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RESEARCH PAPER

Role of Interleukin-6 as an Early Predictor of Bacteremia in Febrile Neutropenia among The Children with Acute Leukemia

Md. Imran Habib[1*], Md. Anwarul Karim[2], Olia Sharmeen Baten[1], Fahmida Begum Mily[3], Lutfor Rahman Molla[1], Yesmin Tanjin jahan[1].

[1]Department of Pediatric Hematology & Oncology, Sir Salimullah Medical College (SSMC), Mitford Hospital, Dhaka, Bangladesh; [2]Department of Pediatric Hematology & Oncology, Bangabandhu Sheikh Mujib Medical University(BSMMU), Dhaka, Bangladesh; [3]Department of Feto-maternal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Abstract

Background: Febrile neutropenia (FN) is a significant complication of acute leukemia, leading to morbidity and mortality. Early detection of bacteremia is crucial for timely management, but traditional culture methods are time-consuming. Previous studies have suggested that Interleukin-6 (IL-6) may serve as an early and convenient marker for predicting bacteremia in children with hematological malignancies and febrile neutropenia. This study aimed to investigate the role of IL-6 in predicting bacteremia among children with acute leukemia and febrile neutropenia.

Methods: A cross-sectional study was conducted at the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), over a 12-month period following ethical approval. A total of 50 children with acute leukemia and febrile neutropenia were enrolled based on specific criteria. Written informed consent was obtained from parents and detailed histories, clinical examinations, and relevant investigations were performed. Data were collected using a semi-structured questionnaire and analyzed using SPSS 22.0.

Results: The study included patients with a mean age of 5.96±3.69 (SD) years, with a male predominance 31(62%). Among the patients, 23(46%) had microbiologically documented infection (MDI),15(30%) had clinically documented infection (CDI), and12(24%) had fever without focus (FWF). Among the isolated organisms in MDI patients,16(69.56%) were gram-negative bacteria .The mean rank of IL-6 was higher in patients with MDI compared to CDI and FWF. IL-6 showed 87% sensitivity and 76% specificity at a cutoff value of 141.95 pg/mL in the ROC curve analysis, with an area under the curve of 0.843. Increasing IL-6 levels were associated with higher odds of bacteremia in both univariate and multivariate logistic regression analyses. No significant difference in IL-6 levels was observed between patients with gram-positive and gram-negative bacteremia.

Conclusion: This study suggests that IL-6 may play a crucial role in predicting bacteremia in febrile neutropenic patients with acute leukemia. However, further multicenter case-control studies are recommended to validate these findings.

Keywords: Children, Febrile neutropenia, Interleukins, Malignancies, C-reactive protein

Introduction

Acute leukemia is the most common type of hematological cancer in children. The cure rate for Acute Lymphoblastic Leukemia in developed countries exceeds 80%, whereas in Low- and Middle-Income Countries (LMIC), it ranges from 40% to 70%.[1,2] Patients with leukemia, particularly those undergoing chemotherapy, are highly susceptible to infections due to various factors associated with the disease and treatment.[3] Febrile Neutropenia (FN) is the most prevalent infection in acute leukemia and has higher mortality rates compared to other malignancies, ranging from 6% to 43%.[3,5] Prompt initiation of antimicrobial treatment within one hour of FN onset is recommended due to its potential to cause hemodynamic instability. However, current diagnostic methods such as blood cultures are time-consuming.[3,6,7] Therefore, there is a need for reliable and readily available biomarkers to diagnose or rule out infection.

