

Study of Significance of Serum Lactate Kinetics in Sepsis as Mortality Predictor

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ABSTRACT

Introduction: Sepsis is one of the leading causes of death worldwide. Serum lactate is being used in sepsis for diagnostic and prognostic purposes for years now. In this study, we shed light over a novel use of lactate in form of various clearance parameters to determine mortality in septic patients at the 28th day.

Materials and method: In our study, 200 patients with sepsis were included using quick sequential organ failure assessment (qSOFA) score and their lactate levels were measured at the time of admission (0 hour) and 24 hours after admission. Lactate clearance parameters (absolute and relative lactate clearance, lactate clearance rate) were calculated. All patients were followed up for a period of 28 days to determine the outcome, and data analysis was done accordingly.

Results and conclusion: Our study showed that higher SOFA score, qSOFA score, and serum lactate levels were associated with increased 28th-day mortality. Low absolute, relative lactate clearance and lactate clearance rate were also associated with poor outcomes. The best cutoffs to predict poor outcomes were serum lactate level at 24 hours ≥ 4 mmol/L and relative lactate clearance $\leq 40.3\%$ with good sensitivity and specificity.

Keywords: Lactate kinetics, Lactate clearance, Mortality prediction, Sepsis, Serum lactate.

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INTRODUCTION

Sepsis is the leading cause of morbidity and mortality and the second commonest cause of death worldwide.¹ Raised blood lactate levels in severe sepsis and septic shock usually indicate impaired oxidative phosphorylation secondary to reduced oxygen availability to the cells (hypoxic hypoxia) and/or tissue hypoperfusion (stagnant hypoxia). Because blood lactate levels can be measured easily and quickly, these have been used as a predictor of tissue hypoperfusion in critically ill patients admitted to the emergency department (ED) or intensive care unit (ICU).²

Serum lactate level has been used for diagnosis of septic shock as well as for targeting fluid resuscitation in patients with sepsis.^{3,4} Usefulness of serum lactate level after the initial 6 hours of resuscitation (so-called golden hours) is still under investigation because many septic patients die even after resuscitation during these golden hours. Systematic studies on serum lactate and lactate clearance are lacking in the Indian subpopulation with sepsis. In the present study, we aim to evaluate lactate clearance in patients with sepsis. We hypothesized that early lactate clearance in patients with sepsis is associated with better outcomes at 28 days.

OBJECTIVES

- **Primary objective:** to determine lactate clearance in septic patients and identify their association and cutoffs to predict the outcome at the 28th day after admission.
- **Secondary objective:** to identify the association between patients' characteristics [e.g. age, Glasgow Coma Scales (GCS), sequential organ failure assessment (SOFA) score, and quick SOFA (qSOFA) score] and outcomes at the 28th day after admission.

MATERIALS AND METHODS

This was a cross-sectional observational study carried out in the Department of General Medicine, ABVIMS and Dr RML Hospital,

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New Delhi, from November 1, 2018, to March 31, 2020, in 200 study participants admitted in wards, emergency and ICU, with suspected infection and having sepsis as defined by qSOFA score and SOFA score. Approval of the ethics and research committee of the hospital was taken by investigators before commencing the study.

Inclusion criteria for our study were age ≥ 18 years and diagnosis of sepsis using qSOFA score (score ≥ 2 points) and SOFA score (rise of ≥ 2 points from baseline). We excluded patients with a history of major surgery, polytrauma, HIV, malignancy, known case of chronic liver disease and chronic kidney disease, new infection acquired during the hospital stay and not present at the time of presentation, pregnancy, and patients taking biguanides or salicylates.

