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Assessment of procalcitonin as a diagnostic marker of infection in pediatrics with cancer complicated by fever and neutropenia

Soheila Zareifar MD[1], Anahita Sanaei Dashti MD[2], Tayebe Masoomzade MSc[1], Mojtaba Anvarinejad MSc[2], Omid Reza Zekavat MD[1], Mohammad Reza Bordbar MD[1], Nader Cohan PhD[1], Sezaneh Haghpanah MD MPH[1,*]

1. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
2. Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
*Corresponding author: Dr Sezaneh Haghpanah, Associate Professor of Community Medicine, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. Email: haghpanah@sums.ac.ir. Orchid ID: 0000-0002-8666-2106.

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Abstract

Background: Febrile neutropenia is still one of the most important complications of treatment in cancer patients. These patients become prone to infection and consequently higher mortality and morbidity. This study aimed to determine the accuracy of serum procalcitonin (PCT) level in the detection of infection in pediatric cancer patients complicated with febrile neutropenia.

Materials and Methods: In this cross-sectional study, all pediatric patients affected by cancer and febrile neutropenia following chemotherapy (n=107) were investigated from August 2014 to August 2015. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum levels of PCT, as well as blood and urine culture, were evaluated in all patients.

Results: The mean age of the patients was 78 ± 55 months (3 - 214 months), and in terms of gender, 53 patients (49.5%) were male. Overall, 25 patients (23.4%) and 13 patients (12%) showed positive blood and urine culture, respectively. The area under the curve (AUC) receiver operating characteristic (ROC) curve was illustrated to determine how much PCT can couldpredict infection.(AUC =0.74, 95% CI: 0.61-0.87, P<0.001). Considering the cut-off of serum PCT levels as 0.70ng/mL, sensitivity, specificity, and positive and negative predictive valueof PCT were 0.76, 0.744, 0.475, and 0.91, respectively. In addition, PCT showed significant correlations with CRP (rs=0.415, P<0.001) and ESR (rs =0.262, P=0.009).

Conclusion: According to the findings of this study, serum PCT levels can be used as a diagnostic test with acceptable sensitivity and specificity and high negative predictive value, but the low positive predictive value in the evaluation of infections in patients affected by cancer and complicated with fever and neutropenia.

Key Words: Fever, Malignancy, Neutropenia, Pediatric, Procalcitonin

Introduction

Febrile neutropenia is still one of the most important clinical problems in patients with cancer (1). These patients become prone to infection due to neutropenia. Consequently, infectious complications can be a leading cause of morbidity and mortality in patients with cancer (2). Neutropenia is the condition of decreased neutrophils counts to less than 500 cells/µl. It is a signal of severe immunosuppression (3-5). Although neutropenia may have many other causes, such as the malignancy itself or the chemotherapy regimen, the most important impression is infection. Infection is among the most common causes of death in malignancies (6, 7). Therefore, early diagnosis and prompt management are not only mandatory but lifesaving (8, 9). The most specific diagnostic method for the presence of an infection is culture, but its result will be prepared with a delay of 24-48 hours which postpones the start of antibiotic therapy (10, 11).

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been used traditionally as diagnostic laboratory

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markers of infection. Nevertheless, the procalcitonin (PCT) level has been reported as a more accurate biomarker in early diagnosis of infection with higher sensitivity and specificity compared to ESR and CRP (12-14).

Procalcitonin (PCT), a precursor of calcitonin, is produced by thyroid gland C-cells in undetectable amounts (<0.1 ng/mL) in normal body conditions (15-18). After inflammatory insults and cytokines release, including interleukin 6, PCT is synthesized by various cell types. The levels rise very rapidly after a few hours and reach a peak of about 12 hours (19-21). Due to its good specificity, it is regarded as a useful marker to predict bacterial sepsis in immunocompromised patients. In immunocompromised Intensive Care Unit (ICU) patients with bacterial sepsis, PCT was determined to predict bacterial infection with the area under the curve (AUC) = 0.85 and at 0.5 ng/mL serum level, with100% sensitivity and 63% specificity(22). Several studies have proved the efficacy of PCT as a marker of critical illness (23-26). The expression of serum PCT varies with a difference in genetic components of the population (27).

