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Research article

The relationship between lactate dehydrogenase to albumin ratio and all-cause mortality during ICU stays in patients with sepsis: A retrospective cohort study with propensity score matching

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ABSTRACT

Background: Sepsis is a prevalent and severe medical condition which is frequently observed in the intensive care unit (ICU). Although numerous biomarkers have been identified to predict the prognosis of sepsis, the lactate dehydrogenase to albumin ratio (LDH/ALB ratio) has not been extensively investigated. The principal objective of this study is to assess the relationship between LDH/ALB ratio and all-cause mortality in patients with sepsis.

Methods: This study included all adult critically ill patients with sepsis from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.0) database. Propensity score matching (PSM) analysis was conducted to mitigate bias, and Kaplan-Meier curves were performed to evaluate the cumulative survival across different groups. The association between the LDH/ALB ratio and mortality was examined through restricted cubic spline (RCS) analysis and Cox regression analysis. The robustness of the findings was confirmed through subgroup analyses. Additionally, the prognostic capability of the LDH/ALB ratio was further evaluated using receiver operating characteristic (ROC) curve analysis.

Results: There were 6059 adult patients with sepsis enrolled in the final analysis. RCS revealed a non-linear relationship between the LDH/ALB ratio and an increased risk of ICU all-cause mortality ($\chi^2 = 46.900$, $P < 0.001$). Following PSM analysis, 1553 matched pairs were obtained. As comparison to the low LDH/ALB ratio group, the mortality rate in the high LDH/ALB ratio group was significantly higher ($P < 0.001$). Kaplan-Meier curves, both before and after PSM, revealed that the ICU cumulative survival rate for patients with sepsis was significantly lower in the high LDH/ALB ratio group compared to the low LDH/ALB ratio group ($\chi^2 = 93.360$, $P < 0.001$; $\chi^2 =$

Abbreviations: ICU, intensive care unit; LDH, lactate dehydrogenase; LDH/ALB ratio, lactate dehydrogenase to albumin ratio; MIMIC-IV, Medical Information Mart for Intensive Care IV; PSM, propensity score matching; RCS, restricted cubic spline; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; MCV, mean corpuscular volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; HR, hazard ratio; CI, confidence interval; AKI, acute kidney injury; AMI, acute myocardial infarction; CA, cardiac arrest; SAH, subarachnoid hemorrhage; AUC, area under the ROC curve.

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14.400, $P < 0.001$). Even after adjusting for a range of potential confounders, multivariate Cox regression analysis indicated that an elevated LDH/ALB ratio was a significant predictor of all-cause mortality in these patients. ROC curve analysis demonstrated that the LDH/ALB ratio had an area under the ROC curve (AUC) of 0.688 for predicting ICU mortality, with a sensitivity of 69.2% and a specificity of 58.6%.

Conclusions: An elevated LDH/ALB ratio (≥10.57) was associated with all-cause mortality in critically ill patients with sepsis, and it might serve as a prognostic marker. Clinicians should pay closer attention to sepsis patients presenting with an LDH/ALB ratio of 10.57 or higher.

1. Introduction

Sepsis, as a significant global public health concern, is characterized as a life-threatening organ dysfunction arising from an impaired host response to infection [1,2]. Despite advancements in sepsis management guidelines and improvements in hemodynamic monitoring technologies within intensive care units (ICUs), sepsis still continues to exhibit substantial rates of morbidity and mortality [3,4]. In 2017, it was estimated that 48.9 million cases of sepsis were diagnosed worldwide, leading to 11.0 million deaths, which accounted for 19.7% of all global fatalities [5]. Effective management of sepsis necessitates early recognition, timely implementation of infection control measures, and optimization of perfusion [4]. Consequently, the identification of reliable prognostic indicators for mortality is crucial in the management of sepsis and represents a significant research focus for the Surviving Sepsis Campaign [6].

Lactate dehydrogenase (LDH) is a crucial enzyme in glycolysis, facilitating the conversion of pyruvate to lactate. It also serves as an indicator of tissue and organ hypoperfusion [7]. Recent research have indicated that an elevated serum LDH level is an independent predictor of mortality within 30 days in patients with sepsis [8]. Albumin, produced by the liver, is essential in various physiological processes, including antioxidation, anti-inflammation, and the regulation of plasma osmolality [9]. One recent study has shown that reduced levels of serum albumin are linked to an increased risk of mortality in critically ill individuals [10]. A meta-analysis has demonstrated that albumin therapy, particularly 20% albumin solutions, significantly lowers 90-day mortality in patients with septic shock (OR 0.81 [0.67, 0.98]; $p = 0.03$) [11]. The LDH to albumin (LDH/ALB) ratio is emerging as a novel biomarker of inflammation. While previous research on LDH/ALB ratio has been centered around malignant tumors [12,13], recent evidence suggests its relevance to the prognosis of patients with lower respiratory tract infection [14] and severe infection requiring monitoring [15]. A specific study explored the correlation between the LDH/ALB ratio and prognosis in patients with sepsis-associated acute kidney injury, revealing that an elevated LDH/ALB ratio was linked to increased mortality rates at 28-day, 90-day, and during hospitalization [16].

Despite the growing interest in the LDH/ALB ratio as a prognostic indicator, the current body of research exploring its association with patient outcomes in the ICU, particularly for those with sepsis, is not extensive. Consequently, this study was designed to examine the relationship between LDH/ALB ratio and all-cause mortality, with the objective of assessing the predictive value of LDH/ALB ratio and providing guidance for clinical management.

2. Methods

2.1. Source of data

A retrospective study was conducted utilizing the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 2.0) database [17], which is a comprehensive and freely accessible repository of intensive care data from 2008 to 2019. The establishment of the database was authorized by the institutional review boards of Beth Israel Deaconess Medical Center in Boston and the Massachusetts Institute of Technology in Cambridge. We obtained authorization to access the database (certification number: 36142713 and 51774135). To protect the privacy of patients, all protected health information in the MIMIC database has been de-identified. Consequently, this study waived consent requirements for individual patients. We identified and extracted data for eligible septic patients and structured the ensuring report in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [18].

2.2. Study population

The retrospective cohort comprised all adult ICU patients diagnosed with sepsis, as defined by Sepsis-3 criteria, from the MIMIC-IV database. In cases where participants had records for multiple ICU admissions, only the initial admission was considered. Additionally, we excluded patients who lacked critical indicators, such as LDH and albumin, or those who were discharged from the ICU within 24 h of admission. Sepsis is diagnosed according to Sepsis 3.0 criteria, which include a Sequential Organ Failure Assessment (SOFA) score of 2 or higher, in conjunction with a confirmed or suspected infection [1].

