Persistent Hyperlactatemia as the Predictor of Poor Outcome in Critically Ill Children: A Single-Center, Prospective, Observational Cohort Study

Vinayak K. Patki¹ Jennifer V. Antin² Shweta H. Khare²

¹Department of Pediatrics, Institute of Medical Education and Research, Vidyagiri, Satara, Maharashtra, India

²Department of Pediatrics, Wanless Hospital, Miraj, Sangli, Maharashtra, India

Address for correspondence Vinayak K. Patki, MB, DNB, FCCP, Department of Pediatrics, Institute of Medical Science and Research, Vidyagiri, 415102 Satara, Maharashtra, India (e-mail: patkivinayak@gmail.com).

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Abstract

Keywords

- ▶ critically ill children
- ▶ hyperlactatemia
- ▶ PICU
- ▶ PRISM
- ▶ normalized lactate load

Objective To study incidence of hyperlactatemia and its correlation with outcome in critically ill children.

Design Single-center, prospective cohort study.

Setting Eight-bedded PICU.

Method Serial serum lactate levels were measured in 140 critically ill children at 0, 12, 24, and 48 hours.

Results A total of 45% children had hyperlactatemia. Lactate levels were significantly ($p = 0.000$) higher in nonsurvivors at all intervals. Lactate levels decreased significantly ($p = 0.000$) in survivors while increased in nonsurvivors. Normalized lactate load was found to be an independent predictor of mortality ($p = 0.023$).

Conclusion Persistent hyperlactatemia serves as a possible predictor of poor outcome in critically ill children.

Introduction

Many variables measured in critically ill patients have been used to estimate severity of illness, predict morbidity and mortality, evaluate costs, and evaluate specific treatment regimens. It is unlikely that any single measurement can perform all of these functions, but in this study we evaluated whether measured lactate could surface.

It is widely believed that in critically ill patients, when oxygen delivery fails to meet oxygen demand, an oxygen debt with global tissue hypoxia ensues. This results in anaerobic metabolism and increased lactate production.^{1,2} An increased blood lactate concentration is therefore regarded as irrefutable evidence of anaerobic metabolism and tissue hypoxia. The normal serum lactate concentration in an unstressed patient is 9 to 10 mg/dL (0.5–1 mmol/L).³ The concentration in arterial blood depends on rate of production and conversion by various organs and is normally maintained below 18 mg/dL (2 mmol/L). The normal lactate production is 0.8 mmol/kg/h (1,300 mmol/day).⁴

Hyperlactatemia is defined as persistent increase in blood lactate concentration (18–45 mg/dL) without metabolic acidosis, whereas lactic acidosis is metabolic acidosis ($\text{pH} < 7.35$) associated with persistently high lactate level ($> 45 \text{ mg/dL}$).^{4,5} High initial serum lactate levels and persistently high lactate levels have been correlated with poor patient outcome.^{6,7}

High blood lactate levels are found in critically ill patients with shock of any etiology including sepsis due to various reasons. In sepsis, there is increased catecholamine production resulting in induced glucose flux apart from tissue hypoperfusion and hypoxia with subsequent increased serum lactate levels.^{8–10} Multiple conditions resulting in inadequate oxygen delivery, disproportionate oxygen demand, and diminished oxygen use may lead to elevated lactate levels.¹¹ The main use of plasma lactate concentration is as an adjunct to a detailed physical examination to detect and monitor evidence of hypoperfusion and as a prognostic indicator. Increased lactate levels may be considered an early

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marker of a potentially reversible state, for example, early septic shock, thus allowing for therapeutic interventions to reverse the condition. In most clinical conditions, failure of lactate to return to normal over 24 to 28 hours is a grave prognostic indicator.^{12–15}

