ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Implementation of the Phoenix Sepsis Score in Vietnamese Pediatric Patients: Prognostic Accuracy and Comparative Analysis with Neutrophil-Lymphocyte Ratio

Phoenix Sepsis Skorunun Vietnamlı Pediatrik Hastalarda Uygulanması: Prognostik Doğruluk ve Nötrofil-Lenfosit Oranı ile Karşılaştırmalı Analiz

Chau Duc Nguyen-Huu (0000-0002-3056-6086), Bich-Ngoc Phan (0000-0001-7887-9172), Van-Tuy Nguyen (0000-0002-6652-9025)

Hue University Faculty of Medicine and Pharmacy, Department of Pediatrics, Hue City, Vietnam

Abstract

Introduction: To evaluate the implementation of the Phoenix sepsis score in the prognosis of pediatric sepsis, and to compare the prognostic accuracy of the Phoenix with that of the NLR.

Materials and Methods: A retrospective cohort analysis was conducted on pediatric patients diagnosed with sepsis. Patients were categorized using the Phoenix and the NLR.

Results: In a cohort of 63 pediatric patients diagnosed with sepsis using established criteria, the Phoenix sepsis score identified 16 as suspected sepsis and 47 as confirmed sepsis. Patients with confirmed sepsis exhibited significantly different clinical and laboratory features, such as pre-existing conditions, lower Glasgow Coma Scale scores, lymphopenia, and lactic acidosis ($p < 0.05$). The Phoenix demonstrated superior prognostic accuracy in predicting mortality compared to the NLR, with an AUC of 0.886 versus 0.649.

Conclusion: The Phoenix sepsis score is a valuable prognostic tool in pediatric sepsis, outperforming NLR in predicting mortality.

Keywords
Pediatric sepsis, classification, prognosis, clinical outcomes

Öz

Giriş: Phoenix sepsis skorunun pediatrik sepsisin prognozundaki uygulanmasını değerlendirmek ve Phoenix'in prognostik doğruluğunu NLR ile karşılaştırmak.

Gereç ve Yöntem: Sepsis tanısı alan pediatrik hastalar üzerinde retrospektif bir kohort analizi yapıldı. Hastalar Phoenix ve NLR kullanılarak kategorize edildi.

Bulgular: Kurulmuş kriterler kullanılarak sepsis tanısı konan 63 pediatrik hastadan oluşan bir kohortta, Phoenix sepsis skoru 16 hastayı şüpheli sepsis ve 47 hastayı doğrulanmış sepsis olarak sınıflandırdı. Doğrulanmış sepsis olan hastalar, önceden var olan durumlar, daha düşük Glasgow Koma Skalası skorları, lenfopeni ve laktik asidoz gibi önemli klinik ve laboratuvar özellikleri sergiledi ($p < 0.05$). Phoenix, NLR ile karşılaştırıldığında mortaliteyi öngörmede üstün prognostik doğruluk gösterdi ve AUC değeri 0.886 iken NLR'nin AUC değeri 0.649 olarak hesaplandı.

Bulgular: Phoenix sepsis skoru, pediatrik sepsiste değerli bir prognostik araç olup, mortaliteyi öngörmede NLR'den daha başarılıdır.

Anahtar kelimeler
Pediatrik sepsis, sınıflandırma, prognoz, klinik sonuçlar

Received/Geliş Tarihi : 24.09.2024
Accepted/Kabul Tarihi : 22.10.2024

DOI:10.4274/jcp.2024.62343

Address for Correspondence/Yazışma Adresi: Van-Tuy Nguyen, Hue University Faculty of Medicine and Pharmacy, Department of Pediatrics, Hue City, Vietnam
E-mail: nvtuy@huemed-univ.edu.vn

Introduction

Sepsis, a life-threatening condition caused by a dysregulated response to infection, poses significant challenges in pediatric populations due to atypical symptoms that complicate early diagnosis (1). Pediatric sepsis, particularly prevalent in neonates and infants with immature immune systems, is a leading cause of morbidity and mortality globally. The incidence varies widely, and early recognition is difficult due to nonspecific symptoms like fever, tachycardia, and lethargy (2). Early and accurate prognosis is crucial for optimizing care, allowing for tailored interventions, risk stratification, and resource allocation, ultimately reducing morbidity and mortality in this vulnerable group (3,4).

