

Prognostic role of mid-regional pro-adrenomedullin in predicting infection in pediatric cancer with febrile neutropenia

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Background: Febrile neutropenia (FN) remains an important complication of cytotoxic chemotherapy for which an urgent and appropriate evaluation is imperative.

Purpose: To assess the diagnostic and prognostic roles of mid-regional pro-adrenomedullin (MR-ProADM) levels in predicting infection in patients with FN.

Methods: This comparative cross-sectional study included 137 patients with chemotherapy-induced FN. Complete blood count, C-reactive protein (CRP), procalcitonin (PCT), and MR-ProADM were evaluated on the 1st day of FN. Chest computed tomography was performed on the 5th day.

Results: MR-ProADM levels were significantly higher in patients with FN than in controls. CRP and MR-ProADM levels were significantly higher and absolute neutrophil count (ANC) was significantly lower in patients with versus without bacterial infections. CRP, PCT, and MR-ProADM levels were significantly negatively correlated with ANC. CRP, PCT, and MR-ProADM levels were significantly and positively correlated with FN degree, FN duration, and hospital stay length. A multivariate regression analysis showed that a longer FN duration and hospital stay length, along with elevated CRP, PCT, and MR-ProADM levels, were significant risk factors for mortality.

Conclusion: MR-ProADM is a reliable prognostic and diagnostic tool for predicting infection in patients with FN.

Key words: Febrile neutropenia, Mid-regional pro-adrenomedullin, Pediatric cancer

are higher among patients with FN and a bacterial infection.

- A longer FN duration and hospital stay length as well as elevated C-reactive protein, procalcitonin, and MR-ProADM levels are significant risk factors for mortality.

Introduction

According to guidelines from the Infectious Diseases Society of America, American Society of Clinical Oncology, and National Comprehensive Cancer Network, febrile neutropenia (FN) is characterized by an oral temperature exceeding 38.3°C or a continuous temperature above 38.0°C for one hour, along with an absolute neutrophil count (ANC) ≤ 500 cells/mm³ within 48 hours.¹⁾ The outcome of an episodic fever and neutropenia is determined by how long the neutropenia and fever last. While some individuals can improve within 48 hours of starting broad-spectrum antibiotics, extended FN lasting over 5 days is often linked to fungal infections, which are harder to treat and have higher death rates.²⁾

Different tools have been examined to identify a prompt detection of bacterial infection by utilizing inflammatory response regulators like C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-10, procalcitonin (PCT), and midregional proadrenomedullin (MR-ProADM).³⁻⁵⁾

CRP is the biomarker that is used most frequently. CRP peaks at its highest level 36–48 hours post the start of the infectious episode. The biomarker's slow kinetics may lead to false negative results during this specific time period in the episode. PCT has been recognized as a sign of bacterial sepsis and severe infection with greater diagnostic precision than CRP.⁶⁾ Because of its favorable kinetics, it is seen

Key message

- Infection remains a leading cause of death in febrile neutropenia (FN).
- Mid-regional pro-adrenomedullin (MR-ProADM) levels

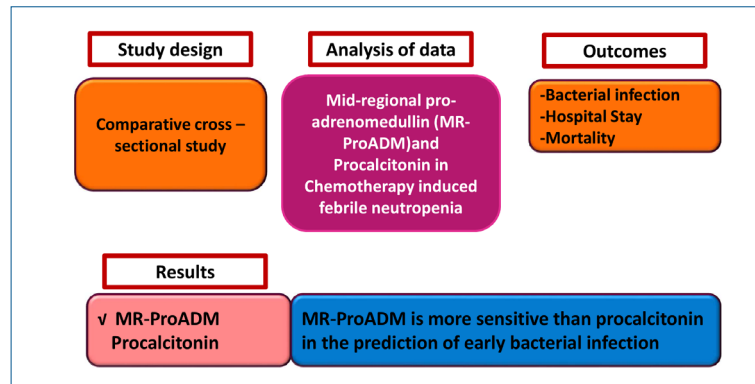
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Graphical abstract. MR-ProADM, midregional proadrenomedullin.

