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Original Article

Kinetics and Role of Pancreatic Stone Protein and Midregional Proadrenomedullin as Predictors of Sepsis and Bacteremia in Children with Hematological Malignancies

Vasiliki Antari[1], Lemonia Skoura[2], Emmanuel Hatzipantelis[1], Vasiliki-Rengina Tsinopoulou[1], Konstantina Papakonstantinou[1], Efthimia Protonotariou[2], Assimina Galli-Tsinopoulou[1] and Athanasios Tragiannidis[1].

[1] Childhood & Adolescent Hematology Oncology Unit, 2nd Pediatric Department, School of Medicine, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece.
[2] Department of Microbiology, School of Medicine, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece.

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Abstract. ***Background*: To investigate the kinetics and prognostic value of pancreatic stone protein (PSP) and mid-regional proadrenomedullin (MR-proADM) during episodes of febrile neutropenia (FN) in children with hematological malignancies.**
***Material and methods*: We evaluated prospectively a total of 70 FN episodes in 70 children with acute leukemias and lymphomas. CRP, PSP, and MR-proADM levels were measured at the onset of the febrile episode (day 1), day 3, and day 7. The outcome and survival of children were evaluated during the study period until day 28. The performance of each marker in identifying sepsis or severe sepsis was assessed as an area under a receiver operating characteristic (ROC) curve. ROC curves were used for each biomarker to derive cut-offs for sensitivity and specificity in distinguishing sepsis from non-sepsis.**
***Results*: During the 2-year study period, 70 febrile neutropenia episodes in 70 children with hematological malignancies were enrolled. Of 70 episodes of febrile neutropenia, in 17 (24%), a bacterial/fungal infection was documented. Criteria for sepsis were fulfilled for 31 (44%) and 7 (10%) patients were admitted to PICU. The median values of all biomarkers on day 1 differed significantly between patients with and without sepsis. PSP, MR-proADM, and CRP specificity were 0.82, 0.70, and 0.57, respectively. The sensitivity of PSP, MR-proADM, and CRP were 0.84, 0.74, and 0.88, respectively.**
***Conclusions*: PSP and MR-proADM are promising biomarkers for early diagnosis of sepsis during FN episodes in children with hematological malignancies. However, PSP has a higher sensitivity and specificity.**

Keywords: Pancreatic stone protein; Midregional proadrenomedullin; Children; Hematological malignancies; Febrile neutropenia; Biomarkers; Pediatric infections.

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Correspondence to: Athanasios Tragiannidis, MD, PhD. Assistant Professor of Pediatrics - Pediatric Hematology-Oncology, Hematology Oncology Unit, 2nd Pediatric Department, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, AHEPA Hospital, Greece. E-mail: atragian@auth.gr, atragian@hotmail.com

Introduction. In the era of multi-modality and targeted therapies, survival of children with cancer has excellent rates that exceed 80% in most European and North American countries.[1] Relapsed and/or refractory diseases are the main cause of treatment failure and are related to low survival rates.[1,2] Infections are still a severe and important complication to therapy and represent the second cause of death and a main cause of morbidity and mortality, especially for children with acute leukemias and those who underwent hematopoietic stem cell transplantation (HSCT).[3-6]

Febrile neutropenia (FN) is the most common adverse event of intensive chemotherapy and cause of treatment delay.[6] In the last two decades, the emergence of newer antiinfectives in combination with the use of novel biomarkers of infection in our arsenal have significantly ameliorated the outcome of febrile episodes and the survival of patients. The prompt initiation of antimicrobial therapy plays a crucial role in managing these episodes. In case of persisting fever and neutropenia, escalation of antimicrobial treatment is advised in combination with empiric use of antifungals.[5-7] Many prognostic models for the outcome of febrile neutropenic episodes have been reported in the literature; however, there is still a strong need for accurate and sensitive biomarkers of infection for distinguishing septic from non-septic and bacteremic from non-bacteremic patients.[8-10]