Lactate has been investigated in adult population in mixed ICU patients. Various illnesses in these patients like acute lung injury, asthma,^{16–18} liver injury,^{19,20} poisoning,²¹ or postcardiac surgery^{22–25} have demonstrated elevated blood lactate levels. In a recent health technology assessment on the use of lactate levels in critically ill patients, both in the emergency department and in the ICU, blood lactate levels have demonstrated as a means to perform risk stratification of these patients.²⁶ Due to the high prevalence of hyperlactatemia in critically ill patients, its association with clinical outcome has been extensively studied over the past two decades.²⁷ Higher lactate value is consistently associated with adverse clinical outcomes and rapid lactate clearance after treatment is associated with improved outcomes.²⁸ Lactate clearance is predictive of lower mortality rate in critically ill patients, and its diagnostic performance is optimal for clinical utility. However, most of these studies are observational studies which, whether it is prospective or retrospective, are subject to confounding bias. Zhang et al demonstrated that initial lactate at ICU admission was associated with death hazard and delayed normalization of lactate was predictive of high risk of death.²⁹ Bakker et al and Kalyanaraman et al have found linear correlation of serial blood lactate levels with outcome of critically ill patients.^{30,31} Lactate clearance is predictive of lower mortality rate in critically ill patients, and its diagnostic performance is optimal for clinical utility. Zhang et al. first coined the term “normalized lactate load” and demonstrated that it was independently associated with prediction of renal injury in cardiopulmonary bypass patients.³²

There are limited studies available about lactate levels in the pediatric age group. Jat et al studied serum lactate levels as a predictor of outcome in pediatric septic shock.¹³ Duke et al correlated lactate with mortality and multiorgan failure in children with sepsis. Hatherill et al³³ and Zhou X et al³⁴ demonstrated that hyperlactatemia on admission to intensive care was associated with a high mortality in children. Koliski et al studied serial lactate concentration as prognostic marker in critically ill children and concluded that the normalization or reduction of lactate levels at and after 24 hours of admission was significantly related with improved outcomes.³⁵ There is paucity of data on lactate levels as prognostic marker in critically ill children from developing countries like India.^{13,25,26} The present study was conducted with an objective to measure serial lactate levels in critically ill children and correlate these levels with their outcome.

Materials and Method

The present study was conducted in Wanless Hospital, Miraj, Maharashtra, India with an eight-bed PICU at a tertiary center. The study population comprised 140 critically ill children who were admitted in PICU over a period of 12 months from

1st January 2012 to 31st December 2012. Children aged 1 month to 18 years with pediatric risk of mortality score (PRISM) of 10 or more at admission were included in the study. Neonates and children who died in less than 24 hours of admission were excluded from the study. Demographic data included age, sex, weight, systemic diagnosis, and duration of the illness. Critical illness variables collected for all children included PRISM III score, inotropes received, and duration of mechanical ventilation (if required). Institutional protocols were used for treating all patients admitted to PICU independent of study participation. The treating PICU team was blind to the results of lactate levels.

The serum lactate levels were measured in arterial blood at 0 hours (lactate 1), 12 hours (lactate 2), 24 hours (lactate 3), and at 48 hours (lactate 4) after admission at ICU by the quantitative lactate oxidase-peroxidase enzymatic colorimetric test by Spinreact which was calibrated every week. The samples were transported in ice-containing containers and processed within 15 minutes of collection at central laboratory. Ethical committee approval and informed consent were taken for all patients. Serum lactate level of 18 mg/dL or more (2 mmol/L) was considered as hyperlactatemia, and serum lactate level of 45 mg/dL or more as severe hyperlactatemia. The study population was compared between hyperlactatemic and non-hyperlactatemic children and also between survivors and nonsurvivors. Sample size was estimated by considering a maximum type I error probability of 5% (α) and a type II error of 20% with an estimated power of 80%, depending on the analysis performed.