as a better option for use in the Emergency Department as its peak only 2–6 hours following the bacterial stimulus, with peak levels appearing at 12–36 hours. MR-ProADM is generated and released by various mammalian organs in response to both normal and disease-related stress.⁷⁾

MR-ProADM levels were found to progressively rise in line with the seriousness of the condition.^{8,9)} A review of studies indicates that MR-ProADM could potentially aid in diagnosing serious bacterial infections in children. Should MR-ProADM show better accuracy than current biomarkers for detecting early bacterial infections in children, it could potentially aid in identifying individuals needing urgent antibiotic treatment, intensive care, and tracking treatment progress.¹⁰⁾

So, we aimed to assess the diagnostic and prognostic role of MR-ProADM in predicting infection in patients with FN.

Methods

1. Study design

A comparative cross-sectional study was conducted on 137 patients with chemotherapy-induced FN. They were selected from the Hematology and Oncology Unit, Pediatric Department, Menoufia University Hospital, and Nasser Institute Hospital. The severity of neutropenia can be classified as mild (ANC: $1.0\text{--}1.5 \times 10^9/\text{L}$), moderate (ANC: $0.5\text{--}1.0 \times 10^9/\text{L}$), severe (ANC: $0.2\text{--}0.5 \times 10^9/\text{L}$),¹¹⁾ and profound neutropenia (ANC $<0.1 \times 10^9/\text{L}$).^{12,13)}

Risk group assessment of neutropenia included low and high-risk groups. Low-risk group includes (1) acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma and solid tumors in remission; (2) duration of neutropenia <7 days; (3) nontoxic appearance; (4) no focal infection, mucositis or diarrhea. High-risk group includes (1) uncontrolled malignancy (i.e., relapse, refractory or induction); (2) acute myeloid leukemia, high-risk ALL in consolidation or delayed intensification; (3) high dose cytarabine; (4) prolonged neutropenia 7 days and profound neutropenia

$<0.1 \times 10^9/\text{L}$; (5) toxic appearance, hypotension, rigors, shock, tachypnea or hypoxia; (6) evidence of infection: pneumonia, cellulitis, diarrhea and mucositis; (7) known colonization with MRSA (methicillin-resistant strains of *Staphylococcus aureus*); (8) prior history of bacteremia/sepsis.¹⁴⁾

2. Ethical consideration

Menoufia University's Faculty of Medicine Ethical Committee approved the study (approval ID number: 8/2023 PEDI 3). Consent was acquired from all patients and their guardians after they were briefed on the advantages and disadvantages of the research.

3. Data collection

All patients underwent clinical assessment, including full history taking and clinical examination. Laboratory investigations such as complete blood count, CRP, PCT, and MR-ProADM were performed on the first day of FN. Blood samples for bacterial and fungal cultures were collected from either peripheral or central lines. Furthermore, tests for sputum culture and complete urine culture were conducted. On the fifth day of having a fever and low ANC, a chest computed tomography (CT) scan was performed.

CBC was examined using the Sysmex KX-21 automated hematology analyzer (Sysmex Corp., Kobe, Japan). CRP levels were assessed using a CRP analyzer (Labcompare, South San Francisco, CA, USA). PCT testing was conducted with a Cobas e 601 analyzer (Roche Diagnostics, Rotkreuz, Switzerland). The Bact/ALERT 3D blood culture system (BioMerieux, Marcy-l'Étoile, France) was used to process blood cultures, and the Vitek-2 compact system (Bio Merieux) was used for colony identification.

Human MR-ProADM SunRed ELISA kits (Catalogue No. 201-12-7275) from Shanghai SunRed Biological Technology Co., Ltd (Shanghai, China) were used to measure MR-ProADM levels, in accordance with the manufacturer's guidelines.

The collection of samples required extracting 5 mL of

venous blood with strict aseptic measures on both the 1st and 5th days of FN. Three milliliters was designated for blood culture, with 2 mL being transferred into a plain tube and spun at 4,000 rpm for 10 minutes. The collected serum was kept at -20°C until MR-ProADM levels were measured with enzyme-linked immunosorbent assay.

