Usage of Plasma Presepsin, C-Reactive Protein, Procalcitonin and Proadrenomedullin to Predict Bacteremia in Febril Neutropenia of Pediatric Hematological Malignancy Patients

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ABSTRACT

Objective: To investigate the value of presepsin and proadrenomedullin (proADM) as new markers for febrile neutropenia, by comparing them with conventional markers.

Methods: Plasma specimens for presepsin, proADM, C-reactive protein (CRP), and procalcitonin (PCT) were collected every 3 days during each episode of febrile neutropenia.

Results: A total of 39 patients experiencing a collective 47 episodes of febrile neutropenia with hematological malignant neoplasms, as well as 40 healthy control patients without infectious disease, were enrolled in this study. Levels of the studied analytes in the presepsin 1 group (with baseline values taken at admission), presepsin 2 group (values recorded on the 3rd day of febrile neutropenia), and presepsin 3 group (values recorded on the 6th day of hospitalization) were all higher in the subgroups with bacteremia. C-reactive protein 1 (baseline value taken at admission), procalcitonin 1 (as recorded at admission), and procalcitonin 2 (recorded on the 3rd day of febrile neutropenia) were higher in the subroups with bacteremia (P =.03, P = .04, and P = .04, respectively). In multivariate logistic regression analysis, presepsin 1 and/or PCT 1/CRP 1 combined analysis was superior in predicting bacteremia.

Conclusion: Presepsin could be used in combination with other biomarkers to detect bacteremia.

Keywords: febrile neutropenia, bacteremia, presepsin, proadrenomedullin, C-reactive protein, procalcitonin

Febrile neutropenia (FN) represents an important complication that affects the clinical outcomes of patients who receive chemotherapy and/or hematopoietic stem-cell transplantation (HSCT). It is assumed that infectious causes are the reason for 80% of FN episodes.[1] Prediction of bacteremia/sepsis in patients with pediatric hematological malignan neoplasms who have febrile neutropenia still remains a challenge for the medical community due to the lack of reliable biomarkers, especially at the beginning of the infection process. In FN episodes, life-threatening complications can develop in a period of several hours, depending on the pathogen. Thus, an accurate and timely diagnostic work-up is mandatory to yield prompt diagnosis and reveal the correct antibiotic treatment.

C-reactive protein (CRP) and procalcitonin (PCT), as biomarkers, have most often been explored to identify patients at risk for complicated course of febrile neutropenia. CRP and PCT both have some limitations, such as nonspecificity and delayed response. High levels of PCT are observed during systemic bacterial infections, and less-elevated PCT levels are observed during localized bacterial infections.[2] PCT is superior to CRP for predictive

Abbreviations:

FN, febrile neutropenia; HSCT, hematopoietic stem-cell transplantation; CRP, C-reactive protein; PCT, procalcitonin; sCD14, soluble CD14 subtype; ADM, adrenomedullin; SIRS, systemic inflammatory response syndrome; ANC, absolute neutrophil count; IDSA, Infectious Disease Society of America; ECLIA, electrochemiluminescence immunoassay analyzer; ROC, receiver operating characteristics; ALL, acute lymphoblastic lymphoma; AML, acute myeloblastic lymphoma; AUC, area under the curve; CI, confidence interval; min, minimum; max, maximum

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purposes and is slightly more pathogen-dependent, especially in gram negative bacteremia.[2] However, there still is a need for more rapid and accurate markers, which also could be used for deescalation strategies involving broad-spectrum antibiotics.

Soluble CD14 subtype (sCD14), known as *presepsin*, is a biomarker that has been demonstrated as a new, emerging, early indicator for the detection of different infections.[3] When a proinflammatory cascade is activated against infectious agents, sCD14 is released after phagocytosis or released into circulation by breakdown of sCD14 via the proteolytic pathway. After this process, presepsin is generated and released. The molecule occurs as early as within 2 hours of inflammation onset, which is even earlier than PCT and CRP.

