



Lactate Level versus Lactate Clearance for Predicting Mortality in critically ill children with Septic Shock admitted in Pediatric Intensive Care Unit of Hi-Tech Medical College and Hospital, Bhubaneswar

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ABSTRACT

BACKGROUND: Arterial lactate is a reflection of balance between lactate production and lactate clearance. Accumulating lactate may be a marker of global hypoxia or hypo-perfusion. Lactate clearance is the reduction of lactate concentration with interventional strategies which has been associated with increased survival.

OBJECTIVE: To compare the prognostic value of lactate level at admission and lactate clearance at 6 hours in critically ill children with sepsis and septic shock.

METHOD: We conducted a prospective cohort study in Paediatric intensive care unit of Hi-Tech Medical College and Hospital from July 2018 to July 2019. We enrolled 58 children who satisfied the criteria for sepsis and septic shock. All of them were followed up until they were discharged from hospital as to whether they survived or died. We performed serial blood lactate measurements early on following their diagnosis of sepsis and after 6 hours following first antibiotic administration. Logistic regression for the multivariate analysis and ROC curves for the accurate analysis of predictive outcome factors were performed.

RESULT: More death occurred in children with low lactate clearance at 6 hours (32%) than in the high lactate clearance group.

CONCLUSION: Lactate clearance at six hours may be used a more effective predictor of mortality in critically ill children than isolated blood lactate level at admission.

KEYWORDS: lactate, lactate clearance, predictor, mortality, septic shock.

I. INTRODUCTION

Septic shock is one of the major causes of admission and death in intensive care units. The

main cause of death in septic shock is organ system failure initiated by cellular hypoperfusion resulting in cellular hypoxia.¹ This condition is caused by the formation of microthrombi in small blood vessels which impair the blood flow.² The knowledge of factors which affect the outcome in septic shock will help in the early recognition of children who are at highest risk of death and may allow timely changes in therapy, which may improve the outcome.³

Prompt identification of inadequate tissue perfusion and its aggressive management is essential in treating patients with septic shock, particularly with the increasing incidence and burden of managing the morbidity and mortality.⁴ The optimal management of pediatric septic shock patients includes early recognition of inadequate tissue perfusion and its timely correction in an effort to prevent anaerobic metabolism, acidosis and cellular death.^{5,6,7}

It is well documented that microvascular flow alterations and organ hypoxia can exist despite normalization of vital signs.^{8,9} Many critically ill patients, who are normotensive and have adequate urine output, may remain in a state of compensated shock.¹⁰ Hence relying solely on the normalization of vital signs such as changes in heart rate, blood pressure and urine output cannot be used as sensitive markers for hypoxia and perfusion disorders, therefore another parameter is needed for monitoring tissue perfusion as an early assessment tool for microcirculation disorders.

Some studies have suggested that blood lactate levels may be used to assess tissue perfusion and be a marker for the onset of tissue hypoxia.^{11,12} There is proportional increase between blood lactate level and severity of tissue hypoxia.^{13,14} In



the recent years, lactate has been studied as a biomarker for sepsis and septic shock.^{15,16,17,18}

Lactic acidosis or hyperlactatemia occurs when lactate production exceeds its clearance which has been confirmed to be associated with worse clinical outcomes in critically ill patients.^{12,19} Lactate measurement in critically ill patients is practical and can provide information on illness severity and prognosis because a high lactate level is most frequently interpreted as resulting from anaerobic metabolism related to cellular hypoxia and is thought to be an important marker of impaired tissue perfusion in patients with sepsis particularly when associated with metabolic acidosis.^{20,21}

Lactate clearance (LC) is the reduction of lactate concentrations with interventional strategies, therapeutic strategies that can potentially decrease arterial lactate which may be associated with improved clinical outcome.²² The aim of such a strategy is to reverse the global tissue hypoxia. The idea of Lactate Clearance is to accommodate this concept. In order to monitor the metabolic consequences of shock and hemodynamic management, plasma lactate levels and lactate clearance can be used in critical illness. Reduced lactate clearance may reflect globally impaired renal and hepatic metabolic function, both of which normally contribute to systemic lactate disposal. Thus lactate clearance biologically reflects homeostasis of the host and provides more meaningful data about the overall adequacy of the resuscitative processes.^{23,24} The Surviving Sepsis Campaign recommends lactate normalization as a target of resuscitation for patients with severe sepsis and septic shock with a recent update.²⁵

II. OBJECTIVE

To compare the prognostic value of lactate level at admission and lactate clearance at six hours in critically ill children with sepsis and septic shock.