***Correspondence:** Md. Imran Habib, Department of Pediatric Hematology & Oncology, Sir Salimullah Medical College (SSMC), Mitford Hospital, Dhaka, Bangladesh*
ORCID: 0009-0006-1026-1775

The current biomarkers with predictive value for diagnosing bacteremia include C-reactive Protein (CRP), Interleukin-6 (IL-6), and Procalcitonin (PCT).[8] IL-6, a multifunctional cytokine, has shown promise as a sensitive and early marker for bacteremia, particularly Gram-negative bacteremia.[9] IL-6 levels have been observed to rise as early as one hour after the infectious stimulus.[10] Febrile neutropenia in cancer patients undergoing chemotherapy prolongs hospital stays, increases treatment costs, and leads to significant morbidity and mortality. Mortality rates for febrile neutropenia have been reported as 5% in solid tumors and 11% in hematological malignancies. Patients with confirmed bacteremia have even worse prognoses, with mortality rates of 18% for Gram-negative bacteremia and 5% for Gram-positive bacteremia.[1,11]

In the context of acute leukemia and febrile neutropenia, the role of IL-6 as an early predictor of bacteremia has not been adequately addressed. Consequently, with this lack of data regarding IL-6 and febrile neutropenia, this study aims to investigate the potential of IL-6 as an early predictor of bacteremia in febrile neutropenia among children with acute leukemia.

Materials and Methods

The study was a cross-sectional study conducted in the Department of Pediatric Hematology and Oncology, Bangladesh Sheikh Mujib Medical University (BSMMU) for a period of twelve months, extending from July 2021 to June 2022.

The study was conducted among the 50 acute leukemia children of 1 to <18 years who developed febrile neutropenia (FN) during any phase of chemotherapy in department of Pediatric Hematology and Oncology, BSMMU, Dhaka during the study period. Patients with any other type of malignancy or getting any palliative chemotherapy will be excluded. Sampling was selected purposively after obtaining informed assent from the parents of the patients before enrollment in this study.

Data were collected by an interview with the help of a pre-tested semi structured questionnaire. At the beginning of the interview the purpose and importance of the study was explained. The questionnaire was filled out by the researcher during the interview. Medical data regarding initial presentation at diagnosis, risk stratification, type of treatment protocol, treatment starting date, complication during treatment were recorded. Blood samples were collected as soon as possible at the onset of fever in inpatients or within 24 hours of presentation to Outdoor Patients Department (OPD) and sent for complete blood counts, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Interleukin 6 (IL-6),blood culture and sensitivity,urine culture and sensitivity, Additional tests and investigative procedures were done if indicated. Serum Interleukin-6 was measured by Siemens Advia Centaur XP based on Chemiluminescence microparticle immunoassay (CMIA) method for quantitative determination of Interleukin-6 with at least 3 ml of venous blood. Values were obtained within 2 hours of the test required. Normal Interleukin-6 value is d”7 pg/mL, Values were obtained within 6 hours of test request and were measured as early as possible of developing FN. All patients were followed up with standard care and procedures and the outcome of the participants were assessed accordingly.

Prior to conducting the study, ethical approval was obtained from the Institutional Review Board (IRB) of BSMMU. The privacy of the participants and confidentiality of data were maintained strictly. The study was conducted in accordance with the guidance and principles of the Declaration of Helsinki.

All data were checked and edited after collection, verified for consistency. Significant tests were done by chi-square tests. To determine the relationship between continuous variables, Kruskal wallis analysis was done. For all analysis a p value d” 0.05 was considered statistically significant and was applied to all statistical tests. Receiver Operating Characteristic (ROC) curves were constructed with 95% CIs. The area under the curve (AUC) was used to evaluate the predictive power of IL-6, CRP & ESR for bacteremia. Using the co-ordinates of curve, the cut off values were determined for the value with best predictive ability.

Results

The collected socio-demographic data of 50 patients with acute leukemia were analyzed and presented in tables and graphs. The majority of the children 38(76%) were 10 years or younger, with an average age of 5.96±3.69 years. Among the patients,31 (62%) were male, and 35(70%) resided in rural areas. Specific information regarding the education level of parents was not available, but data on family income showed that approximately 50% of guardians had a monthly income of 21,000 to 40,000 BDT, while 46% had an income of 10,000 to 20,000 BDT. A small proportion had lower or higher incomes. Regarding leukemia

subtypes, 39(78%) of the cases were Acute Lymphoblastic Leukemia (ALL), with 32(64%) being B-cell ALL and 7(14%) being T-cell ALL. The remaining 11(22%) were Acute Myeloid Leukemia (AML). Mean laboratory values were reported for certain parameters. The mean Hemoglobin level was 9.43±1.66 gm/dl, the mean platelet count was 51,500±46,147/cu.ml, and the mean Absolute Neutrophil Count (ANC) was 179.00±170.76. These values provide insights into the hematological status of the patients and contribute to understanding their overall condition in Table I.

