Serum Lactic Acid: A Predictor of Septic Shock in Childhood Cancers with Febrile Neutropenia in a Tertiary Care Hospital in Bangladesh

ABSTRACT

Background: *Febrile neutropenia (FN) is a common and life-threatening complication in children undergoing treatment for cancer, often leading to septic shock. Early identification of septic shock is critical. Serum lactic acid levels have emerged as a potential biomarker for predicting septic shock. This study aimed to determine the implications of serum lactic acid levels as a predictor of septic shock in childhood cancer patients with febrile neutropenia.* ***Methods:*** *This cross-sectional study was from June 2023 to July 2024. One hundred pediatric oncology patients with neutropenia who were admitted to the Department of Pediatric Hematology and Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU) were enrolled in the study. Clinical examinations and laboratory investigations were conducted for all participants, and the relevant information was recorded. Data were analyzed using SPSS 24.0.* ***Results:*** *Shock patients exhibited significantly higher initial serum lactic acid levels (3.52±0.81 mg/dl) compared to non-shock patients (1.93±0.75 mg/dl). The ROC curve analysis yielded an AUC of 0.934, with a sensitivity of 100.00%, specificity of 81.6%, and a cut-off value of 2.50 mg/dl. The diagnostic performance test demonstrated a PPV of 63.16%, NPV of 100.00%, and overall accuracy of 86.00%.* ***Conclusion:*** *This study demonstrates the potential utility of serum lactic acid levels as a predictive biomarker for identifying febrile neutropenic patients at risk of developing septic shock within 48 hours. Serum lactic acid level >2.5 mmol/L could be considered as a threshold for early risk stratification.*

Keywords: *Childhood cancers, Febrile Neutropenia, Predictor, Sensitivity, Serum lactic acid, Septic shock.*

1. INTRODUCTION

Chemotherapy-related neutropenia is a major dose limiting toxicity of systemic cancer chemotherapy. It is related to mortality, morbidity, and costs. Infection is the main cause of mortality among pediatric patients with cancer and treated with systemic chemotherapy [1]. Patients suffering from fever are classified as high risk due to neutropenia are frequently treated with empiric broad spectrum intravenous (IV) antibiotics due to the risk of rapid clinical deterioration from bacterial infection in this group [2]. Although the most of these patients remain clinically healthy without a known cause of fever, a small percentage of febrile pediatric oncology (PO) patients will decompensate despite the use of empiric antibiotics, with a mortality rate of 12–30% in those who develop sepsis or septic shock as a result [3]. Reduced mortality and organ dysfunction are linked to early diagnosis and management of septic shock. Tools that facilitate early identification of patients who are most at risk for developing septic shock therefore have the potential to better patient outcomes [4]. Due to the absence of reliable, effective tests to risk stratify febrile PO patients, it is difficult to determine which patients will clinically deteriorate as a result of sepsis. When it is related to the development of risk stratification tools, the PO patient group presents particular difficulties because patients frequently do not have the clinical symptoms of a severe infection at the time of the onset of their fever because of an inadequate immune response [5]. Additionally, previous studies have indicated that laboratory markers such as CRP, PCT, and inflammatory cytokines, which are useful in differentiating septic from non-septic patients in general pediatric and adult populations, may have questionable reliability in postoperative (PO) patients. This is due to the altered baseline metabolic status, immune response, and organ function in these patients [6,7]. Elevated serum lactic acid levels are linked to poor results even when arterial blood pressure and oxygenation are sustained [8,9]. It is known that people with cancer have remodeled lactic acid metabolism. This is demonstrated by the fact that people with cancer can develop lactic acidosis without having an infection and that chemotherapy can cause fluctuations in the levels of the enzyme lactate dehydrogenase (LDH), which activate the conversion of pyruvate and lactic acid, as well as serum lactic acid [10]. Several Studies indicate that measuring serum lactic acid in the group of pediatric cancer patients is important. In research conducted in Thailand, found that in 100 hemodynamically stable pediatric oncology patients with fever and neutropenia, initial serum lactic acid >2.5 mmol/L was associated with septic shock [1]. In febrile pediatric oncology patients, a different study found an independent relationship between an elevated initial lactic acid level and a worsening of their illness, indicating that serum lactic acid can be used as a future risk stratification tool for this group [3]. There is a lack of information on the inequitable value of serum lactic acid in PO patients, despite studies in large pediatric populations, including patients with chronic comorbidities, showing an association between increased lactic acid and organ failure,

admission to the pediatric intensive care unit (PICU), bacterial infection, and mortality [11,12]. The objective of this study is to better understand the implications of serum lactic acid levels as a predictor of septic shock in childhood cancers with febrile neutropenia.

