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Original Article

Procalcitonin and proadrenomedullin in pediatric acute leukemia: biomarkers for infection and beyond

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ABSTRACT

Background. The clinical utility of procalcitonin (PCT) and proadrenomedullin (ProADM) in children with malignancies remains inadequately characterized. This study was designed to assess baseline PCT and ProADM levels at the time of leukemia diagnosis and to compare their profiles during subsequent episodes of febrile neutropenia (FN).

Methods. Children aged 18 years or younger with newly diagnosed acute leukemia, including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), were prospectively recruited for this study. Serum levels of PCT and ProADM were measured at baseline, prior to the initiation of chemotherapy at the time of diagnosis, and were reassessed during subsequent episodes of FN.

Results. A total of 80 children with acute leukemia were prospectively enrolled, with a median age of 5 years (interquartile range [IQR]: 3-7 years). The study population comprised of ALL in 67.5% of cases and AML in 32.5%. At the time of diagnosis, prior to chemotherapy initiation (n=80), the median serum PCT level was 0.19 ng/mL (IQR: 0.07–0.54), while the median ProADM level was 0.04 nmol/L (IQR: 0.01–0.07). Among the 80 patients, 32 children subsequently developed FN and had paired serum samples available for comparative analysis. During FN episodes, both biomarkers showed a significant increase relative to baseline values. Median PCT increased from 0.16 ng/mL (0.08–0.52) at diagnosis to 0.32 ng/mL (0.08–0.50) during FN ($P = 0.03$), while median ProADM increased from 0.03 nmol/L (0.006–0.05) to 0.41 nmol/L (0.20–0.81) ($P < 0.001$). At the time of leukemia diagnosis, splenomegaly was the only clinical factor significantly associated with elevated baseline PCT levels ($P = 0.010$). Subgroup analysis revealed distinct biomarker patterns: in children with ALL, PCT levels remained largely unchanged between diagnosis and FN, possibly reflecting an underlying baseline inflammatory state, whereas ProADM showed a significant rise during FN, suggesting greater specificity for infectious events. In contrast, in AML, both PCT and ProADM increased significantly during FN, indicating their potential utility as infection-related biomarkers in this subgroup.

Conclusion. Both PCT and ProADM were significantly elevated in FN when patients with acute leukemia were analyzed as a whole. However, subgroup analysis revealed differing patterns: in ALL, only ProADM remained significantly associated with FN, whereas PCT showed no significant association. In contrast, in AML, both biomarkers were significantly elevated. These findings suggest that ProADM may have greater clinical utility in guiding the management of febrile episodes, particularly in ALL.

Key words: leukemia, procalcitonin, proadrenomedullin, febrile neutropenia, children.

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Infectious complications remain a leading cause of morbidity and mortality in children with acute leukemia. Current management strategies primarily rely on empirical antimicrobial therapy, often resulting in overuse and associated adverse consequences. Procalcitonin (PCT) and proadrenomedullin (ProADM) are infection-related biomarkers that have been extensively studied in the general population; however, their utility in immunocompromised cohorts, such as pediatric patients with acute leukemia, remains underexplored. Given their potential to differentiate between infectious and non-infectious inflammatory states, these biomarkers may serve as valuable adjuncts in the management of febrile episodes in this vulnerable population.[1,2]

Elevated PCT levels serve as a valuable biomarker for assessing the risk of bacterial infections, thereby aiding in the judicious use of antibiotics. This targeted approach to antimicrobial stewardship is crucial for minimizing unnecessary antibiotic exposure, which in turn helps mitigate the emergence of antibiotic resistance.[3] Secmeer et al. demonstrated that serial PCT measurements provide superior diagnostic value compared with C-reactive protein (CRP) in pediatric patients with neutropenic fever, particularly for assessing infection severity, fever duration, and potential etiology.[4] The diagnostic and prognostic significance of PCT has been explored in various malignancies.[5-9] Patients with solid tumors and metastatic disease, even in the absence of clinical or microbiological evidence of infection, exhibited significantly elevated PCT levels. This increase was especially pronounced in individuals with widespread metastatic involvement.[10] Additionally, elevated PCT levels have demonstrated potential utility in the diagnosis and monitoring of various non-infectious conditions, such as hypercalcemia, autoimmune, and immunological disorders.[11] Adrenomedullin (ADM) is a rapidly degraded peptide, and its biologically inactive fragment ProADM is generated as a more stable surrogate marker.[12]

