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Diagnostic Role of sCD14-Subtype as a Sepsis Biomarker in Febrile Neutropenic Pediatric Oncology Patients

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ABSTRACT

Introduction and Objective: Febrile neutropenia (FN) is one of the most common complications of cancer chemotherapy and requires urgent treatment. Upon diagnosis of childhood FN, culture samples should be obtained and a broad spectrum antibiotherapy should be administered immediately. However, bacterial infections are not the only cause of fever in neutropenic pediatric patients; chemotherapeutics, the disease itself, as well as viral and fungal agents can also be the cause of fever. Various biomarkers have been studied to differentiate the cause of fever to date. Infections are mostly lethal in neutropenic patients, early stage differential biomarkers are, therefore, of utmost importance. It is the aim of this study to assess the potential of presepsin as an additional diagnostic tool for the detection of bacteremia/sepsis in childhood Febrile Neutropenia (FN) patients.

Methods: Twenty-four pediatric patients, with a total 29 febrile neutropenic episodes were enrolled in this study. One patient with 3 FN episodes, three patients with 2 FN episodes were admitted to our clinic during the study. Patients were classified into bacteremia/sepsis and fever without origin groups. Serum samples were collected after confirmation of FN and analyzed for presepsin, c-reactive protein (CRP) and procalcitonin (PCT) according to instructions of manufacturers.

Results: Biomarkers failed to display a discriminative value between bacteremia/sepsis and fever without origin groups, whereas presepsin was found to be an indicator of the presence of bacterial growth in hemoculture and was shown to have a potential diagnostic value.

Conclusion: Presepsin might be used as an additional diagnostic tool for the detection of bacteremia/sepsis in childhood FN patients.

Keywords: Biomarker, Febrile Neutropenia, Presepsin, sCD14-subtype

ATEŞLİ NÖTROPENİK PEDİATRİK ONKOLOJİ HASTALARINDA SCD14 ALT TİPİNİN SEPSİS BİYOBELİRTECİ OLARAK TANIDAKİ ROLÜ

ÖZET

Giriş ve Amaç: Bu çalışmada, Çocukluk çağında gelişen Febril Nötropeni (FN) hastalarında presepsin'in bakteriyemi/sepsisin saptanmasında ek bir tanı aracı olarak potansiyelini değerlendirmek amaçlanmıştır. Febril nötropeni kanser kemoterapisinin en yaygın komplikasyonlarından biridir ve acilen bir tedavi gerektirir. FN' de kültür örnekleri alınmalı ve hızlı bir şekilde geniş spektrumlu antibiyoterapi uygulanmalıdır. Nötropenik hastalarda ateşin tek nedeni bakteriyel enfeksiyon değildir. Kemoterapötikler, hastalığın kendisi, viral ve fungal ajanlar ateşin diğer sebepleri olabilir. Ateş nedenini ayırt etmek için çeşitli biyolojik belirteçler araştırılmaktadır. Enfeksiyonlar nötropenik hastalarda çoğunlukla öldürücüdür, bu nedenle erken evredeki farklı biyobelirteçler bulunması son derece önemlidir.

Yöntem: Toplam 29 febril nötropenik atak ve 24 pediatrik hasta çalışmaya alındı. Hastalar, bakteriemi/sepsis ve odağı olmayan ateş grubu olarak sınıflandırıldı. Serum örnekleri, FN teşhisi sonrasında toplandı ve presepsin, c-reaktif protein (CRP) ve prokalsitonin (PCT) konsantrasyonları analiz edildi.

Bulgular: Bilinen biyolojik belirteçler, bakteriemi/sepsis ile odağı olmayan ateş grubu arasında ayırt edici bir değer göstermezken, presepin, hemokültürde bakteri gelişiminin bir göstergesi olarak anlamlı bulundu ve potansiyel bir tanısal değeri olduğu gösterildi.

