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Association between lactate/albumin ratio and 28-day all-cause mortality in critically ill patients with acute myocardial infarction

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Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality worldwide. Early identification of high-risk patients is crucial for timely interventions and improved outcomes. The lactate/albumin ratio (LAR) has been suggest as a significant correlate for assessing the risk of mortality in critically ill patients. This study aimed to utilize the American eICU Collaborative Research Database to explore the association between baseline LAR and all-cause mortality within 28 days in ICU of critically ill patients diagnosed with AMI. We conducted a retrospective cohort study of 989 AMI patients from the eICU Collaborative Research Database. Patients were included based on ICD-9 code 410 and the universal definition of AMI. LAR was calculated as the ratio of baseline lactate to albumin levels within the first 24 h of ICU admission. The outcome was all-cause mortality within 28 days after ICU admission. Multivariable logistic regression models were used to evaluate the independent association between LAR and the risk of death, adjusting for potential confounders including demographics, comorbidities, vital signs, and laboratory parameters. Subgroup analyses and nonlinear modeling were performed to further explore the relationship. Of the 989 AMI patients, 171 (17.3%) died within 28 days after ICU admission. Patients who died had significantly higher LAR compared to survivors (1.66 vs. 0.96, $p < 0.001$). Multivariable analysis showed that each unit increase in LAR was associated with a 2.15-fold higher risk of all-cause mortality within 28 days after ICU admission (95% CI: 1.64–2.83, $p < 0.001$). Subgroup analyses confirmed the consistent association across different patient characteristics. Nonlinear modeling revealed a threshold effect, where LAR above 2.15 was no longer significantly associated with mortality. Kaplan-Meier survival analysis demonstrated lower survival probabilities for patients with higher LAR(1.0526–5.8235). The findings suggest that a higher LAR was associated with an increased risk of 28-day all-cause mortality for critically ill patients with AMI after ICU admission.

Keywords Acute myocardial infarction, Lactate/albumin ratio, Critically ill patients, ICU 28-day mortality, eICU-CRD

Acute myocardial infarction(AMI) is a leading cause of morbidity and mortality worldwide, characterized by myocardial ischemia and injury due to various underlying mechanisms[1]. Globally, AMI is a major health burden, particularly in industrialized countries. It is estimated that approximately 7.8 million deaths annually are attributable to myocardial infarction[2]. As lifestyles change and populations age, these numbers continue to rise. In China, cardiovascular diseases(CVD) are the leading cause of death, with AMI constituting a significant proportion[3]. AMI can rapidly result in severe cardiac dysfunction, such as heart failure, ventricular septal rupture, and papillary muscle dysfunction, all of which can lead to acute mortality[4]. In clinical practice, the vast majority of patients with AMI are admitted to the intensive care unit(ICU) or critical care unit(CCU), which is also recommended in Japanese and European guidelines[5].

Lactate, a product of anaerobic metabolism, typically increases during tissue hypoxia or ischemia[6]. AMI leads to myocardial ischemia, potentially causing local and systemic metabolic abnormalities, thus elevating blood lactate levels[7]. Albumin, a major plasma protein synthesized by the liver, reflects nutritional status and hepatic

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synthetic function[8]. In patients with AMI and other cardiovascular diseases, albumin levels may decrease due to malnutrition, inflammatory responses, or impaired liver function[9].

The lactate/albumin ratio (LAR) is a composite indicator that integrates changes in both lactate and albumin levels, reflecting the patient's metabolic state and physiological stress. A high LAR may indicate more severe tissue hypoxia and metabolic disorder, as well as lower physiological reserve and worsened clinical prognosis. Some studies have demonstrated a positive correlation between LAR and the risk of death in ICU patients, especially in severe illnesses such as septicemia and heart failure[10,11]. Although current data on the application of LAR in patients with AMI are limited, existing research indicates that patients with high LAR have a higher mortality rate in the ICU, likely due to more severe myocardial injury and systemic metabolic disorder. Future research is needed to further validate the association of LAR and clinical outcomes in critically ill patients with AMI.

Thus, this study aims to utilize the American eICU Collaborative Research Database(eICU-CRD) to explore the association between LAR and 28-day all-cause mortality for critically ill patients with AMI after ICU admission.

Methods

Data source

This study was a retrospective observational analysis utilizing data from the eICU Collaborative Research Database (eICU-CRD), a comprehensive, multicenter ICU database developed by the Massachusetts Institute of Technology (MIT) and released under version 2.0 in 2019. The eICU-CRD contains detailed, deidentified data from over 200,000 admissions across 335 ICU units in 208 hospitals in the United States during the years 2014 to 2015[12]. Research has utilized the eICU-CRD for various observational studies[13,14].Access to the eICU-CRD is governed by strict data usage agreements in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Safe Harbor provisions. Researchers must complete the Collaborative Institutional Training Initiative (CITI) program and pass an examination to obtain certification for database access. In this study, the data extraction was performed in accordance with these guidelines, with access approved by the PhysioNet review committee. One author (Ping Jin) obtained the access and was responsible for the data extraction (certification number: 62661740). As all data were fully anonymized, the institutional review board of MIT determined that the research was exempt from further ethical review and waived the requirement for informed consent from patients or their legal guardians. This exemption was supported by the security measures ensuring the minimal risk of reidentification, as certified by Privacert (Cambridge, MA). The study was conducted in full compliance with the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study population

All patients diagnosed with AMI on admission to the ICU were included in the study, and the AMI was based on the ICD-9 code 410 from the eICU-CRD. The diagnosis of AMI was derived from pre-existing conditions. The definition of AMI[15] applies when there is evidence of acute myocardial injury, accompanied by clinical signs of acute myocardial ischemia, and a rise and/or fall in cardiac troponin (cTn) levels, with at least one value exceeding the 99th percentile upper reference limit (URL). The diagnosis is further supported by one or more of the following criteria: symptoms indicative of myocardial ischemia, new ischemic changes on electrocardiogram (ECG), the appearance of pathological Q waves, imaging that shows new loss of viable myocardium or new regional wall motion abnormalities consistent with an ischemic origin, or the detection of coronary thrombi via angiography or post-mortem examination.The following exclusion criteria were applied: (1) patients under the age of 18; (2) not first ICU admissions; (3) missing measurements for lactate and albumin; (4) Outliers, defined as observations with Z-scores beyond ± 3 for variable X, were excluded to minimize extreme value impacts, enhancing the dataset's consistency and reliability. In this study, we excluded 3 cases because of outliers of LAR, and LAR of all included samples was ≤ 6. The study cohort consisted of 989 AMI patients, including 818 survivors (82.7%) and 171 non-survivors (17.3%). The study flowchart is shown in Fig. 1.

