

Relationship Between Serial Lactate Testing and Clinical Outcome of Critically Ill Patients With Sepsis

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Abstract

Objective Our study was to investigate the relationship between serial lactate testing (SLT) and the clinical outcome of critically ill patients with sepsis.

Materials and Methods This was a retrospective cohort study. We extracted the clinical data of patients with sepsis from the Medical Information Mart for Intensive Care version III, 1.4 database. Kaplan-Meier survival curves and multivariate logistic regression models were used to predict the relationship between clinical indicators and 28-day mortality. Receiver operating characteristic curves (ROCs) were used to analyze the impact of the maximum, minimum, and initial values of lactate on 28-day mortality; calculate the Youden index to take the best cutoff value; and then perform a subgroup analysis.

Results In total, 2367 patients with sepsis were enrolled, including 1961 in the SLT group and 406 in the non-SLT group. Clinical indicators seemed to be more serious in the SLT group than in the non-SLT group. ROC analysis results showed that the initial value, maximum value and minimum value of blood lactate had a significant impact on the 28-day mortality of patients, $P < 0.001$; multivariate logistic regression analysis indicated that SLT had a negative impact on 28-day mortality [OR=2.03, 95% CI (1.67, 3.60)], $p < 0.05$.

Conclusion We found that SLT was correlated with sepsis severity but might not improve the clinical outcome of critically ill patients with sepsis. Clinicians should pay attention to differential diagnosis of the source of lactate elevation; our study results need randomized controlled trials for further verification.

Introduction

Sepsis is a life-threatening organ dysfunction disease caused by the host's unregulated response to infection¹ and has the characteristics of high morbidity and mortality.²⁻⁴ Serial lactate testing (SLT) is essential for the risk stratification and management of sepsis.⁵ In addition, SLT is also an important indicator for evaluating the prognosis of patients with sepsis.⁶ Although recent guidelines recommend that patients with sepsis should have their blood lactate levels assessed every 2-4 hours until the lactate value is normal,⁵ whether SLT can predict the prognosis of patients with sepsis is still controversial.⁷⁻⁸

Some researchers have found that SLT can be used as a target for fluid resuscitation in patients with emergency sepsis, reducing pulmonary complications⁹ and 28-day mortality,¹⁰ shorting the ICU length of stay (ICULOS), and reducing vasoactive drugs and ventilator use.¹¹ In addition, veterinary studies have shown that SLT is a more useful prognostic indicator than single lactate monitoring for adult horses diagnosed with septic shock.¹² However, some studies have found that SLT does not improve the clinical outcomes of patients, including hospital mortality, because SLT is not the only factor in the sepsis bundle and may be affected by other measures.¹³ Some scholars believe that SLT performed within 6 hours in patients with sepsis is highly correlated with hospital mortality, but the patient's initial lactate value should be greater than 4 mmol/L.¹⁴

Therefore, the purpose of our study was to investigate the relationship between SLT and the clinical outcomes of patients with sepsis based on the MIMIC-III database. The primary observation endpoint was 28-day mortality, and the secondary observation endpoints were hospital mortality, ICU mortality, ICU length of stay (ICULOS), hospital length of stay (HLOS) and other outcome indicators, which provided clinicians with reliable medical decision-making.

Materials And Methods

1.1 Data Sources

This was a retrospective cohort study. All sepsis patient data were obtained from the MIMIC-III 1.4 database. MIMIC is a large, single-center, public critical care database of more than 40,000 ICU inpatients who were admitted to the intensive care unit of the Massachusetts Institute of Technology Affiliated Hospital from 2001 to 2012.¹⁵ We had applied for access to the database, and the qualification certificate number was 9730539. The sepsis diagnostic codes are 99591 and 99592. The diagnostic criteria for sepsis were based on meeting the third international consensus definition of sepsis and septic shock.¹ Data on patients with recurrent sepsis are only recorded on their first admission. We extracted clinical data through structured query language (SQL). Our research was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology.

We collected baseline data of patients within 24 hours of admission to the ICU, including age, sex, sequential organ failure assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) score, comorbidities (congestive heart failure, paralysis, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, rheumatoid arthritis, coagulopathy, obesity, deficiency anemias, alcohol abuse, drug abuse and depression), laboratory tests (the maximum/minimum value of serum creatinine, red blood cell distribution width [RDW], serum lactate [including the initial value], white blood cells [WBCs], platelets, hemoglobin, blood glucose, anion gap), and hemodynamic parameters (the maximum/minimum of the mean arterial pressure [MAP], dobutamine duration, norepinephrine duration and vasopressin duration). SLT was defined as more than 2 measurements within 24 hours of the patient's admission to the ICU. The primary endpoint of the study was the 28-day mortality of patients, and the secondary endpoints were hospital mortality, ICU mortality, HLOS, ICULOS, ventilator and continuous renal replacement therapy (CRRT) use within 24 hours of admission to the ICU.

