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Predictive Potential of Interleukin-6, Pentraxin-3, and Procalcitonin in Identifying Sepsis and Septic Shock Among High-Risk Fever and Neutropenia Pediatric Cancer Patients Running Head: Biomarkers Predictive Value for Septic Shock

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Abstract

Background: This study aimed to assess the role of interleukin-6(IL-6), Pentraxin-3(PTX-3), and procalcitonin (PCT) in predicting pediatric cancer patients who may develop sepsis or septic shock.

Aim: The study aimed to determine which biomarker has the highest diagnostic value for sepsis/septic shock and to analyze the correlation of the biomarkers with the severity of organ dysfunction represented by the pediatric sequential organ failure assessment (PSOFA) scores.

Methods: Serum levels of interleukin-6, Pentraxin-3, and procalcitonin were measured in 86 pediatric cancer patients who presented with FN, sepsis, and septic shock. Blood samples for IL-6, PTX3, and PCT were obtained within 6 hours of presentation. Patients were categorized into septic and non-septic groups and PSOFA scores at D1, D3, and D28 were calculated. Optimal cut-off values for sepsis and prognostic PSOFA scores were determined.

Results: IL-6, as a single biomarker had the highest ability to predict sepsis at a cut-off value of 89.8 pg/mL with 100% sensitivity and 60.3% specificity (P value <0.001). Combining biomarkers increased the sensitivity and specificity for predicting septic shock and mortality at D28. There was a positive relationship between delta PSOFA and in-hospital mortality. The median levels of IL-6, PTX3, and procalcitonin in gram-negative MDR septic shock patients were significantly higher than the medians in septic shock patients without gram-negative MDR (P value was < 0.05).

Conclusion: Novel biomarkers can help predict sepsis and guide protocols for managing high-risk fever and neutropenia.

Keywords: Predictive; Interleukin-6; Pentraxin-3; Procalcitonin; Septic Shock; Fever and Neutropenia; Cancer

Abbreviations: IL-6: Interleukin-6; PTX-3: Pentraxin-3; PCT: Procalcitonin; PSOFA: Pediatric Sequential Organ Failure Assessment; CNS: Central Nervous System; CVS: Cardiovascular; AEs: Adverse Events; CTC: Common Toxicity Criteria; ALL: Acute Lymphoblastic Leukemia; GIT: Gastrointestinal Infections; MDR: Multi-Drug Resistant; ICU: Intensive Care Unit; IRB: Institutional Review Board

Background

There is limited data on the incidence of sepsis and septic shock in neutropenic pediatric cancer patients. Studies suggest that there are common causes of critical illness in children with cancer, with mortality rates between 41% and 64% [1]. Initial manifestations of sepsis in children include fever, tachycardia, tachypnea, hypotension, and hypothermia. They are highly variable, nonspecific, and are often unnoticed. The most striking feature of pediatric sepsis is that children can sustain tachycardia for long periods, and hypotension may not occur until advanced sepsis compared to adults with sepsis [2,3]. Early administration of empiric intravenous broad-spectrum antibiotics successfully reduced the mortality rate associated with infection in pediatric patients to <1 % [4]. Sepsis is a complex condition involving various immune responses, making it challenging to improve outcomes with drugs targeting single events [5].

This emphasizes the importance of early and precise sepsis detection. Effective biomarkers are crucial for the timely identification and management of sepsis, but no single laboratory test can accurately diagnose or assess its severity [6,7]. IL-6 production is stimulated by various factors, including IL-1, interferons, TNF, viruses, and pathogen-associated molecular patterns. High IL-6 level during inflammation is a poor prognostic factor [6,8]. The determination of IL-6 on the first day of FN was associated with high sensitivity (90%) and specificity (85%) in identifying patients who will develop sepsis or a long-lasting fever episode. Furthermore, IL-6 measurements had a positive predictive value of 94% with the cutoff value accepted at 42 pg/ml [9,10].

Many researchers identified that the extremely high level of IL6 in children with FN while on chemotherapy is strongly related to gram-negative bacteremia [9,11]. Other studies also provided evidence for the utility of IL-6 in the risk stratification of febrile cancer patients [9,12-14]. PTX 3 plays an important role in recognizing pathogens and damaged cells, activating the classical complement pathway, and stimulating phagocytosis [15-17]. Huttunen et al found that PTX 3 concentration exceeding 15 ng/ml is an independent risk factor in patients with bacteremia (sensitivity 72%, specificity 81%) [18]. Also, many researches demonstrated that high concentrations of PTX 3 lasting for the first five days of infection correlated inevitably with high mortality risk [17-21].