Table I: Distribution of the respondents by age (n=50)

Characteristic	No. of patient (%)
Age groups (years)	
>10 Years	12 (24%)
≤10 Years	38 (76%)
Gender distribution	
Male	31 (62%)
Female	19 (31%)
Area of residence	
Rural	35 (70%)
Urban	15 (30%)
Monthly income	
<10000	01 (02%)
10,000-20,000 BDT	23 (46%)
21000-40000BDT	25 (50%)
>40,000 BDT	01 (02%)
Type of acute leukemia	
ALL-B-cell	32 (64%)
ALL-T-cell	7 (14%)
AML	11 (22%)
Hemoglobin (gm/dl) Mean±SD	9.43±1.66
Platelet (cu.mm) Mean±SD	51500±46147
ANC Mean±SD	179.00±170.81

Values are expressed as percentage (%) over column in total and with mean±SD*

ALL- Acute Lymphoblastic Leukemia, AML- Acute Myeloid Leukemia, ANC- Absolute Neutrophil Count.

Among the patients, 23(46%) had a microbiologically documented infection, confirmed through laboratory tests. Another 15(30%) had a clinically documented

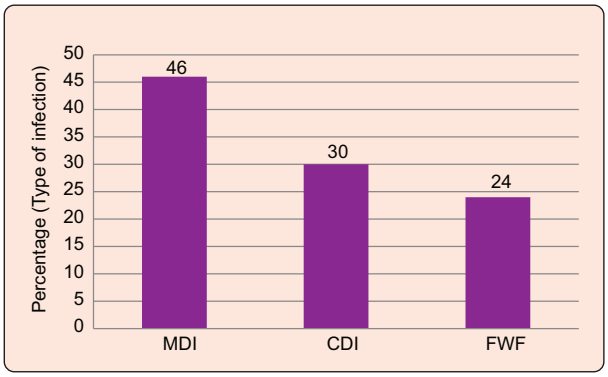

Figure 1: Type of infection among study subjects (n=50)

MDI: Microbiologically documented infection, CDI: Clinically documented infection,

FWF: Fever Without Focus.

infection based on clinical signs and symptoms. Additionally, 12(24%) of the patients had fever without a specific focus, indicating an elevated body temperature without a clear source of infection. These classifications help categorize the different types of infections seen in the patient population and the corresponding diagnostic methods used (Figure 1).

Analysis of Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) levels showed elevated levels in all infection groups. However, there were no statistical differences when comparing the infection groups, suggesting similar elevation of ESR and CRP across all groups. In contrast, analysis of Interleukin-6 (IL-6) levels revealed significant differences. Patients with microbiologically documented infections (MDI)

Table II: Relationship ESR, CRP and Interleukin-6 with types of infection (n=50)

	MDI (n=23) mean rank	CDI (n=15) mean rank	FWF (n=12) mean rank	*p* value
ESR	27.28	26.43	18.96	0.236
CRP	26.5	27.36	19.38	0.287
Interleukin-6	34.65	21.83[a]	12.54[a,b]	<.001

MDI: Microbiologically documented infection, CDI: Clinically documented infection, FWF: Fever Without Focus, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein. p value was determined by Kruskal wallis test. [a]Denotes significant difference of interleukin6 among patients with MDI and CDI. [a,b]Denotes significant difference of Interleukin-6 among patients with MDI and FWF.

had significantly different IL-6 levels compared to patients with clinically documented infections (CDI) (P=0.024) and fever without focus (FWF) patients (P<0.001). However, there was no statistical difference in IL-6 levels between CDI patients and FWF patients.

These findings suggest that IL-6 may serve as a more discriminatory biomarker for differentiating between different types of infections, particularly between MDI patients and both CDI and FWF patients. However, IL-6 alone may not be sufficient to distinguish between CDI and FWF patients, and further analysis using additional biomarkers may be necessary for better differentiation (Table-II).

