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The Role of Lactate Level as Predictor of Mortality Critically Ill Children at Moewardi Hospital

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ABSTRACT

Background: The prevalence of mortality among critically ill children worldwide, particularly in Indonesia, remains alarmingly high. Numerous studies have indicated that elevated lactate levels serve as a significant predictor of mortality in this vulnerable population. The primary objective of this study is to elucidate the predictive value of lactate levels in determining mortality risk among critically ill children.
Subjects and Method: A cohort prospective study was conducted in children aged between 1 month and 18 years old who met the criteria for critically ill children treated in the Pediatric High care unit (PHCU) of Dr. Moewardi General Hospital, Surakarta from January to June 2023. The dependent variable was the mortality. The independent variable was lactate level serum. The data were collected using questionnaire and observation sheet. The cut off point of lactate level was determined with ROC curve.
Results: Among thirty critically ill pediatric patients, 43.3% died, while 56.7% survived. The deceased predominantly comprised females, with a mean age of 5.62 years (SD= 4.14). The mean lactate levels of those who died in the first hour, 6 hours, and 24 hours (Mean= 2.94; SD= 0.90) with a cut-off value of ≥2.35 mmol/L, (Mean= 3.20; SD= 0.50) with a cut-off value of ≥ 2.35 mmol/L and (Mean= 3.65; SD= 0.53) with a cut-off value of ≥2.95 mmol/L, respectively. The 24th hours lactate levels (persistence hyperlactatemia) had the highest sensitivity (92.3%) and specificity (100%) for predicting mortality ($p<0.001$).
Conclusion: In critically ill children, lactate level of ≥2.95 mmol/L is a good predictor of mortality.

Keywords: lactate level, mortality, critically ill children.

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BACKGROUND

Critical illness is the condition requiring support for the failure of a vital organ function which can cause death (WHO, 2016). The support can be in the form of mechanical assistance such as mechanical ventilation, hemodialysis, filtration or heart pump aids, and/ or pharmacological assistance like inotropic or vasoactive-inotropic

(Patki et al., 2017). Response to stress involves the hypothalamic-pituitary-adrenal axis. The catabolism of carbohydrates, proteins and fats exceeds the capacity of the pyruvate dehydrogenase (PDH) enzyme resulting in an increase in lactate level. The catabolism process also increases oxygen consumption and causes a perfusion deficit, so that metabolism runs in an anaerobic state (Dharma et al., 2008).

A Study in Indonesia reported that the mortality rate of critically ill children treated in the PICU of Dr. Cipto Mangunkusoma Hospital was 10.7% with an estimated mean length of stay (LOS) in pediatric intensive care unit (PICU) of ≤ 7 days (75%) and sepsis (20.8%), as well as malignant disease (20.8%) was the most common cause of death (Dewi, 2019).

The Pediatrics risk of mortality (PRISM) III score can be used to determine the LOS in PICU. The PRISM score can assess the severity of a patient's disease by using its 17 components (Pollack et al., 2015). A study by Bramantyo et al at revealed that critically ill children who had a PRISM score of ≥ 8 had a mortality rate of 3.5 folds greater than critically ill children who had a PRISM score of < 8 (Bramantyo et al., 2018).

Lactic acid is a metabolic waste product of pyruvic acid metabolism, a reaction catalysed by lactate dehydrogenase involving the conversion of NADH to NAD+ and oxidized nicotine adenine dinucleotides. The conversion of pyruvate to lactate will continue along with tissue hypoxia and several other clinically relevant conditions (Molan et al, 2017). Hence, Lactate level can be used to measure inadequate perfusion and tissue hypoxia, as it has been proven in several studies.

High lactate levels can predict death and poor neurological outcomes. In patients who experiencing hyperlactatemia, monitoring lactate level with targeted hyperlactatemia therapy significantly reduces the LOS in the PICU. However, up to date there has not been any standard cutoff value as a predictor of mortality in critically ill children. Thus, we conducted a study to assess lactate level for predicting mortality in critically ill children.