Sonuç: Presepsin, çocukluk çağı FN'li hastalarda bakteriyemi/sepsis tespiti için ilave bir tanı aracı olarak kullanılabilir.

Anahtar sözcükler: Biyobelirteç, Febril Nötropeni, Presepsin, sCD14-alt tipi

Absolute neutrophil count (ANC) under 500 / mm^3 in peripheral blood, is an important risk factor for infection. ANC under 100 / mm^3, described as severe neutropenia, may result in lethal circumstances. Neutropenia is more commonly observed in patients with more malignant disease and in those receiving myelosuppressive therapy. FN is considered when a single axillary temperature measurement is ≥38 C° or fever continuing for , at least 1 hour at 37,5 C° (1). Children with FN may display only fever as a main symptom. Therefore, urgent hospitalization and empirical treatment with broad spectrum antimicrobials are necessary until neutropenia resolves (2). In order to prevent overuse of antimicrobials which causes selection of multi-drug resistant pathogenic microorganisms and undesired side-effects, biomarkers become indispensable for prediction of infections in FN patients. Several studies demonstrated the assessment of various biomarkers related to inflammation for prediction of infections in FN patients. Various biomarkers are already in clinical use, although limitations in their specificity and selectivity reduces their predictive value (3). CRP and PCT are the most commonly used biomarkers, but their bacteremia/sepsis differentiation and prognosis determination potentials are limited. In recent years, CRP and PCT levels have been used to define sepsis (4). Monitoring lactate levels in patients with sepsis has become an important treatment parameter in the last 10 years (5). Various types of biomolecules such as coagulation factors (fibrin degradation products, antitrombin-III, D-dimer), hormones (cortisol, ACTH), cytokines (IL-6, IL-8, IL-10, TNF-α), cell membrane markers (HLA-DR, E-selectin), soluble receptors (sCD-14, sTNFRI) are also being investigated in terms of their biomarker potentials but none of them has been found superior to CRP and PCT (6). Based on recent studies, CD-14 subtypes (Presepsin), is considered as a successful biomarker in early diagnosis of sepsis and determination of prognosis (7). In this study, we assessed the predictive value of presepsin in sepsis/bacteremia compared to traditional counterparts, CRP and PCT in FN patients.

Patients and methods

Patient characteristics

This study was performed in the Division of Pediatric Hematology and Oncology Children Hematology and Oncology Department. After written informed consent was obtained from the parents of all patients, plasma samples were collected during each FN episode at presentation. Permission for this study was provided by the Regional Committee of Bioethics.

ANC less than $0.5x10^9$ /l at the onset of fever was defined as neutropenia. Fever was defined as a single body temperature measurement was more than 38.5°C. Bacteremia was defined when a positive blood culture growth was observed. None of the patients were administered antibiotics before enrollment. Multiple FN episodes for a patient were also recorded as individual FN episodes.

According to microbiological and clinical evidences, patients were categorized into two groups; 1- Fever without origin (FWO) – patients with negative blood culture with no sepsis and 2- bacteremia/sepsis (BS) group – patients with positive blood culture or with sepsis diagnosis.

Laboratory analysis

Venous blood samples were collected into 5 ml EDTA containing tubes for routine blood counts and hemoculture in accordance with international FN guidelines. The tubes were centrifuged for plasma separation. Separated plasma was stored at -20°C until measurement. Blood samples were taken on admission day. In addition to routine blood and urine analyses, CRP, PCT and presepsin blood concentrations were also evaluated. Presepsin was measured with an immunoassay analyzer PATHFAST (Mitsubishi Chemical Medience Corporation). Plasma concentrations of presepsin above 60 pg/ml was considered as significantly high. CRP was evaluated by using BNII system (Dade Behring Marburg GMBH, Marburg, Germany). Concentrations of PCT were evaluated by enzyme-linked fluorescent immunoassay (Vidas BRAHMS PCT, Biomerieux).Serum and plasma concentrations under 0.5 mg/dl and 0.05 ng/ml were considered as normal levels for CRP and PCT respectively. Hemogram analysis was done by using Cell-Dyn 3700 device (Abbott Diagnostics Division, United States of America). Finally, venous blood samples of febrile neutropenic patients were collected and incubated in the Bactec 9240 incubator (Becton Dickinson) for microbiological analysis. Identification of microorganisms was performed by using standard methods. All samples for the microbiological assessment were taken before the antimicrobial treatment started.