Data extraction

We utilized Structured Query Language (SQL) to extract variables within the first 24 h of admission from the eICU-CRD. The extracted variables included basic demographic information, comorbidities, vital signs, and other relevant variables. Comorbidities encompassed conditions such as congestive heart failure, cardiac arrhythmias, diabetes, and pneumonia. Basic demographic information was extracted from the patient and apachePatientResult tables. Vital signs, including temperature (°C); respiratory rate (bpm); heart rate (bpm); and mean arterial pressure (MAP, mmHg), were obtained from the apacheApsVar table. Additionally, baseline laboratory data such as platelets, white blood cell(WBC, k/mcl), red blood cell(RBC, k/mcl), hemoglobin(g/dl), blood urea nitrogen(BUN, mg/dl), creatinine(mg/dl), prothrombin time(PT, sec), brain natriuretic peptide(BNP, pg/ml), troponin-I(ng/mL), total cholesterol(mg/dl), triglycerides(mg/dl), low-density lipoprotein cholesterol(LDLc, mg/dl), high-density lipoprotein cholesterol(HDLc, mg/dl), glucose(mg/dl), aspartata transminase(ALT, U/L), alanine transminase(AST, U/L), total protein(g/dl), albumin(g/dl), and lactate(mmol/L) were obtained from the laboratory tables. LAR was calculated as the ratio of lactate to albumin, of which were measure for the first time within 24 h after ICU admission. The outcome of the present study was all-cause ICU mortality within 28 days after admission to the ICU of critically ill patients with AMI.

Statistical analysis

Continuous variables are described using mean $\pm$ standard deviation(SD). Categorical data are presented as frequencies and percentages. To compare differences between survivor and non-survivor group, we used the

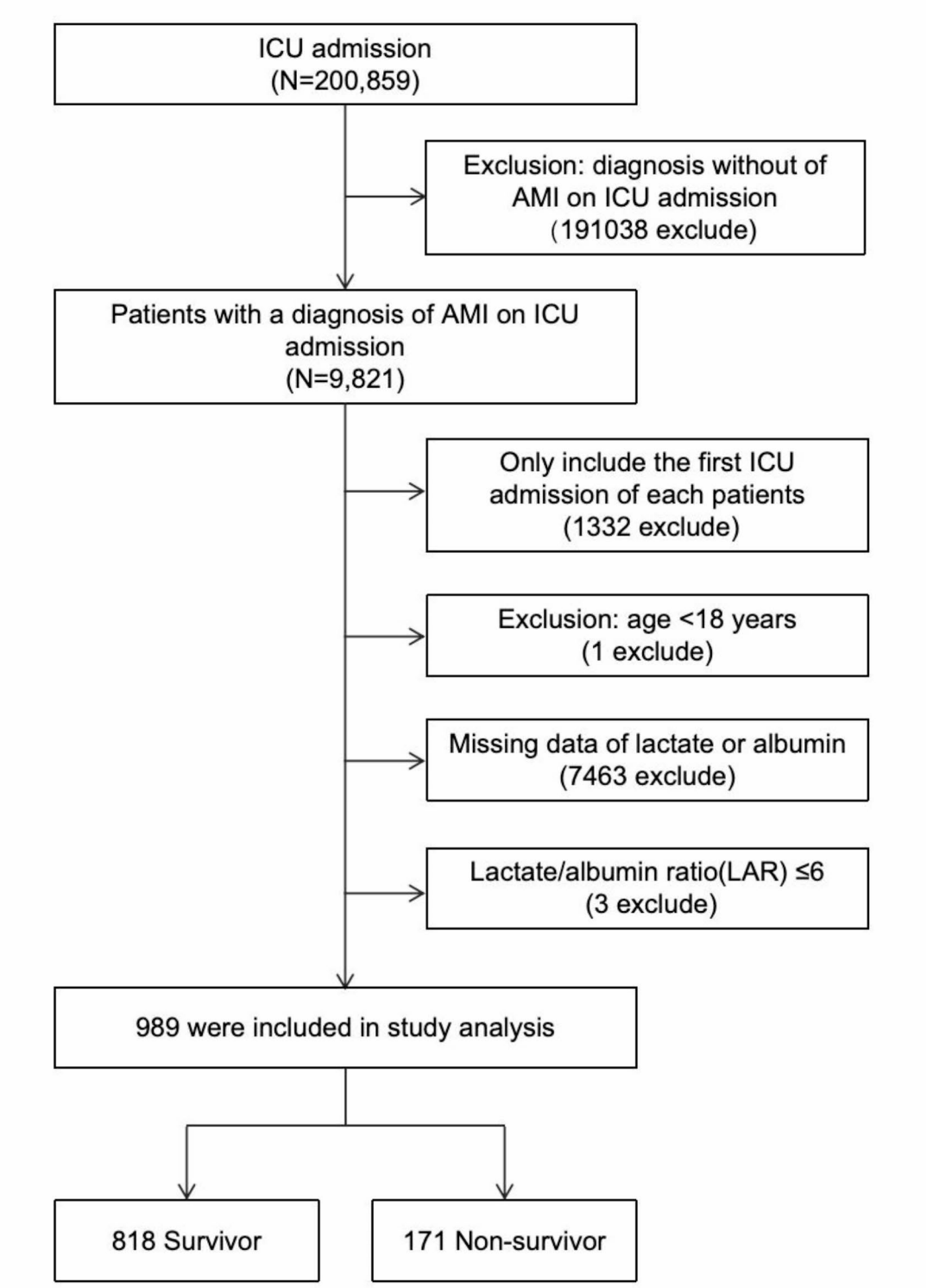

Fig. 1. Flow chart for participants. *ICU* intensive care unit.

chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. One-way analysis of variance was used to compare the differences in continuous variables among tertiles, and the chi-square test was used for categorical variables. We used a multivvariable logistic regression model to estimated the association between LAR and 28-day ICU all-cause mortality, and results are presented as odds ratio(OR) and their 95% confidence intervals(95%CIs). To examine the robustness of the results, we conducted sensitivity analyses by using a Cox proportional hazards model using ICU length of stay as time scale to account for potential modification of results by different statistical method, and the results are presented as hazard ratios (HRs) and

their 95%CIs. Unadjusted and adjusted regression estimates are provided. We adjusted potential confounding factors according to the findings of univariate analysis, literature reports and clinical experiences. In Model I, adjustments were made for age, gender, and ethnicity. In Model II, adjustments were made for gender, age, ethnicity, cardiac arrhythmias, WBC, BUN, creatinine, PT, glucose, AST and ALT. We used a generalized additive model (GAM) to investigate the dose-response relationship between LAR and mortality. Two-piecewise linear regression models were used to test the threshold saturation effect of LAR on mortality. Exploratory analysis was used to determine the turning point of LAR, and the point with the maximum likelihood of the model was selected. We also performed a likelihood ratio test to compare a linear regression model with a two-piecewise linear model. Stratified analysis and interaction tests were conducted to determine whether the effect of LAR differed across subgroups, and the results are presented in the form of a forest plot. Kaplan-Meier survival curves and the log-rank test were used to describe the survival distribution. All reported p-values are two-sided, and a p-value less than 5% is considered statistically significant. All data were analyzed using R software (v3.61) and Empower Stats (http://www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Baseline characteristics of the study population

