RESEARCH ARTICLE

Initial lactate levels versus lactate clearance for predicting mortality in sepsis: A prospective observational analytical study

Mayang Indah Lestari, Rudyanto Sedono, Zulkifli

Abstract

Objective: Lactate is a useful prognostic marker, as its level increases in hypoxic tissue and/or during accelerated aerobic glycolysis due to excessive beta-adrenergic stimulation and decreased lactate clearance. The Surviving Sepsis Campaign Bundle 2018 Update suggested re-measurement of lactate within 2-4 hours so as to conduct/ help/administer /introduce lactate-guided resuscitation to reduce mortality due to sepsis. The aim of this study was to compare initial lactate levels and lactate clearance at 4 h of recognition of sepsis as mortality predictors in sepsis

Methods: It was a prospective study performed with ethical approval in a single tertiary care centre. Patients aged 18 years or older who were diagnosed with sepsis by the Sepsis-3 definition were included in the study while patients who were not admitted to the ICU were excluded Dropout criteria was death of pateints within 4 hours of recognition of sepsis. Baseline demographic data was obtained and subjects were treated with an hour-1 bundle and examined for initial lactate levels. At 4 hours, lactate was re-measured and patients were observed for 28 days then after Lactate clearance was calculated by the following formula:

([initial lactate - hour-4 lactate]/initial lactate) × 100.

Results: Of the 41 subjects included in the study; 27 died (28-day mortality --65.9%). Age, sex, diagnosis of the patient and Charlson's Comorbidities scores between survivors and non-survivors showed no significant differences. Non-survivors had higher Sequential (sepsis-related) Organ Function Assessment (SOFA) scores (11.41±3.46 versus 8.77±2.92; p=0.02). Initial lactate levels and lactate clearance did not differ in prognostic value (AUC 0.67 versus 0.5; p=0.086), but initial lactate levels of >2 mmol/L had the greatest sensitivity (81.5%).

Conclusion: Initial lactate level and lactate clearance did not differ in predicting mortality in patients with sepsis

Keywords: Lactate, Sepsis, Mortality. (JPMA 71: S-25 [Suppl. 1]; 2021)

Introduction

Lactate serves as a tissue perfusion marker in sepsis,[1] but the etiology of hyperlactatemia in sepsis is complex. Under normal conditions, the lactate concentration is less than 2 mmol/L,[2] and arterial lactate concentrations are determined by the balance between lactate production and its clearance. In sepsis, as a result of tissue hypoxia and/or high levels of aerobic glycolysis due to excessive beta-adrenergic stimulation, the lactate level increases due to lactate overproduction[1] and decreased clearance.[3]

Hypoxic conditions hamper the process of mitochondrial oxidative phosphorylation, resulting in the accumulation of pyruvate and an increase in lactate production. Gore et al. found increased levels of pyruvate and its oxidation products in patients with sepsis.[4] By contrast, Levraut et al. showed that hyperlactatemia in stable patients with sepsis was caused by a decreased lactate clearance rather than overproduction.[3] A strong correlation was also been observed between blood lactate concentration and clearance[3] and studies have shown that lactate-guided resuscitation can reduce the mortality rate in patients with sepsis.[5-7]

Despite these differences in etiology, lactate levels can be used as a prognostic marker in patients with sepsis. The Surviving Sepsis Campaign Bundle 2018 Update suggested re-measurement of lactate levels within 2-4 hours of recognition of sepsis to reduce mortality.[1] A previous study by Ryoo et al. found that the initial lactate levels had a prognostic value significantly higher than that of lactate clearance at 6 hours of recognition of sepsis.[8] However, our current knowledge about lactate as a prognostic marker is limited since no study has yet compared initial lactate levels and lactate clearance at 4 hours of recognition of sepsis in terms of predicting mortality in patients with sepsis.

This study analysed all patients with sepsis who met the Sepsis-3 definition and our study inclusion criteria. All subjects were treated with an hour-1 bundle for sepsis.

The aim of the study was to compare the initial lactate

Department of Anesthesiology and Intensive Care, Universitas Indonesia, Rumah Sakit Cipto Mangunkusumo, Jakarta, Indonesia.

Correspondence: Mayang Indah Lestari. Email: mayangindah@fk.unsri.ac.id

levels and lactate clearance at 4 hours of recognition of sepsis as predictors of mortality due to sepsis.

Patients and Methods

It was a prospective observational analytical study conducted in a single tertiary care centre after ethical approval from Health Research Review Committee of Mohammad Hoesin Central Hospital and Faculty of Medicine, Sriwijaya University, Palembang, Indonesia, in the time duration between February till June 2019.