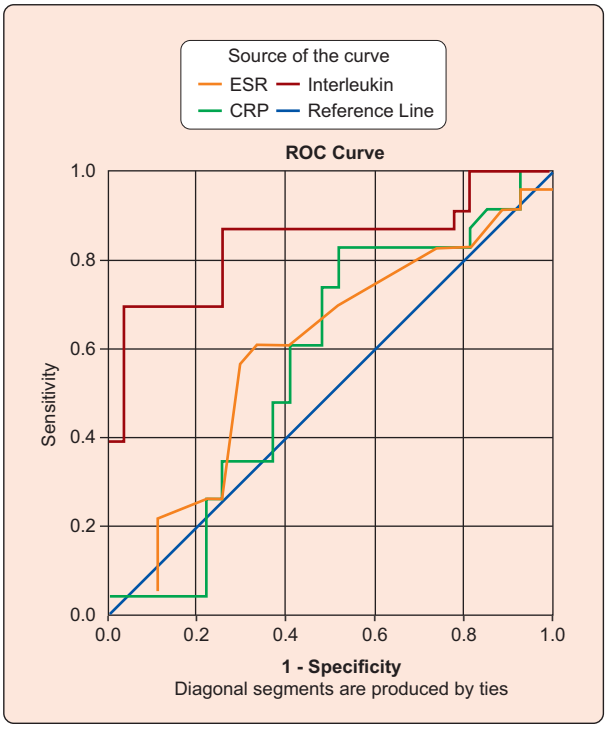

Figure 2: Receiver's Operating Characteristics (ROC) curve of ESR, CRP and Interleukin-6 for detecting the presence of bacteremia among the acute leukemia patients with febrile neutropenia (n=50)

The ROC curve analysis revealed the performance of different biomarkers in diagnosing infections. For Erythrocyte Sedimentation Rate (ESR), a cut-off value of 35 showed 60.9% sensitivity and 64% specificity, with an area under the curve (AUC) of 0.587. C-reactive Protein (CRP) had a cut-off value of 56.50, with 60.9% sensitivity and 56% specificity, and an AUC of 0.547. Interleukin-6 (IL-6) demonstrated a cut-off value of 141.95, with 87% sensitivity and 76% specificity, and an AUC of 0.843 (Figure 2).

Kruskal-Wallis analysis indicated significant differences in IL-6 levels among the infection groups. Patients with microbiologically documented infections (MDI) had significantly different IL-6 levels compared to patients with clinically documented infections (CDI) (P=0.024) and fever without focus (FWF) patients (*P*<0.001). However, no statistical difference in IL-6 levels was observed between CDI patients and FWF patients, as shown in Table III.

The analysis of Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) levels revealed elevated levels in all infection groups. However, when comparing the infection groups, no statistical difference was observed, suggesting that ESR and CRP levels were similarly elevated across all groups.

Regarding Interleukin-6 (IL-6), the data presented in Table IV indicate that there was no statistically significant difference in IL-6 levels between patients with Gram-positive bacteremia and patients with Gram-negative bacteremia. This suggests that IL-6 levels may not differ significantly based on the type of bacteremia.

Table III: Assessment of AUC, 95%CI, p value, sensitivity and specificity of ESR, CRP and IL-6 (n=50)

Markers	Area under curve	95% Confidence interval (lower limit-upper limit)	*p* value	Cutoff value	sensitivity	specificity
ESR	.587	.422-.752	.302	35	60.9%	64%
CRP	.547	.379-.714	.577	56.50	60.9%	56%
Interleukin-6	.843	.724-.963	<.001	141.95	87%	76%

Table IV: Difference of interleukin-6 among patients with gram-positive bacteremia and gram-negative bacteremia (n=50)

	Gram-positive bacteremia (mean±SD)	Gram-negative Bacteremia (mean±SD)	*p* value
Interleukin-6	687.50±616.53	792.65±569.18	0.695

*p value was determined by independent student t test.

