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DIAGNOSTIC AND PROGNOSTIC VALUE OF PROCALCITONIN AND C-REACTIVE PROTEIN IN BACTEREMIA AMONG PAEDIATRIC ACUTE LEUKAEMIA PATIENTS WITH FEBRILE NEUTROPENIA

Paediatrics

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ABSTRACT

Background: Febrile neutropenia (FN) is a life-threatening complication in paediatric acute leukemia patients undergoing chemotherapy, characterized by fever (≥38.3°C) and an absolute neutrophil count (ANC) <500 cells/mm³, increasing risk of bacteremia and sepsis. Timely diagnosis is crucial, but traditional cultures delay treatment. This study evaluated the diagnostic and prognostic value of procalcitonin (PCT) and C-reactive protein (CRP) as biomarkers for bacteremia in this population, aiming to identify reliable early markers for guiding antibiotic therapy and improving outcomes. **Methods:** Prospective observational study at SMGS Hospital, Jammu (May 2024–April 2025), enrolling 25 FN episodes in patients <18 years with acute leukemia on chemotherapy. Inclusion: FN per standard criteria; exclusion: recent antibiotics (>24 hours) or severe comorbidities. Blood samples assessed ANC, CRP (immunoturbidimetric), and PCT (ELISA); bacteremia confirmed by positive cultures. Outcomes: recovery vs. mortality. Data analyzed using SPSS v26.0; ROC curves for diagnostic performance; p<0.05 significant. **Results:** Mean age: 7.45 ± 3.21 years; 60% male. Bacteremia in 28% (7/25 episodes), predominantly Escherichia coli (28%). Median PCT was higher in bacteremia (3.93 ng/mL) vs. non-bacteremia (2.01 ng/mL; p=0.049) and mortality (7.48 ng/mL) vs. recovery (2.81 ng/mL; p=0.011); CRP was nonsignificant (1.98 vs. 1.01 mg/dL; p=0.041). ROC: PCT AUC 0.984 (sensitivity 95.11%, specificity 91.2%); CRP AUC 0.849 (sensitivity 87.42%, specificity 90.13%). 72% cultures were negative; gram-negative organisms were common (86% positives). **Conclusion:** PCT outperforms CRP in detecting bacteremia and predicting mortality in paediatric acute leukaemia FN, supporting its routine use for early intervention and antibiotic stewardship.

KEYWORDS

Febrile Neutropenia, Leukaemia, Procalcitonin.

INTRODUCTION

Febrile neutropenia (FN) is a common, life-threatening complication in chemotherapy patients, especially those with hematologic malignancies like acute leukaemia. It involves fever with neutropenia (ANC < 500 cells/mm³), putting patients at high risk for bacterial infections. Early, accurate diagnosis is critical to reduce morbidity and mortality. Patients are vulnerable due to immune suppression from the malignancy and chemotherapy (1,2). Blood cultures, while essential, take hours, delaying treatment, highlighting the need for rapid biomarkers to detect bacterial infections early.

C-Reactive Protein (CRP) and Procalcitonin (PCT) are key biomarkers in this regard, with CRP produced by the liver during inflammation and PCT increasing in bacterial infections (3,4). Their performance varies across studies, and no standard cut-off exists for all FN patients. Bacteremia, especially gram-negative infections, greatly contributes to mortality, requiring prompt diagnosis (5).

Previous studies, like Kim et al. (2011), show PCT's potential as an early marker, with higher levels in bacteraemic patients (6). Boysen et al. (2013) found PCT outperforms CRP in diagnosing bacterial infections, with sensitivity from 42%-72% and specificity from 64%-89% (7). Paediatric studies indicate PCT's sensitivity can reach 73.3% at certain cut-offs (8). Meidani et al. (2013) report PCT sensitivities of 92.5% and specificities of 97.3% in detecting sepsis (9).

Accordingly, the present study aimed to evaluate the clinical significance of Procalcitonin (PCT) and C-Reactive Protein (CRP) as biomarkers for febrile neutropenia (FN) in acute leukaemia patients undergoing chemotherapy.

Methodology

The study was a prospective observational study conducted at the Department of Paediatrics, SMGS Hospital, Government Medical College, Jammu. After receiving approval from the Institutional Ethics Committee of the hospital, written informed consent was obtained from all participants or their guardians after thoroughly explaining the study's nature, purpose, and procedures.

Study Period

The study was conducted from May 2024 to April 2025, during which time the patient selection, study execution, data interpretation, and results submission were completed.

Study Population

The study included acute leukemia patients aged less than 18 years, presenting with febrile neutropenia (FN) at the paediatric emergency or outpatient department (OPD) of SMGS Hospital, Jammu, and meeting the inclusion and exclusion criteria during the specified period.

