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Blood lactate level as a predictor of outcome in pediatric septic shock and its correlation with PRISM III score.

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I. Introduction

Severe sepsis and septic shock causes significant mortality, morbidity and high cost of care.

Traditionally, normalization of vital signs, such as blood pressure, urine output, and heart rate has been used as endpoints of resuscitation. However, critical analysis of these endpoints has revealed the inadequacy of relying solely upon vital signs in resuscitation of critically ill patients[1]. In the presence of normal vital parameters there is persistence of tissue hypoperfusion which leads to MODS and death.[2] Many critically ill patients who are normotensive and have adequate urine output, may remain in a state of compensated shock.[1]
The optimal management of pediatric septic shock patients includes early recognition of inadequate tissue perfusion and its timely correction in an effort to prevent anaerobic metabolism, acidosis, and cellular death.[3-5]

Lactate is a byproduct of anaerobic metabolism after glycolysis[6]. Lactate is produced in the majority of tissues in human beings, but the main producers include red blood cells, intestine, brain and muscles.[7-8] Several studies have shown an elevated lactate-to-pyruvate ratio in septic shock, suggesting tissue hypoxia is the cause of lactic acidosis.[9]

Increased lactate levels may be considered an early marker of a potentially reversible state, e.g., early septic shock, possibly indicating that "there is still room" to boost fast intervention[10]. Single measurement of lactate is a static variable however it can serve as a risk stratification biomarker[11].

Majority of research with blood lactate has been conducted in adults. In literature, there has been paucity of data on lactate as a prognostic marker of mortality in pediatric population with shock.

Hence, the present study done to evaluate the prognostic value of lactate in children with septic shock to stratify the management of high risk and to assess mortality.

II. Materials and Methods

This study was a prospective observational study conducted in the PICU of tertiary care centre of North India, over a period of 18 months. Total 100 cases of septic shock between the ages of 1 month to 17 years were enrolled for the study.

Septic shock[12] is defined as confirmed or presumed infection, having two or more systemic inflammatory response criteria and hypoperfusion evidenced by either a systolic blood pressure lower than – 2 standard deviation (SD) adjusted for age or at least one manifestation of inadequate organ perfusion, that is, altered mentation, hypoxia (PaO_2<45 mmHg while breathing room air or PaO_2 /FiO_2<350), metabolic acidosis (arterial pH <7.35 or base deficit >5), or oliguria (i.e., urine output <0.5 ml/kg/h), along with signs of poor peripheral perfusion.

Following patients were excluded from the study-

1. Other causes of shock, eg- cardiogenic shock, neurogenic shock, anaphylactic shock, dengue shock syndrome, obstructive shock.
2. Patient with known malignancies and immunosuppressive treatment.
3. Other Condition known to cause elevated lactate for example:-

a) Chronic medical illness
b) Inborn error of metabolism
c) Liver disease

4. Post-operative patients

In all cases detailed history and physical examination was done. Routine hematological investigations, biochemical profile and Arterial blood gas analysis were done. To assess the severity of illness and organ dysfunction, the Pediatric Risk of Mortality III (PRISM III) score was calculated. Blood lactate level at admission was measured, which was done by VITROS LAC slide method using VITROS LAC Slides and the VITROS Chemistry Product Calibrator kit 1 in which there is enzymatic conversion of lactate to pyruvate and hydrogen peroxide. The hydrogen peroxide is converted to nascent oxygen which then oxidizes 4-amino-phenazone to a coloured compound, which is measured spectrophotometrically. Requirement of mechanical ventilation and duration was also noted.

Primary outcome was Survival or non-survival of patient at the end of hospital stay. Serum lactate level was compared between survivor and nonsurvivors. Secondly correlation between blood lactate level and PRISM III score was also established.