2. METHODOLOGY

This study was a cross-sectional analytical study conducted from June 2023 to July 2024 at the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU). A total of 100 pediatric oncology patients diagnosed with febrile neutropenia were included in the study after obtaining written informed consent from either the patients or their legal guardians. Purposive sampling was used to select participants based on specific inclusion and exclusion criteria. Children under 18 years of age, undergoing chemotherapy for cancer treatment and developing febrile neutropenia, were included. Patients who were hemodynamically unstable at the onset of febrile neutropenia or had prolonged fever lasting more than 72 hours were excluded from the study. The study assessed various socio-demographic, clinical, and laboratory variables. Socio-demographic variables included age, sex, height, weight, and socio-economic status. Clinical variables included body temperature, respiratory rate, heart rate, and blood pressure. Laboratory variables consisted of serum lactic acid, complete blood count (CBC), C-reactive protein (CRP), blood culture, and urine culture. Prior to data collection, ethical approval was obtained from the Institutional Review Board (IRB) of BSMMU. Demographic and clinical data, along with the main vital signs, were recorded at the time of febrile neutropenia development. After the initial data collection, patients were closely monitored, and a follow-up was conducted after 48 hours. Data were recorded in a semi-structured questionnaire, and the data were entered and analyzed using SPSS version 24.0. Statistical significance was considered at a p-value of <0.05.

3. RESULT

Among the participants, the majority fell into the age groups of 7-12 years (54.0%) and up to 6 years (28%), with a smaller proportion in the 13-18 year's category (18%). In terms of gender distribution, males constituted 67.0% of the sample, while females accounted for 33.0%. Among the total 100 patients included in the study, 24 patients (24%) experienced shock, while the majority, comprising 76 patients (76%), did not. Shock patients exhibited a lower mean weight of 17.6 kg (±6.7) compared to 22.5 kg (±8.4) in non-shock patients, with a statistically significant ($p<0.05$). Furthermore, shock patients demonstrated a higher mean body temperature of 100.0°F (±1.3) compared to 98.8°F (±0.9) in non-shock patients, with a highly significant ($p<0.001$). Notably, shock patients also exhibited significantly lower mean SBP (77.1±5.3) and DBP (42.9 ±5.3) compared to non-shock patients (SBP: 90.3 ±9.8, DBP: 55.1±9.5), $p<0.001$ for both parameters. However, no significant differences were observed in respiratory rate ($p=0.647$) and heart rate ($p=0.902$) between shock and non-shock patients. In this study, shock patients displayed significantly elevated mean serum lactic acid level of 3.52±0.81 mmol/L compared to 1.93±0.75 mmol/L in non-shock patients ($p<0.001$). Receiver Operating Characteristic (ROC) curves to predict developing septic shock within 48 hours based on the initial serum lactic acid was produced. The curve represents values of sensitivity and specificity for each measurement of serum lactic acid level at the time of developing febrile neutropenia. The Area Under the Curve (AUC) is calculated as 0.934, indicating a high predictive accuracy of serum lactate levels in identifying patients at risk of developing septic shock. The cut-off value determined is 2.50 mmol/L, with a sensitivity of 100% and a specificity of 81.6%. These findings suggest that serum lactic acid levels serve as a robust predictor for the early detection of septic shock in febrile neutropenia patients. The diagnostic performance test results of febrile neutropenia patients to predict the development of septic shock within 48 hours based on initial serum lactic acid levels was assed. The sensitivity of the test is calculated as 100.00%, the specificity of the test is determined as 81.58%, the Positive Predictive Value (PPV) is calculated as 63.16%, the Negative Predictive Value (NPV) is determined as 100.00%, the overall accuracy of the test is calculated as 86.00%.