1.2 Inclusion and exclusion criteria

According to ICD_9 codes (99591 and 99592), patients with sepsis were screened out. Exclusion criteria: only the first hospitalization data for patients who have been admitted to the ICU repeatedly; age <18 years or >75 years; ICULOS <24 hours; acquired immunodeficiency syndrome, lymphoma, metastatic cancer and solid tumors.

1.3 Statistical methods

We used Stata 16.0 statistical software. Continuous variables and normally distributed data are represented by the mean \pm standard deviation, nonnormally distributed data are represented by the median (interquartile range), and categorical variable data are represented by the percentage (rate). The Kaplan-Meier survival analysis method was used to predict the relationship between SLT and 28-day mortality. The receiver operating characteristic curve (ROC) was used to analyze the impact of the maximum, minimum and initial value of lactate on 28-day mortality, and the Yoden index was calculated to take the best cutoff value, and then a subgroup analysis was performed. The multivariate logistics regression model was used to predict the relationship between the dependent variables and 28-day mortality. The processing methods used for outliers included the median method, average method, missing value conversion method, and winsorization. Variables with missing values greater than 20% were directly deleted. Variables with missing values less than 20% were processed by the regression filling method and multiple interpolation method.

Results

2.1 General characteristics

A total of 5185 sepsis patients were enrolled, and only the first hospitalization data were retained for each patient (720 cases were excluded); other excluded cases included patient age <18 years or >75 years (1373 cases), ICULOS < 24 hours (64 cases), acquired immunodeficiency syndrome (39 cases), lymphoma (109 cases), metastatic cancer (327 cases) and solid tumors (186 cases). Therefore, 2367 patients were enrolled in the group, 1961 in the SLT group, and 406 in the non-SLT group (Figure 1). The SOFA score, SIRS score, serum creatinine, RDW, serum lactate, WBC, hemoglobin, blood glucose and anion gap in the SLT group were significantly higher than those in the non-SLT group ($P < 0.05$). Compared with the non-SLT group, the MAP of the SLT group was significantly lower, and the durations of dopamine, norepinephrine and vasopressin were significantly prolonged ($P < 0.05$). However, there were no significant differences in age, sex, comorbidities or platelets between the two groups ($p > 0.05$) (Table 1).

Table 1
General character of patients between the SLT group and non-SLT group

Variables	SLT n=1961	Non-SLT n= 406	P- value
Age, years,[IQR]	59.0(49.3,67.1)	60.6(49.1,66.9)	0.752
Male sex, n (%)	1133(57.8)	230(56.7)	0.676
SOFA score Within 24 hours of admission, [IQR]	6(4,9)	4(2,7)	<0.001
SIRS score Within 24 hours of admission,[IQR]	3(3,4)	3(2,4)	0.014
Comorbidities			
Congestive heart failure, n (%)	572(29.2)	103(25.4)	0.123
Paralysis,n (%)	101(19.2)	18(16.5)	0.574
Chronic pulmonary disease, n (%)	406(20.7)	77(19.0)	0.429
Diabetes, n (%)	220(11.2)	42(10.3)	0.609
Hypothyroidism, n (%)	219(11.2)	43(10.6)	0.736
Renal failure, n (%)	447(22.8)	80(19.7)	0.173
Liver disease, n (%)	386(19.7)	79(19.5)	0.917
Rheumatoid arthritis, n (%)	80(4.1)	20(4.9)	0.440
Coagulopathy, n (%)	525(26.8)	106(26.1)	0.783
Obesity, n (%)	180(9.2)	38(9.4)	0.909
Deficiency anemias, n (%)	564(28.8)	104(25.6)	0.200
Alcohol abuse, n (%)	215(11.0)	52(12.8)	0.285
Drug abuse, n (%)	106(5.4)	16(3.9)	0.224
Depression, n (%)	229(11.7)	39(9.6)	0.230
Laboratory tests(within 24 hours of admission)			
Serum creatinine _{max} ,mg/dl,[IQR]	1.7(1.0,3.5)	1.4(0.9,2.8)	<0.001
Serum creatinine _{min} ,mg/dl,[IQR]	0.9(0.5,1.2)	0.6(0.5,1.1)	0.011
RDW _{max} ,%,Mean±SD	17.2±3.0	16.7±3.0	0.002
RDW _{min} ,%,Mean±SD	15.1±1.9	14.9±1.9	0.040