Methodology

After taking informed written consent, 200 patients with sepsis admitted to ED were included in this study. In patients with suspected infection, detailed clinical history and examination were done and sepsis was diagnosed using qSOFA score.^{3,5} Samples for the following laboratory investigations were taken before initiation of antimicrobial and resuscitative therapy: serum

lactate, complete hemogram, kidney function test, liver function test, serum electrolytes, blood culture, urine routine microscopy, urine culture, sputum gram stain and culture, sputum acid-fast bacilli, and arterial blood gas analysis. Radiological investigations, like chest X-ray and ultrasound (if required), were carried out to localize the site of infection. To calculate SOFA score, data like mean arterial pressure, $\text{PaO}_2/\text{FiO}_2$, platelet count, creatinine, urine output, total bilirubin, and GCS were obtained. SOFA score was calculated to confirm the diagnosis of sepsis. Two samples for serum lactate levels were drawn, the first sample at the time of diagnosis of sepsis (0 hour) and the second sample after 24 hours. At least 2 mL of whole venous blood was collected in a heparinized green-topped vial for measuring serum lactate levels. All samples were transported to the Department of Biochemistry, ABVIMS and Dr RML Hospital immediately on an ice slurry and processed without any delay. In all samples, serum lactate levels were measured using a colorimetric test by the VITROS LAC slide method (using lactate oxidase). Patients were managed according to Surviving Sepsis Campaign international guidelines for the management of sepsis and septic shock.⁶ Patients were followed up for 28 days to document the outcomes in terms of mortality. Then data were collected and statistical analysis was carried out.

As mentioned in a study done by Filho et al., lactate clearance was calculated by below-given formulas²:

- Absolute Lactate Clearance = Initial lactate value (0 hour) – delayed value (24 hours) (mmol/L)
- Relative Lactate Clearance = Absolute lactate clearance/Initial value multiplied by 100 (%)
- Lactate Clearance Rate = Relative lactate clearance/clearance time (% per hour).

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm standard deviation (SD) and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then a nonparametric test was used.

Statistical tests were applied as follows:

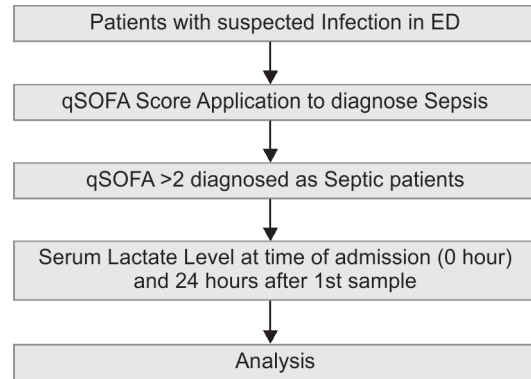
- Quantitative variables were compared using the independent *t*-test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups and the Kruskal Wallis test was used for comparison between more than two groups.
- Qualitative variables were correlated using the Chi-square test/Fisher's exact test.
- Spearman's rank correlation coefficient was used to assess the correlation of various parameters with lactate.
- A receiver-operating characteristic (ROC) curve was used to find out the cutoff point of parameters for predicting mortality. A diagnostic test was used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

A *p* value of <0.05 was considered statistically significant.

The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Study Plan

Flowchart 1: Study plan



RESULTS

The analysis and observation of the study were as follows:

Patient Characteristics

Demographic characteristics of the study population are depicted in Table 1. The age distribution of the study population varied from 19 to 85 years. Maximum patients were in the age-group between 51 and 60 years (26.5%). Advancing age was significantly associated with poor outcomes (*p* value 0.0001, Supplementary Table 1). Higher qSOFA, SOFA scores, and poor GCS were associated with increased 28th-day mortality (*p* value <0.0001). All three patients with GCS of less than six died, while out of 76 total patients with GCS of 15, only nine patients died (Supplementary Tables 2 and 3).

Association between Lactate Kinetics and Outcome

High serum lactate levels were significantly associated with poor outcomes (*p* value <0.0001). Low absolute lactate clearance, relative lactate clearance, and lactate clearance rate were associated with poor outcomes (*p* value <0.0001). Association between lactate kinetics and outcomes at the 28th day is depicted in Table 2.