4. Sample size determination

After reviewing previous studies¹⁾ that showed MR-ProADM's AUC in FN was 0.94, the sample size of 124 parti-

cipants was calculated using statistics and Sample Size Pro Tool version 6. Having a confidence level of 95% and a power of 80%, the sample size was raised to 137 participants.

5. Statistical analysis

The data were encoded, inputted, and analyzed on a computer utilizing IBM SPSS ver. 18.0 (IBM Co., Armonk, NY, USA). The findings were displayed in tables and graphs and explained. Mean, standard deviation, range (minimum and maximum values), and percentage were utilized for descriptive statistics. The Spearman correlation test was utilized to determine the correlation among the parameters. A study was conducted using multiple linear regression to explore the correlation between the dependent variable MR-ProADM and various independent variables. Receiver operating characteristic (ROC) was developed to assess biomarker effectiveness by pinpointing areas where sensitivity and specificity reach their highest levels for accuracy. The significance test was conducted with a *P* value < 0.05.

Results

The demographic data and laboratory investigations for

Table 1. Demographic data, malignancy type, chemotherapy stage, and febrile neutropenia characteristics among the studied patients (n=137)

Variable	Value
Age (yr)	
Mean±SD	8.65±4.83
Range	2–16
Sex	
Male	92 (67.2)
Female	45 (32.8)
Type of malignancy	
Neuroblastoma	15 (10.9)
AML	24 (17.5)
ALL-pre-B	60 (43.8)
ALL-T-cell	29 (21.2)
Burkitt lymphoma	6 (4.4)
Wilms tumor	3 (2.2)
Chemotherapy stage	
Induction	67 (48.9)
Consolidation	13 (9.5)
Continuation (reinduction)	57 (41.6)
Septic focus	
No septic focus	47 (34.3)
Pneumonia	23 (16.8)
Typhlitis	28 (20.4)
Gastroenteritis	16 (11.7)
Oral mucositis	12 (8.8)
Perianal fissure	11 (8.0)
Degree of febrile neutropenia	
Mild (ANC: 1.0–1.5×10 ⁹ /L)	6 (4.4)
Moderate (ANC: 0.5–1.0×10 ⁹ /L)	22 (16.1)
Severe (0.2–0.5×10 ⁹ /L)	53 (38.7)
Profound (ANC <0.1×10 ⁹ /L)	56 (40.9)
Risk of febrile neutropenia	
Low risk	107 (78.1)
High risk	30 (21.9)
Duration of febrile neutropenia (day)	
Mean±SD	5.20±1.70
Range	2–21
Duration of hospital stay (day)	
Mean±SD	20.50±3.40
Range	5–40

Values are presented as number (%) unless otherwise indicated. SD, standard deviation; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Table 2. Blood, urine, and sputum culture results and radiological findings of the studied cases (n=137)