Variables	SLT n=1961	Non-SLT n= 406	P- value
Serum lactate ₀ ,mmol/L,[IQR]	1.8(1.2,2.9)	1.6(1.1,2.4)	<0.001
Serum lactate _{max} ,mmol/L,[IQR]	3.9(2.5,6.3)	2.0(1.5,3.2)	<0.001
Serum lactate _{min} ,mmol/L,[IQR]	1.1(0.9,1.6)	0.9(0.7,1.3)	<0.001
WBC _{max} ,*10 ⁹ /L,[IQR]	14.8(9.2,20.1)	13.1(8.6,18.9)	0.011
WBC _{min} ,*10 ⁹ /L,[IQR]	10.8(6.7,15.9)	10.0(6.3,14.5)	0.020
Platelet _{max} ,*10 ⁹ /L,[IQR]	216.0(139,313.0)	213.5(133.0,296.0)	0.347
Platelet _{min} ,*10 ⁹ /L,[IQR]	147.0(100.0,258.0)	179.5(108.0,279.0)	0.196
Hemoglobin _{max} ,g/dL,Mean±SD	11.4±2.1	10.9±1.8	<0.001
Hemoglobin _{min} ,g/dL,Mean±SD	9.8±1.8	9.6±1.9	0.012
Blood glucose _{max} ,mg/dL,[IQR]	162.0(124.0,211.0)	140.0(115.0,186.0)	<0.001
Blood glucose _{min} ,mg/dL,[IQR]	110.0(93.0,130.0)	102.0(85.0,125.0)	<0.001
Anion gap _{max} ,mmol/L,[IQR]	17.6±5.4	15.8±4.0	<0.001
Anion gap _{min} ,mmol/L,[IQR]	13.6±3.9	13.2±3.5	0.032
Haemodynamics			
MAP _{max} ,mmHg,Mean±SD	100.1±23.6	104.0±29.9	0.014
MAP _{min} ,mmHg,Mean±SD	53.7±14.7	57.1±13.5	<0.001
Dopamine duration,h,[IQR]	5.9(2.4,37.6)	4.4(1.8,16.5)	0.024
Noradrenaline duration,h,[IQR]	13.0(4.6,19.0)	9.9(4.7,22.3)	0.009
Vasopressin duration,h,[IQR]	17.4(5.5±44.8)	13.0(4.0,37.0)	0.041
SLT, serial lactate testing; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; RDW, red blood cell distribution width; WBC, white blood cell; serum lactate ₀ ,initial value of serum lactate; serum lactate _{max} , maximum value of serum lactate; serum lactate _{min} , minimum value of serum lactate; MAP, mean arterial pressure.			

2.2 Clinical outcome

Twenty-eight-day mortality [282 (14.1) vs. 39 (9.6)], hospital mortality [314 (16.0) vs. 47 (11.6)], and ICU mortality [227 (11.6) vs. 27 (6.7)] were increased significantly in the SLT group compared with the non-SLT group ($P < 0.05$). In addition, HLOS [12.5 (6.6, 23.9) vs. 9.7 (5.4, 18.8)] and ICULOS [4.0 (2.0, 10.1) vs. 3.0 (1.6, 8.5)] were significantly prolonged in the SLT group ($P < 0.001$). Finally, the use of ventilators [1026 (52.3) vs. 101 (24.9)] and the use of CRRT [227 (11.6) vs. 32 (7.9)] increased significantly in the SLT group ($P < 0.05$) (Table 2).

Table 2
Clinical outcomes analysis between the SLT group and non-SLT group

Variables	SLT n=1961	Non-SLT n= 406	P-value
Primary outcome			
28-day mortality,n(%)	282(14.4)	39(9.6)	0.011
Secondary outcomes			
In-hospital mortality,n(%)	314(16.0)	47(11.6)	0.024
In-ICU mortality,n(%)	227(11.6)	27(6.7)	0.004
Hospital length of stay,day,[IQR]	12.5(6.6,23.9)	9.7(5.4,18.8)	<0.001
ICU length of stay,day,[IQR]	4.0(2.0,10.1)	3.0(1.6,8.5)	<0.001
Mechanical ventilation use _{1st day} ,n(%)	1026(52.3)	101(24.9)	<0.001
CRRT use _{1st day} ,n(%)	227(11.6)	32(7.9)	0.030
SLT, serial lactate testing; ICU,intensive care unit; CRRT,continuous renal replacement therapy.			

