Research Article

Validation of lactate clearance at 6 h for mortality prediction in critically ill children

Rajeev Kumar, Nirmal Kumar

Abstract

Background and Aims: To validate the lactate clearance (LC) at 6 h for mortality prediction in Pediatric Intensive Care Unit (PICU)-admitted patients and its comparison with a pediatric index of mortality 2 (PIM 2) score. **Design:** A prospective, observational study in a tertiary care center. **Materials and Methods:** Children <13 years of age, admitted to PICU were included in the study. Lactate levels were measured at 0 and 6 h of admission for clearance. LC and delayed or nonclearance group compared for in-hospital mortality and compared with PIM 2 score for mortality prediction. **Results:** Of the 140 children (mean age 33.42 months) who were admitted to PICU, 23 (16.42%) patients died. For LC cut-off (16.435%) at 6 h, 92 patients qualified for clearance and 48 for delayed or non-LC group. High mortality was observed (39.6%) in delayed or non-LC group as compared to clearance group (4.3%) (P = 0.000). LC cut-off of 16.435% at 6 h (sensitivity 82.6%, specificity 75.2%, positive predictive value 39.6%, and negative predictive value 95.7%) correlates with mortality. Area under receiver operating characteristic (ROC) for LC at 6 h for mortality prediction was 0.823 (P = 0.000). The area under ROC curve for expected mortality prediction by PIM 2 score at admission was 0.906 and at 12.3% cut-off of PIM 2 Score was related with mortality. The mean PIM 2 score was high in delayed or non-LC group (25.25%) compared to LC group (10.95%) (P = 0.004). **Conclusion:** LC cut-off <16.435% at 6 h was associated with high mortality.

Keywords: Lactate clearance, mortality prediction, pediatric index of mortality 2 score, Pediatric Intensive Care Unit

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.192040

Quick Response Code:

Introduction

Hyperlactatemia are common findings in critically ill patients and have significant prognostic implications. Lactate levels are frequently cited as an indicator of inadequate tissue perfusion or oxygenation, particularly in sepsis.[1] The severity and duration of lactic acidosis in critically ill patients correlate with overall oxygen debt, potential organ dysfunction, and mortality.[2]

Single lactate level, particularly those measured on Intensive Care Unit (ICU) entry or arrival at the emergency department (ED), has been thought to be a strong predictor of subsequent organ dysfunction and mortality. Trzeciak *et al*. showed that an initial lactate level of more than 4 mmol/L was associated with substantial increases in the probability of acute-phase death.[3] The predictive value of initial lactate has been confirmed in several large cohort or database studies.[4-6] However, a single measurement of lactate is a static variable and can only serve as a risk-stratification biomarker. Serial measurements or lactate clearance (LC) over time may be better prognosticators of organ failure and mortality than a single lactate measurement.[7-12]

From:
Department of Pediatrics, St. Stephen's Hospital, New Delhi, India

Correspondence:
Dr. Nirmal Kumar, 4, Rajpur Road, Quarter No. B-2, Tis-Hazari, New Delhi - 110 054, India.
E-mail: nsk9_2000@Yahoo.com

How to cite this article: Kumar R, Kumar N. Validation of lactate clearance at 6 h for mortality prediction in critically ill children. Indian J Crit Care Med 2016;20:570-4.

Nguyen *et al*. and Jansen *et al*. have suggested the role of LC as a marker of mortality prediction in adults.[13,14] LC is closely associated with capillary perfusion independent of hemodynamic variables, and it is thought to be a good biomarker of microcirculation[13] representative of impaired diffusion of oxygen capacity. Serial lactate measurements may also aid in assessing the adequacy of resuscitation.[13] Various studies have shown that persistent hyperlactatemia beyond 24–48 h was associated with mortality, poor neurological outcome, and organ failure.[13-16]

A study by Nguyen *et al*. comparing survivors with nonsurvivors had an LC of 38.1% ± 34.6% versus 12.0% ± 51.6%, respectively (P = 0.005). There was an approximately 11% decrease likelihood of mortality for each 10% increase in LC.[13] A recently completed multicenter, randomized, controlled trial demonstrated that LC of 10% or more is noninferior to the use of continuous $ScvO_2$ monitoring in determining the adequacy of resuscitation and oxygen supply/demand relationship during the early resuscitation of severe sepsis and septic shock.[17] Taken together, these data demonstrate the utility of LC not only as a prognostic marker in sepsis but also as a valuable endpoint of early resuscitation, it can be used as a tool to predict the outcome.

