



Prognostic implication of lactic dehydrogenase-to-albumin ratio in critically ill patients with acute kidney injury

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Abstract

Background No studies have been published on the correlation between lactic dehydrogenase-to-albumin ratio (LAR) and poor prognosis of acute kidney injury (AKI) patients, warranting further research. This analysis sought to investigate the prognostic implication of LAR in critically ill patients with AKI.

Methods The present study enrolled 11,046 and 5180 adults with AKI from the Medical Information Mart for Intensive Care III (MIMIC III) and MIMIC IV, respectively. Data from MIMIC IV were identified as the training cohort, and those from MIMIC III were identified as the validation cohort. We applied multivariate regression analysis to identify the link between LAR and all-cause mortality. Restricted cubic spline (RCS) was conducted to figure out the correlation between LAR and in-hospital mortality. Furthermore, we carried out stratification analyses to examine if the effects of LAR on in-hospital mortality were consistent across various subclasses.

Results The level of LAR was remarkably higher in the in-hospital non-survivor group ($p < 0.001$). Furthermore, the increased LAR group presented a remarkably higher rate of in-hospital mortality at AKI stages 1, 2, and 3 compared with the decreased LAR group (all $p < 0.001$). Multivariate regression analyses exhibited the independent prognostic significance of LAR for all-cause mortality (all $p < 0.001$). MIMIC III observed concordant results. RCS indicated a non-linear correlation between LAR and in-hospital death (P for non-linearity < 0.001). The relationship between LAR and in-hospital mortality was still significant in patients with various subclasses.

Conclusions Elevated LAR at admission is a prognostic risk factor for critically ill patients with AKI.

Keywords Lactic dehydrogenase · Albumin · Acute kidney injury · Mortality · Intensive care unit

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Introduction

Acute kidney injury (AKI) is a prevalent comorbidity in intensive care unit (ICU) patients, with an incidence of up to 50%, correlated with prolonged hospital stays, increased mortality, and excess healthcare costs [1, 2]. Thus, identifying high-risk AKI individuals is essential for timely and effective interventions to improve patient outcomes. In recent years, new AKI prognostic predictors have been documented [3–5]. Unfortunately, applying these biomarkers in clinical practice still faces significant limitations.

Lactate dehydrogenase (LDH) is a key enzyme of glycolysis that has associated with worse outcomes in patients with severe acute diseases, including sepsis [6], severe acute pancreatitis [7], and severe COVID-19 [8]. Besides, studies have revealed an association between LDH and the progression of diabetic kidney disease [9], and mortality in incident

hemodialysis patients [10]. Serum albumin, a commonly used marker of nutritional status, has been demonstrated to be correlated with the development of AKI and death after AKI [11, 12]. An increasing body of evidence suggests that the LDH-to-serum albumin ratio (LAR), the combination of them, is strongly related to poor outcomes in patients with cancer [13, 14] and infectious diseases [15, 16]. Nevertheless, no studies have hitherto assessed the relationship between LAR and AKI patient mortality. Accordingly, this paper sought to examine the relationship between LAR upon admission and AKI patient mortality in the ICU using data from two public databases.

Materials and methods

Study design

Data were collected from two large open critical care databases, the Medical Information Mart for Intensive Care III (MIMIC III) and MIMIC IV. MIMIC IV, which includes ICU patients treated at Beth Israel Deaconess Medical Center from 2008 to 2019, was employed to examine the relationship between LAR at admission and mortality in ICU patients with AKI [17]. MIMIC III, which contains data from 2001 to 2012, was carried out to validate the results [17]. The authors were entitled to extract data from the two databases after completion of the course "Protecting Human Research Participants".

Population selection criteria

This analysis enrolled adult patients (18 years or older) diagnosed with AKI. We excluded patients with missing data for serum albumin or LDH, multiple ICU admissions, having stayed in the ICU less than 2 days, and duplicated records in both databases. In the case of multiple ICU admissions, only the first admission was selected.

Data extraction and definitions

Variables extracted contained demographic data (age and sex), vital signs (heart rate and blood pressure), comorbidities (heart failure, liver cirrhosis, malignancy, sepsis, etc.), laboratory parameter [white blood cell (WBC), hemoglobin, etc.], scoring systems [simplified acute physiology score (SAPS) II, sequential organ failure assessment (SOFA)], and intervention measures [continuous renal replacement therapy (CRRT), vasopressors, and mechanical ventilation]. The laboratory indicators were taken from the first measurement recorded after admission. AKI was defined and staged according to the "Kidney Disease Improving Global Outcomes" criteria [18]. The LAR was calculated by initial

serum LDH (U/L) /serum albumin (g/L). The in-hospital mortality was the primary outcome, while ICU mortality, 30-day, 90-day, and 365-day all-cause mortality from the date of admission were regarded as secondary outcomes.

