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Association of Serum Lactate Levels with Disease Severity and Outcome in Critically Ill Children Admitted to PICU.

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Abstract

Background: Serum lactate is a readily available biochemical marker of impaired tissue perfusion and altered cellular metabolism. Persistently elevated lactate and inadequate lactate clearance may indicate ongoing physiological dysfunction and an unfavourable response to treatment. This study assessed the association of serum lactate with disease severity and clinical outcomes among critically ill children admitted to the Pediatric Intensive Care Unit. ***Aim:*** To determine the association of serum lactate levels with disease severity and clinical outcomes among critically ill children admitted to the PICU. ***Materials and Methods:*** This hospital-based prospective observational cohort study included 200 critically ill children admitted to the PICU. Serum lactate was measured within one hour of admission and repeated after six hours. Six-hour lactate clearance was calculated as the percentage reduction from the admission value. Disease severity was assessed using the PRISM III score. Participants were followed until PICU discharge to record mortality, mechanical ventilation, vasoactive support, multiple-organ dysfunction, and length of PICU stay. Associations were analysed using the chi-square test, paired and independent-samples t tests, correlation analysis, multivariable regression, and odds ratios with 95% confidence intervals. A p-value <0.05 was considered statistically significant. ***Results:*** Mean serum lactate decreased significantly from 3.72±2.41 mmol/L at admission to 2.84±2.16 mmol/L at six hours, with a mean reduction of 0.88 mmol/L (95% CI: 0.66-1.10; p<0.001). Mean six-hour lactate clearance was 21.64%, and 132 children (66.0%) achieved clearance ≥10%. Admission lactate showed a strong positive correlation with PRISM III score (r=0.660), while six-hour lactate demonstrated a stronger correlation (r=0.720; both p<0.001). Lactate clearance was negatively correlated with PRISM III score (r=-0.580; p<0.001). Mortality increased from 3.8% among children with admission lactate <2 mmol/L to 42.9% among those with lactate >4 mmol/L. Increasing lactate was also significantly associated with mechanical ventilation, vasoactive support, multiple-organ dysfunction, and prolonged PICU stay. Children with six-hour lactate ≥4 mmol/L had higher odds of mortality (OR=6.81; 95% CI: 2.95-15.72), mechanical ventilation (OR=4.32), vasoactive support (OR=5.07), multiple-organ dysfunction (OR=4.22), and PICU stay >7 days (OR=4.85); all p<0.001. Nonsurvivors had higher six-hour lactate than survivors (6.48±2.74 versus 2.12±1.39 mmol/L) and negative lactate clearance (-4.82±24.61% versus 26.87±29.18%; p<0.001). ***Conclusion:*** Elevated admission and six-hour serum lactate levels were significantly associated with greater PRISM III severity, mortality, organ-support requirements, multiple-organ dysfunction, and prolonged PICU stay. Persistent six-hour hyperlactatemia and failure of lactate clearance were particularly associated with poor outcomes. Serial lactate measurement may be used as a practical adjunct to clinical assessment and established severity scores for early prognostication in critically ill children.

Keywords: Serum lactate; PRISM III score; PICU mortality.

INTRODUCTION

Critical illness in children is frequently accompanied by disturbances in tissue perfusion, oxygen delivery, and cellular metabolism, which may progress to multiple-organ dysfunction and death. Early identification of children at increased risk of deterioration is therefore essential for timely resuscitation, appropriate allocation of intensive-care resources, and improved outcomes. Although clinical examination, hemodynamic parameters, urine output, and pediatric severity scores are routinely used for assessment, these indicators may not detect occult tissue hypoperfusion during the early stages of critical illness. Serum lactate is a readily measurable biochemical marker produced during glycolysis. Its concentration may increase because of tissue hypoxia, accelerated aerobic glycolysis, impaired hepatic or renal clearance, mitochondrial

dysfunction, or the effects of catecholamines. Consequently, hyperlactatemia can occur in children with sepsis, shock, respiratory failure, cardiac disease, trauma, seizures, and other critical conditions.

Elevated serum lactate has been associated with organ dysfunction and mortality among critically ill patients. However, a single lactate measurement may be affected by the underlying diagnosis, hepatic function, medications, sampling technique, and timing of resuscitation. Serial measurements and lactate clearance may provide additional information by reflecting changes in tissue perfusion and the response to treatment. Lactate clearance represents the percentage reduction in serum lactate over a specified period; failure to clear lactate may indicate persistent circulatory or metabolic dysfunction. Vincent et al. demonstrated that lactate kinetics were useful for prognostication in critically ill patients [1]. Pediatric studies have similarly reported an association of persistently elevated lactate and reduced lactate clearance with mortality [2,3]. The Surviving Sepsis Campaign guidelines recommend interpreting serial lactate trends together with clinical assessment when managing children with septic shock or sepsis-associated organ dysfunction [4].

Despite its clinical utility, the prognostic thresholds and performance of serum lactate vary considerably across pediatric populations and clinical settings. Recent evidence suggests that six-hour lactate levels and lactate clearance may predict mortality more accurately than admission lactate alone [5]. Further evaluation in a heterogeneous PICU population is therefore required. The present study assessed the association of admission and serial serum lactate levels with disease severity and clinical outcomes among critically ill children admitted to the PICU.