ROC analysis showed that the initial, maximum, and minimum values of serum lactate had a significant impact on the patient's 28-day mortality ($P < 0.001$). The areas under the curve were 0.694, 0.679 and 0.748, and the best cutoff values were 1.9, 2.7, and 1.3 (Figure 2). Survival analysis of subgroup variables showed that the initial value of serum lactate < 1.9 mmol/L was significantly better than that of serum lactate ≥ 1.9 mmol/L, the initial value of serum lactate < 2.7 mmol/L was significantly better than that of serum lactate ≥ 2.7 mmol/L, the initial value of serum lactate < 1.3 mmol/L was significantly better than that of serum lactate ≥ 1.3 mmol/L, and non-SLT was significantly better than SLT, $P < 0.05$ (Figure 3). In addition, further survival analysis based on hospital and ICU mortality revealed that there was no significant benefit for SLT patient survival (Figure 4).

Multivariate logistic regression analysis showed that some indicators had a significant impact on 28-day mortality, including age [OR= 1.02, 95% CI (1.01, 1.03)], SOFA score [OR= 1.19, 95% CI (1.15, 1.25)], initial value of serum lactate [OR= 1.43, 95% CI (1.02, 2.00)], maximum value of serum lactate [OR= 1.39, 95% CI

(1.94, 3.05)], minimum value of serum lactate [OR= 3.65, 95% CI (2.69, 4.97)], SLT [OR= 2.03, 95% CI (1.67, 3.60)], vasopressin duration [OR= 1.01, 95% CI (1.00, 2.49)] and ventilator use [OR= 2.28, 95% CI (1.65, 3.15)], $p < 0.05$. However, congestive heart failure, red cell distribution width, white blood cell count, serum creatinine, norepinephrine duration, and CRRT use had no significant effect on 28-day mortality ($P > 0.05$) (Table 3).

Table 3
Association between variables and 28-day mortality by logistics regression model.

Variables	OR	Z-value	95%CI	P-value
Age	1.02	3.33	1.01-1.03	0.001
SOFA score	1.19	8.33	1.15-1.25	<0.001
Congestive heart failure	1.01	0.04	0.73-1.38	0.971
RDW _{max}	0.92	-2.25	0.85-0.99	0.071
RDW _{min}	1.34	5.21	1.20-1.031.50	0.060
Wbc _{max}	0.97	-2.3	0.94-1.00	0.123
Wbc _{min}	1.05	2.62	1.01-1.09	0.109
Serum creatinine _{max}	1.13	1.13	0.92-1.39	0.258
Serum creatinine _{min}	0.82	-1.57	0.63-1.05	0.117
Serum lactate ₀	1.43	2.10	1.02-2.00	0.006
Serum lactate _{max}	1.39	2.64	1.94-3.05	0.001
Serum lactate _{min}	3.65	8.24	2.69-4.97	<0.001
SLT _{within 24h}	2.03	7.13	1.67-3.60	0.021
Norepinephrine duration	1.00	-0.29	0.79-1.00	0.770
Vasopressin duration	1.01	3.38	1.00-2.49	0.010
CRRT use _{1st day}	0.82	-0.82	0.50-1.32	0.410
Mechanical ventilation use _{1st day}	2.28	5.02	1.65-3.15	<0.001
OR, odds ratio; CI, confidence interval; SOFA, sequential organ failure assessment; RDW, red blood cell distribution width; Wbc, white blood cell; SLT, serial lactate testing; CRRT, continuous renal replacement therapy.				

Discussion

Few researchers have studied the effect of SLT on the clinical outcomes of critically ill patients with sepsis. The results of several randomized controlled trials are also contradictory. Some researchers believe that hyperlactic acidemia is related to the severity of sepsis in patients, mainly due to impaired tissue oxygen utilization.¹⁶ Therefore, other factors that lead to increased serum lactate need to be considered when formulating a serum lactate-oriented fluid resuscitation strategy. In addition, when comparing the effects of serum lactate and peripheral capillary perfusion-oriented fluid resuscitation strategies on the 28-day mortality of patients with sepsis, it was found that there was no significant difference between the two approaches.¹⁷ Other researchers have also found that serum lactate monitoring within 1 hour of admission can reduce the length of hospitalization and mortality of patients with sepsis, but this requires complete life monitoring and timely antibiotic infusion within 1 hour.¹⁸ A serum lactate kinetics-oriented fluid resuscitation strategy might improve the 90-day mortality of patients with high lactate-associated sepsis.¹⁹ Our study found that SLT was related to sepsis severity and did not significantly improve the clinical outcomes of patients with sepsis.