Statistical analysis

Continuous variables were summarized as medians with an interquartile range, and differences were examined using the Mann–Whitney *U* test, since the variables exhibited a skewed distribution. Categorical data were described as frequencies with proportions, and the differences between groups were identified by the Chi-square test. We generated a receiver-operating characteristic (ROC) curve to identify the optimal cut-off point of LAR for predicting in-hospital mortality. The cut-off value was used to split patients into two groups. 365-Day cumulative survival between the two groups was compared by the Kaplan–Meier (KM) curve with the log-rank test. We employed multivariate logistic and Cox proportional hazards regression analysis to identify the link between LAR and all-cause mortality. LAR was examined as both a continuous and a categorical variable. Factors related to in-hospital death during univariate analyses in the MIMIC IV database were applied to establish a multivariable regression model. These covariates included age, systolic blood pressure, heart rate, hypertension, coronary heart disease, chronic kidney disease, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, sodium, potassium, anion gap, bicarbonate, SAPS II, SOFA score, CRRT, vasopressors, and ventilation. A restricted cubic spline with three knots was established to figure out the correlation between LAR and in-hospital mortality. Further analysis was conducted after stratification according to AKI stages, age, gender, comorbidities, and intervention measures. We performed all statistical analysis by R software (version 3.6.3). A *P* value < 0.05 was statistically significant.

Results

Basic characteristics

After screening patients based on the inclusion and exclusion criteria, 5180 and 11,046 patients were included from the MIMIC III and MIMIC IV databases, respectively (Supplementary Fig. 1). A comparison of the characteristics of patients from the two databases at baseline is presented in Supplement Table 1. The two databases were heterogeneous to some extent. The patient characteristics in the survival and mortality groups are presented in Table 1. Overall, LDH and LAR levels were remarkably higher in the in-hospital

Table 1 Baseline clinical characteristics of patients based on in-hospital mortality