Adrenomedullin (ADM) is a 52-amino-acid peptide produced from cultured vascular smooth-muscle cells and vascular endothelial cells; its production is generally augmented by inflammatory agents such as lipopolysaccharide, tumor necrosis factor, and interleukin-1.[3] ADM has regulatory effects on inflammation, infection, angiogenesis, mineralized tissue formation, and development.[4,5]

ADM has been found to be beneficial as a prognostic marker for high sepsis, pneumonia, systemic inflammatory response syndrome (SIRS), and febrile neutropenia. Its precursor molecules are pre–proADM, which consists of 185 amino acids, and proADM, which contains 164 amino acids. After its release, ADM is rapidly eliminated from the serum, so it is hard to measure its serum levels. However, proADM remains stable for longer periods of time.[6,7] To date, to our knowledge, there have been no published studies in pediatric patients with cancer regarding proADM as a biomarker, compared with presepsin, CRP, and PCT.

Herein, we aimed to analyze the utility of presepsin, pro-ADM, CRP, and PCT as biomarkers of bacteremia during febrile episodes that occurred in patients with neutropenia harboring hematological malignant neoplasms. Our goal was to define reliable tools to predict bacteremia and derive the correct prognosis.

Material and Methods

We conducted a prospective, case-control study to examine the utility of presepsin and proADM levels, compared the CRP and PCT levels, for detecting bacterial infections in the FN of pediatric patients in the hematology department. The present study was approved by the ethical committee of the Faculty of Medicine, Hacettepe University, Ankara, Turkey. FN is often defined as having oral temperature of 38.3 or greater, or 38°C or greater, for more than 1 hour, with absolute neutrophil count (ANC) less than 500 per μL or the reduction of ANC to 500 per μL in the next 24 to 48 hours. *Severe neutropenia* has been defined as ANC less than 100 per μL.[8]

The inclusion criteria were age of less than 18 years and presence of hematological malignant neoplasms without a history of antibiotic therapy in the past week. Exclusion criteria were declining to participate in the study, age greater than 18 years, having oncological malignant neoplasms, having nonhematological malignant neoplasms, and not undergoing chemotherapy treatment.

The patients were selected for the study based on the criteria of the Infectious Disease Society of America (IDSA) for the definition of FN. Written consent was given by the parents of each patient to participate in this study. All the patients were subjected to full medical history-taking, thorough clinical examination, and radiological studies (if indicated).

Routine total blood count, biochemical analysis, and blood culture were performed on all patients with febrile neutropenia. Plasma specimens for presepsin, proADM, CRP, and PCT were collected concomitantly during each febrile neutropenic episode at presentation before the first dose of antibiotic treatment (day 0; presepsin 1, proADM1, CRP1, PCT1), at the 3rd day (day 3; presepsin 2, proADM2, CRP2, PCT2) and at the 7th day of antibotic treatment (day 7; presepsin 3, proADM3, CRP3, PCT3). We also checked serum presepsin and proADM levels inm healthy pediatric patients.

None of the included patients had been administered antibiotics before enrollment. *Bacteremia* was defined as a microbial growth in one of the blood culture bottles. For coagulase negative *Staphylococcus* species, 2 positive blood culture results from different sites were required; otherwise, the result was considered to indicate possible contamination. In this study, an individual patient may have had multiple FN events. The serum specimens, taken at the same time as PCT and CRP specimen gathering, were allowed to clot for 10 to 20 minutes at room temperature and then centrifuged (at 492*g* –1107*g*) for 20 minutes. We collected the supernatants carefully. After centrifugation within 2 hours of phlebotomy, the plasma was preserved at –80°C until measurement.

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We measured plasma presepsin levels using a rapid chemiluminescent enzyme immunoassay on the fully automated PATHFAST immunoanalyzer (Mitsubishi Chemical Europe GmbH). ProADM was measured via quantitative sandwich enzyme immunoassay technique, using the Human Pro-ADM ELISA Kit. ProADM levels were measured by ELISA (pg/mL). PCT levels were measured by electrochemiluminescence immunoassay analyzer (ECLIA; ng/mL; local inflammation/infection, 0–0.5; moderate systemic inflammatory response, 0.5–2.0; severe systemic inflammatory response, 2.1–10.0; severe bacterial sepsis/septic shock, >10.0). CRP levels were measured by immunoturbidimetry (mg/L; threshold >5).