Cutoffs of Serum Lactate and Clearances for Predicting Mortality

Using the ROC curve, cutoffs to predict mortality at the 28th day were predicted and they were as follows (Table 3, for ROC curve see Supplementary Figs 1 to 5):

- Serum lactate level at 0 hour > 5.9 mmol/L (sensitivity 83, specificity 69.3, PPV 45.3, NPV 93)
- Serum lactate level at 24 hours > 3.9 mmol/L (sensitivity 91.5, specificity 90.2, PPV 74.1, NPV 97.2)
- Absolute lactate clearance \leq 1.5 mmol/L (sensitivity 63.8, specificity 85, PPV 56.6, NPV 88.4)
- Relative lactate clearance \leq 40.2985% (sensitivity 91.5, specificity 92.8, PPV 79.6, NPV 97.3)
- Lactate clearance rate \leq 1.679% per hour (sensitivity 91.5, specificity 92.8, PPV 79.6, NPV 97.3)

Table 1: Characteristics of patients included in the study

Characteristics	Total population (N = 200)	Survivors (N = 153)	Nonsurvivors (N = 47)	p value
Gender, N (M/F)	109/91	86/67	23/24	
Age (years, Mean ± SD)	51.38 ± 15.9	48.9 ± 15.5	59.45 ± 14.38	0.0001
Quick SOFA (Mean ± SD)	2.19 ± 0.39	2.09 ± 0.29	2.51 ± 0.51	<0.0001
SOFA score (Mean ± SD)				
At 0 hours	4.92 ± 2.2	4.32 ± 1.76	6.85 ± 2.53	<0.0001
At 24 hours	2.97 ± 2.6	2 ± 1.5	6.13 ± 2.92	<0.0001
Etiology of sepsis, N (%)				
Pneumonia	78 (39)	51	27	
Urinary tract infections	50 (25)	30	20	
Liver abscesses	36 (18)	30	6	
Skin and soft tissue infections	24 (12)	14	10	
Others	47 (23.5)	39	8	

Table 2: Association of lactate kinetics with outcomes

Lactate	Died (n = 47)	Survived (n = 153)	Total	p value
Lactate at 0 hour (mmol/L)				
Mean ± SD	8.3 ± 2.55	5.21 ± 2.22	5.93 ± 2.65	<0.0001
Median (IQR)	8.5 (6.7–9.9)	4.6 (3.55–6.7)	5.35 (3.8–7.8)	
Range	1.8–14.6	2.1–12.6	1.8–14.6	
Lactate at 24 hour (mmol/L)				
Mean ± SD	7.16 ± 2.54	2.39 ± 1.48	3.51 ± 2.7	<0.0001
Median (IQR)	7.4 (5.4–8.8)	2.1 (1.55–2.8)	2.4 (1.7–4.875)	
Range	2.2–13.6	0.5–9.4	0.5–13.6	
Absolute lactate clearance (mmol/L)				
Mean ± SD	1.14 ± 1.79	2.82 ± 1.24	2.43 ± 1.56	<0.0001
Median (IQR)	1.2 (0.4–2.2)	2.5 (1.85–3.5)	2.3 (1.5–3.3)	
Range	–3.4 to 4.7	0.8–6.7	–3.4 to 6.7	
Relative lactate clearance (%)				
Mean ± SD	10.68 ± 34	55.49 ± 12.08	44.96 ± 27.23	<0.0001
Median (IQR)	15.31 (4.938–25)	57.35 (48.665–63.197)	51.86 (37.729–60.767)	
Range	–172.22 to 52.17	7.84–89.58	–172.22 to 89.58	
Lactate clearance rate (% per hour)				
Mean ± SD	0.44 ± 1.42	2.31 ± 0.5	1.87 ± 1.13	<0.0001
Median (IQR)	0.64 (0.214–1.042)	2.39 (2.029–2.633)	2.16 (1.577–2.531)	
Range	–7.18 to 2.17	0.33–3.73	–7.18 to 3.73	

