Influence of Lactate on Prognostic Value of Patients with Septic Shock

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Abstract: The latest time for lactate measurement in patients with septic shock in the intensive care unit (ICU) is still controversial, and there is little mention of the significant impact of lactate levels on patient mortality. This study aims to use statistical methods to analyze and predict the prognosis of patients with septic shock using lactate measurement values. All data comes from the eICU collaborative research database. This study first used statistical methods to describe the baseline characteristics of patients. Then, the optimal judgment threshold for lactate measurement was determined using the Jordan index, and patients were divided into two groups based on the optimal threshold. Based on this, survival analysis was conducted using the Kaplan Meier curve and the binary values of lactate levels, while conducting a multivariate analysis. Finally, the relationship between the latest measurement time of lactate and outcome was found through smooth curve fitting. The main exposed factor is lactate measurement, and the main outcome is 28 days mortality. The study included 5776 eligible patients with septic shock, including 4920 surviving patients and 856 deceased patients. Observations have confirmed that patients with severe sepsis or septic shock whose lactate value exceeds 2.29 mmol/L after entering the ICU have an increased risk of death. At the same time, the latest lactate measurement time after entering the ICU is 0.42 days, which is about 10 hours before entering the ICU ward; otherwise, it will endanger the patient's life.

Keywords: Septic Shock; Lactate; Prognosis; Mortality Rate; eICU Collaborative Research Database

1. Introduction

1.1 Research Background and Significance

Septic shock is one of the most common critical situations in emergency departments and ICUs. Septic shock, also known as septic shock, is mainly caused by the invasion of various pathogenic microorganisms into the body. Septic shock can also be induced by diseases such as bacteremia, pneumonia, cholangitis, abdominal infections, and skin and soft tissue infections. Professor Du Bin of Peking Union Medical College Hospital in China found that the incidence rate of sepsis in China is very high, with nearly 2.5 million people suffering from sepsis. Among them, the annual death toll from severe septic shock is about 700000, bringing a huge burden to society and families.

Early prediction and timely treatment are crucial for patients with septic shock. Early prediction and timely treatment are crucial. Ji Meiling provided the diagnostic criteria for sepsis: infection+Sequential Organ Failure Assessment (SOFA) score>=2 points. Diagnostic criteria for septic shock: Those who meet the above diagnostic criteria for sepsis and experience sustained hypotension, still require vasopressor medication to maintain mean arterial pressure (MAP)>=65 mmHg (1 mmHg=0.133 kPa), and lactate (Lac)>2.0 mmol/L [1]. Blood lactate concentration is an important parameter for evaluating the prognosis of critically ill patients, and the use of serum lactate can help clinical doctors make more appropriate decisions in the prognosis management of septic shock patients. In addition, lactic acid may also increase due to other reasons, such as comorbidity, including diabetes and liver disease, and overemphasizing the level of lactic acid without considering clinical conditions may also lead to unnecessary intervention, hospitalization or higher level of care. Given the high mortality rate of septic shock and the necessity of early prediction, it is reasonable to include lactate monitoring in clinical decision-making in order to facilitate the management of septic shock and consider patient prognosis.