One pediatric study looked at LC at 24 h for mortality prediction is published. The study suggested that persistent hyperlactatemia >2 mM after 24 h was associated with 93% mortality as compared to 30% in normalized lactate level.[8]

Pilot study to look at LC for mortality prediction in children showed LC <30% at 6 h was significantly associated with mortality.[18] Hence, we planned to validate this finding of LC at 6 h for mortality prediction.

Aims and objectives

To validate the LC at 6 h for prediction of mortality in Pediatric ICU (PICU)-admitted patients and its comparison with expected mortality prediction by pediatric index of mortality 2 (PIM 2) score.

Materials and Methods

It was a prospective, observational study in a tertiary care PICU, New Delhi, between May 2014 and June 2015. Institutional Ethical Committee approval was obtained prior to undertaking the study. Informed and written consents were obtained from the parents of all participating children. Inclusion criteria: Children of >1 month and <13 years of age, who were admitted in PICU during study period.

Children with do not resuscitate orders, inborn errors of metabolism, trauma patients, and those who refused consent were excluded from the study.

Sample size

By taking confidence level of 95% and confidence interval (CI) of 10%, the sample size required was 138 children.

Methodology

A three-step approach was used.

Step 1

All children admitted in PICU not meeting any of the exclusion criteria were included in the study after taking written and informed consents.

Step 2

All enrolled patients underwent following:

- Detailed history and physical examination were recorded. All preliminary investigations for detecting organ failure including those necessary to calculate PIM 2 score were done at admission
- Blood gas analysis (including lactate) was measured first at admission (0) and then after 6 h of admission using a "Radiometer Copenhagen ABL 555" blood gas analyzer.

Step 3

All patients were managed as per our unit standard clinical practice. PIM 2 score was measured, and PIM 2 risk of mortality was calculated using a web-based calculator (www.sfar.org/scores2/pim22.html) for calculation of predicted mortality rate. The system computes the predicted mortality rate based on standard methods using logistic regression equation.

LC (%) is defined using the following formula: lactate at ED presentation (h 0) minus lactate at h 6, divided by lactate at ED presentation, then multiplied by 100. A positive value denotes a decrease or clearance of lactate whereas a negative value denotes an increase in lactate after 6 h of ED intervention.[18]

$$\text{Lactate clearance} = \frac{\text{lactate ED presentation} - \text{lactate h 6}}{\text{lactate ED presentation}} \times 100$$

Final diagnosis and outcome were recorded.

Statistical analysis

We compared the two groups (clearance vs. nonclearance) for in-hospital mortality. Expected

mortality by PIM 2 score at admission was compared with LC versus nonclearance group by Mann–Whitney U-test.

Quantitative data were presented as mean ± standard deviation (SD). The values results were not normally distributed and thus were analyzed nonparametrically. Survivors and nonsurvivors were compared by the Mann–Whitney U-test for continuous variables and by Fisher's exact test for categorical variables. Pair-wise comparisons were made using Wilcoxon's signed-rank test. A $P < 0.05$ was taken as statistically significant. Sensitivity, specificity, positive predictive value, and negative predictive value of LC for mortality were calculated.

SPSS version 17.0, USA was used for statistical analysis.

Observations and Results

One hundred and forty children admitted to PICU who fulfilled inclusion criteria were included in this study. The mean age of the study population (n = 140) was 33.42 months. Of the 140 children, 98 (70%) were males and 23 (16.4%) patients died. Mean lactate (mmol/L) at admission was low in those who survived in comparison to nonsurvivors (3.117 vs. 5.017) (P 0.009).

Wilcoxon signed-rank test showed statistically significant difference in lactate levels at 0 and 6 h of admission in those who survived (mean lactate at 0 h: 3.117; SD: 2.840 and at 6 h: 1.968; SD: 1.821, P = 0.000) compared to the nonsurvived group (mean at 0 h: 5.017; SD: 3.615) at 6 h (mean: 5.726; SD: 3.3724%, P = 0.070) [Table 1]. The area under receiver operating characteristic (ROC) curve for mortality prediction was 0.823 (95% CI: 0.715–0.931) [P = 0.000, Graph 1]. Based on ROC curve, a cut-off value of 16.435% LC at 6 h was associated with mortality. An optimal LC cut-off was defined as that LC with the maximum sum of sensitivity plus specificity for predicting in-hospital mortality.