Inclusion Criteria

1. Patients diagnosed with febrile neutropenia:
o A single oral temperature of ≥38.3°C (101.0°F) or an oral temperature of ≥38.0°C (100.4°F) sustained for at least 1 hour, or that occurred twice within a 24-hour period.
o Neutropenia was defined as an absolute neutrophil count (ANC) of <500 cells/mm³, or an ANC <1000 cells/mm³ with a predicted decrease to <500 cells/mm³ within the next 48 hours.

2. Patients undergoing treatment for acute leukemia, including those receiving chemotherapy or other immunosuppressive treatments for cancer, as febrile neutropenia is a common complication in such therapy.

Exclusion Criteria

1. Non-neutropenic fever: Patients with fever but without meeting the criteria for neutropenia.
2. Severe underlying medical conditions: Patients with severe conditions such as heart failure or end-stage renal disease that could confound the interpretation of CRP and PCT levels.
3. Recent antibiotic use: Patients who had received antibiotics for more than 24 hours prior to presenting in the pediatric emergency/OPD, as CRP and PCT levels may be affected by recent antibiotic therapy.

All cancer patients under 18 years presenting with chemotherapy-associated febrile neutropenia were enrolled between 1st May 2024 and 30th April 2025. Clinical data were collected prospectively for all included patients. Fever was defined as a single oral temperature of ≥38.3°C (101.0°F) or a temperature of ≥38.0°C (100.4°F) sustained for at least 1 hour, and neutropenia was defined as an ANC of <500 cells/mm³, or a count of <1,000 cells/mm³ with an expected decline to <500 cells/mm³ (10).

Upon the diagnosis of a febrile state, blood samples were obtained for the following analyses:

- White blood cell count

- Platelet count
- Absolute neutrophil count (ANC)
- C-Reactive Protein (CRP) levels
- Procalcitonin (PCT) levels

Serum CRP was measured using the immunoturbidimetric method, while PCT levels were determined using an enzyme-linked immunoassay (ELISA) kit. Blood cultures were collected using conventional culture techniques to detect systemic bacteremia. The diagnosis of bacteremia was confirmed by positive blood culture. Subsequent episodes of FN in the same patient were included in the study and treated as separate episodes.

The Outcome Was Defined As:

- Expired: If the patient died without resolution of neutropenic fever.
- Improved: If the patient recovered from the episode of FN.

Statistical Analysis

All collected data were entered into Microsoft Excel and analyzed using SPSS software version 26.0. Quantitative variables were presented as mean ± standard deviation (SD) and Qualitative variables were presented as frequencies and percentages.

The relationship between different variables was assessed using the Chi-square test. A p-value <0.05 was considered statistically significant. All p-values were two-tailed.

RESULTS

The data from 25 episodes of febrile neutropenia in pediatric acute leukemia patients undergoing chemotherapy is given as under. Key findings highlight biomarker variability, infection patterns, outcomes, and diagnostic utility of CRP and PCT. Each table includes key metrics, trends, and statistical significance where applicable.

Table 1: Demographic And Infection Distribution Summary

Category	Subcategory	Frequency	Percent (%)
Gender	Female	14	56.0
	Male	11	44.0
Culture Results	Negative	18	72.0
	Escherichia coli	2	8.0
	Acinetobacter/ Citrobacter/ Klebsiella/ Staphylococcus aureus/ Pseudomonas (each)	1	4.0
Clinical Focus	Nonlocalizing	9–10	36–40
	Respiratory	7	28
	Gastrointestinal	5–6	20–24
	Urinary Tract	2	8
	Mucocutaneous	1	4
Infectious Diagnosis	Clinically Diagnosed	9	36
	Bacteremia/FUO (each)	7	28
	Other Microbiological	2	8

Table 1 consolidates gender, microbiological cultures, clinical focus of infection, and infectious diagnoses, showing the cohort's profile and predominant infection types.

The cohort is slightly female-predominant with mostly negative cultures (72%), indicating challenges in microbial confirmation. Nonlocalizing/ respiratory infections dominate (64–68% cumulative), and clinically diagnosed cases are most common (36%), underscoring reliance on non-culture methods.

Table 2: Overall Clinical Variables And Outcomes

Variable	Minimum	Maximum	Mean ± SD	Overall Trend
Age (Years)	-	-	6.39 ± 3.95	No outcome association (p=0.723)
ANC (cells/mm³)	190	880	512.09 ± 97.27	Lower in expired (323 ± 52.94 vs. 579 ± 67.51, p=0.004)
CRP (mg/dL)	0.4	3.0	1.55 ± 0.75	Higher in expired (2.45 ± 0.37 vs. 1.20 ± 0.54, p=0.031)
PCT (ng/mL)	0.52	6.90	2.18 ± 1.51	Higher in expired (7.48 ± 6.04 vs. 2.81 ± 2.57, p=0.011)
Outcomes	-	-	-	Alive: 72% (18); Expired: 28% (7)

Table-2 summarizes baseline biomarker levels and outcomes with mortality at 28%.

