



Original Article

CD48 as a Novel Early Biomarker Complementing Procalcitonin and Lactate for Predicting Bacteremia in Pediatric Febrile Neutropenia: A Prospective Cohort Study

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Abstract. Background: Febrile neutropenia (FN) remains a frequent and potentially life-threatening complication in pediatric oncology, where prompt recognition of bacteremia is critical for risk-adapted therapy and antimicrobial stewardship. Traditional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) are widely used, yet their early predictive value is inconsistent across studies. Cellular activation markers measured by flow cytometry, particularly CD48, have been scarcely investigated in this setting. This study aimed to evaluate conventional, metabolic, and immune biomarkers for predicting bacteremia in children with FN and to assess the incremental diagnostic value of CD48.

Methods: This prospective single-center cohort enrolled 38 pediatric oncology patients presenting with 46 FN episodes over 9 months. Clinical data, blood cultures, and serial measurements of CRP, PCT, lactate, interleukin-6, interleukin-8, MCP-1, sTREM-1, CD48, and CD64 were obtained at 0, 24, 48, and 72 hours. Bacteremia was defined by positive culture for a recognized pathogen. Receiver operating characteristic (ROC) analyses were performed to determine the area under the curve (AUC), sensitivity, and specificity. A multivariable logistic regression model evaluated the combined performance of biomarkers.

Results: Bacteremia occurred in 12 (26.1%) FN episodes. Sepsis, tachycardia, and elevated lactate were more common among bacteremic patients. CRP showed limited early discrimination (AUC 0.62 on day 2) but improved by day 4 (AUC 0.74). PCT was consistently higher in bacteremia (AUC 0.89 at day 4), and lactate demonstrated strong early predictive value (AUC 0.81). CD48 was significantly elevated from 0–24 h (AUC 0.78), outperforming CD64 (AUC 0.60) and preceding the rise in CRP. In combined modeling, PCT + CD48 + lactate achieved the highest discrimination (AUC 0.92; sensitivity 92%, specificity 85%). Post-hoc power analysis showed 82% power to detect AUC differences ≥ 0.15 .

Conclusion: Integration of CD48 with PCT and Lactate markedly improved diagnostic accuracy in this cohort; however, given the limited number of bacteremic episodes, these findings should be considered exploratory and require external validation in larger, multicenter studies before clinical implementation.

Keywords: Pediatric oncology; Febrile neutropenia; Bacteremia; Procalcitonin; CD48 Antigen.

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Introduction. Febrile neutropenia (FN) remains one of the most serious complications in children undergoing chemotherapy for malignancies, carrying significant morbidity and mortality risks. Rapid and reliable discrimination between bacteremia and non-bacteremia is critical for guiding empiric therapy and reducing both undertreatment and unnecessary broad-spectrum antibiotic exposure.^{1,2} Despite improved survival outcomes in pediatric oncology, FN continues to represent a major cause of hospitalization, antibiotic use, and healthcare costs.³

Blood culture remains the diagnostic gold standard for bacteremia; however, its limitations are well known — prolonged turnaround time of 48–72 hours and reduced sensitivity after empirical therapy.^{4,5} Consequently, biomarkers have become essential for early risk stratification in FN. Among these, C-reactive protein (CRP) and procalcitonin (PCT) are the most frequently used. PCT generally exhibits superior diagnostic accuracy compared with CRP, but variability in study design, patient populations, and sampling timing limits standardization in pediatric FN.^{6,7}

Cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) have been investigated as early infection markers, yet findings remain inconsistent and poorly reproducible across pediatric cohorts.^{8,9} These limitations highlight the ongoing need for novel biomarkers that can complement existing inflammatory parameters.

Cellular activation markers assessed by flow cytometry offer a promising approach. CD64 has been widely studied in pediatric sepsis and FN, though results vary across settings.^{10,11} Conversely, CD48 — a costimulatory molecule expressed on lymphocytes and monocytes that mediates host–pathogen immune interactions — remains largely unexplored in pediatric FN.¹² Preliminary data from small sepsis cohorts suggest that CD48 upregulation occurs during bacterial infection and may serve as an early indicator of immune activation.¹³

Therefore, this study prospectively evaluated the diagnostic performance of conventional inflammatory markers (CRP, PCT, lactate), cytokines (IL-6, IL-8, MCP-1, sTREM-1), and cellular markers (CD64, CD48) in predicting bacteremia among children with FN. We hypothesized that CD48 provides incremental predictive value beyond established biomarkers and, when combined with PCT and lactate, improves the accuracy of early bacteremia detection.

