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Original Research Article

Analysis of serum lactate levels to predict in hospital mortality in critically ill children admitted to pediatric intensive care unit

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ABSTRACT

Background: The predictive significance of lactate measurement at admission for mortality in critically ill children remains uncertain. Authors objectives was to study evaluated the predictive value of blood lactate levels at admission and determined the cut-off values for predicting in-hospital mortality in the critically ill pediatric population.
Methods: A prospective observational study was done in 100 critically ill admissions to the pediatric intensive care unit (PICU), requiring hemodynamic/respiratory support. The chi-square test for categorical variables performs the comparison.
Results: Out of 100 patients, 22 (22%) expired. Mortality is highest in 10-16 age (7%). In the non-survivor group, the majority of patients were diagnosed as pneumonia (7.5%). Median lactate levels in non-survivors are 4.5 at admission when compared to 2.0 in survivors ($p<0.001$). The mortality rates left rate in the high lactate group (73%) is more when compared to intermediate (20%) and low-level groups (7%). Blood lactate was 75% sensitive and 90% specific at the optimal cut-off value of 33.7 mg/dl. The positive likelihood ratio of predicting death is more with a high lactate level (7.5) when compared to intermediate (0.8) and low levels (0.08). Sensitivity and Specificity with elevated lactate levels is the mortality 24 hrs (89%, 92%) than at admission (75%, 90%). The AUROC values with the admission lactate level are 0.86, and after 24 hrs are 0.95.
Conclusions: Blood lactate levels at admission predict mortality in critically ill children requiring hemodynamic/respiratory support.

Keywords: Blood lactate, Critically ill children, Cut-off value, In-hospital mortality

INTRODUCTION

Critically ill children, due to various underlying disease processes, often have diminished tissue perfusion. Delay in recognition of hypoperfusion leads to the development of multi-organ dysfunction syndrome (MODS), which results in morbidity and increased mortality until it is timely recognized and promptly reversed.[1]

Lactic acid (LA), a by-product of anaerobic metabolism, has been used as a biomarker and indicator of tissue hypoxia.[2] This tissue hypoxia may result from respiratory or circulatory disorders. Hyperlactatemia is associated with worse outcome in critically ill patients.[3]

Only a few studies have been conducted in children to evaluate the role of measurement of LA in the general population of critically ill children in a pediatric intensive care unit (PICU).[4,5]

Hence the present study was taken to reinforce the other paediatric studies and also to see if elevated levels of

lactate are in predictive for in-hospital mortality in ill patients admitted to PICU and also to see if sustained hyperlactatemia has prediction for mortality by measuring lactate at admission and 24 hrs, and by correlating these levels with the outcome.

METHODS

Study subjects

A total of 100 critically ill pediatric subjects admitted to PICU in Narayana medical college, Nellore, from January 2018 to December 2018. Venous blood of the patients is collected and sent for serum lactate analysis using an auto-analyzer at admission and after 24 hrs and their outcome is observed.

Inclusion criteria

Critically ill patients admitted to pediatric ICU at Narayana general hospital between the age of 2 months to 18 years.

Exclusion Criteria

- Three patients in whom death occurred before 24 hrs. of admission
- Trauma patients.
- Post-operative surgical care patients.
- Age less than 28 days (neonatal age).

Parameters

Data was collected on a structured sheet, which included demographic details (age, gender) and clinical variables like values of serum creatinine, blood gas analysis, serum electrolytes, and lactate levels. Median lactate levels in survivor and non-survivor groups. Mortality rates in different lactate groups i.e. low group (<2mmol/l), Intermediate group(2.1-3.9mm0l/l), High group ≥4mmol/l. Sensitivity and specificity of lactate in different lactate groups at admission and after 24 hrs. Predictive value and likelihood ratio of lactate in different lactate groups at admission and after 24 hrs. ROC curves of lactate at admission and after 24 hrs.

Statistical analysis

All the data were expressed by a median with interquartile range for continuous variables and as frequencies and contingency tables for categorical variables. The Chi-square test for categorical variables performs a comparison among variables. Sensitivity, specificity, and predictive values of lactate are calculated to show lactate as a biomarker. The likelihood ratio of predicting death is calculated to estimate the likelihood of predicting death in different lactate levels. ROC curves are used for calculating the strength of lactate as a biomarker with admission and after 24 hrs lactate levels. All the statistical analyses were performed SPSS Version 20.