III. METHODS

This study was a prospective cohort study conducted on children >1 month and <13 years admitted to Pediatric Intensive Care Unit of Hi-Tech Medical College and Hospital in critically ill condition with suspected sepsis and septic shock. Study period was from July 2018 to July 2019.

Inclusion criteria:

Children within age >1 month and <13 years admitted to PICU with suspected sepsis and septic shock. Sepsis is defined as clinical or laboratory evidence of infection in presence of more than two of the following findings:

1. Temperature more than 38 °C or less than 36 °C
2. WBC count abnormalities (>15000 cells/mm³ or <4000 cells/mm³ or 10% immature neutrophils)
3. Increased acute phase reactants (ESR>20mm/hr, CRP>20mg/l)

Septic shock is defined as sepsis with either hypotension (i.e. systolic BP< 2SD adjusted for age) or at least one manifestation of inadequate perfusion:²⁶

1. Altered mentation (irritability, lethargy/coma)
2. Hypoxia (PaO₂/FiO₂<300)
3. Metabolic acidosis (arterial pH<7.35 or Base deficit>5)
4. Oliguria (urine output<0.5ml/kg/hr)
5. Along with signs of poor peripheral perfusion CRT>3 sec, cyanosis)

Exclusion criteria:

1. Patients with other causes of shock like
-Hypovolemic shock
-Cardiogenic shock
-Anaphylactic shock
-Neurogenic shock
-Endocrinological shock
2. Known malignancies and immunosuppressive treatment.
3. Chronic kidney diseases
4. Post operative state.

The Glasgow coma scale score of all the children admitted was calculated. Under all aseptic precautions 0.5 ml of arterial blood was withdrawn using 1 ml pre-heparinised syringe from the radial or femoral artery and were immediately analysed using ABL 80 Flex Radiometer Blood Gas Analyser. Thus at admission (0 hour) pH along with blood lactate levels were recorded. Later, blood gas analysis was repeated at 6 hours of admission for serum lactate level. In interval period of 6 hours resuscitation measures to treat hypoperfusion, hypotension and antibiotic administration were undertaken as per the standard treatment protocol.

Lactate clearance has been incorporated into the initial resuscitation target in the 2016 Surviving Sepsis Campaign.²⁷ Lactate clearance at six hours was calculated based on the following formula:²⁸

Initial lactate level - lactate level at 6 hours x 100 initial lactate level

The subjects were classified into two groups based on lactate clearance: low lactate clearance or high lactate clearance. The clearance groups were based on the lactate level attenuation of more or less than 20% at six hours after administration of the first antibiotic. Then the outcome was evaluated whether they survived or died during the hospitalization.



IV. STATISTICAL ANALYSIS

Logistic regression for the multivariate analysis and ROC curves for the accurate analysis of predictive outcome factors were performed. Survivors and non-survivors were compared by the Mann-Whitney test for continuous variables and by Fisher's exact test for categorical variables. Variables with p value <0.2 in the univariate analysis were included in the multivariate analysis to determine the effect of predictor on outcome of septic shock. For continuous variables, t-test was

used. A p-value<0.05 was taken as statistically significant.

V. RESULTS

A total of 58 children were included in the study. Glasgow coma scale score was calculated at admission. The blood lactate level at admission to be taken as serum lactate at 0 hours and then again was measured at 6 hours following various resuscitative measures to improve outcome. The baseline characteristics of the study subjects are presented in **Table 1**:

| Characteristics | SURVIVORS (46) | NON-SURVIVORS (12) | p value | RR | 95% CI |
|---|-------------------|-----------------------|---------|------|--------------|
| Gender Male:Female | 30:16 | 7:5 | 0.464 | 1.2 | 0.7 to 2.05 |
| Mean age, months(SD) | 20.1+-41.7 | 12.8+-29.8 | 0.586 | 1.1 | 1.07 to 3.06 |
| GCS AT PICU | 9.1+-3.2 | 7.1+-2.7 | 0.084 | 1.42 | 2.0 to 45 |
| pH at admission | 7.24+-0.13 | 7.20+-0.19 | 0.479 | 0.96 | 0.5 to 1.7 |
| Lactate ,(SD) at admission | 8.44(3.27) | 7.29(3.31) | 0.180 | 1.21 | 28-43% |
| Lactate clearance,(SD) at 6 hours | 4.54(2.5) | 6.8(3.74) | 0.001 | 3.4 | 2.3-78% |

Table 1: Baseline characteristics of study subjects

There were 12 deaths out of 58 cases with case fatality rate of 20.7%. the initial lactate was not significantly different between those who died [8.44(SD 3.27)] and those who survived [7.29(SD 3.31)] , p=0.18. But the lactate clearance at 6 hours was significantly lower in those who died [(-4.01%), mean -6.8(SD 3.74)] than those who survived [(35.53%, mean-4.54(SD 2.5)] p<0.001.