SUBJECTS AND METHOD

1. Study Design

This is a cohort prospective study. It was performed in Dr. Moewardi General Hospital, Surakarta, Indonesia from January 2023 to June 2023

2. Population and Sample

The population of this study were pediatric patients diagnosed with sepsis aged between 1 month old and 18 years old who were treated at the PHCU. We used consecutive sampling technique. We excluded patients suffering from inborn error of metabolism, type 1 or type 2 diabetes mellitus and certain syndromes.

3. Study Variables

The dependent variable was the mortality. The independent variable was lactate level.

4. Operational Definition of Variables

PRISM Score III was a scoring to determine predictions mortality in critically ill children and categorized as < 10 and ≥ 10.

Lactate Level was the end results of the glycolysis process in anaerobic conditions. It is said increase if the lactate level in the serum is ≥ 2 mmol/L and it was taken from the blood sample. Lactate levels categorized as ≥ 2 mmol/L and < 2 mmol/L.

Mortality was determined as death occuring during hospitalization. It can be measured with ECG monitoring and sign of death such as mydriasis of pupil or no pulse of arteries.

5. Study Instruments

The demographic data were obtained by

interviewing the patients or caregivers. The patient's medical status data were taken from medical record of patient. The lactate levels were examined in clinical pathology laboratory of Dr. Moewardi General Hospital, Surakarta, Indonesia

5. Data analysis

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6. Research Ethics

This study was approved by the Ethics Committee of Dr. Moewardi General Hospital, Surakarta, Indonesia with the number was 761/VI/HREC/2022.

RESULTS

There were 30 critically ill pediatric patients who met our inclusion criteria, comprising 17 survived patients 13 deceased patients. Of these who died 61.5% were females. The most common diagnoses on admission of the deceased ones were malignancies (30.8%) and pneumonia (30.8%), Respiratory failure (30.8%) was the predominant organ dysfunction among those who died. The baseline lactate levels were significantly higher in the deceased patients then those of in the survived patients (Mean= 2.94; SD= 0.90 vs Mean= 2.10; SD= 0.87; p= 0.0011). The PRISM score was also greater in patients who died than that of in those who survived (Mean= 19.46; SD= 9.29 vs Mean= 6.18; SD= 5.10; p < 0.001) (Table 1.)

Table 1. The Subjects characteristics (Continuous data)

Characteristics	Total (N=30)		Deceased (N=13)		Survivor (N=17)		p
	Mean	SD	Mean	SD	Mean	SD	
Age [b]	5.87	4.96	5.62	4.14	6.06	5.26	0.814
LOS in PHCU	3.87	2.22	2.54	2.03	4.88	1.83	<0.001*
PRISM Score [c]	11.93	9.73	19.46	9.25	6.18	5.10	<0.001*
Baseline Lactate level [b]	2.46	0.97	2.94	0.90	2.10	0.87	0.011*

Note [a] Chi square test; [b] Independent t test; [c] Mann Whitney test; * significantly with p<0.05

Table 2. The Subjects characteristics (Categorical data)

Characteristics	Total (N=30)		Deceased (N=13)		Survivor (N=17)		p
	N	%	N	%	N	%	
Sex[a]							0.153
Male	16	53.3	5	38.5	11	64.7	
Female	14	46.7	8	61.5	6	35.3	
Nutritional Status[c]							0.126
Malnourished	1	3.3	1	7.7	0	0.0	
Undernourished	13	43.3	7	53.8	6	35.3	
Well nourished	16	53.3	5	38.5	11	64.7	
Admission Diagnosis							0.263
CNS Infection	2	6.7	0	0.0	2	11.8	
Malignancy	9	30.0	4	30.8	5	29.4	
Pneumonia	9	30.0	4	30.8	5	29.4	
Post Operation	1	3.3	0	0.0	1	5.9	
Sepsis	3	10.0	3	23.1	0	0.0	
Others	6	20.0	2	15.4	4	23.5	
Function Problems [b]							0.066