Low LC group (≤16.435%) had 39.6% mortality compared to 4.3% in high clearance group (>16.435%) (P = 0.000). Measure of agreement by kappa statistics between LC <16.435% at 6 h and mortality was 0.402. LC ≤16.435% at 6 h for mortality prediction had sensitivity of 82.6%, specificity 75.2%, positive predictive value of 39.6%, and negative predictive value of 95.7% [Table 2].

PIM 2 score cut-off of 12.3% was associated with mortality. Above this cutoff value, high mortality was observed (42.2%) than in those below this cut-off (4.2%) (P = 0.000).

In delayed/non-LC group, the mean PIM 2 score was 25.2583% (SD: 27.94219) whereas in clearance group was 10.9522% (SD: 16.92542).

Comparison of expected mortality by PIM 2 score at admission in LC versus non-LC group by Mann–Whitney U-test was significant [P = 0.004, Table 3].

Discussion

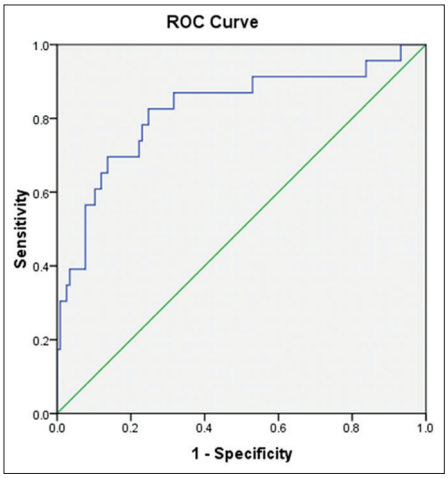
The predictive value of initial lactate has been confirmed in several large cohort or database studies.[4-7] However, a single measurement of lactate is a static variable and can only serve as a risk-stratification biomarker. To make it more clinically useful, trend of "lactate clearance," during treatment at 6 h of hospital stay, was explored and its association with mortality was found.

Various studies have shown high lactate levels in serial measurements and prolonged time to normalize lactate and predicted a higher mortality rate.[7-11,13-15,19] There are very few studies which look at the outcome of LC at 6 h of admission.[13,18,20,21] We observed higher mortality in non-LC group (39.6% vs. 4.3%; P = 0.000) which is similar to the study by Arnold *et al*.[17] (60% vs. 19% at LC cut-off of 10% at 6 h of hospital stay, P < 0.001) and also similar to the study by Nguyen *et al*.[13] who observed that clearance <10% in 6 h was associated with

Table 1: Mean lactate (mmol/L) levels in two groups (died vs. survived) group

	Mean lactate level at admission (SD)	Mean lactate level at 6 h (SD)	*P*
Survived (n=117)	3.117 (2.840)	1.968 (1.821)	0.000
Died (n=23)	5.017 (3.615)	5.726 (3.372)	0.070

SD: Standard deviation



Graph 1: Receiver operating characteristic curve for lactate clearance at 6 h for mortality prediction. Area under curve 0.823 (95% confidence interval: 0.715–0.931)

Table 2: Outcome based on cut-off level of lactate clearance (16.435%)

Lactate clearance test	Mortality		
	Died (*n*=23)	Survived (*n*=117)	Total
≤16.435 (*n*=48)	19	29	48
>16.435 (*n*=92)	4	88	92
Total	23	117	140
Sensitivity		82.6%	
Specificity		75.2%	
Positive predictive value		39.6%	
Negative predictive value		95.7%	

Table 3: Comparing expected mortality by pediatric index of mortality 2 score at admission in lactate clearance versus nonlactate clearance groups

	Expected mortality by PIM 2 score at admission		
	n	Mean	SD
LC at 6 h			
Delayed or non-LC group (LC at 6 h ≤16.435)	48	25.258	27.9421
LC group (LC at 6 h >16.435)	92	10.952	16.9254

Mann-Whitney U-test, *P*=0.004. PIM 2: Pediatric index of mortality 2; SD: Standard deviation; LC: Lactate clearance

a higher mortality ($P = 0.007$). The cut-off value of LC to predict mortality at 6 h by Nguyen *et al*. was 10%, while in our study it is higher (16.435%), probably because they studied LC only in cases with severe sepsis and septic shock, while in our study we considered cases irrespective of underlying etiology.

Hatheril *et al*.[8] showed that persistent hyperlactatemia >2 mM after 24 h was associated with 93% mortality as compared to 30% in those children whose lactate level had normalized, (likelihood ratio of 7, sensitivity 78%, and specificity 89%). The area under the ROC curve for lactate >2 mM at 24 h after admission was 0.86. Although area under ROC curve of 0.823 and sensitivity of 82.6% in our study is comparable to their study, specificity of 75.2% in ours is low compared to their study because they did not look at LC but they looked at persistent hyperlactatemia >2 mM after 24 h for the association of mortality.