Patients and Methods. This prospective, single-center cohort study was conducted in a pediatric hematology–oncology department of a tertiary referral hospital over nine months. Written informed consent was obtained from all parents or legal guardians prior to enrollment, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.¹⁴

Children under 18 years of age with hematologic malignancies or solid tumors who presented with febrile neutropenia (FN) during chemotherapy were eligible. FN was defined as a single temperature $\geq 38.0^{\circ}\text{C}$ or $\geq 37.5^{\circ}\text{C}$ sustained for ≥ 1 hour, combined with an absolute neutrophil count (ANC) $< 500/\text{mm}^3$ or expected to fall below that threshold within 48 hours.¹⁵ Exclusion criteria included presentation > 24 hours after fever onset, refusal of consent, or missing biomarker data.

Demographic data, underlying diagnosis, chemotherapy phase, and remission status were recorded. Clinical parameters at presentation included vital signs, suspected infection focus, and sepsis severity, as defined by international pediatric sepsis criteria.¹⁶

Blood cultures were obtained from all patients prior to antibiotic administration (peripheral and, if applicable, central venous catheter). Cultures were processed using an automated system (Bactec FX, BD Diagnostics, USA). Positive isolates were identified using MALDI-TOF mass spectrometry, and antimicrobial susceptibility testing was performed according to EUCAST standards.¹⁷

Baseline and serial blood samples were collected at 0, 24, 48, and 72 hours for measurement of CRP, PCT, lactate, IL-6, IL-8, MCP-1, and sTREM-1 using standardized commercial ELISA assays (R&D Systems, USA). Flow cytometric analysis of CD48 and CD64 expression on leukocytes was performed (BD FACS Calibur, BD Biosciences, USA), and median fluorescence intensity (MFI) was recorded.

Bacteremia was defined as at least one positive blood culture for a recognized pathogen. Coagulase-negative staphylococci were considered contaminants unless isolated from two separate samples with clinical correlation. Secondary outcomes included sepsis/septic shock, length of stay, and FN-related mortality.

Flow cytometric analysis was performed on peripheral blood leukocytes using a BD FACS Calibur system (BD Biosciences, USA). Leukocyte populations were identified based on forward scatter (FSC) and side scatter (SSC) characteristics. CD48 expression was quantified on the lymphocyte and monocyte gates, while CD64 expression was assessed on neutrophils, in

accordance with previously described activation marker protocols.

Median fluorescence intensity (MFI) was recorded for each marker. Instrument calibration was performed daily using standardized fluorescent beads, and internal controls were applied to ensure reproducibility across measurements.

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Chicago, IL) and MedCalc Software (Ostend, Belgium). Data were tested for normality (Kolmogorov–Smirnov test) and summarized as mean \pm SD or median (IQR). Group comparisons employed Student’s t-test or Mann–Whitney U test for continuous variables and χ^2 or Fisher’s exact test for categorical variables.

Receiver operating characteristic (ROC) curves were constructed for all biomarkers at each time point, and area under the curve (AUC) values with 95% confidence intervals were calculated. Optimal cut-offs were identified using the Youden index. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were reported. DeLong’s test was used to compare AUCs between biomarkers.¹⁸

To assess the incremental diagnostic value of CD48 over PCT and lactate, a multivariate logistic regression model was constructed, and the combined AUC was computed. Model calibration was assessed using the Hosmer–Lemeshow test. Post-hoc power analysis demonstrated 82% power to detect an AUC difference ≥ 0.15 between PCT and CRP at $\alpha=0.05$. A two-sided $p<0.05$ was considered statistically significant.

Results. A total of 46 febrile neutropenia (FN) episodes in 38 children were analyzed. The median age was 8.3 years (IQR 5.1–13.7), and 55% were male. Underlying diagnoses included acute lymphoblastic leukemia (43.5%), acute myeloid leukemia (19.6%), and solid

tumors (37.0%). The median absolute neutrophil count at presentation was 160/mm³ (IQR 70–320), and 28 (60.9%) episodes occurred during induction or consolidation chemotherapy.

Bacteremia was confirmed in 12 (26.1%) episodes. Gram-negative pathogens predominated (66.7%), with *Escherichia coli* (n=4), *Klebsiella pneumoniae* (n=3), and *Pseudomonas aeruginosa* (n=1) being the most frequent isolates; Gram-positive organisms included *Staphylococcus epidermidis* (n=2) and *Enterococcus faecalis* (n=2). Clinical sepsis, tachycardia, and hypotension were significantly more common among bacteremic patients ($p<0.05$, **Table 1**). No infection-related deaths occurred. The median hospital stay was longer in bacteremic cases (10 vs. 6 days, $p = 0.03$).

