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

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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.

1. INTRODUCTION

Febrile neutropenia (FN) is a severe complication in pediatric oncology, commonly arising from the immunosuppressive effects of chemotherapy. It significantly increases the susceptibility to infections, including septic shock, which is a major contributor to morbidity and mortality in this population (Mishra et al., 2021). Early risk stratification and identification of septic shock in FN are essential to prevent adverse outcomes (Ammann et al., 2010). Among the biomarkers available, serum lactic acid has gained importance as a cost-effective and accessible tool for predicting the severity of septic shock (Mariani et al., 2023). Serum lactic acid reflects tissue hypoxia and anaerobic metabolism, both of which are characteristic of septic shock. Elevated lactic acid levels have been shown to correlate with worse outcomes, including increased mortality and prolonged hospital stays, particularly in pediatric patients (Guarino et al., 2023; Slatnick et al., 2022). It is now recommended as a critical parameter in the initial assessment and ongoing monitoring of sepsis severity (Jouza et al., 2022). However, despite its utility in high-resource settings, data on its effectiveness in low-resource contexts, such as Bangladesh, remain limited (Sakakushev, 2022). Childhood cancers, including leukemia and lymphoma, are frequently associated with FN, placing children at significant risk of developing life-threatening complications. Managing FN in resource-constrained settings is further complicated by limited access to intensive care and advanced diagnostic tools (Shampa et al., 2023). Biomarkers like serum lactic acid offer a practical solution to these challenges, providing clinicians with actionable insights for early intervention (Mendelson, 2021). Recent studies have highlighted the prognostic value of lactic acid levels in predicting outcomes in pediatric sepsis and septic shock, yet the relevance of these findings to FN patients with cancer in developing countries is underexplored (Jariyasakoolroj et al., 2024). There is a growing need for region-specific data to guide clinical decision-making and improve outcomes for these vulnerable patients (Islam et al., 2022). This study aimed to evaluate the effectiveness of serum lactic acid levels as a predictor of septic shock in pediatric cancer patients with febrile

neutropenia in a tertiary care hospital in Bangladesh. By correlating lactic acid levels with clinical outcomes, this research seeks to provide evidence-based recommendations for early identification and management of septic shock in this population (Tuan et al., 2024).

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). Purposive sampling was used to select participants based on specific inclusion and exclusion criteria. Children within the age of 18 years, undergoing chemotherapy for cancer treatment and developing febrile neutropenia, were included. Patients aged over 18 years and contraindicated to chemotherapy 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 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. RESULTS

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

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

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%.
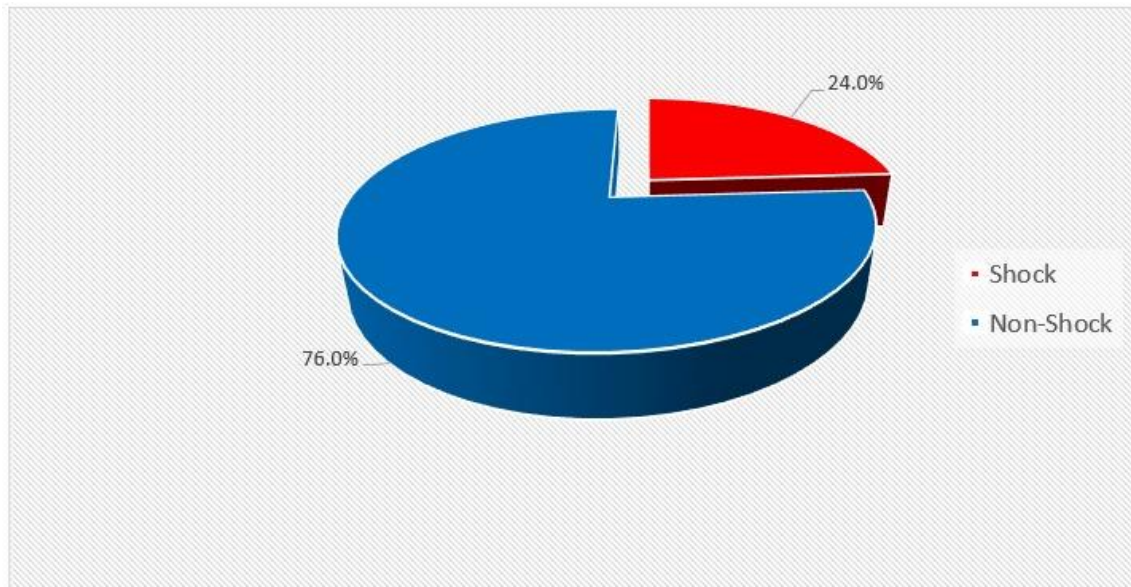