The aim of this study was to determine the accuracy of serum PCT level in the diagnosis of infection and its correlation with CRP and ESR in a population of Iranian pediatric with cancer complicated by fever and neutropenia.

Materials and Methods

This cross-sectional study was conducted from August 2014 to August 2015. All pediatric patients (under 18 years old) diagnosed with malignancy and neutropenic fever, hospitalized in oncology and hematology wards of "Amir Oncology Hospital ", Shiraz, Iran, were studied. Amir Oncology Hospital is a tertiary academic center affiliated to Shiraz University of medical sciences, Shiraz, Iran. Fever was defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 h, and neutropenia was defined as is an absolute neutrophil count $<0.5 \times 10^9$/l or expected to fall below 0.5×10^9/l.

Demographic data consisting of gender, age, type of cancer, and laboratory findings of the patients were collected from their medical records through data gathering form and filled by the professional nurses.

All patients with localized infections, such as various wounds and abscess, and -neutropenic patients, and pediatrics with bone marrow transplantation were excluded from the study.

After enrolling in the study, the blood sample was collected and sent to the laboratory to measure the ESR, CRP, and PCTserum levels. Simultaneously, blood cultures in BACTEC bottles and urine culture were obtained from patients and sent to the laboratory of Amir Oncology Hospital. Positive urine culture was defined by a bacterial growth of equal to or more than 10^5 colonies forming unit per milliliter. The isolates were identified by standard methods. The design and protocol of the study were also approved by the ethics committee of Shiraz University of Medical Sciences (Ethics Committee Code=86-1030).

Laboratory examinations

Blood culture samples (aerobic) were collected by sterile venipuncture and processed using the BACTEC fluorescent series 9240 automated blood culture system (Becton Dickinson, USA). Serum PCT levels were measured by the VIDAS B.R.A.H.M.S PCT assay (bioMérieux, France) based on the Enzyme-Linked Fluorescent Assay (ELFA). Serum CRP concentrations were quantitatively determined by a commercially available immunoturbidimetric kit (Biorexfars, Iran). Whole blood ESR levels were evaluated by the reference Westergren method. Citrated blood samples were mixed well and placed into Westergren tube according to the ICSH

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recommendations (28). The results were obtained after one hour as mm/hr.

Inflammatory marker dosages were obtained within a 24h window when patients were diagnosed with sepsis.

Statistical analysis

Data analysis was performed using the statistical package for the social sciences (SPSS) software, version23.0 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to check the normal distribution of data. Comparison of quantitative variables between the two groups was done by the Mann-Whitney test. $P < 0.05$ was considered statistically significant. The diagnostic accuracy of each inflammatory marker was specified using the following parameters: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).The Cutcut-off point based on the receiver operating characteristics (ROC) curve was set to detect positive culture. The area under the curve was used to assess diagnostic accuracy. The correlation between PCT level and CRP and ESR was evaluated by the Spearman correlation test.

Results

Over the study period, 107 patients with cancer and febrile neutropenia were investigated. Overall, 53(49.5%) of patients were male and 54(50.5%) were female. The mean age of the patients was 78 ± 55 months (From 3 to 214 months). Malignancies were divided into4 groups; acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin's and non-Hodgkin's lymphomas, and solid tumors including neuroblastoma, histiocytosis, rhabdomyosarcoma, and miscellaneous (Table I).