A total of 989 critically ill patients with AMI were enrolled, including 818 survivors and 171 non-survivors. Comparison of demographics, comorbidities, vital signs and laboratory parameters between these two groups are shown in Table 1. The average age of non-survivors (71.45 ± 10.66 years) was significantly higher than that of survivors (67.62 ± 13.34 years, $P < 0.001$), and non-survivors also had a slightly higher BMI (29.85 vs. 28.50 kg/m^2, $P = 0.023$). Cardiac arrhythmias were more common in the non-survivor group (43.27% vs. 30.68%, $P = 0.001$). Non-survivors had significantly higher Apache IV scores (90.34 vs. 73.06, $P < 0.001$). Patients in non-survivors had higher levels of temperature, WBC, BUN, creatinine, PT, troponin-I, glucose, AST, ALT and lactate(all $P < 0.05$); and lower levels of MAP, total cholesterol, HDLc, total protein, albumin(all $P < 0.05$). Additionally, the LAR was significantly higher in non-survivors (1.66 vs. 0.96, $P < 0.001$).

Univariate logistic analysis for 28-day mortality

Univariate logistic analysis was performed to evaluate the association between variables and 28-day all-cause mortality. As shown in Table S1, a higher level of age, BMI, Apache IV score, WBC, BUN, creatinine, PT, troponin-I, total cholesterol, HDLc, glucose, AST, ALT, lactate, LAR, and a lower level of total protein, albumin, and cardiac arrhythmias proportion were significantly associated with 28-day all-cause mortality (all $P < 0.05$). Other variables, including gender, ethnicity, congestive heart failure, diabetes, pneumonia, temperature, respiratory rate, heart rate, MAP, platelets, RBC, hemoglobin, BNP, triglycerides, LDLc showed no statistically relationship with 28-day all-cause mortality for critically ill patients with AMI after ICU admission.

Association between LAR and 28-day mortality in different models

Multivariable logistic regression model was used to evaluate the independent relationship between LAR and 28-day all-cause mortality. Table 2 displays the OR(95%CI) for 28-day mortality associated with LAR in different models. LAR was significantly associated with an increased mortality rate. As a continuous variable, an unit increase in LAR was associated with a higher mortality rate, showing OR of 1.86 (95%CI: 1.59–2.16, $P < 0.0001$), 1.87(95%CI: 1.60–2.19, $P < 0.0001$) and 2.15 (95%CI: 1.64–2.83, $P < 0.0001$) higher mortality rate in crude model(Model 1), minimally adjusted model(Model 2), and fully adjusted model(Model 3), respectively. When LAR was divided into tertiles, compared to the low LAR group, the 28-day mortality rate was slightly higher in the medium LAR group (Model 2: OR = 1.69, $P = 0.0424$), and significantly higher in the high LAR group (Model 2: OR = 4.92, $P < 0.0001$). After adjusting the covariates, the 28-day mortality rate was still higher in the high LAR group when compared with the low LAR group (Model 3: OR = 4.62, $P < 0.0001$).

Cox proportional hazards regression was utilized for sensitivity analyses. The results indicated that without adjusting for any covariates (Model 1), each unit increase in LAR was associated with a 54% increase in the risk of death(HR 1.54,95%CI: 1.38–1.72, $P < 0.0001$). After adjusting for gender, age, and ethnicity(Model 2), the risk of death increased by 58%(HR 1.58,95%CI: 1.41–1.77, $P < 0.0001$). With further adjustment for additional variables(Model 3), the risk of death increased by 64%(HR 1.64,95%CI: 1.36–1.99, $P < 0.0001$). Regarding LAR as tertiles, the positive correlation between high LAR levels and the risk of death was highly significant, whereas the middle LAR levels was no longer significant in Model 3.

Association between LAR and 28-day mortality in subgroups

To further explore whether the association with LAR and 28-day all-cause mortality might vary under multiple conditions, we performed a subgroup analysis of gender, age, BMI, congestive heart failure, cardiac arrhythmias, diabetes, WBC and glucose(Table 3; Fig. 2). No significant interaction was observed across the subgroups.

Nonlinear relationship exploration between LAR and 28-day mortality

Smooth curve fitting analysis and GAM were performed to explore the nonlinear relationship between the LAR and 28-day all-cause mortality for critically ill patients with AMI after ICU admission. As shown in Fig. 3., a threshold, nonlinear association between the LAR and 28-day mortality was found. As shown in Table 4, one line effect showed that when LAR increases per unit or per SD, the mortality increased 1.15-fold ($P < 0.0001$) and 1.23-fold ($P < 0.0001$) respectively. In Model II, a turning point (K) of 2.15 were identified. When the LAR was < 2.15, the mortality rate increased with an adjusted OR of 3.52(95%CI: 2.14,5.81, $p < 0.0001$), and per-SD increase showed an OR of 3.72(95%CI: 2.21,6.25, $P < 0.0001$). When LAR was ≥ 2.15, the association with mortality was OR of 1.15 (95% CI: 0.65, 2.04, $P = 0.6351$) and OR 1.15 (95% CI: 0.63, 2.11, $P = 0.6458$) respectively, indicating statistical insignificance. The log-likelihood ratio was 0.020 ($P = 0.020$), indicating that the difference

