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ORIGINAL ARTICLE

Association between Lactate Dehydrogenase and 30-Day Mortality in Patients with Sepsis: a Retrospective Cohort Study

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SUMMARY

Background: **Sepsis is one of the major causes of death in intensive care unit patients, so it is urgent to explore indicators for rapid and effective screening of sepsis mortality risk. The purpose of this study is to explore the association of LDH level with 30-day mortality in sepsis patients to improve patient survival outcomes.**
Methods: **In this retrospective cohort study, a total of 5,275 patients with sepsis from the Medical Information Mart for Intensive Care IV (MIMIC-IV). LDH level at admission was obtained, and the outcome indicator was the 30-day mortality. Multivariate Cox regression and Kaplan-Meier survival curve analysis were used to assess the relationship between LDH level and 30-day mortality in patients with sepsis.**
Results: **A total of 5,275 patients with sepsis were screened, the 30-day mortality was 51.5%. In multivariate regression models, hazard ratio [HR] and 95% confidence interval [CI] for Log_2 and LDH ≥ 250 UI/L were 1.33 (1.29 - 1.37) and 1.69 (1.54 - 1.85), respectively. Kaplan-Meier survival curve analysis suggested that LDH level is associated with prognosis in patients with sepsis.**
Conclusions: **LDH level was associated with 30-day mortality, which can be used as an important predictor of clinical outcomes for patients.**
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KEYWORDS

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INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by host dysfunction against infection, which imposes a heavy healthcare and economic burden worldwide [1,2]. According to the research reports, the prevalence of sepsis is as high as 247 cases per 100,000 person-years and is increasing, and mortality due to sepsis in ICU patients was estimated at 41.9% [3]. Diagnosis of sepsis can be evaluated with various scores, but the study of prognostic factors still lacks valuable indicators. Therefore, there is a need to explore rapid and effective risk markers associated with sepsis death to improve patient outcomes.

Serum lactate dehydrogenase (LDH) levels, which reflect the degree of cell damage, tend to increase with the

severity of infection. Therefore, some studies mention LDH level as a prognostic factor in many diseases such as sepsis, malignancies, infection, metabolic syndrome etc. [4-6]. In addition, recent studies have found that glucose metabolism reprogramming is closely related to disease progression in patients with sepsis, and that lactate dehydrogenase plays a vital role in the conversion of pyruvate to lactate [7-9]. Therefore, it is of interest to study the level of LDH and early mortality in patients with sepsis to improve the survival and prognosis of patients.

In this study, we performed a large-scale real-world study using the MIMIC-IV database to investigate the association between LDH levels and 30-day mortality in sepsis.

MATERIALS AND METHODS

Database

The data were derived from the MIMIC-IV database, which was released on June 12, 2022 (version 2.0). The MIMIC-IV database was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA) and the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA). The database can be consulted by any researcher who complies with the data usage requirements.

Study design

Adult patients who had been diagnosed with sepsis according to sepsis-3 were included in our study. The exclusion criteria were: 1) not admitted to the hospital for the first time; 2) not first ICU admission; 3) length of ICU stay < 24 hours; 4) age < 18 years; 5) no demographic data; 6) patients with incomplete LDH measurement within the first day of ICU admission; 7) patients with incomplete data. Patients were divided into normal LDH group (LDH < 250 IU/L) and elevated LDH group (LDH ≥ 250 IU/L).

Data extraction

Data were queried and extracted using Structured Query Language (SQL) with the open-source PostgreSQL (v 9.6) software and its GUI software, Navicat [v.15.0.12 (654-bit)-premium].

