



The predictive performance of the lactate clearance rate combined with the APACHE II score in the prediction of sepsis-associated acute kidney injury in 7 days

Yezhou Shen^{1^}, Jiaoyang Yu¹, Fei Zhou¹, Juzhen Yan², Jing Yang³, Ying Guo^{4,5}, Leqing Lin¹

¹Intensive Care Unit, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China; ²Department of Kidney Disease, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China; ³Center of Translational Medicine, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China; ⁴Department of Emergency Medicine, Faculty of Medicine, Hangzhou Normal University, Hangzhou, China; ⁵Intensive Care Unit, Jingmen No. 1 People's Hospital, The Affiliated Hospital of Hubei Minzu University, Jingmen, China

Contributions: (I) Conception and design: Y Shen, L Lin; (II) Administrative support: J Yan, J Yang; (III) Provision of study materials or patients: J Yu, F Zhou; (IV) Collection and assembly of data: Y Guo; (V) Data analysis and interpretation: L Lin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Leqing Lin. Intensive Care Unit, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China.
Email: happylin67@126.com.

Background: The purpose of this study was to evaluate the accuracy of the lactate clearance rate (LCR) combined with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score in the prediction of sepsis-associated acute kidney injury (SAKI).

Methods: Sepsis patients were divided into the SAKI group and non-SAKI group. Arterial blood lactate was collected at 0 h (before treatment), 2 h, 4 h, 6 h, and 8 h (after treatment), and the LCR was calculated. The physiological parameters and laboratory test results were used to calculate the APACHE II score and the Sequential Organ Failure Assessment (SOFA) score. The receiver operating characteristic (ROC) curves of LCR, APACHE II score and SOFA score for predicting patients with SAKI were drawn. Two single indicators with high areas under the curves (AUCs) were selected to calculate the joint probability through regression analysis, and the prediction efficiency corresponding to each curve was analyzed.

Results: There were significant differences in LCR between different groups and time periods ($F^{\text{group}}=17.44$, $P^{\text{group}} \leq 0.0001$, $F^{\text{time}}=11.71$, $P^{\text{time}}=0.0014$). After 8 h of treatment, there was a significant difference in the overall compliance rate between the 2 groups ($P < 0.0001$). In addition, after 24 h of treatment, the APACHE II score in the SAKI group was significantly higher than that in the non-SAKI group ($P=0.0007$), and SOFA score was also significantly higher than that in the non-SAKI group ($P=0.0001$). ROC curve showed that the 0–8 h LCR and APACHE II scores had a high predictive performance for the acute kidney injury (AKI) occurrence in sepsis patients, and AUCs were 0.7637 and 0.7517, respectively, while the combined AUC of the 2 indicators was 0.7975.

Conclusions: The 0–8 h LCR combined with APACHE II score can improve the early predictive value of SAKI, reduce the risk of AKI in patients with sepsis/septic shock, and reduce the social and family burden, which is worthy of clinical application.

Keywords: Lactate clearance rate (LCR); Acute Physiology and Chronic Health Evaluation II (APACHE II) score; sepsis-associated acute kidney injury (SAKI)

Submitted Feb 15, 2022. Accepted for publication Apr 22, 2022.

doi: 10.21037/tau-22-225

View this article at: <https://dx.doi.org/10.21037/tau-22-225>

[^] ORCID: 0000-0002-8567-8624.

Introduction

Sepsis is one of the most common critical infections in intensive care units (ICUs), resulting in extremely high mortality, poor prognosis, and financial stress for patients. When a patient develops sepsis, the kidney is one of the most vulnerable target organs. Findings from a database of 500,000 patients in western Pennsylvania suggested that 40% of patients with sepsis had concomitant acute kidney injury (AKI). The real life percentage would be even higher due to the low rate of detection of AKI (1). With the continuous improvement of fluid management, internal environment monitoring, infection control, and renal replacement therapy in recent years, progress has been made in the treatment of septic AKI. Yet, when sepsis is complicated by AKI, the mortality rate is still as high as 70% (2). How to detect renal injury caused by sepsis in the early stages is key to improving the survival rate and prognosis of patients.

Lactic acid is a product formed by anaerobic glycolysis of glucose in a hypoxic environment. The production rate of lactic acid in the normal human body should be within 15–30 mmol/kg/d. The liver and kidney can remove lactic acid and maintain human arterial blood lactic acid at 0.5–1.0 mmol/L. In patients with sepsis/septic shock, due to the severe impairment of microcirculation function, severe ischemia and hypoxia of cells lead to a large accumulation of lactic acid in the body (3,4). Serum lactate is an indicator used to reflect the perfusion and hypoxia of cells. In the ICU, serum lactate is often used to evaluate the resuscitation effect (5). Serum lactate has also been considered as an independent prognostic predictor of mortality in patients with sepsis (6).

There are many novel molecular markers, such as: neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM-1), liver fatty acid binding protein (L-FABP), interleukin-18 (IL-18), insulin-like growth factor binding factor 7 (IGFBP7), tissue inhibitor of matrix metalloproteinase 2 (TIMP-2), in the field of predicting sepsis associated AKI, but these molecular markers have limitations. First of all, current studies on these molecular markers are mainly aimed at patients with AKI with a relatively single disease type. However, for ICU patients with sepsis related organ dysfunction or frequently complicated with other systemic diseases, it is uncertain whether these indicators still have good sensitivity and specificity. Second, cutoff values for new biomarkers are difficult to determine in cases of normal, abnormal or

unknown baseline renal function. Taking into account the patient's clinical status, such as non-renal conditions and severity of systemic disease, lactate clearance rate (LCR) and Acute Physiology and Chronic Health Evaluation II (APACHE II) were superior to these markers in predicting AKI.