Variables	MIMIC IV				MIMIC III			
	Total N=11,046	Survivors N=8894	Non-survivors N=2152	P	Total N=5180	Survivors N=4077	Non-survivors N=1103	P
Age, years	66.0 (55.0, 77.0)	66.0 (54.0, 76.0)	68.0 (57.0, 79.0)	<0.001	67.5 (54.2, 78.1)	66.3 (53.5, 77.3)	71.0 (57.0, 80.8)	<0.001
Male, n (%)	6382 (57.8%)	5157 (58.0%)	1225 (56.9%)	0.385	2927 (56.5%)	2307 (56.6%)	620 (56.2%)	0.850
SBP, mmHg	135 (110, 160)	136 (110, 160)	133 (108, 160)	0.047	120 (104, 138)	120 (105, 138)	116 (100, 137)	<0.001
DBP, mmHg	78.0 (60.0, 90.0)	78.0 (60.0, 90.0)	77.0 (60.0, 90.0)	0.230	61.0 (51.0, 72.0)	61.0 (51.0, 72.0)	59.0 (48.0, 69.0)	<0.001
Heart rate, bpm	89.0 (73.0, 110)	88.0 (72.0, 109)	93.0 (76.0, 113)	<0.001	90.0 (78.0, 105)	89.0 (77.0, 104)	93.0 (79.0, 110)	<0.001
Hypertension, n (%)	4409 (39.9%)	3631 (40.8%)	778 (36.2%)	<0.001	1926 (37.2%)	1604 (39.3%)	322 (29.2%)	<0.001
Diabetes, n (%)	3332 (30.2%)	2714 (30.5%)	618 (28.7%)	0.109	1383 (26.7%)	1134 (27.8%)	249 (22.6%)	<0.001
CHD, n (%)	3431 (31.1%)	2875 (32.3%)	556 (25.8%)	<0.001	1312 (25.3%)	1158 (28.4%)	154 (14.0%)	<0.001
Heart failure, n (%)	3776 (34.2%)	3026 (34.0%)	750 (34.9%)	0.483	2041 (39.4%)	1554 (38.1%)	487 (44.2%)	<0.001
CKD, n (%)	2680 (24.3%)	2120 (23.8%)	560 (26.0%)	0.036	699 (13.5%)	554 (13.6%)	145 (13.1%)	0.740
Liver cirrhosis, n (%)	1300 (11.8%)	905 (10.2%)	395 (18.4%)	<0.001	466 (9.0%)	312 (7.7%)	154 (14.0%)	<0.001
Malignancy, n (%)	2713 (24.6%)	2050 (23.0%)	663 (30.8%)	<0.001	937 (18.1%)	679 (16.7%)	258 (23.4%)	<0.001
Sepsis, n (%)	3131 (28.3%)	2079 (23.4%)	1052 (48.9%)	<0.001	901 (17.4%)	554 (13.6%)	347 (31.5%)	<0.001
WBC, k/ul	10.4 (7.3, 15.1)	10.1 (7.20, 14.6)	11.7 (7.9, 17.1)	<0.001	10.6 (7.4, 15.4)	10.3 (7.3, 15.0)	11.7 (7.8, 17.2)	<0.001
Hemoglobin, g/dl	11.4 (9.7, 13.2)	11.6 (9.80, 13.3)	10.9 (9.3, 12.7)	<0.001	11.8 (10.3, 13.3)	11.9 (10.4, 13.4)	11.2 (10.0, 12.9)	<0.001
BUN, mg/dl	22.0 (15.0, 38.0)	21.0 (15.0, 36.0)	27.0 (17.0, 46.0)	<0.001	23.0 (15.0, 38.0)	22.0 (15.0, 35.0)	29.0 (18.0, 48.0)	<0.001
SCr, mg/dl	1.1 (0.8, 1.7)	1.1 (0.8, 1.7)	1.3 (0.9, 2.0)	<0.001	1.1 (0.8, 1.7)	1.1 (0.8, 1.6)	1.3 (0.9, 2.0)	<0.001
Sodium, mEq/l	138 (135, 141)	138 (135, 141)	137 (134, 141)	<0.001	138 (135, 141)	138 (135, 141)	138 (134, 141)	<0.001
Potassium, mEq/l	4.2 (3.8, 4.8)	4.2 (3.8, 4.7)	4.3 (3.8, 4.9)	<0.001	4.2 (3.8, 4.7)	4.1 (3.8, 4.6)	4.3 (3.8, 4.9)	<0.001
Anion gap, mEq/L	16.0 (13.0, 19.0)	15.0 (13.0, 18.0)	16.0 (14.0, 20.0)	<0.001	15.0 (13.0, 18.0)	15.0 (13.0, 18.0)	16.0 (14.0, 19.0)	<0.001
Bicarbonate, mEq/L	23.0 (20.0, 26.0)	23.0 (20.0, 26.0)	22.0 (18.0, 25.0)	<0.001	24.0 (21.0, 27.0)	24.0 (21.0, 27.0)	23.0 (20.0, 27.0)	<0.001
ALT, u/l	27.0 (17.0, 56.0)	26.0 (16.0, 53.0)	32.0 (19.0, 74.0)	<0.001	27.0 (16.0, 55.0)	27.0 (16.0, 51.0)	31.0 (18.0, 72.3)	<0.001
AST, u/l	39.0 (23.0, 86.0)	36.0 (23.0, 77.0)	52.0 (28.0, 130)	<0.001	36.0 (22.0, 78.0)	34.0 (22.0, 71.0)	46.0 (25.8, 109)	<0.001
Serum albumin, g/dl	3.3 (2.8, 3.8)	3.4 (2.8, 3.8)	3.0 (2.5, 3.5)	<0.001	3.1 (2.6, 3.6)	3.2 (2.7, 3.7)	2.9 (2.4, 3.3)	<0.001
LDH, u/l	277 (209, 412)	265 (204, 382)	353 (245, 578)	<0.001	271 (203, 396)	258 (197, 371)	323 (232, 518)	<0.001
LAR	8.8 (6.2, 14.0)	8.2 (5.9, 12.6)	12.2 (8.1, 21.2)	<0.001	9.0 (6.2, 14.3)	8.5 (5.9, 12.9)	11.7 (7.7, 20.1)	<0.001
SAPS II	41.0 (32.0, 51.0)	39.0 (31.0, 48.0)	49.0 (39.0, 59.0)	<0.001	40.0 (31.0, 50.0)	38.0 (30.0, 47.0)	48.0 (40.0, 58.0)	<0.001
SOFA score	3.0 (1.0, 5.0)	3.0 (1.0, 5.0)	4.0 (1.0, 8.0)	<0.001	5.0 (3.0, 8.0)	5.0 (3.0, 7.0)	7.0 (4.0, 10.0)	<0.001
CRRT, n (%)	1535 (13.9%)	967 (10.9%)	568 (26.4%)	<0.001	622 (12.0%)	439 (10.8%)	183 (16.6%)	<0.001
Vasopressors, n (%)	5116 (46.3%)	3557 (40.0%)	1559 (72.4%)	<0.001	2840 (54.8%)	2090 (51.3%)	750 (68.0%)	<0.001
Ventilation, n (%)	6107 (55.3%)	4455 (50.1%)	1652 (76.8%)	<0.001	1868 (36.1%)	1317 (32.3%)	551 (50.0%)	<0.001