These two biomarkers, PCT and ProADM, are not neutrophil-specific and are primarily derived from thyroidal C cells and the adrenal medulla, respectively. Consequently, their measurement remains valid and reliable even in the context of profound neutropenia.[13] No study has specifically evaluated the role of PCT and ProADM at the time of diagnosis in pediatric acute leukemia. This study aimed to assess their baseline levels before chemotherapy initiation and to compare them with levels measured during subsequent episodes of febrile neutropenia (FN).

Materials and Methods

Study population

A prospective observational study was conducted from June 2020 to March 2023 at the Department of Pediatrics of a tertiary care referral institute. Ethical clearance for this study was obtained from the Institute Ethics Committee (IEC-459/01.09.2017, RP-09/2017, OP-13/06.12.2019, RP-43/2019). Children aged ≤18 years with newly diagnosed acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were eligible for enrollment, provided that informed consent was obtained from a parent or legally authorized representative (LAR), along with assent from children aged over 7 years. Patients who had received antibiotic therapy within the 14 days preceding their acute leukemia diagnosis were excluded from the study.

Data collection

At the time of leukemia diagnosis, data collection included demographic and clinical parameters, the underlying malignancy subtype, complete blood counts, and, following the initiation of chemotherapy, detailed information related to episodes of febrile neutropenia (FN).

Outcome assessment

The primary objective of the study was to evaluate PCT and ProADM levels at the time

of leukemia diagnosis and to compare them with those measured during episodes of febrile neutropenia. The secondary objective was to identify clinical and laboratory determinants associated with elevated levels at the time of acute leukemia diagnosis.

Sample collection and processing

Baseline investigations, including complete blood counts (CBC), serum electrolytes, renal function tests (RFTs), and liver function tests (LFTs), were obtained at the time of acute leukemia diagnosis. During episodes of FN, the routine diagnostic work-up included CBC, serum electrolytes, RFTs, LFTs, chest radiography (CXR), blood cultures, and sensitivity testing, along with other microbiological investigations as indicated. In addition, 2 mL of serum samples were collected for biomarker estimation of PCT and ProADM at the time of leukemia diagnosis, and subsequently during FN presentation. All patients presenting with FN were monitored for overall clinical outcomes.

Serum PCT levels were measured using the ARCHITECT BRAHMS PCT assay, a chemiluminescent microparticle immunoassay (CMIA) with a quantification range of 0.02 to 100 ng/mL. ProADM levels were estimated using the Human Proadrenomedullin ELISA Kit (MBS3803630; MyBioSource, USA) in the Department of Reproductive Biology.[2] Threshold values of PCT ≥ 0.21 ng/mL and ProADM ≥ 0.18 nmol/L were considered clinically significant in this analysis, as these cutoffs have been previously associated with systemic infections and adverse clinical outcomes in pediatric populations with cancers.[2] Serum samples were also collected from age- and sex-matched healthy children to serve as controls.

Definitions

- Febrile neutropenia (FN)[14]: This was defined as either a single axillary temperature ≥38.5 °C, or ≥38.0 °C on two occasions at least 1 hour apart, in the presence of an absolute neutrophil count (ANC) <500/mm^3.
- Classification of FN: Febrile neutropenia episodes were categorized into three groups based on clinical and microbiological findings:
  - Microbiologically documented infection (MDI): Isolation of a pathogenic microorganism from blood or another normally sterile site.
  - Clinically documented infection (CDI): Presence of a clinically identifiable focus of infection on physical examination, without microbiological confirmation.
  - Unexplained fever (NF): Fever without an identifiable clinical focus or microbiological documentation.
- In cases where both clinical evidence and microbiological confirmation were present, the episode was classified as MDI.