Previous studies found that the rate of SLT within 6 hours in patients with sepsis increased from 23–69%, and the rate of SLT within 24 hours increased from 59–94%,⁷ which was generally consistent with our research results (1961/2367, 82.8%) from 2003 to 2013. We also found that the disease severity score, laboratory indicators and hemodynamic parameters of the SLT group seemed to be worse than those of the non-SLT group. In fact, the initial, maximum, and minimum values of serum lactate in the SLT group were significantly higher than those in the non-SLT group. This seemed to indicate that SLT, similar to hyperlactemia, was related to the severity of sepsis. We believed that SLT would not improve the clinical outcomes of patients regardless of whether the lactate value was reduced to a normal level. This result might be inconsistent with the conclusions of some researchers.^{20–23} However, we maintain that SLT of critically ill patients must be combined with effective treatment so that critically ill patients might have a beneficial prognosis.

We believe that hyperlactemia can occur in anaerobic glycolysis or in the absence of hypoxia. The latter might be affected by the adrenergic state and the use of beta agonists.^{24–25} Hyperlactemia can also be seen in liver cirrhosis or end-stage liver disease,²⁶ with metformin use²⁷ or propofol use,²⁸ and in toxic diseases.^{29–30} For critically ill patients with sepsis, the serum lactate-oriented fluid resuscitation program should clarify the reason for the initial value increase in serum lactate and facilitate the adoption of a targeted treatment strategy. The treatment of lactic acidosis caused by insufficient tissue perfusion should focus on restoring local or overall tissue perfusion. Therefore, fluid resuscitation is the core principle, and hemodynamics are supported by vasoactive drugs and source control.³¹ The increasing serum lactate caused by other factors usually needs to be treated by removing harmful substances and correcting the primary metabolic defect as much as possible. Usually, the source of the elevated serum lactate is difficult to determine, but we believe that it is necessary to continually reassess the patient's volume status after the initial guided volume resuscitation to prevent fluid overload. A study confirmed that for every liter of fluid added by fluid resuscitation, the patient's mortality will increase by 2.3%.³²

Therefore, if serum lactate cannot be eliminated, clinicians should pay attention to the differential diagnosis of the source of insidious serum lactate elevation.

Our study has several limitations. First, it is a retrospective observational study and thus is subject to the limitations of this type of study. However, we believe that the MIMIC-III database contains a large amount of data for this entire group, so it is a good representation of the characteristics of patients with sepsis. In addition, our research is not perfect because we only studied the impact of categorical variables on patient outcomes. Although the results are representative, the investigation does not include parameters such as the number of lactate monitoring events within 24 hours or within 6 hours; ultimately, we believe that prospective studies are still needed to further verify our results.

In summary, we found that SLT was correlated with the severity of sepsis. SLT might not improve the clinical outcomes of critically ill patients with sepsis. Clinicians should pay attention to the differential diagnosis of the source of lactate elevation. Our study results need to be verified further in randomized controlled trials.

Declarations

4.1 Ethics approval and consent to participate

We confirmed that all methods were performed in accordance with the Declaration of Helsinki. Ethics was approved by the Institutional Review Board of the Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology and all participants had signed informed consent.

4.2 Consent for publication

Not applicable

4.3 Availability of data and materials

The datasets generated during and/or analyses during the current study are available in the Medical Information Mart for Intensive Care version III, 1.4 database(MIMICIII,1.4).

4.4 Competing interests

The authors declare that they have no competing interests.

4.5 Funding

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4.6 Authors' contributions

GL, and YW contributed to determining variables, extracting variables from the trauma registry, providing input, and finally approving the manuscript. Besides, YL was a contributor to the research design, responsible for providing input data and finalizing the draft.