MIMIC Medical Information Mart for Intensive Care, SBP systolic blood pressure, DBP diastolic blood pressure, CHD coronary heart disease, CKD chronic kidney disease, WBC white blood cell count, BUN blood urea nitrogen, SCr serum creatine, ALT alanine aminotransferase, AST aspartate aminotransferase, LDH lactate dehydrogenase, LAR lactic dehydrogenase-to-albumin ratio, SAPS simplified acute physiology score, SOFA sequential organ failure assessment, CRRT continuous renal replacement therapy

non-survivor group, whereas serum albumin levels were lower ($p < 0.001$). Compared with survivors in the MIMIC IV database, patients who died during hospitalization had higher age, SAPS II, SOFA score, faster heart rate, lower SBP, higher prevalence of CKD, liver cirrhosis, malignancy, sepsis, lower proportions of hypertension, and CHD, and were more likely to receive CRRT, mechanical ventilation, and used more vasopressors. In terms of laboratory indices, patients with in-hospital death exhibited higher levels

of WBC, BUN, SCr, potassium, anion gap, ALT, and AST, but lower levels of bicarbonate, sodium, and hemoglobin. Analysis of patients from the MIMIC III database showed that the levels of heart rate, WBC, BUN, SCr, potassium, anion gap, ALT, AST, SAPS II, and SOFA score were significantly higher, but SBP, DBP, hemoglobin, sodium, bicarbonate were lower in the in-hospital death group when compared with the survival group. Besides, mechanical ventilation, vasopressors, and CRRT were more common in

patients who died during hospitalization. Moreover, remarkable differences in the history of hypertension, diabetes, CHD, heart failure, liver cirrhosis, malignancy, and sepsis were also observed between both groups.

Association between LDH and outcomes

Patients were categorized into low (≤ 10.6) and high (> 10.6) LAR groups based on the best cut-off score determined by ROC curve analysis (Supplementary Fig. 2). MIMIC IV database showed that the incidence of in-hospital, ICU, 30-day, 90-day, and 365-day mortality increased significantly in patients with increased LAR compared with those with decreased LAR, in line with results in the MIMIC III database (Supplementary Table 2). When stratified by the AKI stage, in-hospital mortality rates of the increased LAR group at stages 1, 2, and 3 were remarkably higher than the decreased LAR group in both databases (all $p < 0.001$; Fig. 1A, B).

The predictive significance of LAR for all-cause mortality was verified by multivariate regression analyses. During analysis of the MIMIC IV database showed that, even after controlling confounding factors, a one-unit increase of LAR was strongly correlated with increased risk of in-hospital, ICU, 30-day, 90-day, and 365-day mortality (all $p < 0.001$, Table 2). The results also exhibited that high LAR was an important predictor of all-cause mortality [OR (95% CI) for in-hospital mortality: 2.14 (1.91–2.40), $p < 0.001$; OR (95% CI) for ICU mortality: 2.21 (1.95–2.50), $p < 0.001$; HR (95% CI) for 30-day mortality: 1.91 (1.75–2.08), $p < 0.001$; HR (95% CI) for 90-day mortality: 1.91 (1.74–2.08), $p < 0.001$; HR (95% CI) for 365-day mortality: 1.86 (1.71–2.03), $p < 0.001$, Table 2]. Similar outcomes were noted during the analysis of the MIMIC III database for the impact of LAR on clinical outcomes. Multivariate regression analysis revealed the independent prognostic significance of LAR for all-cause mortality, whether considered LAR as a nominal or

Fig. 1 In-hospital mortality of patients between high and low LAR groups at different AKI stages in MIMIC IV (A) and MIMIC III (B). LAR, lactic dehydrogenase-to-albumin ratio; AKI, acute kidney injury; MIMIC, Medical Information Mart for Intensive Care