In a systematic review and meta-analysis, PCT was found to be more specific for differentiating bacterial infections among hospitalized patients [22]. Another meta-analysis showed that PCT is a useful marker for early diagnosis of sepsis in critically ill patients with sensitivity and specificity of 77% and 79%, respectively [23-25]. It was shown that sepsis caused by Gram-negative bacteria was associated with a significantly higher level of PCT than sepsis caused by Gram-positive bacteria [26-29]. PCT has drawn attention because it can be used for guidance of antibiotic stewardship to reduce inappropriate use of antibiotics [30]. Combining multiple biomarkers has been shown to compensate for the low prediction efficiency of a single marker [31].

Materials and Methods

The study was an observational prospective cross-sectional study conducted from June 2022 to December 2022 at the National Cancer Institute Cairo-Egypt. A total of 92 episodes of fever and neutropenia were analyzed in 86 pediatric cancer patients who presented to the ER with fever and neutropenia, sepsis, and septic shock after receiving chemotherapy. Patients who refused to be included in the study or to give blood samples within 24 hours from the initial presentation to the ER were excluded. The study followed the adapted pediatric version of Sequential Organ Failure Assessment (pSOFA scores) that was validated by Matics et al to facilitate the evaluation of the international sepsis-3 definitions in children [31]. The pSOFA score is a prompt bedside method that can identify patients with suspected infection who are at greater risk of a poor outcome outside the ICU. Each organ system has a score ranging from 0 to 4, the sum of the 6 sub scores for 6 organ systems (range, 0-24 points; higher scores indicate a worse outcome).

The studied organ systems in pSOFA scores were the central nervous system (CNS), cardiovascular (CVS), respiratory, hepatic, and renal systems. The coagulation system was excluded from our study as the assessment of the coagulation system in the score includes platelet count. All our patients were thrombocytopenic either disease or chemotherapy-related, so this will have a negative impact on the scoring system. The sum of the 5 sub scores for 5 organ systems ranges from 0-20 points. The patients were divided into septic and non-septic groups based on defined criteria. The pediatric SOFA score was calculated for each group at D1, D3, and D28. Delta pSOFA was calculated by subtracting pSOFA D3 from pSOFA D1. The study followed the standardized definitions for adverse events (AEs), known as the Common Terminology Criteria for Adverse Events (CTCAE, also called "common toxicity criteria" [CTC]), to describe the severity of organ toxicity for patients receiving cancer therapy [32].

Sampling for biomarkers and clinical data collection

All data were collected through medical records and conducting laboratory tests. Routine laboratory investigations were done, and blood gas analysis was performed as needed. Additional tests, such as CRP and blood cultures were carried out. Imaging tests were also done if fever persisted or specific infections were suspected. Bloodstream infection was confirmed through microbiological culture.

Blood sampling for biomarkers

All blood samples for initial IL-6, PTX3, and PCT measurements were obtained within 6 hours of initial presentation to the ER (or during admission into the department) with FN, sepsis, or septic shock. The samples were collected from all subjects as follows: venous blood samples were withdrawn by venipuncture using dry sterile vacutainers. All blood samples for IL-6 and PTX-3 were divided into five milliliters and distributed into 2 sterile vacutainers with gel for the ELISA technique. Procalcitonin was measured on cobas e411 (Electrochem luminescence immunoassay).

Results

Eighty-six patients with 92 episodes of fever and neutropenia were included. Patients were divided by age into four groups: <= 2 years, 2-6 years, 6-12 years, and 12-18 years. The majority of patients (38%) belonged to the group of >6-12 years old. Sixty-two patients had hematological malignancies, while thirty patients had solid malignancies. The most common hematological malignancy was acute lymphoblastic leukemia (ALL) (33.7%).

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The majority of patients (86%) were denovo cases of malignancy. High-risk FN was observed in 90% of patients. Most patients had severe infections (88%) and exhibited apparent clinical foci (78.3%). Gastrointestinal infections (GIT) were the most common type of infections (31.5%), followed by respiratory tract infections. Necrotizing enterocolitis was documented in 23 (25%)episodes. Positive blood cultures were documented in 47.8% of the episodes, while forty-eight (52.2%) episodes did not yield positive blood culture. Gram-negative E-coli was the most commonly documented organism (21.7%). Thirty (32.6%) episodes had documented a multi-drug resistant (MDR) spectrum and susceptibility. Sepsis was documented in fifty-five episodes (61.7%), however in 24 (26.1%) episodes, patients presented with septic shock, and finally in 7 (7.6%) episodes, sepsis was not documented.