Fig. 1. Distribution of febrile neutropenia patients by shock

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

Table 4. Sensitivity and Specificity status

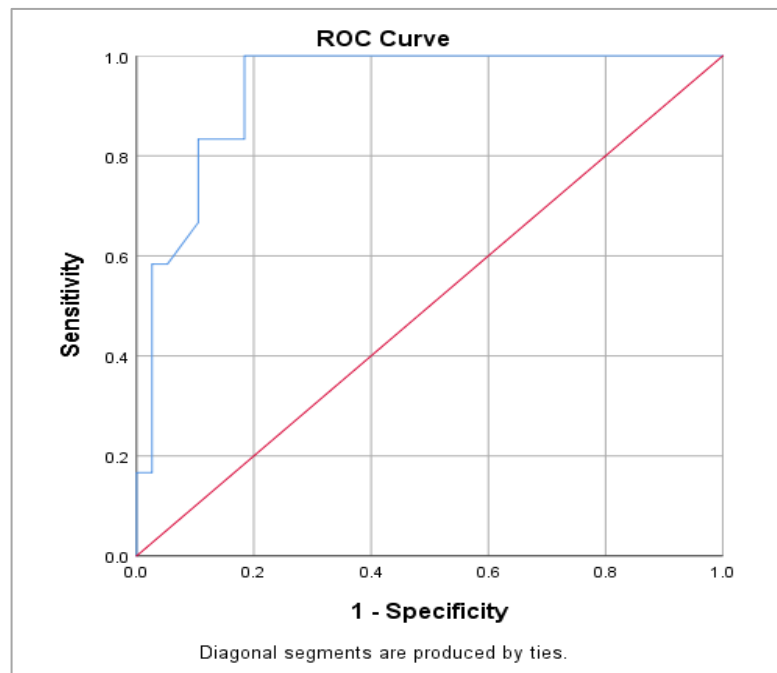| AUC	SE	Cut off value	Sensitivity	Specificity	p-value	95%CI	
						Lower	Upper
0.934	0.024	2.5	100%	81.60%	<0.001	0.888	0.98

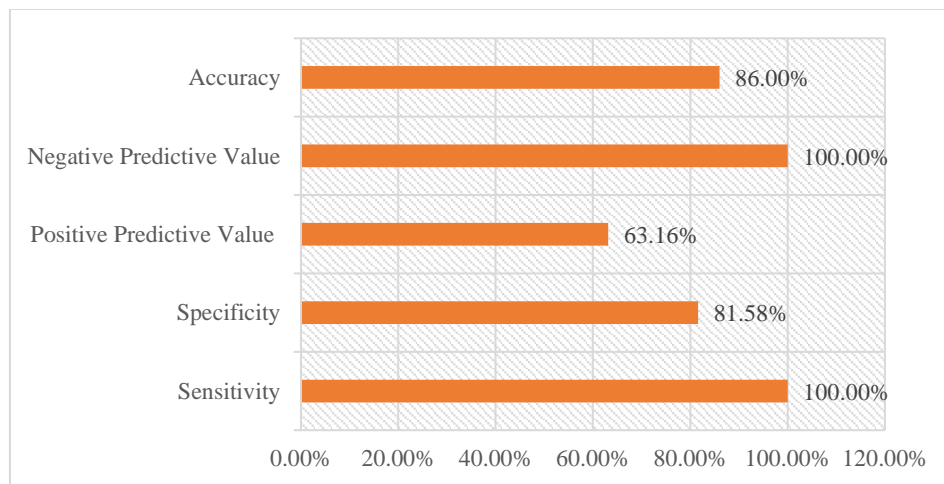**Fig. 2. ROC Curve on the specificity**

Fig. 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) reported a median age of 13 months (range: 6-26) and equal gender distribution (50% males and 50% females) in their case 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. Comparative findings were observed in some other recent studies (Silva et al., 2021; La Via et al., 2024). 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. 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 neutropenic 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) 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) 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) 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) 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. (2010) 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) 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. (2010), 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.

5. 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.

6. CONCLUSION AND RECOMMENDA-TION

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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology Details of the AI usage are given below:

1. Large Language Models have been used to clarify some issues and manuscript development.

CONSENT

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.