2.3. Variable extraction

Structured Query Language (SQL) was utilized to extract data from the MIMIC-IV database. The variables were extracted included age, sex, SOFA score, utilization of norepinephrine, existing comorbidities at ICU admission, length of ICU stay, and mortality.

Simultaneously, laboratory parameters such as LDH, albumin, bicarbonate, white blood cell (WBC), hemoglobin, mean corpuscular volume (MCV), platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, blood urea nitrogen (BUN), glucose, potassium, calcium, and prothrombin time (PT) were also gathered. The LDH/ALB ratio was calculated based on serum levels of LDH and albumin. All laboratory variables were collected within 6 h prior of ICU admission to the first 24 h following ICU admission, and the SOFA score was obtained within 24 h of ICU admission.

2.4. Groups and outcomes

Patients were classified based on survival outcomes during the ICU stay into two groups: the survival group (n = 5049) and the death group (n = 1010). Additionally, the study population was divided into two groups according to the LDH/ALB ratio threshold of 10.57, which corresponded to a hazard ratio (HR) of 1 in the restricted cubic spline (RCS) analysis. This resulted in a low LDH/ALB ratio group (<10.57, n = 3244) and a high LDH/ALB ratio group (≥10.57, n = 2815). The primary endpoint was all-cause mortality during the ICU stay.

2.5. Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as percentages (%). Depending on the data distribution and the type of variables, comparisons of patient characteristics were made using *t*-test, Wilcoxon rank-sum test, or Chi-squared test, as appropriate.

The relevance between LDH/ALB ratio and the risk of ICU all-cause mortality in patients with sepsis was visualized using RCS analysis. An LDH/ALB ratio corresponding to a HR of 1 was identified as the optimal cut-off value. Based on this value, the study population was divided into low and high LDH/ALB ratio groups. To mitigate potential bias between these groups, propensity score matching (PSM) analysis was conducted. This analysis included all relevant variables such as gender, age, SOFA score, norepinephrine usage, various laboratory parameters, and existing comorbidities at ICU admission. The PSM analysis employed a 1:1 nearest-neighbor matching algorithm with a caliper width of 0.03 to ensure close matching of the pairs.

The ICU cumulative survival rates of patients with low and high LDH/ALB ratio groups, both before and after PSM, were compared using Kaplan-Meier survival curves. The differences in survival rates between the two groups were statistically analyzed using the log-rank test.

Variables that attained a *P* value of less than 0.10 in the univariate analysis, comparing the survival and death groups, were subsequently included in the multivariate regression analysis. Cox proportional-hazards models were constructed to evaluate the association between the LDH/ALB ratio and ICU all-cause mortality. The results were expressed as HRs with 95% confidence intervals (CIs). Subgroup analyses were conducted to assess the stability and consistency of our findings across different groups.

To assess the prognostic capability of the LDH/ALB ratio, receiver operating characteristic (ROC) curve analysis was performed.

Data analysis was conducted using Stata software version 14.0 and the R programming language version 4.2.0. A two-tailed P-value of less than 0.05 was considered to indicate statistical significance.

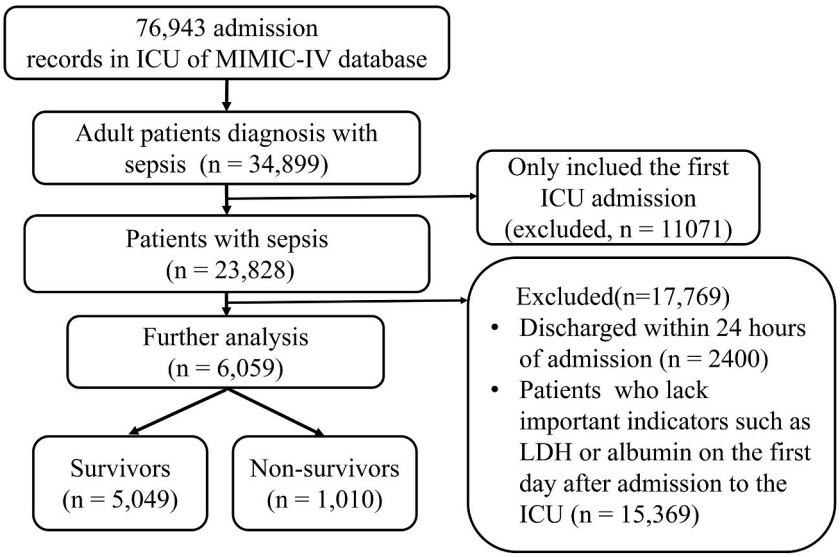

Fig. 1. Flow chart of patients' extraction.

3. Results

3.1. Study population and general characteristics

In the final analysis, a total of 6059 adult patients with sepsis were included from an initial cohort of 76,943 ICU admissions in the MIMIC-IV database, following the application of exclusion criteria. The flow chart of data extraction was depicted in Fig. 1. The average age of the participants was 63.96 (17.02) years, and males constituted 56.86% of the study population. It was observed that the death group exhibited higher mean values of age, SOFA score, LDH, LDH/ALB ratio, WBC, MCV, ALT, AST, creatinine, BUN, glucose, potassium, and PT compared to the survival group. Additionally, the death group had a higher incidence of norepinephrine administration, malignancy, acute kidney injury (AKI), acute myocardial infarction (AMI), cardiac arrest (CA), and subarachnoid hemorrhage (SAH). Conversely, the survivors typically had shorter ICU stays and significantly higher levels of albumin, bicarbonate, platelet, and calcium. Table 1 provided a summary of the general characteristics of the included patients.

Table 1
General characteristics of patients in the survival and death groups before and after propensity score matching (PSM).