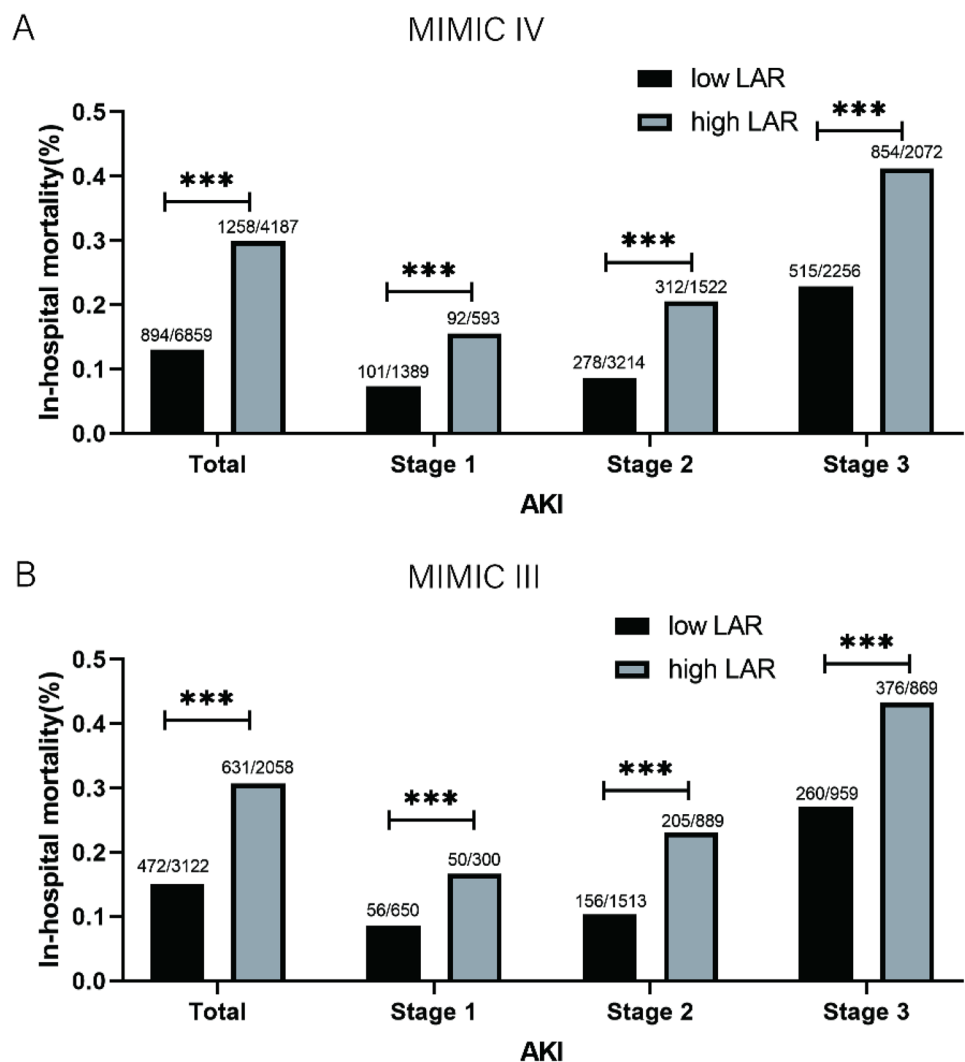


Table 2 Adjusted odds ratios/hazard ratios of LAR for all-cause mortality

	Unadjusted		Adjusted	
	OR/HR (95% CI)	<i>P</i>	OR/HR(95% CI)	<i>P</i>
MIMIC IV [#]				
LAR as continuous variable ^a				
In-hospital mortality	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001
ICU mortality	1.02 (1.02–1.02)	<0.001	1.02 (1.01–1.02)	<0.001
30-day mortality	1.01 (1.01, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001
90-day mortality	1.01 (1.01, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001
365-day mortality	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001
LAR as nominal variable ^b				
In-hospital mortality	2.87 (2.60–3.16)	<0.001	2.14 (1.91–2.40)	<0.001
ICU mortality	3.12 (2.80–3.49)	<0.001	2.21 (1.95–2.50)	<0.001
30-day mortality	2.49 (2.29, 2.70)	<0.001	1.91 (1.75, 2.08)	<0.001
90-day mortality	2.49 (2.29, 2.70)	<0.001	1.91 (1.74, 2.08)	<0.001
365-day mortality	2.39 (2.21, 2.59)	<0.001	1.86 (1.71–2.03)	<0.001
MIMIC III [#]				
LAR as continuous variable ^a				
In-hospital mortality	1.01(1.01- 1.01)	<0.001	1.01(1.00- 1.01)	<0.001
ICU mortality	1.01 (1.01–1.01)	<0.001	1.01(1.00- 1.01)	<0.001
30-day mortality	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.01)	<0.001
90-day mortality	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.01)	<0.001
365-day mortality	1.01 (1.00, 1.01)	<0.001	1.00 (1.00–1.01)	<0.001
LAR as nominal variable ^b				
In-hospital mortality	2.48 (2.17–2.84)	<0.001	1.89 (1.60–2.22)	<0.001
ICU mortality	2.58 (2.22–3.00)	<0.001	1.82 (1.52–2.18)	<0.001
30-day mortality	1.90 (1.72, 2.10)	<0.001	1.55 (1.39, 1.74)	<0.001
90-day mortality	1.90 (1.72, 2.10)	<0.001	1.55 (1.38, 1.73)	<0.001
365-day mortality	1.73 (1.59, 1.89)	<0.001	1.48 (1.35, 1.64)	<0.001

