failure Guidelines, the diagnosis of HFpEF requires: (1) the presence of clinical signs and/or symptoms of heart failure, (2) a left ventricular ejection fraction of ≥ 50%, and (3) objective evidence of structural and/or functional cardiac abnormalities consistent with left ventricular diastolic dysfunction and/or elevated left ventricular filling pressures [1]. Only patients over the age of 18 who fulfilled all of participants who fulfilled the following conditions were included in the study: clinical signs and symptoms of heart failure, left ventricular ejection fraction (EF) ≥ 50%, an N-terminal probrain natriuretic peptide (NT-proBNP) level exceeding 125 pg/mL, and at least one of the following findings detected by echocardiography: Left ventricular enlargement, dilation of the left atrium or impaired diastolic function. Only the data from the initial admission were included for patients with multiple hospital visits. Exclusion criteria for the patients were incomplete or unavailable data, length of stay less than 3 days, history of malignancy, detection of arrhythmia on electrocardiography during hospitalization,

and the presence of valve pathology on conventional echocardiography (ECHO). Transthoracic echocardiograms (TTE), interpreted by a cardiology specialist, were retrospectively reviewed in compliance with the American Society of Echocardiography's established protocols [27]. Clinical parameters, including age, gender, comorbidities, laboratory values, LAR, and the mortality status of the patients, which was the final outcome of the study, were evaluated. Laboratory data were obtained frrom venous and artery blood samples at admission. GE vivid T8 (Vingmed Ultrasound AS, Horten, Norway) was used for TTE imaging. The Institutional Ethics Committee granted approval for this study (Approval Date: June 12, 2024; Decision No: 2024/06-118), and it was conducted following the ethical guidelines set by the Declaration of Helsinki.

Statistical Analysis

SPSS version 23.0 (Chicago, Illinois, USA) was used for the data analysis. A comparison was made between the baseline characteristics of survivors and non-survivors. The Kolmogorov-Smirnov test was performed to evaluate the normality of the data. For continuous variables with a normal distribution, the mean and standard deviation were used, while for variables that did not follow a normal distribution, the median and interquartile range were presented. Categorical variables were expressed as frequencies and percentages. For numerical data, either Student's t-test or Mann-Whitney U test was employed, depending on the data distribution. The chi-square test was applied for categorical variables. Both univariate and multivariate regression analyses were performed. ROC curve analysis was used to assess the relationship between HFpEF and the LAR across the entire study population. Statistical significance was defined as p-values below 0.05.

Results

Study group data were obtained from the hospital patient information database. Data from 1,910 heart failure patients, who either visited the emergency department or were sent to the cardiology clinic, were utilized in this study. According to the variables determined for the study, 110 patients had missing data. The remaining 1297 patients were excluded as they have at least one of the exclusion criterias. 503 patients were selected for inclusion in the study based on meeting the study’s criteria. A total of 74 patients (6.9% of those included) died while hospitalized during the course of the study (Table-1). Among the patients who died in the hospital, the admission LAR was significantly higher. Significant differences were found in additional variables when comparing the groups. The average age of the deceased patients was 77.5 ± 5 years ($p < 0.001$). The group with in-hospital mortality had a notably higher comorbidity rate compared to the other group. Although lactate levels were similar between the two groups, albumin levels showed a significant difference. Sodium and potassium levels did not show significant differences between the deceased and surviving patients, creatinine levels were markedly higher in the deceased patients ($p < 0.001$).