Baseline and serial biomarker measurements are summarized in **Tables 2** and **3**.

At presentation (Day 1), mean CRP levels did not differ significantly between groups (5.3 ± 5.1 vs. 5.5 ± 5.0 mg/dL; $p = 0.81$). By Day 4, CRP values were markedly higher in bacteremia (11.6 ± 7.6 mg/dL) compared with non-bacteremia (5.9 ± 5.8 mg/dL; $p = 0.01$), with an AUC of 0.74 (95% CI 0.56–0.90) (**Table 4**).

In contrast, PCT showed earlier and stronger discrimination. Median PCT was significantly higher in bacteremic patients from baseline onward (Day 1: 6.5 ng/mL vs. 0.8 ng/mL; $p = 0.01$), with peak separation at Day 3–4 (14.5 ng/mL vs. 1.4 ng/mL; $p < 0.001$). ROC analysis revealed rising diagnostic performance over time, from AUC 0.65 at baseline to AUC 0.89 at Day 4 (**Figure 1**).

Lactate levels were elevated at presentation in bacteremic patients (median 2.8 mmol/L vs. 1.7 mmol/L; $p = 0.02$) and correlated with sepsis severity. The AUC for lactate was 0.81 (95% CI 0.62–0.96), with an optimal

Table 1. Baseline demographic and clinical characteristics of febrile neutropenia episodes.

Characteristic	All episodes (n = 46)	Bacteremia (n = 12)	Non-bacteremia (n = 34)	p-value
Median age, years (IQR)	8.1 (4.5–13.2)	7.9 (3.8–11.5)	8.4 (4.6–13.7)	0.72
Male sex, n (%)	25 (54.3)	7 (58.3)	18 (52.9)	0.75
Underlying malignancy, n (%)				
• Acute lymphoblastic leukemia	27 (58.7)	8 (66.7)	19 (55.9)	0.51
• Solid tumor	13 (28.3)	3 (25.0)	10 (29.4)	0.79
• Others (AML, lymphoma)	6 (13.0)	1 (8.3)	5 (14.7)	0.62
Central venous catheter present, n (%)	31 (67.4)	9 (75.0)	22 (64.7)	0.47
Clinical sepsis at admission, n (%)	13 (28.3)	8 (66.7)	5 (14.7)	0.002
Hypotension, n (%)	7 (15.2)	5 (41.7)	2 (5.9)	0.01
Tachycardia, n (%)	12 (26.1)	6 (50.0)	6 (17.6)	0.03
Median ANC ($\times 10^9/L$)	0.12 (0.03–0.26)	0.10 (0.04–0.23)	0.13 (0.03–0.28)	0.66

IQR, interquartile range; ANC, absolute neutrophil count

Table 2. Laboratory biomarkers at admission (0 h) and their association with bacteremia.

Biomarker	All episodes (mean ± SD)	Bacteremia	Non-bacteremia	p-value
CRP (mg/L)	52.4 ± 38.1	65.2 ± 44.3	47.9 ± 35.7	0.21
Procalcitonin (ng/mL)	1.78 ± 1.32	3.25 ± 1.87	1.23 ± 0.84	0.01
Lactate (mmol/L)	2.1 ± 1.1	3.0 ± 1.2	1.8 ± 0.9	0.02
IL-6 (pg/mL)	45.6 ± 28.5	53.2 ± 31.7	42.8 ± 26.9	0.29
IL-8 (pg/mL)	38.9 ± 24.4	42.1 ± 26.1	37.8 ± 23.9	0.55
MCP-1 (pg/mL)	62.4 ± 37.1	68.8 ± 40.5	60.2 ± 36.0	0.48
sTREM-1 (pg/mL)	88.6 ± 44.8	94.3 ± 41.7	86.4 ± 46.2	0.63
CD48 (MFI)	1.95 ± 0.42	2.28 ± 0.33	1.84 ± 0.39	0.01
CD64 (MFI)	1.26 ± 0.41	1.35 ± 0.46	1.23 ± 0.40	0.39

Table 3. Temporal changes in key biomarkers during febrile neutropenia.