Table 1: Demographic data

Variables	n	%
Age group (Years)		
≤6	28	28
7-12	54	54
13-18	18	18
Sex		
Male	67	67
Female	33	33

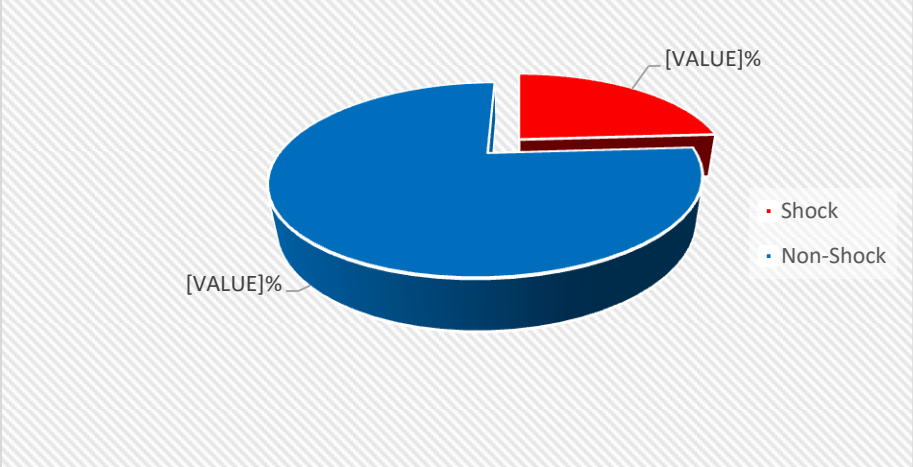

Figure 1: *Distribution of febrile neutropenia patients by shock*

Table 2: Comparison of clinical parameters of patients with febrile neutropenia with and without shock.

Clinical parameters	Shock (n=24)	Non-Shock (n=76)	p-value
Weight (Kg)	17.6±6.7	22.5±8.4	0.011
Body temperature (°F)	100.0±1.3	98.8±0.9	<0.001
Respiratory rate (per minute)	28.6±3.9	32.6±43.0	0.647
Heart rate (per minute)	127.5±9.4	131.1±144.2	0.902
SBP (mmHg)	77.1±5.3	90.3±9.8	<0.001
DBP (mmHg)	42.9±5.3	55.1±9.5	<0.001

p-value obtained by Unpaired t- test, p<0.05 considered as a level of significant

Table 3: Comparison of initial serum lactic acid level in patients with febrile neutropenia with and without shock.

Laboratory parameters	Shock (n=24)	Non-Shock (n=76)	p-value
Initial serum lactic acid (mmol/L)	3.52±0.81	1.93±0.75	<0.001

p-value obtained by Unpaired t- test between groups, p<0.05 considered as a level of significant

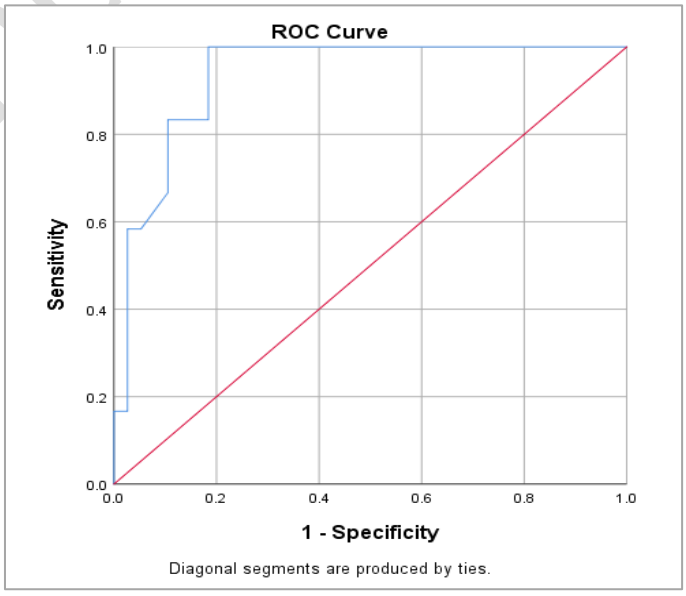

Figure 2: *ROC Curve on the specificity*

Table 4: Sensitivity and Specificity status

AUC	SE	Cut off value	Sensitivity	Specificity	p-value	95%CI	
						Lower	Upper
0.934	0.024	2.5	100%	81.60%	<0.001	0.888	0.98