The process of inclusion and exclusion of data is shown in Figure 1. Following basic characteristics were extracted: age, gender, subject id, ICU stay id, length of hospital stay, length of ICU stay, survival time, and the sequential organ failure assessment (SOFA) score. Then, vital signs, including heart rate (HR), mean arterial pressure (MAP), respiratory rate (RR), temperature (T), systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SpO2), were collected during the first 24 hours of ICU stay. Afterwards, first day laboratory results, such as glucose (GLU), blood sodium, blood potassium, blood white blood cell count (WBC), blood red blood cell count (RBC), platelet count (PLT), hemoglobin (HGB), blood creatinine (Cr), blood urea nitrogen (BUN), red blood cell distribution width (RDW), blood calcium were extracted. Furthermore, concomitant diseases including myocardial infarct, congestive heart failure, chronic pulmonary disease, diabetes, liver disease, renal disease, malignant tumor were identified.

Statistics

Categorical variables are available in numbers and percentages. Continuous variables are expressed as the mean and standard deviation (SD) for a normal distribution, or the median and interquartile range (IQR) for a skewed distribution. Substitution method was applied for missing data in very rare cases. For baseline characteristics analysis, data were compared using of *t*-test for continuous variables and the chi-squared test for categorical variables.

The correlation between LDH level and 30-day mortality was analyzed by univariate Cox regression analysis and multivariate Cox regression analysis. According to the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement, analyses were first performed without adjustment. Further analyses cumulatively included adjustment for age and gender. Finally, the analysis was modified for all variables. Survival analysis based on the Kaplan-Meier (KM) method was carried out to explore the relationships between the LDH levels and 30-day mortality in patients with sepsis.

All analyses were performed using R Statistical Software, version 3.4.3 (The R Foundation, Vienna, Austria) and Free Statistics version 1.7. p-values < 0.05 (two-sided) were considered statically significant.

RESULTS

Study population and baseline features

A total of 5,275 patients met the definition of sepsis 3.0 in the MIMIC-IV database, including 1,761 patients in the LDH < 250 IU/L group and 3,514 patients in the LDH ≥ 250 IU/L group. The baseline characteristics are summarized in Table 1. The average age of all patients was 68.0 ± 14.9 years, and 56% were male. Differences in age, temperature, HR, MAP, DBP, RR, SpO_2, GLU, BUN, Cr, Sodium, Potassium, WBC, HGB, RBC, RDW, and PLT between two groups were statistically significant. The incidence of myocardial infarct, congestive heart failure, and the score of SOFA in the elevated LDH group were significantly higher than those in the normal LDH group. In addition, up to 2,714 of the 5,275 patients died within 30 days after ICU admission, yielding a mortality rate of 51.5%, compared with the survival group, the proportion of patients with high LDH level (LDH ≥ 250 IU/L) in the 30-day death group was significantly increased. The difference was statistically significant ($p < 0.05$).

Table 1. Baseline characteristics of the study participants.