Twenty-five individuals (23.4%) of the patients had positive blood cultures. Among them, 48% (12) were caused by gram-negative bacteria and others by gram-positive bacteria. Totally, 13 patients (12%) had a positive urine culture. The most frequent causative bacterial species isolated from blood and urine were S.epidermidis and E.coli, respectively. The diagnostic accuracy of PCT was determined by the ROC curve illustration for urine and blood culture separately. The results for urine culture was not statistically significant (AUC=0.616, 95% CI: 0.45-.78, P= 0.176). The results of the diagnostic accuracy of PCT for blood culture were presented in figure 1(AUC =0.74, 95% CI: 0.61-0.87, P<0.001). Considering the cut-off point of serum PCT levels as 0.70ng/mL, sensitivity, specificity, and positive and negative predictive value of PCT for diagnosis of infection in pediatric with malignancy and the fever were 0.76, 0.744, 0.475and 0.91, respectively.

PCT serum levels and CRP were significantly higher in patients with positive blood culture compared to negative blood cultures (P<0.001 and P=0.018 respectively); however, ESR showed no significant difference between the two groups (P>0.05) (Table II). In addition, PCT serum levels showed significant moderate positive correlation with CRP (rs=0.415, P<0.001) and significant mild positive correlation with ESR (rs=0.262, P=0.009).

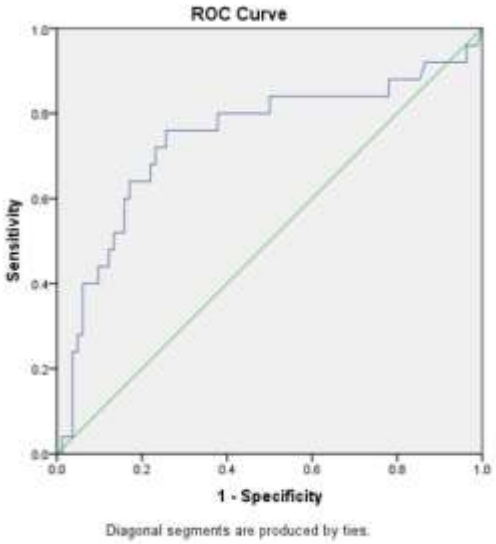

Figure 1. Receiver operating characteristic curve to illustrate the diagnostic value of procalcitonin to predict infection considering blood culture as a gold standard diagnostic test

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Table I: The demographic and characterization of the patients

Parameter	Values	Number and percent (%)
Age(Year)	≤1	7(6.5)
	1-5	42(39.3)
	≥5	58(54.2)
Gender	Male	53(49.5)
	Female	54(50.5)
Cancer Type	ALL	43(40.2)
	AML	9(8.4)
	Hodgkin´s and non-Hodgkin´s lymphomas	15(14)
	Solid Tumor	40(37.4)
WBC per microliter	≤500	9(8.4)
	500-1000	24(22.4)
	≥1000	74(69.2)

Table II: Comparison of biomarkers levels in patients with and without positive blood cultures

Biomarkers	Positive blood cultures Median (range)	Negative blood cultures Median (range)	P value
Procalcitonin ng/ml	2.17(0.09-35.9)	0.32 (0.06-40)	<0.001
CRP mg/l	96 (0-192)	24 (0-192)	0.018
ESR mm/hr	66 (11-125)	44 (3-131)	0.129

Discussion

In this study, the accuracy of serum PCT level in the diagnosis of infection was determined in a group of Iranian pediatrics with cancer complicated by febrile neutropenia. Moreover, the correlation of serum PCT level with ESR and CRP were assessed.

In patients with cancer with or without chemotherapy, neutropenia and fever may have different etiologies. One of the lethal causes of neutropenia and fever is an infection that must be promptly diagnosed and managed (8). In our study, 25 (23.4%) and 13 (12%) patients with fever and neutropenia had positive blood and urine cultures, respectively. Due to the lack of acceptable sensitivity of cultures especially in developing countries, efforts are done to find and evaluate much simpler and more sensitive inflammatory markers in febrile neutropenia.