Lactate load was defined as the product of time and lactate value, and normalized lactate load was the lactate load divided by the time (► Fig. 1).³³ Normalized lactate load (L) was calculated by the equation:

$$L = \frac{1}{2(t_n - t_0)} \sum_{i=0}^n (V_i + V_{i+1}) \times (t_{i+1} - t_i)$$

$$\text{lactate load} = \frac{1}{2} \sum_{i=0}^n (v_i + v_{i+1}) \times (t_{i+1} - t_i)$$

$$\text{Normalized lactate load} = \frac{\text{lactate load}}{t_i - t_0}$$

Fig. 1 Schematic illustration of the calculation of lactate load and normalized lactate load. (Adapted from Zhang et al³².)

where t_i was time point for lactate measurement and v_i was the value of lactate. For instance, if there were three measurements of lactate defined as v_1 , v_2 , and v_3 , with corresponding measurement time of t_1 , t_2 , and t_3 , then the lactate load and normalized lactate load would be given by the equations lactate load = $[(v_1 + v_2) \times (t_2 - t_1) + (v_2 + v_3) \times (t_3 - t_2)]/2$ and normalized lactate load = $[(v_1 + v_2) \times (t_2 - t_1) + (v_2 + v_3) \times (t_3 - t_2)]/[2 \times (t_3 - t_1)]$, respectively. Due to an expected skewed distribution of the normalized lactate load, the results were log transformed to improve its normality. Thus, L was transformed by natural log ($\ln$) to improve its normality. The log transformed values are denoted as $\ln$ throughout the manuscript. Lactate load was used to account for cumulative effect of hyperlactatemia in predicting outcome.

The data were presented as mean $\pm$ standard deviation. Normally distributed continuous variables were compared with Student's t -test, and categorical variables were compared with chi-square test or Fisher's exact test. Non-normally distributed data were compared with Mann-Whitney test and Kruskal-Wallis test. Repeated lactate measurement was studied as longitudinal data analysis using linear mixed models. After determination of individual factors associated with mortality by univariate analysis, a binary logistic regression model of significant factors associated with mortality was developed. The results of regression model were presented as adjusted odds ratio with 95% confidence intervals. Wald's chi-square value was used to test unique contribution of each predictor. Regression model adequacy was tested by Omnibus test of model coefficients, Nagelkerke R square, and Hosmer and Lemeshow chi-square test. Receiver operating characteristic curve (ROC curve) was used to validate predicted probabilities of death. In all comparisons, p value less than 0.05 was considered significant. An IBM SPSS software 19.0 was used for statistical analysis.

The study was performed with an objective to determine incidence of hyperlactatemia and to correlate degree of hyperlactatemia with severity of illness and outcome in critically ill children.

Results

During the study period of 1 year, out of the total 210 patients who were admitted to PICU, 152 patients had a PRISM score of 10 and more. Out of those 152 patients, seven died and five

were discharged against medical advice within 24 hours of admission. The remaining 140 patients were included in the study. Overall patient cohort had median age of 48 months (IQR 1.0–168.0), median weight of 13.5 months (IQR 2.0–47), and median PRISM score of 12 (10–23). Male-to-female ratio was 1.54:1. Incidence of hyperlactatemia was 45%. Incidence of hyperlactatemia was 38.2% in age group of 1 to 12 months, 49.0% in age group of 13 to 59 months, and 39.6% in age group of more than 60 months. Incidence of hyperlactatemia for specific diagnosis was 53% in patients with sepsis, 52% in gastrointestinal cases, 50% in cardiac cases, 37.5% in respiratory cases, 41.3% in neurological cases, and 40% in renal diseases. Incidence of hyperlactatemia was nearly similar among different diseases without significant association with particular disease (**►Table 1**).

The hyperlactatemic group had significantly higher PRISM III score (14.95 ± 3.43 vs. 12.38 ± 2.39) than that of nonhyperlactatemic group. Hyperlactatemic group had higher requirement of ventilation (44.4% vs. 15.6%), inotropes (38.1% vs. 7.8%), and steroid (20.6% vs. 6.5%). Of those who received mechanical ventilation they also had a longer duration of mechanical ventilation (43.27 ± 24.17 vs. 29.47 ± 11.19 h), but the length of PICU stay (68.90 ± 18.63 vs. 67.17 ± 25.43 h) was not higher than that of hyperlactatemics (**►Table 2**).