Variables	Before PSM				After PSM			
	Survival group (n = 5049)	Death group (n = 1010)	t/Z/χ2	*p*	Survival group (n = 2621)	Death group (n = 485)	t/Z/χ2	*p*
Age (years)	63.66 ± 17.15	65.47 ± 16.25	−3.079	0.002	63.27 ± 17.08	66.97 ± 15.97	−4.426	<0.001
Male, n (%)	2831 (56.07)	614 (60.79)	7.649	0.006	1434 (54.71)	279 (57.53)	1.310	0.252
SOFA score	7.36 ± 3.89	11.33 ± 4.55	−28.716	<0.001	7.53 ± 3.76	10.79 ± 4.33	−17.110	<0.001
LDH (U/L)	283 (207, 432)	433 (279, 808)	−17.751	<0.001	298 (220, 415)	353 (252, 539)	−7.411	<0.001
Albumin (g/L)	31.31 ± 6.88	29.32 ± 7.57	8.222	<0.001	30.24 ± 6.75	29.05 ± 7.09	3.539	<0.001
LDH/ALB ratio	9.25 (6.56, 14.93)	15.69 (9.26, 30.77)	−18.846	<0.001	10.28 (7.33, 14.29)	12.13 (8.79, 19.09)	−8.287	<0.001
Bicarbonate (mmol/L)	21.77 ± 5.34	19.96 ± 6.03	9.606	<0.001	21.73 ± 5.32	20.92 ± 5.73	3.023	0.003
WBC (× 10^9/L)	11.40 (7.60, 16.80)	13.30 (8.50, 19.20)	−6.329	<0.001	11.80 (7.70, 17.30)	13.30 (8.50, 18.40)	−2.626	0.009
Hemoglobin (g/L)	108.61 ± 25.70	108.41 ± 26.42	−0.232	0.817	105.84 ± 25.69	106.33 ± 24.62	−0.392	0.695
MCV (fl)	92.22 ± 8.11	94.16 ± 8.55	−6.891	<0.001	92.44 ± 8.27	93.93 ± 8.15	−3.652	<0.001
Platelet (× 10^9/L)	186.00 (121.00, 266.00)	179.00 (103.00, 264.00)	2.600	0.009	179.00 (113.00, 269.00)	170.00 (108.00, 262.00)	1.497	0.135
ALT (U/L)	32.00 (18.00, 74.00)	43.00 (22.00, 119.00)	−7.238	<0.001	31.00 (19.00, 61.00)	31.00 (18.00, 54.00)	0.509	0.611
AST (U/L)	48.00 (27.00, 110.00)	83.00 (37.00, 245.00)	−11.613	<0.001	50.00 (29.00, 91.00)	53.00 (31.00, 105.00)	−1.753	0.080
Creatinine (umol/L)	106.08 (70.72, 167.96)	123.76 (88.40, 212.16)	−7.883	<0.001	106.08 (70.72, 167.96)	114.92 (79.56, 203.32)	−3.220	0.001
BUN (mmol/L)	8.54 (5.34, 14.60)	10.68 (6.41, 18.16)	−7.761	<0.001	8.54 (5.34, 14.95)	11.39 (6.41, 18.16)	−5.471	<0.001
Glucose (mmol/L)	7.17 (5.78, 9.56)	7.83 (5.83, 11.06)	−4.113	<0.001	7.11 (5.72, 9.44)	7.67 (5.89, 10.56)	−2.393	0.017
Potassium (mmol/L)	4.31 ± 0.96	4.55 ± 1.06	−7.126	<0.001	4.29 ± 0.96	4.45 ± 1.00	−3.450	<0.001
Calcium (mg/dl)	8.20 ± 1.04	8.12 ± 1.12	2.091	0.037	8.10 ± 0.97	8.20 ± 1.03	−2.172	0.030
PT (s)	14.60 (12.70, 17.70)	16.25 (13.40, 23.10)	−11.054	<0.001	14.60 (12.90, 17.70)	15.90 (13.20, 21.60)	−5.397	<0.001
Norepinephrine use, n (%)	1487 (29.45)	668 (66.14)	494.311	<0.001	815 (31.10)	323 (66.60)	222.214	<0.001
Comorbidities, n(%)								
Hypertension	1842 (36.48)	356 (35.25)	0.555	0.456	895 (34.15)	172 (35.46)	0.315	0.575
Diabetes	1526 (30.22)	291 (28.81)	0.799	0.371	757 (28.88)	147 (30.31)	0.404	0.525
Malignancy	855 (16.93)	241 (23.86)	27.259	<0.001	511 (19.50)	127 (26.19)	11.220	0.001
CPD	1236 (24.48)	268 (26.53)	1.904	0.168	657 (25.07)	148 (30.52)	6.328	0.012
CHF	1507 (29.85)	312 (30.89)	0.436	0.509	813 (31.02)	156 (32.16)	0.251	0.617
AKI	3288 (65.12)	893 (88.42)	213.521	<0.001	1765 (67.34)	422 (87.01)	76.004	<0.001
AMI	436 (8.64)	131 (12.97)	18.646	<0.001	246 (9.39)	49 (10.10)	0.245	0.621
Acute pancreatitis	241 (4.77)	40 (3.96)	1.257	0.262	140 (5.34)	19 (3.92)	1.709	0.191
CKD	1116 (22.10)	215 (21.29)	0.327	0.567	596 (22.74)	108 (22.27)	0.052	0.820
CA	198 (3.92)	166 (16.44)	233.416	<0.001	112 (4.27)	56 (11.55)	42.316	<0.001
SAH	70 (1.39)	39 (3.86)	29.183	<0.001	33 (1.26)	18 (3.71)	15.239	<0.001
LOS ICU (days)	3.55 (2.03, 7.04)	4.49 (2.20, 9.18)	−5.303	<0.001	3.63 (2.10, 7.11)	5.06 (2.37, 9.61)	−4.945	<0.001

Abbreviations: SOFA, Sequential Organ Failure Assessment; LDH, lactate dehydrogenase; LDH/ALB ratio, lactate dehydrogenase to albumin ratio; WBC, white blood cell; MCV, mean corpuscular volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; CPD, chronic pulmonary disease; CHF, congestive heart failure; AKI, acute kidney injury; AMI, acute myocardial infarction; CKD, chronic kidney disease; CA, cardiac arrest; SAH, subarachnoid hemorrhage; ICU, intensive care unit; LOS, ICU length of ICU stay.

3.2. RCS analysis

The RCS analysis demonstrated a significant nonlinear relationship between LDH/ALB ratio and the risk of all-cause mortality in the ICU ($\chi^2 = 46.900$, $P < 0.001$). The LDH/ALB ratio was found to have a HR of 1 at the optimal cut-off value of 10.57. As illustrated in Fig. 2, the risk of all-cause mortality in the ICU increased with a higher LDH/ALB ratio, but the rate of this increase diminished over time, eventually reaching a plateau.