The Phoenix sepsis score aims to establish a standardized, evidence-based approach to defining pediatric sepsis. Recognizing the limitations of existing sepsis definitions in accurately identifying children at risk for severe illness, the Phoenix sepsis score was developed through a rigorous process involving a multidisciplinary team of experts. By incorporating a comprehensive assessment of clinical, laboratory, and organ dysfunction parameters, these criteria seek to improve early identification, risk stratification, and subsequent management of pediatric sepsis (5).

The Phoenix sepsis score offers a significant advancement in the clinical management of pediatric sepsis. By providing a standardized, evidence-based approach to defining and identifying sepsis, clinicians can more accurately assess disease severity, initiate timely interventions, and improve patient outcomes. The criteria's emphasis on organ dysfunction and the inclusion of both clinical and laboratory parameters enhance early recognition, facilitating appropriate triage, resource allocation, and therapeutic decision-making. Ultimately, the Phoenix sepsis score have the potential to reduce morbidity and mortality associated with pediatric sepsis (5).

The neutrophil-to-lymphocyte ratio (NLR) is a readily available and inexpensive biomarker that reflects the complex interplay between inflammation and immune suppression during sepsis (6). Derived from routine complete blood count parameters, NLR quantifies the balance between neutrophils, primarily involved in the innate immune response, and lymphocytes, essential for adaptive immunity. Elevated NLR values are associated with increased severity and mortality in sepsis patients, suggesting its potential role as a prognostic indicator. However, the precise mechanisms underlying the correlation between NLR and sepsis outcome remain to be fully elucidated, necessitating further research to establish its clinical utility in different patient populations (7).

Current gaps in the literature reveal a lack of research on the newly established Phoenix sepsis score, particularly within pediatric populations in resource-limited countries. Introduced in 2024, the Phoenix sepsis score has not yet been extensively studied in these settings, where unique challenges may affect their applicability and effectiveness. This gap is especially concerning as resource-limited countries often face constraints that could influence the implementation and outcomes of such criteria. Additionally, there is a need for comparative studies that evaluate the Phoenix sepsis score alongside other established markers, such as the NLR, to better understand their utility in optimizing diagnostic and treatment strategies for pediatric patients in these contexts.

To address these gaps, our study is designed with two primary objectives: (1) to evaluate the implementation of the Phoenix sepsis score in the prognosis of pediatric sepsis, and (2) to compare the prognostic accuracy of the Phoenix sepsis score with that of the NLR.

Material and Methods

Study Design

This study is a retrospective cohort analysis based on data derived from our previous research (8) on pediatric patients diagnosed with sepsis according to the criteria established by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005.

Study Population

The study population includes all pediatric patients from our previous research (8) conducted between 2022 and 2023 who met the necessary criteria for classification under the Phoenix framework.

Data Collection

This retrospective study includes all patients from our previous research (8) who met the full criteria for Phoenix classification.

Patients initially diagnosed with sepsis based on the IPSCC criteria were reclassified utilizing the Phoenix sepsis score. This classification system categorizes patients into three groups: sepsis suspected (0-1 points), sepsis (2 or more points), and septic shock (sepsis with at least one point in the cardiovascular criteria).

Clinical and laboratory data, including Phoenix sepsis score and NLR, were utilized to evaluate patient outcomes, specifically focusing on survival or mortality.

Phoenix Sepsis Score

The criteria for respiratory dysfunction were mechanical ventilation, the Pao2:Fio2 and Spo2:Fio2 ratios; cardiovascular dysfunction was assessed using the mean arterial pressure, lactate level, and vasoactive medications; coagulation dysfunction was assessed using the platelet count, international normalized ratio, D-dimer, and fibrinogen; and neurologic dysfunction was assessed using the Glasgow Coma Scale (GCS) and pupillary reaction (5).

The revised definition for sepsis is a Phoenix Sepsis Score of 2 or higher in patients with probable infection, and a score of 1 or more in the cardiovascular domain for sepsis meeting the requirements for septic shock.

NLR Calculation

The Neutrophil-to-Lymphocyte Ratio (NLR) was calculated using the following formula (7):

NLR = Neutrophil count (cells/μL) / Lymphocyte count (cells/μL)

Neutrophil and lymphocyte counts were obtained from complete blood count (CBC) results of the study participants.