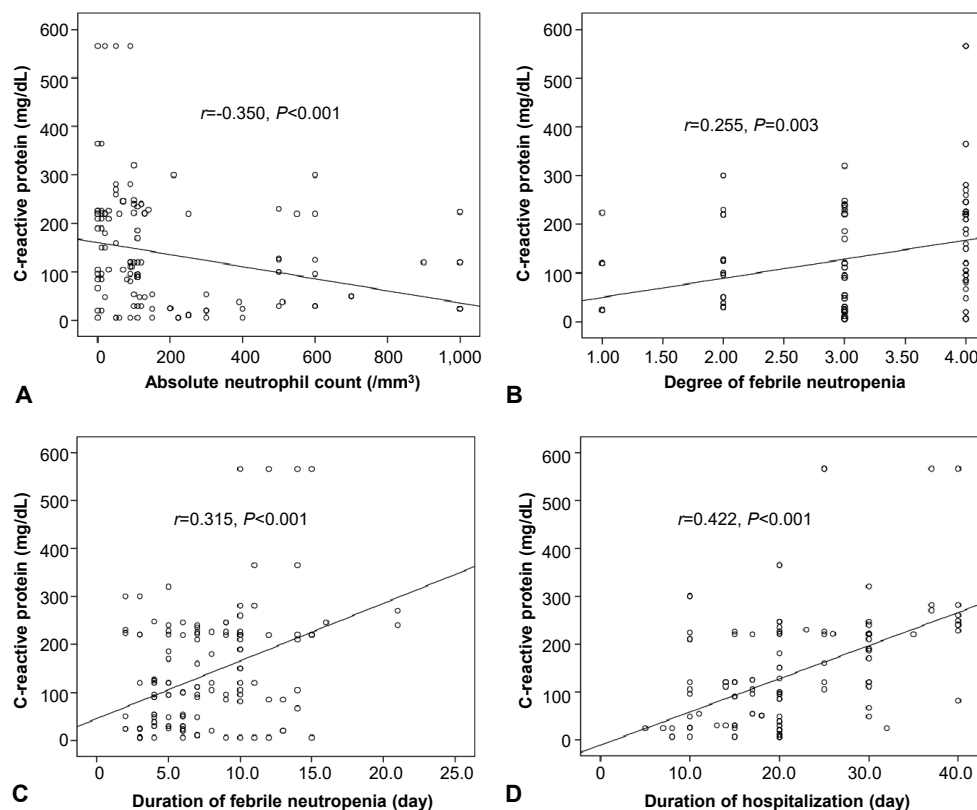
Variable	No. (%)
Blood culture	
No growth	100 (73.0)
<i>Klebsiella</i>	29 (21.2)
<i>E. coli</i>	6 (4.4)
<i>Actinobacter</i>	2 (1.5)
Urine culture	
No growth	126 (92.0)
<i>E. coli</i>	2 (1.5)
<i>Candida</i>	9 (6.6)
Sputum culture	
No growth	130 (94.9)
<i>Pseudomonas</i>	5 (3.6)
<i>Actinobacter</i>	2 (1.5)
Chest x-ray	
Normal	99 (72.3)
Pneumonia	31 (22.6)
Cardiomegaly	2 (1.5)
Pleural effusion	5 (3.6)
CT chest on the fifth day of FN	
Not done	7 (5.1)
Normal	97 (70.8)
Pneumonia	26 (19.0)
Pleural effusion	7 (5.1)

CT, computed tomography; *E. coli*, *Escherichia coli*; FN, febrile neutropenia.

Table 3. Laboratory investigation results of patients with versus without bacterial infections (n=137)

Variable	Cases with bacterial infection (n=49)	Cases without bacterial infection (n=88)	t test	P value
CRP (mg/dL)			4.494	<0.001
Mean±SD	114.2±12.16	68.9±10.56		
Range	6–356	6–120		
Midregional proadrenomedullin (pg/mL)			16.047	<0.001
Mean±SD	703.65±100.3	492.04±124.9		
Range	540–900	300–600		
Procalcitonin (ng/mL)			0.509	0.612
Mean±SD	17.6±2.81	18.19±3.2		
Range	0–100	0–100		
Absolute neutrophil count (ANC) (/mm ³)			7.565	<0.001
Mean±SD	214.85±96.87	611.83±192.27		
Range	0–500	0–1,100		

CRP, C-reactive protein; SD, standard deviation.

Boldface indicates a statistically significant difference with $P<0.05$.**Fig. 1.** Correlation between C-reactive protein level and different parameters: (A) absolute neutrophil count, (B) febrile neutropenia degree, (C) febrile neutropenia duration (days), (D) hospitalization length (days).

the studied groups are shown in Table 1.

Pre-B ALL was the most common type of pediatric cancer, making up 43.8%, followed by T-cell ALL at 21.2%. 49% of cases were in the induction stage of chemotherapy. Typhlitis was the most frequent septic focus, then pneumonia, oral mucositis, and perianal fissure. FN lasted from 2 to 21 days, and hospitalization ranged from 5 to 40 days. Profound FN was the predominant type in 40.9% of cases. The majority of cases (78.1%) were associated with low-risk

FN as revealed in Table 1.

Regarding cultures and radiological imaging, a standard CT chest on the 5th day for FN cases showed that 70.8% had a normal CT chest, 19% had pneumonia, and 5.1% had pleural effusion. The findings from the blood cultures indicated that *Klebsiella* was present in 21.2% of cases, *Escherichia coli* in 4.4%, and *Actinobacter* in 1.5%. The results of the urine culture revealed *Candida* in 6.6% of the samples and *E. coli* in 1.5% of the samples.