Patients aged 18 years or older and diagnosed with sepsis using the Sepsis-3 definition were included while patients who were not admitted to the ICU were excluded from the study. Dropout criteria was death within 4 hours of recognition of sepsis. Trained investigators, under intensivist supervision, identified all eligible patients for enrolment in this study. Sample size was calculated by purposive sampling technique.

Baseline demographic data was measured for all subjects including age, sex, diagnosis of the patient, Charlson's Comorbidity score and Sequential Organ Failure Assessment (SOFA) score.

The treatment protocol started with using the hour-1 bundle of sepsis which included 1) measuring initial/basal lactate levels; 2) obtaining blood for blood culture examination in less than one hour before antibiotics administration 3) administering intravenous broad-spectrum antibiotics; 4) rapid administration of 30 mL/kg BW crystalloid and /or lactate (4 mmol/L or more) for conditions of hypotension.; 5) and introducing vasopressors during or after fluid resuscitation in case compensatory hypotension occurs to maintain Mean Arterial Pressure (MAP)of $\geq$65 mmHg.[1] Lactate was re-measured at 4 hours. A microbiological examination was also conducted to record the source of infection. Patients were observed for 28 days, for outcomes; survival or non-survival(death). Lactate clearance was calculated using the formula ([initial lactate — hour-4 lactate]/initial lactate) $\times$ 100. Lactate was measured using a Stat Profile pHOx® Series blood gas analyser (Nova Biomedical, Waltham, U.S.).

Data was expressed as mean $\pm$ standard deviation or median (min-max) for continuous variables (depending on the data distribution) and numbers (percentages) for categorical variables. A normality test was carried out using the Shapiro-Wilk test. Each subjects' characteristics were analysed using the $\chi 2$ test to compare categorical variables, the independent t-test to compare normally distributed continuous variables and the Mann-Whitney test to compare non-normally distributed continuous variables or categorical variables which did not meet the $\chi 2$ test criteria. The performance was evaluated using the Receiver Operating Characteristic (ROC) curves with the Area Under the Curve (AUC). The significance level was 5%. Data was analysed using SPSS Statistics version 21.0 (IBM, New York, U.S.).

Results

The aim of this study was to compare lactate levels and lactate clearance 4 hours after recognition of sepsis as predictors of mortality due to sepsis. A total of 44 patients met the inclusion criteria and were enrolled in our study. Three patients were dropped out due to death within 4 h of sepsis recognition, leaving a total of 41 subjects whose data were analysed in this study.

The patients in our study had a 28-day mortality rate of 65.9% (27 subjects died). No considerable differences were evident between non-survivors and survivors in terms of age, sex, diagnosis of the patient, microbiology results or comorbidity score based on Charlson classification (Table-1). The only variable that showed a clear difference between non-survivors and survivors was the SOFA score. The initial lactate levels were higher in non-survivors than in survivors (2.7 [0.5-14.7] versus 2.5 [1-8]), although the difference was not statistically significant (p = 0.16).

We analysed Area Under the Receiver Operating

Table-1: Subject characteristics.

Variable	Total N = 41 (100%)	Non-survivor N = 27 (65.9%)	Survivor N = 14 (34.1%)	p-value
Age	50.88±2.35	51.44 ± 15.28	49.79 ± 15.08	0.974
Sex				
Female	22 (53.7%)	13 (48.1%)	9 (64.3%)	0.51
Male	19 (46.3%)	14 (51.9%)	5 (35.7%)	
Diagnosis				
Medical	27 (65.9%)	17 (63%)	10 (71.4%)	0.73
Surgical	14 (34.1)	10 (37%)	4 (28.6%)	
Microbiology				
Gram-positive	2 (4.9%)	2 (7.4%)	0 (0%)	0.53
Gram-negative	21 (51.2%)	8 (29.6%)	13 (92.9%)	
Fungal	1 (2.4%)	0 (0%)	1 (7.1%)	
Other	17 (41.5%)	17 (63%)	0 (0%)	
Charlson's Comorbidities score				
0	3 (7.3%)	1 (3.7%)	2 (14.3%)	0.53
2-Jan	29 (70.7%)	20 (74.1%)	9 (64.3%)	
4-Mar	5 (12.2%)	3 (11.1%)	2 (14.3%)	
>5	4 (9.8%)	3 (11.1%)	1 (7.1%)	
SOFA score*	10.55±0.55	11.41±3.46	8.77±2.92	0.02
Initial lactate levels	2.7 (0.5–14.7)	3.1 (0.5–14.7)	2.5 (1–8)	0.16
Lactate clearance	8.33 (-350–70.15)	8.7 (-350–70.15)	5.19(-76.47–62.5)	0.92

*SOFA: Sequential (sepsis-related) Organ Function Assessment.