	Total	LDH < 250IU/L	LDH ≥ 250IU/L	*p*
Variables	**(n = 5,275)**	**(n = 1,761)**	**(n = 3,514)**	
Gender, n (%)				**0.352**
Female	**2,321 (44.0)**	**759 (43.1)**	**1,562 (44.5)**	
Male	**2,954 (56.0)**	**1,002 (56.9)**	**1,952 (55.5)**	
Age (years), mean ± SD	**68.0 ± 14.9**	**69.3 ± 14.2**	**67.3 ± 15.2**	**< 0.001**
30-day mortality, n (%)				**< 0.001**
No	**2,561 (48.5)**	**1,089 (61.8)**	**1,472 (41.9)**	
Yes	**2,714 (51.5)**	**672 (38.2)**	**2,042 (58.1)**	
Vital signs, mean ± SD				
Temperature (℃), mean ± SD	**36.6 ± 1.0**	**36.7 ± 0.9**	**36.6 ± 1.1**	**0.044**
Heart rate (bpm), mean ± SD	**93.7 ± 21.5**	**91.8 ± 21.2**	**94.7 ± 21.6**	**< 0.001**
MAP (mmHg), mean ± SD	**80.6 ± 19.8**	**79.8 ± 18.8**	**81.0 ± 20.3**	**0.037**
Respiratory rate (bpm), mean ± SD	**21.1 ± 6.4**	**20.4 ± 6.1**	**21.5 ± 6.4**	**< 0.001**
SpO_2 (%), mean ± SD	**96.2 ± 4.8**	**96.5 ± 4.2**	**96.1 ± 5.0**	**< 0.001**
SBP (mmHg), mean ± SD	**119.9 ± 25.3**	**120.5 ± 25.2**	**119.6 ± 25.3**	**0.243**
DBP (mmHg), mean ± SD	**66.6 ± 19.0**	**65.9 ± 18.1**	**67.0 ± 19.4**	**0.048**
Laboratory tests				
GLU (mg/dL), median (IQR)	**134.0 (106.0, 179.0)**	**129.0 (104.0, 169.0)**	**137.0 (107.0, 185.0)**	**< 0.001**
BUN (mg/dL), median (IQR)	**29.0 (18.0, 48.0)**	**27.0 (16.0, 44.0)**	**30.0 (19.0, 50.0)**	**< 0.001**
Cr (ng/dL), median (IQR)	**1.3 (0.9, 2.2)**	**1.2 (0.8, 2.0)**	**1.3 (0.9, 2.2)**	**< 0.001**
Sodium (mmol/L), mean ± SD	**137.6 ± 6.9**	**137.1 ± 6.7**	**137.8 ± 7.0**	**< 0.001**
Potassium (mmol/L), mean ± SD	**4.4 ± 1.0**	**4.3 ± 0.9**	**4.5 ± 1.0**	**< 0.001**
Calcium (mmol/L), mean ± SD	**8.3 ± 1.1**	**8.3 ± 1.0**	**8.3 ± 1.1**	**0.464**
WBC (10^9/L), median (IQR)	**12.1 (7.8, 17.3)**	**10.9 (7.1, 15.8)**	**12.7 (8.3, 18.2)**	**< 0.001**
Hemoglobin (g/dL), mean ± SD	**10.5 ± 2.5**	**10.2 ± 2.4**	**10.6 ± 2.5**	**< 0.001**
RBC (10^{12}/L), median (IQR)	**3.5 (2.9, 4.1)**	**3.4 (2.8, 4.0)**	**3.5 (2.9, 4.1)**	**< 0.001**
RDW (%), mean ± SD	**16.2 ± 2.7**	**16.0 ± 2.5**	**16.3 ± 2.8**	**0.002**
Platelet (10^9/L), median (IQR)	**187.0 (117.0, 271.0)**	**198.0 (128.0, 280.0)**	**181.5 (111.0, 265.0)**	**< 0.001**
Accompanied diseases (comorbidity)				
Myocardial infarct, n (%)	**1,060 (20.1)**	**236 (13.4)**	**824 (23.4)**	**< 0.001**
Congestive heart failure, n (%)	**1,908 (36.2)**	**569 (32.3)**	**1,339 (38.1)**	**< 0.001**
Chronic pulmonary disease, n (%)	**1,547 (29.3)**	**526 (29.9)**	**1,021 (29.1)**	**0.54**
Diabetes, n (%)	**579 (11.0)**	**193 (11)**	**386 (11)**	**0.978**
Renal disease, n (%)	**1507 (28.6)**	**528 (30)**	**979 (27.9)**	**0.107**
Malignant cancer, n (%)	**1240 (23.5)**	**426 (24.2)**	**814 (23.2)**	**0.407**
Severe liver disease, n (%)	**743 (14.1)**	**271 (15.4)**	**472 (13.4)**	**0.054**
Score system				
SOFA, mean ± SD	**4.2 ± 2.4**	**3.9 ± 2.1**	**4.4 ± 2.5**	**< 0.001**

Abbreviations: LDH - lactate dehydrogenase, MAP - mean arterial pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, GLU - Glucose, BUN - blood urea nitrogen, Cr - creatinine, WBC - white blood cell count, RBC - red blood cell count, RDW - red blood cell distribution width.