Twenty eight (20%) children died in study population. Mortality was significantly higher (34.9% vs. 7.8%) among hyperlactatemic than nonhyperlactatemic children. Serum lactate levels at 0, 12, 24, and 48 hours and normalized lactate load ($\ln$) ($p=0.000$) were significantly higher in nonsurvivors than that of survivors (**►Table 3**). Lactate levels in survivors were decreased significantly during hospital stay, whereas lactate levels were increased in nonsurvivors (**►Tables 4 and 5**). Repeated lactate measurement in both survivors and nonsurvivor groups demonstrated significant ($p=0.000$) estimates of fixed effects and significant ($p=0.000$) estimates of covariance parameters using linear mixed models with covariance structure either as unstructured or compound symmetry (not shown in tables).

Normalized lactate load ($\ln$) (adjusted odds ratio of 7.213, Wald of 5.206, $p = 0.023$) was found as an independent factor to predict death-like PRISM score in the multivariate analysis (Omnibus test of model coefficient 117.209 at $df=2$ with $p=0.000$, Nagelkerke R square 0.909, and Cox and Snell R square 0.570) (**►Table 6**). The area under ROC curve for lactate at 12, 24, and 48 hours and for normalized lactate load ($\ln$)

Table 1 Distribution according to primary system involved in both groups

System involved	Hyperlactatemic ($n = 63$)		Nonhyperlactatemic ($n = 77$)		p value
	No	deaths	No	deaths	
Sepsis	18	4	16	1	0.844
Neurological	12	6	17	0	0.817
Cardiovascular	10	3	10	0	0.808
Gastrointestinal	8	3	10	2	0.839
Respiratory	9	4	15	1	0.558
Renal	6	2	9	2	0.890

Table 2 Demographics in hyperlactatemic vs non- hyperlactatemic children

Parameter	Hyperlactatemic (n = 63)	Nonhyperlactatemic (n = 77)	p value
Median weight in kg	14 (3–42)	13 (2–47)	0.497
Male/female	41/22	44/33	0.339
Median age in months	48 (2–168)	48 (1–156)	0.683
PRISM score	14.95 ± 3.43	12.35 ± 2.33	0.000
Ventilation required n (%)	28 (44.4%)	12 (15.6%)	0.000
Duration of ventilation in hours	43.27 ± 24.17	29.47 ± 11.19	0.000
Use of inotropes n (%)	24 (38.1%)	6 (7.8%)	0.000
Use of steroid n (%)	13 (20.6%)	5 (6.5%)	0.023
Length of PICU stay in days	68.90 ± 18.63	67.1725.43	0.652
Mortality n (%)	22 (34.9%)	6 (7.8%)	0.000

Table 3 Demographics: survivors versus nonsurvivors

Diagnosis	Survivors (n = 112)	Nonsurvivors (n = 28)	p value
Median weight in kg	12 (2–40)	14 (2.5–47)	0.899
Male/female ratio	64/48	17/11	1.000
Median age in months	36 (1–156)	48 (2–168)	0.526
PRISM score	12.21 ± 1.68	18.75 ± 2.01	0.000
Lactate at 0 h	20.08 ± 13.13	74.11 ± 40.42	0.000
Lactate at 12 h	18.27 ± 11.58	77.82 ± 40.09	0.000
Lactate at 24 h	15.40 ± 10.05	79.27 ± 38.71	0.000
Lactate at 48 h	13.20 ± 9.60	81.37 ± 39.20	0.000
Normalized lactate load (Lln)	2.72 ± 0.56	4.098 ± 0.80	0.000

Table 4 Alteration in serial lactate levels in nonsurvivors (n = 28) by paired t-test

Lactate values	Paired differences					t	df	Sig. (two-tailed)
	Mean	Std. deviation	Std. error mean	95% CI				
				Lower	Upper			
0–12 h	–3.71071	7.67417	1.45028	–6.68645	–.73498	–2.559	27	.016
12–24 h	–3.1667	8.8821	1.7094	–6.6803	.3470	–1.853	26	.075
24–48 h	.2087	9.5262	1.9864	–3.9108	4.3281	.105	22	.917