AIM

To determine the association of serum lactate levels with disease severity and clinical outcomes among critically ill children admitted to the PICU.

OBJECTIVES

1. To measure serum lactate levels at admission and six hours after admission among critically ill children admitted to the PICU.
2. To determine the association of admission lactate, six-hour lactate, and lactate clearance with disease severity assessed using the PRISM III score.
3. To evaluate the association of serum lactate parameters with mortality, mechanical ventilation, vasoactive support, and length of PICU stay.

MATERIALS AND METHODS

Source of Data

The study participants were critically ill children admitted to the Pediatric Intensive Care Unit during the study period. Clinical information was obtained through direct examination, interviews with parents or legally authorised representatives, medical records, bedside monitoring charts, laboratory reports, and PICU outcome records.

Study Design

The study was a hospital-based prospective observational cohort study.

Study Location

The study was conducted in the Pediatric Intensive Care Unit of the Department of Pediatrics. The PICU provided intensive monitoring, respiratory support, vasoactive therapy, and management of critically ill children with medical and surgical conditions.

Study Duration

The study was conducted over a period of 18 months after approval from the Institutional Ethics Committee.

Sample Size

A total of 200 critically ill children who fulfilled the eligibility criteria were enrolled. Participants were recruited consecutively until the required sample size was achieved.

Inclusion Criteria

- Children aged one month to 18 years admitted to the PICU.
- Children expected to remain in the PICU for at least six hours.
- Children for whom the first serum lactate sample could be collected within one hour of PICU admission.
- Children whose parents or legally authorised representatives provided written informed consent.
- Assent was obtained from older children whenever applicable.

Exclusion Criteria

- Neonates younger than one month.
- Children transferred from another healthcare facility after prolonged resuscitation when the pretreatment lactate level was unavailable.
- Children who died or were discharged against medical advice before the second lactate measurement.
- Children with known inborn errors of metabolism associated with persistent lactic acidosis.
- Children with chronic severe hepatic failure or receiving metformin, antiretroviral drugs, or other medications known to alter lactate metabolism.
- Children in whom adequate blood samples could not be obtained.
- Children whose parents or legally authorised representatives declined participation.

Procedure and Methodology

Approval was obtained from the Institutional Ethics Committee before commencement of the study. Written informed consent was obtained from the parent or legally authorised representative. Participants were enrolled consecutively according to the predefined eligibility criteria.

At admission, a detailed clinical history was recorded, including age, sex, presenting complaints, duration of illness, referral status, underlying disease, comorbidities, treatment received before admission, and primary diagnosis. Each child underwent a comprehensive clinical examination. Temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, capillary-refill time, peripheral pulse quality, level of consciousness, urine output, and signs of respiratory distress or shock were documented.

The primary diagnosis was categorised as sepsis or septic shock, respiratory illness, neurological illness, cardiovascular illness, gastrointestinal or hepatic illness, renal illness, trauma, poisoning, postoperative condition, or another critical illness. Relevant investigations, including complete blood count, blood glucose, arterial or venous blood gas analysis, serum electrolytes, renal-function tests, liver-function tests, coagulation profile, C-reactive protein, cultures, and radiological investigations, were performed as clinically indicated.

Disease severity was assessed using the Pediatric Risk of Mortality III (PRISM III) score, calculated from the required physiological and laboratory parameters recorded during the first 24 hours of PICU admission. A higher PRISM III score indicated greater disease severity and predicted mortality risk.

The first serum lactate level, designated Lactate-0, was measured within one hour of PICU admission and preferably before major therapeutic interventions whenever this did not delay emergency management. A second sample, designated Lactate-6, was obtained six hours after the initial measurement. Patient management, including fluid resuscitation, antimicrobial therapy, oxygen therapy, mechanical ventilation, and vasoactive support, was undertaken according to the PICU protocol and was not altered by study participation.

Six-hour lactate clearance was calculated as:

A positive value represented a reduction in lactate, whereas a zero or negative value indicated failure of clearance or an increase in lactate. Admission hyperlactatemia was defined according to the laboratory reference range and was additionally analysed using clinically relevant categories such as <2 mmol/L, 2-4 mmol/L, and >4 mmol/L.

Participants were followed throughout their PICU stay. The need for invasive or non-invasive mechanical ventilation, duration of ventilation, requirement and duration of vasoactive support, development of multiple-organ dysfunction, length of PICU stay, and final outcome were recorded. The principal outcome was PICU mortality. Secondary outcomes included mechanical ventilation, vasoactive-agent requirement, multiple-organ dysfunction, prolonged PICU stay, transfer to the ward, discharge, and discharge against medical advice.

Sample Processing

Approximately 1-2 mL of venous or arterial blood was collected aseptically with minimal tourniquet application and without repeated fist clenching. The sample was collected in a fluoride-oxalate or heparinised tube, according to the laboratory protocol. Samples were appropriately labelled and transported immediately to the central laboratory.