CRP is an acute inflammatory protein produced by the liver by proinflammatory cytokines IL-1, IL-6, and IL-17 and increases 6-10 hours after the onset of acute infections and inflammation.[11] Measurement of CRP is highly recommended by infectious disease societies.[12,13] In the pediatric setting, there have been many attempts to incorporate predictive models, including CRP, for the initial assessment of children with FN.[8,10] In a recent systematic literature review, 37 studies evaluated CRP as a biomarker of bacterial infection in high-risk febrile immunocompromised children. CRP was related to high sensitivity, ranging from 77.7 to 92.3%, but poor specificity (15.5–72.2%).[9] Contrarily, higher cut-off values have been related to a decrease in sensitivity (24.2–77.8%) and a slight increase in specificity (63–87.3%).[9]

Originally, lithostatic and regenerating protein 1 (Reg 1), later renamed pancreatic stone protein (PSP), has been studied in patients with pancreatitis and diabetes.[14] PSP is a 14kDa insoluble polypeptide encoded by the reg gene secreted by the pancreas, and its response is induced by systemic inflammation and sepsis. As an acute-phase protein, it is involved in cell proliferation during regenerative processes through proinflammatory cytokines and in the inflammatory response to infection. PSP has widely been used in adults as a biomarker of sepsis in the clinical setting and has a higher diagnostic impact in identifying infection than other used biomarkers.[14] Due to its unique characteristic of increasing before the onset of signs and symptoms of infection and sepsis (pre-symptomatic diagnosis), PSP has widely been studied in different populations and age groups and has shown to be more accurate and with higher sensitivity and specificity than CRP, procalcitonin (PCT) and IL-6 for diagnosis and outcome of sepsis.[15] Data on neonates and children are scarce. In children, the combination of PSP with PCT and CRP has been shown to be superior to each isolated biomarker for children with sepsis and osteomyelitis.[16-17] In neonates, PSP has been evaluated as a sepsis biomarker. It has been found that, alone or when combined with PCT, it has a high negative predictive value that rules out sepsis and helps de-escalate antibiotic treatment.[18-19] This is the first study evaluating PSP in the pediatric hematology oncology setting.

Adrenomedullin is a peptide with immunomodulating effects that have been shown to have a role in the integrity and stability of the vascular endothelium after severe infection. It seems to downregulate many processes, including inflammation and sepsis. Its serum levels show rapid elevations during sepsis, followed by rapid circulation clearance, making it difficult to detect because of its half-life of 22 min.[2] Due to its increased stability, the precursor mid-regional pro adrenomedullin (MR-proADM) is measured in clinical practice. MR-proADM is predictive for poor clinical outcomes in patients with sepsis, severe respiratory and urinary infections, and heart and kidney failure in adult and pediatric settings.[20-23] As a precursor amino acid sequence that splits from proadrenomedullin, MR-proADM is used as a surrogate marker for adrenomedullin. In the pediatric setting, MR-proADM has widely been used as a biomarker and prognostic marker in children with lower respiratory (mainly community-acquired pneumonia), urinary tract infections, and malignancy.[20-23]

To date, no combined studies have investigated the role of the standard biomarker CRP compared to the newer (PSP, MR-proADM) for predicting bacteremia, sepsis, and outcome in febrile neutropenic children with hematological malignancies. Therefore, we aimed to evaluate all the above-mentioned biomarkers in this setting.

Material and Methods.

Patients and study design. At the Pediatric Hematology-Oncology Unit of the 2nd Pediatric Department of the Aristotle University of Thessaloniki, Greece, 70 febrile neutropenic consecutive episodes in 70 children with hematological malignancies were collected and analyzed prospectively from January 2020 to December 2022. For each patient, only one FN episode was included in the study. Inclusion criteria were age under 18 years and diagnosis of acute leukemia or lymphoma without a

history of fever and antibiotic use in the last 7 days. For each patient/episode, we collected demographic data, underlying disease, treatment, fever characteristics (temperature, days until defervescence), duration and severity of neutropenia, positivity of blood cultures collected during the onset of the FN episode, and antimicrobial treatment. Total blood counts and biochemical exams were routinely performed in all patients during each febrile neutropenic episode. Plasma specimens for CRP and MR-proADM and whole blood for PSP were collected at the onset of each episode and before administering the first antibiotic treatment. All the abovementioned biomarkers were measured on day 1, day 3, and day 7. Samples collected for each patient were centrifugated (3000r/min for 10min) and stored at -80 ºC. CRP levels were measured by immunoturbidimetry (mg/dl; normal values <0.8mg/dl). PSP values were measured with the CE-marked IVD PSP capsule on the abioSCOPE® platform (Abionic SA, Epalinges, Switzerland). This nanofluidic immunoassay technology measures a point-of-care PSP value within 7 min via a fingerstick test. The abioSCOPE platform can measure PSP values of up to 600 ng/mL.[24] Higher values were displayed as >600 ng/mL. Serum MR-ProADM was measured by the new sandwich immunoassay method (Novus Biologicals, USA). The assay (normal reference range 0.33 ± 0.7 nmol/l) has an analytical detection limit of 0.05 nmol/l. Values of MR-proADM were provided as nmol/l, and the assay had a functional sensitivity of 0.47 nmol/L.[25]