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Figures

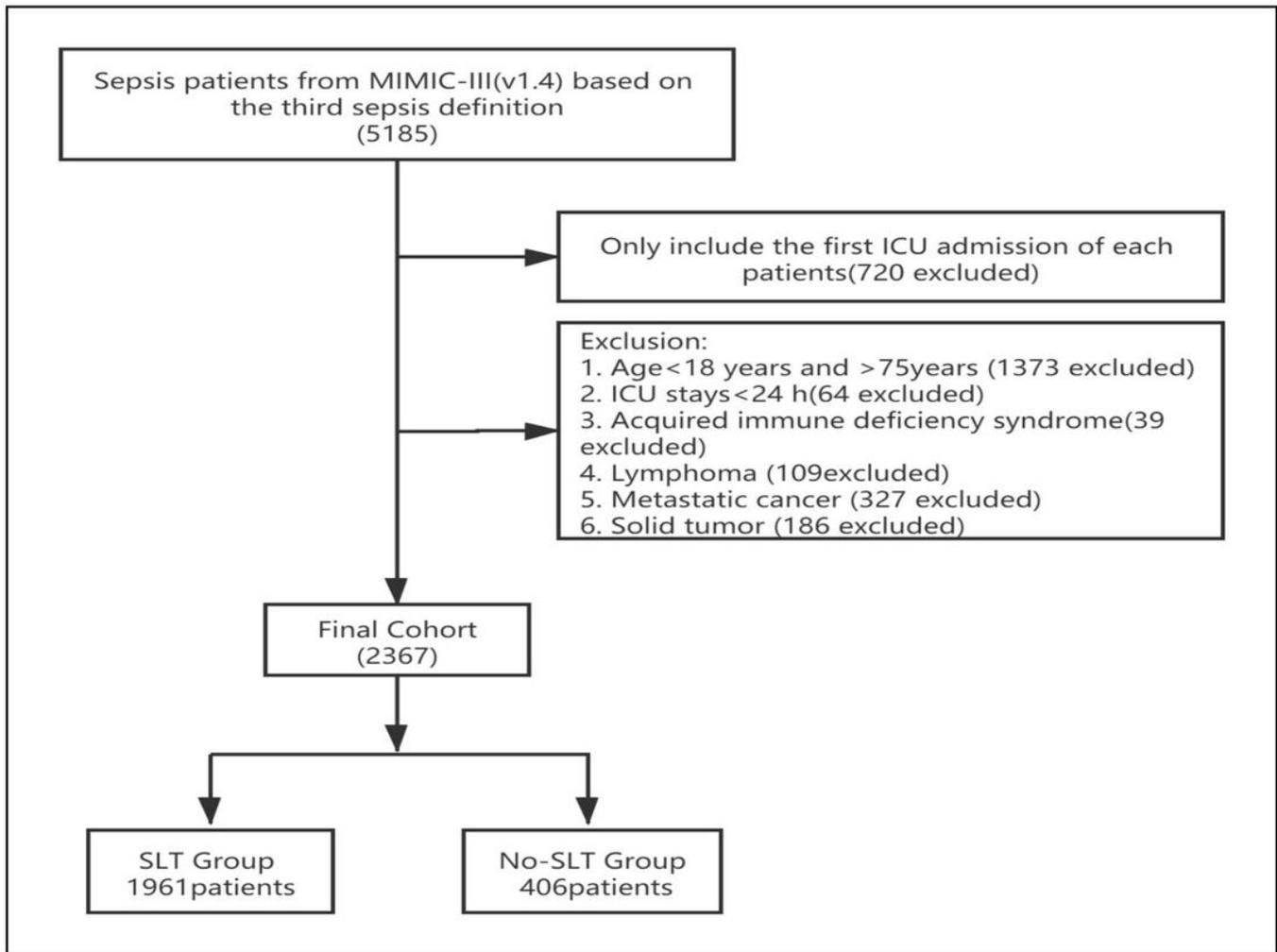


Fig.1 Patient selection and flow chart design; MIMIC-III,medical information mark for intensive care-III. ICU,Intensive care unit. SLT,serial lactate testing.

Figure 1

See image above for figure legend.

