Original Article

The value of lactate/albumin ratio for predicting the clinical outcomes of critically ill patients with heart failure

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Background: Previous studies have shown that the lactate/albumin (L/A) ratio plays a role in predicting the outcomes of septic shock or severe sepsis. However, the role of the L/A ratio in predicting the outcomes of critically ill patients with heart failure remains unclear. We therefore performed a retrospective study to clarify this issue.

Methods: The study was based on the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database and included critically ill adult patients with heart failure. The primary endpoints were 28-day and 1-year all-cause mortality after admission at the intensive care unit.

Results: We analyzed 4,562 patients in this study. We divided the participants into five groups according to the L/A ratio: quintile (Q)1 (L/A ratio ≤0.40, n=913), Q2 (0.40< L/A ratio ≤0.51, n=912), Q3 (0.51< L/A ratio ≤0.66, n=912), Q4 (0.66< L/A ratio ≤0.92, n=912), and Q5 (L/A ratio >0.92, n=913). After stratifying by L/A ratio, the risk of 28-day and 1-year mortality were significantly different between the groups (log-rank P<0.001). Compared with the first quintile, the second, third, fourth, and fifth quintiles of the L/A ratio were associated with higher 28-day [hazard ratio (HR) 1.57, 95% confidence interval (CI): 1.21–2.03 for Q3, HR 1.72, 95% CI: 1.34–2.21 for Q4, and HR 3.15, 95% CI: 2.47–4.01 for Q5) and 1-year mortality (HR 1.19, 95% CI: 1.00–1.41 for Q2, HR 1.36, 95% CI: 1.15–1.60 for Q3, HR 1.42, 95% CI: 1.20–1.67 for Q4, and HR 2.46, 95% CI: 2.09–2.89 for Q5). The restricted cubic spline showed that the L/A ratio positively correlated with both 28-day and 1-year all-cause mortality.

Conclusions: The L/A ratio could serve as a predictor of short and long-term mortality in critically ill patients with heart failure.

Keywords: Lactate/albumin ratio; prognosis; heart failure

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Introduction

Heart failure is a costly disease with a poor prognosis, and there are approximately 23 million heart failure patients worldwide (1). Previous studies have shown that the 30-day and 1-year mortality rates for heart failure are 10.4% and 22%, respectively (2-4). In another study, the 3-year mortality rate was 40% in patients with New York Heart Association class IV or stage D heart failure (5).

Considering these reports, predictive biomarkers play a vital role in improving disease management in critically

ill patients with heart failure. The lactate/albumin (L/A) ratio is a biomarker with good discrimination for predicting short-term survival outcome in patients with septic shock or severe sepsis (6-8). Additionally, the study by Shin *et al.* showed that the area under the receiver operating characteristic curve (AUROC) of the L/A ratio for predicting the outcomes of severe sepsis was better than that of lactate alone (7). Other studies have assessed the usefulness of the L/A ratio as a predictor in other diseases. Kong *et al.* suggested that the L/A ratio was superior to lactate alone for predicting favorable neurologic outcomes and survival to discharge after out-of-hospital cardiac arrest (9).

However, the role of the L/A ratio in predicting outcomes in critically ill patients with heart failure remains unclear. Therefore, we performed a retrospective study to resolve this issue. We hypothesized that the L/A ratio could predict survival outcomes in critically ill patients with heart failure.

We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4519).

Methods

Data source

We performed a retrospective study based on the open-source Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III) database, which includes health data for more than 40,000 patients who were admitted to the intensive care unit (ICU) of Beth Israel Deaconess Medical Center from 2001 to 2012 (10). We used version 1.4 (most recent at the time of the study) for this research. The database contains comprehensive clinical data, including patient characteristics, laboratory outcome, medication, international classification of diseases-ninth revision (ICD-9) codes, and medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We completed the National Institutes of Health online course and passed the Examination for Protecting Human Research Participants and applied for data access (No. 29790341). The project was approved by Beth Israel Deaconess Medical Center and the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, Massachusetts, USA). The requirement for written informed consent was waived due to the retrospective study design. The identification information of the participants was hidden to protect their privacy.

Inclusion and exclusion criteria

We included critically ill adult patients with heart failure (≥18 years) at first ICU admission from the database. The exclusion criteria were as follows: (I) non-adult patients and (II) missing lactate and albumin values at ICU admission.

Primary endpoint

Survival information (including survival outcome and time of death) was obtained from the Social Security Death Index records. Our study endpoints were all-cause mortality at 28 days and 1 year after the date of ICU admission.

