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Relationship between lactate albumin ratio and mortality in patients with ischemia and non-obstructive coronary artery disease (INOCA)

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Abstract

Aim: Ischemia with non-obstructive coronary artery disease (INOCA) is when there is myocardial ischemia without occlusive coronary artery disease. Over time, this could result in a reduced quality of life, frequent hospital visits, and a higher risk of cardiovascular-related deaths. Diagnosis, management, and prognosis of INOCA pose challenges. Lactate-albumin ratio (LAR) has been associated with mortality from many cardiovascular diseases. The study examined the link between LAR and mortality in patients with INOCA.

Materials and Methods: The study analyzed data from 987 patients diagnosed with ischemia through myocardial perfusion imaging using single photon emission computed tomography (MPI-SPECT) at our center between 2017 and 2023. After applying the exclusion criteria, we included 279 patients in the study. Medical histories, laboratory parameters, and patient death information were recorded.

Results: The mean follow-up time was 20547 days. Mortality occurred in 5% of patients (14 patients). Patients were divided into two groups: mortality and non-mortality. The LAR was 0.65 ± 0.26 in the non-mortality group and 1.05 ± 0.32 in the mortality group, indicating a meaningful disparity between the two groups (p=0.017). Cox regression analysis was conducted to determine mortality predictors. In INOCA patients, mortality was independently predicted by age and LAR (p=0.03, and p=0.005, respectively). To evaluate the efficacy of LAR in predicting mortality, we executed the Receiver Operating Characteristic (ROC) analysis. The examination revealed an area under the curve (AUC) of 0.689 (0.519-0.858), a cut-off of 0.656, a sensitivity of 57.1%, and a specificity of 52.8% (p=0.017).

Conclusion: Our study found that LAR performs as an independent predictor of mortality in patients with INOCA.

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Introduction

Ischemia with non-obstructive coronary artery disease (INOCA) is described as the presence of myocardial ischemia without occlusive coronary artery disease [1]. INOCA has been considered a chronic coronary syndrome. Ischemia in patients with INOCA can be detected through stress electrocardiogram, abnormal cardiac stress imaging, and elevated troponin levels. This specific patient population can experience long-term complications like heart failure with preserved ejection fraction, myocardial infarction, decreased quality of life, repeated hospitalizations, and increased cardiovascular mortality [2,3]. Although INOCA causes symptoms more frequently in women, it can also be seen in men and even has a worse prognosis in men [4]. The pathophysiology of INOCA is not clear, but it is evident that most patients experience coronary vascular dysfunction [5]. INOCA can be ignored due to the absence of obstructive coronary lesions. However, it can be a significant cause of cardiovascular morbidity and mortality. It is one of the diseases that is difficult to diagnose and predict prognosis because it has a heterogeneous patient group [6]. Therefore, new tools to predict INOCA prognosis are needed.

Lactate is an end product of anaerobic glycolysis. Although the increase in lactate levels may be due to various factors such as decreased excretion due to liver and kidney disease and acceleration of anaerobic glycolysis, in clinical practice, it is thought that the lactate level increases due to tissue perfusion disorder [7,8]. Recent studies have sug-

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gested that high serum lactate levels may be associated with short- and long-term mortality from cardiovascular diseases like acute myocardial infarction and heart failure [9].

Albumin levels have proven to be a reliable indicator in clinical practice, effectively reflecting nutrition, liver function, and inflammation status for many years. Hypoalbuminemia is strongly linked to a poor prognosis, especially in diseases where inflammation is involved in their pathophysiology [10]. Similarly, hypoalbuminemia indicates a poor prognosis in many cardiovascular diseases in which inflammation has been implicated [11].

The Lactate-Albumin Ratio (LAR) is calculated by dividing the lactate level by the albumin level. This ratio was first employed to evaluate the prognosis of individuals with sepsis [12]. Recent studies have linked it to a poor prognosis for cardiovascular diseases like heart failure and acute myocardial infarction [13,14].

INOCA mortality has become a growing problem in recent years. Identification of mortality predictors may provide insight into prognosis. Therefore, the study investigated the association between mortality and LAR in patients with INOCA.