In addition, because the monitoring of lactate is easier to perform in daily clinical practice, serum lactate concentration is also a readily available and inexpensive clinical marker for patients with sepsis/septic shock. However, a single serum lactate value will be affected by many factors, and it could be misleading in the clinical assessment of the resuscitation status of patients with sepsis/septic shock, as well as the perfusion and hypoxia of cells. LCR reflects dynamic changes in lactate concentration and has been shown to be superior to absolute lactate values in predicting outcomes and evaluating quality (7). This study is the first attempt to combine the LCR and APACHE II score, using the Sequential Organ Failure Assessment (SOFA) score as a reference, to predict sepsis-associated acute kidney injury (SAKI), that is, whether patients with sepsis will develop renal injury in the future and improve the early prediction value of SAKI. Moreover, we attempt to evaluate the effectiveness of early lactate, LCR, APACHE II score, and SOFA score in predicting the prognosis of patients with sepsis/septic shock and SAKI. We present the following article in accordance with the STARD reporting checklist (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-225/rc>)

Methods

Subjects

According to the cluster sampling method, perform descriptive analysis and predictive performance analysis. 80 patients with sepsis/septic shock admitted to ICU, The Affiliated Hospital of Hangzhou Normal University from January 2019 to September 2021 were selected. All patients signed the informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Affiliated Hospital of Hangzhou Normal University (No. 2019-HS-37). Patients who developed SKI within 7 days after admission were included in the SAKI group (39 cases), and those who did not develop SKI within 7 days after admission were included in the non-SAKI group (41 cases). The inclusion criteria were as follows: (I) Met

the diagnostic criteria for sepsis and septic shock issued by the Save Sepsis Campaign (SCC) in 2016; (II) clearly diagnosed with sepsis/septic shock; (III) aged 18–90 years old; (IV) survival time after clear diagnosis >24 h; (V) the patient received all necessary treatments deemed necessary by the ICU physician; (VI) the information of the patient was not lost within 90 days. The exclusion criteria were as follows: (I) patients <18 years old or >90 years old; (II) pregnant women, with congenital metabolic diseases; (III) patients who died within 24 h after admission; (IV) patients who discontinued treatment and were discharged suddenly, and patients (or their family members) who refused to participate; (V) patients with end-stage diseases such as malignant tumors; (VI) patients with underlying kidney disease or other potential kidney damage factors; (VII) patients with incomplete clinical data; (VIII) patients with non-infectious acute diseases (cardiogenic shock, myocardial infarction, pulmonary embolism) and patients with severe chronic diseases (respiratory failure, heart failure, and end-stage liver disease) accompanied by organ dysfunction; (IX) long-term use of drugs that affect blood lactate levels (hydroxyacids, biguanides), and a large number of catecholamines were used before admission. The AKI diagnostic criteria were as follows: According to the Kidney Disease Improving Global Outcomes (KDIGO) AKI diagnostic criteria guideline developed by the KDIGO in 2012, AKI can be diagnosed if one of the following conditions is met: (I) Serum creatinine (SCr) rises ≥ 0.3 mg/dL within 48 h (≥ 26.5 $\mu\text{mol/L}$); (II) confirmed or presumed that the SCr increased to ≥ 1.5 times the baseline value within 7 days; (III) the urine output was less than 0.5 mL/kg/h, and lasted for more than 6 h. The diagnostic criteria of SAKI were as follows: According to the KDIGO AKI guideline diagnostic criteria formulated by the KDIGO in 2012, the occurrence of SAKI was judged according to the occurrence of AKI.

Treatment methods

Patients who met the inclusion criteria were immediately treated in accordance with the 2016 SCC and 2018 SCC bundle guidelines, which included the following contents: (I) monitoring blood lactate level, taking blood culture specimens before using antibiotics, and taking broad-spectrum antibiotic treatment empirically in the ICU for 1 h. Targeted anti-infective treatment was taken according to the etiological basis after 48–72 h; (II) when low blood pressure or blood lactate ≥ 4 mmol/L, a crystalloid solution

was administered at 30 mL/kg. For patients with septic shock, within 6 h of initial resuscitation, if the central venous pressure (CVP) was 8–12 mmHg (12–15 mmHg for mechanically ventilated patients), the average arterial pressure ≥ 65 mmHg, urine output ≥ 0.5 mL/kg/h, central venous oxygen saturation (ScvO₂) or mixed venous oxygen saturation (SvO₂) was greater than or equal to 0.7 or 0.65, fluid resuscitation should be used, with first choice of crystalloid solution. For patients with severe infection or septic shock and CVP reached the target within the first 6 h, but ScvO₂ or SvO₂ did not meet the target requirements, packed red blood cells would be transfused to make hematocrit (HCT) $\geq 30\%$, and/or dobutamine should be given (≤ 20 $\mu\text{g/kg/min}$); (III) if the patient needed mechanical ventilation, the initial upper limit of the airway plateau pressure was set to 30 cm H₂O to avoid ventilator-related lung injury; (IV) after the hemodynamics were stable, early nutritional support was provided first. Enteral nutrition was combined with parenteral nutrition if necessary; (V) for severe patients with stress hyperglycemia, the level of blood sugar was controlled at 8.0–10.0 mmol/L; (VI) water and electrolyte balance were maintained.