Statistical Analysis

The data were analyzed using SPSS Statistics, version 20.0 (IBM Corporation). Comparisons between measures (mean [SD]) of the 2 groups were performed using the Student *t* test, and comparisons between measures (mean [SD]) of multiple groups were performed by 1-way ANOVA testing (*F*). Kruskall-Wallis test (*K*) was used instead of ANOVA in nonparametric data (SD >50% mean).

Mann-Whitney testing was used for nonparametric data, and χ^2 testing was used for comparing categorical variables. We used correlation coefficient rank testing to rank different variables against each other in linear correlation, which was positive or negative. The capacity of CRP, PCT, presepsin, pro-ADM, and serum thrombocyte values were analyzed using ROC (receiver operating characteristics) curve analysis. When we observed a significant cutoff value, sensitivity, specificity, and positive and negative predictive values were presented. While we investigated the associations between non-normally distributed and/or ordinal variables, we calculated the correlation coefficients and their significance using the Spearman test. A *P* value of less than .05 was considered statistically significant, and a *P* value of .05 or greater was considered statistically insignificant.

Results

A total of 29 patients with acute lymphoblastic lymphoma (ALL; 33.3%), 18 with acute myeloblastic lymphoma (AML; 20.7%), and 40 control individuals (46.0%) with no known underlying disease or fever were included in this study. The median age of the patients with hematological malignant neoplasms was 77 months (21–216 months), and the median age of the control group was 71.5 months (10.0–215.0 months; *P* = .72).The median age of the 47 patients with hematological malignant neoplasms was 77 months (21–216 months), and the median age of the control group was 71.5 months (10–215 months; *P* = .72). In total, 23 of the 47 patients (48.9%) and 18 of 40 (45.0%) in the control group were male (*P* = .44). The median (minimum–maximum) duration of hospitalization was 13 days (6–75 days). Patients with AML were more prone to longer hospitalization than patients with ALL: 19 days (6–75) vs 10 days (6–38; *P* = .01). In 36 FN episodes (41.4%), patients had severe neutropenia (ANC <100/μL).

In 26 of 47 FN episodes (55.3%), at least 1 infectious cause was found: 18 (69.2%) were due to bacteria, 5 (19.2%) were due to viruses, and 3 (11.6%) were due to fungal infections (**Table 1**). Patients with FN who had severe neutropenia more commonly had bacteriemia: of 8 of 9 (88.9%) patients with gram negative bacteremia, 7 of 9 (77.8% patients with gram positive bacteremia) had severe neutropenia.

The median (minimum–maximum) presepsin levels of control individuals were statistically significantly higher than those levels in the patient group (2555 pg/mL [670–7010] vs 1870 pg/mL [140–7010], respectively [*P* = .04]). Median (minimum–maximum) presepsin levels were higher in patients with FN episodes caused by bacterial infections than in patients with FN episodes with no underlying infectious etiology; however, the difference was not statistically significant (*P* = .10, *P* = .67, and *P* = .75, respectively; **Table 2**). In 9 patients with gram negative bacteriemia, median presepsin 1, -2, and -3 levels were all higher than in the patients with gram-positive bacteremia (*n* = 9); however, the difference was not statistically significant (*P* = .13, *P* = .89, and *P* = .42, respectively; **Table 3**, **Figure 1**).

Serum proADM1 levels of patients with FN who harbored bacteremia was statistically significantly higher than those in the control group: 58.24 pg per mL (58.24–69.13) vs 46.13 pg/mL (20.16–70.45), respectively (*P* <.001.) Median (minimum–maximum) proADM levels were similar between patients with bacteremia and those without bacteremia (*P* = .90, *P* = .67, and *P* = .70, respectively; **Table 2**). Median serum proADM levels (1, 2, and 3) of patients with gram positive bacteremia were not statistically different from those levels in patients with gram negative bacteremia (**Table 3**).

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Median CRP1, -2, and -3 levels of patients with FN were 5.82 mg/dL (0.16–31.5 mg/dL), 5.99 mg/dL (0.42–52.1 mg/dL), and 1.67 mg/dL (0.18–51.1 mg/dL), respectively; change was statistically significant during hospitalization (P <.001).