Materials and Methods

Study design and patient selection

This study was a retrospective, single-center, and observational study. The evaluation began by examining the data of patients who presented to the cardiology outpatient clinic with chest pain, had a medium-high probability of coronary artery disease before the test, and had myocardial ischemia detected on myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT). Data from 987 patients diagnosed with ischemia using MPI with SPECT and who underwent coronary angiography at our center between 2017 and 2023 were examined for the study. Two cardiologists monitored the patients' coronary angiography. If they could not agree on the percentage of coronary lesions, a third cardiologist viewed the images. Patients with stenosis greater than $\geq$50% in at least one epicardial coronary artery were excluded from the study because they did not meet the INOCA criteria. When the coronary angiography records of 987 patients were reviewed, 638 patients were eliminated from the trial due to the presence of a lesion of 50% or greater in at least one epicardial coronary artery. The medical history and laboratory parameters of the remaining 349 patients were thoroughly analyzed. Six patients were excluded from the study due to severe heart valve disease. One patient was eliminated from the trial due to pericardial effusion. Three participants were eliminated from the research due to diabetic ketoacidosis. Seven patients were eliminated from the trial due to severe liver and kidney disease. Sixteen participants were eliminated from the research because of active malignancy. Five participants were eliminated from the research because of chronic inflammatory disease. Three participants were excluded from the trial due to a diagnosis of malnutrition. Nineteen patients were eliminated from the trial because of missing data. In addition, the sample size required for G power analysis is 184, according to a 5% error and 95% confidence level. Also, considering a 10% loss, it was planned to include 200 patients. Nevertheless, the sample size was found to be greater, and a total of 279 participants participated in the study. Figure 1 presents the flow chart. Medical history, hemogram, biochemistry, and venous blood gas information were recorded. Patient death information was obtained from the hospital registration system and the Ministry of Health's death notification system. The local ethics committee approved the study and adhered to the Declaration of Helsinki's principles.

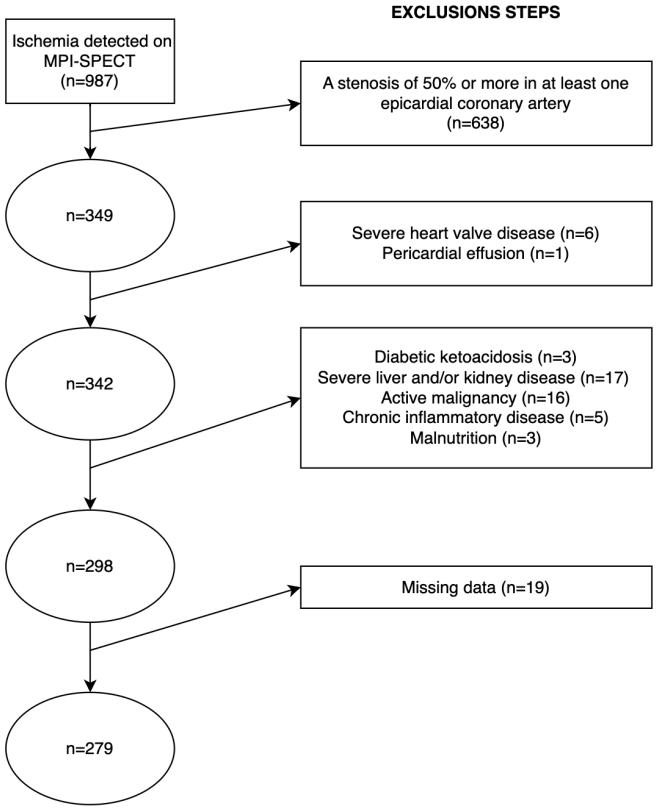

Figure 1. Flow chart of exclusion steps.

Collection of blood samples

Blood samples were collected within the 24 hours after patients were admitted to our clinic for coronary angiography. Samples were drawn from either the left or right antecubital vein following the application of mild venous stasis using a tourniquet on the upper arm. The samples were collected in potassium EDTA tubes for a complete blood count. We measured hemoglobin, hematocrit, platelet, and white blood cell counts using the Beckman Coulter LH 780 with the electrical impedance method. Standard laboratory methods were used to assess the biochemical parameters. The blood gas test was examined using an ABL 800 FLEX blood gas analyzer (Radiometer).

Definitions

According to the 2021 American Heart Association, INOCA is defined as the demonstration of coronary dysfunction by invasive means or the demonstration of ischemia by non-invasive methods in addition to <50% stenosis in the

epicardial coronary arteries. Stress cardiac magnetic resonance imaging (CMR) and MPI-SPECT are non-invasive examinations [15].

Hypertension (HT) is represented as having an arterial blood pressure of 140/90 mmHg or higher or using at least one antihypertensive drug [16].