Table 5 Alteration in serial lactate levels in survivors (n = 112) by paired t-test

Lactate values	Paired differences					t	df	Sig. (two-tailed)
	Mean	Std. deviation	Std. error mean	95% CI				
				Lower	Upper			
0–12 h	1.80795	4.28664	.40505	1.00531	2.61058	4.464	111	.000
12–24 h	2.8687	3.5517	.3356	2.2037	3.5338	8.548	111	.000
24–48 h	2.2054	6.1584	.5819	1.0523	3.3585	3.790	111	.000

Table 6 Multivariate analysis of factors associated with mortality by logistic regression

Variable	Wald	SE	df	p value	Odds ratio
Normalized lactate load	5.206	.866	1	0.023	7.213
PRISM score	11.849	.486	1	0.001	5.321
Constant	12.803	9.508	1	0.000	0.000

was comparable with that of PRISM score. The normalized lactate load (Lln) had fairly good sensitivity and specificity and was comparable with that of PRISM score in predicting death (—Table 7).

Discussion

Recent studies have demonstrated a good correlation of lactate levels with prognosis during critical illness; thus, the parameter has become established as an important marker in intensive care units. While the initial studies had demonstrated increased mortality associated with peak serum lactate,¹⁰ subsequent studies have failed to correlate this finding and demonstrated the significance of serial lactate levels over single value.^{6,13} Although arterial lactate values have been used as an indicator of severity and prognosis both in patients with acute shock¹⁰ and in general critically ill patients,⁵ recent data have demonstrated a good correlation of the arterial lactate level with lactate levels in venous and mixed venous (pulmonary artery) blood.^{6,7} It is important to note that the predictive ability of utilizing serum lactate levels in critical illness depends more on how the serum lactate value decreases overtime rather than the measured peak level.

In the present study, the incidence of hyperlactatemia was 45%, which was comparable with past studies.^{12,13,24,25,35} Our study population of critically ill children was heterogeneous. These patients demonstrated various illnesses and system involved. However, we could not find higher incidence of lactate levels in any particular disease; this finding was consistent with Koliski et al.³⁵ In our study population, 53% of cases of sepsis had hyperlactatemia, 66.7% (12 out of 18) of these cases had demonstrated signs of hypoperfusion and were supported on inotropic agents. All these cases demon-

strated signs of hypoperfusion and were supported on inotropic agents. It is important to note that in sepsis, there may be inadequate tissue perfusion in the absence of clinical signs (occult hypoperfusion). The mechanism for occult hypoperfusion has not been clearly described and may result from a combination of many factors including change in distribution of blood flow by vasodilation or increase in diffusion distance between capillary and cell as a result of interstitial edema or associated capillary injury.⁷

Hyperlactatemic children had high morbidity as demonstrated by a greater incidence of mechanical ventilation, longer duration of mechanical ventilation, higher use of inotropes, and steroids with a subsequent higher mortality. These findings were consistent with prior studies.^{13,24,25,35} We could not demonstrate longer duration of PICU stay in these children unlike Koliski et al.

In our study, 34.9% of hyperlactatemic children died as compared with 7.8% of patients with nonhyperlactatemics. This incidence of mortality among hyperlactatemics was comparable with previous published studies.^{26,33–35} The lactate levels at all intervals were significantly higher in nonsurvivors than survivors. The lactate levels decreased in survivors overtime while increased in nonsurvivors. In a previous study, Vincent et al. demonstrated that shock patients with the best prognosis were those in whom lactate levels had considerably decreased within 1 hour after resuscitation.¹¹ This finding may encourage clinicians to check serum lactate as an early prognostic marker for risk of death among critically ill patients after resuscitation.^{1,6,12,14,22}