Table 3: Receiver-operating characteristic curve of lactate at 0 hour, 24 hours, absolute lactate clearance, relative lactate clearance, and lactate clearance rate for predicting mortality

	Area under the ROC curve (AUC)	Standard error	95% confidence interval	p value	Cutoff
Lactate at 0 hour (mmol/L)	0.823	0.0353	0.763–0.873	<0.0001	>5.9
Lactate at 24 hour (mmol/L)	0.948	0.0158	0.908–0.975	<0.0001	>3.9
Absolute lactate clearance (mmol/L)	0.793	0.043	0.730–0.847	<0.0001	≤1.5
Relative lactate clearance (%)	0.963	0.0137	0.926–0.984	<0.0001	≤40.2985
Lactate clearance rate (% per hour)	0.963	0.0137	0.926–0.984	<0.0001	≤1.6792

DISCUSSION

Demographics and Etiology

In the present study, 200 patients were included out of which 109 (54.5%) were males and 91 (45.5%) were females. The mean age was 51.38 ± 15.9 years. Advancing age was significantly associated with poor outcomes (p value 0.0002). This study showed multiple etiologies of sepsis with pneumonia (39%) being the commonest followed by urinary tract infections (25%) and liver abscesses (18%). Out of 200 patients, in 147 patients, no organism could be isolated from cultures. Most common isolated organisms were *E. coli* (14 patients) followed by *Klebsiella* species (10 patients).

In a study done by Nguyen et al. in Detroit, a total of 111 patients were included where 59 were males (53.2%) and 52 were females (46.8%). This gender distribution was comparable to our study. Mean age of patients was 64.9 ± 16.7 years. However, advancing age was not associated with poor outcomes or low lactate clearance. Most common etiologies of sepsis in this study were pneumonia (47.7%) and urosepsis (12.6%), which was comparable to our study.⁷

In another study conducted by Ryoo et al. in South Korea, mean age of the study population was 65 ± 12.2 years. Old age was not a significant risk factor for poor outcomes. This study included a total of 1,060 patients out of which 662 (62.5%) were males and 398 (37.5%) were females. The etiology of sepsis was not included in data collection in this study.⁸

In a retrospective cohort study in 443 patients done by Filho et al. in Sao Paulo, Brazil, the study population included 273 (61.6%) male patients, while our study had 109 (54.5%) male patients. Old age was not having a significant association with poor outcomes. Source of sepsis in this study was the respiratory system (50.6%) followed by the urinary system (20.3%), which was comparable to our study (pneumonia 39% and urinary tract infections 25%).²

Age distribution in our study was different, and our study had more patients in younger age-groups. This could be due to the fact that all three abovementioned studies mainly included ICU patients with sepsis, while our study had ED, general ward, as well as ICU patients. An interesting observation in our study was older age population had a significant association with mortality.

Outcome

In the present study, out of 200 patients, 47 (23.5%) did not survive. Gender was not associated with poor outcomes. Low GCS was significantly associated with poor outcomes. None of the abovementioned studies included comparison between GCS and lactate parameters or outcomes. Our study indicated that patient's consciousness level in the form of GCS could be a prognostic factor in predicting mortality.

In our study, qSOFA score was calculated for all patients at the entry point and sepsis was defined by using clinical history, examination, and utilization of this score. Higher qSOFA score was significantly associated with poor outcomes at the 28th day (p value <0.0001).

SOFA score had a significant association with outcomes at the 28th day. High SOFA scores were significantly associated with 28th-day mortality (p value <0.0001). In a study done by Ryoo et al., high SOFA scores were significantly associated with poor outcomes in terms of 28th-day mortality (p value <0.01). Mean SOFA score for nonsurvivors was 9.68 ± 3.56 compared to survivors, which was 8.36 ± 2.98 .⁸ These findings were comparable to our study in which mean SOFA score for nonsurvivors was 6.85 ± 2.53 and for survivors was 4.32 ± 1.76 .