3.3. PSM analysis

The ICU all-cause mortality was 16.67% among all participants in this study. Following the determination of the optimal cut-off value using RCS analysis, the study population was divided into groups with low and high LDH/ALB ratios. The mortality rate in the high LDH/ALB ratio group was significantly higher at 24.87%, in contrast to the lower mortality of 9.56% observed in the low LDH/ALB ratio group ($\chi^2 = 254.345$, $P < 0.001$).

After PSM, a total of 1553 pairs were successfully matched, achieving well-balanced baseline demographic characteristics between groups. In this matched cohort, the group with a low LDH/ALB ratio maintained a lower mortality rate of 11.78%, compared to the mortality rate of 19.45% in the high LDH/ALB ratio group ($\chi^2 = 34.601$, $P < 0.001$), as presented in Table 2.

3.4. Kaplan-Meier survival curves

To assess the cumulative survival across different levels of the LDH/ALB ratio, Kaplan-Meier survival curves were constructed for the ICU cumulative survival rates in both the low and high LDH/ALB ratio groups. Analysis of the Kaplan-Meier curves, both before and after matching, revealed that patients with sepsis had a considerably lower ICU cumulative survival rate in the high LDH/ALB ratio group ($\chi^2 = 93.360$, $P < 0.001$; $\chi^2 = 14.400$, $P < 0.001$), as depicted in Fig. 3a and b.

3.5. Elevated LDH/ALB ratio was related to ICU all-cause mortality

The matched cohort was re-grouped based on survival and death for the univariate analysis, as presented in Table 2. Variables that exhibited a P value less than 0.10 in the univariate analysis were subsequently included in the multivariate regression analysis. Table 3 provided an adjusted examination of the association between the LDH/ALB ratio and ICU all-cause mortality in patients with sepsis, utilizing the Cox proportional hazards model for analysis.

Compared to the group with a low LDH/ALB ratio, the group with a high LDH/ALB ratio had a HR of 1.916 (95%CI: 1.676–2.191), indicating that an elevated LDH/ALB ratio (≥10.57) was an independent risk factor for ICU all-cause mortality in patients with sepsis. The multivariate Cox regression analysis, adjusted for various confounders both before and after PSM, consistently demonstrated that an elevated LDH/ALB ratio (≥10.57) was a significant predictor of ICU all-cause mortality in patients with sepsis (before PSM, HR = 1.544, 95 %CI: 1.337–1.783, $P < 0.001$; after PSM, HR = 1.498, 95 %CI: 1.243–1.805, $P < 0.001$). These findings were presented in Table 3.

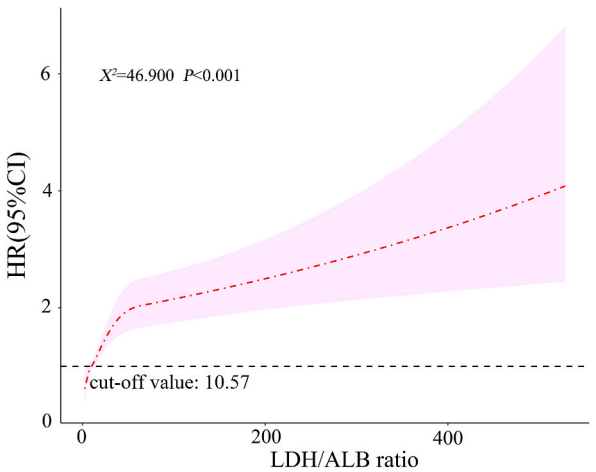

Fig. 2. RCS analysis of the LDH/ALB ratio with ICU all-cause mortality in patients with sepsis. The RCS was obtained by constructing a Cox proportional risk model, revealing a nonlinear correlation between the LDH/ALB ratio and the risk of mortality. The optimal cut-off value for the LDH/ALB ratio was 10.57. Data are shown as HRs with 95% CIs. The shaded areas on each side of the regression line are the 95%CIs. Abbreviations: LDH/ALB ratio, lactate dehydrogenase to albumin ratio; ICU, intensive care unit; RCS, restricted cubic spline; HR, hazard ratio; CI, confidence interval.

Table 2
General characteristics for included patients between low and high LDH/ALB ratio groups before and after propensity score matching (PSM).