1.2 Current Research Status at Home and Abroad

Septic shock is a subtype of sepsis, which is essentially caused by tissue ischemia and hypoxia due to insufficient effective circulating blood volume. Usually, metabolic disorders occur in the body before clinical hemodynamic changes, and blood lactate levels are an important indicator. In recent years, research on lactic acid and sepsis has shown that early identification and appropriate management can improve the prognosis of patients with septic shock. Ji et al. showed that in shock patients, the death group showed sustained high lactate levels within the first 24 hours, while in patients with good prognosis, lactate levels gradually decreased[1]. Ma and Lu. proposed that sepsis and septic shock are related to hyperlactatemia, and the higher the lactate concentration, the worse the prognosis [2]. When the serum lactate concentration is greater than 10 mmol/L, the patient mortality rate can reach 80%, as recorded by Bai Huiying in the compilation of critical illness emergency medicine in China [3]. The medical journal compiled by Yang Mingxing shows that if severe lactic acidosis persists for 48 hours, the mortality rate can reach 100% [4]. Li et al. found that blood lactate concentration is an important parameter for evaluating the prognosis of critically ill patients [5]. Howell et al. [6], Mikkelsen et al. [7], Wacharasint et al. [8] also confirmed that lactate levels can serve as a predictive indicator of mortality in sepsis patients. Nichol et al. [9], Dellinger et al.[10]. The existing evidence from Kang YR et al. suggests that current guidelines may be overly conservative in recommending resuscitation only for sepsis patients with a blood lactate concentration of at least 4.0 mmol/L [11]. Although lactate levels above 4.0 mmol/L are significantly associated with high mortality in sepsis patients, lactate levels between 2.0 and 4.0 mmol/L are often ignored to differentiate septic shock, which may lead to over diagnosis and unnecessary incidence rate and mortality.

In order to effectively evaluate the prognostic value of lactate in predicting septic shock patients, this study conducted a retrospective observational cohort study on adult patients with sepsis. The research results indicate that lactate levels exceeding 2.29 mmol/L are the optimal threshold for predicting 28 day mortality in sepsis patients.

2. Materials and Methods

2.1 Data Source and Introduction

The research data in this article comes from the eICU collaborative research database. The eICU database consists of ICU ward data from numerous hospitals in the United States. The current version is v2.0, released on May 17, 2018, and covers routine data from over 200000 patients admitted to intensive care units in 2014 and 2015. It collects a large amount of high-quality clinical information, including vital signs, care plans, disease severity, diagnostic information, treatment information, etc, It effectively solves the current situation of medical personnel lacking big data for clinical research. This article selects complete information of septic shock patients from the database for research.

2.2 Study Population

Due to incomplete or biased data or errors in patient related information, in order to ensure that experimental data is not affected by these factors. It is necessary to use data processing software to conduct a screening and select subjects that meet the standards. Exclusion criteria: Patients under the age of 18 or who have been in the ICU for less than 48 hours are excluded. For patients who have been admitted to the ICU more than once, only the first admission to the ICU is included in the analysis. Patients with leukemia and metastatic tumors are also excluded and only sepsis patients are included. Finally, this article did not perform missing value filling, which excluded invalid values. In the end, 5776 patients were included in our study. The flowchart of the discharge standard is shown in Figure 1.