Covariates of interest

After applying and obtaining permission, we downloaded the database to the local database and used Structured Query Language (SQL) with PostgreSQL (version 9.6) to extract related variables, outcomes, and data. The variables included physical characteristics [including age, ethnicity, gender, height, and weight), vital signs [including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiration rate, and oxygen saturation (SPO_2)], laboratory outcomes [including white blood cells (WBC), hemoglobin, neutrophils, lymphocytes, hematocrit, platelets, alanine, aspartate, albumin, blood urea nitrogen, creatinine, creatine kinase, potassium, sodium, pH, PO_2, partial pressure of CO_2 (PCO_2), lactate, base excess (BE), glucose], left ventricular ejection fraction (LVEF), medications [including digoxin, beta blocker, angiotensin-converting-enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and diuretics], comorbidities [including peripheral vascular disease, hypertension, chronic obstructive pulmonary disease (COPD), diabetes, renal failure, atrial fibrillation, myocardial infarction, and stroke], and scores [including Glasgow Coma Scale (GCS), Simplified Acute Physiology Score (SAPS), Oxford Acute Severity of Illness (OASIS), and Sequential Organ Failure Assessment (SOFA)]. Missing values were imputed using the multiple imputation approach (11).

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as

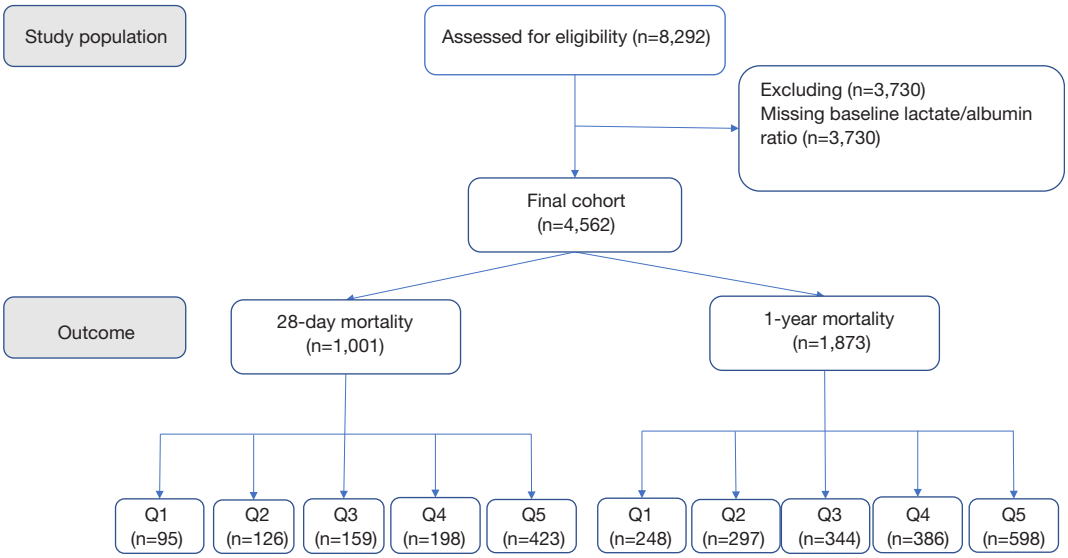

Figure 1 Study flow diagram depicting exclusion criteria and outcomes.

number (percentages). Differences in baseline variables between groups stratified by the value of the L/A ratio were ascertained using analysis of variance or Kruskal-Wallis test for continuous variables, or with the chi-squared test or Fisher's exact test for dichotomous variables. The Kaplan-Meier method was used to calculate the cumulative incidence of all-cause mortality by L/A ratio quintiles (12). Univariate and multivariate Cox proportional-hazards models were used to examine the association between the quintiles of the L/A ratio with the outcomes (with the first quintile as the reference group) (13). Variables with P≤0.1 in the univariate Cox proportional-hazards model were entered into separate multivariate models for 28-day and 1-year all-cause mortality. Variables common to both models included age, ethnicity, weight, SBP, DBP, heart rate, respiration rate, SPO_2, WBC, hematocrit, platelets, alanine, creatinine, N-terminal pro B-type natriuretic peptide (NT-proBNP), potassium, glucose, pH, LVEF, beta-blockers, ACEI, ARB, diuretics, hypertension, COPD, diabetes, stroke, GCS, SAPS, OASIS, and SOFA. The multivariate model for 28-day mortality also included creatine kinase. The multivariate model for 1-year mortality also included height, hemoglobin, lymphocytes, digoxin, and atrial fibrillation. The relationship between baseline BE values (modeled as continuous variables), and the risk of all-cause mortality was evaluated using a Cox regression model with a restricted cubic spline (14). A two-sided P value of <0.05 was considered statistically significant in all analyses. All analyses were performed using R version 3.5.2 (R Foundation for Statistical Computing, Austria, Vienna).