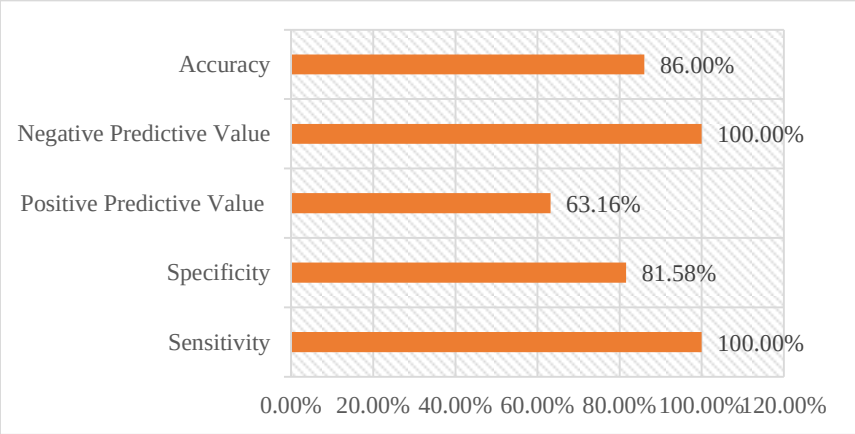

Figure 3: *The diagnostic performance test of febrile neutropenia patients to predict developing septic shock within 48 hours based on the serum lactic acid level*

4. DISCUSSION

In this study, 54% of participants were aged 7-12 years, 28% were up to 6 years old, and 18% were 13-18 years. Males constituted 67% of the sample, while females made up 33%. Similarly, Mohamed et al. (2021) [13] reported a median age of 13 months (range: 6-26) and equal gender distribution (50% males and 50% females) in their cases group. In the control group, the average age was 13 months (range: 6-34), with 41.7% males and 58.3% females. This study found a 24% prevalence of shock among neutropenic patients, affecting 24 out of 100 individuals. This study aligns with previous research by Jat et al. (2011) [14], which reported a 4.8% prevalence of septic shock, and Llorens et al. (1995) [15], who noted a 24% incidence of septic shock without a specific infection source. Among shock patients in this study, 50% had ALL, 25% AML, 16.7% hepatoblastoma, and 8.3% APML, with no cases of Infantile leukemia, NHL, or ES. In contrast, non-shock patients had varied diagnoses: 65.8% ALL, 21.1% AML, 5.3% NHL, 2.6% each for Infantile leukemia, hepatoblastoma, and ES (p=0.015). These results indicate that the type of underlying diagnosis may play a role in the development of shock in this population. This study aligns with previous research by Jat et al. (2011) [14], which reported a 4.8% prevalence of septic shock, and Llorens et al. (1995) [15], who noted a 24% incidence of septic shock without a specific infection source. Among shock patients in this study, 50% had ALL, 25% AML, 16.7% hepatoblastoma, and 8.3% APML, with no cases of Infantile leukemia, NHL, or ES. In contrast, non-shock patients had varied diagnoses: 65.8% ALL, 21.1% AML, 5.3% NHL, 2.6% each for Infantile leukemia, hepatoblastoma, and ES (p=0.015). These results indicate that the type of underlying diagnosis may play a role in the development of shock in this population. This study compared laboratory parameters in febrile neutropenia patients with and without shock, finding significantly higher mean ANC (665.8±492.3 vs. 307.3±381.6 cells/μL, p<0.001) and CRP levels (140.6±43.9 vs. 92.6±81.7 mg/L, p=0.007) in shock patients. Hemoglobin levels and WBC counts showed no significant differences (p=0.144). Aligned with these findings, Xiang et al. (2021) [16] observed significant differences in ANC, CRP, and other blood parameters between septic shock and control groups, emphasizing abnormalities in inflammatory markers. Similarly, Suwanpakdee et al. (2021) [1] reported higher WBC counts, ANC, CRP, lactic acid levels, and positive blood cultures in febrile neutropenia patients with shock. These studies highlight ANC and CRP as vital indicators for early shock detection, stressing timely management to enhance outcomes and lower mortality in this high-risk group. This study found significantly higher initial serum lactic acid levels in febrile neutropenia patients with shock (3.52±0.81 mmol/L) compared to those without shock (1.93±0.75 mmol/L) (p<0.001), highlighting its importance in assessing tissue perfusion and metabolic status during shock. Similarly, Suwanpakdee et al. (2021) [1] reported elevated lactate levels in shock patients (3.1±1.0 mmol/L) versus non-shock patients (1.7±0.06 mmol/L) (p<0.001). These findings underscore serum lactic acid's role as a vital indicator for identifying shock in febrile neutropenia cases. This consistent evidence highlights the significance of elevated serum lactic acid levels as a critical marker for identifying shock in febrile neutropenia patients. Xiang et al. (2021) [16] also reported significant differences in lactic acid levels between septic shock and control groups at the 24-hour observation point, emphasizing its role in septic shock evaluation. However, Mato et al. (2015) [17]