Characteristics	Total (N=30)		Deceased (N=13)		Survivor (N=17)		p
	N	%	N	%	N	%	
Respiratory Distress	5	16.7	0	0.0	5	29.4	
Loss of Consciousness	5	16.7	2	15.4	3	17.6	
Hypovolemia Shock	1	3.3	0	0.0	1	5.9	
Sepsis Shock	3	10.0	3	23.1	0	0.0	
No	16	53.3	8	61.5	8	47.1	
Organ Failure [b]							0.188
Kidney Failure	1	3.3	0	0.0	1	5.9	
Hepatic Failure	1	3.3	1	7.7	0	0.0	
Heart Failure	1	3.3	1	7.7	0	0.0	
Respiratory Failure	5	16.7	4	30.8	1	5.9	
Blood Disorder	8	26.7	3	23.1	5	29.4	
No	14	28.0	4	30.8	10	58.8	

Note [a] Chi square test; [b] Independent t test; [c] Mann Whitney test; * significantly with p<0.05

The Spearman rank obtained a correlation value of r= 0.34 for the correlation test between increased lactate level a PRISM III score (p= 0.066). A Scatter plot of the relationship between lactate levels and PRISM score is shown in figure 1.

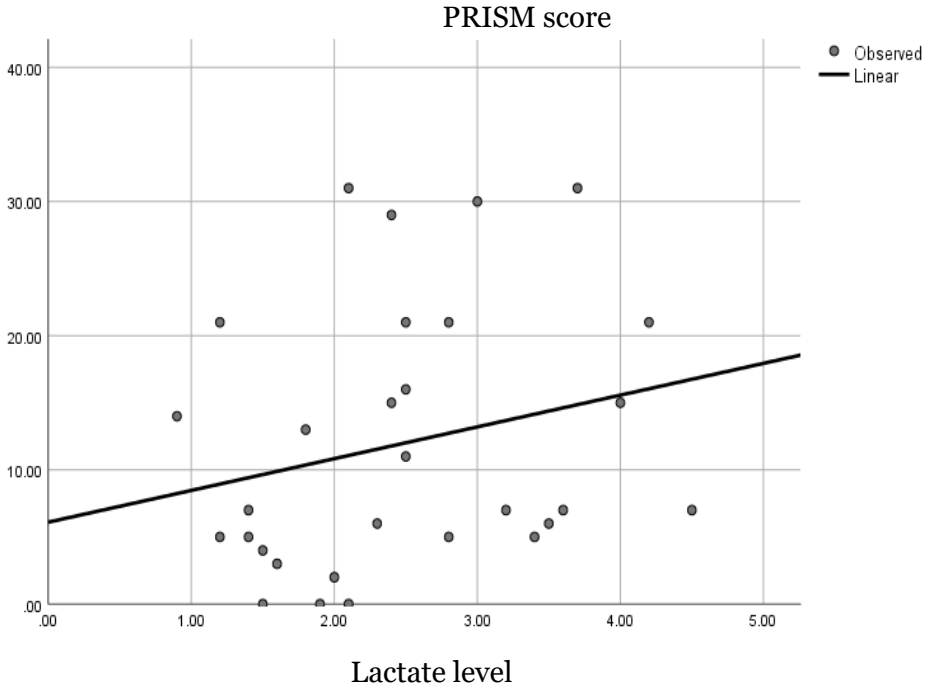

Figure 1. The Scatter plot of relationship between lactate level and PRISM score

The lactate levels of the 1th, 6th, and 24th hours in the patients who died were significantly higher than those of the survived ones. They were 2.94 mmol/l, 3.20 mmol/l, and 3.65 mmol/l, respectively in the deceased group as compared to 2.10 mmol/l, 1.91 mmol/l, and 2.06 mmol/l, respectively. (p=0.011; p<0.001, and p<0.001) (Table 2).