Statistical Analysis

To evaluate the prognostic accuracy of the Phoenix sepsis score, we employed several statistical methods using SPSS version 20.0. Receiver Operating Characteristic (ROC) curves, which graph the true positive rate against the false positive rate to assess diagnostic performance, were used to measure prognostic accuracy. To measure the Phoenix sepsis score's overall discriminatory power, the area under the ROC curve (AUC) was computed. Additionally, sensitivity and specificity were computed to assess the criteria's effectiveness in correctly identifying true positives and true negatives, respectively. A comparative analysis between the Phoenix sepsis score and the NLR was conducted using these metrics to determine their relative prognostic effectiveness. Statistical significance of the comparisons was assessed using appropriate tests in SPSS 20.0 to ensure robust and reliable results.

Results

Demographic and Clinical and laboratory Characteristics

A retrospective analysis was conducted on a cohort of 63 pediatric patients with a previous diagnosis of sepsis. Employing the Phoenix sepsis score, participants were subsequently categorized into two groups: sepsis suspected (n=16, 25.4%) and sepsis (n=47, 74.6%), with a subset of 39 cases fulfilling the criteria for septic shock.

As outlined in Table 1, demographic factors including age and sex did not exhibit significant disparities between the sepsis and sepsis suspected groups. Conversely, a statistically significant difference was observed in the prevalence of underlying diseases, with patients in the sepsis group demonstrating a higher incidence (p=0.036). Additionally, patients with sepsis were found to have significantly lower GCS (p=0.000) compared to those with suspected sepsis.

Laboratory findings revealed significant differences between the sepsis and sepsis-suspected groups. Patients with sepsis exhibited lower white blood cell and lymphocyte counts ($p<0.05$) and elevated lactate levels (p=0.013). Although a trend towards decreased neutrophil counts and increased neutrophil-to-lymphocyte ratios was observed in the sepsis group, these differences did not attain statistical significance. Platelet count, C-reactive protein, and creatinine levels did not vary significantly between the two groups. Coagulation profiles indicated higher international normalized ratios (INRs) and D-dimer levels in the sepsis group compared to the sepsis-suspected group (Table 1), while fibrinogen levels remained comparable.

Clinical outcomes demonstrated a marked disparity between the groups. Patients with sepsis had a significantly higher incidence of mechanical ventilation (66% vs. 6.2%) and mortality (61.7% vs. 6.2%, p=0.000).

Table 1. Demographic and clinical characteristics of the study population				
Parameter	**Total (n=63)**	**Sepsis suspected (n=16)**	**Sepsis (n=47)**	**p-value**
Age (month)	36 (10-96)	42 (18-108)	36 (8-96)	ns^{+}
Sex (M/F)	36/27	7/9	29/18	ns*
Underline disease (%)	47.6	25.0	55.3	0.036*
WBC (x10^3/mm^3)	13.41 (7.6-18.4)	14.25 (12.11-19.7)	12.1 (3.3-17.88)	0.042^{+}
Neutrophils (x10^3/mm^3)	9.77 (2.13-13.58)	9.99 (7.11-15.51)	8.14 (2.08-12.75)	ns^{+}
Lymphocytes (x10^3/mm^3)	1.98 (0.97-3.4)	3.19 (2.09-7.66)	1.73 (0.44-2.79)	0.001^{+}
Platelets (x10^3/mm^3)	169 (100-305)	236.5 (169-296)	148 (77-305)	ns^{+}
NLR	5.2 (2.59-7.31)	3.86 (0.92-7.05)	5.29 (2.9- 7.31)	ns^{+}
GCS	14 (12-15)	15 (15-15)	13 (10-15)	0.000^{+}
Mechanical ventilation (%)	50.8	6.2	66.0	0.000*
CRP	86.8 (34.08-84.1)	94.9 (70.62-127.2)	85.07 (21.1-161)	ns^{+}
Creatinine	47.34 (31-84.1)	42.64 (32-62.08)	49 (30.1-89.65)	ns^{+}
Lactate	3.0 (1.9-5.0)	2.05 (1.9-2.5)	3.32 (2-6.7)	0.013^{+}
INR > 1.3 (%)	47.6	18.8	57.4	0.007*
D-dimer > 2mg/L (%)	25.4	0.0	34.0	0.006$^{\#}$
Fibrinogen < 100mg/dL (%)	1.6	0.0	2.1	ns$^{\#}$
PHOENIX	4 (1-6)	0 (0-1)	5 (3-6)	0.000^{+}
Death (%)	52.4	6.2	61.7	0.000*