observed no significant difference in lactic acid levels between cases and controls at baseline, suggesting similar initial metabolic statuses. These contrasting findings underscore the need for continuous lactic acid monitoring to identify shifts in tissue perfusion and metabolic function, enabling early detection and management of shock in at-risk patients. The present study utilized ROC curves to evaluate the predictive power of initial serum lactate levels for septic shock onset within 48 hours in febrile neutropenia patients. An AUC of 0.934 demonstrated high predictive accuracy, with a cut-off value of 2.50 mmol/L yielding 100% sensitivity and 81.6% specificity, affirming the role of serum lactate in early shock detection. Similarly, Suwanpakdee et al. (2021) [1] found that initial serum lactate levels above 2.5 mmol/L showed the highest AUC for predicting septic shock within 48 hours, with excellent sensitivity, specificity, and overall diagnostic performance. These findings highlight serum lactate's clinical utility in identifying high-risk patients promptly. Both studies highlight the significance of serum lactic acid levels in early septic shock detection in febrile neutropenia patients. Our findings further underscore serum lactic acid as a valuable marker for identifying septic shock risk in hemodynamically stable pediatric oncology patients after febrile neutropenic episodes, emphasizing the importance of routine measurement of serum lactic acid in this group. Additionally, these results are consistent with those of Mato et al. (2015) [17], reinforcing the clinical relevance of serum lactic acid levels in predicting septic shock. The study also used ROC curve analysis to establish an optimal cut-off value for serum lactic acid in pediatric oncology patients. The results highlight that a serum lactic acid level above 2.0 mmol/L has the highest true positive rate for predicting septic shock within 48 hours, underscoring its high sensitivity. Additionally, a 2.5 mmol/L cut-off for serum lactic acid demonstrated the highest true negative rate and specificity, suggesting its role in guiding proactive hemodynamic monitoring in at-risk patients. This threshold may prompt early actions such as transferring patients to semi-intensive care units, ensuring proper vascular access, and initiating timely interventions like intravenous fluid adjustments to optimize tissue perfusion. In conclusion, both studies reinforce the crucial role of serum lactic acid levels as a predictive marker for septic shock in febrile neutropenia patients, aiding clinical decision-making and patient management strategies.

Limitation of the study:

This study has several limitations. The small sample size of 100 patients may limit the generalizability of the findings. Conducted at a single tertiary care hospital in Bangladesh, the study may introduce selection bias and may not reflect other healthcare settings. Additionally, potential confounding factors, such as comorbidities and medications, were not considered, which could influence serum lactic acid levels and septic shock development. While elevated serum lactic acid levels are associated with septic shock, other factors like tissue hypoperfusion and underlying conditions could also contribute, necessitating careful interpretation. Finally, the study did not assess long-term outcomes, such as mortality or length of hospital stay, limiting the evaluation of the clinical impact of serum lactate measurement.

5. CONCLUSION & RECOMMENDATION

This study highlights the clinical significance of serum lactic acid levels as a predictive marker for septic shock in childhood cancer patients with febrile neutropenia. A significant association was found between elevated initial lactate levels and the occurrence of shock, with high sensitivity, specificity, and accuracy. These findings suggest that measuring serum lactate could aid in early risk stratification and prompt intervention, improving clinical decision-making and outcomes. Incorporating serum lactate measurement into routine practice may optimize patient management and reduce septic shock-related morbidity and mortality in this vulnerable population.

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