LDH level and 30-day mortality in patients with sepsis

In this study, we performed univariate cox regression analysis of the base-line variables, including vital signs, laboratory test, comparability, and Score system, as shown in Table 2. The universal analysis indicated that

Table 2. Univariate COX regression analysis of risk factors and 30-day mortality in patients with sepsis.

Variables	HR (95% CI)	p
Gender		
Male	ref.	
Female	0.9916 (0.9192, 1.0696)	0.826
Age	0.9987 (0.9962, 1.0013)	0.336
MBP (mmHg)	0.9985 (0.9965, 1.0005)	0.132
Temperature (℃)	0.88 (0.85, 0.91)	< 0.001
SBP (mmHg)	0.9966 (0.9951, 0.9982)	< 0.001
DBP (mmHg)	1.0001 (0.9981, 1.0021)	0.916
SpO_2 (%)	0.98 (0.97, 0.99)	< 0.001
Respiratory rate (bpm)	1.02 (1.02, 1.03)	< 0.001
Heart rate (bpm)	1.0045 (1.0028, 1.0062)	< 0.001
GLU (mg/dL)	1 (1, 1)	0.005
BUN (mg/dL)	1.0032 (1.0019, 1.0044)	< 0.001
Cr (ng/dL)	1.0045 (0.9841, 1.0253)	0.667
Sodium (mmol/L)	1.0019 (0.9965, 1.0074)	0.484
Potassium (mmol/L)	1.06 (1.02, 1.1)	0.001
Calcium (mmol/L)	0.98 (0.95, 1.02)	0.28
Hemoglobin (g/dL)	1.04 (1.02, 1.05)	< 0.001
Platelet (10^9/L)	0.9997 (0.9994, 1)	0.06
RBC (10^{12}/L)	1.07 (1.02, 1.12)	0.003
RDW (%)	1.02 (1.01, 1.04)	0.002
WBC (10^9/L)	1.003 (1.0012, 1.0048)	0.001
LDH (Log_2)	1.36 (1.33, 1.4)	< 0.001
Myocardial Infarct		
No	ref.	
Yes	1.14 (1.04, 1.25)	0.004
Congestive heart failure		
No	ref.	
Yes	0.91 (0.84, 0.98)	0.013
Chronic pulmonary disease		
No	ref.	
Yes	0.91 (0.84, 0.99)	0.036
Diabetes		
No	ref.	
Yes	0.75 (0.66, 0.86)	< 0.001
Renal disease		
No	ref.	
Yes	0.84 (0.77, 0.91)	< 0.001
Malignant cancer		
No	ref.	
Yes	0.92 (0.84, 1.01)	0.071
Severe liver disease		
No	ref.	
Yes	1.19 (1.08, 1.32)	< 0.001
SOFA	1.07 (1.06, 1.09)	< 0.001

Note: data presented as HR and 95% CI.
Abbreviations: LDH - lactate dehydrogenase, MAP - mean arterial pressure, SBP - systolic blood pressure, DBP - diastolic blood pressure, GLU - Glucose, BUN - blood urea nitrogen, Cr - creatinine, WBC - white blood cell count, RBC - red blood cell count, RDW - red blood cell distribution width.

Table 3. Relationship between LDH and 30-day mortality of sepsis.

Variable	Non-adjusted		Adjustment I		Adjustment II	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
LDH (Log_2)	1.36 (1.33 - 1.4)	< 0.001	1.37 (1.33 - 1.41)	< 0.001	1.33 (1.29 - 1.37)	< 0.001
Binary variable						
LDH < 250 IU/L	1 (ref.)		1 (ref.)		1 (ref.)	
LDH ≥ 250 IU/L	1.86 (1.7 - 2.03)	< 0.001	1.86 (1.7 - 2.02)	< 0.001	1.69 (1.54 - 1.85)	< 0.001

Note: data presented are HR and 95% CI.
Non-adjusted: no covariances were adjusted; adjustment I model: adjusted for age and gender; adjustment II model: adjusted for all covariances in Table 1.
Abbreviations: LDH - lactate dehydrogenase, HR - hazard ratio, CI - confidence interval.