When plasma-based analysis was used, the sample was centrifuged promptly, and plasma was separated to minimise continued glycolysis and falsely elevated lactate values. Serum or plasma lactate was measured using an enzymatic lactate-oxidase method on a calibrated automated biochemical analyser. When blood-gas analysis was used, lactate was measured immediately using a calibrated blood-gas analyser. Internal quality-control procedures were performed according to laboratory standards. Lactate values were reported in mmol/L.

Data Collection

Data were collected prospectively using a predesigned and pretested case-record form. The form included:

- Demographic characteristics.
- Presenting symptoms and primary diagnosis.
- Pre-existing illnesses and treatment before PICU admission.
- Vital signs and clinical indicators of perfusion.
- Admission and six-hour serum lactate levels.
- Six-hour lactate clearance.
- PRISM III score.
- Laboratory and microbiological findings.
- Requirement for ventilation and vasoactive support.
- Development of organ dysfunction.
- Duration of ventilation and PICU stay.
- Final outcome at PICU discharge.

The completed forms were checked daily for accuracy and completeness. Each participant was assigned a unique identification number, and personally identifiable information was kept confidential.

Statistical Methods

Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics, version 26.0, or equivalent statistical software. Continuous variables were summarised as mean and standard deviation when normally distributed and as median and interquartile range when skewed. Categorical variables were presented as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test and graphical methods.

Admission lactate, six-hour lactate, lactate clearance, and PRISM III scores were compared between survivors and nonsurvivors using the independent-samples t test or Mann-Whitney U test. Categorical lactate groups were compared with mortality, mechanical ventilation, vasoactive support, and multiple-organ dysfunction using the chi-square test or Fisher's exact test.

The relationship between lactate parameters and PRISM III score was assessed using Pearson's or Spearman's correlation coefficient. Changes between admission and six-hour lactate levels were analysed using the paired t test or Wilcoxon signed-rank test. Multivariable binary logistic regression was performed to identify whether lactate parameters independently predicted mortality after adjustment for age, diagnosis, comorbidities, PRISM III score, mechanical ventilation, and vasoactive support. Adjusted odds ratios with 95% confidence intervals were reported.

Receiver-operating-characteristic curve analysis was performed to evaluate the ability of admission lactate, six-hour lactate, and lactate clearance to predict PICU mortality. Area under the curve, optimal cut-off value, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Association of admission serum lactate categories with disease severity and clinical outcomes (N=200)

Parameter	Lactate <2 mmol/L (n=78)	Lactate 2-4 mmol/L (n=73)	Lactate >4 mmol/L (n=49)	Effect estimate (95% CI)	Test of significance	P value
PRISM III severity category				Cramér's V=0.281	χ^2=31.60, df=4	<0.001*
Mild, n (%)	44 (56.4)	28 (38.4)	7 (14.3)			
Moderate, n (%)	23 (29.5)	31 (42.5)	18 (36.7)			
Severe, n (%)	11 (14.1)	14 (19.2)	24 (49.0)			
PRISM III score, Mean (SD)	7.12 (3.46)	11.84 (4.72)	18.63 (6.18)	Mean difference, >4 vs <2: 11.51 (9.70-13.32)	One-way ANOVA, F=90.17	<0.001*
PICU mortality, n (%)	3 (3.8)	9 (12.3)	21 (42.9)	RR, >4 vs <2: 11.14 (3.48-35.67)	χ^2=34.69, df=2	<0.001*
Mechanical ventilation, n (%)	19 (24.4)	35 (47.9)	36 (73.5)	RR, >4 vs <2: 3.02 (1.97-4.61)	χ^2=29.73, df=2	<0.001*

Vasoactive support, n (%)	11 (14.1)	22 (30.1)	31 (63.3)	RR, >4 vs <2: 4.49 (2.51-8.03)	χ^2=33.61, df=2	<0.001*
Multiple-organ dysfunction, n (%)	7 (9.0)	17 (23.3)	27 (55.1)	RR, >4 vs <2: 6.14 (2.89-13.04)	χ^2=34.00, df=2	<0.001*
PICU stay, days, Mean (SD)	4.71 (2.68)	6.42 (3.81)	9.36 (5.27)	Mean difference, >4 vs <2: 4.65 (3.13-6.17)	One-way ANOVA, F=25.84	<0.001*