Results

Overall, 8,292 critically ill patients with heart failure were screened in the database. Among them, 3,730 patients had missing baseline L/A ratios. Thus, the final analysis included 4,562 participants. Altogether, 1,001 participants (22%) died at 28 days, and 1,873 participants (41%) died at 1 year after the date of ICU admission (*Figure 1*).

We divided the participants into five groups according to the L/A ratio: quintile (Q)1 (L/A ratio ≤0.40, n=913), Q2 (0.40< L/A ratio ≤0.51, n=912), Q3 (0.51< L/A ratio ≤0.66, n=912), Q4 (0.66< L/A ratio ≤0.92, n=912), and Q5 (L/A ratio >0.92, n=913). The comparison of baseline clinical characteristics between the five groups is shown in *Table 1*. Age and heart rate increased with increasing L/A ratio. The SBP, DBP, weight, and height decreased with increasing L/A ratio. Blood sample data showed that the WBC, alanine, creatinine, NT-proBNP, creatine kinase, potassium, PO_2, lactate, and glucose levels were higher, while hemoglobin, lymphocytes, hematocrit, platelet, albumin, sodium, BE, pH, and PCO_2 were lower with increasing L/A ratio. In the echocardiographic data, the LVEF decreased with increasing L/A ratio. Regarding drugs, the use of diuretics and ACEI decreased and the use of digoxin increased with increasing L/A ratio. Concerning comorbidities, the incidence of atrial fibrillation and myocardial infarction were higher, while the incidence of