Variables	Before PSM					After PSM				
	All patients (n = 6059)	Low LDH/ALB ratio group (n = 3244)	High LDH/ALB ratio group (n = 2815)	t/Z/χ2	*p*	All patients (n = 3106)	Low LDH/ALB ratio group (n = 1553)	High LDH/ALB ratio group (n = 1553)	t/Z/χ2	*p*
Death, n (%)	1010 (16.67)	310 (9.56)	700 (24.87)	254.345	<0.001	485 (15.61)	183 (11.78)	302 (19.45)	34.601	<0.001
Age (years)	63.96 ± 17.02	65.75 ± 16.68	61.91 ± 17.17	8.815	<0.001	63.85 ± 16.96	63.45 ± 17.34	64.25 ± 16.58	−1.322	0.186
Male, n (%)	3445 (56.86)	1873 (57.74)	1572 (55.84)	2.203	0.138	1713 (55.15)	864 (55.63)	849 (54.67)	0.293	0.588
SOFA score	8.02 ± 4.27	6.91 ± 3.74	9.31 ± 4.48	−22.773	<0.001	8.04 ± 4.03	8.18 ± 4.04	7.90 ± 4.01	1.960	0.050
LDH (U/L)	298 (214, 478)	222 (181, 269)	505 (375, 811)	−61.667	<0.001	306 (226, 431)	229 (184, 277)	430 (343, 576)	−42.235	<0.001
Albumin (g/L)	30.98 ± 7.04	33.17 ± 6.49	28.46 ± 6.80	27.556	<0.001	30.05 ± 6.82	31.91 ± 6.46	28.19 ± 6.66	15.814	<0.001
LDH/ALB ratio	9.96 (6.86, 16.88)	7.05 (5.53, 8.52)	17.68 (13.29, 29.45)	−67.236	<0.001	10.57 (7.55, 15.04)	7.55 (6.13, 8.87)	15.04 (12.39, 20.27)	−48.257	<0.001
Bicarbonate (mmol/L)	21.47 ± 5.50	22.43 ± 5.29	20.36 ± 5.53	14.881	<0.001	21.60 ± 5.39	21.57 ± 5.50	21.64 ± 5.28	−0.367	0.713
WBC (× 109/L)	11.70 (7.70, 17.10)	10.90 (7.30, 15.70)	12.90 (8.30, 18.90)	−9.809	<0.001	12.05 (7.80, 17.50)	12.00 (7.50, 17.40)	12.10 (7.90, 17.50)	−0.535	0.593
Hemoglobin (g/L)	108.58 ± 25.82	109.60 ± 25.58	107.40 ± 26.05	3.321	<0.001	105.91 ± 25.52	105.27 ± 26.02	106.56 ± 25.01	−1.404	0.160
MCV (fl)	92.54 ± 8.22	92.00 ± 7.86	93.16 ± 8.57	−5.475	<0.001	92.67 ± 8.27	92.69 ± 8.15	92.64 ± 8.39	0.164	0.870
Platelet (× 109/L)	185.00 (117.00, 266.00)	195.00 (130.50, 273.00)	173.00 (102.00, 257.00)	7.698	<0.001	177.50 (112.00, 267.00)	178.00 (116.00, 268.00)	177.00 (108.00, 266.00)	0.387	0.699
ALT (U/L)	33.00 (18.00, 79.00)	24.00 (15.00, 44.00)	54.00 (26.00, 165.00)	−28.639	<0.001	31.00 (18.00, 60.00)	29.00 (18.00, 58.00)	33.00 (20.00, 61.00)	−2.969	0.003
AST (U/L)	51.00 (28.00, 128.00)	34.00 (22.00, 60.50)	102.00 (46.00, 300.00)	−37.951	<0.001	51.00 (30.00, 93.00)	45.00 (26.00, 88.00)	55.00 (35.00, 96.00)	−6.716	<0.001
Creatinine (umol/L)	106.08 (70.72, 176.80)	97.24 (70.72, 159.12)	114.92 (79.56, 203.32)	−7.080	<0.001	106.08 (70.72, 176.80)	106.08 (70.72, 176.80)	106.08 (70.72, 176.80)	1.884	0.060
BUN (mmol/L)	8.90 (5.70, 15.31)	8.19 (5.34, 13.88)	9.61 (5.70, 16.73)	−6.852	<0.001	9.08 (5.34, 15.66)	8.90 (5.34, 15.66)	9.26 (5.70, 15.66)	−0.520	0.603
Glucose (mmol/L)	7.28 (5.78, 9.78)	7.17 (5.78, 9.39)	7.39 (5.78, 10.28)	−2.526	0.012	7.17 (5.78, 9.61)	7.17 (5.78, 9.44)	7.17 (5.78, 9.78)	−0.286	0.775
Potassium (mmol/L)	4.35 ± 0.98	4.28 ± 0.90	4.44 ± 1.06	−6.461	<0.001	4.31 ± 0.97	4.32 ± 0.98	4.31 ± 0.95	0.043	0.966
Calcium (mg/dl)	8.19 ± 1.05	8.38 ± 0.97	7.96 ± 1.10	15.933	<0.001	8.11 ± 0.98	8.11 ± 0.96	8.12 ± 1.00	−0.470	0.638
PT (s)	14.70 (12.80, 18.40)	14.30 (12.50, 17.10)	15.30 (13.20, 20.10)	−12.300	<0.001	14.70 (12.90, 18.20)	14.70 (13.00, 18.30)	14.70 (12.90, 18.10)	1.261	0.207
Norepinephrine use, n (%)	2155 (35.57)	947 (29.19)	1208 (42.91)	123.808	<0.001	1138 (36.64)	585 (37.67)	553 (35.61)	1.420	0.233
Comorbidities, n(%)										
Hypertension	2198 (36.28)	1226 (37.79)	972 (34.53)	6.944	0.008	1067 (34.35)	518 (33.35)	549 (35.35)	1.372	0.241
Diabetes	1817 (29.99)	1048 (32.31)	769 (27.32)	17.859	<0.001	904 (29.10)	450 (28.98)	454 (29.23)	0.025	0.874
Malignancy	1096 (18.09)	503 (15.51)	593 (21.07)	31.447	<0.001	638 (20.54)	327 (21.06)	311 (20.03)	0.505	0.477
CPD	1504 (24.82)	824 (25.40)	680 (24.16)	1.251	0.263	805 (25.92)	393 (25.31)	412 (26.53)	0.605	0.437
CHF	1819 (30.02)	974 (30.02)	845 (30.02)	0.000	0.995	969 (31.20)	486 (31.29)	483 (31.10)	0.014	0.908
AKI	4181 (69.00)	2061 (63.53)	2120 (75.31)	97.755	<0.001	2187 (70.41)	1094 (70.44)	1093 (70.38)	0.002	0.969

(*continued on next page*)

Table 2 (*continued*)

Variables	Before PSM					After PSM				
	All patients (n = 6059)	Low LDH/ALB ratio group (n = 3244)	High LDH/ALB ratio group (n = 2815)	t/Z/χ2	*p*	All patients (n = 3106)	Low LDH/ALB ratio group (n = 1553)	High LDH/ALB ratio group (n = 1553)	t/Z/χ2	*p*
AMI	567 (9.36)	209 (6.44)	358 (12.72)	69.962	<0.001	295 (9.50)	151 (9.72)	144 (9.27)	0.184	0.668
Acute pancreatitis	281 (4.64)	110 (3.39)	171 (6.07)	24.544	<0.001	159 (5.12)	75 (4.83)	84 (5.41)	0.537	0.464
CKD	1331 (21.97)	766 (23.61)	565 (20.07)	11.029	0.001	704 (22.67)	358 (23.05)	346 (22.28)	0.265	0.607
CA	364 (6.01)	114 (3.51)	250 (8.88)	76.877	<0.001	168 (5.41)	85 (5.47)	83 (5.34)	0.025	0.874
SAH	109 (1.80)	62 (1.91)	47 (1.67)	0.498	0.480	51 (1.64)	25 (1.61)	26 (1.67)	0.020	0.888
LOS ICU (days)	3.71 (2.05, 7.35)	3.13 (1.91, 6.14)	4.44 (2.39, 8.95)	−12.225	<0.001	3.80 (2.12, 7.65)	3.51 (2.02, 6.98)	4.14 (2.25, 8.40)	−4.532	<0.001

Abbreviations: SOFA, Sequential Organ Failure Assessment; LDH, lactate dehydrogenase; LDH/ALB ratio, lactate dehydrogenase to albumin ratio; WBC, white blood cell; MCV, mean corpuscular volume; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time; CPD, chronic pulmonary disease; CHF, congestive heart failure; AKI, acute kidney injury; AMI, acute myocardial infarction; CKD, chronic kidney disease; CA, cardiac arrest; SAH, subarachnoid hemorrhage; ICU, intensive care unit; LOS, ICU length of ICU stay.