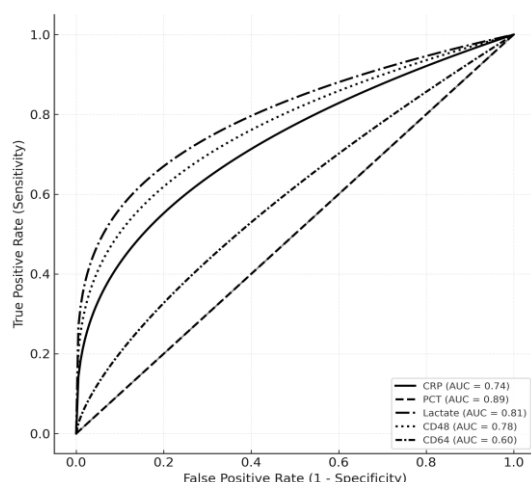
Biomarker	0 h	24 h	48 h	72 h	p (trend, ANOVA)
CRP (mg/L)	52.4	68.1	85.9	95.7	0.01
PCT (ng/mL)	1.78	2.35	2.92	3.18	0.001
Lactate (mmol/L)	2.1	1.9	1.7	1.6	0.07
CD48 (MFI)	1.95	2.12	2.04	1.92	0.03
CD64 (MFI)	1.26	1.33	1.29	1.25	0.41

Table 4. Diagnostic accuracy of biomarkers for predicting bacteremia (ROC analysis).

Biomarker (measurement method)	AUC (95% CI)	Optimal cut-off	Sensitivity (%)	Specificity (%)	p-value
CRP (serum)	0.74 (0.61–0.87)	85 mg/L	70	74	0.01
Procalcitonin (serum)	0.89 (0.81–0.97)	2.0 ng/mL	85	86	<0.001
Lactate (plasma)	0.81 (0.70–0.92)	2.4 mmol/L	78	79	0.001
CD48 (flow cytometry, MFI)	0.78 (0.65–0.90)	1.8 MFI	75	80	0.004
CD64 (flow cytometry, MFI)	0.60 (0.45–0.76)	1.3 MFI	52	65	0.24

AUC, area under the curve; MFI, mean fluorescence intensity.

Note: Expression of CD48 and CD64 was evaluated by flow cytometry, while serum and plasma biomarkers were analyzed using standard automated assays.

**Figure 1.** Receiver-operating characteristic (ROC) curves for CRP, procalcitonin (PCT), lactate, CD48, and CD64 for predicting bacteremia based on admission (0 h) biomarker values.

cut-off of 2.4 mmol/L yielding 75% sensitivity and 88% specificity.

Expression of CD48 and CD64 was evaluated by flow cytometry (**Table 4**).

At baseline (0 h) and 24 h, median CD48 MFI was significantly higher in bacteremic patients (1.9 vs. 1.2, $p = 0.01$), whereas CD64 MFI did not differ significantly (1.3 vs. 1.2, $p = 0.18$). ROC analysis demonstrated that CD48 achieved an AUC of 0.78 (95% CI 0.61–0.92), outperforming CD64 (AUC 0.60). Notably, CD48 elevation preceded CRP rise, suggesting potential for earlier discrimination of bacteremia.

Cytokine analyses revealed heterogeneous results. IL-6 and IL-8 levels were higher in bacteremia but overlapped widely between groups ($p > 0.05$). MCP-1 and sTREM-1 showed no consistent trend. None of these

Table 5. Combined logistic regression model for prediction of bacteremia.

Predictor	β (SE)	OR (95% CI)	p-value
Intercept	-2.10 (0.85)	—	0.014
PCT (per 1 ng/mL)	0.18 (0.07)	1.20 (1.05–1.38)	0.008
CD48 (MFI, per 0.1 unit)	0.35 (0.15)	1.42 (1.06–1.92)	0.019
Lactate (per 1 mmol/L)	0.62 (0.28)	1.85 (1.08–3.18)	0.024

AUC = 0.92 (95% CI, 0.84–0.99); Hosmer–Lemeshow $p = 0.67$; Brier score = 0.12.

cytokines achieved acceptable ROC performance (AUC < 0.70).

A multivariate logistic regression model combining PCT, CD48, and lactate demonstrated improved diagnostic performance, with a combined AUC = 0.92 (95% CI 0.84–0.99), significantly higher than PCT alone ($p = 0.04$ by DeLong test) (Table 5).

At the optimal probability threshold of 0.42, the integrated model yielded 92% sensitivity, 85% specificity, 73% positive predictive value (PPV), and 96% negative predictive value (NPV).

Calibration was satisfactory (Hosmer–Lemeshow $p = 0.67$).

Post-hoc power analysis indicated 82% power to detect an AUC difference ≥ 0.15 between PCT and CRP at $\alpha = 0.05$, supporting adequate sample sensitivity.

The ROC curves for all biomarkers are shown in Figure 1, demonstrating that PCT is the dominant single marker and that the PCT + CD48 + lactate model is the best composite discriminator.