Diabetes mellitus (DM) is diagnosed when the glycated hemoglobin is 6.5% or higher and/or the fasting blood glucose level is ≥126 mg/dL after an 8-hour fast [17].

Statistical analysis

We employed numbers and percentages to effectively represent categorical data, providing a clear and concise visualization of our findings. For normal distributions, continuous variables were recorded as mean ± standard deviation (SD); for non-normal distributions, they were recorded as median (interquartile range [IQR]). Nonparametric data was analyzed using the χ^2 test. Before conducting significance tests, we assessed the normality of all variables using the Kolmogorov–Smirnov test and scrutinized the homogeneity of variances with the Levene test. T-tests for independent groups were confidently utilized for data exhibiting a normal distribution and homogeneity. In cases where parameters did not adhere to a normal distribution between two groups, we relied on the Mann–Whitney U test. Univariable and multivariable Cox regression analyses were conducted to thoroughly examine risk factors for mortality and decide independent risk factors. All analyses were executed using the SPSS statistical package version 23.0 (IBM Corp., NY, USA), with a significance level of $p<0.05$ for all statistical assessments. We assessed LAR's effectiveness in predicting mortality among patients with INOCA. This was accomplished by carefully examining receiver operating characteristic (ROC) curves and determining the area under the curve (AUC) value.

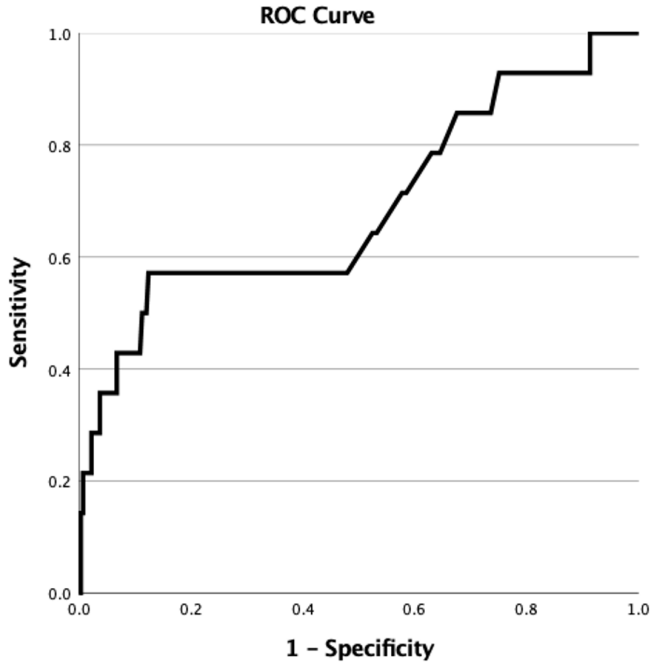

Figure 2. ROC-AUCs for LAR's prediction of mortality development in INOCA.

Table 1. Baseline demographic characteristics.

Variables	Mortality (-) (n=265)	Mortality (+) (n=14)	P value
Gender, male (%)	104 (39.2)	8 (57.1)	0.184
Age (years)	62.49 ± 12.87	74.59 ± 9.02	**<0.001**
HT, n (%)	174 (65.7)	6 (42.9)	0.083
DM, n (%)	48 (18.1)	5 (35.7)	0.102
CAD, n (%)	232 (87.5)	10 (71.4)	0.084
CVE, n (%)	3 (1.1)	0 (0)	0.689
LVEF (%)	56.3 ± 2.1	55.6 ± 1.8	0.726
LAd (mm)	35.7± 4,8	36± 4.6	0.402
RAd (mm)	34.8± 4.3	34.9± 4.5	0.776
pH	7.39 ± 0.83	7.41 ± 0.39	0.089
HCO_3 (mmol/L)	23.61 ± 4.05	19.37 ± 6.95	**0.044**
PCO_2 (mmHg)	43.6 ± 9.4	52.4 ± 13.6	0.070
Lactate (mmol/L)	2.1 (1.5-3.1)	5.8 (3.6-8.0)	**0.005**
Albumin (g/dL)	4.30 ± 0.42	4.21 ± 0.60	0.992
WBC (10^3/μL)	8.6 (6.7-10.9)	10.9 (7.2-12.5)	0.190
Hemoglobin (g/dL)	14.2 ± 2.1	13.9 ± 2.1	0.782
Platelet (10^3/μL)	252 (209-298)	228 (157-258)	0.085
CRP (mg/L)	1.9 (0.43-6.65)	8.6 (4.9-15.3)	0.188
Glucose (mg/dL)	104 (90-130)	103 (98-157)	0.401
ALT (U/L)	23 (17.5-32)	16 (14-27)	**0.040**
Total Cholesterol (mg/dL)	170.8 ± 42.1	151.8 ± 48.9	0.197
HDL (mg/dL)	39.7 ± 12.2	37.2 ± 11.8	0.358
LDL (mg/dL)	118.5 ± 39.7	98.7 ± 25.6	**0.049**
Triglyceride (mg/dL)	146 (103-222)	120 (97-230)	0.793
Creatinine (mg/dL)	0.84 ± 0.27	0.89 ± 0.26	0.450
Sodium (mg/dL)	139.3 ± 4.3	138.8 ± 2.6	0.357
Potassium (mg/dL)	4.22 ± 0.49	4.23 ± 0.30	0.703
LAR	0.65 ± 0.26	1.05 ± 0.32	**0.017**