Statistical methods

Dichotomous variables were presented as proportions (%), while continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as median with interquartile range (IQR) for non-normally distributed data. The Wilcoxon signed-rank test was employed to compare biomarker levels (PCT and ProADM) between the time of acute leukemia diagnosis and during febrile neutropenia episodes. Associations between categorical variables were assessed using the chi-square or Fisher s exact test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

Results

At the time of acute leukemia diagnosis, a total of 80 patients were enrolled in the study after excluding 13 patients due to the following reasons: lack of informed consent (n = 2), recent antibiotic use within the preceding 14 days (n =6), and sampling errors (n = 5).

Baseline demographic and clinical characteristics of all included patients at the time of acute leukemia diagnosis (n=80) are summarized in Table I. The median age of the study cohort (n=80) was 5 years (IQR: 3-7 years), with a male predominance. The majority of patients (67.5%) were diagnosed with ALL. The most common presenting symptoms included fever in 70 patients (87.5%), anorexia in 45 (56.3%), bleeding in 22 (27.5%), lethargy in 20 (25%), abdominal pain in 21 (26.3%), and cough in 9 (11.3%).

In our cohort of 80 patients, at the time of acute leukemia diagnosis, the median PCT was 0.19 ng/ml (IQR: 0.07-0.54), and the median ProADM was 0.04 nmol/L (IQR: 0.01-0.07). Serum levels of PCT and ProADM in age- and gender-matched healthy controls (n = 40) were below the targeted cutoff values. Table I summarizes the baseline demographic and clinical characteristics of patients with acute leukemia who developed febrile neutropenia (n = 32). Among the 32 patients who developed FN, the most common presenting symptoms were fever (28; 87.5%), anorexia (14; 43.8%), lethargy (10; 31.3%), and abdominal pain (7; 21.9%). Of these patients, 80% had an identifiable focus of infection, with respiratory involvement being the most common (45%), followed by gastrointestinal (30%) and other sites (25%). Overall, 77% were classified as clinically documented infection (CDI), 3% as microbiologically documented infection (MDI), and 20% as fever of unknown origin (NF). Two patients succumbed to sepsis, and blood culture in one of them yielded Haemophilus influenzae.

Primary outcomes

At the time of leukemia diagnosis (n=32), the median serum PCT level was 0.16 ng/

Table I. Baseline demographics and laboratory characteristics of children with acute leukemia at diagnosis (N=80) and those who subsequently developed febrile neutropenia (N=32).

	All patient with acute leukemia (N=80)	Acute leukemia patients who developed febrile neutropenia (N=32)
Demographics		
Median age (years)	5 (3-7)	4.8 (2-8)
Male : Female ratio	7:1	2.2:1
Median weight (Kg)	15 (12-20)	14 (11-19.8)
Mean height (cm)	108.6 (23)	107.3 (23.3)
BMI (kg/m^2)	14.4 ± 4	13.9 ± 4
Primary diagnosis		
ALL	54 (67.5%)	20 (62.5%)
AML	26 (32.5%)	12 (37.5%)
Baseline laboratory parameters		
Hemoglobin (g/dL)	7.7 ± 2	8 ± 2
TLC (/mm^3)	9,600 (3400-27,300)	8,885 (2180-20,320)
ANC (/mm^3)	750 (283-2,000)	760 (321-1,524)
Platelets (/mm^3)	33,000 (16,000-56,500)	26,000 (15,850-50,000)
Biomarkers at leukemia diagnosis		
Median PCT (ng/ml)	0.19 (0.07-0.54)	0.16 (0.08-0.52)
Median ProADM (nmol/L)	0.04 (0.01-0.07)	0.03 (0.006-0.05)

Continuous variables are presented as mean ± SD or median (Q1-Q3) according to their distribution characteristics and categorical variables are presented as number (percentage).
ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count; BMI: Body mass index; IQR: Interquartile range; PCT: Procalcitonin, ProADM: Proadrenomedullin; TLC: Total leukocyte count.

mL (IQR: 0.08 0.52), and the median ProADM level was 0.03 nmol/L (IQR: 0.006 0.05). At the presentation of febrile neutropenia (Day 1) (n=32), the median PCT increased to 0.32 ng/mL (IQR: 0.08 0.50; p=0.03), while the median ProADM rose substantially to 0.41 nmol/L (IQR: 0.20 0.81; p=<0.001) (Table II).