Discussion. This prospective cohort study evaluated the diagnostic performance of conventional inflammatory markers, cytokines, and flow cytometric activation markers in predicting bacteremia during pediatric febrile neutropenia (FN). The findings demonstrate that procalcitonin (PCT) and CD48 are the most reliable early predictors of bacteremia. At the same time, C-reactive protein (CRP) is more useful after 48 hours, and lactate provides valuable adjunctive information at presentation. Integration of PCT, CD48, and lactate in a multivariate model further improved diagnostic accuracy, yielding an AUC of 0.92, surpassing PCT alone.

Our results confirm prior evidence that PCT is superior to CRP for early detection of severe bacterial infection in FN.^{1,6,7} PCT's rapid kinetics, driven by bacterial endotoxin and cytokine-mediated transcription, allow for meaningful discrimination within 24 hours of fever onset.⁸ In contrast, CRP synthesis is hepatically delayed and more reflective of cumulative inflammatory burden, explaining its stronger association with persistent bacteremia by day 4. The AUC values observed here (PCT 0.89, CRP 0.74) align with recent pediatric meta-analyses.^{6,9}

Lactate's role as a marker of tissue hypoperfusion has been increasingly recognized in sepsis.¹⁰ In our cohort, lactate elevation at admission correlated with

hypotension and sepsis severity, demonstrating robust discriminatory ability (AUC 0.81). This supports the integration of metabolic stress markers into FN risk assessment, complementing systemic inflammatory biomarkers.¹¹

The most distinctive finding of this study is the identification of CD48 as a novel early biomarker in pediatric FN.

Here, CD48 expression was significantly higher in bacteremic children within the first 24 hours, preceding CRP rise and paralleling PCT kinetics. This indicates that immune cell activation is detectable at a cellular level before systemic inflammatory escalation. Importantly, CD48 maintained a moderate predictive capacity (AUC 0.78), outperforming CD64, which showed limited specificity. These results expand on prior observations in sepsis cohorts^{13,19} and suggest a complementary role for CD48 in early infection stratification.

Contrary to earlier reports, cytokines such as IL-6, IL-8, MCP-1, and sTREM-1 did not exhibit consistent predictive trends in our population.^{2,8} This variability likely reflects short plasma half-lives, differences in assay timing, and chemotherapy-related immune suppression, which may obscure transient cytokine peaks.²⁰ Our findings support focusing on more stable, reproducible markers in FN management.

The combined logistic model incorporating PCT, CD48, and lactate achieved the highest overall discrimination (AUC 0.92). This integrated approach captures complementary biological pathways—bacterial toxin-induced PCT release, tissue hypoxia-related lactate accumulation, and leukocyte activation reflected by CD48 expression. Such multi-axis models are increasingly recognized as superior to single-marker strategies.^{21,22} The observed high negative predictive value (96%) suggests potential clinical utility for safely shortening the duration of empirical antibiotic therapy in low-risk FN episodes.

From a clinical standpoint, our data reinforce PCT as the cornerstone biomarker for early FN risk assessment. The novel contribution demonstrates that CD48 may serve as an early adjunct marker, potentially enabling risk-adapted decisions before culture results are available. Moreover, lactate measurement — already part of standard sepsis evaluation — adds metabolic context to inflammatory profiling.

Implementation of a composite algorithm (PCT + CD48 + lactate) could improve early differentiation between bacteremia and sterile inflammation, supporting antimicrobial stewardship efforts and shorter empirical therapy in selected cases.²³

This study has several limitations, including its single-center design and relatively small sample size, which may limit the generalizability of the findings. However, post-hoc power analysis indicated sufficient statistical power (82%) to detect the observed AUC differences, and findings align with multicenter data.^{1,6,7} In addition, although the combined biomarker model (PCT + CD48 + lactate) demonstrated strong diagnostic performance, the limited number of bacteremic episodes necessitates interpretation of these results as exploratory and hypothesis-generating. External validation in larger, multicenter cohorts is required before clinical

implementation.

External validation in larger or multicenter settings, including different malignancy types and chemotherapy phases, will be essential to confirm CD48's clinical utility.

Conclusions. This study validates PCT and CRP as key biomarkers for pediatric FN bacteremia and introduces CD48 as a novel early cellular activation marker with complementary diagnostic value. The combination of PCT, CD48, and lactate achieved superior accuracy in predicting early bacteremia, suggesting a potential role in future FN risk algorithms. Integration of cellular biomarkers into clinical decision frameworks may advance individualized antimicrobial management and reduce overtreatment in pediatric oncology.

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