Variables	Survivor	Non-survivor	*P*-value
Sample size	818	171	
Demographics			
Age (years)	67.62 ± 13.34	71.45 ± 10.66	< 0.001
BMI(kg/m^2)	28.50 ± 6.84	29.85 ± 7.36	0.023
Male(%)	371 (45.35%)	65 (38.01%)	0.079
Ethnicity			0.052
Caucasian(%)	658 (80.74%)	148 (87.06%)	
Other/Unknown(%)	157(19.26%)	22 (12.94%)	
Comorbidities			
Congestive heart failure (%)	178 (21.76%)	43 (25.15%)	0.334
Cardiac arrhythmias (%)	251 (30.68%)	74 (43.27%)	0.001
Diabetes (%)	151 (18.46%)	31 (18.13%)	0.919
Pneumonia (%)	211 (25.79%)	46 (26.90%)	0.764
Scoring systems			
Apache IV score	73.06 ± 24.65	90.34 ± 20.94	< 0.001
Vital signs			
Temperature (℃)	36.37 ± 0.74	36.24 ± 0.99	0.017
Respiratory rate (bpm)	27.53 ± 14.78	29.21 ± 14.43	0.178
Heart rate (/min)	107.89 ± 29.65	111.24 ± 35.54	0.198
MAP (mmHg)	82.65 ± 45.04	80.56 ± 50.20	0.033
Laboratory data			
Platelets (k/mcl)	204.65 ± 85.99	204.38 ± 93.71	0.971
RBC (k/mcl)	3.89 ± 0.80	3.98 ± 0.77	0.163
Hemoglobin (g/dl)	11.54 ± 2.41	11.93 ± 2.41	0.061
WBC (k/mcl)	14.73 ± 6.71	16.82 ± 7.17	< 0.001
BUN (mg/dl)	31.54 ± 18.56	35.48 ± 18.37	0.014
Creatinine (mg/dl)	1.73 ± 1.15	1.97 ± 1.06	0.015
PT (sec)	16.62 ± 5.45	18.96 ± 7.00	< 0.001
BNP (pg/ml)	2895.76 ± 4656.00	1497.80 ± 2032.44	0.270
Troponin-I (ng/mL)	9.57 ± 14.33	14.70 ± 19.16	0.002
Total cholesterol (mg/dl)	143.79 ± 45.98	125.36 ± 45.15	0.015
Triglycerides (mg/dl)	126.78 ± 78.28	112.52 ± 52.02	0.227
LDLc (mg/dl)	78.48 ± 36.75	72.55 ± 38.23	0.433
HDLc (mg/dl)	39.72 ± 15.23	33.25 ± 13.51	0.009
Glucose (mg/dl)	167.75 ± 70.41	189.11 ± 78.30	< 0.001
AST (U/L)	201.64 ± 329.25	342.26 ± 440.06	< 0.001
ALT (U/L)	99.59 ± 164.68	148.08 ± 201.78	0.001
Total protein (g/dl)	6.03 ± 0.87	5.84 ± 0.83	0.014
Albumin (g/dl)	2.89 ± 0.63	2.78 ± 0.67	0.046
Lactate (mmol/L)	2.57 ± 1.89	4.36 ± 2.83	< 0.001
LAR	0.96 ± 0.85	1.66 ± 1.16	< 0.001

Table 1. Baseline characteristics of participants. Mean ± SD for continuous variables; P-value was calculated by Kruskal-Wallis test. N(%) for categorical variables; P-value was calculated by chi-square test. *BMI* body mass index, *MAP* mean arterial pressure, *RBC* red blood cell, *WBC* white blood cell, *BUN* blood urea nitrogen, *PT* prothrombin time, *BNP* brain natriuretic peptide, *LDLc* low-density lipoprotein cholesterol, *HDLc* high-density lipoprotein cholesterol, *ALT* aspartata transminase, *AST* alanine transminase, *LAR* the ratio of lactate to albumin.

between the two models was not statistically significant. This means that adjusting for the additional covariates in Model II (gender, age, ethnicity, cardiac arrhythmias, WBC, BUN, creatinine, PT, glucose, AST and ALT) did not significantly improve the fit of the model compared to the simpler Model I.

Survival curve analysis

Kaplan-Meier survival analysis in Fig. 4. showed significant differences in 28-day survival probability among the three groups (Log rank test: $P < 0.0001$), with the high LAR group (LAR range: 1.0526–5.8235) exhibiting the lowest survival probability.

Exposures	Multivariable logistic regression			Cox proportional hazards regression		
	Model 1 OR (95%CI) *P*	Model 2 OR (95%CI) *P*	Model 3 OR (95%CI) *P*	Model 1 HR (95%CI) *P*	Model 2 HR (95%CI) *P*	Model 3 HR (95%CI) *P*
LAR	1.86 (1.59, 2.16) < 0.0001	1.87 (1.60, 2.19) < 0.0001	2.15 (1.64, 2.83) < 0.0001	1.54 (1.38, 1.72) < 0.0001	1.58 (1.41, 1.77) < 0.0001	1.64 (1.36, 1.99) < 0.0001
LAR tertiles						
Low	Reference	Reference	Reference	Reference	Reference	Reference
Middle	1.71 (1.03, 2.84) 0.0366	1.69 (1.02, 2.82) 0.0424	1.48 (0.70, 3.13) 0.3000	1.63 (1.01, 2.63) 0.0462	1.65 (1.02, 2.67) 0.0403	1.44 (0.71, 2.92) 0.3129
High	5.00 (3.16, 7.92) < 0.0001	4.92 (3.09, 7.82) < 0.0001	4.62 (2.25, 9.50) < 0.0001	3.52 (2.30, 5.39) < 0.0001	3.58 (2.34, 5.49) < 0.0001	3.16 (1.62, 6.16) 0.0007

Table 2. Multivariable logistic regression and Cox proportional hazards regression for effect of LAR. *OR*: odds ratio. *95%CI*: confidence interval. Model 1 = no covariates were adjusted. Model 2 = gender, age, ethnicity were adjusted. Model 3 = gender, age, ethnicity, cardiac arrhythmias, WBC, BUN, creatinine, PT, glucose, AST and ALT were adjusted. The range of LAR is (0.1053–0.5455) in low group, (0.5455–1.0526) in Middle group and (1.0526–5.8235) in high group.

Characteristic	*N*	OR(95%CI)	*P*-value	*P* for interaction
Stratified by gender				0.5946
Male	436	1.80 (1.15, 2.83)	0.0107	
Female	553	2.72 (1.82, 4.05)	< 0.0001	
Stratified by age (years)				0.3304
22–62	316	2.95 (1.43, 6.09)	0.0034	
63–74	333	1.95 (1.28, 2.98)	0.0019	
75–89	340	3.23 (1.63, 6.40)	0.0008	
Stratified by BMI (kg/m^2)				0.8230
13.93–25.35	320	2.25 (1.20, 4.19)	0.0109	
25.38–30.69	320	2.70 (1.45, 5.02)	0.0017	
30.71–53.82	321	2.58 (1.45, 4.59)	0.0013	
Stratified by congestive heart failure				0.3188
No	768	2.11 (1.56, 2.86)	< 0.0001	
Yes	221	3.40 (1.33, 8.70)	0.0106	
Stratified by cardiac arrhythmiacs				0.9966
No	664	2.12 (1.48, 3.04)	< 0.0001	
Yes	325	2.19 (1.36, 3.51)	0.0012	
Stratified by diabetes				0.9927
No	807	2.20 (1.63, 2.98)	< 0.0001	
Yes	182	3.20 (1.21, 8.46)	0.0191	
Stratified by WBC (k/mcl)				0.5943
0.1–11.47	315	2.41 (1.33, 4.36)	0.0036	
11.5–16.88	324	3.30 (1.69, 6.42)	0.0004	
16.9–39.3	324	1.94 (1.15, 3.26)	0.0124	
Stratified by Glucose (mg/dl)				0.2235
42–128	307	3.65 (1.80, 7.41)	0.0003	
129–185	309	2.21 (1.11, 4.42)	0.0247	
186–386	310	1.69 (1.10, 2.60)	0.0167	

Table 3. Subgroup regression analysis between LAR with 28-day all-cause mortality and interaction analysis. *OR*: odds ratio. *95%CI*: confidence interval. *BMI* body mass index, *WBC* white blood cell.