OR odds ratio, HR hazard ratio, 95% CI 95% confidence interval, MIMIC Medical Information Mart for Intensive Care, LAR lactic dehydrogenase-to-albumin ratio, ICU intensive care units

^aThe OR was examined by per 1-point increase of LAR

^bThe OR was examined regarding the low LAR as reference

[#]The baseline model includes variables that are significant in univariate logistic proportional hazard analysis in MIMIC IV, including age, SBP, heart rate, hypertension, CHD, CKD, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, BUN, sodium, potassium, anion gap, bicarbonate, ALT, AST, SAPS II, SOFA score, CRRT, vasopressors, and ventilation (details shown in Supplementary Table 2)

continuous variable (all $p < 0.001$, Table 2). KM curves for the 365-day cumulative survival rate based on the best cut-off score of LAR in both databases are illustrated in Fig. 2. KM curves for 365-day death in the two databases presented a significant statistical difference between the increased and decreased LAR group (Fig. 2A, B; both log-rank $P < 0.001$). A non-linear correlation between LAR and in-hospital mortality was obtained in Fig. 2C (P for non-linearity < 0.001). The probability of in-hospital mortality increased rapidly with the LAR level up to 18.05 (OR (95% CI):1.09 (1.08–1.10), $p < 0.001$, Table 3). When the level of LAR is more than 18.05, the probability of in-hospital death increased relatively slowly.

Subgroup analyses

Subgroup analyses were carried out to assess the risk stratification performance of LAR for in-hospital mortality using the MIMIC IV database (Fig. 3). The high LAR was consistently associated with increased in-hospital death in different subgroups, including AKI stage 1 to 3, age ≤ 65 or > 65 years, female or male, with or without hypertension, diabetes, CHD, heart failure, CKD, liver cirrhosis, malignancy, sepsis, CRRT, vasopressors, and mechanical ventilation. Notably, the predictive value of LAR was more pronounced in patients without CKD ($P_{\text{interaction}} = 0.035$) and patients with malignancy ($P_{\text{interaction}} = 0.033$), and patients

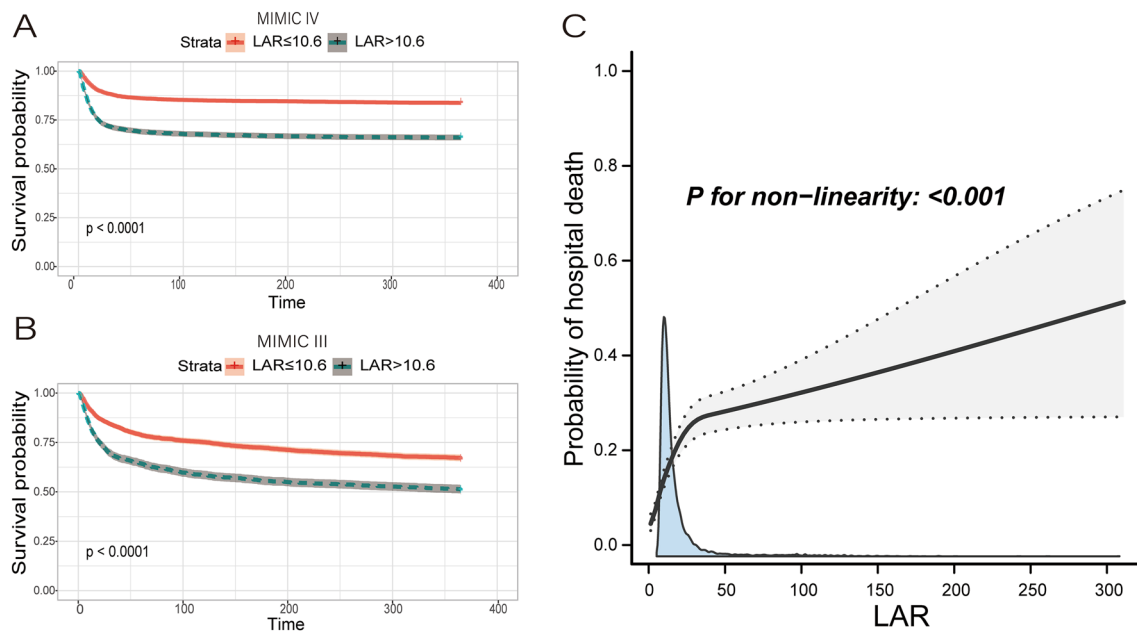


Fig. 2 Kaplan–Meier curves and restricted cubic spline analysis. Kaplan–Meier curves for 365-day accumulative survival rates stratified by high and low LAR in MIMIC IV (A) and MIMIC III (B) databases. The association between LAR and in-hospital death in MIMIC IV using restricted cubic spline analysis (C). A non-linear association between LAR and in-hospital mortality was observed after adjusting

for age, SBP, heart rate, hypertension, CHD, CKD, liver cirrhosis, malignancy, sepsis, WBC, hemoglobin, BUN, sodium, potassium, anion gap, bicarbonate, ALT, AST, SAPS II, SOFA score, CRRT, vasopressors, and ventilation. LAR, lactic dehydrogenase-to-albumin ratio; MIMIC, Medical Information Mart for Intensive Care