ETHICAL APPROVAL

Prior to data collection, ethical approval was obtained from the Institutional Review Board (IRB) of BSMMU.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

Ammann, R. A., et al. (2010). Predicting adverse events in children with fever and chemotherapy-induced neutropenia: The prospective multicenter SPOG 2003 FN study. *Journal of Clinical Oncology, 28*(12), 2008-2014. https://doi.org/10.1200/JCO.2009.27.9057

Guarino, M., et al. (2023). 2023 update on sepsis and septic shock in adult patients: Management in the emergency department. *Journal of Clinical Medicine, 12*(9), 3188. https://doi.org/10.3390/jcm12093188

Islam, M. A., et al. (2022). A review on measures to rejuvenate immune system: Natural mode of protection against coronavirus infection. *Frontiers in Immunology, 13*, 837290. https://doi.org/10.3389/fimmu.2022.837290

Jariyasakoolroj, T., Chattipakorn, S. C., & Chattipakorn, N. (2024). Potential biomarkers used for risk estimation of pediatric sepsis-associated organ dysfunction and immune dysregulation. *Pediatric Research*. https://doi.org/10.1038/s41390-023-02395-6

Jouza, M., et al. (2022). MicroRNA as an early biomarker of neonatal sepsis. *Frontiers in Pediatrics, 10*, 854324. https://doi.org/10.3389/fped.2022.854324

La Via, L., et al. (2024). The global burden of sepsis and septic shock. *Epidemiologia, 5*(3), 456-478. https://doi.org/10.3390/epidemiologia5030041

Mariani, S., De Piero, M. E., & Haverich, A. (2023). Future noninvasive monitoring. In *Cardiopulmonary Bypass* (pp. 65-83). Academic Press. https://doi.org/10.1016/B978-0-12-820944-1.00008-2

Mato, A. R., et al. (2010). Elevation in serum lactate at the time of febrile neutropenia (FN) in hemodynamically-stable patients with hematologic malignancies (HM) is associated with the development of septic shock within 48 hours. *Cancer Biology & Therapy, 9*(8), 585-589. https://doi.org/10.4161/cbt.9.8.12209

Mendelson, A. (2021). Experimental, theoretical, and translational studies of RBC distribution in capillary networks (Doctoral dissertation). The University of Western Ontario, Canada. https://ir.lib.uwo.ca/etd/7828

Mishra, K., et al. (2021). The clinical profile, management, and outcome of febrile neutropenia in acute myeloid leukemia from resource constraint settings. *Therapeutic Advances in Infectious Disease, 8*, 20499361211036592. https://doi.org/10.1177/2049936121103659 2

Mohamed, N. A., & Youness, E. R. (2021). Clinical role of serum lactate dehydrogenase assessment in critically ill pediatric patients with sepsis. *Biomedical and Pharmacology Journal, 14*(4), 1941-1954. https://doi.org/10.13005/bpj/2334

Sakakushev, B. E. (2022). MOF management in low-resource settings. In *Postinjury Multiple Organ Failure* (pp. 241-260). Springer International Publishing. https://doi.org/10.1007/978-3-030-70181-7_13

Shampa, M. T. A., et al. (2023). A comprehensive review on sustainable coastal zone management in Bangladesh: Present status and the way forward. *Heliyon.* https://doi.org/10.1016/j.heliyon.2023.e136 49

Silva, M. M. M., Oliveira-Figueiredo, D. S. T., & Cavalcanti, A. D. C. (2021). Prevalence and factors associated with sepsis and septic shock in oncological patients in intensive therapy. *Revista Brasileira de Enfermagem, 75*, e20201338. https://doi.org/10.1590/0034-7167-2020-0138

Slatnick, L. R., et al. (2022). Serum lactate is associated with increased illness severity in immunocompromised pediatric hematology oncology patients presenting to the emergency department with fever. *Frontiers in Oncology, 12*, 990279. https://doi.org/10.3389/fonc.2022.990279

Tuan, D. A., Uyen, P. V. N., & Masak, J. (2024). Hybrid quorum sensing and machine learning systems for adaptive synthetic biology: Toward autonomous gene regulation and precision therapies. https://doi.org/10.1016/B978-0-12-821305-9.00003-2

Xiang, L., et al. (2021). Machine learning for early warning of septic shock in children with hematological malignancies accompanied by fever or neutropenia: A single center retrospective study. *Frontiers in Oncology, 11*, 678743. https://doi.org/10.3389/fonc.2021.678743

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