For each patient, data about clinical signs and symptoms, vital signs, focal infection (pneumonia, urinary tract infection, bloodstream infection, colitis, CNS infection), transfer to ICU, and outcome on day 28 (survival, death) were prospectively collected. The study protocol was approved by the Ethics Committee of the Medical School of Aristotle University of Thessaloniki, Greece (42/2022).

Definitions. Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock were based on those published by the International Consensus Conference on Pediatric Sepsis[26]. Bacteremia was defined by positive blood cultures in patients with FN. In the case of coagulase-negative *Staphylococcus* spp, two positive blood cultures were required. Localized infection was defined as the presence of clinical and/or radiological findings of infection in febrile neutropenic patients without positive bloodstream infection (BSI). Additionally, fever was defined as a single axillary temperature ≥38.0 C° for more than one hour or ≥38.3 C° or greater and neutropenia as absolute neutrophil count (ANC) of <500cells/μL or the decrease of ANC to 500cells/μL in the next 24-48 hours according to the definitions of the American Society of Clinical Oncology and Infectious Diseases Society of America.[27]

Statistical analysis. Continuous variables were described using the mean ± SD for normally distributed data or the median (interquartile range (IQR)) for non-normally distributed data. Comparisons of group differences for continuous variables were made by one-way ANOVA or Mann-Whitney test as appropriate. Categorical data were described as the number of patients in each category with corresponding percentages. The significance of differences in proportions was tested by the Chi-squared test. The performance of each marker in identifying sepsis or severe sepsis was assessed as an area under a receiver operating characteristic (ROC) curve. ROC curves were used for each marker to derive cut-offs for sensitivity and specificity in distinguishing sepsis from non-infective SIRS. Statistical analyses were performed in SPSS 17.0 (IBM Corporation Somers, NY, USA) and Prism 5 (GraphPad Software Inc. La Jolla, CA, USA). All P-values were two-sided, and statistical significance was set at an a-value of 0.05.

Results. During the 2-year study period, 70 FN episodes in 70 consecutive children with hematological malignancies were enrolled. Seventy patients' underlying diseases were: acute lymphoblastic leukemia (55 patients), acute myeloid leukemia (11 patients), and non-Hodgkin lymphoma (4 patients). The study population consisted of 41 females and 29 males, and the median age of patients was 5 (range: 1-18 years). Patients' demographic data and clinical characteristics are shown in **Table 1**. Of 70 FN episodes enrolled, no focus of infection was documented in 45 (64%) cases, while in 17 (24%) episodes a BSI was detected. Gram-negative bacteria were obtained in 13 (19%) episodes, Gram-positive in 2 (3%) episodes, and an invasive fungal infection (candidemia) was documented in 2 (3%) episodes. Gram-negative organisms isolated were *Pseudomonas aeruginosa* (5), *E. coli* (4), *Klebsiella pneumonia* (2), and *Citrobacter koseri* (2). A coagulase-negative *Staphylococcus* spp and a *Candida* spp were detected both in 2 episodes. Criteria for sepsis were fulfilled for 31 patients (44%), and 7 (10%) were admitted to the ICU. Overall, all-cause mortality on day 28 was 4% (3 patients), while 67 patients (96%) underwent defervescence, bacteremia eradication, and infection resolution. The median temperature value at the onset of the FN episode was 38.5 (range: 37.5-40.0 C°). All patients were neutropenic at onset, and the median value of WBC and absolute neutrophil count (ANC) were 1300 (range: 10-14000/μL) and 100 (range: 0-500/μL), respectively. The mean hemoglobin value at day 1 was 8.5 (5.9-13.1g/dl), and the mean platelets value was 44000/μL (4000-393000/μL). All demographic characteristics, clinical data, laboratory findings, focus of infection, and outcomes of patients are

Table 1. Demographics, clinical characteristics, the focus of infection, and outcome of children with haematological malignancies.