Table 1. Patient Characteristics[a]

Hematological Malignancy, No. (%)	
Acute myeloid leukemia	18 (61.7)
Acute lymphoblastic leukemia	29 (38.3)
Absolute Neutrophil Count During FN (Day 0), No. (%)	
<100/μL	36 (76.6)
100–500/μL	11 (23.4)
Focus of Infection, No. (%)	
No focus of infection	21 (44.7)
Bacteriemia	18 (38.3)
Viral upper respiratory infection	5 (10.6)
Fungal infection	3 (6.4)
Pathogens Identified in Blood Cultures, No.	
Gram negative Bacteria	
Escherichia coli	3
Klebsiella pneumonia	2
Pseudomonas aeruginosa	1
Citrobacter freundii	1
Klebsiella oxytoca	1
Gram positive Bacteria	
Staphylococcus epidermidis	5
Staphylococcus hominis	2
Enterococcus faecium	1
Streptococcus mitis	1

FN, febrile neutropenia.
[a]*No. refers to number of episodes of febrile neutropenia.*

Median CRP2 levels were statistically significantly higher (P = .02), but CRP1 and CRP3 levels were similar in patients with bacteremia and without bacteremia (P = .68 and P = .45, respectively). Median CRP2 levels of patients with FN who harbored gram-negative bacteremia were statistically significantly higher than those levels in patients with FN who harbored gram-positive bacteremia (P = .02; **Table 3**, **Figure 1**).

Median (minimum–maximum) PCT1, -2, and -3 levels of patients with FN were 0.43 ng per mL (0.05–40.4 ng/mL), 0.29 ng per mL (0.04–17.6 ng/mL), and 0.22 ng per mL (0.04–11.4 ng/mL), respectively; the change was statistically significant during hospitalization (P <.001). Median PCT1 and -2 values of patients with FN who had documented bacterial infections were higher than in patients with FN who did not have underlying infectious etiology (each P = .04) (**Table 2**). Median PCT1 and -2 values were higher in patients with gram-negative bacteremia than those with gram-positive bacteremia (P = .01 and P = .008, respectively; **Table 3**). A cutoff value of serum pro-ADM1 level of 57.95 pg/mL was found to diagnose FN attacks, with sensitivity of 98% and specificity of 75% (area under the curve [AUC], 0.78; 95% confidence interval [CI], .66–.90; P <.001). A cutoff value of serum presepsin 3 level of 750 pg/mL was found to diagnose bacteremia in FN, with sensitivity of 85% and specificity of 64 % (AUC, 0.74; 95% CI, 0.55-0.93; P = .03).

A cutoff value of serum PCT1 level of 0.36 ng/mL was found to detect bacteremia in patients with FN, with sensitivity of 82%

Table 2. Biomarker Changes in Bacteremic and Nonbacteriemic FN Groups

Variable	Group with Bacteremia, Median (Min–Max)[a]	Group without Bacteremia Median (Min–Max)[b]	*P* Value[c]
Age (mo)	78 (21–216)	81 (21–213)	.85
Presepsin 1 (pg/mL)	2210 (250–7010)	1700 (140–6920)	.10
Presepsin 2 (pg/mL)	2540 (130–7010)	1560 (100–6920)	.67
Presepsin 3 (pg/mL)	4550 (170–6920)	1880 (100–7010)	.75
Pro–ADM 1 (pg/mL)	58.24 (58.24–69.13)	52.44 (53.56–70.45)	.90
Pro–ADM 2 (pg/mL)	56.24 (58.24–70.45)	49.40 (48.55–70.45)	.60
Pro–ADM 3 (pg/mL)	54.44 (58.24–70.45)	48.40 (53.01–70.45)	.70
CRP 1 (mg/dL)	7.00 (0.20–18.80)	8.45 (0.49–31.50)	.68
CRP 2 (mg/dL)	8.25 (0.46–52.10)	5.08 (0.47–17.60)	**.03**
CRP 3 (mg/dL)	6.00 (0.30–18.50)	0.98 (0.40–28.9)	.45
PCT 1 (ng/mL)	0.53 (0.15–10.80)	0.20 (0.05–40.40)	**.04**
PCT 2 (ng/mL)	1.81 (0.08–17.60)	0.20 (0.04–3.67)	**.04**
PCT 3 (ng/mL)	0.23 (0.11–11.40)	0.20 (0.04–3.60)	.26