Table 1 demonstrates a significant graded association between admission serum lactate and disease severity among the 200 critically ill children. Mild illness was most frequent among children with lactate <2 mmol/L (56.4%) and decreased to 14.3% among those with lactate >4 mmol/L. Conversely, severe illness increased from 14.1% in the <2 mmol/L group to 49.0% in the >4 mmol/L group. This association was statistically significant (χ^2=31.60, df=4, p<0.001; Cramér's V=0.281). The mean PRISM III score also increased progressively from 7.12±3.46 in children with lactate <2 mmol/L to 11.84±4.72 in those with lactate 2-4 mmol/L and 18.63±6.18 in those with lactate >4 mmol/L (F=90.17, p<0.001). The mean difference between the highest and lowest lactate groups was 11.51 points (95% CI: 9.70-13.32). Adverse outcomes showed a similar dose-response pattern. Mortality increased from 3.8% to 42.9%, mechanical ventilation from 24.4% to 73.5%, vasoactive support from 14.1% to 63.3%, and multiple-organ dysfunction from 9.0% to 55.1% across the lowest and highest lactate categories. Compared with children having lactate <2 mmol/L, those with lactate >4 mmol/L had 11.14 times the risk of mortality, 3.02 times the risk of mechanical ventilation, 4.49 times the risk of vasoactive support, and 6.14 times the risk of multiple-organ dysfunction. Mean PICU stay also increased significantly from 4.71±2.68 to 9.36±5.27 days, with a mean difference of 4.65 days (95% CI: 3.13-6.17; p<0.001).

Table 2: Serum lactate levels at admission and six hours after PICU admission (N=200)

Serum lactate parameter	Admission value	Six-hour value	Change/clearance (95% CI)	Test of significance	P value
Serum lactate, mmol/L, Mean (SD)	3.72 (2.41)	2.84 (2.16)	Mean reduction: 0.88 (0.66-1.10)	Paired t=8.03	<0.001*
Median serum lactate, mmol/L (IQR)	3.08 (1.72-5.14)	2.19 (1.28-3.76)	Median reduction: 0.63 (0.42-0.82)	Wilcoxon Z=-8.17	<0.001*
Lactate <2 mmol/L, n (%)	78 (39.0)	103 (51.5)	Increase: 12.5% (5.7%-19.0%)	McNemar χ^2=12.25	<0.001*
Lactate 2-4 mmol/L, n (%)	73 (36.5)	61 (30.5)	Reduction: 6.0% (-3.3%-15.2%)	McNemar χ^2=1.72	0.190
Lactate >4 mmol/L, n (%)	49 (24.5)	36 (18.0)	Reduction: 6.5% (-1.4%-14.2%)	McNemar χ^2=4.17	0.041*
Hyperlactatemia ≥2 mmol/L, n (%)	122 (61.0)	97 (48.5)	Absolute reduction: 12.5% (4.8%-20.0%)	McNemar χ^2=12.25	<0.001*
Six-hour absolute lactate reduction, mmol/L, Mean (SD)			0.88 (0.66-1.10)	One-sample t=8.03†	<0.001*
Six-hour lactate clearance, %, Mean (SD)			21.64 (17.29-25.99)	One-sample t=9.77†	<0.001*
Lactate clearance ≥10%, n (%)			132 (66.0%); 95% CI: 59.2%-72.2%	One-sample proportion z=4.53‡	<0.001*
Failure of lactate clearance, n (%)			41 (20.5%); 95% CI: 15.5%-26.6%	One-sample proportion z=-8.34‡	<0.001*

†Tested against a null mean change/clearance of zero.
‡Tested against a reference proportion of 50%.

Table 2 shows a significant reduction in serum lactate during the first six hours after PICU admission. Mean lactate decreased from 3.72±2.41 mmol/L at admission to 2.84±2.16 mmol/L at six hours, giving a mean reduction of 0.88 mmol/L (95% CI: 0.66-1.10; paired t=8.03, p<0.001). Median lactate similarly decreased from 3.08 mmol/L (IQR: 1.72-5.14) to 2.19 mmol/L (IQR: 1.28-3.76), with a median reduction of 0.63 mmol/L (95% CI: 0.42-0.82; Z=-8.17, p<0.001). The proportion of children with lactate <2 mmol/L increased significantly from 39.0% to 51.5% (p<0.001), whereas the proportion with lactate >4 mmol/L decreased from 24.5% to 18.0% (p=0.041). The reduction in the intermediate 2-4

mmol/L category, from 36.5% to 30.5%, was not statistically significant (p=0.190). Overall hyperlactatemia of ≥2 mmol/L decreased from 61.0% at admission to 48.5% at six hours, representing an absolute reduction of 12.5% (95% CI: 4.8%-20.0%; p<0.001). The mean six-hour lactate clearance was 21.64±31.4%, with a 95% CI of 17.29%-25.99% (p<0.001). Adequate clearance of at least 10% occurred in 132 children (66.0%; 95% CI: 59.2%-72.2%), while 41 children (20.5%; 95% CI: 15.5%-26.6%) demonstrated failure of lactate clearance.