Characteristics	Values
Males	29 (41%)
Females	41 (59%)
Median age (range)	5(1-18 years)
Underlying disease	
Acute lymphoblastic leukemia	55 (79%)
Acute myeloid leukemia	11 (16%)
Non-Hodgkin lymphoma	4 (5%)
Length of hospital stay at onset (range)	10 (0-110 days)
White blood cell counts at onset (range)	1300 (10-14000/μL)
Absolute neutrophil count at onset (range)	100 (0-500/μL)
Hemoglobin at onset (range)	8.5 (5.9-13.1g/dl)
Platelets count at onset (range)	44000 (4000-393000/μL)
No focus of infection	45 (64%)
Bacteremia/fungemia	17 (24%)
Gastrointestinal infection (colitis, appendicitis, mucositis, abscess)	5 (7%)
Respiratory tract infection	1 (1.4%)
Skin infection (abscess)	1 (1.4%)
Urinary tract infection	1 (1.4%)
Positive blood culture (BSI)	17 (24%)
Gram-negative bacteria	13 (19%)
Gram-positive bacteria	2 (3%)
Fungemia	2 (3%)
Sepsis	31 (44%)
ICU transfer	7 (10%)
Outcome	
Resolution	67 (96%)
Death	3 (4%)

shown in **Table 1**.

Biomarker median levels and ranges at days 1, 3, and 7 are shown in **Table 2**. CRP and PSP levels were significantly higher at the onset of the febrile episode (day 1) and decreased on days 3 and 7. Of note, for MR-proADM the highest median values were measured on day 7 from the onset of the FN episode. The median length of stay in the hospital at the onset of the FN episode for children who fulfilled the criteria for sepsis was 22 days and differed significantly from those without (10 days) (p=0.01). Patients who fulfilled the criteria for sepsis had a significantly lower median WBC count at onset and differed significantly from those without (700/μL vs 1340/μL; p=0.04). Contrarily, although the median ANC of patients with sepsis was lower than those without, no statistical significance was found (230/μL vs 457/μL; p=0.06). Criteria for sepsis were fulfilled for 31 (44%) and 7 (10%) patients were admitted to PICU. All-cause mortality on day 28 was 4% (3 patients, two with candidemia/invasive candidiasis and one with sepsis due to invasive aspergillosis/COVID-19 infection. All three biomarkers were significantly higher in children with sepsis than in those without at the onset of the FN episode. Of note, the median PSP levels on day 1 were higher in children with sepsis compared to those without [179ng/ml (range: 77-560ng/ml) vs. 80ng/ml (range: 21-600ng/ml)] and differed significantly (p<0.00001).

Similarly, CRP and MR-proADM levels on day 1 were higher in children with sepsis and differed significantly from those without (p=0.06 and p=0.02, respectively). Baseline characteristics, laboratory data, focus of infection, outcome, and median values of PSP, MR-proADR, and CRP in patients with and without sepsis during the onset of the FN episode are shown in **Table 3**. Additionally, we compared biomarker levels between patients with and without bloodstream infections (BSI). Patients with BSI had prolonged hospitalization compared to those without (median 20 vs 14 days) but did not differ significantly (p=0.16). Similarly, to patients with sepsis, those with BSI had a lower median value of WBC and ANC but did not differ significantly between the 2 groups (p=0.15 and p=0.10, respectively). Of note, the median value of PSP on day 1 differed significantly between patients with and without a BSI [174ng/ml (range: 81-560ng/ml) vs 89ng/ml (range: 21-600ng/ml)] (p=0.03).

Similarly, the median value of MR-proADR on day 1 differed significantly among patients with BSI and those without (p=0.04). Contrarily to this, the median CRP value was higher for children with BSI but did not differ significantly (p=0.21). **Table 4** shows baseline patients' characteristics, clinical and laboratory data, focus on infection, outcome, median PSP, MR-pro-ADR, and CRP values in patients with and without BSI.