Statistical methods- Categorical/nominal variables were summarized as frequency and percentage and were analyzed using Chi square test/Fischer exact test as applicable. Continuous variables were summarized as mean and standard deviation and were analyzed using student t test. Ordinal variables were summarized as median and range and were analyzed using Mann Whitney test. Correlation between two variables was determined using Spearmann correlation coefficient. ROC curve was used to determine the cutoff value for predicting outcome and area under the curve with 95% Confidence interval was calculated. Diagnostic parameters like sensitivity, specificity, Positive predictive value, negative predictive value, and diagnostic accuracy were calculated at the determined cutoff value. A p value <0.05 was taken as statistically significant. All statistical analyses were done using SPSS version 20 (trial version).

III. Results

Table 1 depicts age and gender distribution of study subjects. Most of the subjects were males (61%). Most of the study subjects (60%) were in age of 1- 12 year. No significant difference was seen in age distribution of male and female subjects with septic shock (p=0.794).

Table 1: Age and Gender Distribution of Study Subjects

Age group	Male		Female		Total	
	N	%	N	%	N	%
1 month – 1year	20	32.8	11	28.2	31	31
(1-12 years)	35	57.4	25	64.1	60	60
(> 12 years)	6	9.8	3	7.7	9	9
Total	61	100	39	100	100	100

Table 2 illustrates the causes of septic shock. Most common cause of septic shock in this study was pneumonia (41%) and pneumonia was also the most common cause of death (43.9 %) in this study. No death was seen in subjects with a diagnosis of gastroenteritis, septic arthritis, UTI or trauma. This difference in survival outcome in different diagnosis was found to be statistically significant

Table 2: Etiological Outcome of Septic Shock

Diagnosis	Survived		Expired		Total	
	N	%	N	%	N	%
Total	67	67	33	33	100	100
Pneumonia	23	56.1	18	43.9	41	100
Meningitis	11	78.6	3	21.4	14	100
Febrile Encephalitis	10	62.5	6	37.5	16	100
Gastroenteritis	7	100	0	0	7	100
Septic arthritis	7	100	0	0	7	100
Cellulitis	4	50	4	50	8	100
UTI	4	100	0	0	4	100
Trauma	1	100	0	0	1	100
Burn	0	0	2	100	2	100

Chi-square = 17.663 with 8 degrees of freedom; P = 0.024 (S)

Table 3 reveals that no significant difference was observed in vitals (heart rate, Respiratory rate, Temperature, systolic or diastolic blood pressure) and hemoglobin and TLC level in patients who survived and in those who expired.

P^H, HCO_3 and Base excess level were found to be significantly lower in patient who expired as compared to those who survived (p<0.001). It can be inferred that P^H, HCO_3 level and base excess were significantly associated with survival outcome. The mean PTT level was 37.58 ± 8.41 min in septic shock

patients who survived and was 44.79± 13.92 in patients who expired. PTT time was significantly longer in patients who expired (p<0.001).

Table 3: Vitals and Laboratory Parameters of Study Subjects at Presentation in Relation to Survival Outcome

Vitals	Survived (N=67)	Expired (N=33)	P value
Heart rate (/min)	140.9 ± 31.81	138 ± 35.7	0.676
Respiratory rate (/min)	36.21 ± 16.63	41.03 ± 3.44	0.204
Temperature (^{0}C)	37.41 ± 1.76	37.44 ± 1.86	0.938
SBP (mmHg)	91.87 ± 15.15	86.12 ± 21.45	0.125
DBP (mmHg)	55.37 ± 13.89	54.3 ± 15.08	0.729
GCS	9.34 ± 2.68	6.96± 1.57	<0.001(S)
S.Hemoglobin level	9.92 ± 1.86	9.53± 1.94	0.328 (NS)
Total Leucocyte count	15.28 ± 9.55	13.89± 8.13	0.45 (NS)
PTT	37.58 ± 8.41	44.79± 13.92	<0.001
P^H (mean ±SD)	7.23 ± 0.13	7.11± 0.17	<0.001
HCO_3 level	17.35 ± 5.42	13.32± 3.50	<0.001
Base excess	-8.88 ± 6.15	-11.45± 5.96	0.042

Among 100 patients of septic shock 67% patients survived and 33% patients expired. **Table 4** shows that the mean arterial lactate level was 2.77 ± 1.77 mmol/L in septic shock patients who survived and 6.54 ± 3.67 mmol/L in those who expired. The mean arterial lactate level was significantly higher in patients who expired. i.e. arterial lactate is significantly associated with survival outcome in septic shock.