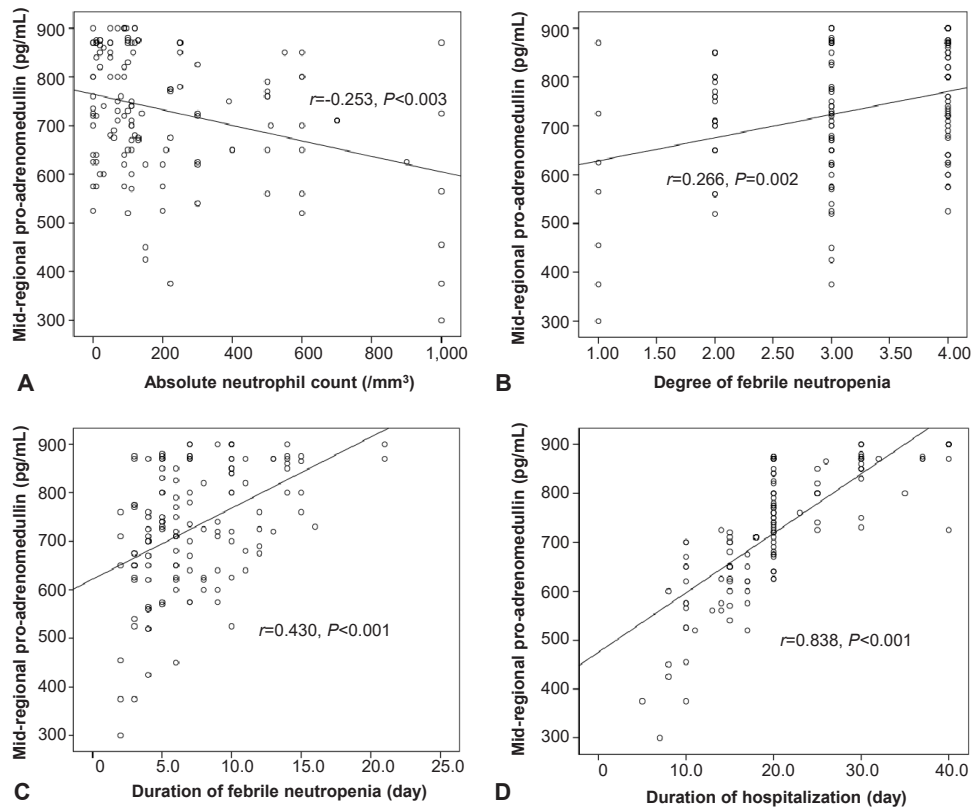


Fig. 2. Correlation between midregional proadrenomedullin level and different parameters: (A) absolute neutrophil count; (B) febrile neutropenia degree; (C) febrile neutropenia duration (days); (D) hospitalization length (days).