Data presented as median and quartile range (25% - 75%). ns: not-significant, *: Pearson chi-square test, $^{\#}$: Fisher's exact test, $^{+}$: Mann-Whitney test, WBC: White blood cells, NLR: Neutrophil to lymphocyte ratio, CRP: C reactive protein, GCS: Glasgow coma score, INR: International normalized ratio

The Phoenix sepsis score, a measure of sepsis severity, exhibited a wider range (3-6) in the sepsis group compared to the sepsis-suspected group (0-1).

Comaparative analysis of Phoenix and NLR

Figure 1 illustrates the correlation between NLR and Phoenix sepsis score. A moderate positive correlation was observed (Pearson r = 0.3514, p = 0.047), suggesting that higher NLR values were associated with increased Phoenix sepsis score. This finding indicates a potential association between NLR and the severity of sepsis.

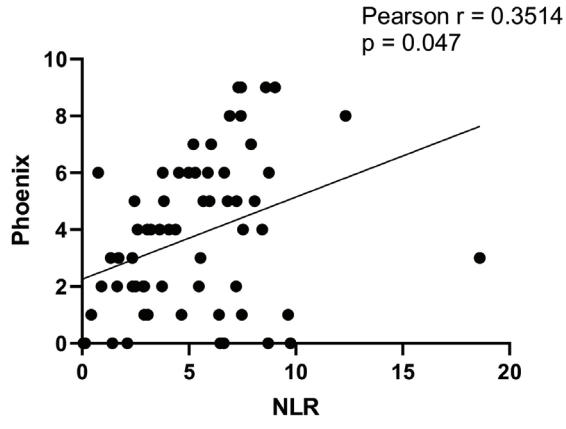

Figure 1. Correlation between Phoenix and NLR

Prognostic Performance of Phoenix Sepsis Score and NLR

Figure 2 presents the ROC curve analysis assessing the predictive performance of the Phoenix sepsis score and NLR for mortality. Both markers demonstrated acceptable discriminatory capacity in differentiating between deceased and surviving patients. Notably, the Phoenix sepsis score exhibited a marginally superior area AUC relative to NLR, implying a potentially

greater accuracy in predicting mortality within this cohort.

Table 2 presents the prognostic performance of the Phoenix sepsis score and NLR in predicting mortality. The Phoenix sepsis score demonstrated superior discriminatory capacity with an AUC of 0.886 compared to NLR with an AUC of 0.649. An optimal cut-off value of 5.5 for the Phoenix sepsis score yielded a sensitivity of 60% and a specificity of 100%, resulting in a perfect positive predictive value. In contrast, NLR, with a cut-off value of 3.7527, achieved a higher sensitivity of 80% but lower specificity of 54.5%, leading to a positive predictive value of 61.5%. Both markers exhibited comparable negative predictive values of approximately 75%.

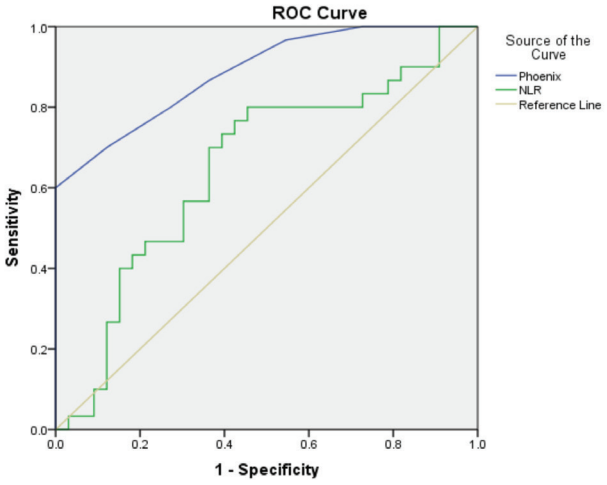

Figure 2. ROC curve analysis of the Phoenix sepsis score and NLR for predicting mortality

Subgroup Analyses

Table 3 presents the prognostic performance of the Phoenix sepsis score and NLR stratified by the presence of underlying diseases. In patients with underlying diseases, the Phoenix sepsis score demonstrated superior discriminatory capacity (AUC 0.885) compared to NLR (AUC 0.745). A cut-off value of 5.5 for Phoenix sepsis score exhibited perfect specificity and a sensitivity of 70%. NLR, with a cut-off of 6.5571, achieved moderate sensitivity and specificity.