Statistical analysis

Comparison between FWO and BS groups was performed for all FN episodes by using Mann–Whitney-U test. Correlations were done by using the Spearman rank test. The diagnostic properties of biomarkers for prediction of hemoculture and urine bacterial growth were evaluated by receiver-operating characteristic (ROC) analysis.P value <0.05 was estimated as statistically significant for all statistical analysis. The MedCalc statistical software was used for calculations (version 13.0, Belgium).

Results

Demographic analysis

Study was conducted with a total of 29 FN episodes in 24 patients. 9 female and 15 male patients with a median age of 7.1 in a range 0-14 years including 7 acute lymphoblastic leukemia, 3 neuroblastoma, 3 medulloblastoma, 2 Burkitt's lymphoma, 2 s-PNET, 1 acute myeloblastic leukemia, 1 anaplastic ependymoma, 1 pinealoma, 1 Ewing's sarcoma, 1 rhabdomyosarcoma, 1 ependymoma and 1 viral suppression were enrolled in this study.

Microbiological analysis

Upon diagnosis of febrile neutropenia, blood and urine cultures were obtained and microbiologically evaluated before antibiotic treatment. Patients with ongoing fever during empirical treatment were followed by repetitive microbiological evaluations. In addition, patients with positive physical examination evidence were requested additional microbiological investigations.

As a result of laboratory analysis, *Aeromonas hydrophila/caviae*, *Streptococcus pneumoniae*, methicillin resistant *Staphilococcus epidermidis*andbroad spectrum beta-lactamaseproducing*Escherichia coli* were identified in positive hemocultures. Moreover, *Escherichia coli* was identified in urine cultures.

Comparison of experimented biomarkers, presepsin, c-reactive protein and procalcitonin

Median presepsin, CRP and PCT levels between FWO and BS groups did not differ significantly (Table 1).

Table 1. Comparison of biomarkers concentration in plasma of patients according to mann–whitney test.

Biomarker	*Groups*	*Median (min-max)*	*p-value*
CRP	FWO	2.4 (0.03-18.9)	0.143
	BS	4.6 (0.1-12)	
PCT	FWO	0.3 (0.1-0.8)	0.537
	BS	0.4 (0.08-0.8)	
Presepsin	FWO	450.5 (68-1026)	0.098
	BS	822 (311-946)	

Correlation between experimented biomarkers, presepsin, c-reactive protein and procalcitonin

Correlations between experimented biomarkers, white blood cell (WBC) and platelet (PLT) counts were done by using the Pearson correlation method shown in Figure 1. A weak correlation between WBC counts and PCT levels ,and a weak negative correlation between PLT counts and presepsin plasma levels were demonstrated. Correlations between other evaluated variables were not significant.

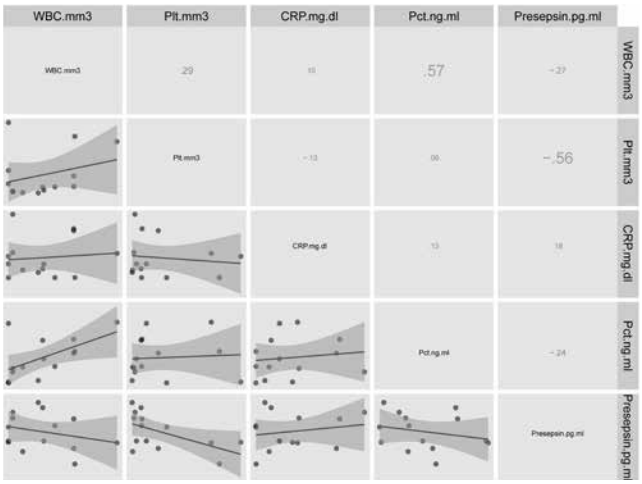

Figure 1. Correlation between presepsin, c-reactive protein, procalcitonin, WBC and Plt counts.