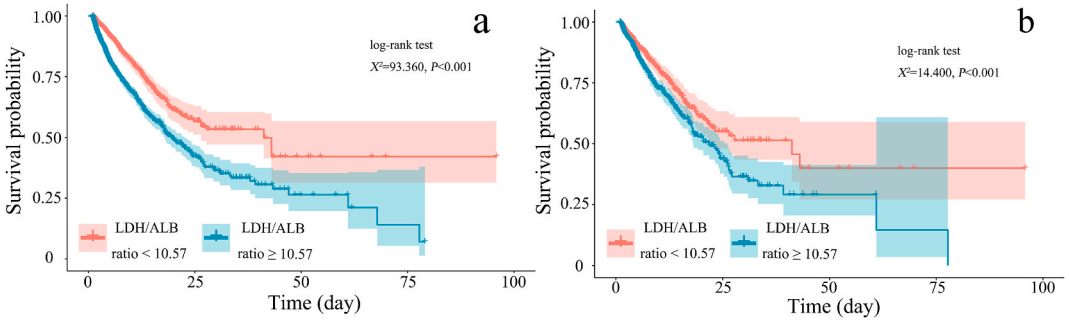

Fig. 3. Kaplan-Meier survival curves for ICU cumulative survival rates in the low and high LDH/ALB ratio groups. A significantly lower ICU survival probability can be identified in the high LDH/ALB ratio group both before (a) and after (b) PSM. Abbreviations: LDH/ALB ratio, lactate dehydrogenase to albumin ratio; ICU, intensive care unit; PSM, propensity score matching.

Table 3
Cox proportional hazards regression analysis of LDH/ALB ratio and ICU all-cause mortality in patients with sepsis.

Variables		model I			model II			model III		
		HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*
Before PSM	Low LDH/ALB ratio	1.0 (ref)			1.0 (ref)			1.0 (ref)		
	High LDH/ALB ratio	1.916	1.676–2.191	< 0.001	1.640	1.421–1.893	< 0.001	1.544	1.337–1.783	< 0.001
After PSM	Low LDH/ALB ratio	1.0 (ref)			1.0 (ref)			1.0 (ref)		
	High LDH/ALB ratio	1.425	1.186–1.712	< 0.001	1.447	1.203–1.742	< 0.001	1.498	1.243–1.805	< 0.001

Before PSM.
Model I adjusted for no variables.
Model II adjusted for age, sex, SOFA score, bicarbonate, WBC, MCV, platelet, ALT, AST, creatinine, BUN, glucose, potassium, calcium and PT.
Model III adjusted for model II plus norepinephrine use, the incidence of malignancy, AKI, AMI, CA and SAH.
After PSM.
Model I adjusted for no variables.
Model II adjusted for age, SOFA score, bicarbonate, WBC, MCV, AST, creatinine, BUN, glucose, potassium, calcium and PT.
Model III adjusted for model II plus norepinephrine use, the incidence of malignancy, CPD, AKI, CA and SAH.
Abbreviations: ICU intensive care unit, PSM propensity score matching, LDH/ALB ratio lactate dehydrogenase to albumin ratio, HR hazard ratio, CI confidence interval, SOFA sequential organ failure assessment, WBC white blood cell, MCV mean corpuscular volume, ALT alanine aminotransferase, AST aspartate aminotransferase, BUN blood urea nitrogen, PT prothrombin time, AKI acute kidney injury, AMI acute myocardial infarction, CA cardiac arrest, SAH subarachnoid hemorrhage, CPD chronic pulmonary disease.

3.6. Subgroup analyses

Subgroup and interaction analyses were conducted to examine the stability of the association between the LDH/ALB ratio and ICU mortality across different subgroups, as depicted in Fig. 4. The results indicated that LDH/ALB ratio was associated with ICU all-cause mortality in most sub-populations of septic patients. Furthermore, no significant interactions were observed among the subgroups (*P* for interaction >0.05), suggesting that the impact of the LDH/ALB ratio on mortality was consistent across different patient characteristics.

3.7. ROC curve analysis

The ROC curve analysis revealed that the optimal threshold for the LDH/ALB ratio in predicting ICU mortality was determined to be 10.683. This threshold demonstrated a sensitivity of 69.2% and a specificity of 58.6%, with the area under the ROC curve (AUC) reaching 0.688. Notably, the prognostic capability of the LDH/ALB ratio was superior to that of LDH alone (AUC = 0.677) and albumin alone (AUC = 0.579). Furthermore, the combination of the LDH/ALB ratio with the SOFA score resulted in the highest predictive performance, with an AUC of 0.754, a sensitivity of 74.6%, and a specificity of 64.5% (Fig. 5, Supplementary Table 1).

4. Discussion

Sepsis is a prevalent and severe condition in the ICU, posing a significant threat to patients' lives. The complexity of the disease and the variety of monitoring methods contribute to substantial costs associated with the management and treatment of sepsis. Clinicians are currently challenged to find a reliable, cost-effective, and easily accessible indicator for the early prognostic assessment of patients with sepsis. This study discovered that the LDH/ALB ratio was higher in the death group, and those with a high LDH/ALB ratio exhibited a significantly higher rate of all-cause mortality. RCS analysis demonstrated a non-linear relationship between the LDH/ALB ratio and the risk of ICU all-cause mortality. Kaplan-Meier survival curves revealed that the ICU cumulative survival rate of patients