FN, febrile neutropenia; min, minimum; max, maximum; No., refers to the number of episodes of FN; pro-ADM, proadrenomedullin; CRP, C-reactive protein; PCT, procalcitonin.
[a]*n = 18.*
[b]*n = 29.*
[c]*Bolding indicates statistical significance.*

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Table 3. Biomarker Changes in Gram Positive and Gram Negative Bacteriemic FN Groups

Variable	Group with Gram Positive Bacteremia[a]	Group with Gram Negative Bacteremia[a]	*P* Value[b]
	Median (Min-Max)		
Presepsin 1 (pg/mL)	1960 (470–4470)	4590 (250–7010)	.13
Presepsin 2 (pg/mL)	2030 (250–5890)	3990 (130–7010)	.89
Presepsin 3 (pg/mL)	2090 (210–6920)	6920 (170–6920)	.42
Pro–ADM 1 (pg/mL)	52.34 (58.24–64.20)	58.24 (58.24–64.20)	.93
Pro–ADM 2 (pg/mL)	52.30 (58.24–66.83)	56.40 (58.24–70.45)	.99
Pro–ADM 3 (pg/mL)	49.45 (58.24–65.06)	52.30 (58.24–70.45)	.68
CRP 1 (mg/dL)	7.31 (0.2–18.8)	5.79 (1.67–16.29)	.89
CRP 2 (mg/dL)	7.01 (0.46–21.1)	18.2 (6.11–52.10)	**.02**
CRP 3 (mg/dL)	2.01 (0.3–17.1)	10.85 (0.47–18.50)	.48
PCT 1 (ng/mL)	0.41 (0.34–40.4)	1.00 (0.15–10.80)	**.01**
PCT 2 (ng/mL)	0.55 (0.08–3.67)	4.40 (1.63–17.60)	**.008**
PCT 3 (ng/mL)	0.22 (0.11–1)	0.48 (0.17–11.40)	.18
Thrombocyte 1, $\times 10^3/\mu L$	41 (11–257)	22.50 (14.00–52.00)	**.004**
Thrombocyte 2, $\times 10^3/\mu L$	49 (16–273)	20.50 (15.00–62.00)	.19
Thrombocyte 3, $\times 10^3/\mu L$	35 (23–376)	40.50 (18.00–183.00)	.09

min, minimum; max, maximum; pro-ADM, proadrenomedullin; CRP, C-reactive protein; PCT, procalcitonin.
[a]$\eta = 9$.
[b]*Bolding indicates statistical significance.*

and specificity of 62% (AUC, 0.74; 95% CI, 0.58-0.90; $P = .01$). A cutoff value of serum CRP2 level of 6.6 mg/dL was found to detect bacteremia in FN, with sensitivity of 67% and specificity of 69% (AUC, 0.70; 95% CI, 0.54-0.86; $P = .02$).

A cutoff value of serum thrombocyte 1 level of 40.5×10^3 μL was found to detect bacteremia in patients with FN, with sensitivity of 80% and specificity of 74% (AUC, 0.28; 95% CI, .09–.46; $P = .04$). A cutoff value of serum thrombocyte 2 level of 54.5×10^3 μL was found to detect bacteriemia in patients with FN, with sensitivity of 80% and specificity of 61% (AUC, 0.21; 95% CI, .02–.40; $P = .01$). The optimal cutoff values for proADM, presepsin, PCT, CRP, and thrombocytes were identified by plotting ROC curves. ROC curves of all patients with febrile neutropenia and bacteremia vs patients with febrile neutropenia who did not have bacteremia are depicted in **Figure 2**.