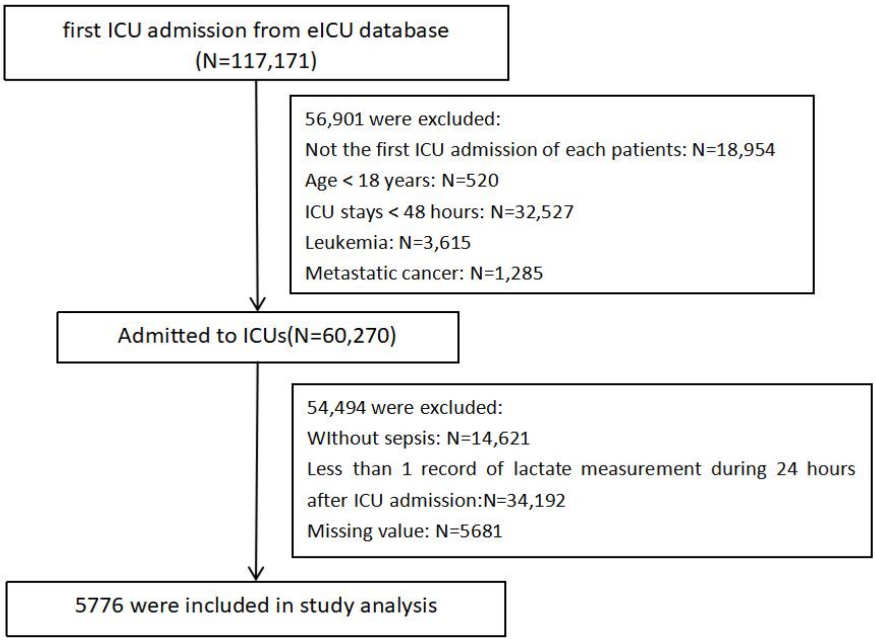

Figure 1. Patient Selection Flowchart

2.3 Data Extraction

This article collects and records the following data: Patientunitstayid, intubated, dialysis, GSC_SCORE (Glasgow Coma Scale is a medical method for assessing the degree of coma in patients. The degree of coma is evaluated by adding the scores of the three factors (vision, muscle, and speech)). The higher the score, the better the state of consciousness. WBC(white blood cell count), temperature, respiratorate, sodium, heart rate, meanbp (mean blood pressure), hematocrit, BUN(urea nitrogen), glucose, and acute physiology score, apache score(acute physiology and chronic health score), diabetes, gender, age, ethnicity, hospital discharge year, Unittype (admission type), Admissionweight, Los.Day (length of hospitalization), D28(28 day mortality rate), LAC(lactate, in hours), LAC_Day (lactate, in days), SEP (septic shock patients). Admitdiagnosis.001 (SEPSISPULM), Admitdiagnosis.005 (SEPSIUTI), Admitdiagnosis.014 (SEPSISGI), Admitdiagnosis.017 (SEPSIUNK), Admitdiagnosis.027 (SEPSICUT), Admitdiagnosis.034 (SEPSISOTH), Admitdiagnosis.236 (SEPSISGYN).

2.4 Statistic Analysis

Continuous variables are represented by mean ± standard deviation (SD), while categorical variables are represented by numbers and percentages. The comparison of continuous variables between groups is conducted using the Student t-test or Mann Whitney U-test (depending on the situation). The comparison of categorical variables between groups was conducted using Pearson chi square test or Fisher's exact test (depending on the situation). Logistic regression analysis is used to evaluate the differences in mortality rates between two groups, while covariance analysis is used to evaluate the differences in consecutive results. EmpowerStats is used for all statistical analysis and calculations (http://www.empowerstats.com X&Y Solutions, Inc, Boston, MA) and R version 4.0.5 (http://www.R-project.org, The R Foundation). A double tailed P value of<0.05 indicates a statistically significant difference.

3. Results

3.1 Study Population Description

A total of 5776 patients with septic shock were screened and included in the study (Figure 1). The general situation of the patient population can be understood through the data in Table 1.