Finally, Sixty-five (65/86) (75.5%) patients improved and were discharged while twenty-one (21/86) (24.4%) patients died. Severe infection was reported in 96.7% and 70.8% of episodes with sepsis and septic shock, respectively. There was a statistically significant correlation between the occurrence of sepsis or septic shock and the degree of infection (P value <0.001). There was a statistically significant correlation between the occurrence of sepsis or septic shock and the gram-negative infection (p < 0.001). The majority (97.2%) of septic shock patients showed an MDR gram-negative spectrum and sensitivity. Median and mean levels of IL6, pentraxin 3, and procalcitonin were significantly higher in the septic shock group than in the non-septic group (Table 1). The medians of IL-6, PTX3, and procalcitonin in gram-negative MDR septic shock patients were significantly higher than the medians of the same biomarkers in septic shock patients without gram-negative MDR (Table 2).

Table 1: Median levels of sepsis biomarkers between septic shock and non- septic shock groups.

	Septic shock					No septic shock					P value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
IL6 D1	366.63	163.03	375.00	96.00	695.00	120.59	170.17	26.20	0.00	729.00	<0.001
PTX3 D1	47.09	14.58	48.00	22.70	67.70	28.71	19.58	24.90	0.00	65.80	<0.001
PROCAL D1	8.24	7.53	7.25	1.40	32.50	3.25	4.34	1.64	0.00	18.60	<0.001

*= p-value <0.05.

Table 2: Correlation between septic shock patients with gram –ve MDR and IL-6.

	septic shock with Gram negative MDR										P value
	yes					no					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
IL6 D1	409.90	151.13	412.70	96.00	695.00	126.18	166.69	33.60	0.00	729.00	<0.001
CRP D1	218.63	136.69	213.00	44.00	549.00	115.38	89.19	92.00	0.60	493.00	0.001
PTX3 D1	48.39	14.72	48.70	22.70	67.70	29.63	19.50	27.60	0.00	65.80	<0.001
PROCAL D1	9.35	8.02	7.97	1.50	32.50	3.30	4.25	1.70	0.00	18.60	<0.001

The AUCs for the prediction of sepsis were 0.86 for IL6, 0.775 for PTX3, and 0.792 for procalcitonin. IL-6 as a single biomarker showed the highest ability for prediction of sepsis with a cut-off value of 89.8 pg/mL with 100% sensitivity and 60.3% specificity (P value <0.001) (Figure 1). Delta pSOFA showed the highest ability for prediction of sepsis when using a cut-off value increasing by more than one point with 95.8 % sensitivity and 94.1% specificity (P value <0.001) (Figure 1). IL 6 was significantly and positively correlated with pSOFA D1, pSOFA D3, and delta pSOFA with correlation coefficients 0.635,0.693 and 0.345, respectively (P value was < 0.001) (Table 3).

Independent Factors for prediction of septic shock

Univariate logistic analysis of PCT, IL-6, PTX-3, CRP, and pSOFA D1 score was performed within the sepsis and non-sepsis groups. Binary logistic regression to predict septic shock in patients with sepsis showed that among PCT (B = -0.036, odds ratio (OR) = 0.964), IL-6 (B =0.05, OR= 1.005, P value <0.05), CRP (B =0.002, OR = 1.002, PTX-3 (B = 0.020, OR = 1.020), and pSOFA D1 score (B= 0.997, OR = 0.2710, P = 0.001), IL6 and pSOFA D1 score were strong and independent predictors of septic shock in patients with sepsis (Table 4). The Hosmer–Lemeshow test for goodness of fit was applied to the multivariate logistic regression related to septic shock and pSOFA D1 and indicated good calibration with a P value estimated as 0.646 for pSOFA D1. Binary logistic regression was conducted to examine whether PCT, IL-6, PTX-3, and pSOFA D1 scores were significantly associated with the odds of non-survival. The findings suggested that IL-6 and pSOFA D1 score were strongly correlated to mortality at day 28 (P value <0.05) .

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Table 3: Correlation of IL6, PTX3, procalcitonin, CRP and pSOFA scores in prediction of sepsis and septic shock patients.

		IL6 D1	PTX3 D1	PROCAL D1
Psofa D1	Correlation Coefficient	0.635	0.473	0.472
	P value	< 0.001	< 0.001	< 0.001
	N	92	92	92
Psofa D3	Correlation Coefficient	0.693	0.461	0.504
	P value	< 0.001	< 0.001	< 0.001
	N	92	92	92
Delta pSOFA	Correlation Coefficient	0.345	0.228	0.287
	P value	0.001	0.029	0.005
	N	92	92	92
	P value	< 0.001	< 0.001	< 0.001
	N	92	92	92

Table 4: Predictive value of IL6, PTX3, procalcitonin and CRP for sepsis.

	Area Under the Curve	P value	95% Confidence Interval				
			Lower Bound	Upper Bound	Cut off	Sensitivity %	Specificity %
CRP D1	0.729	< 0.001	0.609	0.849	169	62.5	80.9
IL6 D1	0.861	< 0.001	0.786	0.935	89.85	100	60.3
PTX3 D1	0.775	< 0.001	0.681	0.87	30.25	91.7	57.4
PROCAL D1	0.792	< 0.001	0.699	0.884	2.175	87.5	64.7

*= p-value <0.05.