Munde *et al*.[18] looked at LC at 6 h and observed that mortality was high in delayed or non-LC group than clearance group (75% vs. 25% with a $P = 0.000$). In their study, LC of <30% at 6 h for prediction of mortality in PICU-admitted children had a sensitivity of 75% and specificity 97%. The area under ROC curve was 0.977 (95% CI: 0.943–1.012) for mortality prediction. Although their sensitivity is comparable to our study, specificity in our study is less, probably because they took a very high cut-off of LC <30% for mortality prediction. The area under ROC curve in their study is high because of high cut-off of LC (<30%) and high mortality (90%) among delayed or non-LC compared to our study.

In delayed/non-LC group, mean PIM 2 score was 25.2583% and in clearance group was 10.9522% (SD: 16.92542%, $P = 0.004$). PIM 2 score of more than 12.3% (cut = off value) for expected mortality and an LC less than cut-off value (16.435%) were comparable.

The limitations of our study is that it includes only patients admitted to the PICU and excludes those admitted in step down units, trauma cases and those who are non critically ill.

Conclusion

We found an lactate clearance cut off cut-off of around 16% at 6 h in critically ill patients is comparable to PIM 2 score for mortality prediction.

Acknowledgment

We would like to thank Dr. R. S. Beri who helped to conduct this study and Dr. D. K. Shukla for data analysis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 1970;41:989-1001.
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
3. Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, *et al.* Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 2007;33:970-7.
4. Green JP, Berger T, Garg N, Shapiro NI. Serum lactate is a better predictor of short-term mortality when stratified by C-reactive protein in adult emergency department patients hospitalized for a suspected infection. Ann Emerg Med 2011;57:291-5.
5. Mikkelsen ME, Miltiades AN, Gaieski DF, Goyal M, Fuchs BD, Shah CV, *et al.* Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med 2009;37:1670-7.
6. del Portal DA, Shofer F, Mikkelsen ME, Dorsey PJ Jr., Gaieski DF, Goyal M, *et al.* Emergency department lactate is associated with mortality in older adults admitted with and without infections. Acad Emerg Med 2010;17:260-8.
7. Cerovic O, Golubovic V, Spec-Marn A, Kremzar B, Vidmar G. Relationship between injury severity and lactate levels in severely injured patients. Intensive Care Med 2003;29:1300-5.

8. Hatherill M, McIntyre AG, Wattie M, Murdoch IA. Early hyperlactataemia in critically ill children. Intensive Care Med 2000;26:314-8.
9. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, *et al.* Relative hyperlactatemia and hospital mortality in critically ill patients: A retrospective multi-centre study. Crit Care 2010;14:R25.
10. Suistomaa M, Ruokonen E, Kari A, Takala J. Time-pattern of lactate and lactate to pyruvate ratio in the first 24 hours of intensive care emergency admissions. Shock 2000;14:8-12.
11. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, *et al.* Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001;27:74-83.
12. Khosravani H, Shahpori R, Stelfox HT, Kirkpatrick AW, Laupland KB. Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill. Crit Care 2009;13:R90.
13. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, *et al.* Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004;32:1637-42.
14. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, *et al.* Early lactate-guided therapy in Intensive Care Unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med 2010;182:752-61.
15. Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, *et al.* Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine (Baltimore) 2004;83:274-9.
16. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996;171:221-6.
17. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, Casner E, *et al.* Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock 2009;32:35-9.
18. Munde A, Kumar N, Beri RS, Puliyel JM. Lactate clearance as a marker of mortality in pediatric Intensive Care Unit. Indian Pediatr 2014;51:565-7.
19. Jansen TC, van Bommel J, Mulder PG, Lima AP, van der Hoven B, Rommes JH, *et al.* Prognostic value of blood lactate levels: does the clinical diagnosis at admission matter? J Trauma 2009;66:377-85.
20. Cardinal Fernández PA, Olano E, Acosta C, Bertullo H, Albornoz H, Bagnulo H. Prognostic value of lactate clearance in the first 6 hours of intensive medicine course. Med Intensiva 2009;33:166-70.
21. Puskarich MA, Trzeciak S, Shapiro NI, Albers AB, Heffner AC, Kline JA, *et al.* Whole blood lactate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest 2013;143:1548-53.