Table 1. Study Population Description

D28	Survived(N=4920)	Died(N=856)	Standardize diff.	P-value
WBC	16.02 ± 10.57	18.14 ± 13.48	0.18 (0.10, 0.25)	<0.001
TEMPERATURE	36.61 ± 1.27	35.99 ± 2.62	0.30 (0.23, 0.37)	<0.001
RESPIRATORYRATE	30.51 ± 14.56	32.55 ± 13.46	0.15 (0.07, 0.22)	<0.001
SODIUM	137.97 ± 6.69	137.30 ± 7.30	0.09 (0.02, 0.17)	0.008
HEARTRATE	114.59 ± 28.04	117.37 ± 28.15	0.10 (0.03, 0.17)	0.008
MEANBP	77.99 ± 45.52	72.69 ± 44.80	0.12 (0.04, 0.19)	0.002
HEMATOCRIT	31.17 ± 6.46	29.89 ± 6.37	0.20 (0.13, 0.27)	<0.001
BUN	37.08 ± 26.66	44.10 ± 26.34	0.26 (0.19, 0.34)	<0.001
GLUCOSE	172.98 ± 112.70	171.29 ± 120.54	0.01 (-0.06, 0.09)	0.689
ACUTEPHYSIOLOGYSCORE	62.89 ± 22.56	77.11 ± 26.42	0.58 (0.51, 0.65)	<0.001
APACHESCORE	75.87 ± 23.59	92.74 ± 26.41	0.67 (0.60, 0.75)	<0.001
AGE	65.15 ± 15.62	69.16 ± 13.09	0.28 (0.21, 0.35)	<0.001
ADMISSIONWEIGHT	84.22 ± 27.92	78.56 ± 25.21	0.21 (0.14, 0.29)	<0.001
LOS.DAY	10.91 ± 8.23	8.07 ± 5.59	0.40 (0.33, 0.48)	<0.001
LAC	2.06 ± 1.76	2.91 ± 2.93	0.35 (0.28, 0.43)	<0.001
LAC_DAY	0.29 ± 0.26	0.33 ± 0.28	0.16 (0.08, 0.23)	<0.001
INTUBATED			0.34 (0.27, 0.41)	<0.001
0	3691 (75.02%)	508 (59.35%)		
1	1229 (24.98%)	348 (40.65%)		
DIALYSIS			0.06 (-0.01, 0.13)	0.099
0	4635 (94.21%)	794 (92.76%)		
1	285 (5.79%)	62 (7.24%)		
GSC_SCORE			0.31 (0.24, 0.39)	<0.001
3	291 (5.91%)	81 (9.46%)		
4	33 (0.67%)	7 (0.82%)		
5	31 (0.63%)	10 (1.17%)		
6	193 (3.92%)	42 (4.91%)		
7	227 (4.61%)	74 (8.64%)		
8	239 (4.86%)	58 (6.78%)		
9	208 (4.23%)	39 (4.56%)		
10	314 (6.38%)	31 (3.62%)		
11	242 (4.92%)	39 (4.56%)		
12	221 (4.49%)	41 (4.79%)		
13	401 (8.15%)	81 (9.46%)		
14	683 (13.88%)	109 (12.73%)		
15	1837 (37.34%)	244 (28.50%)		
DIABETES			0.08 (0.01, 0.15)	0.029
0	3547 (72.09%)	648 (75.70%)		
1	1373 (27.91%)	208 (24.30%)		
ADMITDIAGNOSIS.001			0.20 (0.13, 0.27)	<0.001
0	2962 (60.20%)	431 (50.35%)		
1	1958 (39.80%)	425 (49.65%)		
ADMITDIAGNOSIS.005			0.25 (0.18, 0.33)	<0.001
0	3762 (76.46%)	738 (86.21%)		
1	1158 (23.54%)	118 (13.79%)		

GENDER			0.04 (-0.03, 0.12)	0.226
0	2528 (51.38%)	459 (53.62%)		
1	2392 (48.62%)	397 (46.38%)		
ETHNICITY			0.13 (0.05, 0.20)	0.083
0	3915 (79.57%)	684 (79.91%)		
1	406 (8.25%)	92 (10.75%)		
2	251 (5.10%)	37 (4.32%)		
3	174 (3.54%)	24 (2.80%)		
4	99 (2.01%)	10 (1.17%)		
5	51 (1.04%)	6 (0.70%)		
6	24 (0.49%)	3 (0.35%)		
HOSPITALDISCHARGEYEAR			0.10 (0.03, 0.17)	0.006
2014	2078 (42.24%)	405 (47.31%)		
2015	2842 (57.76%)	451 (52.69%)		
UNITTYPE			0.19 (0.12, 0.26)	<0.001
0	3216 (65.37%)	541 (63.20%)		
1	703 (14.29%)	140 (16.36%)		
2	121 (2.46%)	12 (1.40%)		
3	268 (5.45%)	73 (8.53%)		
4	100 (2.03%)	10 (1.17%)		
5	290 (5.89%)	56 (6.54%)		
6	139 (2.83%)	16 (1.87%)		
7	83 (1.69%)	8 (0.93%)		
ADMITDIAGNOSIS.027			0.14 (0.06, 0.21)	<0.001
0	4528 (92.03%)	816 (95.33%)		
1	392 (7.97%)	40 (4.67%)		
ADMITDIAGNOSIS.014			0.00 (-0.07, 0.08)	0.929
0	4276 (86.91%)	743 (86.80%)		
1	644 (13.09%)	113 (13.20%)		
ADMITDIAGNOSIS.034			0.03 (-0.04, 0.10)	0.415
0	4682 (95.16%)	809 (94.51%)		
1	238 (4.84%)	47 (5.49%)		
ADMITDIAGNOSIS.017			0.08 (0.00, 0.15)	0.035
0	4402 (89.47%)	745 (87.03%)		
1	518 (10.53%)	111 (12.97%)		
ADMITDIAGNOSIS.236			0.00 (-0.07, 0.07)	0.955
0	4908 (99.76%)	854 (99.77%)		
1	12 (0.24%)	2 (0.23%)		