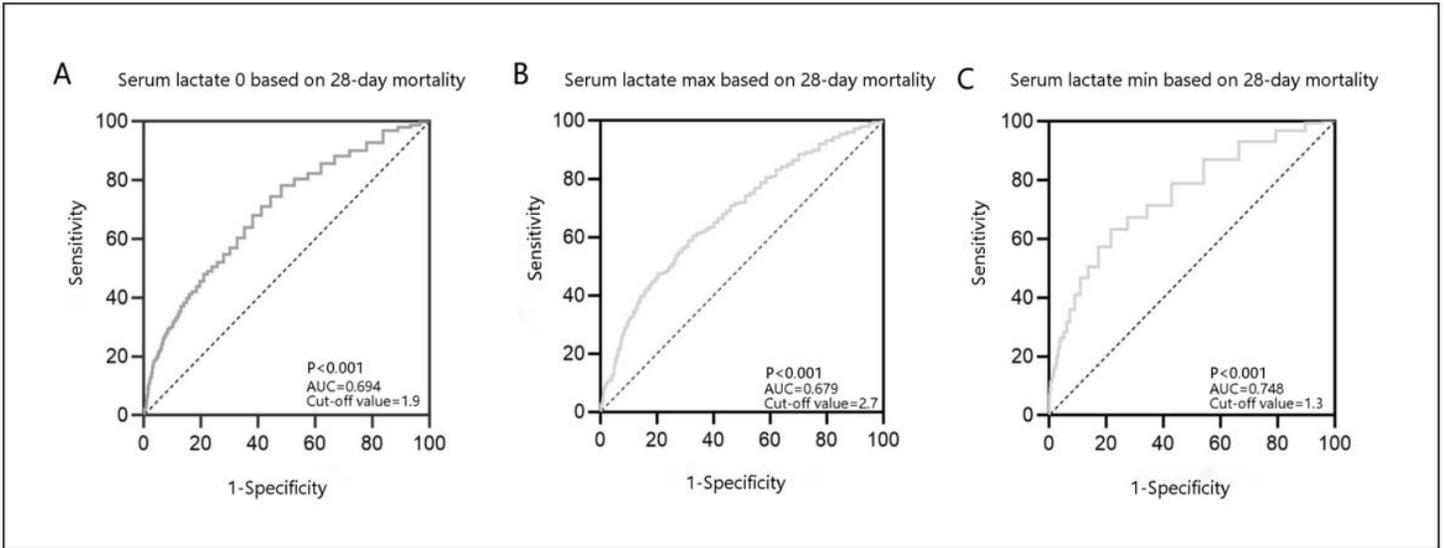


Fig.2 Receiver operating characteristic curve(ROC) analysis of initial, maximum and minimum values of serum lactate based on 28-day mortality of acute pancreatitis patients. serum lactate₀, initial value of serum lactate. serum lactate_{max}, maximum value of serum lactate. serum lactate_{min}, minimum value of serum lactate. AUC, area under the curve.

Figure 2

See image above for figure legend.