Table 1 The characteristic of the population

Variables	Lactate/albumin ratio quintile					P value
	First (L/A ratio ≤0.40)	Second (0.40< L/A ratio ≤0.51)	Third (0.51< L/A ratio ≤0.66)	Fourth (0.66< L/A ratio ≤0.92)	Fifth (L/A ratio >0.92)	
Number of patients	913	912	912	912	913	–
Male, n (%)	509 (55.8)	518 (56.8)	497 (54.5)	514 (56.4)	501 (54.9)	0.846
Age	69.88 (12.77)	70.46 (12.50)	71.49 (12.34)	71.37 (12.71)	70.41 (13.20)	0.031
Ethnicity, n (%)						0.078
White	656 (71.9)	682 (74.8)	660 (72.4)	675 (74.0)	625 (68.5)	
Black	87 (9.5)	59 (6.5)	73 (8.0)	65 (7.1)	79 (8.7)	
Asian	20 (2.2)	21 (2.3)	28 (3.1)	16 (1.8)	24 (2.6)	
Hispanic	13 (1.4)	21 (2.3)	17 (1.9)	20 (2.2)	18 (2.0)	
Other	24 (2.6)	16 (1.8)	15 (1.6)	14 (1.5)	12 (1.3)	
Height (cm), mean (SD)	168.83 (10.69)	168.68 (10.26)	168.40 (10.44)	168.49 (10.77)	167.24 (11.04)	0.012
Weight (kg), mean (SD)	86.12 (28.28)	83.27 (25.75)	81.65 (23.57)	80.36 (23.82)	80.10 (22.67)	<0.001
Heart rate, mean (SD)	83.01 (14.44)	85.08 (14.87)	86.51 (15.85)	89.02 (15.49)	90.97 (17.00)	<0.001
SBP (mmHg), mean (SD)	120.31 (17.54)	116.89 (16.40)	115.71 (16.01)	114.41 (16.18)	110.47 (15.97)	<0.001
DBP (mmHg), mean (SD)	58.81 (10.49)	58.35 (10.31)	57.52 (9.79)	57.83 (10.34)	56.85 (10.21)	0.001
Respiration rate (beats/min), mean (SD)	19.09 (3.76)	19.30 (3.96)	19.88 (4.32)	20.04 (4.38)	20.15 (4.58)	<0.001
SPO_2 (%), mean (SD)	96.89 (1.94)	97.08 (2.10)	97.11 (2.07)	97.14 (2.01)	96.56 (4.18)	<0.001
WBC (K/μL), mean (SD)	10.31 (4.81)	11.14 (4.36)	11.43 (4.88)	12.38 (6.19)	13.59 (9.94)	<0.001
Hemoglobin (g/dL), mean (SD)	10.46 (1.50)	10.32 (1.31)	10.35 (1.26)	10.30 (1.30)	10.37 (1.32)	0.124
Lymphocyte (%), mean (SD)	19.15 (61.39)	15.27 (26.24)	13.75 (24.30)	13.85 (22.37)	17.44 (52.38)	0.016
Hematocrit (%), mean (SD)	31.42 (4.39)	30.93 (3.79)	31.03 (3.75)	30.88 (3.78)	31.13 (3.98)	0.031
PLT (K/uL), mean (SD)	244.32 (101.91)	242.51 (103.34)	238.33 (105.24)	229.53 (104.81)	199.45 (101.90)	<0.001
Albumin (g/dL), mean (SD)	3.44 (0.51)	3.26 (0.54)	3.12 (0.55)	2.95 (0.57)	2.72 (0.58)	<0.001
Alanine (IU/L), mean (SD)	39.12 (90.25)	49.77 (110.66)	67.27 (199.08)	94.89 (347.97)	209.74 (502.18)	<0.001
Creatinine (mg/dl), mean (SD)	1.72 (1.68)	1.65 (1.49)	1.59 (1.36)	1.71 (1.38)	1.88 (1.46)	0.001
NT-proBNP (pg/mL), mean (SD)	10,080.35 (13,012.94)	10,486.02 (12,691.18)	10,775.59 (12,760.69)	12,567.41 (13,557.44)	12,507.56 (14,478.59)	<0.001
CK (IU/L), mean (SD)	288.07 (711.03)	271.18 (566.75)	299.90 (633.58)	290.44 (556.89)	531.81 (1105.35)	<0.001
Sodium (mmol/L), mean (SD)	138.85 (3.63)	138.53 (3.63)	138.63 (3.56)	138.53 (3.71)	138.28 (4.06)	0.027
Potassium (mmol/L), mean (SD)	4.17 (0.39)	4.17 (0.37)	4.15 (0.37)	4.14 (0.36)	4.22 (0.46)	<0.001
BE (mEq/L), mean (SD)	1.25 (4.78)	0.52 (3.89)	0.33 (3.73)	−0.22 (4.20)	−2.43 (4.83)	<0.001
pH, mean (SD)	7.38 (0.06)	7.39 (0.05)	7.39 (0.05)	7.39 (0.05)	7.36 (0.08)	<0.001
PO_2 (mmHg), mean (SD)	100.47 (26.38)	104.36 (25.82)	102.38 (26.09)	104.29 (25.62)	102.22 (25.98)	0.007
PCO_2 (mmHg), mean (SD)	45.56 (11.80)	42.33 (8.50)	41.51 (7.70)	40.87 (8.37)	39.66 (8.57)	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Lactate/albumin ratio quintile					P value
	First (L/A ratio ≤0.40)	Second (0.40< L/A ratio ≤0.51)	Third (0.51< L/A ratio ≤0.66)	Fourth (0.66< L/A ratio ≤0.92)	Fifth (L/A ratio >0.92)	
Lactate (mmol/L), mean (SD)	1.09 (0.24)	1.48 (0.26)	1.82 (0.34)	2.27 (0.49)	4.29 (2.39)	<0.001
Glucose (mg/dL), mean (SD)	128.57 (30.03)	130.04 (27.77)	134.18 (31.57)	134.89 (31.70)	142.87 (43.87)	<0.001
LVEF, n (%)						0.003
<10%	156 (17.1)	127 (13.9)	137 (15.0)	121 (13.3)	113 (12.4)	
10–35%	62 (6.8)	61 (6.7)	69 (7.6)	79 (8.7)	95 (10.4)	
35–55%	299 (32.7)	346 (37.9)	342 (37.5)	334 (36.6)	354 (38.8)	
55–70%	317 (34.7)	306 (33.6)	278 (30.5)	297 (32.6)	257 (28.1)	
>70%	79 (8.7)	72 (7.9)	86 (9.4)	81 (8.9)	94 (10.3)	
ACEI, n (%)	301 (33.0)	257 (28.2)	264 (28.9)	239 (26.2)	192 (21.0)	<0.001
ARB, n (%)	24 (2.6)	19 (2.1)	17 (1.9)	11 (1.2)	10 (1.1)	0.076
Digoxin, n (%)	74 (8.1)	85 (9.3)	107 (11.7)	102 (11.2)	108 (11.8)	0.031
Beta blocker, n (%)	402 (44.0)	444 (48.7)	420 (46.1)	439 (48.1)	408 (44.7)	0.185
Diuretic, n (%)	721 (79.0)	717 (78.6)	728 (79.8)	701 (76.9)	643 (70.4)	<0.001
Peripheral vascular disease, n (%)	122 (13.4)	147 (16.1)	153 (16.8)	153 (16.8)	149 (16.3)	0.231
Hypertension, n (%)	612 (67.0)	590 (64.7)	542 (59.4)	533 (58.4)	423 (46.3)	<0.001
COPD, n (%)	163 (17.9)	137 (15.0)	123 (13.5)	117 (12.8)	118 (12.9)	0.011
Diabetes, n (%)	369 (40.4)	342 (37.5)	360 (39.5)	326 (35.7)	315 (34.5)	0.049
Renal impairment, n (%)	276 (30.2)	218 (23.9)	221 (24.2)	241 (26.4)	198 (21.7)	<0.001
AF, n (%)	407 (44.6)	443 (48.6)	455 (49.9)	466 (51.1)	398 (43.6)	0.003
MI, n (%)	171 (18.7)	210 (23.0)	214 (23.5)	208 (22.8)	248 (27.2)	0.001
Stroke, n (%)	35 (3.8)	31 (3.4)	29 (3.2)	29 (3.2)	36 (3.9)	0.843
GCS, mean (SD)	13.75 (2.59)	13.65 (2.81)	13.77 (2.65)	13.82 (2.61)	13.35 (3.30)	0.002
OASIS, mean (SD)	32.87 (8.52)	33.99 (8.41)	34.62 (8.38)	35.73 (8.72)	38.28 (9.78)	<0.001
SAPS, mean (SD)	19.14 (4.51)	19.92 (4.73)	20.04 (4.68)	20.77 (4.74)	22.87 (5.90)	<0.001
SOFA, mean (SD)	4.71 (2.56)	5.09 (2.83)	5.18 (2.88)	5.80 (3.20)	7.40 (3.81)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; CK, creatine kinase ; CK-MB, creatine kinase-MB; BE, base excess; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; AF, atrial fibrillation; GCS, Glasgow Coma Scale; OASIS, Oxford Acute Severity of Illness; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; L/A, lactate/albumin; SD, standard deviation.