Observation indicators

The arterial blood lactate of patients at 0h (before treatment) and 2, 4, 6, and 8 h (after treatment) was collected, and the LCR was calculated. Whether the LCR met the standard was determined, the APACHE II and SOFA scores of patients were collected, then patients were tracked after the diagnosis of sepsis. Descriptive analysis and predictive power analysis were performed on whether AKI occurred within 7 days and mortality occurred within 7 days and 28 days.

For arterial blood lactate, arterial blood samples were collected from patients at 0h (before treatment) and at 2, 4, 6, and 8 h (after treatment). The GEM Premier3000 blood gas analyzer was used to measure arterial blood lactate. For LCR, the patient's LCR was calculated based on the lactate values collected above: 2, 4, 6, or 8 h $\text{LCR} = [(\text{lactate value in the Department of Intensive Medicine} - \text{lactate value in the Department of Intensive Medicine 2 or 4 or 6 or 8 h}) / \text{lactate value in the Department of Intensive Medicine} \times 100\%]$. According to the patient's arterial lactate value and LCR value, it was determined whether the patient's LCR was up to the standard. The criterion was as follows: if the initial lactate was >2.0 mmol/L, it would decrease by $\geq 10\%$; or the initial and repeated lactate levels were both <2.0 mmol/L.

Using the APACHE II scoring scale as a measuring tool,

Table 1 Comparison of general data between the SAKI group and non-SAKI group

Subjects	SAKI group (n=39)	Non-SAKI group (n=41)	t/ χ^2	P
Age ($\bar{x}\pm s$, year)	72.10 \pm 16.67	67.13 \pm 16.99	1.320	0.1907
Gender, n (%)				
Male	19 (48.72)	24 (58.54)	0.8804	0.3786
Female	20 (51.28)	17 (41.46)		
Underlying conditions				
Hypertension, n (%)	17 (43.59)	11 (26.93)	2.468	0.1162
Diabetes, n (%)	2 (5.13)	2 (4.88)	0.0026	0.9591
Coronary atherosclerotic heart disease, n (%)	1 (2.56)	0 (0.00)	1.065	0.3200
Combined underlying disease (≥ 2), n (%)	11 (28.21)	9 (21.95)	0.4169	0.5185
Source of infection, n (%)				
Abdominal and intestinal origin	3 (7.69)	8 (19.51)	2.355	0.1249
Lung infection	12 (30.77)	11 (26.93)	0.1515	0.6971
Bloodstream infection	2 (5.13)	3 (7.32)	0.1643	0.6860
Urinary tract infection	2 (5.13)	1 (2.44)	0.4005	0.5268
Liver abscess, cyst secondary infection	2 (5.13)	0 (0.00)	2.156	0.1420
Multi-origin: (≥ 2 sources), n (%)	18 (46.15)	18 (43.90)	0.0409	0.8397

SAKI, sepsis-associated acute kidney injury.

all patients were scored by a third-party specialist 24 h after admission, and the scores were recorded. The raters were not members of the study and had conflicts of interest.

Using the SOFA score scale as a measuring tool, all patients were scored by a third-party specialist immediately after admission and 24 h after admission, and the scores were recorded. The raters were not members of the study and had no conflicts of interest.

Statistical analysis

SPSS 26.0 statistical software was used for data processing. Measurement data conforming to a normal distribution were expressed as mean \pm standard deviation. Non-normally distributed measurement data were expressed as median and interquartile range. Categorical variables were expressed as a percentage of the total sample. The overall difference of LCR at each time point was analyzed by the repeated measures method. Intra-group comparisons were performed by the LSD *t*-test. Inter-group comparisons of other indicators were performed by the independent *t*-test. Enumeration data was analyzed by the chi-square

test. Receiver operating characteristic curve (ROC) analysis of the predictive efficacy of LCR (0–6 h), LCR (0–8 h), APACHE II score, SOFA score research variables on the occurrence of AKI in patients with sepsis. The area under the curve (AUC), its 95% confidence interval, standard error and P value were calculated, and the Youden index was used to find the best cutoff point. $P < 0.05$ indicated that the difference was statistically significant.

Results

Descriptive analysis of the clinical data of SAKI and non-SAKI patients

In this study, 39 of the 80 patients had SAKI, with an incidence rate of 48.75%, while 41 did not have SAKI, accounting for 51.25% of the total. Statistical analysis was performed on the age, gender, past medical history, and source of infection of the 2 groups of patients, and the results showed that there were no significant differences ($P > 0.05$), and the 2 groups were considered to be equal at baseline (Table 1).

Statistical analysis of clinical data such as ICU admission

Table 2 Comparison of clinical data between the SAKI group and non-SAKI group

Subject	SAKI group (n=39)	Non-SAKI group (n=41)	t	P
ICU admission time (d)	13.33±8.91	12.78±9.54	2.662	0.7908
MAP (mmHg)				
Immediately in ICU	71.95±19.02	82.95±19.56	2.548	0.0128
8 h of treatment	76.67±11.88	77.20±11.57	0.8403	0.2021
Oxygenation index				
Immediately in ICU	230.32±112.53	238.71±158.18	2.721	0.7862
8 h of treatment	228.06±114.79	216.93±106.83	0.6546	0.6546
Mechanical ventilation time (h)	12.58±9.94	9.65±8.35	1.430	0.1567
Types of vasoactive drugs (types)	2.33±1.13	2.05±1.36	0.9989	0.3210
Vasoactive drug use time (d)	7.86±7.19	3.19±2.76	3.871	0.0002
Albumin level (g/L)				
Immediately in ICU	28.73±4.80	26.81±6.24	1.537	0.1284

SAKI, sepsis-associated acute kidney injury; MAP, mean arterial pressure; ICU, intensive care units.

time, mean arterial pressure (MAP), albumin level, oxygenation index, mechanical ventilation time, vasoactive drug use type and time, albumin level, and other clinical data of the 2 groups of patients was conducted. It was found that vasoactive drug use time was significantly different between the 2 groups ($P<0.05$; *Table 2*).