RESULTS

In 100 patients, 58 are males, and 42 are females. The majority of patients are between 10 to 16 years (45%), followed by less than one year (27%). Out of 100 patients, 22(22%) expired. Mortality is highest in 10-16 age (7%) and least in 1 to 4 years age group (4%). In the-survivor group, the majority of patients were diagnosed as pneumonia (7.5%), followed by meningitis and shock. No significant association is observed with the disease in the no survivor group (p=0.4) (Figure 1).

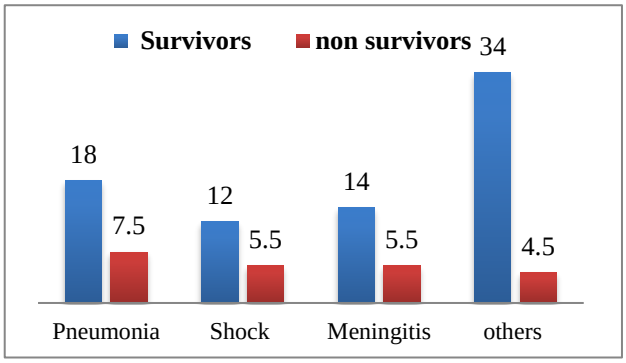

Figure 1: Analysis of diagnosis among survivors and non-survivors.

Diagnosis among survivors and non-survivors shows the majority of patients in the non-survivor group were diagnosed as pneumonia (7.5%) followed by meningitis and shock. No significant association is seen with the disease in the non-survivor group.

Table 1 shows analysis of different parameters among survivors and non-survivors p-value is significant in all the components showing significant difference among survivors and non-survivors.

Median lactate levels in non-survivors are 4.5 at admission when compared to 2.0 in survivors(p<0.001). Median lactate after 24 hrs is 5.8 in non-survivors when compared to 1.8 in survivors.

Lactate levels are divided into three groups: Low levels 0 to 2.0mmol/l, Intermediate levels 2.1mmol/l to 3.9mmol/l; High levels ≥4mmol/l.

The mortality rate in the high lactate group (73%) is more when compared to intermediate (20%) and low-level groups (7%) (Table 1).

Lactate levels measured after 24 hrs also show high sensitivity and specificity in high lactate level group (≥4mmol/l), i.e.,89% and 92%, respectively, which are higher than the values measured with admission lactate levels in the same group (75% and 90%). Increased

specificity is observed in the high lactate group with 24 hrs lactate levels when compared to the admission lactate level (Table 2).

Table 1: Analysis of different parameters among survivors and non-survivors.

	Survivors M(IQR)	Non-survivors M(IQR)	p-value
pH	7.3(7.30-7.35)	7.2(7.15-7.24)	<0.001
Bicarbonate in mmol/l	16.5(14.7-19.2)	13.1(9.7-15.14)	<0.001
Pa02 in mmHg	89.5(85-102)	74.8(55-98)	<0.001
Paco2 in mmHg	36.8(31-45)	75.2(56-98)	<0.001
Sodium in meq/l	133(131-139)	135(125-140)	<0.001
Potassium in meq/l	4.5(4.3-4.92)	5.7(4.5-6.0)	<0.001
Chloride in meq/l	109(104-108)	105(100-110)	<0.001
WBC count	15334(12500-18500)	18000(14500-25500)	<0.01
Urea	43.0(35-60)	70(50-110)	<0.001
Creatinine	0.42(0.4-0.6)	0.82(0.6-1.5)	<0.01
AST	45(35-61)	62(42-75)	<0.01
ALT	33(28-43)	52(30-73)	<0.01

All values in the table are shown in the median with their interquartile range m(IQR).
p-value<0.001 is significant M=median IQR=inter quartile range.

Table 2: Sensitivity and specificity analysis in three lactate groups with lactate levels after 24 hrs.

Serum lactate after 24 hrs	Mortality %(n)	Sensitivity %(95%CI)	Specificity%(95%CI)
<2mmol/l	7%	0.77% (0.02% to 3.35%)	43.25% (32.08% to 55.20%)
2 to 3.9mmol/l	20%	11.14% (3.45% to 27.45%)	75.90% (68.25% to 82.21%)
≥4mmol/l	73%	89.25% (78.25% to 98.15%)	92.84% (89.51 to 98.89%)

Sensitivity and specificity are shown in percentage with 95%confidence intervals.