Table 3: Association of serum lactate parameters with disease severity assessed using PRISM III (N=200)

Lactate parameter	PRISM III association	Effect estimate (95% CI)	Test of significance	P value
Admission lactate, mmol/L	Positive correlation	Pearson r=0.660 (0.572-0.732)	t=12.37	<0.001*
Six-hour lactate, mmol/L	Positive correlation	Pearson r=0.720 (0.646-0.780)	t=14.60	<0.001*
Six-hour lactate clearance, %	Negative correlation	Pearson r=-0.580 (-0.668 to -0.478)	t=-10.03	<0.001*
Absolute lactate reduction, mmol/L	Negative correlation	Pearson r=-0.431 (-0.536 to -0.313)	t=-6.72	<0.001*
Admission lactate: adjusted change in PRISM III score per 1 mmol/L increase	Higher PRISM III score	B=1.28 (1.02-1.54)	Multivariable linear regression, t=9.69	<0.001*
Six-hour lactate: adjusted change in PRISM III score per 1 mmol/L increase	Higher PRISM III score	B=1.61 (1.32-1.90)	Multivariable linear regression, t=10.95	<0.001*
Lactate clearance: adjusted change in PRISM III score per 10% increase	Lower PRISM III score	B=-0.74 (-1.03 to -0.45)	Multivariable linear regression, t=-5.03	<0.001*

PRISM III score according to admission lactate category

Admission lactate category	n	PRISM III score, Mean (SD)	Mean difference versus <2 mmol/L (95% CI)	Test of significance	P value
<2 mmol/L	78	7.12 (3.46)	Reference		
2-4 mmol/L	73	11.84 (4.72)	4.72 (3.22-6.22)	Post-hoc t=6.22	<0.001*
>4 mmol/L	49	18.63 (6.18)	11.51 (9.70-13.32)	Post-hoc t=12.58	<0.001*
Overall comparison	**200**	**11.66 (6.42)**		**One-way ANOVA, F=90.17**	**<0.001***

The multivariable model was adjusted for age, sex, primary diagnosis, comorbidity, mechanical ventilation, and vasoactive support.

Table 3 demonstrates strong and statistically significant relationships between serum lactate parameters and disease severity measured using the PRISM III score. Admission lactate showed a strong positive correlation with PRISM III score (r=0.660; 95% CI: 0.572-0.732; p<0.001), while six-hour lactate demonstrated an even stronger positive correlation (r=0.720; 95% CI: 0.646-0.780; p<0.001). Therefore, higher admission and persistent six-hour lactate levels were associated with greater physiological derangement. In contrast, six-hour lactate clearance was negatively correlated with PRISM III score (r=-0.580; 95% CI: -0.668 to -0.478; p<0.001), as was the absolute lactate reduction (r=-0.431; 95% CI: -0.536 to -0.313; p<0.001), indicating that better lactate clearance was associated with lower disease severity. After adjustment for age, sex, primary diagnosis, comorbidity, mechanical ventilation, and vasoactive support, each 1 mmol/L increase in admission lactate was associated with a 1.28-point increase in PRISM III score (95% CI: 1.02-1.54), while each 1 mmol/L increase in six-hour lactate was associated with a 1.61-point increase (95% CI: 1.32-1.90). Conversely, every 10% increase in lactate clearance was associated with a 0.74-point reduction in PRISM III score (95% CI: 0.45-1.03); all adjusted associations were statistically significant (p<0.001). Mean PRISM III scores also increased progressively across admission lactate categories, from 7.12±3.46 in the <2 mmol/L group to 11.84±4.72 in the 2-4 mmol/L group and 18.63±6.18 in the >4 mmol/L group (F=90.17, p<0.001).

Table 4: Association of six-hour serum lactate ≥4 mmol/L with PICU outcomes (N=200)

Clinical outcome	Six-hour lactate ≥4 mmol/L (n=71)	Six-hour lactate <4 mmol/L (n=129)	Effect estimate (95% CI)	Test of significance	P value
PICU mortality, n (%)	24 (33.8)	9 (7.0)	OR=6.81 (2.95-15.72)	χ^2=23.92	<0.001*
Mechanical ventilation, n (%)	48 (67.6)	42 (32.6)	OR=4.32 (2.33-8.02)	χ^2=22.73	<0.001*

Vasoactive support, n (%)	39 (54.9)	25 (19.4)	OR=5.07 (2.67-9.61)	χ^2=26.60	<0.001*
Multiple-organ dysfunction, n (%)	31 (43.7)	20 (15.5)	OR=4.22 (2.16-8.24)	χ^2=19.11	<0.001*
PICU stay >7 days, n (%)	43 (60.6)	31 (24.0)	OR=4.85 (2.60-9.06)	χ^2=26.22	<0.001*
PICU stay, days, Mean (SD)	8.72 (5.11)	5.14 (3.06)	Mean difference=3.58 days (2.26-4.90)	Welch t=5.39	<0.001*

Comparison of serum lactate parameters according to major outcomes

Outcome comparison	Outcome present, Mean (SD)	Outcome absent, Mean (SD)	Mean difference (95% CI)	Test of significance	P value
Admission lactate: nonsurvivors (n=33) vs survivors (n=167), mmol/L	7.12 (2.96)	3.05 (1.72)	4.07 (2.99-5.15)	Welch t=7.65	<0.001*
Admission lactate: ventilation required (n=90) vs not required (n=110), mmol/L	4.81 (2.61)	2.83 (1.84)	1.98 (1.34-2.62)	Welch t=6.07	<0.001*
Admission lactate: vasoactive support required (n=64) vs not required (n=136), mmol/L	5.29 (2.78)	2.98 (1.96)	2.31 (1.54-3.08)	Welch t=5.98	<0.001*
Six-hour lactate: nonsurvivors vs survivors, mmol/L	6.48 (2.74)	2.12 (1.39)	4.36 (3.51-5.21)	Welch t=10.09	<0.001*
Lactate clearance: nonsurvivors vs survivors, %	-4.82 (24.61)	26.87 (29.18)	-31.69 (-41.17 to -22.21)	Welch t=-6.62	<0.001*

Abbreviations: CI, confidence interval; OR, odds ratio; PRISM III, Pediatric Risk of Mortality III; PICU, Pediatric Intensive Care Unit; SD, standard deviation.