In order to determine the capability of biomarkers to detect severe infection and sepsis, ROC curve analysis was conducted for each biomarker. The specificity of PSP, MR-proADM, and CRP were 0.82, 0.70, and 0.57 respectively. The sensitivity of PSP, MR-proADM,

Table 2. Biomarkers levels at time points.

	Day 1	Day 3	Day 7
PSP (ng/ml)	179 (77-560)	80 (21-600)	75 (22-219)
CRP (mg/dl)	7.08 (0.33 – 32)	3.04 (0 – 30.6)	4.60 (0.12-27.82)
MR-pro-ADR (nmol/L)	0.314 (0.05-2.729)	0.333 (0.05-2.306)	0.609 (0.05-3.015)

Table 3. Baseline characteristics of patients with and without sepsis.

	Sepsis	Non sepsis	p value
Males	14	15	0.46
Females	17	24	
Median age (years)	5(1-18 years)	5(1-18 years)	0.5
Length of stay at onset (days)	22 (1-110)	10 (0-28)	0.01
White blood cell count (onset) (/µL)	770	1340	0.04
Absolute neutrophil count (onset) (/µL)	236	457	0.06
Focus of infection			
No focus of infection	0	33	
Focus of infection	31	6	
Positive blood culture (BSI)			
Gram negative bacteria	14	0	
Gram positive bacteria	1	1	
Fungemia (candidemia)	2	0	
CRP (mg/dl)	7.08 (0.33-32)	3.04 (0-30.6)	0.06
PSP (ng/L)	179 (77-560)	80 (21-600)	<0.00001
MR-proADR (nmol/L)	0.559 (0.05-2.729)	0.196 (0.05-0.858)	0.02
ICU transfer	7	0	
Death	2	1	

Table 4. Baseline line characteristics of patients with BSI.

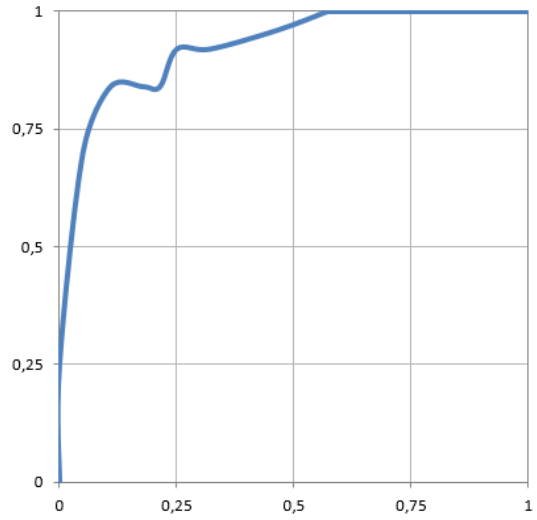
	BSI	Non BSI	p value
Males	7	23	0.3
Females	10	30	
Median age (years)	6 (1-18 years)	4.5 (1-18 years)	0.5
Length of stay at onset (days)	20 (1-95)	14 (0-110)	0.16
White blood cell count (onset) (/µL)	940	1868	0.15
Absolute neutrophil count (onset) (/µL)	210	406	0.10
CRP (mg/dl)	6.77 (4.14-32.0)	5.46 (0-30.6)	0.21
PSP (ng/L)	174 (81-560)	89 (21-600)	0.03
MR-proADR (nmol/L)	0.526 (0.05-2.729)	0.297 (0.05-0.858)	0.04
Sepsis	15	16	
ICU transfer	2	5	
Outcome			
Resolution	18	49	
Death	2	1	

and CRP were 0.84, 0.74, and 0.88, respectively. The positive predictive value (PPV) of PSP, MR-proADM, and CRP were 0.81, 0.64, and 0.68, respectively. The negative predictive value (NPV) of PSP, MR-proADM, and CRP were 0.85, 0.84, and 0.78, respectively. The AUC (area under the curve) of PSP, MR-proADR, and CRP were 0.80 (CI 95%: 0.67 – 0.92), 0.68 (CI 95%: 0.50 – 0.86) and 0.67 (CI 95%: 0.52 – 0,82), respectively. The AUC for PSP, MR-proADR, and CRP are shown in **Figure 1-3**.