Conversely, in patients without underlying diseases, while Phoenix sepsis score maintained a strong discriminatory ability (AUC 0.861), NLR exhibited a markedly decreased performance (AUC 0.587). A lower Phoenix sepsis score cut-off of 1.5 achieved perfect sensitivity but reduced specificity, whereas

Table 2. Prognostic performance of Phoenix sepsis score and NLR

	Phoenix	**NLR**
AUC	0.886	0.649
Cut off	5.5	3.7527
Sensitivity	60%	80%
Specificity	100%	54.5%
Positive predictive value	100%	61.5%
Negative predictive value	73.7%	75%

NLR: Neutrophil to lymphocyte ratio, AUC: Area under the curve

Table 3. Prognostic performance of Phoenix sepsis score and NLR in patient with and without underline diseases

	With underline disease		**Without underline disease**	
	Phoenix	**NLR**	**Phoenix**	**NLR**
AUC	0.885	0.745	0.861	0.587
Cut off	5.5	6.5571	1.5	4.0815
Sensitivity	70%	50%	100%	80%
Specificity	100%	100%	52.2%	56.5%
Positive predictive value	100%	100%	47.6%	44.4%
Negative predictive value	62.5%	50%	100%	86.7%

NLR: Neutrophil to Lymphocyte Ratio, AUC: Area Under the Curve

NLR's cut-off of 4.0815 yielded moderate sensitivity and specificity.

These findings suggest that the Phoenix sepsis score may be a more robust predictor of mortality across different patient subgroups, particularly in those with underlying diseases.

Discussion

This retrospective study aimed to evaluate the prognostic performance of the Phoenix sepsis score and NLR in a pediatric sepsis population. This study represents the pioneering application of the Phoenix sepsis score to pediatric sepsis patients at a tertiary hospital in Vietnam. Our findings indicate that patients with sepsis exhibited distinct clinical and laboratory characteristics compared to those with sepsis suspicion. Notably, underlying diseases and lower GCS were significantly associated with sepsis.

Laboratory abnormalities, including lymphopenia and lactic acidosis, were prominent in the sepsis group, aligning with previous studies (9,10). While the NLR did not reach statistical significance in this study, its correlation with the Phoenix sepsis score suggests a potential role in sepsis severity assessment. While several studies have demonstrated the potential of the NLR as a prognostic biomarker for pediatric sepsis severity, others have yielded inconclusive results. This variability may be attributed to age-related changes in lymphocyte and neutrophil counts, which can influence the NLR's predictive value (7,11). In our subgroup analysis, the NLR was found to be a prognostic indicator in pediatric patients with sepsis and underlying diseases.

The Phoenix sepsis score demonstrated superior prognostic performance in predicting mortality compared to NLR, as evidenced by the higher AUC and superior diagnostic metrics. Furthermore, the Phoenix sepsis score maintained its predictive ability across different patient subgroups, including those with and without underlying diseases, highlighting its potential as a robust prognostic tool in pediatric sepsis.

Study Limitations

The present study has several limitations that warrant consideration. Firstly, the retrospective design inherent to this research limits the ability to establish definitive causal relationships between variables. Secondly, the relatively small sample size might have influenced the statistical power to detect certain effects, potentially leading to type II errors.

Additionally, while the Phoenix sepsis score and NLR demonstrated significant prognostic value, the study did not delve into the impact of early intervention based on these markers on patient outcomes. Furthermore, the focus on pediatric patients limits the generalizability of the findings to other age groups.

Future Research Directions

Expanding on the results of this investigation, other directions for further study can be pursued. Larger sample numbers are necessary for prospective studies to verify the predictive validity of the NLR and Phoenix sepsis score, as well as to assess how they affect patient outcomes. Investigating the potential of combining the Phoenix sepsis score with other biomarkers or clinical variables to enhance predictive accuracy could be a promising direction.