Univariate analysis indicated that GCS score, lactate at admission and lactate clearance had p- value < 0.2, therefore those variables were included in multivariate analysis. The multivariate

analysis revealed that lactate clearance at 6 hours was a statistically significant outcome predictor of septic shock in children [RR 3.4, 95% CI- 2.3-78].

Out of 12 children who died , 9 children (75%) had low lactate clearance <30 and 3 children (25%) had high lactate clearance >30 as shown in **Figure 1**.

Out of 14 children in the low lactate clearance group (LC<30), 9 children (64.3%) died whereas in high lactate clearance group(LC>30), out of 46 children only 3 children (6.5%) died as shown in **Figure 2**.

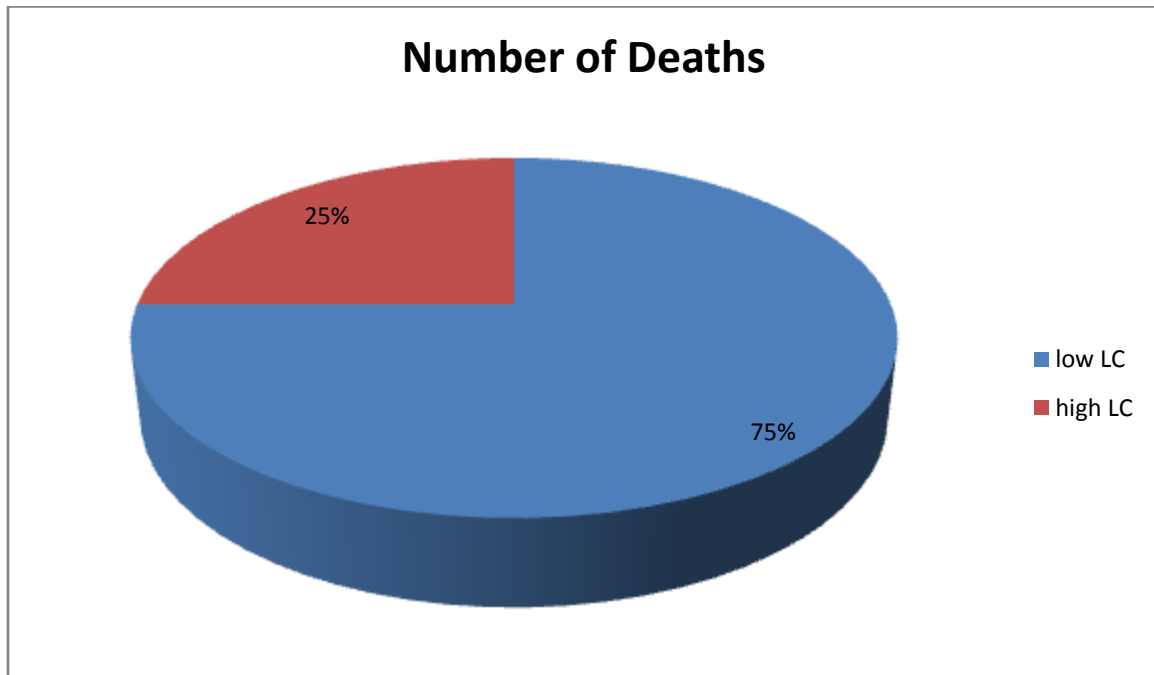


Figure 1: Pie chart showing amount of lactate clearance in dead children

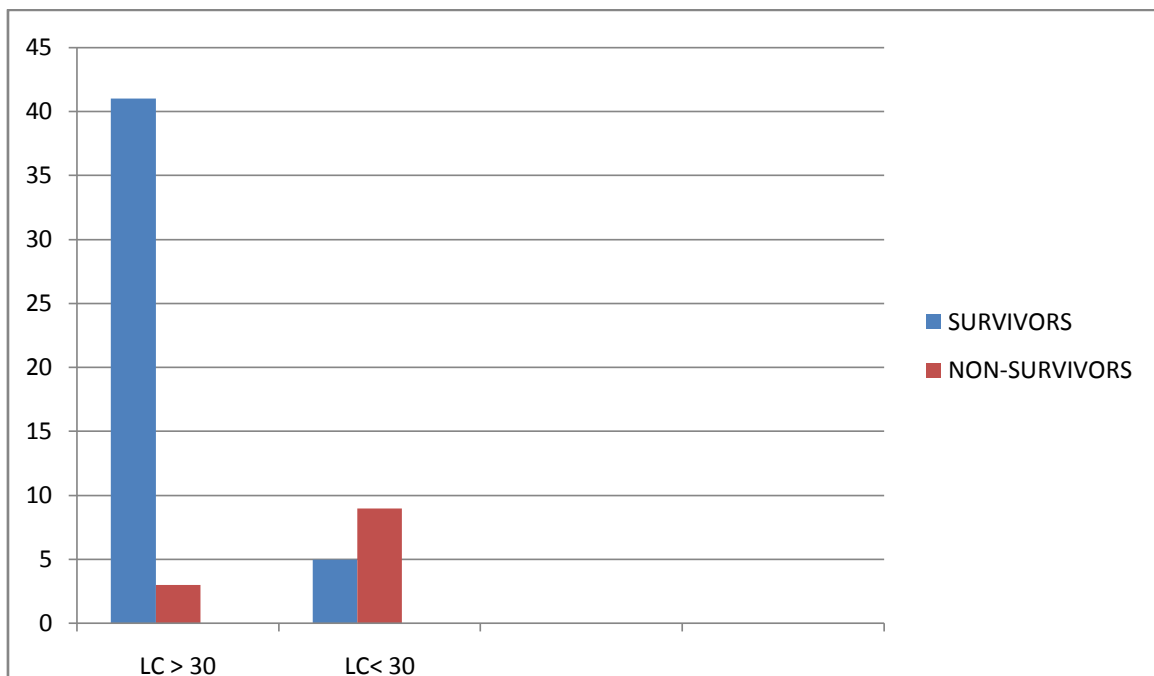


Figure 2: Bar diagram showing proportion of deaths in various subgroups of lactate clearance.

ROC curve analysis for six hour lactate showed an area under curve (AUC) of 97% ($p < 0.05$), suggesting that six hour lactate clearance

measurement had good strength as a predictor of outcome in septic shock in critically ill children, as shown in **Figure 3**.

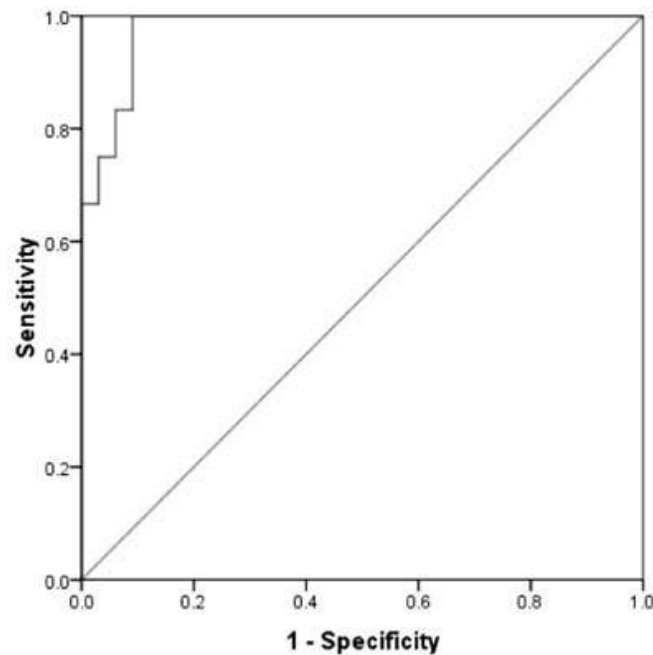


Figure 3. ROC curve of six hours lactate clearance as a predictive indicator of mortality in septic shock.

VI. DISCUSSION