Table-1 Demographic and Clinical Data

N (%)	All Patients N = 503 (%)	Survivors N = 429 (%)	Deceased N = 74 (%)	P-value
Gender (F)	259 (51.5)	224 (52.2)	35 (47.3)	0.43
Age	58 ± 12	55 ± 10	77.5 ± 5	< 0.001
Coronary Artery Disease (CAD)	185 (36.8)	123 (28.7)	62 (83.8)	< 0.001
Diabetes Mellitus (DM)	102 (20.3)	73 (17)	29 (39.2)	< 0.001
Atrial Fibrillation (AF)	38 (7.6)	21 (4.9)	17 (23)	< 0.001
Hypertension (HT)	288 (57.3)	233 (54.4)	55 (74.3)	0.01
Stroke (SVO)	11 (2.2)	9 (2.1)	2 (2.7)	0.74
Hemoglobin (HGB)	15 ± 1.6	15.1 ± 1.6	14 ± 1.7	< 0.001
White Blood Cell (WBC)	9.4 ± 3.2	9.3 ± 3	9.8 ± 3.9	0.58
Platelet (PLT)	291 ± 89	293 ± 80	281 ± 128	0.67
Lactate	2.6 ± 1.7	2.5 ± 1.7	2.9 ± 1.4	0.07
Albumin	44 ± 6	45 ± 5.6	42 ± 7.4	< 0.001
Aspartate Aminotransferase (AST)	28 ± 16	27 ± 15	30 ± 19	0.82
Alanine Aminotransferase (ALT)	32 ± 18	33 ± 18	25 ± 17	< 0.001
Glucose	117 ± 69	119 ± 73	105 ± 41	0.65
Cholesterol	192 ± 44	170 ± 40	190 ± 51	0.81
Low-Density Lipoprotein (LDL)	124 ± 43	120 ± 41	121 ± 52	0.42
High-Density Lipoprotein (HDL)	45 ± 11	44 ± 10	47 ± 14	0.49
Triglycerides	185 ± 118	188 ± 116	169 ± 125	0.05
Creatinine	0.9 ± 0.5	0.9 ± 0.5	1.9 ± 0.3	< 0.001
Sodium	142 ± 3.1	141 ± 3	142 ± 3	0.32
Potassium	4.5 ± 0.4	4.5 ± 0.4	4.6 ± 0.5	0.22

N (%)	All Patients N = 503 (%)	Survivors N = 429 (%)	Deceased N = 74 (%)	P-value
Magnesium	2.5 ± 1.9	2.6 ± 1.9	1.9 ± 0.3	< 0.001
C-Reactive Protein (CRP)	6.1 ± 1.9	1.4 ± 0.7	1.5 ± 0.8	0.15
Uric Acid	5.6 ± 1.6	5.5 ± 1.6	6 ± 1.7	0.01
Lactate/Albumin Ratio (LAR)	0.05 ± 0.04	0.05 ± 0.03	0.07 ± 0.05	0.03

In the study, statistically significant variables were included in both univariate and multivariate regression analysis (Table-2). In this analysis, higher admission LAR (OR, 1.59; 95% CI, 1.23–2.05; P < 0.001), older age (OR, 1.46; 95% CI, 1.318–1.617; P < 0.001), presence of coronary artery disease (CAD) (OR, 0.351; 95% CI, 0.140–0.883; P < 0.026), presence of diabetes mellitus (DM) (OR, 0.267; 95% CI, 0.108–0.661; P < 0.004), and presence of atrial fibrillation (AF) (OR, 0.018; 95% CI, 0.003–0.106; P < 0.001) were found to be independent factors associated with in-hospital mortality.

Table-2 The effects of different prognostic variables on mortality in univariate and multivariate logistic regression analyses.

Prognostic Variables	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
Age	2.030	1.645–2.505	< 0.001	1.460	1.318–1.617	< 0.001
CAD	0.078	0.041–0.149	< 0.001	0.351	0.140–0.883	0.026
DM	0.318	0.187–0.541	< 0.001	0.267	0.108–0.661	0.004
AF	0.173	0.086–0.346	< 0.001	0.018	0.003–0.106	< 0.001
HT	0.411	0.236–0.715	0.002	0.251	0.061–1.037	0.560
HGB	0.770	0.661–0.898	< 0.001	1.226	0.829–1.812	0.307
ALT	0.971	0.953–0.988	< 0.001	0.935	0.892–0.980	0.005
Magnesium	0.193	0.067–0.561	0.003	0.779	0.142–4.264	0.774
Uric Acid	1.212	1.047–1.404	0.010	1.020	0.724–1.736	0.910
LAR	1.460	1.15–1.85	0.002	1.59	1.23–2.05	< 0.001

(*Abbreviations: OR: Odds Ratio, CI: Confidence Interval, CAD: Coronary Artery Disease, DM: Diabetes Mellitus, AF: Atrial Fibrillation, HT: Hypertension, HGB: Hemoglobin, ALT: Alanine Aminotransferase, LAR: Lactate/Albumin Ratio*)

The ROC curve for predicting hospital mortality with LAR is shown in Figure-1. The AUC value of LAR at admission was 0.636; 95% CI (0.520–0.752); p = 0.035, with a sensitivity of 66% and specificity of 60% at a cutoff value of 0.48, making L/A a predictor for mortality in HFpEF (Figure-1).