*Statistically significant at p<0.05.

Table 4 shows that persistent hyperlactatemia at six hours was strongly associated with adverse PICU outcomes. Among children with six-hour lactate ≥4 mmol/L, mortality was 33.8%, compared with 7.0% among children with lactate <4 mmol/L. These children had approximately sevenfold greater odds of mortality (OR=6.81; 95% CI: 2.95-15.72; p<0.001). They also had significantly greater odds of requiring mechanical ventilation (67.6% versus 32.6%; OR=4.32), vasoactive support (54.9% versus 19.4%; OR=5.07), and developing multiple-organ dysfunction (43.7% versus 15.5%; OR=4.22). A PICU stay longer than seven days occurred in 60.6% of children with lactate ≥4 mmol/L compared with 24.0% of those with lower lactate, corresponding to an OR of 4.85 (95% CI: 2.60-9.06; p<0.001). Mean PICU stay was also 3.58 days longer in the elevated-lactate group (8.72±5.11 versus 5.14±3.06 days; 95% CI: 2.26-4.90; p<0.001).

Outcome-based comparisons further supported the prognostic importance of serum lactate. Nonsurvivors had a significantly higher mean admission lactate than survivors (7.12±2.96 versus 3.05±1.72 mmol/L), with a mean difference of 4.07 mmol/L (95% CI: 2.99-5.15; p<0.001). Admission lactate was also significantly higher among children requiring mechanical ventilation (4.81±2.61 versus 2.83±1.84 mmol/L) and vasoactive support (5.29±2.78 versus 2.98±1.96 mmol/L). The difference between nonsurvivors and survivors was more pronounced for six-hour lactate, which was 6.48±2.74 and 2.12±1.39 mmol/L, respectively (mean difference 4.36 mmol/L; p<0.001). Nonsurvivors demonstrated negative mean lactate clearance of -4.82±24.61%, indicating increasing lactate, whereas survivors showed positive clearance of 26.87±29.18%. The difference in clearance was -31.69 percentage points (95% CI: -41.17 to -22.21; p<0.001).

DISCUSSION

The present prospective observational cohort study demonstrated that serum lactate was strongly associated with disease severity and adverse outcomes among critically ill children admitted to the PICU. Admission lactate, persistent hyperlactatemia at six hours, and inadequate lactate clearance were associated with higher PRISM III scores, mortality, mechanical ventilation, vasoactive support, multiple-organ dysfunction, and prolonged PICU stay. The overall pattern supports serial lactate measurement as a practical adjunct to clinical assessment and established pediatric severity scores.

Admission lactate, disease severity, and outcomes

In Table 1, increasing admission lactate showed a clear dose-response relationship with disease severity. Mean PRISM III score increased from 7.12±3.46 among children with lactate <2 mmol/L to 11.84±4.72 among those with lactate 2-4

mmol/L and 18.63±6.18 among those with lactate >4 mmol/L. Severe illness occurred in 49.0% of children with lactate >4 mmol/L, compared with only 14.1% among those with lactate <2 mmol/L. This graded relationship suggests that increasing lactate reflects progressively greater physiological and metabolic derangement.

These observations agree with Gorgis et al. (2019)[1], who found a significant positive relationship between early lactate and PRISM III score among children with severe sepsis or septic shock. In their study, every 1 mmol/L increase in lactate was associated with an approximately 1.12-point increase in the PRISM III score. Although initial lactate did not significantly predict mortality in their relatively small cohort, it remained an important early indicator of disease severity. The stronger relationship in the present study—an adjusted increase of 1.28 PRISM III points per 1 mmol/L increase in admission lactate—may be related to its larger sample size and broader distribution of disease severity.

Mortality in the present study increased from 3.8% in the lactate <2 mmol/L group to 12.3% in the 2-4 mmol/L group and 42.9% in the >4 mmol/L group. Children with admission lactate >4 mmol/L had an 11.14-fold higher risk of mortality than children with lactate <2 mmol/L. Choudhary et al. (2017)[2] similarly reported that admission lactate ≥4 mmol/L predicted mortality in pediatric septic shock, with an odds ratio of 5.4. Nonsurvivors in their study had a mean admission lactate of 5.12 mmol/L, compared with 3.13 mmol/L among survivors. The present findings therefore reinforce the clinical relevance of 4 mmol/L as a high-risk threshold, although it should not be considered universally diagnostic because lactate production and clearance vary according to diagnosis, organ function, treatment, and sampling time.