Table 2. Differences in lactate levels based on outcomes of critically ill pediatric patients

Parameter	Deceased		Survived		p
	Mean	SD	Mean	SD	
The 1th hour lactate [b]	2.94	0.90	2.10	0.87	0.011
The 6th hour lactate [a]	3.20	0.50	1.91	0.46	<0.001
The 24th hour lactate [b]	3.65	0.53	2.06	0.49	<0.001

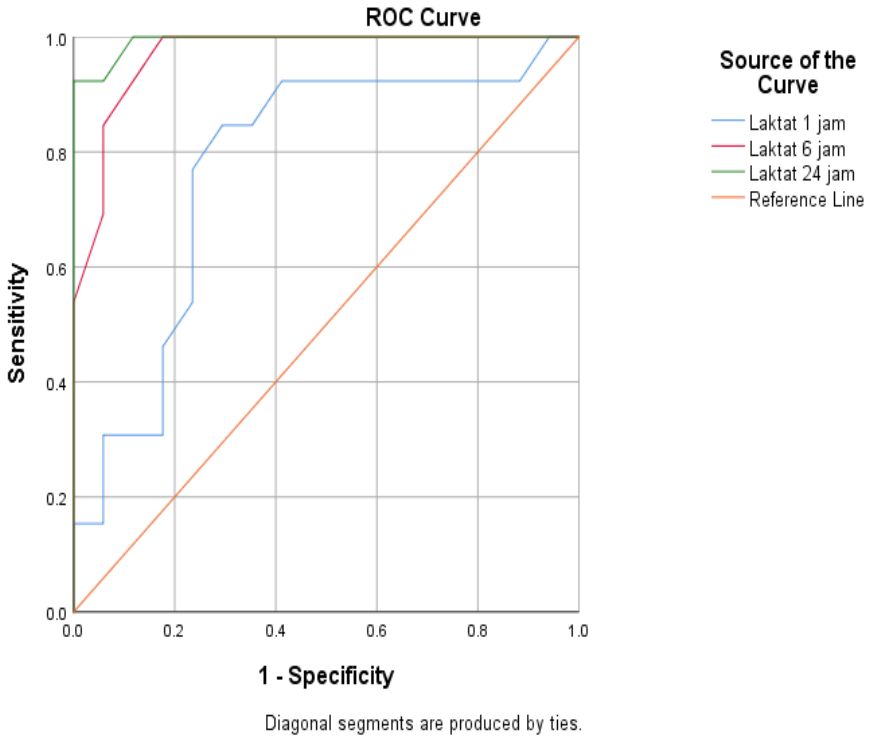

Figure 2. ROC Curve of Lactate level

The results of the examination of lactate levels compared with the outcomes of critically ill pediatric patients showed the ROC curve results in Figure 2. Using the lactate levels of the patients who died, the AUC value in the 1th hour was 0.774 with a cut-off point of >2.35 mmol/l obtaining the sensitivity of 84.6%, a specificity of 70.6%, a positive predictive value (PPV) of 68.8%, and a negative predictive value (NPV) of 85.7% (p = 0.011). The AUC of the lactate level in the 6th hour was 0.968 with a cut-off point of >2.35 mmol/l, having a sensitivity of 100% and a Specificity of 82.4%, a positive predictive value (PPV) of 81.2%, and a negative predictive value (NPV) of 100 % (p<0.001). In addition, the AUC of the lactate level in the 24th hour was 0.993 with a cut-off point of >2.95 mmol/l, showing a sensitivity of 92.3%, a specificity of 100%, a positive predictive value (PPV) of 100%, and a negative predictive value (NPV) of 94.4 % (p<0.001) (Figure 2 and Table 3).

Table 3. Determination of Cut-off Lactate Levels as a Predictor of Mortality in Critically Ill Children.