Discussion

In this study, we assessed the prognostic significance of the LAR in HF patients whose data were available through the hospital information system. The data obtained indicate that a higher LAR at admission can predict the mortality level of hospitalized patients in a linear fashion.

The prognosis of such patients is poor and, at the same time, poses significant economic and public health burdens [28]. As a result, the LAR could be employed as an easy-to-use and practical tool for risk assessment, aiding clinicians in forecasting the outcomes for these patients. Elevated LAR is linked to high lactate and low albumin levels. Initially, it was observed that LAR was more valuable than lactate or albumin on its own in forecasting mortality in critically ill patients such as sepsis [24]. However, both

lactate and albumin levels can vary in many cases. Since we know that lactate metabolic levels are influenced by various mechanisms [21], it may not play a determining role for a disease in isolation. On the other hand, serum albumin is frequently employed for the clinical assessment and monitoring of diseases [29]. Due to its anti-inflammatory, anticoagulant preventing coagulation and inhibiting clot formation, serum albumin may have a potential role in cardiovascular diseases [30]. Low albumin levels are known to indicate poor prognosis in many diseases. Due to the reverse changes in lactate and albumin induced by different mechanisms, the LAR allows for more accurate predictions in determining the prognosis of heart failure patients [31]. In HFpEF patients, hypoalbuminemia, which develops due to causes such as proteinuria, liver dysfunction, malnutrition, and chronic inflammation, in addition to the increase in lactate caused by inadequate perfusion, hypoxia, peripheral congestion, and renal dysfunction, can help identify mortality risk early in this group.

When lactate was first discovered, it was considered a metabolic by product of glycolysis with no significant physiological purpose [32]. In addition to being a metabolic waste, lactate plays an essential role in the development of organs and the coordination of cellular activities [33]. Lactate serves not only as a metabolic by product but also as a crucial signaling molecule involved in maintaining cellular homeostasis, inter-neuronal signaling, immune modulation, and regulation of proliferation-related protein functions [34, 35]. It is now understood that the mechanisms involving lactate transport and signaling play a pivotal part in the emergence and escalation of diverse pathologies, notably cancer [36, 37]. Alterations in lactate concentrations have been documented across a range of cardiovascular diseases, such as AF, including ischemic heart events, chronic heart dysfunction, and vascular hardening, based on findings from both basic and clinical research [38]. Numerous clinical studies have further emphasized the significance of lactate as a prognostic marker in cardiovascular diseases [39]. Emerging data indicate that increased levels of blood lactate may be linked to poorer clinical outcomes in individuals with heart failure [40].

In conditions like heart failure, which are classified as cardiovascular diseases, increased lactate levels and hypoalbuminaemia are present [41]. The evaluation of lactate and albumin levels is crucial in cardiovascular diseases. Studies have shown that lactate levels are linked to survival in heart failure [42]. Furthermore, in individuals who exhibit comparable lactate concentrations, the lactate/albumin ratio has been found to more clearly determine the high risk of mortality [24].

In particular, by evaluating using lactate and albumin in conjunction, the LAR can be utilized as a potential biomarker to predict fatality risk associated with heart failure [43]. In a retrospective study, the importance of a high LAR in determining mortality in heart failure was emphasized [44]. In another study involving heart failure patients, it was found that the LAR could be an early predictor of prognosis [45]. Furthermore, a different study showed that, in predicting mortality, the LAR was more valuable than lactate alone [46].

Conclusion

Our findings indicated that a higher LAR significantly contributed to increased mortality risk in patients diagnosed with HFpEF. This predictive value arises from the increase in lactate levels and the decrease in albumin.

In conclusion, in this study, the LAR, which is inexpensive, easily accessible, and applicable, was found to be a significant biochemical parameter in predicting mortality in HFpEF. Close monitoring should be ensured in HFpEF patients with LAR during hospital admission.