Abbreviations: HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CVE: Cerebrovascular event, LVEF: left ventricular ejection fraction, LAd: left atrial diameter, RAd: right atrial diameter, HCO_3: Bicarbonate, PCO_2: Partial carbon dioxide, WBC: White blood cells, CRP: C-reactive protein, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, LAR: Lactate-albumin ratio.

Results

Our research involved a total of 279 patients diagnosed with INOCA. The mean follow-up time was 205±47 days. Mortality was observed in 5% (14 patients) of the patients. Patients were split into two groups: mortality and non-mortality. The age difference between the mortality and non-mortality groups was 74.59 ± 9.02 and 62.49 ± 12.87 years, respectively. The age in the mortality group was statistically significantly older ($p<0.001$). HT, DM, and coronary artery disease (CAD) appeared statistically similar in the two groups. The pH was comparable in both groups, but the HCO_3 levels were statistically significant, measuring 19.37 ± 6.95 in the mortality group ($p=0.044$). While lactate level was 2.1 mmol/L in the non-mortality group, it was 5.8 mmol/L in the mortality group. The two groups had a statistically significant difference in lactate levels ($p=0.005$). Alanine aminotransferase (ALT) and low-density lipoprotein (LDL) levels were considerably reduced in the mortality group ($p=0.04$ and $p=0.049$, respectively). While LAR was 0.65 ± 0.26 in the non-mortality group, it was 1.05 ± 0.32 in the mortality group, indicating a meaningful significant disparity between the two groups

Table 2. Univariable and Multivariable Cox Regression Analysis.

Variables	Univariable HR (%95 CI)	P value	Multivariable HR (%95 CI)	P value
Age	1.089 (1.036-1.144)	**<0.001**	1.074 (1.006-1.146)	**0.032**
ALT	0.970 (0.923-1.020)	0.238	0.986 (0.935-1.040)	0.605
LDL	0.986 (0.970-1.001)	0.067	0.987 (0.966-0.1003)	0.074
LAR	4.069 (1.946-8.510)	**<0.001**	3.148 (1.417-6.992)	**0.005**

Abbreviations: ALT: Alanine aminotransferase, LDL: Low-density lipoprotein, LAR: Lactate- albumin ratio, HR: Hazard ratio, CI: Confidence interval.

(p=0.017). Please refer to Table 1 for the details.

To identify mortality factors, Cox regression studies, both univariable and multivariable, were conducted. Age and LAR emerged as independent predictors of mortality in INOCA patients (p=0.03 and p=0.005, respectively). The outcomes of the regression analysis are presented in Table 2.

We conducted a ROC analysis to consider LAR's capability to predict mortality. The analysis yielded an AUC of 0.689 (0.519-858) with a cut-off value of 0.656. The sensitivity was established at 57.1%, while the specificity was recorded at 52.8% (p=0.017) (Figure 2).

Discussion

Our study found a considerable connection between LAR and mortality in patients with INOCA. Our study is the first to investigate the association between INOCA mortality and LAR, according to our knowledge.