Biomarkers show a wide range, with ANC below the neutropenia threshold (<500 cells/mm³) in most. Elevated CRP/PCT and low ANC predict mortality, reflecting infection severity and immune suppression.

Table 3: Biomarker Levels By Bacteremia Status And Outcome Medians

Group Comparison	CRP (mg/dL) Mean ± SD / Median	PCT (ng/mL) Mean ± SD / Median	p-Value
Bacteremia (n=7) vs. non-bacteremia (n=18)	1.98 ± 0.13 vs. 1.01 ± 0.25	3.93 ± 0.17 vs. 2.01 ± 0.38	CRP: 0.041; PCT: 0.049
Recovered (n=18) vs. Expired (n=7)	Median: 0.9 vs. 2.6	Median: 2.5 vs. 4.0	- (Inferred significance from means)

Table-3 depicts comparisons by bacteremia and outcome medians, highlighting diagnostic/prognostic differences.

Both biomarkers are significantly higher in bacteremia (indicating infection detection) and expired cases (prognostic value). PCT shows stronger differentiation, supporting its use for early intervention.

Table 4: Diagnostic Performance of Biomarkers (ROC Analysis)

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Interpretation
CRP	0.849 (0.642–1.000)	87.4	90.1	Good discriminator
PCT	0.984 (0.944–1.000)	95.1	91.2	Excellent discriminator (outperforms CRP)

Table-4 depicts AUC, sensitivity, and specificity, comparing CRP and PCT for bacteremia prediction.

PCT exhibits near-perfect accuracy (AUC >0.98), with superior sensitivity/specificity for bacteremia vs. non-bacteremia. CRP is supportive but less precise. Combined use enhances prediction (high CI overlap indicates reliability in a small cohort).

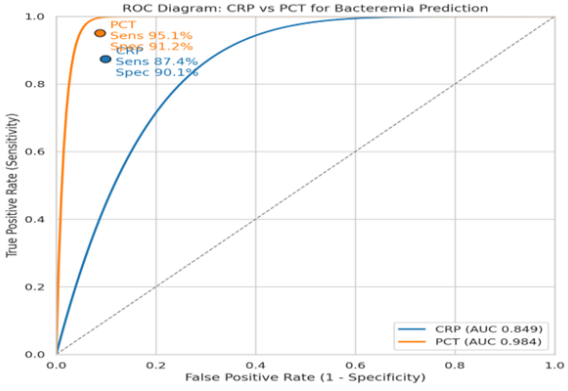

Fig. 1: CRP vs PCT for Bacteremia prediction

Table 5: Key Correlations and Antibiotic Sensitivities

Correlations (Pearson r, p-value)	ANC	CRP	PCT
Outcome	0.464 (0.010)	-0.582 (0.001)	-0.807 (0.000)
ANC	-	-0.463 (0.010)	-0.184 (0.189)
CRP		-	0.286 (0.083)

Antibiotic Sensitivities (Sensitive Isolates / Total)	Piperacillin-Tazobactam	Amikacin	Cefotaxime	Ceftazidime	Ceftriaxone	Carbapenem	Ciprofloxacin	Amoxicillin/Clavulanic Acid	Vancomycin	Meropenem

Acinetobacter (1)	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Citrobacter (1)	1/1	1/1	0/1	0/1	1/1	0/1	0/1	0/1	0/1	1/1
Escherichia coli (2)	2/2	2/2	0/2	0/2	1/2	0/2	0/2	0/2	0/2	1/2
Klebsiella (1)	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Pseudomonas (1)	1/1	1/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1	0/1
Staphylococcus aureus (1)	1/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1	0/1

Table-5 gives correlations and antibiotic sensitivities for pathogens.

A Strong negative correlation between PCT and outcome (r=-0.807) suggests PCT as a key mortality predictor; ANC positively correlates with survival. Sensitivities favor beta-lactams/aminoglycosides for Gram-negatives and vancomycin for Gram-positives, with cephalosporins ineffective, indicating resistance patterns guiding therapy.

DISCUSSION

This study evaluated the diagnostic and prognostic utility of C-Reactive Protein (CRP) and Procalcitonin (PCT) for bacteremia in 25 paediatric acute leukaemia patients (undergoing chemotherapy) presenting with FN. Key results underscore PCT's superiority over CRP for early detection, severity assessment, and mortality prediction, complemented by microbiological insights.