An increase in the mortality has been observed among patient with lactate levels greater than 22 mg/dL.¹⁶ Broder and Weil noted that only 11% of those with serum lactate greater than 36 mg/dL survived.¹⁰ Moreover, Smith et al. suggested that hyperlactatemia can identify patients at risk of death and can also be used as indicator of the need for ICU admission.⁶ Besides these studies in adult patients, Siegel et al. observed that in children admitted to ICU after a cardiac surgery, high levels of lactate had a positive predictive value of 100% and negative predictive value of 97% for death.²³ By using multivariate logistic regression, Duke et al found that lactate level allowed distinguishing survivors from nonsurvivors among children with sepsis at 12 and 24 hours of admission.¹⁴ Hatherill et al suggested that

Table 7 ROC curve analysis of factors associated with mortality

Variable	AUC	SE	p value	95% CI	Sensitivity	Specificity	Criterion
Lactate at 0 h	0.855	0.0502	0.001	0.786–0.901	71.4%	96.4%	> 54.3
Lactate at 12 h	0.887	0.0417	0.001	0.822–0.934	75.0%	99.1%	> 57.9
Lactate at 24 h	0.921	0.0302	0.001	0.864–0.960	77.8%	96.4%	> 39.8
Lactate at 48 h	0.954	0.0202	0.001	0.904–0.983	100%	77.4%	> 17.8
PRISM score	0.991	0.0589	0.001	0.958–1.000	96.4%	96.4%	> 15
Normalized lactate load	0.893	0.0391	0.0001	0.830–0.939	74.1%	99.1%	> 3.95

Abbreviations: AUC, area under curve; ROC, receiver operating characteristic.

hyperlactatemia can indicate death on admission and if it persists after 24 hours of treatment.²² Jat et al found that lactate of 45 mg/dL or greater at 24 hours had 8.6 times (odds ratio 8.6) risk of predicting death in children with sepsis.¹³ Koliski et al documented that normalization or reduction of lactate levels at and after 24 hours of admission was significantly related with higher chances of survival.³⁵

Zhang et al have demonstrated that both lactate level and time influenced clinical outcome.^{28,29,32} The rationale is that a patient with persistent hyperlactatemia may have worse outcome than those with transient hyperlactatemia, given the magnitude of hyperlactatemia is the same. Lactate load considers both magnitude and time of hyperlactatemia. Other studies considered lactate and time separately, which was subject to the problem of multiple testing.^{30,31} However, it may not be valid in the situation because the patient had a prolonged measurement of lactate, as compared with a short time of lactate measurement. For example, patient A has low magnitude of lactate but is measured over a greater time period versus patient B who has a high magnitude of lactate but is measured over a shorter time of period. Their lactate loads could be equal. In our study to accommodate this situation, we used normalized lactate load to account for difference in the measurement duration.

In the present study, normalized lactate load (Lln) was found to be only significant independent risk factor for mortality with odds ratio of 7.213. The normalized lactate load (Lln) and lactate value at 24 and 48 hours have shown fairly good sensitivity, specificity, and area under ROC curve which were comparable with that of PRISM score in predicting mortality.

Previous data from India have demonstrated the relationship of elevated serum lactate levels to poor outcome in specific group of patients, that is, either septic shock,¹³ postcardiac surgery²⁵ rather than the diverse critically ill patients in PICU studied in our study.

Limitations of this study included the small sample size due to the diverse population resulting in small subgroups when patients were stratified by diagnosis, exclusion of numerous patients due to low PRISM scores, and missing values during this longitudinal study. Further the inclusion of severely ill patients may have skewed the mortality among those with hyperlactatemias and may be higher than stated. Therefore, further studies are necessary to confirm the predictive value of lactate in pediatric patients admitted in ICUs. Until new biochemical markers are discovered, our study demonstrates that serum lactate may be a useful prognostic marker.

Conclusion

Incidence of hyperlactatemia is high among critically ill children. Serial serum lactate level is superior to isolated measurements in estimating the clinical status of critically ill children in the PICU. Persistent hyperlactatemia serves as the predictor of poor outcome in critically ill children. Normal-

ized lactate load can be used as predictor of death consistent with the PRISM score.

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