Furthermore, exploring the role of the Phoenix sepsis score in guiding therapeutic decisions and its correlation with specific interventions would provide valuable insights into optimizing patient management. Expanding the study population to include different age groups would contribute to a broader understanding of the generalizability of the findings.

Finally, investigating the cost-effectiveness of implementing the Phoenix sepsis score in clinical practice would provide crucial information for resource allocation and healthcare policy decisions.

A more thorough understanding of the function of the Phoenix sepsis score and NLR in pediatric sepsis management can be attained by resolving these limitations and following the suggested research initiatives, which will ultimately improve patient outcomes.

Conclusion

This study underscores the importance of early and accurate sepsis identification in pediatric patients. The Phoenix sepsis score emerged as a valuable prognostic tool, exhibiting superior discriminatory capacity for mortality prediction compared to NLR. The consistent performance of the Phoenix sepsis score across different patient subgroups strengthens its potential clinical utility. Further prospective studies are warranted to validate these findings and explore the impact of early intervention based on the Phoenix sepsis score on

patient outcomes. By implementing the Phoenix sepsis score in clinical practice, healthcare providers may be able to identify high-risk patients earlier, facilitating timely and appropriate interventions, ultimately improving patient outcomes.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Ethics

Ethics Committee Approval: Animal and human rights statement.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Acknowledgments

We are grateful to Professor Tran Kiem Hao, Head of the Pediatric Center, Hue Central Hospital for his invaluable support throughout this project from its inception. We extend our sincere thanks to Dr. Nguyen Dac Luong, Dr. Pham Kieu Loc, and the other esteemed doctors in the Pediatric Intensive Care Unit (PICU) and the Pediatric Tropical Department for their dedicated care and follow-up of the patients involved in the study. Finally, we acknowledge all individuals who played a role in the implementation of the survey. Their contributions are deeply appreciated.

Footnote

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Schuller KA, Hsu BS, Thompson AB. The Rate of Sepsis in a National Pediatric Population, 2006 to 2012. Clin Pediatr. 2017;56:1001-7.
2. Massaud-Ribeiro L, Silami PHNC, Lima-Setta F, Prata-Barbosa A. Pediatric Sepsis Research: Where Are We and Where Are We Going? Front Pediatr. 2022;10.
3. Le S, Hoffman J, Barton C, Fitzgerald JC, Allen A, Pellegrini E, Calvert J, Das R. Pediatric Severe Sepsis Prediction Using Machine Learning. Front Pediatr. 2019;7:413.
4. Oak S, Stempowski M, Frank E. Implementation of the Early-Onset Sepsis Risk Calculator at a Community Level I Nursery. Clin Pediatr. 2021;61:259-65.
5. Sanchez-Pinto LN, Bennett TD, DeWitt PE, Russell S, Rebull MN, Martin B, et al. Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock. JAMA. 2024;331:675-86.
6. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy. 2021;122:474-88.
7. Wu H, Cao T, Ji T, Luo Y, Huang J, Ma K. Predictive value of the neutrophil-to-lymphocyte ratio in the prognosis and risk of death for adult sepsis patients: a meta-analysis. Front Immunol. 2024;15:1336456.
8. Nguyen-Huu CD, Nguyen V-T. Main clinical and laboratory features of children with sepsis: A single-center prospective study in central Vietnam. Journal of Medicinal and Pharmaceutical Chemistry Research. 2024;6:1708-15.
9. Scott HF, Donoghue AJ, Gaieski DF, Marchese RF, Mistry RD. The utility of early lactate testing in undifferentiated pediatric systemic inflammatory response syndrome. Acad Emerg Med. 2012;19:1276-80.
10. Podd BS, Banks RK, Reeder R, Telford R, Holubkov R, Carcillo J, et al. Early, Persistent Lymphopenia Is Associated With Prolonged Multiple Organ Failure and Mortality in Septic Children. Crit Care Med. 2023;51:1766-76.
11. Zhong X, Ma A, Zhang Z, Liu Y, Liang G. Neutrophil-to-lymphocyte ratio as a predictive marker for severe pediatric sepsis. Transl Pediatr. 2021;10:657-65.