Discussion

This retrospective cohort study found a higher LAR was independent associated with a higher risk of 28-day all-cause in critically ill patients with AMI in the eICU-CRD database. Multivariate analysis indicated that each unit increase in LAR raised the 28-day mortality risk by 2.15 times. Patients in the highest LAR tertile faced a mortality risk 4.62 times greater than those in the lowest. The relationship persisted across subgroups. Nonlinear analysis showed a threshold effect; LAR below 2.15 correlated with a 3.52-fold increase in mortality per unit,

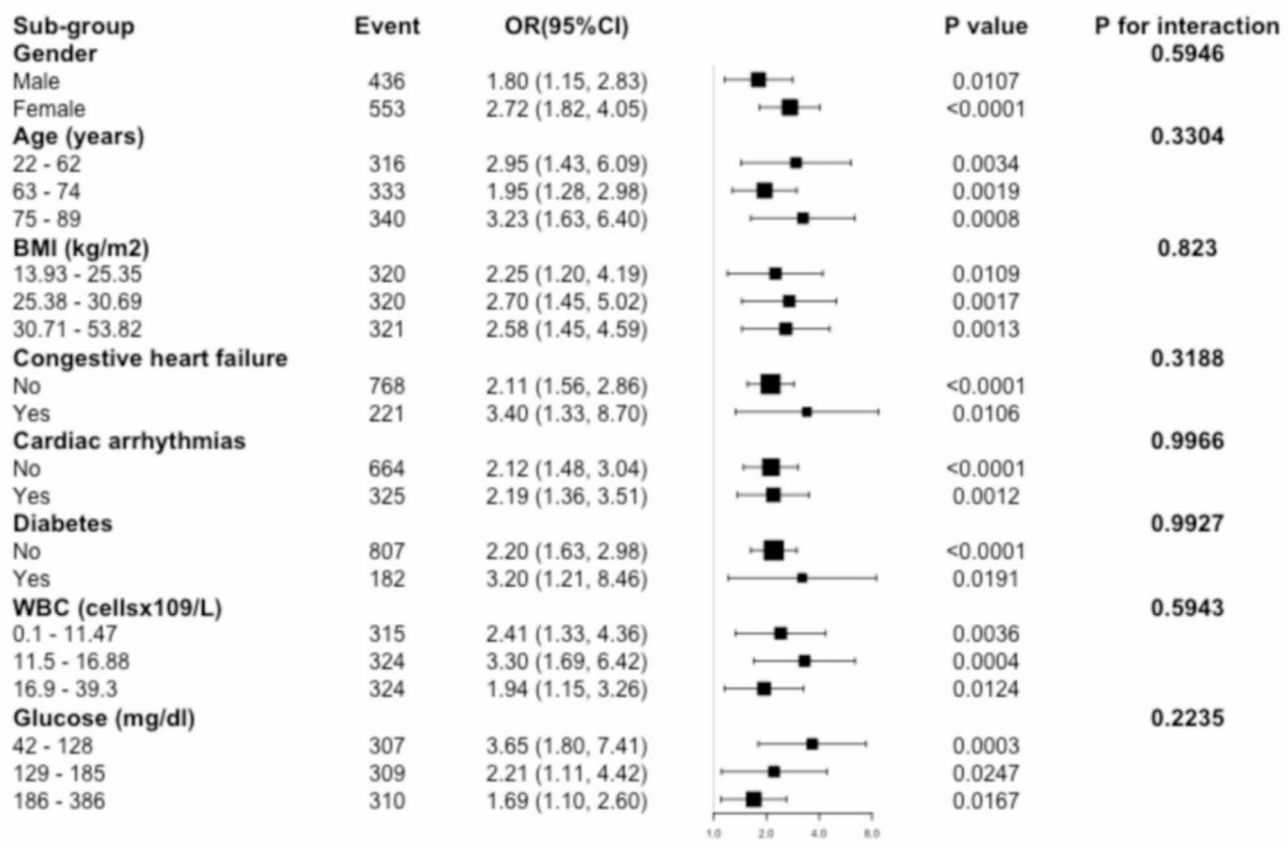

Fig. 2. Association between LAR and 28-day all-cause mortality in subgroups. Forest plot and adjusted OR(95%CI) for 28-day mortality. *OR*: Odds ratio. *95%CI*: confidence interval. *BMI* body mass index, *WBC* white blood cell.

with no significant impact above this level. Kaplan-Meier analysis confirmed lower survival probabilities for patients with higher LAR. To our knowledge, this study is the first to explore the association between LAR and 28-day all-cause mortality for critically ill patients with AMI after ICU admission.

The elevated LAR has been shown to be associated with increased mortality in critically ill patients with AMI in this study. The underlying mechanisms linking LAR to adverse outcomes in AMI patients are multifactorial and can be explained by the following pathways: (1) Elevated lactate levels reflect anaerobic metabolism due to insufficient oxygen supply to tissues, which is common in the setting of AMI. Tissue hypoperfusion and hypoxia can lead to myocardial injury, ventricular dysfunction, and ultimately, poor clinical outcomes[16]. (2) Hypoalbuminemia, a component of the elevated LAR, is a marker of systemic inflammation. Inflammatory cytokines can impair endothelial function, promote thrombosis, and exacerbate myocardial damage in AMI patients[17]. (3) The combination of increased lactate and decreased albumin indicates a state of metabolic acidosis and dysregulation of homeostasis[18]. These metabolic disturbances can further compromise cardiac function and worsen the prognosis of AMI. (4) The high LAR may reflect a state of global tissue hypoperfusion and multi-organ dysfunction, which are associated with increased mortality in AMI patients[19], especially among critically ill patients with AMI.