Table 3 Threshold effect analysis of LAR on in-hospital mortality using piecewise linear regression in MIMIC IV

Inflection point of LAR	OR (95% CI)	<i>P</i>
LAR < 18.05	1.09 (1.08, 1.10)	< 0.001
LAR ≥ 18.05	1.00 (1.00, 1.01)	0.002

OR odds ratio, 95% CI 95% confidence interval, MIMIC Medical Information Mart for Intensive Care, LAR lactic dehydrogenase-to-albumin ratio

who did not undergo CRRT ($P_{\text{interaction}} = 0.009$) and mechanical ventilation ($P_{\text{interaction}} < 0.001$).

Discussion

The principal finding was that LAR at admission was remarkably correlated with an increased risk of all-cause mortality in critically ill patients with AKI after multiple covariates' adjustment. Most importantly, these correlations remained significant after stratifying according to AKI stages. The correlation of LAR with all-cause mortality was further confirmed using data from the MIMIC III database.

Prior studies have detected that LDH is strongly related to poor prognoses in various clinical settings, including

infectious diseases [6, 8], cancer [19, 20], cardiovascular disease [21], cardiac surgery [22], and hypoxic hepatitis [23]. Recent work has established the relationship between LDH and long-term mortality in incident hemodialysis patients [10]. Besides, LDH and hypoalbuminemia have been demonstrated to be crucial markers for predicting prognosis in critically ill patients [24, 25]. Moreover, the relationship between hypoalbuminemia and unfavorable endpoints in patients with AKI in multiple clinical scenarios has been established [26, 27]. To our knowledge, no research has focused on the predictive implications of LAR in ICU patients with AKI. Our analysis substantiated that LAR is a vital predictor of all-cause mortality in ill critical patients with AKI. The prognostic significance of LAR was further verified in the external validation, indicating the reliability of our results. Besides, the correlation between LAR and in-hospital mortality was still observed after stratification according to the AKI stages, which showed that the prognostic implication of LAR was not affected by the severity of kidney injury.

LDH is widely acknowledged as a prognostic risk factor for multiple diseases. There is a rich literature substantiating that hypoalbuminemia is correlated with poor prognosis in various diseases, such as cancer [28, 29], cardiovascular diseases [30], heart failure [31], and sepsis [32]. The findings of subgroup analysis suggested that the predictive significance