In multivariate logistic regression analysis, presepsin 1 and PCT1 combined analysis was superior in detecting bacteriemia than PCT1 by itself (R^2: 0.18 vs 0.09, respectively). Presepsin 2 and PCT2 combined analysis was superior in detecting bacteremia, compared with PCT1 by itself (R^2: 0.58 vs 0.05, respectively). Presepsin 2 and PCT2 combined analysis was superior in detecting gram negative bacteremia, compared with PCT 1 by itself (R^2: 0.15 vs 0.002, respectively). In multivariate logistic regression analysis, presepsin 1 and CRP1 combined analysis was superior in detecting bacteremia, compared with CRP1 by itself (R^2: 0.34 vs 0.05, respectively). Presepsin 1 and CRP1 combined analysis was superior in detecting gram negative bacteremia, compared with CRP1 by itself (R^2: 0.13 vs 0.08, respectively).

Discussion

In the results of this study, we discovered that presepsin, when combined with CRP and PCT, can discriminate among bacterial infections, especially gram negative bacteriemia, in FN episodes of pediatric hematological malignancy. Also, presepsin 1 and -2, when combined with PCT1 and PCT2, were superior predictors of bacteremia, especially in gram negative bacteriemia. Median plasma presepsin levels were statistically significantly higher in the control group than in the FN group. This difference of serum presepsin levels between the control and FN groups might be explained by the fact that CD14 is expressed in neutrophils or monocytes and neutropenia in patients with FN, hence the lower serum presepsin levels. It was reported[9] that patients with hemophagocytic syndrome had higher levels of serum presepsin than those patients without hemophagocytic syndrome.

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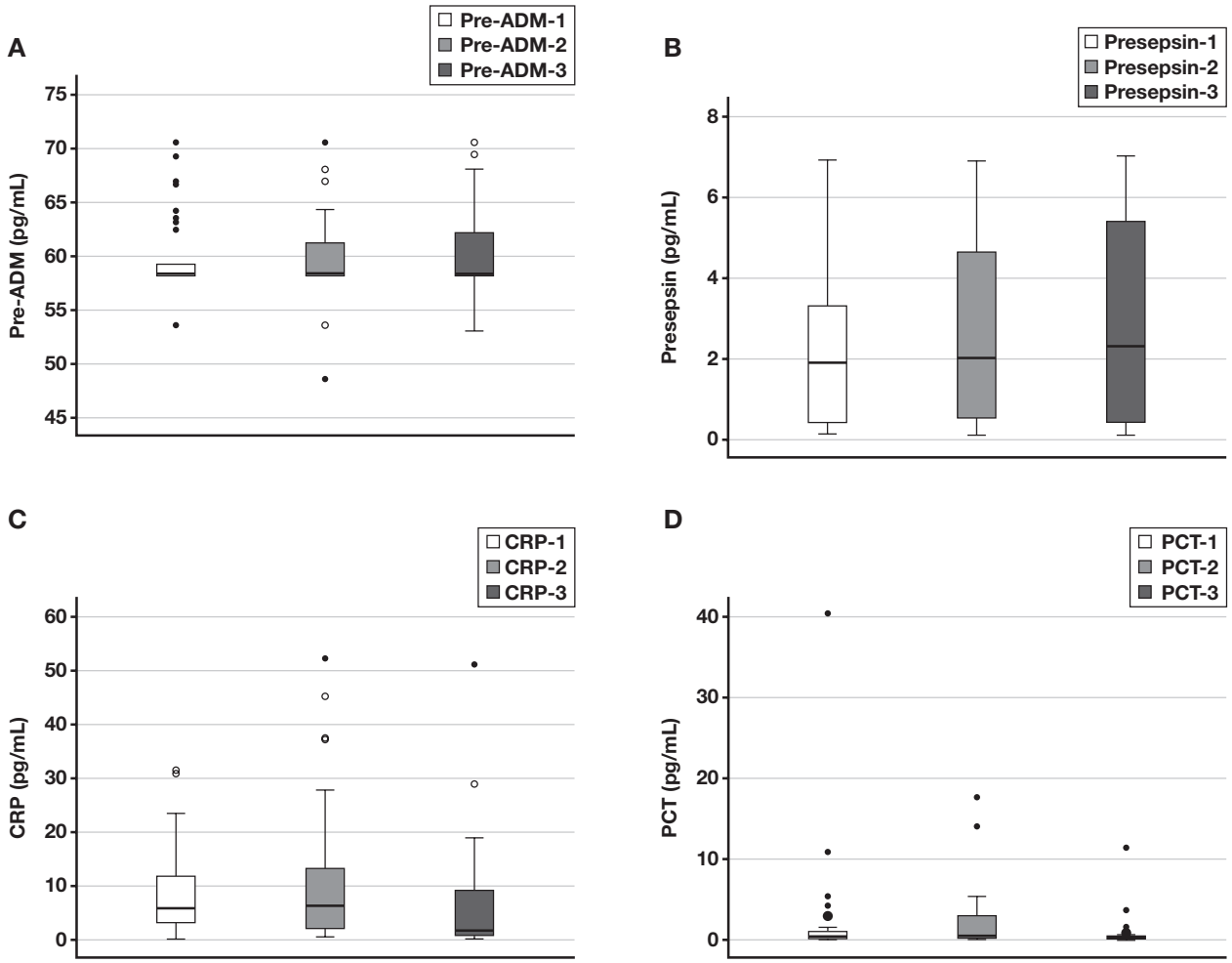