The most commonly used traditional inflammatory marker, ESR, measures the rate of red blood cell precipitation. In our study, ESR showed no significant difference between the two groups of patients with and without infection. Because it is inexpensive and the result gets ready in about 2 hours, it is widely used worldwide. ESR has some disadvantages like being nonspecific. It rises in noninfectious conditions like chronic renal, burns, malignancies, inflammatory conditions like systemic lupus erythematosus, and vasculitis (9,

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10). It also varies with gender, age, temperature, immunoglobulin levels, hyperlipidemia, hypoalbuminemia, severe anemia, and the number and morphology of red blood cells present (3). ESR is naturally low in neonates, decreased fibrinogen state, sickle cell disease, polycythemia, or congestive heart failure (12). It is probably only superior to white blood cells count in identifying inflammatory conditions (10).

CRP is a very sensitive marker of inflammation and produced in the liver after the secretion of cytokine release in insults like infection, inflammation, and chemical or physical reactions (18-20). CRP upsurges rapidly within 6 hours and peaks at about 48 hours with a half-life of about 19 hours. Its level decreases abruptly if the initial insult stops (18). Viral infections cause mild elevation of CRP, making it a rather useful tool to differentiate bacterial from viral infections. Its negative predictive value is probably the most useful aspect of CRP and it would be more if be checked and assessed serially (21, 29). In our study, CRP was significantly higher in patients with positive blood culture compared to negative blood cultures.

Diagnostic accuracy of PCT in our study (0.74, 95% CI: 0.61-0.87) was similar to Lin et al.'s study (30). Considering the cut-off point of serum PCT levels as 0.70 ng/mL, sensitivity, specificity, and positive and negative predictive value of PCT for diagnosis of infection in pediatric with malignancy and the fever were 0.76, 0.744, 0.475, and 0.91, respectively. A systematic review and meta-analysis that assessed the value of some biomarkers in predicting adverse outcome in febrile neutropenic episodes in pediatric and young people with cancer showed that in documented infection, CRP> 50 mg/l had the sensitivity of 0.65 and specificity of 0.73 (7 studies, 731 episodes) and PCT> 0.2 ng/ml had the sensitivity of 0.96 and the specificity of 0.85 PCT (3 studies, 216 episodes)(31). Cut off points of our study as well as sensitivity and specificity differed from this review.

Lin et al., evaluated the role of procalcitonin in the diagnosis of severe infection in pediatric patients with fever and neutropenia in a systematic review and meta-analysis, PCT and CRP had similar diagnostic accuracy equivalent and area under the receiver operating characteristic curve: 0.75 versus 0.74, respectively. CRP test was more sensitive than PCT; the pooled sensitivity of PCT and CRP was 0.59 and 0.75, respectively. PCT was more specific; the pooled specificity was 0.76 for PCT and 0.62 for CRP. PCT had a superior positive likelihood ratio and a better test for a rule-in test (30). Likewise, in our study, PCT showed a significant moderate positive correlation with CRP.

In a large study, PRORATA trial, 621 ICU patients were investigated. Antibiotic therapy encouraged when PCT levels were $\geq$ 0.5 ng/mL and strongly encouraged in the case of $\geq$ 1 ng/mL. This led to more days without antibiotics in the PCT-guided patients than those in the control group (14.3 ± 9.1 vs. 11.6 ± 8.2 days; absolute difference 2.7 days, 95% CI 1.4–4.1; $P < 0.0001$) (32).Hemming reported that PCT >2 ng/mL in pediatrics with cancer presenting with febrile neutropenia was strongly associated with an increased risk of severe infection (33).

Conclusion

Based on the results, serum PCT levels can be used as a diagnostic test with acceptable sensitivity and specificity and good negative predictive value, but the low positive predictive value in the evaluation of infections in patients affected by cancer who complicated with fever and neutropenia.

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related to the thesis by Dr. Tayebeh Masoomzade for receiving her medical degree by the Ethics Committee Code of 86-1030.

Conflict of interest

The authors declare no conflict of interest.

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