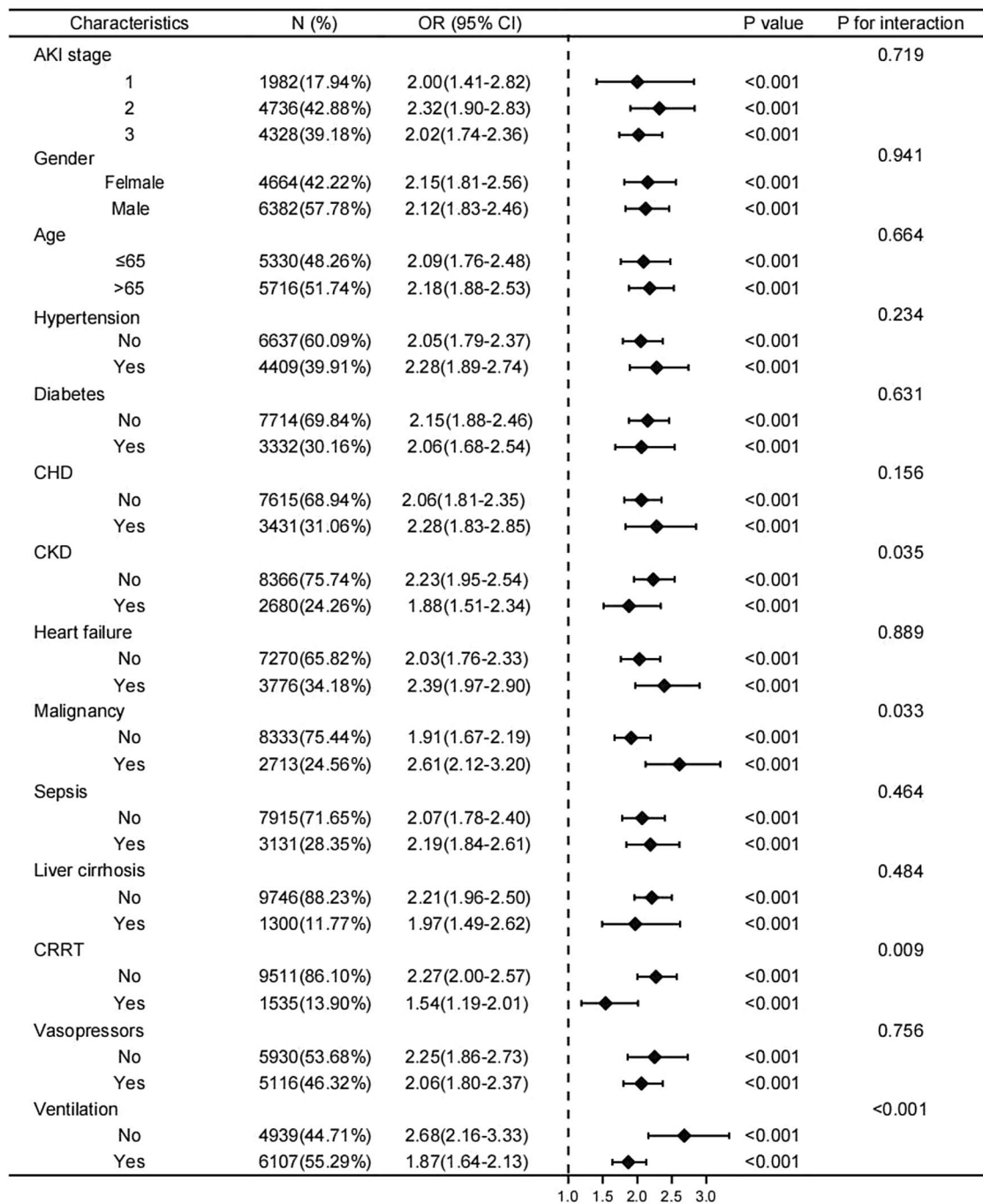


Fig. 3 The association between LAR and in-hospital mortality in various subgroups in MIMIC IV. The OR was examined regarding the low LAR as reference. LAR, lactic dehydrogenase-to-albumin ratio;

OR, odds ratio; 95%CI, 95% confidence interval; MIMIC, Medical Information Mart for Intensive Care

of LAR seemed not to be affected by disease types. Indeed, it is well established that albumin is susceptible to changes at age [33]. Subgroup analysis by age showed no differences in the prognostic ability of LAR. There is a possibility that LAR can reduce these uncertainty biases. LAR, which combines LDH and albumin, may yield a better predictive value than the individual indicators. However, it remains unclear

why LAR exhibited more significant predictive value in patients that did not receive CRRT and mechanical ventilation. We speculate that LAR might serve as a useful biomarker for relatively low-risk AKI patients.

At present, the specific mechanism regarding the link of LAR with all-cause mortality remains uncertain. The following are some speculations. It is widely thought that

albumin possesses anti-inflammatory properties [34] and exhibits significant value as an inflammation indicator in infectious diseases [35]. LDH has also been reported as an inflammation marker of pulmonary diseases [36, 37]. These studies showed that albumin and LDH were associated with inflammation, which is a vital pathogenic mechanism in the development and progression of AKI [38, 39]. Hypoperfusion is another significant cause of AKI progression [38, 39]. Hypoalbuminemia could cause leakage of intravascular fluid which results in a further decrease of blood volume and exacerbate renal hypoperfusion [26, 39]. LDH is a crucial enzyme in anaerobic glycolysis that can catalyze pyruvate to lactate [40]. Hypoperfusion is often accompanied by tissue ischemia and hypoxia, which contribute to the rapid accumulation of lactate. Legouis et al. revealed that impaired lactate clearance is closely correlated with the mortality of AKI patients [41].

Although the present study used data from two large critical care databases, some limitations remain. First, LAR was only evaluated at admission; thus, it is unclear whether dynamic changes in LAR can predict prognosis. Second, despite controlling several confounding variables during multivariate analysis, selection bias may affect our findings' robustness to a certain extent. Third, finally, the present study did not explore the mechanism behind the relationship between all-cause mortality and elevated LAR.

Conclusion

The LAR upon admission is a crucial predictor for all-cause mortality of AKI patients in the ICU.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10157-023-02321-5>.

Declarations

Conflict of interest All the authors have declared no competing interest.

Ethical approval The Institutional Review Boards of the Massachusetts Institute of Technology exempted the MIMIC III/IV database from ethics review, given that patient information was hidden to protect privacy.

Consent for publication Not applicable.

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