INOCA is a chronic coronary syndrome diagnosed by the presence of ischemia detected by invasive or non-invasive methods in addition to non-obstructive epicardial coronary arteries. Studies have found that INOCA is associated with deterioration in quality of life, recurrent hospitalization, and increased cardiovascular mortality [18,19]. Diagnosis, patient management, and prediction of prognosis are challenging due to the absence of obstructive lesions in the coronary arteries and patient heterogeneity [3]. The pathophysiology of patients with INOCA is believed to be epicardial coronary artery dysfunction or coronary microvascular dysfunction, which coronary spasms can sometimes accompany. Although the pathophysiology is not clearly understood, increased inflammation and oxidative stress, in addition to cardiometabolic risk factors may cause epicardial coronary and coronary microvascular dysfunction. In addition, recurrent angina, even in the absence of coronary obstruction, can linked to cardiac autonomic dysfunction [20]. It is estimated that approximately 3-4 million people worldwide have angina attacks each year, even though they do not have obstructive coronary artery disease [21]. Until recently, the medical community widely believed that INOCA had a favorable prognosis. Recent studies have revealed that patients with INOCA face a raised risk of significant unfavorable cardiac events, stroke, and cardiovascular mortality [22]. In addition, patients with single-vessel obstructive coronary artery disease and those without it demonstrate comparable one-year mortality and myocardial infarction rates [18]. Advanced age, HT, DM, and smoking history are associated with increased mortality in INOCA patients [3]. In our study, advanced age predicted INOCA mortality similarly to the literature. However, our study did not detect HT and DM as a mortality predictor. Additionally, we did not have information about the smoking history of the patients in our study.

Myocardial ischemia is caused by an imbalance in heart oxygen supply. As a result, cardiac myocytes show decreased mitochondrial oxidative phosphorylation and a shift toward the glycolytic pathway. In this case, an increase in lactate level is observed due to an increase in the glycolytic pathway due to impaired oxidative phosphorylation [7]. Lactate is the end product of the anaerobic glycolytic pathway. Its level may increase in cases where oxygenation is impaired at the cellular level. Increased serum lactate levels have been linked to numerous cardiovascular diseases, such as cardiac arrest, acute myocardial infarction, heart failure, atrial fibrillation, atherosclerosis, and silent myocardial ischemia [23-28]. Lactate also has significant predictive value for mortality in many cardiovascular diseases [9]. In our study, similar to the literature, serum lactate levels were statistically significantly higher in INOCA patients with mortality.

Hypoalbuminemia has long been recognized as a negative acute-phase reactant. It has been used to determine the prognosis of acute diseases, especially sepsis [29]. Significant liver disorders, inflammatory conditions, and malnutrition may affect serum albumin levels [30]. Recent studies have shown that hypoalbuminemia may be associated with mortality from cardiovascular diseases such as heart failure and acute myocardial infarction [31,32]. In our study, albumin level was lower in the mortality group, However, no statistically significant change was seen. This may be because INOCA does not present with acute and severe signs such as acute myocardial infarction and heart failure.

LAR was initially utilized to assess the prognosis of patients with sepsis, and it is believed to offer superior predictive value compared to the sole measurement of serum lactate level [33]. Since both high serum lactate level and hypoalbuminemia indicate poor prognosis in cardiovascular diseases such as heart failure and coronary artery disease, LAR has been used to predict poor prognosis in cardiovascular diseases [14,32]. Patients with INOCA commonly experience coronary vascular dysfunction. The resulting oxygen-supplying imbalance may trigger hypoxia, increased inflammation, and oxidative stress at the cellular level. At the cellular level, hypoxia may cause cardiomyocytes to shift to anaerobic glycolysis rather than oxidative phosphorylation, increasing serum lactate levels [9]. Hypoalbuminemia may also be a sign of increased inflammation [10]. Inflammation and oxidative stress un-

deniably play a pivotal role as pathophysiological causes of atherosclerotic heart diseases [34]. Considering all these mechanisms, it may not be surprising that a practical, easily applicable, and inexpensive parameter such as LAR stands out in predicting the prognosis of a chronic coronary syndrome such as INOCA.

We faced several limitations in our study. First, our study was limited by a relatively small sample size and by being a retrospective, single-center study. Secondly, our limitations were that we did not use an invasive method to detect coronary dysfunction, and patients' medical treatment data and smoking information could not be accessed. Finally, another limitation was that only the initial value of LAR was included in the study, and dynamic change was not monitored.

Conclusion

Our research suggests that LAR could potentially be a key factor in predicting mortality among patients with INOCA. INOCA still presents significant challenges in diagnosis, prognosis, and treatment. Using a cheap and easily calculable parameter such as LAR to estimate prognosis in INOCA patients may provide clinical benefits.

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Declaration of conflicting interests

Regarding this paper's research, writing, and publication, the authors declare they have no conflicts of interest.

Ethical approval

The Health Sciences University, Erzurum City Hospital, Ethical Committee approved this study (Ethics Committee Decision Date: 11/09/2024, Ethics Committee Decision Number: 2024/09-169).

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