Variable	AUC (95% CI)	p	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Lactate 1 h	0.77 (0.58 - 0.90)	0.011*	≥2.35	84.6 (54.6 - 98.1)	70.6 (44.0 - 89.7)	68.8 (50.4 - 82.6)	85.7 (61.8 - 95.7)
Lactate 6 h	0.96 (0.83 - 0.99)	<0.001*	≥2.35	100 (75.3 - 100.0)	82.4 (56.6 - 96.2)	81.2 (60.8 - 92.4)	100
Lactate 24 h	0.99 (0.87 - 1.00)	<0.001*	≥2.95	92.3 (64.0 - 99.8)	100 (80.5 - 100.0)	100	94.4 (72.1 - 99.1)

Note: AUC = Area Under Curve; * significantly with p<0.05

DISCUSSION

In 30 critically ill children who were treated in the PHCU at Dr. Moewardi, there were 13 patients deceased and 17 patients survived in PHCU and most of those were female. The mean age of patients who died was younger than those who lived. Malnutrition status was also found most frequently in patients who died. The most common disease experienced by patients is pneumonia. These three things are different from previous research conducted in India, where male gender and good nutritional status were more likely to die, while the most common disease was sepsis (Meher et al, 2018).

We found that the mean initial lactate level in 1th hour was >2.95 mmol/l higher Lactate (Mean= 2.94; SD= 0.90) compared. Meanwhile, the average PRISM score in patients who died was >10 with an average PRISM IIII Score (Mean= 19.46; SD= 9.25). This is slightly different from the study before. In study conducted by Meher et al, the average initial lactate level of patients who died was 6.19 mmol/L, whereas in study conducted in Indonesia by Gunawan et al, the average lactate level was 4.77 mmol/l (Gunawan et al., 2017). In these results have the same conclusion that lactate levels >2 mmol/l can increase patient mortality. The difference in lactate level values in each study is assumed to depend on the type of disease in each subject studied.

This study also assessed differences in lactate levels in the 1th hour, 6th hours and 24th hours after admission. The initial lactic level in this study obtained a cutoff of ≥ 2.35 mmol/L with an AUC value for mortality of 0.774, which can predict 68.8% mortality with a sensitivity value of 84.6% and a specificity of 70.6%. This is different from research conducted by Meher et al, where a cutoff value of ≥ 5.42 was obtained with an AUC value of 0.898, the sensitivity in this study was 75%, specificity was 100% and could predict mortality by 100% (Meher et al., 2018).

The incidence of persistent hyperlactatemia for 24 hours with a cutoff value of >2.95 mmol/L with an AUC value of 0.993, sensitivity in this study was 92.3%, specificity was 100% and could predict death by 100%. This is in line with research conducted by Meher et al, where the incidence of persistent hyperlactatemia was >3.02 mmol/l with a value of 0.986, the sensitivity in this study was 95%, the specificity was 100%, and could predict 100% death. These results are also in line with study conducted by Patki et al. (2017) the incidence of persistent hyperlactatemia >2.8 mmol/L can increase the mortality rate. This research also shows things that are in line with the theory which states that the relationship between the incidence of persistent hyperlactatemia 24 to 48 hours can cause increased mortality, poor neurological outcomes and indicate the occurrence of organ failure (Meher et al., 2018).

The relationship between lactate levels and PRISM III scores in this study via the scarlet plot was depicted as having a positive relationship but not statistically significant (r = 0.34; p = 0.666). This shows that the use of lactate levels cannot describe the presence of multi-organ disorders as can be described by the PRISM III score. However, lactate levels have a fairly strong relationship in assessing the outcome of critically ill pediatric patients, especially 24-hour lactate levels (persistent hyperlactatemia) (Bei et al., 2014).

Lactate levels can predict mortality in critically ill children. Persistent hyperlactatemia (lactate levels within 24 hours) is better predicting mortality than initial lactate levels. There is a positive relationship between increasing lactate levels and the PRISM III score, but it does not have statistical significance.

AUTHOR CONTRIBUTION

Reza Ervanda Zilmi is the lead author who conducted the research, conducted data analysis, and wrote the manuscript. Pudjiastuti examined the background and discussion of the research. Rustam Siregar formulated the research framework.

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This research was funded independently.

CONFLICT OF INTEREST

In this study there was no conflict of interest.

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