LCR, LCR compliance rate, APACHE II score, and SOFA score between the 2 groups

The LCR, compliance rate, APACHE II score, and SOFA score were compared between the 2 groups at 2, 4, 6, and 8 h (after treatment). The results showed that there were significant differences in the LCR between different groups and different time periods ($F^{\text{group}}=17.44$, $P^{\text{group}}\leq 0.001$, $F^{\text{time}}=11.71$, $P^{\text{time}}=0.0014$), but there was no interaction effect between the 2 factors of group and time ($F^{\text{interaction}}=1.776$, $P^{\text{interaction}}=0.1516$). The LCR of each time period was further compared, and the results showed that the 0–6 h LCR and 0–8 h LCR of the non-SAKI group were significantly higher than those of the SAKI group ($P<0.05$), but no difference between the LCR of the 2 time periods of 0–2 h and 0–4 h in the 2 groups was found ($P>0.05$). After 8 h of treatment, there was a significant difference in the overall compliance rate between the 2 groups ($P<0.05$). In addition, after 24 h of treatment, the APACHE II score in the SAKI group was significantly higher than that in the non-SAKI

group ($P<0.05$), and the SOFA score was also significantly higher than that in the non-SAKI group ($P<0.05$; *Table 3*, *Figure 1*).

ROC curve of LCR, APACHE II score, and SOFA score in predicting AKI in patients with sepsis

Based on the previous descriptive analysis, it is known that the 0–6 h LCR, 0–8 h LCR, APACHE II score, and SOFA score (at 24 h) have a greater correlation with the occurrence of AKI in sepsis patients, and can be used as predictive factors for whether sepsis patients will develop AKI. Therefore, ROC curves of the above 4 indicators in predicting AKI occurrence in patients with sepsis were drawn, and the 2 single indicators with higher AUCs were selected to calculate the joint probability through regression analysis. The ROC curve of the joint prediction was drawn to analyze the corresponding prediction performance of each curve.

The ROC curve showed that the use of LCR and APACHE II scores had high predictive performance in predicting AKI occurrence in patients with sepsis, and their AUCs were 0.6310 for 0–6 h LCR, 0.7637 for 0–8 h LCR, 0.7517 for APACHE II score, and 0.7367 for SOFA score, with significant differences ($P<0.05$). The AUC of the 0–8 h LCR combined with the APACHE II score for predicting AKI occurrence in sepsis patients was 0.7975, which was

Table 3 Comparisons of LCR, APACHE II score, and SOFA score between the SAKI group and non-SAKI group

Index	SAKI group (n=39)	Non-SAKI group (n=41)	t/ χ^2	P
LCR ($\bar{x}\pm s$, %)				
0–2 h	-16.82±58.17	-13.99±67.53	0.2004	0.8417
0–4 h	-31.43±69.98	-15.69±72.07	0.9903	0.3251
0–6 h	2.41±54.99	26.40±20.15	2.616	0.0107
0–8 h	10.85±51.21	53.10±23.37	4.786	<0.0001
LCR, n (%)	31 (79.49)	39 (95.12)	4.467	0.0346
APACHE II score ($\bar{x}\pm s$, points)	24.95±6.24	19.49±7.46	3.541	0.0007
SOFA score ($\bar{x}\pm s$, points)				
Immediately in ICU	9.05±3.42	7.64±3.51	1.819	0.0728
24 h of treatment	9.90±3.94	6.58±3.32	5.083	0.0001

LCR, lactate clearance rate; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SAKI, sepsis-associated acute kidney injury; ICU, intensive care units.

significantly higher than that of LCR, APACHE II score, and SOFA score separately. The Youden index suggested that the best cut-off points of the 0–6 h LCR, 0–8 h LCR, APACHE II score, and SOFA score for predicting AKI occurrence in sepsis patients were 1.32, 32.57, 18.50, and 10.50, respectively (Figure 2, Table 4).

Comparison of blood lactate level and LCR in patients with different prognosis

The lactate levels in the survival group and the death group were analyzed, and the results showed that there was no significant difference in blood lactate levels in different groups and at different times ($F^{\text{group}}=4.390$, $P^{\text{group}}=0.2680$; $F^{\text{time}}=4.390$, $P^{\text{time}}=0.6650$). There was no interaction effect between group and time ($F^{\text{interaction}}=0.3036$, $P^{\text{interaction}}=0.8755$). The LCR of the patients in the survival group and the death group was analyzed, and the results showed that the LCR of the death group was significantly lower than that of the survival group ($F^{\text{group}}=10.22$, $P^{\text{group}}<0.0001$), but there was no significant difference between different times ($F^{\text{time}}=2962$, $P^{\text{time}}=0.5867$). In addition, no difference in interaction effect between group and time was observed ($F^{\text{interaction}}=1.736$, $P^{\text{interaction}}=0.1596$). Further analysis found that the 0–8 h LCR of the death group was significantly lower than that of the survival group ($P=0.0351$; Table 5, Figure 3).