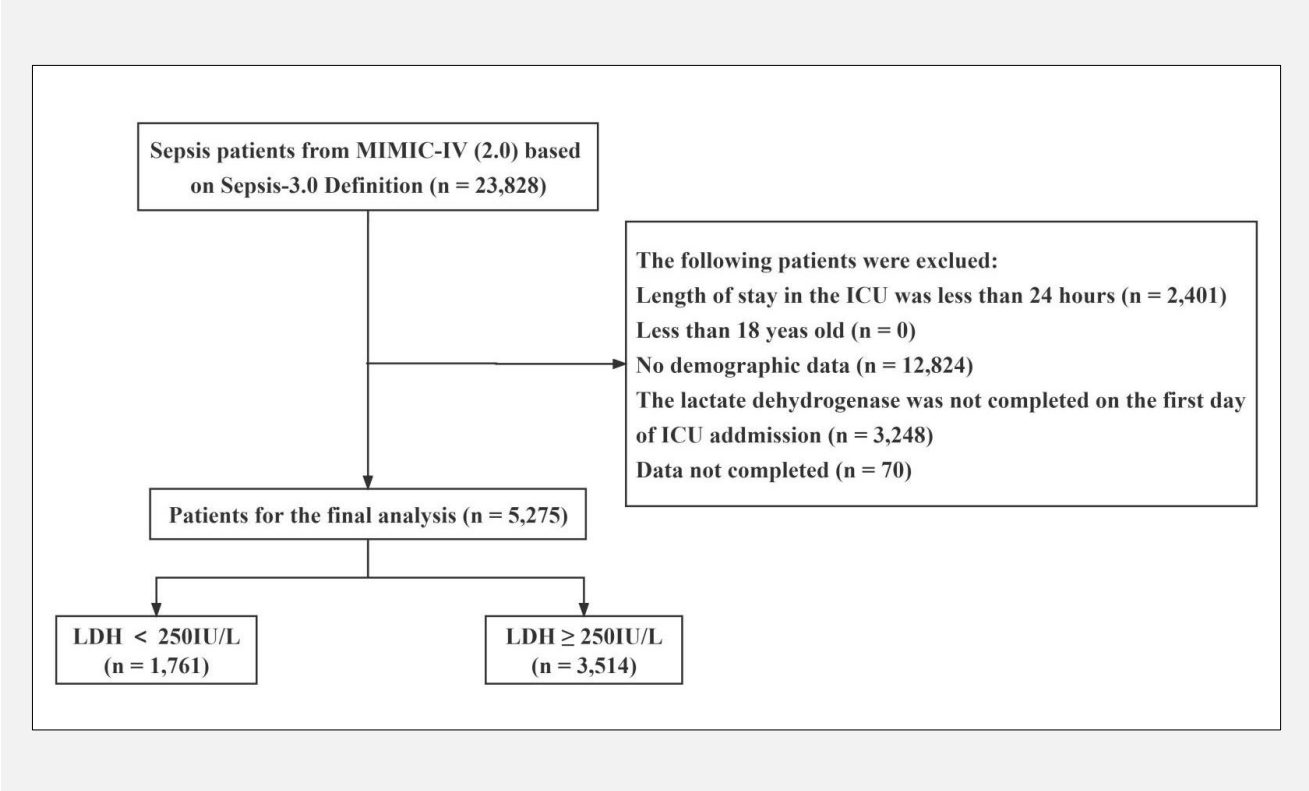

Figure 1. Flow chart of patient disposition.

temperature, SBP, SpO_2, RR, HR, BUN, HGB, Diabetes, Renal disease, Severe liver disease and SOFA were associated with 30-day mortality ($p < 0.001$).