hypertension, COPD, diabetes, and renal impairment were lower with increasing L/A ratio. In the scores data, the GCS, SAPS, OASIS, and SOFA scores were higher with increasing L/A ratio.

The 28-day mortality

The Kaplan-Meier curve showed that the time-event curves of the five groups of patients were significantly different over time (*Figure 2*). The log-rank test showed a statistically significant difference in 28-day mortality between the five groups (P<0.001). *Table 2* shows the results of the Cox proportional-hazards model. In the unadjusted Cox model, the patients in the second, third, fourth, and fifth L/A ratio quintile had higher 28-day mortality than those in the first quintile [hazard ratio (HR) 1.36, 95% confidence interval (CI): 1.04–1.77 for Q2, HR 1.73, 95% CI: 1.34–2.23 for Q3, HR 2.23, 95% CI: 1.75–2.85 for Q4, and HR 5.96, 95% CI: 4.77–7.44 for Q5]. After adjustment for the confounding factors, the risk of 28-day mortality was significantly higher in the third, fourth, and fifth quintiles than in the first quintile (HR 1.57, 95% CI: 1.21–2.03 for Q3, HR 1.72, 95% CI: 1.34–2.21 for Q4, and HR 3.15, 95% CI: 2.47–4.01 for Q5). The Cox regression model with a restricted cubic spline showed a linear relationship between L/A ratio and the risk of 28-day mortality in the patients (*Figure 3*). We divided the participants into five groups according to the lactate level: Q1 (lactate ≤1.27 mmol/L, n=924), Q2 (1.27 mmol/L < lactate ≤1.6 mmol/L, n=960), Q3 (1.6 mmol/L < lactate ≤2.0 mmol/L, n=852), Q4 (2.0 mmol/L < lactate ≤2.7 mmol/L, n=917), and Q5 (lactate >2.7 mmol/L, n=909). The Kaplan-Meier curve showed that the time-event curves of the five groups of patients were significantly different over time (log-rank P<0.001) (Figure S1). The Cox regression model with a restricted cubic spline showed a positive linear relationship between lactate and the risk of 28-day mortality (Figure S2). We divided the participants into five groups according to the albumin level: Q1 (albumin ≤2.57 g/dL, n=918), Q2 (2.57 < albumin ≤2.93 g/dL, n=902), Q3 (2.93 < albumin ≤3.27 g/dL, n=930), Q4 (3.27 < albumin ≤3.6 g/dL, n=930), and Q5 (albumin >3.6 g/dL, n=882). The Kaplan-Meier curve showed that the time-event curves of the five groups of patients were significantly different over time (log-rank P<0.001) (Figure S3). The Cox regression model with a restricted cubic spline showed a negative linear relationship between albumin and the risk of 28-day mortality (Figure S4).