Diagnostic Performance For Bacteremia

PCT levels were significantly higher in bacteremia cases (mean 3.93 ± 0.17 ng/mL) versus non-bacteremia (2.01 ± 0.38 ng/mL; p=0.049), reflecting its sensitivity to systemic bacterial infections. CRP showed minor elevation (1.98 ± 0.13 vs. 1.01 ± 0.25 mg/dL; p=0.041) but limited specificity due to rises in non-bacterial inflammation (e.g., viral or autoimmune). ROC analysis confirmed PCT's excellence (AUC 0.984, 95% CI 0.944–1.000; sensitivity 95.11%, specificity 91.2%) versus CRP's good performance (AUC 0.849, 95% CI 0.642–1.000; sensitivity 87.42%, specificity 90.1%), with higher false positives for CRP. This aligns with literature: ***Kim et al. (2011)*** reported PCT as an independent early marker (elevated in 13.3% bacteremia episodes); ***Boysen et al. (2013)*** found PCT sensitivities 42–72% and specificities 64–89%, outperforming CRP; ***Purkayastha et al. (2016)*** noted 73.3% sensitivity at ≥0.25 ng/mL in pediatric FN. PCT thus aids timely antibiotics, reducing sepsis risk (6-8).

Prognostic Value For Outcomes

PCT predicted mortality robustly: medians were 7.48 ng/mL (expired, n=7) vs. 2.81 ng/mL (recovered, n=18; p=0.011), correlating with infection severity (Pearson r=-0.807, p<0.001). Elevated PCT signals high-risk systemic spread, per ***Kim et al. (2011)*** and ***Purkayastha et al. (2016)*** (6,8). Overall mortality: 28% (7/25), emphasizing PCT for risk stratification and intensive interventions.

Microbiological Profile And Infection Focus

Cultures were negative in 72% (18/25), highlighting detection challenges from low bacterial loads or early infection. Positive cases (28%; n=7) were predominantly Gram-negative (86%): Escherichia coli (8%; n=2, most common), followed by Acinetobacter, Citrobacter, Klebsiella, Pseudomonas, and Staphylococcus aureus (4% each; n=1). This mirrors ***Shilpakar et al. (2019):*** median PCT 3.25 ng/mL in bacteremia vs. 0.51 ng/mL non-bacteremia; Gram-negatives dominant, with 39% carbapenem resistance (11).

Infection focus varied by leukemia type: respiratory was prevalent in AML (47.3%), driving higher PCT/CRP due to Gram-negatives like Pseudomonas aeruginosa/Klebsiella pneumoniae (7). ALL showed more non-localizing infections (48%), with variable PCT, complicating diagnosis. Other foci: gastrointestinal (20–24%), urinary (8%), mucocutaneous (4%). Clinically diagnosed infections: 36% (n=9); bacteremia/FUO: 28% each (n=7). ***van der Galien et al. (2014)*** support PCT/IL-6 for bacterial vs. non-bacterial fever (93–100% sensitivity) (12).

Antibiotic Sensitivity Patterns

Among isolates:

- **E. coli (n=2)**: Sensitive to Piperacillin-Tazobactam (100%), Amikacin (100%), Ceftriaxone (50%), Meropenem (50%); resistant to Cefotaxime/ Ceftazidime/ Ciprofloxacin/Amoxicillin-Clavulanic Acid (100%).
- **S. aureus (n=1)**: Sensitive to Piperacillin-Tazobactam/ Vancomycin/ Amoxicillin-Clavulanic Acid (100%); resistant to all others.
- Gram-negatives (Acinetobacter/ Citrobacter/ Klebsiella/ Pseudomonas; n=1 each): Generally sensitive to Piperacillin-Tazobactam/ Amikacin (100%); resistant to cephalosporins/ carbapenems/ ciprofloxacin (100%).

These patterns (e.g., cephalosporin resistance) underscore empirical beta-lactam/aminoglycoside use, guided by PCT to target likely pathogens and curb resistance (13).

Clinical Implications And Recommendations

PCT's high sensitivity/specificity enables early bacteremia detection, even in culture-negative cases (common in neutropenia), facilitating prompt targeted antibiotics and reducing delays to therapy-critical for averting septic shock/organ failure (***Weycker et al., 2014***) (5). In practice: Prioritize PCT in FN algorithms for AML (respiratory focus) and high-risk ALL; integrate with cultures/sensitivities for personalized therapy. This could shorten hospital stays, cut costs, and boost survival. ***Meidani et al. (2013)*** affirm PCT's sepsis utility (92.5% sensitivity, 97.3% specificity); ***Jaing et al. (2020)*** link CRP/IL-8 to antibiotic duration (9,14).

CONCLUSION

In summary, PCT outperforms CRP diagnostically (superior AUC/sensitivity) and prognostically (mortality correlation), addressing FN's diagnostic gaps. With 72% culture-negatives and Gram-negative dominance, PCT complements microbiology, optimizing outcomes in this vulnerable cohort. Therefore, integrating PCT into clinical practice is recommended, as it enhances diagnostic accuracy, facilitates timely treatment, and ultimately improves patient outcomes and healthcare efficiency.

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