The results of our study demonstrated that a greater proportion of deaths occurred in the group of low lactate clearance at six hours (64.3%) as compared to those with high lactate clearance at six hours (6.5%). Logistic regression analysis showed that lactate clearance at six hours was a significant predictor of mortality [RR 3.4, 95% CI 2.3-78]. Many clinical studies have demonstrated that patients with lactate clearance showed better clinical outcomes as compared with those without lactate clearance.²⁹ Furthermore, patients with rapid lactate clearance were more likely to survive than those with slow lactate clearance.³⁰

Low lactate clearance at six hours indicates a state of high blood lactate level that occurred within the preceding six hours. Such a condition accounts for hypoxia that persists in the tissues, causing organ dysfunction and death.³¹ High lactate clearance indicates the return of lactate levels to normal values after treatment.

VII. CONCLUSION

There was a significant correlation between lactate clearance, outcome and prognosis. Hence clearance directed therapy should be initiated as soon as child suspected with sepsis and septic shock is admitted in pediatric intensive care unit. Limitation of this study was that the initial lactate levels were not significantly different between the survivors and non-survivors. But low lactate clearance clearly predicted the mortality in

the non-survivors. Thus, lactate clearance at six hours may be used as a more effective predictor of mortality in critically ill children than isolated blood lactate level at admission.

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