HR and corresponding 95% CI for risk for 30-day mortality according to LDH (Log2) and LDH ≥ 250 IU/L are summarized in Table 3. In the minimally adjusted model adjusted for age and gender, the 30-day mortality was increased in the LDH ≥ 250 IU/L group compared with the LDH < 250 IU/L group, with an HR of 1.86 (95% CI: 1.7 - 2.02). After adjusting all covariances, the HR and 95% CI was 1.69 (1.54 - 1.85). The statistical results of all models are robust.

Kaplan-Meier survival curve analysis

According to the LDH level, the Kaplan-Meier survival curve was used to show the 30-day mortality of sepsis patients. The results showed that there was a statistically significant difference between LDH level and the 30-day mortality in sepsis patients ($p < 0.001$).

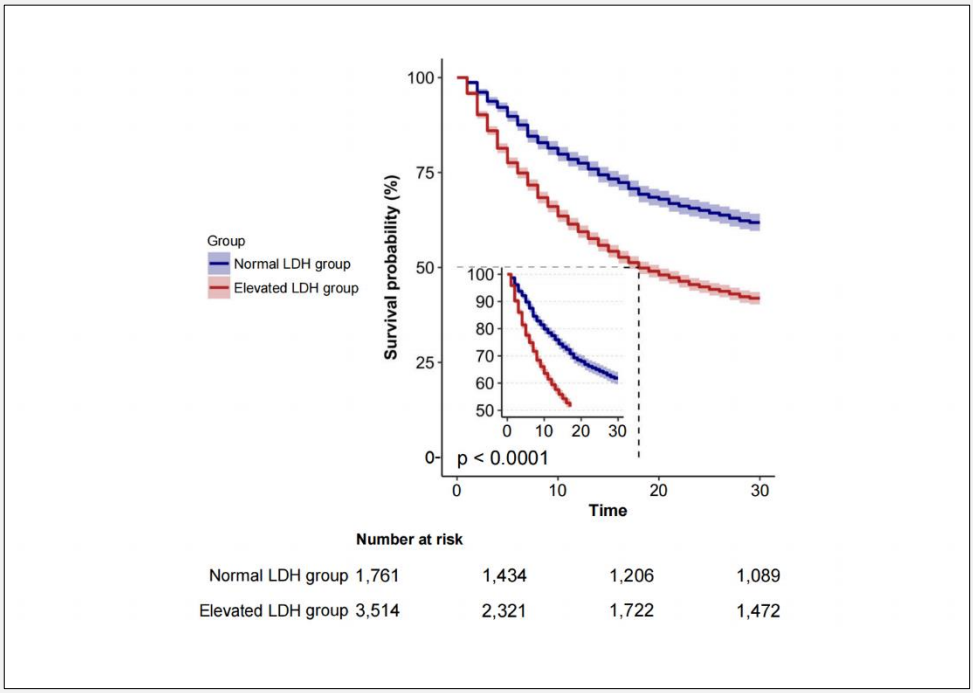

Figure 2. Kaplan-Meier survival curves at day 30 in sepsis patients.

DISCUSSION

Sepsis remains a major burden worldwide, with an estimated 31.5 million cases and 5.3 million deaths worldwide each year [10,11]. A meta-analysis of morbidity and mortality in patients with sepsis by Fieischmann-Struzek et al. found that the mortality rate for sepsis in hospitalized and ICU patients was 26.7% and 41.9%, respectively [3]. In this study, the estimated mortality in the ICU accounted for 51.5%, which is higher than the proportion reported in the literature, but similar to that reported by Ali Duman [12], which illustrated that sepsis remains the leading cause of death from ICU infections. At present, although many studies have been devoted to finding effective predictors of premature mortality and severity of sepsis, there are still no widely recognized markers.