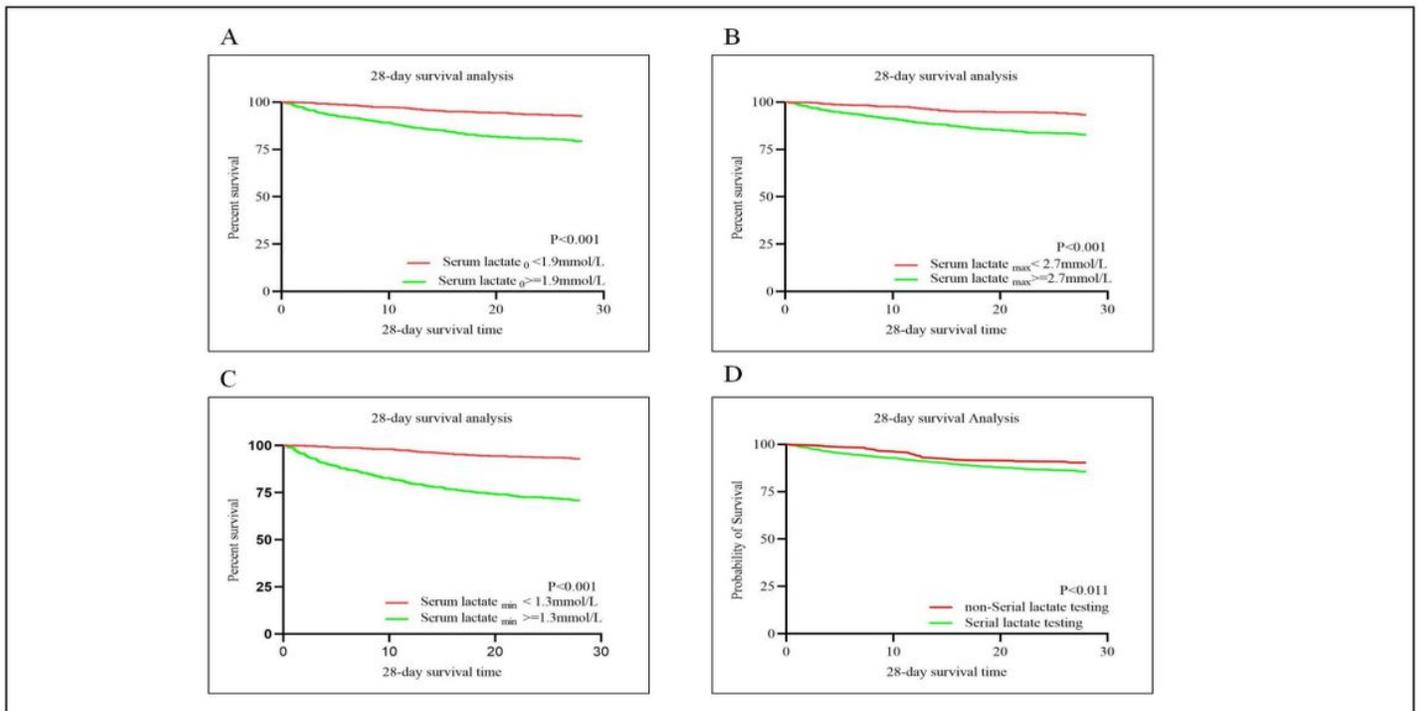
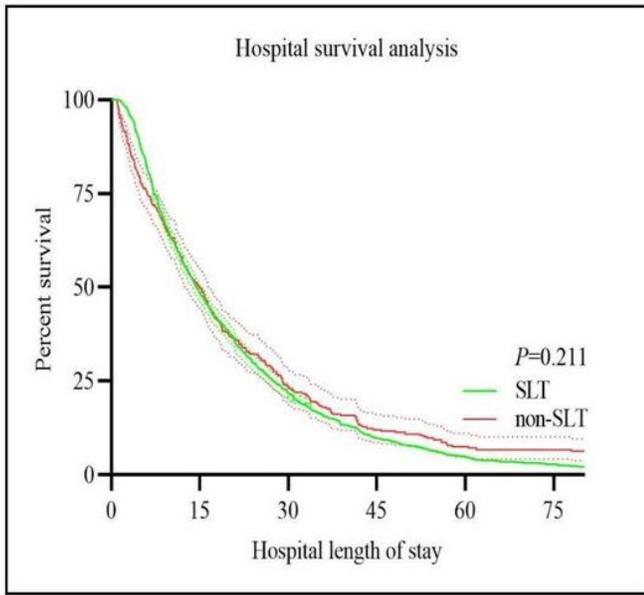


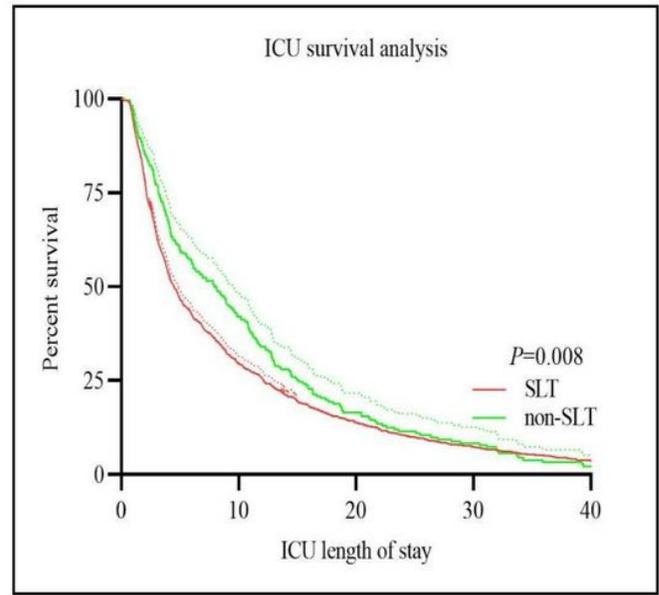
Fig.3 Subgroup survival analysis of initial, maximum and minimum values of serum lactate based on 28-day mortality of acute pancreatitis patients(A,B,C). Survival analysis of serial lactate testing and non-serial lactate testing on 28-day mortality of acute pancreatitis patients(D). serum lactate₀, initial value of serum lactate; serum lactate_{max}, maximum value of serum lactate; serum lactate_{min}, minimum value of serum lactate.

Figure 3

See image above for figure legend.



A



B

Fig.4 Survival analysis of serial lactate testing and non-serial lactate testing on hospital mortality of acute pancreatitis patients(A). Survival analysis of serial lactate testing and non-serial lactate testing on ICU mortality of acute pancreatitis patients(B). ICU,intensive care unit. SLT, serial lactate testing.

Figure 4

See image above for figure legend.