Limitations

First, while our study demonstrated that the LAR is a dependable early indicator of mortality in HFpEF patients, the retrospective and single-center nature of our study limits our ability to establish causal relationships with certainty. Although multivariable adjustments and subgroup analyses were applied, potential confounders may still influence the clinical prognosis. The authors acknowledge this and have exercised caution in interpreting the results. Secondly, in our study, the patient's admission lactate and albumin levels were recorded, and the relationship between these values and prognosis was investigated. In conclusion, it was not possible to evaluate the effect of dynamic lactate and albumin changes on prognosis during the follow-up of the patient. Conducting more comprehensive evaluations alongside these data may yield much stronger results in the future.

Abbreviations

HFrEF
Heart failure with reduced ejection fraction
HFmrEF
Heart failure with mildly reduced ejection fraction
HFpEF
Heart failure with preserved ejection fraction
NYHA
New Yor Heart Association
DM
Dİyabetes mellitus
NT-proBNP
N-terminal pro-natriuretic peptide
TTE
Transthoracic Echocardiography
LAR
Lactat/Albumin ratio

Declarations

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Competing Interests

The authors have no financial or proprietary interests in any material discussed in this article.

Ethics approval and consent to participate

This study was approved by the Erzurum Faculty of Medicine Scientific Research Ethics Committee (Approval Date: June 12, 2024; Decision No: 2024/06-118).
Due to the retrospective study design and the use of anonymized patient data, the requirement for obtaining individual informed consent was waived.

Author contributions: CRediT

SGU: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Conceptualization. **MCŞ:** Writing – review & editing, Methodology, Data curation, Conceptualization. **MÖ**: Writing – review & editing, Methodology, Data curation, Conceptualization. **FKŞ:** Writing – review & editing, Methodology, Conceptualization**.**

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Clinical trial number

Not applicable

Data availability

Data that support the findings of this study are available from the authors upon request.

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Figures

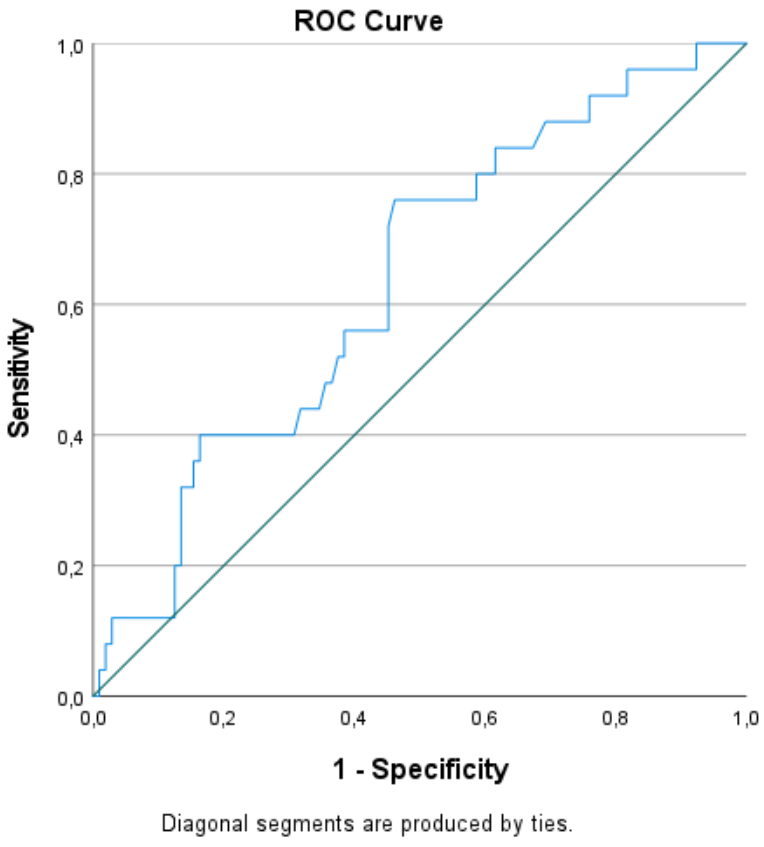


Figure 1

ROC curve analysis of L/A for predicting mortality in HFpEF.