The LAR, which combines lactate and albumin, integrates inflammatory and nutritional factors, suggesting its significance in the association with patients outcomes. LAR has been identified as a critical predictor of mortality, emphasizing its role as a robust prognostic indicator among patients admitted to a German ICU for sepsis between 2004 and 2009[20]. Study from a single-center retrospective cohort showed that the LAR outperforms initial serum lactate in predicting in-hospital mortality among adult septic patients in terms of prognostic efficacy[10]. Previous investigators found that the LAR was positively correlated both 28-day and 1-year all-cause mortality in critically ill patients with heart failure[11]. Huang et al. found that higher LAR levels were linked to a greater risk of in-hospital mortality among atrial fibrillation patients admitted to the ICU[21]. Study by Ren et al. found that LAR exhibited a nonlinear association with in-hospital mortality among ICU patients with acute respiratory failure. Below the turning point, there was a positive correlation between LAR and in-hospital mortality, while above this point, no correlation was observed[22].

According to previous research, Wang et al. analyzed MIMIC III database and found that LAR was significantly associated with 14-day, 28-day, 90-day all-cause mortality in critically ill patients with AMI. A higher LAR would be considered an independent risk factor for higher mortality in AMI patients[23]. Study from Chen analyzed MIMIC IV database and also found that LAR was an independent predictor of increased all-cause

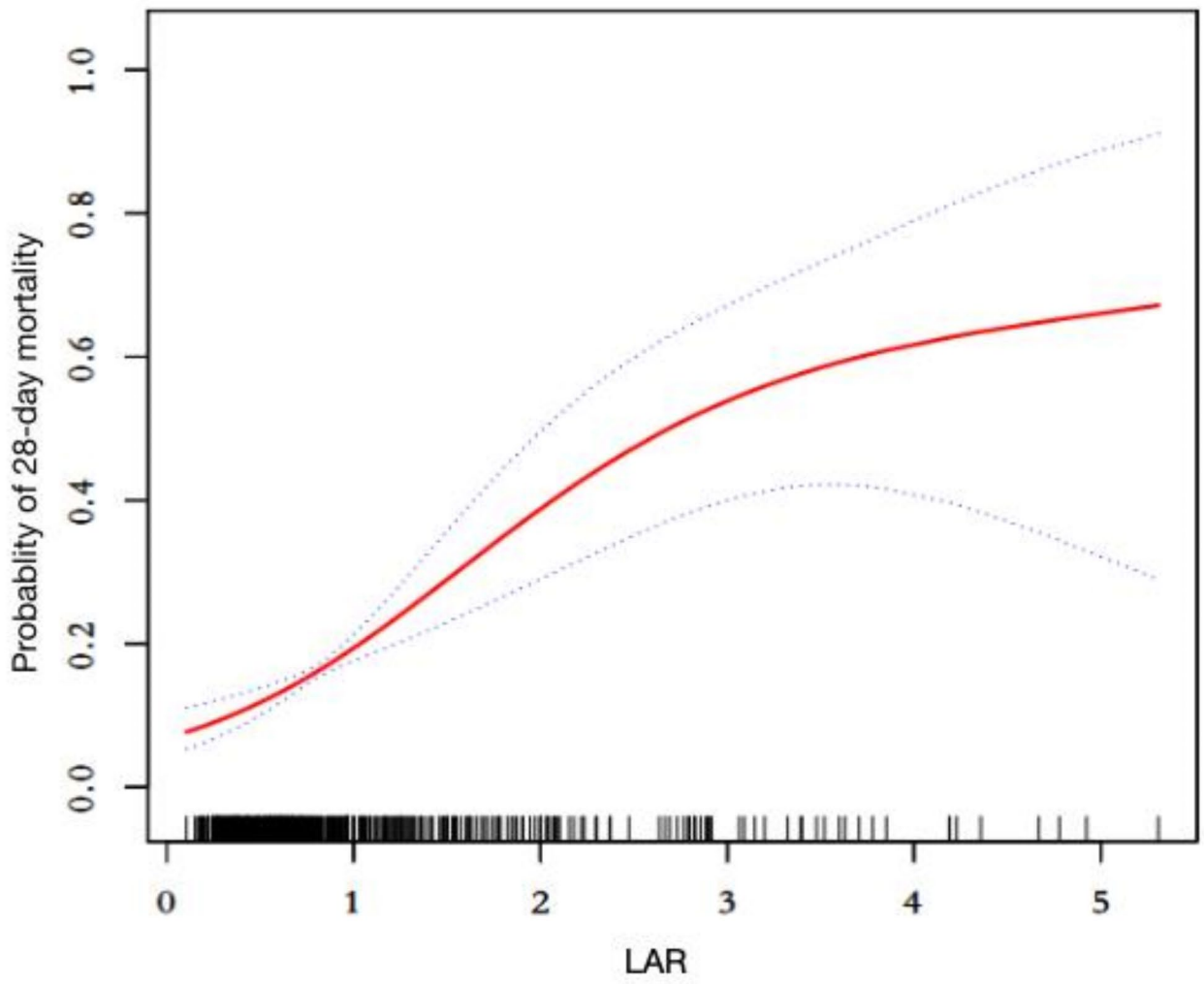

Fig. 3. The non-linear relationship between LAR and 28-day all-cause mortality. Solid red line represents the smooth curve fit between variables and blue bands represent the 95% of confidence internal from the fit. Adjusted for gender, age, ethnicity, cardiac arrhythmias, WBC, BUN, creatinine, PT, glucose, AST and ALT.

	LAR per-unit increase		LAR per-SD increase	
Models	**OR(95%CI)**	***P*-value**	**OR(95%CI)**	***P*-value**
Model I				
One line effect	2.15 (1.64, 2.83)	< 0.0001	2.23 (1.67, 2.96)	< 0.0001
Model II				
Turning point (K)	2.15		1	
LAR < K	3.52 (2.14, 5.81)	< 0.0001	3.72 (2.21, 6.25)	< 0.0001
LAR ≥ K	1.15 (0.65, 2.04)	0.6351	1.15 (0.63, 2.11)	0.6458
Log-likelihood ratio	0.020		0.020	

Table 4. Threshold effect analysis of LAR and 28-day all-cause mortality. Model I, linear analysis. Model II: non-linear asalysis. Adjusted for gender, age, ethnicity, cardiac arrhythmias, WBC, BUN, creatinine, PT, glucose, AST and ALT. *OR*: odds ratio. *95%CI*: confidence interval.