Discussion. Children and adolescents with hematological malignancies represent a particular population at risk for developing FN after conventional antitumoral therapies due to defects in immunity and mucosal integrity.[6] Many prognostic models for febrile neutropenic episodes have been reported in the literature; however, it remains still challenging to predict outcomes and distinguish septic from non-septic and bacteremic from non-bacteremic patients.[8-10]

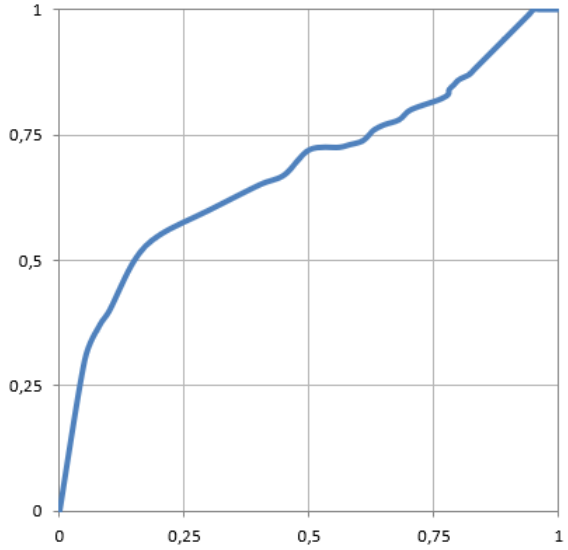
Our study evaluated the role of the newer biomarkers PSP and MR-proADM compared to CRP in febrile neutropenic children with hematological malignancies. According to our findings, PSP is a promising biomarker

Figure 1. AUC for PSP.



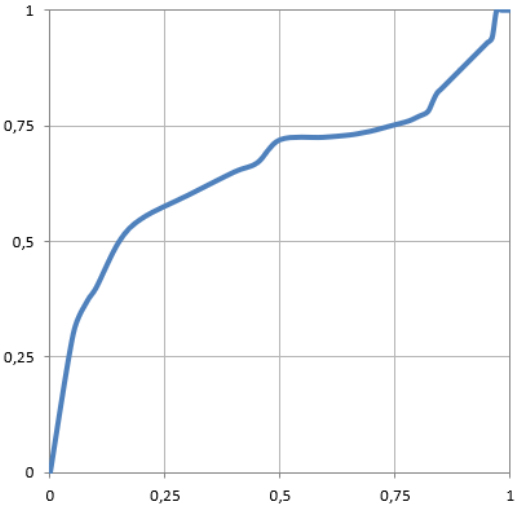
AUC Graph PSP = 0.80 (CI 95%: 0.67 – 0.92).

Figure 2. AUC for MR-proADR.



AUC mid-proADM Graph = 0.68 (CI 95%: 0.50 – 0.86).

Figure 3. AUC for CRP.



AUC CRP Graph = 0.67 (CI 95%: 0.52 – 0,82).

for early diagnosis of sepsis during FN episodes in children with hematological malignancies. PSP has the best AUC compared to MR-proADM and CRP, with high sensitivity and specificity. For both biomarkers, sensitivity and specificity were high, although CRP presented the highest sensitivity (0.88) but poor specificity (0.57), as already reported in the literature in single studies but also in the recent systematic review by Van der Velden et al.[9]

PSP has been studied and compared to other biomarkers in neonates and children with infection, sepsis, osteomyelitis, and in those admitted to pediatric ICU. To our knowledge, no data about kinetics and the role of PSP in febrile neutropenic children with hematological malignancies are available in the literature. In a recent review, Eggimann et al. concluded that in 12 out of 13 studies performed in different clinical settings in the adult population, PSP proved to be more accurate and with a higher specificity and sensitivity in comparison to CRP, PCT, and IL-6.[15] Apart from the adult setting, PSP has been evaluated as a diagnostic marker of sepsis-related organ failure in 62 pediatric patients admitted in the ICU and has shown high specificity and a low sensitivity value (0.92 and 0.50, respectively). Based on their results, the authors of the abovementioned study concluded that PSP values did not differ between patients with systemic inflammatory response syndrome and sepsis; however, those who died had higher PSP levels compared to survivors.[16] Another study in the pediatric setting evaluated and compared PSP, CRP, and PCT as prognostic factors in children with sepsis and septic shock, and according to their findings, the accuracy (AUC) to predict death was for PSP=0.83, for PCT=0.76, and for CRP=0.73. These findings are similar to ours regarding PSP and CRP, although patients were non-neutropenic. The authors concluded that all the abovementioned biomarkers can predict the outcome, and combining all three improves the prediction significantly.[17] In the setting of the neonatal population, various studies have evaluated PSP as a predictor of sepsis and have shown that its accuracy (AUC) for infection and sepsis is high alone or in combination with PCT.[18,19] To our knowledge, only a recent study by de Guadiana-Romualdo et al. evaluated biomarkers' role in adult cancer patients. In this study, like ours, 105 febrile neutropenic adult patients with cancer and PCT, PSP, and sCD25 were measured at presentation to evaluate these markers' ability to diagnose infection and outcome. All biomarkers were significantly higher in infected patients, and PCT presented the highest diagnostic accuracy for infection (AUC: 0.901), whereas PSP and sCD25 had a lower and similar performance (AUC: 0.751 and 0.730, respectively).[28] In our study, the AUC of PSP was superior (0.80); however, the methodology differed as we focused particularly on the diagnostic performance of