Comparing the 7-day and 28-day deaths of the 2 groups, the SAKI group had 2 deaths in 7 days (5.13%) and 15

deaths in 28 days (38.46%), while the non-SAKI group had 1 death in 7 days (2.44%) and 7 deaths in 28 days (17.07%). There was a significant difference in the 28-day mortality between the 2 groups ($P=0.0332$; Table 6).

Discussion

Lactic acid can be used as a useful indicator of perfusion, but there are many causes of non-perfusion due to elevated lactate concentrations, such as muscle hyper-function, accelerated aerobic glycolysis, systemic diseases, and inhibition of pyruvate dehydrogenase, among others. Moreover, a single serum lactate value will be affected by many factors and may mislead physicians when drawing a clinical judgment of the resuscitation status of patients with sepsis/septic shock, as well as the accurate assessment of cell perfusion and hypoxia. LCR, that is, the ratio of the difference between the initial arterial blood lactate concentration and the observation point arterial blood lactate concentration, can dynamically reflect the changes in blood lactate concentration. In sepsis/septic shock-related AKI, especially at high levels of intrarenal oxygen shunt, lactate levels are more reflective of arterial perfusion than oxygen supply, and lactate is a strong independent predictor of mortality in SAKI patients. Compared with traditional perfusion parameters and oxygen-derived variables, blood lactate concentration and LCR have certain advantages in predicting effectiveness in different populations (8). This conclusion was also verified in this study, in that LCR

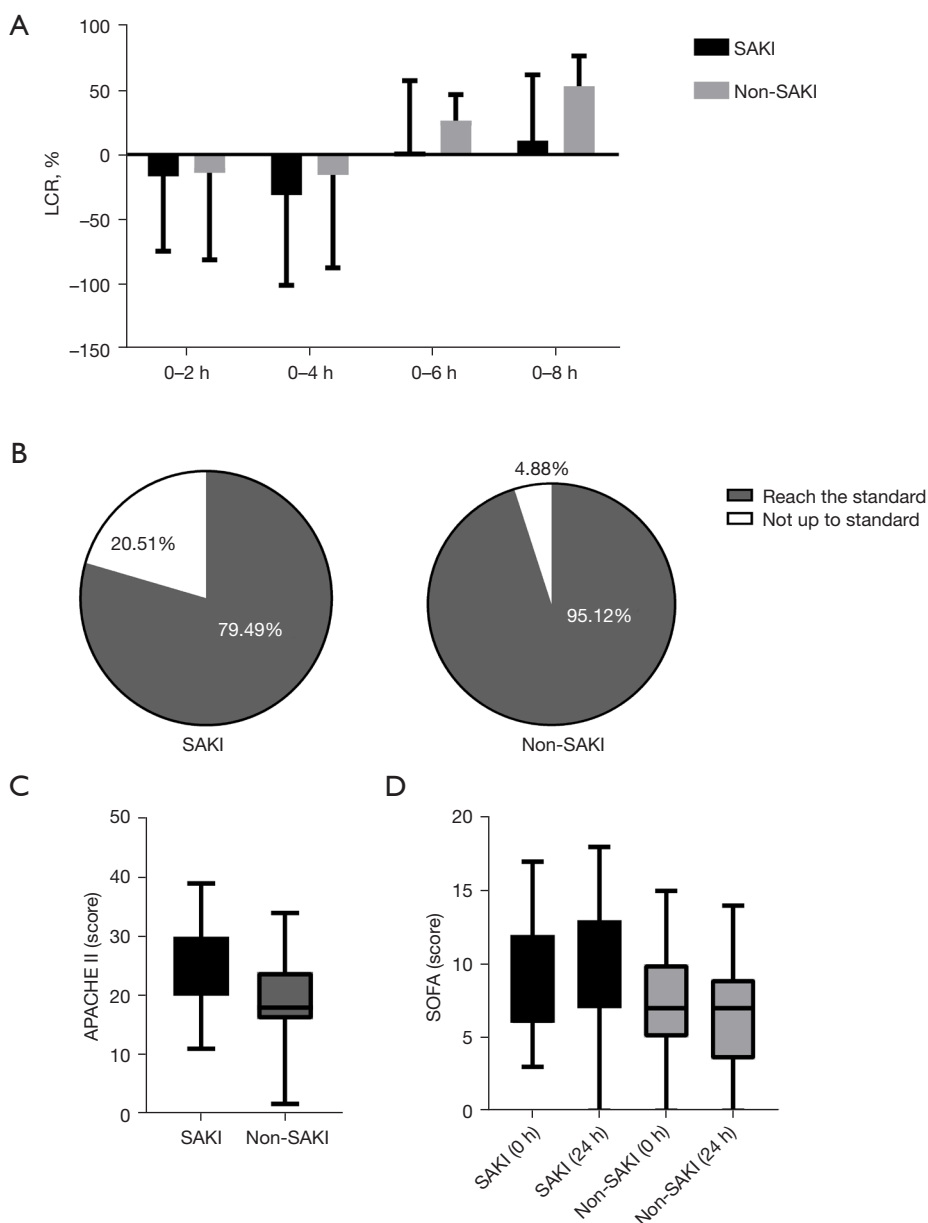


Figure 1 Comparison of LCR, APACHE II score, and SOFA score between the 2 groups. (A) The LCR of the 2 groups of patients at 0-2h, 0-4h, 0-6h, and 0-8 h after treatment. (B) The lactate clearance of the 2 groups of patients at 8 h after treatment. (C) The APACHE II scores of the 2 groups of patients after 24 h of treatment. (D) The SOFA scores of the 2 groups of patients immediately after admission and 24 h after treatment. LCR, lactate clearance rate; SAKI, sepsis-associated acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