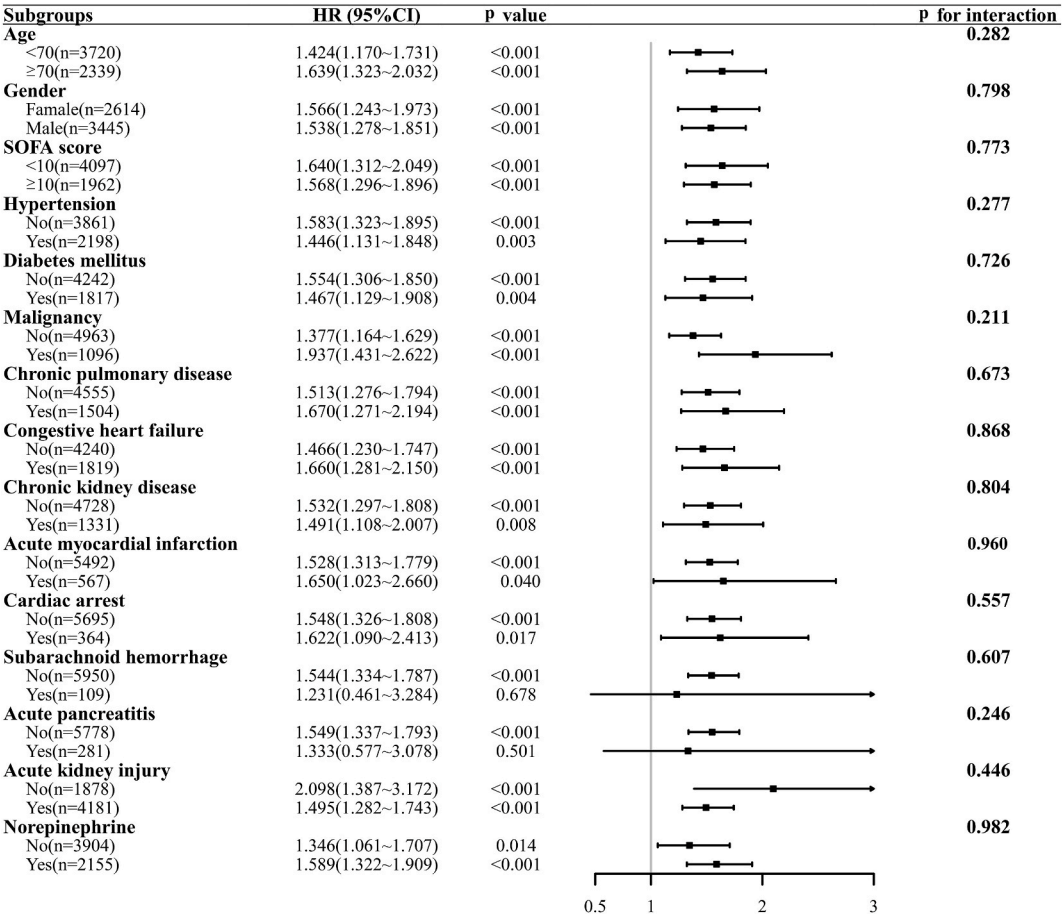

Fig. 4. Subgroup analyses of the LDH/ALB ratio in patients with sepsis. Abbreviations: LDH/ALB ratio, lactate dehydrogenase to albumin ratio; HR, hazard ratio; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

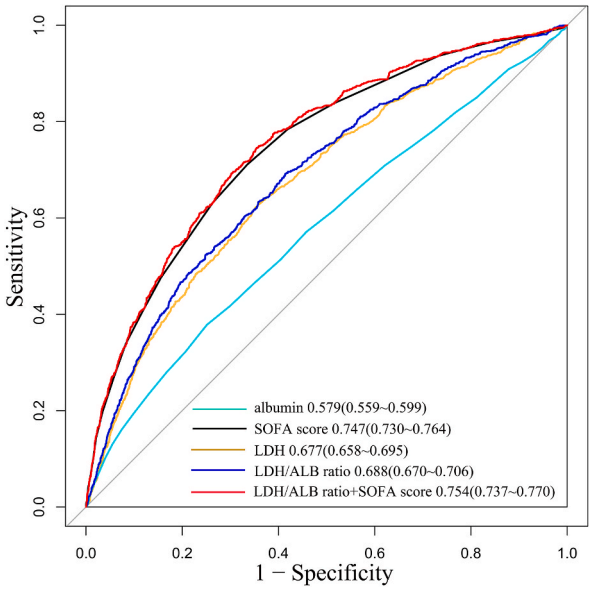

Fig. 5. ROC curves of LDH, albumin, LDH/ALB ratio and SOFA score for predicting ICU all-cause mortality in patients with sepsis. Abbreviations: SOFA, Sequential Organ Failure Assessment; LDH, lactate dehydrogenase; LDH/ALB ratio, lactate dehydrogenase to albumin ratio; ROC, receiver operating characteristic; ICU intensive care unit.

with sepsis was significantly lower in the group with a high LDH/ALB ratio. Furthermore, Cox regression analysis identified that an elevated LDH/ALB ratio (≥10.57) was a significant predictor of ICU all-cause mortality. ROC curve analysis showed that the LDH/ALB ratio had a predictive accuracy for ICU mortality with an AUC of 0.688, a sensitivity of 69.2%, and a specificity of 58.6%.

Serum albumin, recognized as the negative acute phase reactant, is part of the globulin protein family and plays a pivotal role in systemic inflammation. A decrease in albumin levels can be triggered by a variety of clinical conditions including gastrointestinal protein loss, malabsorption, nephrotic syndrome, systemic inflammatory diseases, and sepsis. Previous research has established a correlation between reduced albumin levels and unfavorable outcomes in patients with sepsis [19–21]. This finding was further confirmed by our study, which showed that patients in the death group had a significantly lower albumin levels compared to the survival group. Nevertheless, albumin, as a critical indicator of inflammation and nutritional status, can be influenced by a range of factors such as malnutrition, chronic illnesses, and lifestyle choices (including smoking, alcohol consumption, and obesity). Consequently, in addition to its utilization as an individual prognostic marker, albumin is frequently combined with other variables to improve the accuracy of prognostic evaluations in sepsis. Albumin-based ratios, like the lactate to albumin ratio, the C-reactive protein to albumin ratio, and the BUN to albumin ratio, have been recognized as prognostic tools for patients with infection or sepsis [22–25].

LDH, as an essential glycolytic enzyme, plays a pivotal role in the cellular metabolism by facilitating the conversion of pyruvate to lactate. It is ubiquitously produced in various types of living cells within the human body. Clinically, elevated LDH levels are indicative of conditions such as ischemia hypoxia and inflammatory response, and they generally reflect the degree of tissue damage. Consequently, LDH holds potential as a prognostic marker for the early detection of severe ailments characterized by substantial tissue or cellular impairment, including infections, tumors, and hematologic diseases [26–29]. A particular study on patients with COVID-19 [28] revealed a negative correlation between the duration of lung lesion absorption as observed through imaging (5.57 ± 0.65 days) and the time required for LDH levels to normalize (5.67 ± 0.55 days, $r = 0.53$, $P < 0.05$). These findings validated the potential utility of serum LDH as a marker for evaluating the severity of COVID-19 pneumonia and monitoring the response to treatment. Additionally, our study supported this by showing that LDH levels were significantly higher in non-survivors of sepsis in the ICU compared to survivors.