Table 4: Arterial Lactate Level in Relation to Survival Outcome

Outcome	Arterial lactate in mmol/L (mean ±SD)	P value
Survived (67)	2.77 ± 1.77	<0.001(S)
Expired (33)	6.54± 3.67	

Table 5 reveals that the mean PRISM III score was 8.88 ± 2.56 in septic shock patients who survived and was 18.06 ± 4.71 in those who expired. Mean PRISM III score was significantly higher in patients who expired. i.e. Mean PRISM III score was significantly associated with survival outcome in septic shock.

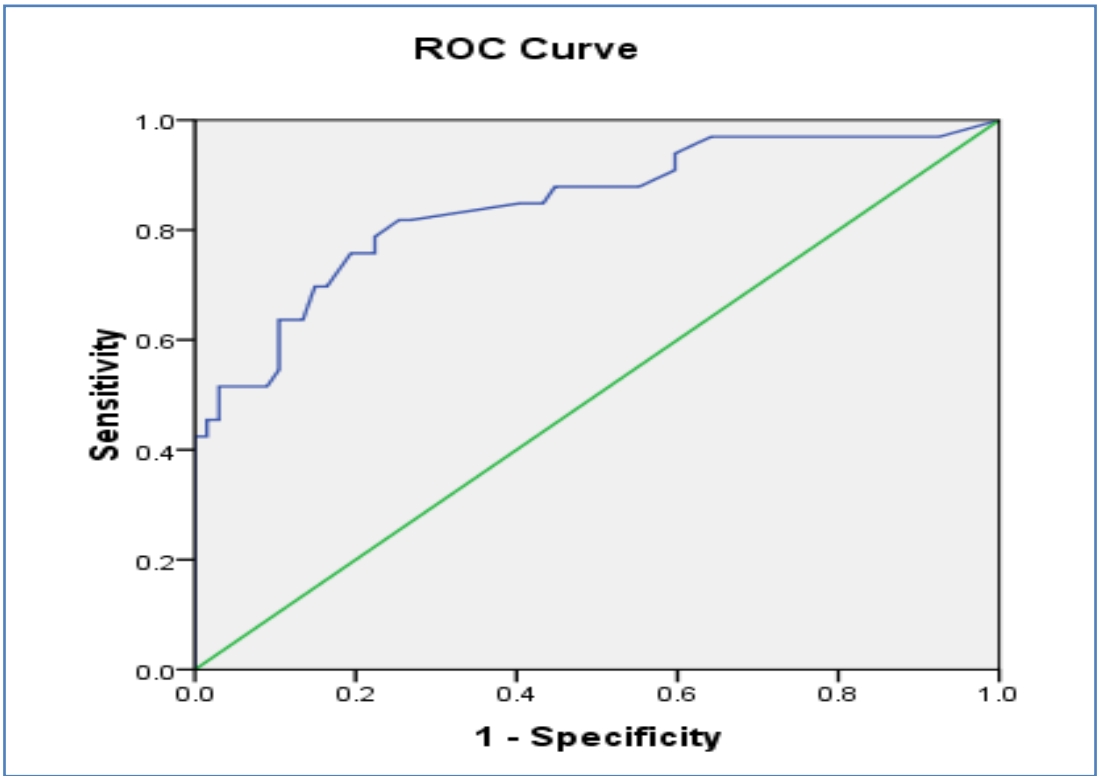
Table 5: PRISM III Score in Relation to Survival Outcome of Study Subjects

Outcome	PRISM III Score (mean ±SD)	Median (range)	P value
Survived	8.88 ± 2.56	8 (4 – 17)	<0.001(S)
Expired	18.06 ± 4.71	19 (7 – 27)	

Table 6 shows that the area under the curve for PRISM III score for predicting death in septic shock patients is 0.941 (0.885 – 0.997). The area under the curve for arterial lactate level for predicting death in septic shock is 0.845 (0.758 – 0.932). It can be inferred that both PRISM III score and arterial lactate level are good predictor of survival outcome in septic shock.