Aramburo et al. (2018)[3], studying severely ill febrile children in East Africa, also observed that hyperlactatemia was associated with increased mortality and that children who cleared lactate within eight hours had a better probability of survival. These results are particularly relevant because they demonstrate the value of lactate in resource-constrained pediatric settings, where rapid and inexpensive biochemical indicators may assist early risk stratification.

Admission lactate >4 mmol/L in the present study was also associated with mechanical ventilation, vasoactive support, multiple-organ dysfunction, and longer PICU stay. Compared with children having lactate <2 mmol/L, the highest lactate group had 3.02 times the risk of mechanical ventilation, 4.49 times the risk of vasoactive support, and 6.14 times the risk of multiple-organ dysfunction. These associations are biologically plausible because elevated lactate may reflect circulatory failure, adrenergic stress, impaired oxygen utilization, hepatic dysfunction, or a combination of these abnormalities. Lactate may therefore function as an integrated indicator of systemic physiological stress rather than solely as a marker of anaerobic metabolism.

Morris et al. (2022)[4] reported that lactate measured at PICU admission was more strongly associated with intensive-care mortality than absolute base excess. Their findings support the use of lactate as an early severity marker, while also emphasizing that its prognostic value is enhanced when interpreted alongside physiological risk models. El-Mekkawy et al. (2020)[5] similarly found that elevated plasma lactate was associated with mortality in a general PICU population and that incorporating lactate improved the predictive performance of the pediatric Sequential Organ Failure Assessment score.

Changes in lactate during the first six hours

Table 2 demonstrated a significant overall improvement in lactate during the first six hours. Mean serum lactate decreased from 3.72±2.41 mmol/L at admission to 2.84±2.16 mmol/L at six hours, representing a mean reduction of 0.88 mmol/L. The prevalence of hyperlactatemia ≥2 mmol/L decreased from 61.0% to 48.5%, while the proportion with lactate <2 mmol/L increased from 39.0% to 51.5%. These findings suggest that resuscitative and disease-specific interventions resulted in improved perfusion or metabolic recovery in a substantial proportion of children.

The mean six-hour lactate clearance was 21.64%, and 66.0% of children achieved clearance ≥10%. Nazir et al. (2019)[6] found that six- and 24-hour lactate clearance were significantly associated with mortality among children with septic shock. Their study demonstrated that survivors had greater reductions in lactate, whereas persistent or rising lactate identified children at greater risk of death. The present study supports this conclusion and shows that clinically useful information can be obtained as early as six hours after admission.

Moustafa et al. (2021)[7] also concluded that six-hour lactate clearance independently predicted mortality among critically ill children. Their results support the present selection of a six-hour interval, because it provides prognostic information sufficiently early to allow reassessment of resuscitation and escalation of treatment. A six-hour interval may be more clinically actionable than waiting for 24- or 48-hour measurements.

Alam and Gupta (2021)[8], in an Indian cohort of children with severe sepsis, reported that the six-hour lactate value was more strongly associated with early mortality and need for a higher level of care than the admission value. This closely parallels the present findings, in which the correlation with PRISM III was stronger for six-hour lactate than admission

lactate. It suggests that persistent hyperlactatemia after initial treatment may distinguish transient stress-related lactate elevation from continuing circulatory or metabolic dysfunction.

The findings are also consistent with the systematic review by Vincent et al. (2016)[9], which concluded that decreasing lactate over time was consistently associated with lower mortality across different groups of critically ill patients. Nevertheless, the review emphasized variability in measurement intervals, clearance definitions, disease populations, and prognostic thresholds. Thus, the 10% clearance threshold used in the present study should be interpreted as a clinically useful risk-stratification value rather than a universal therapeutic target.

Relationship with PRISM III score

Table 3 showed strong positive correlations of PRISM III score with admission lactate (r=0.660) and six-hour lactate (r=0.720). Six-hour lactate clearance was negatively correlated with PRISM III score (r=-0.580), while absolute lactate reduction showed a moderate negative correlation (r=-0.431). Therefore, children with more severe physiological disturbance had higher initial lactate, greater persistence of hyperlactatemia, and poorer lactate clearance.

The stronger correlation for six-hour lactate than for admission lactate is clinically important. Admission lactate can be influenced by seizures, struggling during sampling, catecholamine exposure, delayed referral, hepatic dysfunction, or treatment before arrival. A persistently elevated value after six hours may more accurately reflect unresolved pathophysiology and inadequate response to treatment. Abdelaziz et al. (2024)[10] similarly found that admission lactate did not differ significantly between survivors and nonsurvivors, whereas six-hour lactate and six-hour lactate clearance were strongly associated with mortality. Their optimal thresholds—six-hour lactate ≥4 mmol/L and clearance <10%—are directly consistent with the thresholds applied in the present study.

After adjustment for demographic and clinical factors, every 1 mmol/L increase in six-hour lactate was associated with a 1.61-point increase in PRISM III score, whereas every 10% increase in clearance was associated with a 0.74-point reduction. Rocha et al. (2023)[11] likewise observed that elevated lactate on the first and second PICU days was associated with mortality and higher PIM3 scores. Children with increasing or minimally decreasing lactate had fewer ventilation-free days, more frequent renal replacement therapy, longer hospitalization, and an almost eightfold greater probability of death.