Figure 1

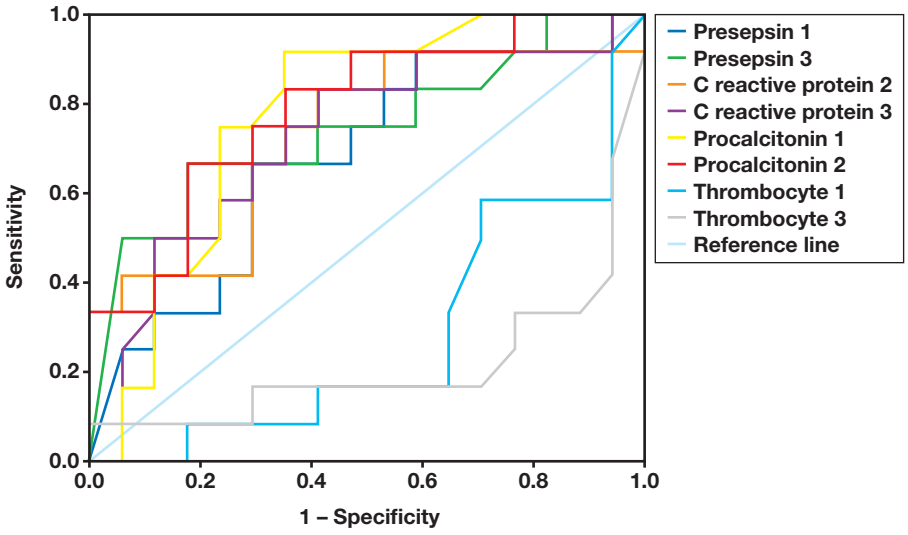
Box-and-whisker plots showing levels of various analytes in patients with febrile neutropenia. Plots show the median (solid black line), 25th and 75th percentiles (ends of boxes), and range (whiskers). **A**, Proadrenomedullin (proADM). **B**, Presepsin. **C**, C-reactive protein (CRP). **D**, Procalcitonin (PCT) levels of patients with febrile neutropenia.

These results show that serum presepsin might have less diagnostic value in patients with neutropenia because of less phagocytosis. However, in our study findings, the baseline and the lowest plasma presepsin levels were not extremely low, as we had expected in patients with severe neutropenia. Thus, we can say that presepsin stays at an appropriate level even in cases of severe neutropenia. This theory might be explained by the recent finding[9] that monocytes, rather than neutrophils, are the dominant producer of presepsin. Production from tissue macrophages or resident monocytes might play a role in maintaining plasma presepsin levels. Another result is that plasma presepsin levels were elevated in the early phase of most bacteremia episodes.

The data have shown a clear relationship between presepsin level and CRP, suggesting the sensitivity and validity of presepsin testing in the evaluation of infection. Median presepsin levels were higher in FN episodes caused by bacterial infections than in FN episodes with no underlying infectious etiology. Correlations between presepsin and CRP values were also discovered in an other study conducted by Koizumi et al.[10] In those study results, serum presepsin level and very low neutrophil count were reliable markers of FN, similar to our findings.