better reflects renal perfusion compared with ScvO₂, and improving LCR can improve the prognosis of patients. Hsu and Hsu (9) have suggested that higher blood lactate is associated with the progression of AKI. In a recent animal experiment, Tan *et al.* (10) reported that lactate-directed

treatment reduced the occurrence of AKI in mice. Zhao and Duan (11) proposed that lactic acid is an independent risk factor for death in patients with septic shock. However, it cannot accurately predict the death of the patients without integrating LCR, SOFA score, APACHE II score, and

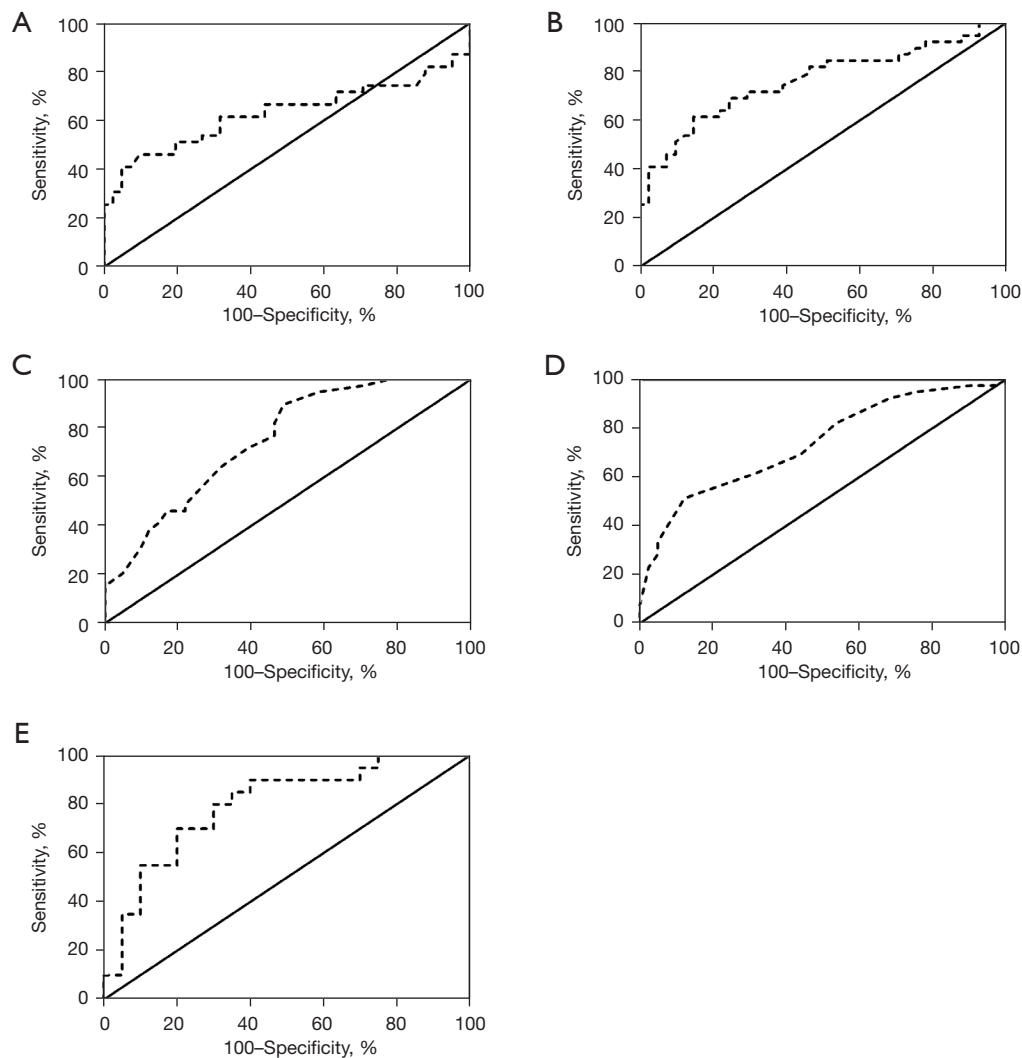


Figure 2 ROC curves. (A) 0–6 h LCR; (B) 0–8 h LCR; (C) APACHE II score; (D) SOFA score (24 h); (E) 0–8 h LCR combined with SOFA score (24 h). The diagonals in the figure are reference lines. ROC, receiver operating characteristic; LCR, lactate clearance rate; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

Table 4 Area under the curve of each index for predicting AKI in patients with sepsis

Index	Cut-off	AUC	P	95% CI	
				Upper bound	Lower bound
LCR (0–6 h)	1.32	0.6310	0.0438	0.5002	0.7618
LCR (0–8 h)	32.57	0.7637	<0.0001	0.6567	0.8705
APACHE II score	18.50	0.7139	0.0010	0.6009	0.8268
SOFA score (24 h)	10.50	0.7340	0.0003	0.6242	0.8438
LCR (0–8 h) combined with SOFA score (24 h)	–	0.7975	0.0013	0.6571	0.9379

AKI, acute kidney injury; AUC, areas under the curves; LCR, lactate clearance rate; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