In the subgroup analysis, among patients with ALL, the median PCT level at diagnosis was 0.25 ng/mL (IQR: 0.12 0.65) and remained comparable during the FN episode (Day 1), with a median of 0.26 ng/mL (IQR: 0.07 0.50; p = 0.50). However, the median ProADM level increased significantly from 0.03 nmol/L (IQR: 0 0.05) at diagnosis to 0.42 nmol/L (IQR: 0.24 0.80) during FN presentation (p = 0.001) (Table II).

In patients with AML, the median PCT level increased significantly from 0.07 ng/mL (IQR: 0.09 0.30) at diagnosis to 0.33 ng/mL (IQR: 0.19 2.70) during FN (p < 0.001). Similarly, the median ProADM level rose from 0.02 nmol/L (IQR: 0 0.05) at diagnosis to 0.40 nmol/L (IQR: 0.16 0.83) during FN (p = 0.002) (Table II).

Secondary outcomes

Positive procalcitonin at the time of leukemia diagnosis was significantly associated only with splenomegaly (p=0.010). Age, sex, type of malignancy, hepatomegaly, and ANC were not significantly associated with PCT positivity. Notably, all patients had undetectable ProADM levels at diagnosis; therefore, an analysis of determinants associated with elevated ProADM was not performed. Table III presents the clinical and laboratory factors associated with elevated PCT levels at the time of leukemia diagnosis.

Discussion

This study assessed the utility of two biomarkers PCT and ProADM at the time of acute leukemia diagnosis and compared their levels during episodes of febrile neutropenia in pediatric patients. A statistically significant increase in both PCT and ProADM levels was observed during FN episodes compared with baseline levels at leukemia diagnosis, prior to the initiation of chemotherapy. These findings underscore the potential of PCT and ProADM as biomarkers for infection-related conditions, capable of distinguishing infectious episodes from baseline inflammatory states associated with malignancy. PCT, in particular, has been extensively studied as a marker of systemic bacterial infections and sepsis, with growing evidence supporting its role in antibiotic stewardship by guiding the initiation and discontinuation of antimicrobial therapy.[15,16] Similarly, ProADM has shown promise as a prognostic indicator in infectious

Table II. Comparison of biomarkers at acute leukemia diagnosis and during febrile neutropenia, and subgroup analysis of comparison of biomarkers (n=32).

Laboratory parameters	Biomarkers at diagnosis	Biomarkers at Day 1 of FN presentation	P-value
PCT (ng/mL)	0.16 (0.08-0.52)	0.32 (0.08-0.50)	0.03
ProADM (nmol/L)	0.03 (0.006-0.05)	0.41 (0.2-0.81)	<0.001
Subgroup analysis			
Acute lymphoblastic leukemia (n=20)			
PCT (ng/mL)	0.25 (0.12-0.65)	0.26 (0.07-0.50)	0.5
ProADM (nmol/L)	0.03 (0-0.05)	0.42 (0.24-0.80)	<0.001
Acute myeloid leukemia (n=12)			
PCT (ng/mL)	0.07 (0.09-0.30)	0.33 (0.19-2.7)	0.001
ProADM (nmol/L)	0.02 (0-0.05)	0.40 (0.16-0.83)	0.002

Variables are presented as median (Q1-Q3).
ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, FN: Febrile neutropenia, IQR: Interquartile range, PCT: Procalcitonin, ProADM: Proadrenomedullin.

Table III. Summarizing the determinants of positive procalcitonin (PCT) at leukemia diagnosis (cutoff ≥ 0.21 ng/mL) (n=32).