Discussion

This cross-sectional observational study involved 50 children with acute leukemia and febrile neutropenia to investigate the role of Interleukin-6 (IL-6) in predicting bacteremia. The study population had an age range of 1 year to <18 years, with the majority 38(76%) falling into the age group <10 years. The mean age was 5.96±3.69 years, which is consistent with findings from previous studies where mean age was 6.5±4.4 (SD) years. The study observed a male predominance, with 31(62%) of the patients being male and 19(38%) being female, aligning with the findings. (2020) study focused on Acute Lymphoblastic Leukemia (ALL)[12]. The majority of the study population (70%) resided in rural areas, while 30% came from urban regions. This difference in infection rates between urban and rural areas may be due to variations in healthcare facilities and delayed access to appropriate treatment options in rural settings as found study[13].

Regarding clinical presentations, all patients had a fever, with a mean duration of 4.46±2.23 days. Other common symptoms included vomiting, headache, abdominal pain, loose stools, respiratory distress/ cough, bleeding manifestations, difficulty/burning sensation during urination, and convulsions. These presentations are typical in patients with febrile neutropenia and malignancy. Vital parameters, such as blood pressure, pulse rate, respiratory rate, and temperature, were within a range indicative of infection. These features were similar to the typical presentations of febrile neutropenia patients with malignancy[3]. In terms of leukemia subtypes, 39(78%) of the patients had Acute Lymphoblastic Leukemia (ALL), with 32(64%) being B-cell precursor ALL and 7(14%) T-cell precursor ALL. The remaining 11(22%) had Acute Myeloid Leukemia (AML). These proportions are consistent with the overall distribution of ALL and AML in leukemia cases.[4,6]

The study (Figure 1) classified the patients into three infection groups: Microbiologically Documented Infection (MDI), Clinically Documented Infection (CDI), and Fever Without Focus (FWF). The prevalence of MDI was 23(46%), CDI was 15(30%), and FWF was 12(24%), aligning with the findings of previous studies on febrile neutropenia. Among the patients with bacteremia, 16(69.56%) had Gram-negative (Gm-ve) bacteremia, while 7(30.44%) had Gram-positive (Gm+ve) bacteremia. Pseudomonas, Acinetobacter, and Klebsiella were the most common Gram-negative bacteria isolated. Similar results were seen (2018)[14,15]. Statistical analysis revealed that IL-6 levels were significantly higher in MDI patients compared to CDI and FWF patients. However, no significant difference was observed between CDI and FWF patients. Erythrocyte Sedimentation Rate (ESR) and C-reactive Protein (CRP) levels were higher in both MDI and CDI patients compared to FWF patients, although statistical significance was not achieved. Other studies found similar significant IL-6 level result to prediction of bacteremia.[1,16]

ROC curve analysis revealed that IL-6 had a statistically significant area under the curve (AUC) of 0.843, indicating its potential as a marker for predicting bacteremia. In contrast, CRP had an AUC of 0.547, and ESR had an AUC of 0.587, indicating lower predictive ability. Similar findings were reported.[17-18]

Although our study also has some limitations such as a small sample size and the absence of serial evaluation of Interleukin-6 (IL-6) due to financial constraints of the study. However, this study suggests that IL-6 could serve as a potential marker for predicting the presence of bacteremia among children with acute leukemia and febrile neutropenia.

Conclusion

In febrile neutropenic children undergoing chemotherapy, IL-6 proves to be a superior predictor of Gram-negative bacteremia compared to CRP. However, due to the small sample size, the statistical significance of this association remains uncertain. Despite this, CRP remains a valuable and cost-effective test for sepsis when IL-6 testing is not feasible. IL-6 emerges as the most effective parameter in

predicting bacteremia. Further studies are needed to determine the clinical relevance of these findings and their potential application in early discharge, outpatient therapy with once-daily intravenous antibiotics (e.g., Ceftriaxone) or even the use of oral antimicrobial therapy. These approaches have the potential to yield significant cost savings, reduce exposure to hospital-acquired pathogens, improve the quality of life for children, and minimize disruption to family life.

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Conflict of interest: The authors declare that they have no competing interests.

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