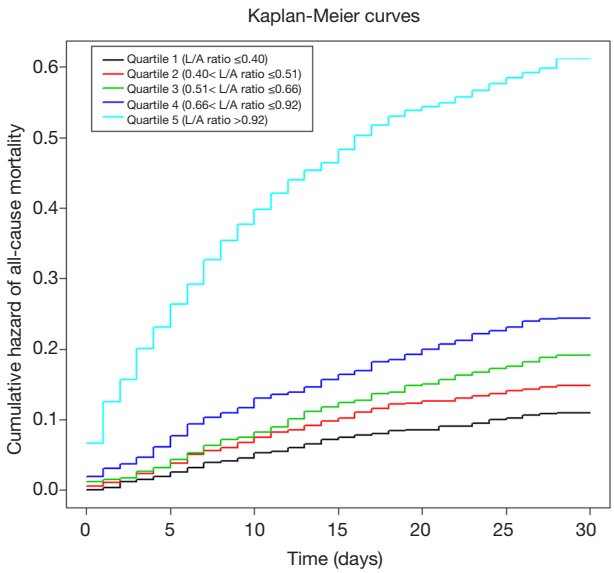

Figure 2 Kaplan-Meier plot showing the cumulative incidence of 28-day all-cause mortality by lactate/albumin (L/A) ratio quintiles among critically ill patients with heart failure.

Table 2 Hazard ratio (95% confidence interval) of 28-day all-cause mortality according to quartiles of lactate/albumin ratio score

Variable	L/A ratio quintile				
	First (L/A ratio ≤0.40)	Second (0.40< L/A ratio ≤0.51)	Third (0.51< L/A ratio ≤0.66)	Fourth (0.66< L/A ratio ≤0.92)	Fifth (L/A ratio >0.92)
N	913	912	912	912	913
Events	95	126	159	198	423
Model 1 (HR and 95% CI)	Reference	1.36 (1.04–1.77)	1.73 (1.34–2.23)	2.23 (1.75–2.85)	5.96 (4.77–7.44)
Model 2 (HR and 95% CI)	Reference	1.30 (0.99–1.70)	1.57 (1.21–2.03)	1.72 (1.34–2.21)	3.15 (2.47–4.01)

Model 1: univariable analysis; Model 2: multivariable analysis. L/A, lactate/albumin; HR, hazard ratio; CI, confidence interval.

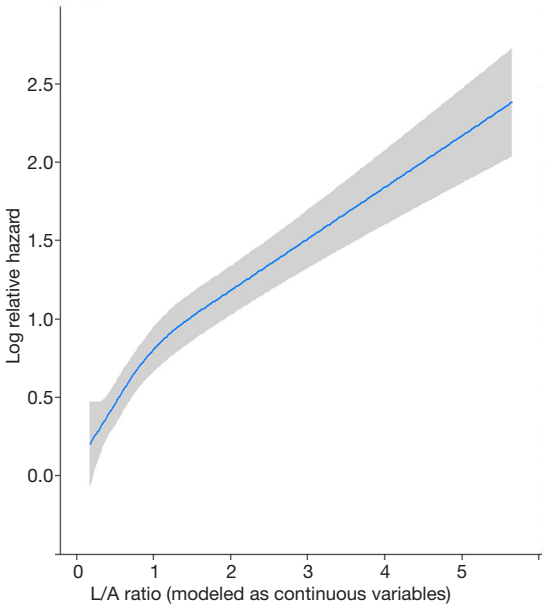

Figure 3 Lactate/albumin (L/A) ratio was modeled as a continuous variable and fitted in an adjusted Cox proportional hazard model using restricted quadratic spline regression for 28-day all-cause mortality.

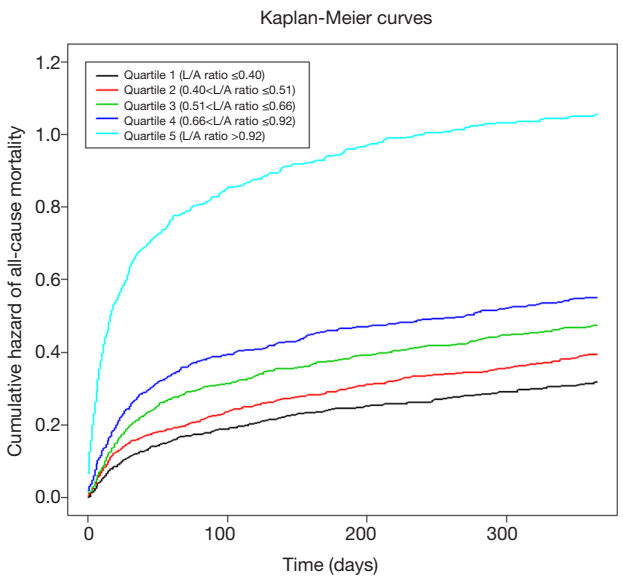

Figure 4 Kaplan-Meier plot showing the cumulative incidence of 1-year all-cause mortality by lactate/albumin (L/A) ratio quintiles among critically ill patients with heart failure.