Table-2: Comparison of initial lactate levels and lactate clearance at 4 h for predicting mortality in septic patients.

Variable	Area under the Receiver Operating Curve (95% CI)	Confidence Interval (CI) 95% Lower	Upper	p-value
Initial Lactate	0.67	0.490	0.840	0.086
Lactate clearance	0.5			

Characteristic (ROC) curves (AUC) to confirm the accuracy of initial lactate levels or lactate clearance in predicting mortality in patients with sepsis (Figure-1). The initial lactate performance was poor (AUC 0.67), and lactate clearance (AUC 0.5) failed to predict mortality.

We also compared initial lactate levels and lactate clearance at 4 h for predicting mortality due to sepsis (Table-2), but the difference between these two variables was not statistically significant.

The ROC shown in Table-3 indicated that the variable with the highest sensitivity for predicting mortality due to sepsis was an initial lactate level greater than 2 mmol/L, at 81.5%which meant that an initial lactate level of more than 2 mmol/L could correctly predict the death of patients with sepsis within 28 days 81.5% of the time. The variable with the highest specificity was an initial lactate level greater than 4 mmol/L, at 85.7%. meaning that an initial lactate level of more than 4 mmol/L could correctly predict the survival of patients with sepsis within 28 days, 85.7% of the time.

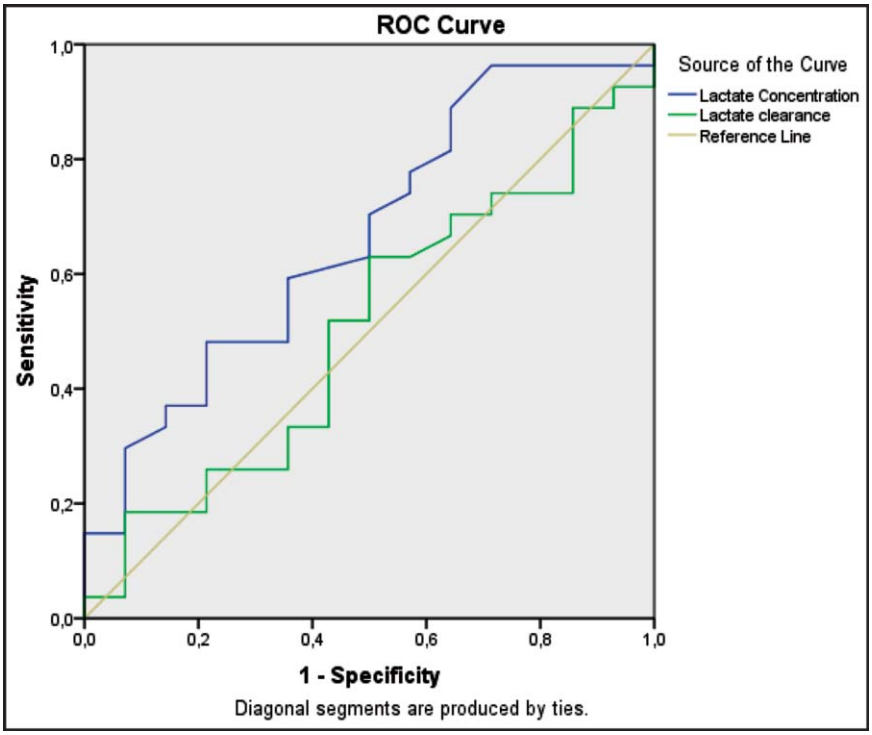

Figure: AUC of initial lactate and lactate clearance for sepsis mortality prediction performance.

Table-3: Sensitivity and specificity of initial lactate levels and lactate clearance at 4 hour for predicting mortality in septic patients.