Note: D28 (28 day mortality rate), WBC (white blood cell count), meanbp (mean blood pressure), BUN (urea nitrogen), apache score (acute physiology and chronic health score), Los.Day (length of hospitalization), LAC (lactate, in hours), LAC_Day (lactate, in days), GSC_SCORE (Glasgow Coma Scale is a medical method for assessing the degree of coma in patients. The degree of coma is evaluated by adding the scores of the three factors (vision, muscle, and speech)), Unittype (admission type), Admitdiagnosis.001 (SEPSISPULM), Admitdiagnosis.005 (SEPSIUTI), Admitdiagnosis.014 (SEPSISGI), Admitdiagnosis.017 (SEPSIUNK), Admitdiagnosis.027 (SEPSICUT), Admitdiagnosis.034 (SEPSISOTH), Admitdiagnosis.236 (SEPSISGYN).

As shown in the above table, among these 5776 patients, 4920 survived and 856 died. This article provides an example to illustrate the meaning of this table. For example, the variable age AGE, the survival group is 65.15 ± 15.62 (mean ± standard deviation) people, and the death group is 69.16 ± 13.09 people, with a P value of<0.001. This indicates that the difference between the two groups is significant and statistically significant. In sepsis patients, age is one of the influencing factors, and the age of the death group is significantly higher than that of the survival group. Therefore, for clinical practice, medical staff should pay attention to the age of ICU patients, Any other variable with a P value<0.05 has statistical significance. Meanwhile, if the P value of the variable gender GENDER is 0.226, which is much greater than 0.05, it indicates that there is no reference value for gender impact in sepsis patients, and other variables with P values greater than 0.05 are also the same.

3.2 ROC Analysis

The receiver operating characteristic curve, abbreviated as ROC curve, has a false positive rate on the horizontal axis and a true positive rate on the vertical axis. The ROC curve evaluates diagnostic performance by measuring the area under the curve (AUC), with values between 1.0 and 0.5. The closer the AUC is to 1, the better the diagnostic performance. Sensitivity refers to the proportion of individuals who are correctly diagnosed as patients by screening methods. Specificity refers to the proportion of individuals who are not actually affected by the disease and can be correctly identified as non patients by screening methods. The Youden Index is the sum of sensitivity and specificity minus 1, reflecting the total ability of true patients and non patients. The higher the Youden Index, the greater the authenticity. Meanwhile, the value of the test variable corresponding to the maximum value of the Jordan index is the diagnostic threshold of the method, which is the optimal threshold corresponding to it in Table 2.

Table 2. ROC Analysis for Continuous Predictor

Test	1	0	ROC area(AUC)	95%CI low	95%CI upp	Best threshold	Specificity	Sensitivity
LAC	856	4920	0.6130	0.5907	0.6340	2.2900	0.7283	0.4334

Note: AUC confidence interval and significance test using non parametric resampling method (Bootstrap resampling times=500).

From the generated Table 2, it can be seen that the AUC is 0.613, which is somewhat persuasive. From the table, it can also be seen that the optimal threshold is 2.29. In our retrospective cohort study of 5776 patients with severe sepsis and septic shock admitted to the ICU, lactate levels exceeding the optimal threshold of 2.29mmol/L showed the highest sensitivity and specificity for 28 day mortality.