Likelihood ratio analysis

The high positive likelihood ratio is observed in high-level lactate group at admission; it is 7.50 and 28.41 after 24 hrs showing that there is more likelihood of predicting death with high lactate levels, and this likelihood ratio is more at 24 hrs when compared to admission levels. The low positive likelihood ratio is observed in the low lactate level group, i.e., 0.08 at admission lactate levels and 0.02 after 24 hrs lactate levels.

The low negative likelihood ratio is observed in the high lactate level group when compared to intermediate and low lactate level groups. The low negative likelihood ratio is required for a good test (Table 3).

Predictive value analysis

High positive predictive value is observed in high-level lactate group at admission; it is 62.25% and 87.54% after 24 hrs showing that there is more chance of predicting death with high lactate levels, and this predictive value is more at 24 hrs when compared to admission levels. Low positive predictive value is observed in low lactate level group, i.e., 6.78% at admission lactate levels and 2.12% after 24 hrs lactate levels (Table 4).

Table 3: Likelihood ratio analysis in different lactate groups with lactate levels at admission and after 24 hrs.

Serum lactate at admission and after 24 hrs	Likelihood ratio positive	Likelihood ratio negative
<2mmol/l		
At admission	0.08	1.45
After 24 hrs	0.02	2.67
2 to 3.9mmol/l		
At admission	0.8	1.07
After 24 hrs	0.47	1.17
>4mmol/l		
At admission	7.50	0.27
After 24 hrs	28.41	0.07

High positive predictive value is observed in high-level lactate group at admission it is 62.25 % and 87.54% after 24 hrs showing that there is more chance of predicting death with high lactate levels and this predictive value is more at 24 hrs when compared to admission levels. Low positive predictive value is observed in low lactate level group, i.e., 6.78 % at admission lactate levels and 2.12% after 24 hrs lactate levels.

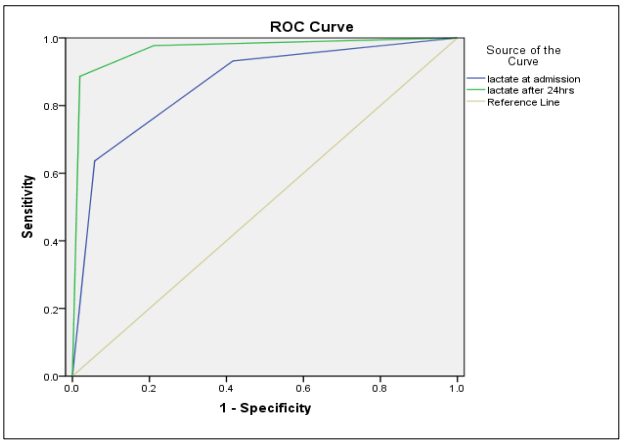

Figure 2: ROC curves of admission and 24 hrs lactate levels.

Out of 22 patients who have not survived, 16 patients showed increasing trend in serum lactate levels i.e., lactate level at 24 hrs is greater than the lactate levels at admission showing poor lactate clearance has high chance of predicting death with sensitivity and specificity of 89% and 92% respectively with high positive likelihood ratio and high positive predictive value (87.54%) (Table 5).

ROC curve (Figure 2) shows the increased area under the curve for 24hrs lactate levels when compared to admission lactate levels, which shows 24 hrs lactate levels have more sensitivity and specificity than admission lactate levels. The AUROC values with the admission lactate level are 0.86, and after 24 hrs, lactate levels are 0.96.

Table 4: Predictive value analysis in different lactate groups with lactate levels at admission and after 24 hrs.

Serum lactate at admission and after 24 hrs	Positive p-value	Negative p-value
<2mmol/l		
At admission	6.78%	41.55%
After 24 hrs	2.12%	21.22%
2 to 3.9mmol/l		
At admission	28.98%	64.10%
After 24 hrs	8.92%	80.77%
>4mmol/l		
At admission	62.25%	95.13%
After 24 hrs	87.54%	98.12%

Table 5: Lactate as a prognostic marker.

Serum lactate in increasing trend	Non-survivors	Sensitivity	Specificity	Likelihood ratio positive	Likelihood ratio negative	Positive p-value
	16 of 22	89%	92%	11.13	0.12	87.54%

Table 6: Comparison of area under curve at admission and 24 hrs lactate levels.