In infectious disease diagnoses, if only relying on symptoms, signs, and imaging manifestations, sometimes are difficult. At this time, the detection of infection-related markers is of profound significance for the reference of differential diagnosis. At present, common biomarkers of infection are CRP, PCT, IL-6, IL-10, IL-8, WBC, BUN, etc. They cannot only judge the severity of infection, but also correspond to the prognosis and mortality of patients. LDH is just an enzyme involved in glucose metabolism, and its final step in aerobic oxidation converts pyruvate to lactate, which produces energy in living organisms [8,13]. LDH is present in almost all types of human cells, with high levels in lung, muscle, kidney, and blood cells, as well as cells in the heart and liver. Serum LDH levels are elevated by cellular damage and systemic inflammatory responses from local infection, and they increase with the severity of the infection [14,15]. Therefore, some studies have reported that LDH level is a prognostic factor for many diseases, including cell damage, malignancy, infarction, certain inflammatory diseases, etc. [6,12,16-18].

At present, there are some studies on the relationship between LDH levels and clinical outcomes in patients, but they are all based on small samples. Hence, it necessary to further investigate this problem using a database. Zein et al. reported that unstable LDH levels within the first 48 hours were an important indicator of mortality in patients with severe sepsis. Jun Lu et al. studied the relationship between LDH and 28-day mortality in 192 patients with sepsis, and the results showed that elevated LDH level was an independent risk factor for death and was significantly associated with increased 28-day mortality in patients with sepsis [5]. So, Yong Jeon et al. proposed LDH/ALB (lactate dehydrogenase-to-albumin ratio) as one of the prognostic factors in patients with sepsis [19]. Unlike previous studies, in this study, we considered the effect of several covariance indica-

tors, including vital signs, validation measures, and underlying disease of the patient, when examining LDH and early sepsis mortality. In this way, this study may provide a more comprehensive understanding of whether LDH has an effect on early death from sepsis. Interestingly, our findings were robust, both before and after adjustment, indicating that LDH was a prognostic factor for sepsis, and higher LDH levels were associated with higher risk of death in patients

In addition, survival analysis indicated that the elevated LDH group had earlier death time compared with the normal LDH group. The result suggested that LDH level was associated with the in-hospital 30-day mortality and survival of sepsis patients. Thus, early and effective treatment is of great importance. Previous studies have shown that a high concentration of LDH and age is associated with a high risk of early death in patients with sepsis. Studies have shown that LDH is associated with hypoxia conditions and glycolysis, converting pyruvate into lactic acid and NADH into NAD+ [20]. Some studies suggested that the reprogramming of glucose metabolism in immune cells is related to the mortality of sepsis. In the process of utilizing LDH for glycolysis, immune cells produce a large number of inflammatory factors and accumulation of lactic acid, which promotes the progression of sepsis. Most previous studies reported that serum LDH was an independent prognostic indicator in patients with sepsis, the higher the LDH level, the shorter the survival time.

This large retrospective study collected a large number of factors associated with sepsis mortality and adjusted them to assess their impact on prognosis. The results suggest that LDH level was associated with death in patients with sepsis and may be an independent risk indicator for the prognosis of sepsis. The LDH levels obtained in this study were all the results of the first day of septic patients after entering the ICU, which avoided the changes in LDH levels caused by disease progression and treatment to the greatest extent. LDH is a routine biochemical index, which is easier to obtain. However, this study also has some limitations: First, we did not study the correlation of LDH with inflammatory factors and lactate. We also did not further study the role of LDH in glucose reprogramming. Second, some key clinical indicators associated with prognosis, such as albumin, were excluded due to the lack of various specific values in some patients. Third, our research is only based on online data analysis of the database, and further external validation is required.

In summary, LDH level is associated with death in patients with sepsis. The higher the LDH level, the higher the patient mortality rate. Therefore, LDH can be used as an independent risk index to judge the prognosis of patients with sepsis.

CONCLUSION

In conclusion, this study demonstrates that elevated LDH levels are independently associated with increased 30-day mortality in patients with sepsis, but further study is needed to confirm this association.

Declaration of Interest:

The authors declare that there are no conflicts of interest.

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