Table 2. Comparison of biomarker concentrations in fn patients with positive and negative hemoculture according to mann–whitney test.

Growth	*CRP (mg/dl) Median (min-max)*	*PCT (ng/ml) Median (min-max)*	*Presepsin (pg/ml) Median (min-max)*
Growth (+)	3.3 (1.5-12)	0.2 (0.1-0.6)	874 (568-946)
Growth (-)	2.4 (0.03-18.9)	0.3 (0.1-0.8)	427 (68-1026)
p-value	0.365	0.382	**0.012***

Table 3. Comparison of Biomarker Concentrations in FN Patients with Positive and Negative in Urine Culture According to Mann–Whitney Test.

Growth	*CRP (mg/dl) Median (min-max)*	*PCT (ng/ml) Median (min-max)*	*Presepsin (pg/ml) Median (min-max)*
Growth (+)	4.6 (0.1-8.9)	0.4 (0.3-0.8)	354.5 (311-398)
Growth (-)	2.4 (0.03-18.9)	0.3 (0.1-0.8)	632 (68-1026)
p-value	0.758	0.190	0.144

Comparison of presepsin, c-reactive protein and procalcitonin in blood and urine cultures

Median presepsin concentration was found significantly different between patients with positive and negative hemocultures in FN patients whereas CRP and PCT concentrations did not differ significantly (Table 2). None of the biomarker concentrations were found significantly different among patients with positive and negative urine cultures (Table 3).

Bacteremia/Sepsis predictive value of presepsin, c-reactive protein and procalcitonin in blood and urine cultures

The predictive values of presepsin, CRP and PCT for bacteremia/sepsis were evaluated by ROC analysis (Tables 4 and Table 5).

Table 4. Diagnostic utility of biomarkers for ıdentifying bacteremia/sepsis in patients with positive hemoculture according to Receiver-Operating Characteristic (ROC) analysis

Hemoculture	*AUC*	*p-value*	*%95 CI*
CRP	0.639	0.395	0.353-0.925
PCT	0.486	0.932	0.159-0.813
Presepsin	0.861	0.027*	0.676-1.00

Table 5. Diagnostic utility of biomarkers for ıdentifying bacteremia/sepsis in patients with positive urine culture according to Receiver-Operating Characteristic (ROC) analysis

Urine Culture	*AUC*	*p-value*	*%95 CI*
CRP	0.875	0.087	0.730-1.0
PCT	0.850	0.110	0.608-1.00
Presepsin	0.200	0.171	0.019-0.381