3.3 Kaplan Meier Survival Curve

The Kaplan Meier method is the most commonly used method for survival analysis, abbreviated as the KM method. The KM method calculates the survival probability of a patient in a certain period and the survival probability in the next period, and then multiplies each survival probability to obtain the corresponding survival rate for the corresponding period. Meanwhile, as a non parametric estimation method, it does not require the distribution form of the population, making it very suitable for use in survival analysis. The K-M curve can also intuitively display the survival or mortality rates of two or more groups, making it very suitable for presentation in the article. Therefore, the K-M curve has also become one of the most commonly used methods in clinical research. The KM curve of this paper is shown in Figure 2.

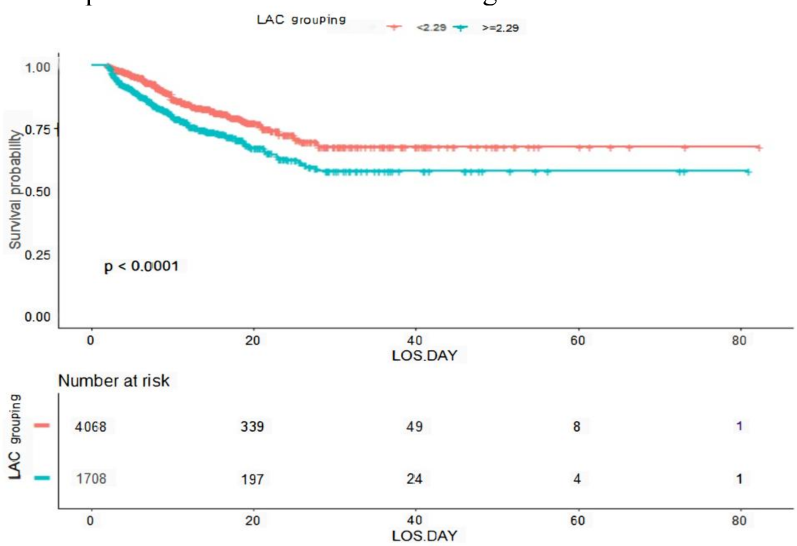

Figure 2. Kaplan Meier survival Curve

From the graph, it can be seen that the lactate value is divided into two groups. The mortality rate of patients with lactate values greater than 2.29 mmol/L is significantly higher than that of patients with lactate values less than 2.29 mmol/L. At the same time, the P value between the two groups is less than 0.0001, indicating a statistical difference. Therefore, for patients entering the ICU, critically ill patients with a lactate value greater than 2.29 mmol/L should be considered first. The critical value of 2.29mmol/L was obtained from the Jordan index in the previous section.

3.4 Smooth Curve Fitting

Smooth curve fitting is a commonly used data analysis method that can obtain a smooth two-point curve through statistical analysis of the data, thereby better reflecting the trend and pattern of the data. Smooth curve fitting is also a very effective method in inflection point analysis. By smoothing curve fitting, the relationship between lactate measurement time and outcome can be found, that is, the inflection point: the optimal measurement time for lactate, as shown in Figure 3.

The horizontal axis in the figure is the lactate value measured in days, the vertical axis is the 28 day mortality rate, the solid line in the middle is the fitting line, and the dashed line on both sides is the 95% confidence interval. It can be seen that the relationship between the two is an increasing curve. This graph confirms that at the optimal inflection point, which is 0.42 days, it is the latest lactate measurement time for patients after entering the ICU. Lactic acid must be measured within 10 hours of entering the ICU ward, otherwise exceeding it will endanger the patient's life. This inflection point can be obtained through threshold effect analysis, as shown in inflection point K in Table 3 below.

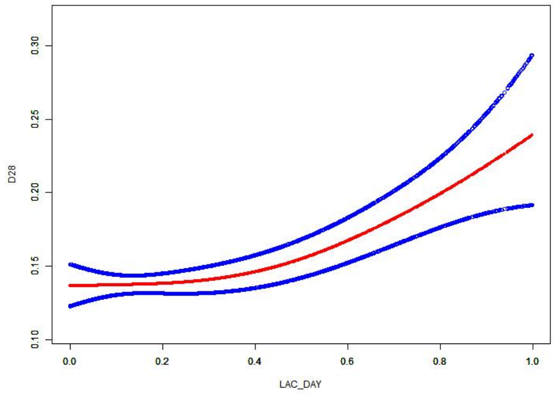

Figure 3. Smooth Curve Fitting

3.5 Multivariate Analysis

Multifactor analysis studies the combined effects of multiple factors on outcome variables simultaneously, considering both the individual effects of each factor and the interaction between multiple factors, as shown in Table 4 below.