Table 6: Area under Receiver Operating Characteristic Curve

Variable	Area under curve	95% Confidence Interval of area under curve	Critical cut off value	P Value
PRISM III	0.941	0.885 – 0.997	10.5	<0.001(S)
Arterial Lactate	0.845	0.758 – 0.932	3.3	<0.001(S)



ROC Curve for Arterial Lactate Level Predicting Outcome

IV. Discussion

Severe sepsis and septic shock are associated with high mortality rate and consumes considerable health care resources.

Septic shock was the most common shock in patients admitted in PICU. Pneumonia was the most common cause of septic shock, accounting for 41% of total cases. Encephalitis was the 2nd most common presentation. In a study done by **Jat et al**[13] also pneumonia was the most common (73% cases) infectious cause of septic shock.

Among 100 patients 67 % survived and 33 % expired. Higher mortality in our study may be due to fact that majority of septic shock patients admitted to PICU were fluid refractory and also refractory to one of inotropes. A study done by **Jat et al**[13] had 50% mortality. Another study done by **Chanderashekher et al**[14] had 24 % mortality. In our study 63 % patient required ventilator support .Out of these 33 % patients did not survived. 37 % patients didn't required ventilator support and all these patients survived. This shows that mortality rate was higher in those who required ventilator support.

In our study in patients who survived mean arterial lactate was 2.77 mmol/L and in those who expired was 6.5 mmol/L. Mean arterial lactate level was significantly higher in patients who expired ($p<0.001$) i.e. arterial lactate was significantly associated with survival outcome in septic shock. A study done by **Chanderashekher et al**[14] also had mean lactate levels of 2.28 and 5.60 mmol/L in survivors and non survivors respectively. From their study it was suggested that higher lactate level was associated with high mortality. Similar results were also seen in study done by **Hatherill et al**[15], they had mean lactate levels of 3.8 and 4.6 mmol/L in survivors and non survivors respectively. They concluded from their study that higher the lactate level, worse the outcome.

Mean PRISM III score in patients who survived was 8.8 and in those who didn't survived was 18.06. Mean PRISM III score was significantly higher in patients who expired ($p<0.001$) i.e. Mean PRISM III score was significantly associated with survival outcome in septic shock. A study done by **Jat et al**[13] also had mean PRISM III score of 9.5 and 21.1 in survivors and non survivors respectively. They showed, higher the PRISM III score, higher the mortality.

The area under the ROC curve for lactate value at presentation is 0.845 with confidence interval of 0.758 – 0.932. This indicates that there was a correlation between lactate levels and mortality. Similar results were seen in study done by **Jat et al**[13] where area under ROC curve for PRISM III score and lactate level was 0.909 and 0.8 respectively. In a similar study done by **Bai et al**[16] Blood lactate achieved an area under-the-receiver-operating-characteristic curve (AUC) of 0.79 ($p <0.001$) for predicting mortality that was similar to that

of PRISM III (AUC = 0.82; p <0.001). Their study suggested that both lactate and PRISM III score were strong predictor of mortality in septic shock.

The relationship between arterial lactate (at presentation) and PRISM III score (done at presentation) was determined by calculating the Spearman correlation coefficient. In this study a highly significant correlation exist between PRISM III and lactate level at presentation (r-0.504; p-0.001). Similar correlation was seen in study done by **Jat et al**[13]. The Spearman correlation coefficient in their study was 0.561 with p value of 0.003. Their study concludes that arterial lactate level was significantly correlated with PRISM III score (done at presentation).

V. Conclusions

Septic shock is amongst common life threatening condition of PICU with high mortality.

The present study demonstrated that most patients who died had higher arterial lactate level than those who survived. A lactate levels (>3.3 mmol/L) and PRISM III (> 10) are good predictors of death in pediatric septic shock. This study also revealed a positive correlation between PRISM III score and arterial blood lactate at presentation. So this study concludes that arterial lactate level at presentation can be a good predictor of outcome in pediatric septic shock.

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