Table 5 Comparison of blood lactate levels and LCR in patients with different prognoses ($\bar{x}\pm s$)

Time	Blood lactate level (mmol/L)				LCR (%)			
	Survival group (n=58)	Death group (n=22)	t	P	Survival group (n=58)	Death group (n=22)	χ^2	P
0 h	2.81±2.62	2.68±2.31	0.2044	0.8386				
2 h	2.86±2.06	2.34±2.09	1.004	0.3184	-20.73±65.92	-1.23±52.65	1.244	0.2174
4 h	2.88±2.36	2.63±2.24	0.4288	0.6692	-23.76±70.70	-22.31±73.54	0.0810	0.9356
6 h	2.16±1.97	2.32±2.28	0.3105	0.7570	18.27±34.75	5.33±57.75	1.225	0.2243
8 h	1.96±1.76	1.57±1.52	0.4500	0.6540	38.93±42.42	15.56±46.35	2.145	0.0351

LCR, lactate clearance rate.

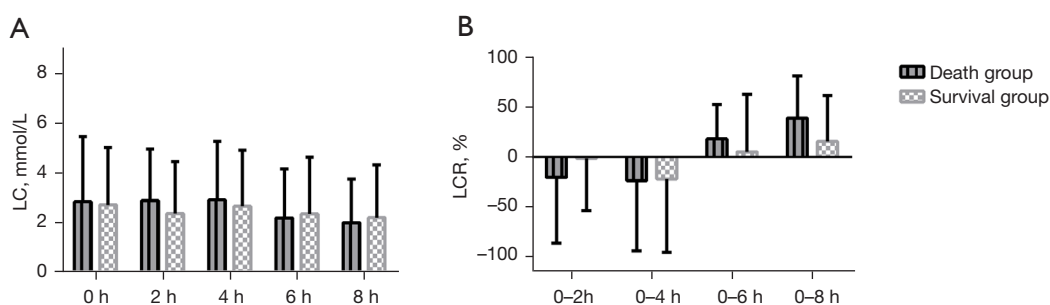


Figure 3 Comparison of blood LC levels and LCR in patients with different prognoses. (A) Blood LC levels of patients with different prognoses at 0 h, 2 h, 4 h, 6 h, and 8 h; (B) LCR of patients with different prognoses at 0–2 h, 0–4 h, 0–6 h, and 0–8 h. LC, lactic acid; LCR, lactate clearance rate.

Table 6 Comparison of prognosis between the SAKI group and non-SAKI group

Subject	SAKI group	Non-SAKI group	χ^2	P
7 d mortality, n (%)	2 (5.13)	1 (2.44)	0.4005	0.5268
28 d mortality, n (%)	15 (38.46)	7 (17.07)	4.586	0.0332

SAKI, sepsis-associated acute kidney injury.

other indicators. The APACHE II score is a scoring system for critically ill patients proposed by Knaus in 1985. Its reliability has resulted in its widespread recognition by the medical community. After various calculations of the patient’s disease state, it can predict the mortality rate of the patient. A higher APACHE II score indicates a more critical condition, greater damage to various organs and systems of the body, and is more likely to cause kidney damage leading to concurrent AKI (12). Sadaka *et al.* (13) conducted a retrospective analysis using the APACHE database to predict the prognosis of organ function in patients with sepsis by using an ROC curve. The results suggested that elevated APACHE II scores and the mortality

of patients with sepsis were significantly correlated, with an AUC of 0.80 (95% CI: 0.78–0.82) for APACHE II. Asada *et al.* (14) proposed that although APACHE II has high predictive performance, the APACHE II score consists of 3 components, each of which represents the corresponding score. It is impossible to know the particular impact of each system component on the kidneys. Therefore, when applying APACHE II for AKI prediction, the clinical environment, such as non-renal conditions and severity of systemic disease, should be considered. Novel molecular markers for predicting AKI can be combined with other clinical monitoring indicators such as lactate or LCR, thereby improving prediction performance for better

clinical application prospects.

In this study, the 2, 4, 6, and 8 h (after treatment) LCR, APACHE II score, and SOFA score were compared between the 2 groups. The results showed that there were significant differences in LCR between groups and time periods ($F^{\text{group}} = 17.44$, $P^{\text{group}} \leq 0.001$, $F^{\text{time}} = 11.71$, $P^{\text{time}} = 0.0014$). Further comparison of LCR in each time period showed that the 0–6 h LCR and 0–8 h LCR of the non-SAKI group were significantly higher than those of the SAKI group ($P < 0.05$). After 8 h of treatment, there was a significant difference in the overall compliance rate between the 2 groups ($P < 0.05$). In addition, the APACHE II score of the SAKI group was significantly higher than that of the non-SAKI group ($P < 0.05$). After 24 h of treatment, the SOFA score of the SAKI group was significantly higher than that of the non-SAKI group ($P < 0.05$). The above results suggest that LCR, APACHE II score, and SOFA score are significantly correlated with the occurrence of AKI in sepsis patients.