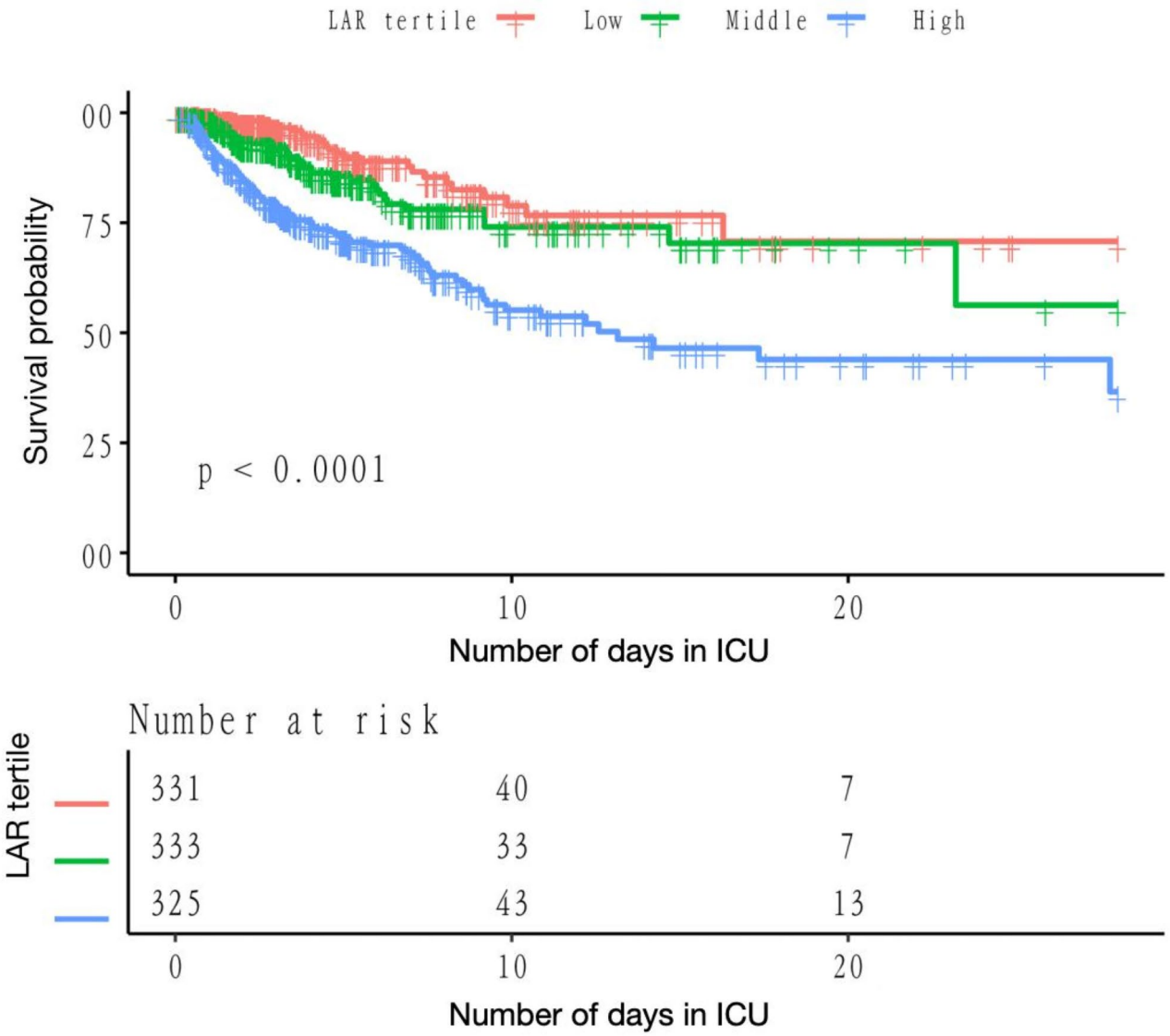

Fig. 4. Kaplan-Meier survival curve of 28-day mortality stratified by LAR. The range of LAR is (0.1053–0.5455) in Low group, (0.5455–1.0526) in Middle group and (1.0526–5.8235) in High group.

mortality in patients with AMI during hospitalization[24]. Our results were consistent with these researches which both indicated that a high LAR levels was associated with higher in-hospital mortality in critically ill patients with AMI. In addition, we also implied multivariable logistic regression model to evaluate the independent relationship between LAR and 28-day mortality after adjusting confounders. Meanwhile, we also performed GAM and smooth curve fitting analysis to explore the nonlinear relationship between the LAR and 28-day mortality, and found a turning point of LAR, which provides a more accurate evidence for clinical assessment and prognosis. Another research showed that that elevated LAR on admission was an independent predictor of high in-hospital mortality in patients with heart failure after myocardial infarction, and was superior to lactate, which show the association of LAR with AMI related clinical outcome[25]. Compared with this research, subgroup analysis performed in our study showed more stable association under multiple stratified variables.

This study has several limitations. First, as the data were derived from the eICU-CRD, which is a multi-center critical care database. The outcome of this study was 28-day all-cause mortality for critically ill patients with AMI after ICU admission, so the mortality may be different from or even higher than the mortality reported in other relevant studies[23,26–28]. Further, the findings of the present study may not be fully representative of the general AMI population who did not admitted into ICU or mortality for more than 28-day. Second, the eICU database lacks detailed information on the type and severity of myocardial infarction, which may influence the association between LAR 28-day all-cause mortality. Third, the database does not provide long-term follow-up data, limiting the assessment of the association between LAR and long-term mortality. Fourth, some potentially important clinical variables, such as the use of specific medications and the time from symptom onset to hospital admission, were not available in the database, which may have affected the analysis. Finally, as this was an

observational study, the causal relationship between LAR and mortality cannot be determined, and further mechanistic studies are warranted.

Conclusion

This study is the first time to explore an independent association between LAR with a higher risk of 28-day all-cause in critically ill patients with AMI in the eICU-CRD database.Higher LAR was associated with increased mortality risk, with the relationship consistent across subgroups. A threshold effect was observed, and Kaplan-Meier analysis confirmed lower survival probabilities for patients with higher LAR. Critically ill patients with AMI after ICU admission should be given appropriate attention about LAR throughout hospitalization.

Data availability

The raw data are fully available in the eICU Collaborative Research Database at https://eicu-crd.mit.edu/. after completing relevant registration and training.