The 1-year mortality

The Kaplan-Meier curve showed that the time-event curves of the five groups of patients were significantly different over time (*Figure 4*). The log-rank test showed a statistically significant difference in 1-year mortality between the five groups (P<0.001). *Table 3* shows the results of the Cox proportional-hazards model. In the unadjusted Cox model, patients in the second, third, fourth, and fifth quintiles of L/A ratio had a higher 1-year mortality than those in the first quintiles (HR 1.24, 95% CI: 1.05–1.47 for Q2, HR 1.50, 95% CI: 1.28–1.77 for Q3, HR 1.78, 95% CI: 1.52–2.08 for Q4, and HR 3.82, 95% CI: 3.29–4.43 for Q5). After adjustment for the confounding factors, the risk of 1–year mortality remained significantly higher in the second, third, fourth, and fifth quintiles than in the first quintile (HR 1.19, 95% CI: 1.00–1.41 for Q2, HR 1.36, 95% CI: 1.15–1.60 for Q3, HR 1.42, 95% CI: 1.20–1.67 for Q4, and HR 2.46, 95% CI: 2.09–2.89 for Q5). The Cox regression model with a restricted cubic spline showed a linear relationship between the L/A ratio and the risk of 1-year mortality in critically ill patients with heart failure (*Figure 5*). The Kaplan-Meier curve showed that the time-event curves of the five groups of lactate level were significantly different over time (log-rank P<0.001) (Figure S5). The Cox regression model with a restricted cubic spline showed a positive linear relationship between lactate and the risk of 1-year mortality (Figure S6). The time-event curves of the five groups of albumin level were significantly different over time (log-rank P<0.001) (Figure S7). The Cox regression model with a restricted cubic spline showed a negative linear relationship between albumin and the risk of 1-year mortality (Figure S8).

Discussion

In this study, we used the open-source MIMIC-III database to evaluate the role of the L/A ratio in predicting the outcomes of critically ill patients with heart failure. The results showed a linear relationship between the L/A ratio and the risk of short-term and long-term all-cause mortality in critically ill patients with heart failure. Notably, the higher the L/A ratio, the higher the risk of short-term and long-term mortality.

Critically ill patients with heart failure have a poor prognosis and are associated with a high economic burden. Therefore, predicting the outcomes of these patients can help clinicians make relevant clinical decisions. Previous

Table 3 Hazard ratio (95% confidence interval) of 1-year all-cause mortality according to quartiles of lactate/albumin ratio score

Variable	L/A ratio quintile				
	First (L/A ratio ≤0.40)	Second (0.40< L/A ratio ≤0.51)	Third (0.51< L/A ratio ≤0.66)	Fourth (0.66< L/A ratio ≤0.92)	Fifth (L/A ratio >0.92)
N	913	912	912	912	913
Events	248	297	344	386	598
Model 1 (HR and 95% CI)	Reference	1.24 (1.05–1.47)	1.50 (1.28–1.77)	1.78 (1.52–2.08)	3.82 (3.29–4.43)
Model 2 (HR and 95% CI)	Reference	1.19 (1.00–1.41)	1.36 (1.15–1.60)	1.42 (1.20–1.67)	2.46 (2.09–2.89)

Model 1: univariable analysis; Model 2: multivariable analysis. L/A, lactate/albumin; HR, hazard ratio; CI, confidence interval.

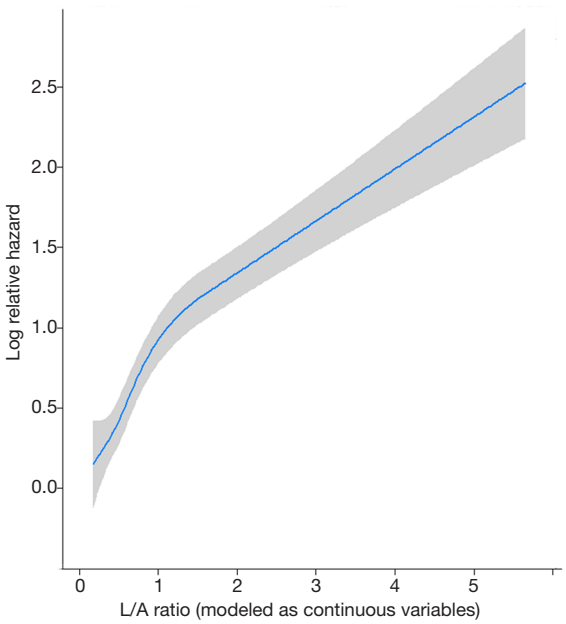

Figure 5 Lactate/albumin (L/A) ratio was modeled as a continuous variable and fitted in an adjusted Cox proportional hazard model using restricted quadratic spline regression for 1-year all-cause mortality.