The LDH/ALB ratio, which combines factors of organ failure, chronic disease, inflammation, and nutritional status, may provide more comprehensive prognostic information than the separate predictive values of LDH or albumin. A prospective study involving 347 patients in the ICU investigated the correlation between three typical biomarkers (LDH, albumin, and magnesium) and organ failure or mortality. The results revealed that the LDH/ALB ratio was significantly associated with organ failure and had a prognostic value that surpassed that of either albumin or LDH [30]. Additionally, a recent cross-sectional study involving 477 individuals with COVID-19 demonstrated that a higher LDH/ALB ratio was linked to longer hospitalizations, greater ICU admission, and increased mortality rates. In comparison to patients with an LDH/ALB ratio of 101.46, those with a ratio of 148.78 exhibited a significantly increased likelihood of mortality and ICU admission, with odds ratios of 7.78 and 4.49, respectively [31]. Lee et al. [14], in a study of individuals with lower respiratory tract infections presented to the emergency department, demonstrated that the LDH/ALB ratio possessed a broader AUC, ranking second only to BUN/albumin ratio. The LDH/ALB ratio also exhibited an independent impact on in-hospital mortality via multivariate logistic regression analysis. These findings suggested that the LDH/ALB ratio may be a potential indicator for the prognosis of septic patients.

It is worth noting that this is further confirmed by our study. A nonlinear relationship between the LDH/ALB ratio and the risk of ICU mortality was found in our study, indicating that an elevated LDH/ALB ratio (≥10.57) was a significant predictor of all-cause mortality among ICU patients with sepsis. The exact pathways linking a raised LDH/ALB ratio to a poor prognosis in patients with sepsis are not fully elucidated. It is well-documented that sepsis triggers tissue damage through inflammatory mechanisms, ensuing organ dysfunction, and an immunosuppressed state. LDH is promptly released into the circulation following tissue injury due to ischemia and hypoxia, highlighting its role as a sensitive marker for cellular damage [32].Additionally, serum albumin possesses anti-inflammatory characteristics and confers protection against sepsis [33].An elevated LDH/ALB ratio suggests either a rise in LDH or a decline in albumin, indicating a systemic imbalance and serving as a prognostic indicator in sepsis. Within the realm of clinical practice, extremely high levels of LDH alongside markedly low levels of albumin often signal the critical state of patients, correlating with a substantially high and stable mortality risk. Our statistical analysis indicated that septic patients with an LDH/ALB ratio greater than 10.57 experienced a heightened risk of death, emphasizing the need for increased clinical vigilance. Moreover, the sharp rise in mortality risk of patients with an LDH/ALB ratio exceeding 50 served as a directive for healthcare practitioners to prioritize their care. Amidst ongoing efforts to refine prognostic tools, researchers are actively exploring novel prognostic indicators beyond traditional scoring systems that provide more direct prognostic insights. ROC curve analysis revealed that a combined index exhibited superior predictive accuracy relative to the use of the LDH/ALB ratio or the SOFA score independently. The aforementioned discovery advocates the integration of the LDH/ALB ratio into existing scoring frameworks to enhance their prognostic power, thus presenting an advanced perspective for healthcare professionals and patient management.

This research possesses several notable strengths. Firstly, it is the first, to our knowledge, to specifically explore the correlation between the LDH/ALB ratio and ICU all-cause mortality among patients with sepsis. The groundbreaking nature of this investigation thus contributes a novel understanding to the field. Secondly, the data utilized in this study was obtained from the well-established MIMIC-IV database. This source is widely recognized for its comprehensive collection of real-world data and high-quality information, lending credence to our findings. Additionally, it is important to acknowledge the potential influence of confounding factors, such as comorbidities, on the outcomes of our study. To address this concern, we employed rigorous statistical techniques, including PSM analysis and detailed subgroup analyses. These methods were utilized to mitigate the impact of confounders, thereby strengthening the validity of our findings. The consistent results obtained through these measures further support the reliability of the LDH/ALB ratio as a prognostic indicator in this specific patient population.

However, our research has several limitations. Firstly, the retrospective nature of the study introduces an inherent drawback in the form of selection bias. Secondly, this study solely focuses on the association between the initial LDH/ALB ratio at ICU admission and all-cause mortality, without delving into the potential relationship between dynamic LDH/ALB ratio during hospitalization and mortality. Additionally, the lack of information regarding sepsis etiologies in the MIMIC database restricts the comprehensiveness and level of detail in our study. Moreover, the fact that LDH is not routinely measured in many laboratories, especially in emergency departments, might restrict the applicability of the LDH/ALB ratio as a prognostic tool in clinical settings. Finally, this study was conducted in a single center, and in future research endeavors , we intend to collect clinical data of sepsis from our own facility to validate the findings. Notwithstanding these limitations, our study has identified a correlation between the LDH/ALB ratio and unfavorable outcomes in patients with sepsis. However, several well-structured, multicenter, and prospective studies are needed in the future to verify the results of our study.

5. Conclusions

In conclusion, the current evidence suggested that an elevated LDH/ALB ratio (≥10.57) was associated with all-cause mortality for patients with sepsis in the ICU, potentially serving as a prognostic marker. However, given the retrospective nature of the study design, the results should be interpreted with caution.

Data availability statement

The datasets generated and analyzed during the current study are available in the Medical Information Mart for Intensive Care IV (MIMIC-IV, v 2.0) database.

The publicly available repository can be found below: https://physionet.org/content/mimiciv/2.0.

Ethics statement

This study was conducted in accordance with Good Clinical Practice (Declaration of Helsinki 2002). MIMIC-IV was an anonymized public database. To apply for access to the database, two of the authors passed the Protecting Human Research Participants exam (Record ID: 36142713 and 51774135). The project was approved by the institutional review boards of the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) and was given a waiver of informed consent.

Consent for publication

Not applicable.

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CRediT authorship contribution statement

Xiaoyue Guan: Writing – original draft, Methodology, Conceptualization. **Lei Zhong:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Jinyu Zhang:** Writing – original draft, Methodology, Conceptualization. **Jianhong Lu:** Writing – original draft, Methodology, Formal analysis. **Meng Yuan:** Writing – review & editing, Methodology, Conceptualization. **Lili Ye:** Writing – review & editing, Methodology, Formal analysis. **Jie Min:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27560.

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