Table 3. Threshold Effect Analysis

Outcome:	D28
model I	
One line effect	1.81 (1.39, 2.37) <0.0001
model II	
inflection point K	0.42
< -segment effect 1	0.93 (0.52, 1.67) 0.8050
> -segment effect 2	3.66 (1.99, 6.72) <0.0001
effect difference between 2 and 1	3.94 (1.34, 11.58) 0.0125
Predicted value of equation at inflection point	-1.86 (-2.02, -1.70)
Log Likelihood Ratio Tests	0.012

Note: Data in the table: β (95% CI) Pvalue/OR (95% CI) Pvalue
Result variable: D28
Exposure variable: LAC_ DAY
Adjusting variable: None

Table 4. Multifactor Analysis

Exposure	Non-adjusted	Adjust I	Adjust II
LAC grouping			
<2.29	1.0	1.0	1.0
>=2.29	2.05 (1.77, 2.38) <0.0001	1.96 (1.68, 2.28) <0.0001	1.54 (1.30, 1.81) <0.0001

Note: Data in the table: β (95% CI) Pvalue/OR (95% CI) Pvalue
Result variable: D28
Exposure variables: LAC grouping
Non-adjusted model adjust for: None
Adjust I model adjust for: AGE; GENDER; ADMISSIONWEIGHT; UNITTYPE
Adjust II model adjust for: GENDER; AGE; HOSPITALDISCHARGEYEAR; UNITTYPE; INTUBATED; DIALYSIS; GSC_SCORE; WBC; TEMPERATURE; RESPIRATORYRATE; SODIUM; HEARTRATE; MEANBP; HEMATOCRIT; BUN; GLUCOSE; ACUTEPHYSIOLOGYSCORE; APACHESCORE; DIABETES
Generalized estimate equation were used, subject ID=WBC (independence).

From the Table, it can be seen that the population with a lactate level exceeding 2.29mmol/L has a higher risk ratio. Based on the population without lactate water reaching 2.29mmol/L, represented by 1, the risk ratio without adjusting variables is 2.05, the adjusted model 1 is 1.96, and the adjusted model 2 is 1.54. The P-values are all less than 0.05, which are statistically significant.

4. Conclusion

Through this study, it has been shown that lactate levels have a high prognostic value for sepsis patients, which can provide reference for clinical doctors and have a positive impact on the prognosis of septic shock patients in the future. In our retrospective observational cohort study, it was confirmed that patients with severe sepsis or septic shock who had a lactate value exceeding 2.29 mmol/L after entering the ICU had a significantly increased risk of death. The study also confirmed that lactate values need to be measured within 0.42 days of entering the ICU, which means lactate must be measured right and left within 10 hours of admission, as exceeding this level can endanger the patient's life. Due to the need to place lactate levels in an appropriate clinical context to demonstrate their value as a prognostic factor for patients with septic shock, this study also has some limitations. This study did not analyze the correlation between another key factor, blood lactate clearance rate, and hospital mortality rate in sepsis patients. Some studies found that low serum lactate clearance rate clearly indicates poor prognosis in sepsis patients. Secondly, relevant research can be further expanded to clarify its value in evaluating the condition and prognosis of pediatric sepsis, thereby further guiding clinical treatment, preventing the deterioration of the disease or the occurrence of complications, and thus prolonging life.

Acknowledgements

The study of Molecular motors and Micro-andnano-heat engines of the non-Markovian dissipation (12365007); Science and Technology planning Project of Yunnan Province (202001AP070046).

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