studies showed that lactate could predict the survival outcome in patients with acute heart failure (15-17). However, lactate levels are also affected by other factors; for instance, liver or kidney dysfunction may lead to abnormal lactate due to clearance disorders. Shin *et al.* evaluated the value of the L/A ratio in predicting the outcomes of patients with severe sepsis (7). The results showed that the AUROC of the L/A ratio was higher than that for lactate alone. Further, in patients with lactate clearance disorder, the AUROC of the L/A ratio was still higher than that of lactate. Therefore, the L/A ratio reflects the reverse changes caused by two different mechanisms and is thus more accurate in predicting the outcome in critically ill patients with heart failure. Normal or moderate levels of lactate are considered a sign of a good prognosis. However, at the same lactate level, using the L/A ratio can further identify high-risk patients (7). The L/A ratio also plays a role in predicting the outcomes of other serious diseases. Wang *et al.* included 54 patients with severe sepsis or septic shock and evaluated the predictive role of the L/A ratio regarding the risk of multiple organ dysfunction syndromes (MODS) and mortality (8). The results showed that the L/A ratio correlated with the risk of MODS and death. Another study by Lichtenauer *et al.* showed that the L/A ratio contributes to the risk stratification for patients with sepsis (6). Therefore, monitoring the L/A ratio may help to manage critically ill patients with heart failure better in clinical practice.

The linear correlation between the L/A ratio and the risk of all-cause death in critically ill patients with heart failure is explained as follows. Poor heart function or long-term and large-scale use of diuretics in critically ill patients with heart failure results in insufficient tissue perfusion and anaerobic metabolism, which increases the level of lactate (18,19). Evidence shows that elevated lactate level is associated with an increased risk of in-hospital mortality in patients with acute decompensation heart failure (17). Lactate level is a marker of hypoperfusion and hypoxia in patients with acute heart failure. Increased lactate levels are associated with hemodynamic instability in patients with acute heart failure. Patients with severe heart failure had chronic consumption or liver congestion, which results in hypoalbuminemia. Previous studies showed that 14% of patients with acute heart failure had hypoalbuminemia, and patients with hypoalbuminemia had a poor prognosis (20,21). In our study, a positive linear relationship was observed between

lactate and the risk of short-term and long-term mortality, and a negative linear relationship was observed between albumin and the risk of short-term and long-term mortality. Therefore, a high L/A ratio reflects increased levels of lactate and hypoalbuminemia, which increase the risk of all-cause mortality in patients with severe heart failure. In future, it will be necessary to ascertain whether the L/A ratio is better than lactate or albumin alone for predicting the outcomes of patients with severe heart failure.

Limitations of the study

First, this study was based on the MIMIC-III database, and there were difficulties in extracting textual information from this database. Therefore, we could not fully extract the patients' cardiac color Doppler ultrasound data, such as the left ventricular end-diastolic diameter and atrial diameter. However, we extracted LVEF as a substitute for cardiac color Doppler ultrasound data, which can also reflect the patient's cardiac function. Second, this study investigated the relationship between the patients' baseline lactate level and prognosis; therefore, it was impossible to assess the impact of the dynamic change of this ratio on the prognosis. Third, the proportion of blacks and whites was high in this study, and there were fewer Asians. Therefore, applying the results of this study to Asian populations requires caution.

Conclusions

The L/A ratio positively correlated with short-term and long-term mortality in critically ill patients with heart failure. The higher the L/A ratio, the higher the short-term and long-term risk of death in these patients. Our findings suggest that the L/A ratio could serve as a predictor of short-term and long-term mortality in critically ill patients with heart failure.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4519

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4519). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We completed the National Institutes of Health online course and passed the Examination for Protecting Human Research Participants and applied for data access (NO. 29790341). The project was approved by Beth Israel Deaconess Medical Center and the Institutional Review Board of the Massachusetts Institute of Technology (Cambridge, Massachusetts, USA). The requirement for written informed consent was waived due to the retrospective study design. The identification information of the participants was hidden to protect their privacy.

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