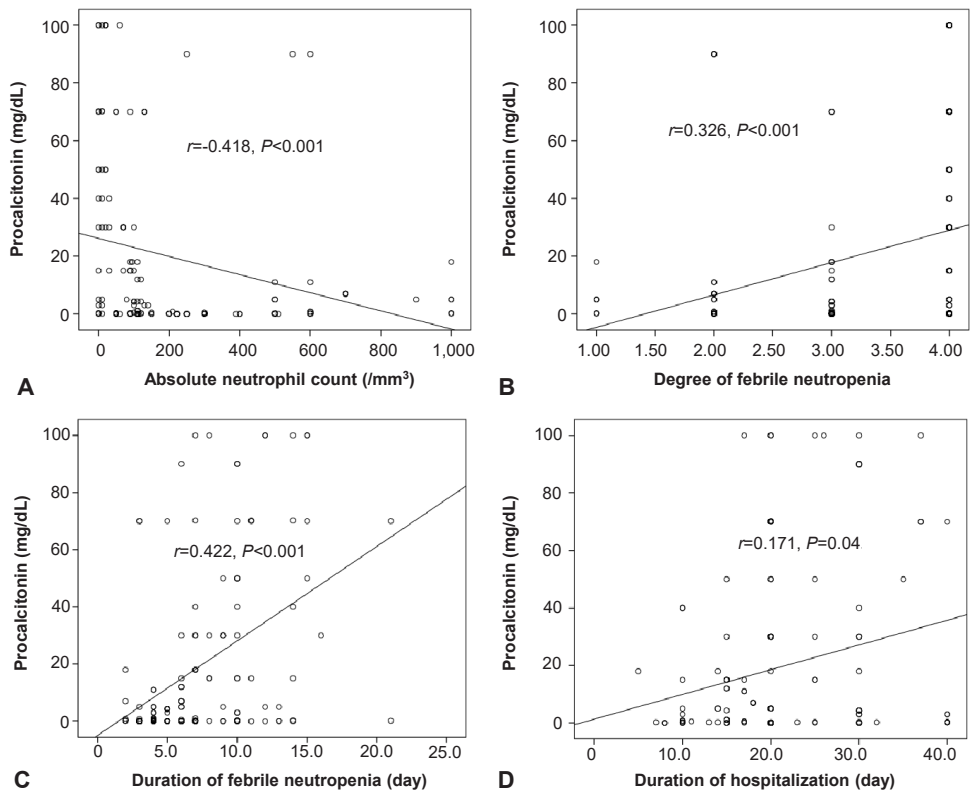


Fig. 3. Correlation between procalcitonin and different parameters: (A) absolute neutrophil count; (B) febrile neutropenia degree; (C) febrile neutropenia duration (days); (D) hospitalization length (days).

Table 4. Comparison between survivors and nonsurvivors according to CRP, procalcitonin, and midregional proadrenomedullin levels (n=137)

Variable	Survivors (n=118)	Nonsurvivors (n=19)	t test	P value
CRP (mg/dL)			3.058	0.003
Mean±SD	101.81±12.57	191.11±44.63		
Range	6–226	105–566		
Midregional proadrenomedullin (pg/mL)			3.867	<0.001
Mean±SD	581.58±69.64	707.2±104.23		
Range	260–700	540–900		
Procalcitonin (ng/mL)			2.725	0.013
Mean±SD	14.03±2.78	39.32±2.66		
Range	0–100	3–100		

CRP, C-reactive protein; SD, standard deviation.

Boldface indicates a statistically significant difference with $P<0.05$.

Pseudomonas was present in 3.6% of sputum cultures, while *Actinobacter* was found in 1.5% as shown in Table 2.

MR-ProADM and CRP were significantly higher and ANC was significantly lower in cases with bacterial infection than those without bacterial infection as shown in Table 3.

CRP, PCT, and MR-ProADM had a significant negative correlation with ANC ($r=-0.350$, $P<0.001$; $r=-0.253$, $P=0.003$; $r=-0.418$, $P<0.001$ respectively). CRP, PCT, and MR-ProADM had a significant positive correlation with the degree of FN, duration of FN, and prolonged hospitalization. MR-ProADM had a significant strong positive correlation with hospitalization ($r=0.838$, $P<0.001$) as shown in Figs. 1-3.

Significantly higher levels of CRP, PCT, and MR-ProADM were observed among nonsurvivors as shown in Table 4.

Multivariate regression analysis for mortality among the studied cases showed that the age, being male, having septic focus, prolonged hospital stay, high levels of CRP, PCT, and MR-ProADM were all significant risk factors contributing to mortality in the FN cases as shown in Table 5.

The ROC curve analysis of PCT indicated a cutoff value of 0.08 ng/dL, with an AUC of 0.780; and sensitivity, specificity, PPV, and NPV values were 82%, 66%, 69.3%, and 78.9 %, respectively. The cutoff value for MR-ProADM was 489 pg/mL, with an AUC of 0.964, and sensitivity, specificity, PPV, and NPV were 90.5%, 82.6%, 87.9%, and 88.2%, respectively, as illustrated in Fig 4.