Parameters	PCT positive, n (%)	PCT negative, n (%)	P-value
Age			0.16
≤ 5 years	3 (15)	3 (15)	
> 5 years	0	0	
Sex			0.96
Male	9 (41)	9 (41)	
Female	4 (40)	4 (40)	
Type of malignancy			0.16
ALL	10 (50)	10 (50)	
AML	3 (25)	3 (25)	
Presence of fever			0.07
Present	13 (46.4)	13 (46.4)	
Absent	0	0	
Hepatomegaly			0.68
Present	5 (45.6)	5 (45.6)	
Absent	8 (38)	8 (38)	
Splenomegaly			0.010
Present	4 (100)	4 (100)	
Absent	9 (32.1)	9 (32.1)	
ANC			0.19
< 500/mm^3	5 (50)	5 (50)	
≥ 500/mm^3	10 (46)	10 (46)	

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; ANC: Absolute neutrophil count.

and inflammatory conditions, including sepsis and pneumonia, due to its vasodilatory and immunomodulatory properties.[17,18] Recently, Meena et al.[2] evaluated the diagnostic and prognostic performance of PCT and ProADM in febrile neutropenic children with both hematological malignancies and solid tumors (n=345). Although PCT demonstrated effectiveness in distinguishing MDI, CDI, and NF, and additionally predicted 30-day mortality, highlighting its potential utility in guiding risk stratification and management of FN in the pediatric oncology setting, this study did not provide subgroup-specific biomarker analysis, in contrast to the index study, which reports biomarker findings separately for ALL and AML. Additionally, Meena et al.[2] measured biomarkers at presentation and on days 3 and 7 of FN, whereas the current study assessed biomarkers at baseline (at the time of leukemia diagnosis) and compared them with values obtained during FN episodes (Day 1).

In the subgroup analysis, patients with ALL showed no significant change in serum PCT levels from baseline (at diagnosis) to during FN episodes. This suggests that PCT may reflect underlying inflammation or para-inflammatory processes associated with the leukemic process itself. Previous studies have reported elevated baseline PCT levels in certain malignancies, including hematological cancers, likely due to cytokine-mediated stimulation independent of infection.[10,19] In contrast, ProADM levels in ALL patients increased significantly during FN episodes compared with baseline, reinforcing its role as a more infection-specific biomarker in this subgroup. ProADM is known to be upregulated in response to microbial toxins and

inflammatory stimuli, with well-documented prognostic value in infections and sepsis.[17,18]

Interestingly, in patients with AML, both PCT and ProADM levels rose significantly during FN episodes compared with levels at diagnosis. This suggests that, unlike in ALL, the baseline inflammatory milieu in AML may not elevate PCT to the same extent, making subsequent increases more reflective of infectious processes. These findings may reflect disease-specific differences in immune and cytokine activation patterns between ALL and AML, with implications for interpreting biomarker kinetics during infectious episodes.

At the time of acute leukemia diagnosis, splenomegaly was the only clinical variable significantly associated with elevated serum PCT levels. This association may reflect subclinical inflammation related to leukemic infiltration and immune activation. However, splenomegaly may also represent a confounding factor, as it can result either from infectious processes or direct disease involvement. Additionally, tissue remodelling or necrosis in the spleen may release damage-associated molecular patterns (DAMPs), stimulating cytokine-mediated PCT production even in the absence of overt infection.[20]

PCT and ProADM have been extensively studied as diagnostic biomarkers for infectious diseases. PCT has consistently demonstrated high sensitivity and specificity for identifying bacterial infections, making it a valuable tool in differentiating bacterial from viral etiologies.[21-23] Similarly, ProADM levels have been shown to be significantly higher in patients with localized bacterial infections and bloodstream infections compared with healthy individuals.[24] Its role in reflecting endothelial dysfunction and systemic inflammatory burden enhances its potential as a marker for infection severity and prognosis.