PSP for diagnosis of early-onset sepsis in pediatric febrile neutropenic patients. Other studies in the adult setting with sepsis-related complications have shown that PSP levels have a high diagnostic accuracy in discriminating the severity and outcome.[29-35] In our study, PSP was superior in discriminating between patients with sepsis and those without and between patients with and without a BSI.

MR-proADR has been demonstrated to have an impact as a prognostic marker for bacteremia, sepsis, FN, and pneumonia.[20-23,36-46] In our study, MR-proADM has shown a sensitivity and specificity value of 0.70 and 0.74, respectively. A recent systematic review evaluated the diagnostic accuracy of MR-pro-ADM in identifying children with invasive bacterial infections. In the meta-analysis, four studies were selected that included 1404 patients aged between day one of life and 12 years. Only one study was of high quality, accounting for the majority of patients. A single study reported the diagnostic accuracy of MR-pro-ADM for invasive bacterial infection, reporting an AUC of 0.69.[21] Agnello et al. investigated the roles of presepsin and MR-proADM in 36 FN episodes of 26 children with cancer and found that both presepsin and MR-proADRM have poor clinical usefulness for the outcome of FN episodes.[38] A recent study that evaluated 36 FN episodes of 14 children with solid tumors has shown that the first-day plasma MR-proADM levels significantly predicted the presence of culture positivity (AUC 0.628) and high risk patients with neutropenic fever (AUC 0.76).[42] Demirkaya et al. compared MR-proADM with CRP and PCT in pediatric cancer patients. Among these biomarkers, PCT demonstrated the highest correlation with the severity of infection, and adrenomedullin levels on day 3 were significantly higher in the microbiologically documented infection group than those in the clinically documented infection group and patients with fever of unknown origin.[43] In the adult setting, the role of MR-proADM and PCT as novel biomarkers for predicting infections in febrile patients with hematogical malignancies has been evaluated on 340 patients, 103 with sepsis and 159 with SIRS. Similarly, to our results, the initial pro-ADM levels were significantly higher in neutropenic patients with BSIs than in those without documented infections. Levels of MR-pro-ADM decreased in response to antimicrobial therapy in patients with bacterial infection (p=0.007), as our results also show.[41]

Our study, although prospective, has several limitations. It is a single-center study with a small number of patients/episodes during a short period (2 years). Despite this, our findings have demonstrated that PSP, in particular, is a promising marker for early diagnosis of sepsis and bacteremia in febrile neutropenic children with cancer. PSP has a higher AUC than CRP and MR-proADM, with a higher sensitivity and specificity, and could predict high-risk patients for sepsis-related complications (ICU transfer, bacteremia, death). Additionally, both can be useful, especially if combined with CRP, for the early diagnosis of severe infection and for triaging patients based on the risk of sepsis. PSP expected from the high sensitivity and specificity, through its negative predictive value, seems to predict patients who develop sepsis. Unfortunately, we had some problems timely performing PCT, so no comparison was possible with this important marker of sepsis. Further studies are required to understand the diagnostic accuracy of both tests, particularly alone and in a minor grade in combination, in predicting the outcome of high-risk febrile neutropenic children with hematological malignancies at the onset of the episode and during its course.

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