Discussion

FN continues to be a significant side effect of cytotoxic chemotherapy treatment. MR-proADM was beneficial for assessing the seriousness and outcome of sepsis and community-acquired pneumonia in children.^{15,16)}

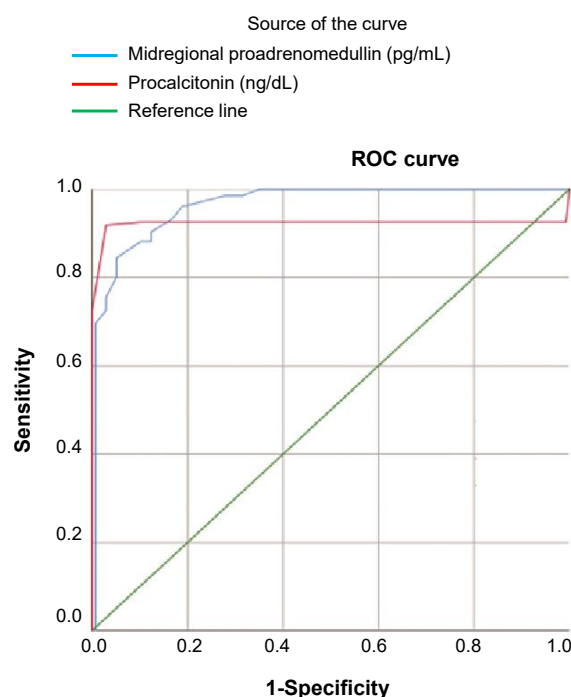
The FN patients showed notable reductions in hemoglobin, platelets, white blood cells, and ANC in comparison

Table 5. Multivariate regression analysis of mortality among study groups

Characteristic	Risk of mortality		
	Exp (B)	95% CI	P value
Age	1.367	1.100–2.005	0.014
Sex	1.116	1.001–2.213	0.036
Septic focus	1.311	1.109–3.164	0.035
Duration of febrile neutropenia	2.519	0.998–4.655	0.003
Degree of fever	0.843	0.791–1.456	0.261
Duration of hospitalization	1.456	1.132–2.961	0.012
CRP	2.089	2.001–4.567	0.036
Procalcitonin	1.834	1.025–2.073	0.038
Midregional proadrenomedullin	2.009	1.842–4.412	0.006

CI, confidence interval; CRP, C-reactive protein

Boldface indicates a statistically significant difference with $P<0.05$.

**Fig. 4.** Receiver operating characteristic curve analysis of both midregional proadrenomedullin and procalcitonin in the prediction of infection in febrile neutropenia patient.

to the control groups. At admission, levels of MR-ProADM were significantly higher in FN cases compared to controls. Furthermore, patients with bacteremia exhibited elevated MR-ProADM and CRP levels in comparison to patients without bacteremia.

This aligns with the findings of Agnello et al.,¹⁷⁾ who observed higher MR-ProADM levels upon admission that decreased over the subsequent days, likely as a result of the response to antibiotic treatment. Antari et al.¹⁸⁾ found increased CRP and MR-ProADM levels in infected children with hematological malignancy experiencing FN. Baumann et al.¹⁹⁾ discovered that MR-ProADM levels were higher on day 1 of admission especially in children with Gram-negative bacteremia. Al Shuaibi et al.²⁰⁾ demonstrated elevated MR-ProADM levels in FN patients with hematological malignancies. Patients with bacteremia had higher levels compared to patients without bacteremia.

The most common type of malignancy was pre-B ALL (43.8%) and T-cell ALL (21.2%). The most cases were in the induction stage of chemotherapy (48.9%). Typhlitis was the most prevalent septic focus at 20.4%, with pneumonia being the second most common at 16.8%. The duration of FN varied from 2 to 21 days leading to an extended hospital stay. The most common type of FN was profound one (40.9%). Most cases (78.1%) show low risk of FN with a duration lasting between 2 to 21 days.

Agnello et al.¹⁷⁾ reported that ALL was the most common type of malignancy, with duration of FN ranging from 6 to 33 days leading to extended hospital stay.

Regarding blood culture *Klebsiella* was present in 21.2% of cases, *E. coli* in 4.4%, and *Acinetobacter* in 1.5%. *Candida* was found in the urine culture of 6.6% of them, while 1.5% had *E. coli* detected. 3.6% of patients tested positive for *Pseudomonas* in sputum culture, while 1.5% tested positive for *Acinetobacter*. A study by Agnello et al.¹⁷⁾ showed that 22% of cases were caused by Gram-positive bacteria, while 7% were attributed to Gram-negative bacteria. Antari et al.¹⁸⁾ found that 19% of FN episodes were due to Gram-negative bacteria, while each Gram-positive bacteria and invasive fungal infections (candidemia) accounted for 3% of episodes. The Gram-negative organisms that were isolated included *Pseudomonas aeruginosa*, *E. coli*, and *Klebsiella*.