There are still some limitations in this study. Firstly, due to the cumbersomeness of extracting lactic acid in the experiment, it is impossible to measure the lactic acid value at 10, 12, 14, and 24 h. The results of this experiment can only explain the best LCR and lactate acid values within 0 to 8 h. For the prediction of the occurrence of AKI in sepsis patients by the clearance compliance rate of LCR and APACHE II, we cannot know whether results within 10, 12, 14, and 24 h are better than the results obtained in this experiment. Secondly, Due to the relatively short study period of this subject, the relatively small sample size made it impossible to compare the severity of renal injury in the SAKI group. It was only concluded that the LCR and APACHE II scores had predictive potential for the subsequent occurrence of AKI in patients with sepsis. If the study period can be extended and the number of cases can be increased in the follow-up study, the LCR and APACHE II scores may be more valuable in predicting septic AKI. It was impossible to explore whether this prediction factor could indicate the severity of AKI for patients with sepsis. Thirdly, the patients included in this experiment were relatively older, and possible organ insufficiency may be associated with the development of the disease. The damage of liver and kidney function may lead to the increase of lactic acid, while sepsis/septic shock itself will inhibit lactate scavenging enzyme and pyruvate dehydrogenase, resulting in impaired lactate clearance. The influence of these possible error factors on the experiment was not considered in the study. Lastly, for the prediction of AKI occurrence, continuous research into new molecular markers of sepsis

may further improve the predictive effectiveness of AKI occurrence in sepsis patients if further tests can be carried out in combination with single or multiple molecular markers. Therefore, based on the above viewpoints, we expect more countries and regions to join forces with critical care medicine departments to conduct multi-center joint experiments to explore the combination of LCR, APACHE II score, SOFA score, and new molecular markers. This will be one of the key research topics of AKI occurrence in patients with sepsis/septic shock.

In conclusion, the LCR combined with the APACHE II score has high predictive effectiveness for SAKI, making it worthy of clinical application. For patients with sepsis/septic shock, in addition to early lactate and other test indicators for the routine treatment of sepsis, more attention should be paid to LCR, APACHE II score, and SOFA score in patients with sepsis. Their utility for the early prediction of sepsis and the evaluation of prognosis in patients with sepsis might improve the patient's LCR and reduce the patient's APACHE II score, leading to the reduction of the risk of subsequent AKI occurrence in patients with sepsis/septic shock. This will ultimately improve the patient's survival rate, reduce the patient's risk of death, and reduce the burden on society and families.

Acknowledgments

Funding: This study was supported by the Science and Technology Planning Project of Hangzhou City (No. 20191203B95) and the Key medical disciplines of Hangzhou (No. 0020200244).

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-225/rc>

Data Sharing Statement: Available at <https://tau.amegroups.com/article/view/10.21037/tau-22-225/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tau.amegroups.com/article/view/10.21037/tau-22-225/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of The Affiliated Hospital of Hangzhou Normal University (No. 2019-HS-37) and informed consent was taken from all the patients.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Peerapornratana S, Manrique-Caballero CL, Gómez H, et al. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019;96:1083-99.
- Klenzak J, Himmelfarb J. Sepsis and the kidney. *Crit Care Clin* 2005;21:211-22.
- Nolt B, Tu F, Wang X, et al. Lactate and Immunosuppression in Sepsis. *Shock* 2018;49:120-5.
- Goyal P, Agarwal R, Srivastava H, et al. Serial Serum Lactic Acid in Pregnancy-Associated Sepsis for Maternal Outcome. *J Obstet Gynaecol India* 2020;70:342-8.
- Pan J, Peng M, Liao C, et al. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: A meta-analysis. *Medicine (Baltimore)* 2019;98:e14453.
- Liu Z, Meng Z, Li Y, et al. Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with Sepsis. *Scand J Trauma Resusc Emerg Med* 2019;27:51.
- Gao X, Cao W, Li P. Pcv-aCO₂/Ca-cvO₂ Combined With Arterial Lactate Clearance Rate as Early Resuscitation Goals in Septic Shock. *Am J Med Sci* 2019;358:182-90.
- Zollo AM, Ayoob AL, Prittie JE, et al. Utility of admission lactate concentration, lactate variables, and shock index in outcome assessment in dogs diagnosed with shock. *J Vet Emerg Crit Care (San Antonio)* 2019;29:505-13.
- Hsu YC, Hsu CW. Septic acute kidney injury patients in emergency department: The risk factors and its correlation to serum lactate. *Am J Emerg Med* 2019;37:204-8.
- Tan C, Gu J, Li T, et al. Inhibition of aerobic glycolysis alleviates sepsis-induced acute kidney injury by promoting lactate/Sirtuin 3/AMPK-regulated autophagy. *Int J Mol Med* 2021;47:19.
- Zhao M, Duan M. Lactic acid, lactate clearance and procalcitonin in assessing the severity and predicting prognosis in sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020;32:449-53.
- He L, Su L, Zhang J, et al. Analysis of factors influencing recovery of renal functions in septic shock patients in intensive care unit with acute kidney injury. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020;32:199-203.
- Sadaka F, EthmaneAbouElMaali C, Cytron MA, et al. Predicting Mortality of Patients With Sepsis: A Comparison of APACHE II and APACHE III Scoring Systems. *J Clin Med Res* 2017;9:907-10.
- Asada T, Isshiki R, Hayase N, et al. Impact of clinical context on acute kidney injury biomarker performances: differences between neutrophil gelatinase-associated lipocalin and L-type fatty acid-binding protein. *Sci Rep* 2016;6:33077.

Cite this article as: Shen Y, Yu J, Zhou F, Yan J, Yang J, Guo Y, Lin L. The predictive performance of the lactate clearance rate combined with the APACHE II score in the prediction of sepsis-associated acute kidney injury in 7 days. *Transl Androl Urol* 2022;11(4):543-553. doi: 10.21037/tau-22-225