Variable	Sensitivity	Specificity
Initial Lactate (mmol/L)		
>2	81.5%	35.7%
>3	48.1%	64.3%
>4	37%	85.7%

Variable	Sensitivity	Specificity
Lactate clearance (%)		
<10%	44.4%	57.1%
<20%	33.3%	64.3%
<30%	25.9%	78.6%

Discussion

In critically ill patients, and especially those who suffer from shock, hyperlactatemia is normally interpreted as an anaerobic metabolism marker indicating inadequate oxygen delivery. In sepsis, the etiology of hyperlactatemia is particularly complex. For example, Ronco et al. demonstrated that increased oxygen delivery fails to decrease lactate levels in patients with sepsis having hyperlactatemia.[9] Similarly, Gattinoni et al. found that supra-normal oxygen delivery in sepsis, as popularised by Shoemaker et al.,[10] did not improve patient outcomes.[11] Apart from its association with hypoxia, hyperlactatemia is also related to many other metabolic processes and other clinical conditions, such aslactate clearance. Gattinoni et al. showed that a more frequent etiology of hyperlactatemia in sepsis is a diminished oxygen utilisation by tissues.[12]

The arterial lactate level is determined by the balance between lactate production and its clearance. Despite their different aetiologies, lactate levels remain clinically important and can be used as a prognostic marker. For example, Mahmoodpoor et al. indicated that patients with sepsis who died within 28 days had higher serum lactate levels at the time of arrival and

required a higher dose of vasopressor.[13] Similarly, Lokhandwala et al. showed that lactate levels ≥4 mmol/L at 6 h after the initial examination and lactate reductions less than 20% were associated with an increased risk of in-hospital mortality due to sepsis.[14] Nguyen et al. found that patients with a higher lactate clearance had significantly decreased in-hospital and 28 or 60-day mortalities.[15] The Surviving Sepsis Campaign Bundle 2018 Update suggested re-measurement of lactate within 2-4 h of recognition of sepsis for lactate-guided resuscitation to reduce mortality.[1]

In our study, no significant differences were noted in age, sex, diagnosis of patient or Charlson's Comorbidities score between survivors and non-survivors, but the SOFA scores were higher in non-survivors (11.41±3.46 versus 8.77±2.92; p = 0.02). Lie et al. also indicated a higher total SOFA score in non-survivors than in survivors (6.7±3.8 versus 4.6±2.9; p < 0.001).[16]

In this study, neither lactate level nor lactate clearance differed between survivors and non-survivors. This result contrasted with a retrospective study by Ryoo et al., who found a lower median 6 h lactate level and a higher lactate clearance in survivors than in non-survivors.[8] This inconsistency between these study findings probably reflected the different patient populations (sepsis versus septic shock). In this study, we included all patients with sepsis diagnosed by using the Sepsis-3 Definition, which included those patients who had initial lactate levels of 2 mmol/L or less.

The initial lactate levels and the lactate clearance at 4 h of recognition of sepsis did not differ in prognostic value (AUC 0.67 versus 0.5; p = 0.086). Unlike the previous retrospective study, Ryoo et al. found that initial lactate levels had a significantly better prognostic value than lactate clearance at 6 h of recognition of sepsis (AUC 0.70 versus 0.65; p <0.01).[8] Singh et al. showed an AUC for serum lactate at 0 h of 0.734 and a lactate clearance at 48 h of 0.91.[17] The inconsistency among these studies probably reflects differences in the timing of the lactate measurements or in the time frame used to calculate the lactate clearance.

An initial lactate level of more than 2 mmol/L had the highest sensitivity for predicting mortality due to sepsis (81.5%). In this study, we also that an initial lactate level of more than 4 mmol/L had a specificity of 85.7% and sensitivity of 37%. This result was consistent with the findings of Fernando et al., who concluded that an initial lactate level of 4 mmol/L or greater had a specificity of 97% and a sensitivity of 27% in predicting the deterioration of patients with sepsis.[18] Ryoo et al. also found that a lactate level above 2 mmol/L had the greatest sensitivity (85.3%) and a level above 4 mmol/L had the greatest specificity (72.3%).[8]

Limitations

Our study had several limitations. One limitation is that we did not examine lactate at 2 h after recognition of sepsis, as suggested in the Surviving Sepsis Campaign Bundle 2018 Update, which recommends re-measurement of lactate within 2-4 h. A second limitation is that we included all patients with sepsis diagnosed by using the Sepsis-3 definition, which included those who had lactate levels of 2 mmol/L or less. A third limitation was that this was a single-centre study, which cannot be generalized to other institutions and populations.

Conclusion

The SOFA score, which serves as a life-threatening organ dysfunction indicator in sepsis, was higher in non-survivor patients. Initial lactate levels and lactate clearance after 4hrs of recognition of sepsis did not differ as predictors of mortality in patients with sepsis. Both initial lactate levels and lactate clearance were found to be poor predictors of mortality in patients with sepsis. Few inconsistencies among previous studies and our findings probably reflected differences in patient populations (sepsis versus septic shock) and in the lactate measurement times used to calculate lactate clearance. Our study limitations necessitate further investigations.

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