Combinations of PCT, IL-6, and PTX-3 for prediction of septic shock and D28 mortality

Combinations of these biomarkers resulted in the following: PCT + IL-6 (AUC = 0.866); PCT + PTX-3(AUC = 0.824); IL-6 + PTX-3 (AUC = 0.888) and PCT + IL-6 + PTX-3 (AUC = 0.895). The sensitivity and specificity of prediction of the septic shock of the combination between IL-6 and PTX-3 were 100% and 77.9%, respectively. There were no significant differences in the sensitivity and specificity of the former combination and other markers combinations (either 2 or 3 combinations). However, there was a significant increase in the sensitivity and specificity of the prediction of septic shock with any combinations of biomarkers than any single marker alone. The same previous results were observed in the prediction of D28 mortality.

Discussion

This study aimed to assess the value of IL-6, PTX-3, and PCT levels in predicting septic complications in pediatric cancer patients with high-risk FN after chemotherapy. The study found that patients with septic shock had higher levels of IL6, PTX3, and procalcitonin compared to those without septic shock. Additionally, the levels of pSOFA D1, D3, and delta pSOFA were significantly higher in the septic shock group. These findings are similar to a previous study conducted by Zhang Y. et al who compared the diagnostic and predictive value of different biomarkers in sepsis patients in an intensive care unit (ICU). He concluded that although the SOFA score is considered the gold standard, analyzing multiple biomarkers can enhance the diagnostic and prognostic capabilities of sepsis in ICU patients [33].

In our study, IL-6 as a single biomarker, showed the highest ability for prediction of sepsis and septic shock when using a cut-off value of 89.8 pg/Ml, the sensitivity was 100% but the specificity was 60.3%. There was a significant correlation between septic shock patients with gram-negative MDR and levels of IL-6, PTX3, and procalcitonin. The medians of IL-6, PTX3, and procalcitonin in gram-negative MDR septic shock patients were significantly higher than the medians of the same biomarkers in septic shock patients without gram-negative MDR. These findings were consistent with previous research conducted by Xu et al. He aimed to compare the efficacy of serum IL-6, procalcitonin, and C-reactive protein in identifying pediatric cancer patients at high risk for infection. The results showed that IL-6 had a higher AUC of 0.89 compared to CRP and procalcitonin. This indicated that IL-6 is a more reliable marker for identifying high-risk patients, distinguishing between Gram-positive and negative bacteremia, assessing the severity of infection, and predicting the outcome for those patients [34]. In another research conducted by Song et al in Korea, he found that septic shock could be distinguished by serum IL-6 levels (AUC, 0.71 to 0.89, 76.1% sensitivity, 78.4% specificity) [35].

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In our study, PTX-3 showed a moderate predictive ability for sepsis in comparison to IL-6, when using a cut-off value of 30.25 ng/mL, the sensitivity was 91.7% but the specificity was 57.4% (P value <0.001). These findings were similar to another study conducted by Hamed et al who aimed to evaluate the diagnostic value of PTX-3 in patients with sepsis and septic shock. The research demonstrated that PTX-3 can serve as a useful diagnostic tool in differentiating between sepsis and septic shock, and its levels in the plasma can be indicative of the severity of the condition [36]. Several prior studies provided significant and beneficial AUCs for PTX-3 for distinguishing sepsis or septic shock from healthy controls [37-39].

Our study found that the combination of IL-6 and PTX-3 had a sensitivity of 100% in predicting septic shock and mortality at D28. This combination also had the highest specificity (77.9%) in predicting septic shock. There were no significant differences in the sensitivity and specificity between the three combined biomarkers (IL-6, PTX-3, and procalcitonin) and any combination of two biomarkers. However, there was a significant increase in sensitivity and specificity for predicting septic shock and mortality at D28 when using any combination of sepsis biomarkers compared to using a single marker [40].

Conclusion

IL-6 as a single biomarker showed the highest ability for prediction of sepsis and septic shock. The combination of IL-6+PTX-3 showed the highest ability for predicting septic shock and D28 mortality.IL 6 was significantly and positively correlated with pSOFA D1, pSOFA D3, and delta pSOFA. This study provides valuable information about the inflammatory response in pediatric cancer patients with high-risk fever and neutropenia following chemotherapy which can aid clinicians in identifying children who are at a higher risk of developing sepsis or septic shock, allowing for earlier intervention and appropriate management. Finally, this study provides a foundation for further research and development in the field of sepsis biomarkers. By identifying IL-6, PTX3, and procalcitonin as potential biomarkers, this study opens avenues for future investigations exploring their mechanisms of action, refining cutoff values, and assessing their performance in different populations.

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