However, lactate and PRISM III should be viewed as complementary rather than interchangeable. PRISM III incorporates multiple physiological and laboratory abnormalities, whereas lactate represents a specific but multifactorial metabolic response. Lactate offers the advantage of rapid availability, while PRISM III provides more comprehensive severity adjustment.

Persistent six-hour hyperlactatemia and mortality

Table 4 indicated that six-hour lactate ≥4 mmol/L was associated with mortality of 33.8%, compared with 7.0% among children with lactate <4 mmol/L. The corresponding odds ratio was 6.81. Elevated six-hour lactate was additionally associated with mechanical ventilation (OR=4.32), vasoactive support (OR=5.07), multiple-organ dysfunction (OR=4.22), and PICU stay longer than seven days (OR=4.85).

These findings strongly agree with Abdelaziz et al. (2024)[10], who identified six-hour lactate ≥4 mmol/L as the best cut-off for predicting PICU mortality. Similarly, Alam and Gupta (2021)[8] demonstrated that the six-hour value provided better prognostic information than admission lactate. These comparisons suggest that persistent lactate elevation after initial resuscitation is more clinically meaningful than a single abnormal admission value.

Nonsurvivors in the present study had substantially higher six-hour lactate than survivors (6.48±2.74 versus 2.12±1.39 mmol/L). They also demonstrated negative mean clearance of -4.82%, whereas survivors achieved positive clearance of 26.87%. Nazir et al. (2019)[6] and Choudhary et al. (2017)[2] similarly found that failure to reduce lactate was associated with mortality. Although Choudhary et al. assessed clearance at 24 hours, their finding that clearance <10% predicted death supports the direction and clinical importance of the present six-hour results.

Loomba et al. (2022)[12] reported an association between elevated serum lactate and mortality across pediatric hospital admissions, indicating that the prognostic significance of lactate is not confined to children with formally diagnosed septic shock. This supports the heterogeneous PICU population used in the present study. Nevertheless, variation in diagnoses can also produce heterogeneity because lactate kinetics may differ among sepsis, respiratory failure, cardiac disease, seizures, trauma, hepatic dysfunction, and postoperative illness.

The international pediatric Surviving Sepsis Campaign guideline by Weiss et al. (2020)[13] suggests using trends in blood lactate, together with clinical assessment, to guide resuscitation in children with septic shock or sepsis-associated organ dysfunction. The guideline cautions that lactate should not be interpreted in isolation because persistent elevation can arise from mechanisms other than inadequate tissue perfusion. The present findings are consistent with this approach: lactate offers useful early prognostic information but should complement capillary refill, blood pressure, mental status, urine output, organ-function measures, and validated severity scores.

CONCLUSION

Elevated serum lactate levels were significantly associated with greater disease severity and poorer clinical outcomes among critically ill children admitted to the PICU. Admission and six-hour lactate levels showed strong positive correlations with PRISM III scores, while lactate clearance was negatively correlated with disease severity. Children with admission lactate >4 mmol/L had substantially higher mortality, mechanical ventilation, vasoactive support, multiple-organ dysfunction, and longer PICU stay. Persistent six-hour lactate ≥4 mmol/L was particularly associated with adverse outcomes, whereas adequate lactate clearance was associated with survival. Serial lactate assessment, especially the six-hour value and lactate clearance, may therefore serve as a simple and useful adjunct to clinical examination and PRISM III scoring for early risk stratification, monitoring treatment response, and predicting outcomes. Serum lactate should, however, be interpreted with the overall clinical condition rather than used as an isolated prognostic marker.

LIMITATIONS OF STUDY

1. The study was conducted at a single tertiary-care centre; therefore, its findings may not be generalisable to PICUs with different patient profiles, referral patterns, resources, and treatment protocols.
2. The observational design established associations but could not confirm a causal relationship between elevated lactate and adverse outcomes.
3. The study population included children with heterogeneous medical and surgical conditions. Differences in the underlying diagnosis and pathophysiology may have influenced lactate production and clearance.
4. Serum lactate was measured only at admission and six hours. Additional measurements at 12, 24, and 48 hours could have provided a more comprehensive assessment of lactate kinetics.
5. Treatment received before PICU admission, including fluids, oxygen, antimicrobial therapy, blood transfusion, and vasoactive medications, may have affected the initial lactate level.
6. Factors unrelated to tissue hypoperfusion, including seizures, hepatic or renal dysfunction, catecholamine administration, metabolic disorders, and sampling difficulties, may have influenced serum lactate.
7. Variations in resuscitation, ventilation, and vasoactive support during the first six hours could have affected lactate clearance.
8. Lactate clearance may have limited clinical meaning in children with normal admission lactate because only a small reduction would be possible.
9. The study evaluated short-term outcomes until PICU discharge and did not assess 28-day mortality, post-discharge mortality, neurological status, functional outcomes, or quality of life.
10. Residual confounding could have persisted despite multivariable adjustment, as all possible clinical, biochemical, and treatment-related variables could not be controlled.

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