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References

1. Falk, E., Nakano, M., Bentzon, J. F., Finn, A. V. & Virmani, R. Update on acute coronary syndromes: The pathologists' view. *Eur. Heart J.* **34** (10), 719–728. https://doi.org/10.1093/eurheartj/ehs411 (2013).
2. Roth, G. A. et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: Update from the GBD 2019 study. *J. Am. Coll. Cardiol.* **76** (25), 2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010 (2020).
3. Zhou, M. et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: A systematic analysis for the global burden of Disease Study 2017. *Lancet.* **394** (10204), 1145–1158. https://doi.org/10.1016/S0140-6736(19)30427-1 (2019).
4. Henry, T. D. et al. Council on arteriosclerosis, thrombosis and Vascular Biology; and Council on Cardiovascular and Stroke nursing. Invasive management of Acute myocardial infarction complicated by cardiogenic shock: A Scientific Statement from the American Heart Association. *Circulation.* **143** (15), e815–e829. https://doi.org/10.1161/CIR.0000000000000959 (2021).
5. Ibanez, B. et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* **39** (2), 119–177. https://doi.org/10.1093/eurheartj/ehx393 (2018).
6. Garcia-Alvarez, M., Marik, P. & Bellomo, R. Stress hyperlactataemia: Present understanding and controversy. *Lancet Diabetes Endocrinol.* **2** (4), 339–347. https://doi.org/10.1016/S2213-8587(13)70154-2 (2014).
7. Park, I. H. et al. Clinical significance of serum lactate in acute myocardial infarction: A Cardiac magnetic resonance imaging study. *J. Clin. Med.* **10** (22), 5278. https://doi.org/10.3390/jcm10225278 (2021).
8. Caironi, P., Langer, T. & Gattinoni, L. Albumin in critically ill patients: The ideal colloid? *Curr. Opin. Crit. Care.* **21** (4), 302–308. https://doi.org/10.1097/MCC.0000000000000223 (2015).
9. Arques, S. Human serum albumin in cardiovascular diseases. *Eur. J. Intern. Med.* **52**, 8–12. https://doi.org/10.1016/j.ejim.2018.04.014 (2018).
10. Bou Chebl, R. et al. Lactate/albumin ratio as a predictor of in-hospital mortality in septic patients presenting to the emergency department. *Front. Med. (Lausanne).* **7**, 550182. https://doi.org/10.3389/fmed.2020.550182 (2020).
11. Guo, W. et al. The value of lactate/albumin ratio for predicting the clinical outcomes of critically ill patients with heart failure. *Ann. Transl Med.* **9** (2), 118. https://doi.org/10.21037/atm-20-4519 (2021).
12. Pollard, T. J. et al. The eICU Collaborative Research Database, a freely available multi-center database for critical care research. *Sci. Data.* **5**, 180178. https://doi.org/10.1038/sdata.2018.178 (2018).
13. Sarkar, R. et al. Performance of intensive care unit severity scoring systems across different ethnicities in the USA: A retrospective observational study. *Lancet Digit. Health.* **3** (4), e241–e249. https://doi.org/10.1016/S2589-7500(21)00022-4 (2021).
14. Hu, C. et al. Kidney function and cardiovascular diseases: A large-scale observational and mendelian randomization study. *Front. Immunol.* **14**, 1190938. https://doi.org/10.3389/fimmu.2023.1190938 (2023).
15. Thygesen, K. et al. Fourth universal definition of myocardial infarction (2018). *J. Am. Coll. Cardiol.* **72** (18), 2231–2264. https://doi.org/10.1016/j.jacc.2018.08.1038 (2018).
16. Kraut, J. A. & Madias, N. E. Lactic acidosis. *N. Engl. J. Med.* **371** (24), 2309–2319. https://doi.org/10.1056/NEJMra1309483 (2014).
17. Soeters, P. B., Wolfe, R. R. & Shenkin, A. Hypoalbuminemia: Pathogenesis and clinical significance. *JPEN J. Parenter. Enter. Nutr.* **43** (2), 181–193. https://doi.org/10.1002/jpen.1451 (2019).
18. Adeva-Andany, M. M., Fernández-Fernández, C., Mouriño-Bayolo, D., Castro-Quintela, E. & Domínguez-Montero, A. Sodium bicarbonate therapy in patients with metabolic acidosis. *ScientificWorldJournal.* **2014**, 627673. https://doi.org/10.1155/2014/627673 (2014).
19. Laghlam, D. et al. Management of cardiogenic shock: A narrative review. *Ann. Intensive Care.* **14** (1), 45. https://doi.org/10.1186/s13613-024-01260-y (2024).
20. Lichtenauer, M. et al. The lactate/albumin ratio: A valuable tool for risk stratification in septic patients admitted to ICU. *Int. J. Mol. Sci.* **18** (9), 1893. https://doi.org/10.3390/ijms18091893 (2017).
21. Huang, T. & Lin, S. Usefulness of lactate to albumin ratio for predicting in-hospital mortality in atrial fibrillation patients admitted to the intensive care unit: A retrospective analysis from MIMIC-IV database. *BMC Anesthesiol..* **24** (1), 108. https://doi.org/10.1186/s12871-024-02470-4 (2024).
22. Ren, J., Kang, Q., Wang, F. & Yu, W. Association of lactate/albumin ratio with in-hospital mortality in ICU patients with acute respiratory failure: A retrospective analysis based on MIMIC-IV database. *Med. (Baltim).* **102** (39), e35410. https://doi.org/10.1097/MD.0000000000035410 (2023).
23. Wang, D. et al. Association between lactate/albumin ratio and all-cause mortality in critical patients with acute myocardial infarction. *Sci. Rep.* **13** (1), 15561. https://doi.org/10.1038/s41598-023-42330-8 (2023).
24. Chen, Y. et al. Association between lactate/albumin ratio and prognosis in patients with acute myocardial infarction. *Eur. J. Clin. Invest.* **54** (1), e14094. https://doi.org/10.1111/eci.14094 (2024).
25. Chen, Y. et al. Association between lactate/albumin ratio and mortality in patients with heart failure after myocardial infarction. *ESC Heart Fail.* **10** (3), 1928–1936. https://doi.org/10.1002/ehf2.14359 (2023).
26. Jian, L., Zhang, Z., Zhou, Q., Duan, X. & Ge, L. Red cell distribution width/albumin ratio: A predictor of In-Hospital all-cause mortality in patients with Acute myocardial infarction in the ICU. *Int. J. Gen. Med.* **16**, 745–756. https://doi.org/10.2147/IJGM.S393393 (2023).
27. Fang, D. & Chen, H. Association between serum calcium level and in-hospital mortality in patients with acute myocardial infarction: A retrospective cohort study. *Sci. Rep.* **12** (1), 19954. https://doi.org/10.1038/s41598-022-24566-y (2022).

28. Zhu, J. L. et al. Association of lactate to albumin ratio and bicarbonate with short-term mortality risk in patients with acute myocardial infarction. *BMC Cardiovasc. Disord.* **22** (1), 490. https://doi.org/10.1186/s12872-022-02902-4 (2022).

Author contributions

Ping Jin & Yitong Bian: Data curation, Formal analysis, Writing-original draft. Qing Cui, Xiying Liang & Yuyu Sun: Data curation. Qiangsun Zheng: Methodology, Design, Writing - review & editing. All authors approved the final version to be published and agree to take responsibility for all aspects of the work.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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