In our research, ANC showed a significant negative correlation with CRP, PCT, and MR-ProADM. CRP, PCT, and MR-ProADM showed a significant positive relationship with the severity of FN, length of FN, and prolonged hospital stay. MR-ProADM showed a strong positive correlation with prolonged hospitalization. The age, being male, having a septic focus, prolonged hospital stay, high CRP, PCT, and MR-ProADM levels were all important factors contributing to mortality.

Agnello et al.¹⁷⁾ discovered a significant positive correlation between MR-ProADM and prolonged hospitalization with no significant correlation with neutrophil count or fever duration. Elevated levels of MR-ProADM upon admission in critical patients have been linked to elevated mortality rates.²¹⁾ Elevated MR-ProADM and PCT levels in critically ill children were linked to higher mortality risk scores.²²⁾ Levels of MR-ProADM and PCT can indicate the seriousness of sepsis in children, aiding in early diagnosis and prognosis evaluation. The diagnostic efficacy of MR-ProADM was superior to PCT.²³⁾ Elevated MR-ProADM levels were found in children with sepsis who needed mechanical ventilation and in those who experienced in-hospital death.²⁴⁾ Levels of MR-ProADM were notably elevated in FN cancer patients who did not respond to antimicrobial treatment compared to those who did respond.²⁵⁾ Fawzi et al.²⁶⁾ found that levels of MR-ProADM were significantly higher in severely neutropenic young patients with hematological malignancies who had bacterial infections.

The AUC for MR-ProADM was 0.964, featuring sensitivity and specificity of 90.5% and 82.6%, respectively, whereas the AUC for PCT was 0.780, with sensitivity and specificity at 82% and 66%, respectively, according to our findings.

Corr et al.²⁷⁾ indicated the diagnostic accuracy of MR-proADM for invasive bacterial infection (IBI), highlighting an AUC of 0.69. On the first day, MR-ProADM levels significantly detecting culture positivity (AUC, 0.628) and identified high-risk patients with neutropenic fever (AUC, 0.76).²⁸⁾ MR-proADM exhibited sensitivity and specificity rates of 0.70 and 0.74, respectively.¹⁸⁾ The AUC of PCT was 0.665, displaying a sensitivity of 38.9% and a specificity of 91.7%, respectively.²⁹⁾

MR-proADM played a role in the clinical pathway of children with IBI and aided in identifying IBI through scoring systems or as a prognostic tool that could highlight children requiring intensive care.²⁷⁾ Lan and Zhang³⁰⁾ showed that MR-ProADM levels can predict the severity of sepsis. MR-proADM has been associated with endothelial injury, indicating organ damage during critical conditions like septic shock.³¹⁾

MR-proADM seems to be a biomarker with significant prognostic value. This conclusion is additionally backed by a collection of experimental evidence highlighting ADM's significant role in controlling vascular permeability, endothelial barrier function, inflammatory mediators, and microcirculation.³²⁾ MR-proADM, a reliable surrogate marker of adrenomedullin, is thought to significantly contribute to decreased vascular permeability and is released following hyperpermeability in the microcirculation and subsequent capillary leakage. It functions as a counter-regulator of disrupted microcirculation, tissue ischemia,

and tissue injury induced by inflammatory agents.³³⁾

MR-proADM might serve as a predictor of the outcomes for high-risk febrile neutropenic children with hematological cancers from the start of the episode and during its progression.

In conclusion, MR-ProADM plays a reliable prognostic and diagnostic role in predicting infection in patients with FN and their outcome.

Footnotes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Author Contribution: Conceptualization: SR, SE, AS, AM; Data curation: SR, SE, AS, AM; Formal analysis: AM, AS; Writing - original draft: SE, AM, AA; Writing - review & editing: SR, SE, AS, AM

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