Discussion

In this study diagnostic value of presepsin (sCD14-ST) in bacteremia/sepsis was explored at the beginning of FN in pediatric oncology patients. Presepsin was shown to be a potential additional diagnostic tool. Although , PCT alone or in combination with other markers was previously shown to be useful for the early prediction of bacterial infections in pediatric oncology patients (2, 8, 9), our results suggest a slight but not significant correlation between PCT and positive culture tests. CRP, one of the most commonly used inflammation markers, was also evaluated for its potential diagnostic value for BS. Increased serum CRP level was previously demonstrated in intensive care patients with fever and known or suspected infection (10), but the correlation was not significantly strong to predict BS either alone or in combination with other markers . In our study, CRP also did not express a significant diagnostic value as discussed before. Presepsin, a recent marker, has been suggested useful for the diagnosis of sepsis and the prediction of its severity (11). The diagnostic value of presepsin in neonatal sepsis was evaluated and presepsin was found to be significantly increased in systemic inflammatory response (12). Although the clinical use of presepsin is limited, a previous study showed the significant test limits and the usefulness of presepsin in inflammation and sepsis (13). In another study by Endo et al. plasma level of presepsin was found to be increased especially in bacteriemic patients compared to PCT and IL-6 (14). In this study, presepsin is also suggested as a potential diagnostic tool specifically for bacteremia and sepsis in pediatric oncology patients (15-18). Median presepsin level was found to be874 pg/ml (min-max;568-946) in FN patients with positive blood culture besides, in those with negative blood culture,it was found to be 427 pg/ml (min-max;68-1026) which is significantly lower (p=0.012). According to urine culture results, presepsin level was not found significantly different between urine culture positive and negative groups. Despite,it was previously discussed that the main source of presepsin is innate immune cells and quantities ofpresepsin might dramatically be reduced in FN patients during the course of chemotherapy (9). According to our results, it is demonstrated that the presepsin level is significantly increased in FN groups with positive blood culture. According to Urbonas et al. (9), median presepsin concentration was previously shown in FN patients defined as bacteremia/sepsis groups as 401 pg/ml which was not a significant increase compared to median presepsin, 356 pg/ml found in those with fever of unknown origin. A cut-off value of 415 mg/L for presepsin was previously suggested to permit sensitivity of 80.1% and specificity of 81% (11). In this study, median presepsin plasma concentration is significantly higher in FN patients with positive blood culture which is above suggested cut-off values shown in Table 2. It is thereforehinted that even if chemotherapy related innate immune system reduction occurs, the plasma level of presepsin can be still increased. PCT was suggested that it has dynamic reference intervals and cut-off ranges, depending on gestational age, postnatal age,clinical conditions and settings (19). PCT results should be interpreted with caution, a cut-off of 0.5 mg/L was previously shown to express good sensitivity and specificity (20). In this study, PCT concentrations were not between suggested range and it could be one of the possible explanations of non-significant PCT diagnostic results among FN groups. Lastly, CRP is specific, but not a sensitive biomarker for bacterial infection. Thus, severe sepsis and septic shock may not be closely correlated with serum CRP concentration(21). In this study, CRP was not found to be correlated to bacteremia/sespis as discussed previously.

Correlations between biomarkers, presepsin, PCT, CRP, white blood cell (WBC) and platelet (PLT) counts were evaluated. We found a weak correlation between WBC counts and PCT levels as was previously demonstrated by Magrini et. al (22). According to the authors, PCT combined with WBC showed the best diagnostic and prognostic power for sepsis in ROC analysis . In addition, a weak negative correlation was also shown between platelet counts and presepsin plasma levels. Correlations between other evaluated variables were not significant (22).

In our study, diagnostic utility of biomarkers for identifying bacteremia/sepsis in patients with positive hemoculture and urine culture were evaluated by using ROC

analysis. According to results, only presepsin showed efficient diagnostic performance in terms of positive hemoculture diagnosis. In previous studies, AUC-ROC$_{presepsin}$; 0.817 (23), AUC-ROC$_{presepsin}$; 0.908 (24), AUC-ROC$_{presepsin}$; 0.845 (11) were demonstated in different patient groups for the diagnosis of bacteremia/sepsis. In our study, AUC-ROC$_{presepsin}$ was found 0.861 (p=0.027 with 0.676-1.00 %CI) which predicted the growth in hemoculture significantly.

This study was performed prospectively to compare the three different biomarkersto in prediction of the growth in hemoculture and urine culture. The limitations of our study is low number of patients of low number of febrile neutropenic episodes.

Conclusion

In this study,CRP and PCT did not show a discriminative prediction value between bacteremia/sepsis and fever without origin groups in febrile neutropenic oncology patients, whereas presepsin was found to be an indicator of positive hemoculture. and was shown to demonstrate a potential diagnostic value, however this data needs to be confirmed in larger studies.

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