Lactate Kinetics and Outcomes

In a study done by Nguyen et al., serum lactate levels at the time of ED admission were significantly associated with 60th-day mortality. Mean serum lactate level in nonsurvivors was 8.0 ± 4.7 mmol/L, while lactate level in survivors was 6.1 ± 4.4 mmol/L.⁷ This was comparable to our study in which mean serum lactate at 0 hour in nonsurvivors was 8.3 ± 2.55 mmol/L and lactate level in survivors was 5.21 ± 2.22 mmol/L. In this study, lactate clearance was calculated by the given formula: (lactate at presentation - lactate after 6 hours/lactate at presentation) * 100 (which was equivalent to relative lactate clearance in our study). It was $12.0 \pm 51.6\%$ in nonsurvivors, and this was comparable to our study (in our study, relative lactate clearance was $10.68 \pm 34\%$).⁷ However, this study used Systemic Inflammatory Response Syndrome (SIRS) criteria as the entry point, 6-hour lactate clearance, and mainly ICU patients, while our study used qSOFA score, 24-hour lactate clearance, and both ICU and non-ICU patients. In both the studies, results showed that low lactate clearance was significantly associated with higher mortality. They have calculated $\leq 10\%$ is the optimal cutoff of relative lactate clearance at 6 hours after admission to predict mortality at the 60th day with sensitivity of 44.7% and specificity of 84.4%.⁷ However, our study showed that relative lactate clearance of $\leq 40\%$ at 24 hours can significantly predict 28th-day mortality (sensitivity 91.5% and specificity 92.8%).

In the study done by Ryoo et al., they used Sepsis 3 guidelines to define sepsis, but they calculated 6-hour lactate clearance. In this study, 0-hour median lactate levels (at the time of admission) were 5.0 mmol/L in nonsurvivors and 3.9 mmol/L in survivors.⁸ In our study, 0-hour median serum lactate levels were 8.5 mmol/L in nonsurvivors and 4.6 mmol/L in survivors. In this study, median 6-hour lactate values were significantly higher in the nonsurvivor group (4.6 mmol/L) compared to survivors (2.5 mmol/L).⁸ This was comparable to our study in which also median 24-hour lactate values were significantly higher in the nonsurvivor group (7.4 mmol/L) compared to the survivor group (2.1 mmol/L) with p value <0.0001 . Thus, higher initial and delayed serum lactate levels were significantly associated with 28th-day mortality. Median relative lactate clearance was also significantly lower in the nonsurvivor groups (14.8% in this study, 15.3% in our study) compared to the survivor group (35.4% in this study, 57.3% in our study). In this study, a 6-hour lactate value of ≥ 2 mmol/L predicted 28th-day mortality with high sensitivity (85%) but low specificity (35%).⁸ In our study, a 24-hour lactate value of ≥ 4 mmol/L predicted 28th-day mortality with sensitivity of 91.5% and specificity of 90.2%.

Limitations

- The sample size was small.
- Comorbidities of patients were not included in this study, which could have affected the outcomes of patients.
- The study only calculated 24-hour lactate clearance. Frequent lactate measuring and then comparing 6-hour, 12-hour, as well as 24-hour lactate clearance could provide more information and insight into lactate kinetics.

CONCLUSION

Low absolute lactate clearance, relative lactate clearance, and lactate clearance rate are significantly associated with mortality at the 28th day. Relative lactate clearance of $\leq 40\%$ at 24-hour is a good predictor of 28th-day mortality in septic patients with sensitivity and specificity of 91.5 and 92.8%, respectively.

Old age and poor GCS are significantly associated with adverse outcomes in septic patients. High SOFA, qSOFA scores, as well as serum lactate levels (0 and 24 hours) are associated with poor outcomes.

Contribution

Nagina Agarwal: Conceptualization, Methodology, Validation, Resources, Supervision, Writing—Review and Editing
Mit Chaudhari: Formal analysis, Investigation, Data Curation, Writing—Original Draft, Visualization, Writing—Review and Editing

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