Lactate	Area under curve	Standard error	95% Confidence interval
At admission	0.860	0.35	0.712 to 0.927
After 24 hrs	0.950	0.24	0.930 to 1.000

DISCUSSION

This study provides information on blood lactate concentration in critically ill children and demonstrates that the blood lactate level upon admission to a general medical PICU is significantly linked with in-hospital mortality. An elevated blood lactate level at PICU admission is predictive of in-hospital mortality in critically ill children.

A limited number of studies established the use of hyperlactatemia as a predictive index in critically ill children who are admitted to the PICU.[6-8] Our results are in order with recently published findings that suggest that blood lactate concentration upon admission to PICU is predictive of mortality. The observation that the degree of absolute hyperlactatemia is considerably related to death independent of illness severity indicates that blood lactate is a useful early predictor in identifying critically ill children who are at high risk of mortality in the pediatric intensive care setting.

Patients admitted to ICU frequently have elevated blood lactate levels than those admitted to other units. This is because these patients frequently present with perfusion disorders, with consequent tissue hypoxia.[9]

Our results show that Median lactate levels in non-survivors are 4.5 at admission when compared to 2.0 in survivors($p<0.001$). Median lactate after 24 hrs is 5.8 in non-survivors when compared to 1.8 in survivors. Hyperlactatemia has been detected in critically ill

patients, and quite a lot of clinical studies have shown an association between its levels and the type of outcome, with higher levels in those patients who will eventually die.[10-12] These Values indicate that decreased clearance of lactate is seen in non-survivors when compared to survivors. Okorie Nduka.[13]

Of the non-survivor group, the majority of patients were diagnosed as pneumonia (7.5%), followed by meningitis and shock. This is similar to that shown by Hatherillet al, but low as compared to previous data from adults, which showed it to be 20-30% in general medical ICU and cardiac surgery.[6] These differences could be due to variation in disease states and or time of presentation or time of checking LA levels. In the present patient population, most cases of sepsis showed signs of hypoperfusion at every assessment.

This study has been conducted in the PICU setting. Several studies 76-79 were done with different cut off values in this study 3 groups were used low, intermediate and high lactate level groups, Lactate levels of two and four were used as cut off values in intermediate and high lactate level groups. Different cut off values was used in different studies; many studies have used cut off value 4. In this study serum, lactate is measured at admission and after 24 hrs.

Lactate levels measured after 24 hrs also show high sensitivity and specificity in high lactate level group (≥4mmol/l), i.e., 89% and 92%, respectively, which are higher than the values measured with admission lactate levels in the same group(75% and 90%). Increased specificity is observed in the high lactate group with 24 hrs lactate levels when compared to the admission lactate level. This is in correlation with the study done by Koliski et al.[8] The high positive likelihood ratio is observed in high-level lactate group at admission; it is 7.50 and 28.41 after 24 hrs showing that there is more likelihood of predicting death with high lactate levels, and this likelihood ratio is more at 24 hrs when compared to admission levels. The low positive likelihood ratio is observed in the low lactate level group, i.e., 0.08 at admission lactate levels and 0.02 after 24 hrs lactate levels.

This study is in correlation with other studies where a positive likelihood ratio increased from 7.5 to 28.4 for serum lactate at admission and after 24 hrs.

Many of the studies showed increased positive predictive value as the lactate cut off value increases, the current study is in correlation with above studies done by Garcia Sanz et al, and Hatherill et al, and the positive predictive values of lactate after 24 hrs is higher than at admission as depicted in study done by Hartel et al.[6,14] The present study also supports this and proves that as cut off lactate level increases there is high positive predictability of death. High positive predictive value is observed in high-level lactate groups at admission. It is 62.25% and 87.54% after 24 hrs showing that there is more chance of predicting death with high lactate levels, and this predictive value is more at 24 hrs when compared to admission levels. Low positive predictive value is observed in low lactate level group, i.e., 6.78% at admission lactate levels and 2.12% after 24 hrs lactate levels.

Of the 22 patients who have not survived, 16 patients showed increasing trend in serum lactate levels i.e. lactate level at 24 hrs is higher than the lactate levels at admission showing poor lactate clearance has high chance of predicting death with sensitivity and specificity of 89% and 92% respectively with high positive likelihood ratio and high positive predictive value (87.54%).

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CONCLUSION

Authors study indicates that the blood lactate level on admission to the PICU was noticeably associated with death in critically ill children, even after adjusting for age, sex, and illness severity. An elevated level of blood lactate upon admission was independently predictive of in-hospital mortality in the pediatric population. These results extend the knowledge of blood lactate as a clinical biomarker of mortality in critical illness.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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