However, the reliability of presepsin in febrile neutropenia has not been well demonstrated so far in the literature. In

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Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower bound	Upper bound
Presepsin 1	0.694	0.099	0.080	0.499	0.888
Presepsin 3	0.743	0.098	0.028	0.550	0.935
C reactive protein 2	0.740	0.099	0.030	0.546	0.935
C reactive protein 3	0.723	0.099	0.044	0.528	0.918
Procalcitonin 1	0.775	0.089	0.013	0.601	0.948
Procalcitonin 2	0.789	0.086	0.009	0.621	0.958
Thrombocyte 1	0.277	0.097	0.044	0.087	0.467
Thrombocyte 3	0.213	0.098	0.010	0.021	0.405

Figure 2

Receiver operating characteristics (ROC) of biomarkers in patients with bacteriemic febrile neutropenia, compared with those in patients with nonbacteremic febrile neutropenia. CRP indicates C-reactive protein; PCT, procalcitonin.

the report of a study conducted in adult patients with FN, Koh et al[11] revealed that plasma presepsin level was a reliable marker of FN, even during aggressive chemotherapy in patients with a very low white blood cell count.

In the findings of another study conducted in patients with FN who were older than 16 years, the authors concluded that in patients with FN, presepsin levels were elevated significantly earlier than were PCT levels. Also, they discovered that presepsin may be a more sensitive indicator of bacterial infection than other analytes. Nevertheless, the ability of presepsin to discriminate septic shock from other conditions was inferior to that of PCT.[12]

We also concluded that procalcitonin is a faster-increasing marker, compared with CRP, in FN. Median PCT1 and PCT2 were statistically significantly higher in bacteriemia-induced FN episodes than in FN episodes without identified bacterial etiology. Median PCT1 and -2 levels were also statistically significantly higher in patients with gram negative bacteriemia than patients with gram positive bacteriemia. In a study of patients with FN pediatric hematologic and oncologic manifestations, it was concluded that a significant elevation of presepsin level was statistically significantly higher in bacteremia than clinically proven infection and fever of unknown origin,[13] as in our study findings. These investigators also reported a significant increase in CRP and PCT, as in our study. However, in contrast with the aforementioned study, we checked serum CRP, PCT, and presepsin levels 3 days apart in patients with FN. In multivariate logistic regression analysis, presepsin 1–CRP1, presepsin 1–PCT1, and presepsin 2–PCT2 combinations

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were superior in distinguishing bacteriemia from nonbacterial FN episodes and gram-negative bacteriemia from gram-positive bacteriemia than CRP or PCT by themselves.

To our knowledge, ours is the first study on using serum proADM levels to predict bacteriemia in pediatric patients with FN who harbor hematologic malignant neoplasms. In a published pediatric study report,[14] serum adrenomedullin was not superior or equal to CRP and/or PCR in detecting the severity of infection in patients with FN. However, in an other published study report[15] on pediatric patients with FN who harbored solid tumors, the authors concluded that increased plasma ADM was correlated with high-risk neutropenic fever and culture-positive results.

Despite those findings, in our study, we did not find any difference between bacterial and nonbacterial FN episodes, nor between gram negative and gram positive bacterial FN episodes. Serum proADM1 levels in patients with FN who had bacteriemia were statistically significantly higher than those levels in the control group (P <.001). Serum proADM levels in patients with FN may alert physicians to bacteremic febril neutropenic episodes in pediatric patients with hematological malignant neoplasms; however, further studies are needed to verify or disprove this hypothesis.

In conclusion, plasma presepsin level is a reliable marker of bacteremic FN episodes, even in patients with extremely low neutrophil counts. Evaluation of the increase rate can aid in early diagnosis of bacteremia in FN, in myeloid and lymphoid disorders. Closer monitoring of this molecule, concomitantly with CRP and/or procalcitonin, may guide physicians to select antibiotics in treatment of patients with FN. Serum presepsin levels may be used and combined with serum CRP and/or PCT levels to predict bacteriemia, especially gram negative bacteriemia, in pediatric patients with hematologic malignant neoplasms. **LM**

Personal and Professional Conflicts of Interest

None reported.

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