Both PCT and ProADM have been extensively studied as biomarkers for prognosticating sepsis, either individually or in combination, alongside established disease severity scoring systems. PCT reflects systemic bacterial infection and is produced in response to proinflammatory cytokines, particularly interleukin-6 and tumor necrosis factor-alpha. In contrast, ProADM has been linked to endothelial dysfunction and vasodilation, both hallmarks of severe sepsis and septic shock.[17,20]

Patients with cancer, including those with neutropenia, often have elevated baseline inflammatory markers due to malignancy or treatment-related complications. Severely immunocompromised individuals may also exhibit a diminished inflammatory response. These factors can limit the reliability of standard inflammatory biomarkers in this population. Most studies on PCT-guided antibiotic therapy have excluded immunocompromised patients due to safety concerns. Hence, the applicability of PCT and ProADM in cancer patients remains uncertain and requires further evaluation.

Several studies have demonstrated that baseline PCT levels are higher in cancer patients than in healthy individuals.[10,25,26] Among afebrile cancer patients, those with stage IV disease tend to have significantly elevated PCT levels relative to those with early-stage cancer.[10,25] Additionally, in the absence of fever, PCT levels are generally higher in patients with hematologic malignancies than in those with solid tumors.[25] PCT concentrations are elevated in medullary thyroid carcinoma, probably due to ectopic production and release by tumor cells into the bloodstream.[27] Baseline PCT elevations have also been reported in individuals with hepatocellular carcinoma[28], ovarian cancers[29], gastrointestinal neuroendocrine tumors[5,30] and lung cancer.[7,31-33]

Existing studies involving immunocompromised cancer patients are limited and highly heterogeneous in cancer type, comorbidities, and immunosuppression levels. Further research in well-defined, homogeneous populations is needed for clearer insights. PCT and ProADM may serve as valuable, complementary biomarkers for diagnosing sepsis and bacterial infections in

oncology settings. However, it is important to recognize that malignancy itself can contribute to elevated baseline levels of these biomarkers, particularly PCT. In the present study, however, no significant baseline elevation of PCT or ProADM was observed at the time of acute leukemia diagnosis, suggesting minimal non-infectious upregulation in this cohort.

Strengths and limitations

A key strength of this study is its prospective design. It is the first to evaluate and compare biomarker levels (PCT and ProADM) both at the time of acute leukemia diagnosis and during febrile neutropenia episodes. Another notable strength is the recruitment of a homogenous patient cohort, limited to children with acute leukemia, thereby reducing clinical variability and enhancing the internal validity of the findings. However, the study has certain limitations. A major limitation is the absence of biomarker measurements during leukemia remission, which could have provided additional insights by enabling comparisons across disease states diagnosis, remission, and infection. Additionally, the relatively small sample size may limit both the statistical power and the generalizability of the findings, particularly for subgroup analyses. Future studies with larger cohorts and the inclusion of remission-phase sampling are needed to validate and expand upon these findings.

In conclusion, this study underscores the potential of PCT and ProADM as biomarkers to distinguish infectious episodes from baseline inflammatory states in children with acute leukemia. Compared with levels at diagnosis, ProADM was significantly elevated during febrile neutropenia in both ALL and AML. In contrast, PCT showed a significant rise only in the AML subgroup, with no significant elevation observed in ALL. These findings suggest that ProADM may serve as a more consistent and reliable biomarker across leukemia subtypes. Taken together, these results support the integration of biomarker assessment into standard FN evaluation protocols in pediatric oncology. Future studies should aim to validate these findings in larger, multicenter cohorts and assess the clinical utility of these biomarkers in real-time therapeutic algorithms. Research should also focus on dynamic trends of these markers over the course of infection, stratified by leukemia subtype and treatment phase, to refine their diagnostic and prognostic accuracy.

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Ethical approval

The study was approved by the Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi, India (date: 17.12.2019, number: IEC-459/01.09.2017, RP-09/2017, OP-13/06.12.2019, RP-43/2019).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: JPM; data collection: HM, SB, RSPR; analysis and interpretation of results: JPM, HM; draft manuscript preparation: JPM, HM, SB, RSPR, AKG, AH, RS. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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