ORIGINAL ARTICLE

Clinical profile and factors associated with mortality in febrile neutropenia among children with acute lymphoblastic leukemia: A single-center study in Indonesia

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ABSTRACT

Background and aim: Febrile neutropenia (FN) is a life-threatening oncologic emergency in children with acute lymphoblastic leukemia (ALL), associated with substantial morbidity and mortality. This study aimed to describe the clinical profile of FN and identify factors associated with mortality in a resource-limited pediatric oncology setting.

Methods: An observational analytic study with a cross-sectional design was conducted using secondary data from electronic medical records of pediatric ALL patients with FN at Dr. Soetomo General Academic Hospital between January 2023 and July 2025. The unit of analysis was FN episodes. Demographic, clinical, microbiological, and outcome data were collected. Mortality-associated factors were analyzed using chi-square, Mann–Whitney U, and independent t-tests.

Results: A total of 135 patients with 206 FN episodes were analyzed (mean 1.52 episodes/patient). Most episodes occurred in children aged <5 years (51.9%) and males (58.3%). Febrile neutropenia most commonly developed during induction chemotherapy (42.2%), with high-risk ALL protocol predominating (52.9%). Profound neutropenia was present in 36.9% of episodes. Culture positivity was found in 28.6% of episodes, with

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gram-negative bacteria predominating (54.9%), particularly Pseudomonas aeruginosa (15.69%). Overall episode mortality rate was 16.5% (34/206 episodes; 25.2% per patient). Factors significantly associated with mortality included high-risk protocol, profound neutropenia, positive cultures, prolonged hospitalization, prolonged fever, delayed ANC recovery, lower hemoglobin, lower platelet count, and lower ANC ($p<0.05$).

Conclusions: High-risk protocol, severe neutropenia, bacteremia, and unfavorable hematological parameters were associated with mortality, highlighting the need for tailored risk stratification and antimicrobial stewardship in pediatric oncology settings. (www.actabiomedica.it)

Key words: febrile neutropenia, acute lymphoblastic leukemia, clinical profile, pediatric, mortality, Indonesia

Introduction

Febrile neutropenia (FN) is one of the most serious and common complications of chemotherapy in children with hematological malignancies, particularly acute lymphoblastic leukemia (ALL). It is characterized by a single axillary temperature measurement of ≥38.3–38.5°C, or a sustained temperature of ≥38°C more than one hour, in the presence of an absolute neutrophil count (ANC) of ≤500 cells/mm³, or ≤1,000 cells/mm³ with an anticipated decline to <500 cells/mm³ within 24–48 hours (1). In children with ALL, the combined effects of disease-related immunosuppression and myelosuppressive chemotherapy create a profound vulnerability to infectious complications, rendering FN a true oncologic emergency. The incidence of FN is notably higher in hematological malignancies compared to solid tumors, with reported rates varying by disease type, treatment intensity, and center-specific protocols (2). Children with ALL experience recurrent FN episodes across the treatment continuum, from induction through maintenance, each episode carrying a risk of severe infectious complications including bacteremia, septic shock, and death (3). Current pediatric FN guidelines classify patients into low-risk and high-risk groups according to the severity and duration of neutropenia, underlying disease, treatment intensity, and comorbidities. This classification guides clinical management, including antimicrobial therapy and supportive care, as children with acute leukemia are at increased risk of severe infectious complications and mortality (1). Globally, mortality rates from FN in pediatric oncology range from 2% to over 20%, depending on the country's resources and treatment capabilities (4). In Indonesia, data on the clinical profile and mortality burden of FN in children with ALL remain limited. Dr. Soetomo General Academic Hospital in Surabaya, the largest referral center in East Java, manages a high volume of pediatric ALL patients, providing a unique opportunity to study this condition in a middle-income country context. Understanding the local epidemiology, microbiological landscape, and mortality-associated factors is critical for developing context-appropriate clinical management protocols. This study aimed to describe the clinical profile of FN in children with ALL at a single tertiary center in Indonesia, characterize the microbiological findings, and identify clinical and laboratory factors significantly associated with mortality.

Methods

This was an observational analytic study with a cross-sectional design using secondary data from electronic medical records. The study was conducted at the Pediatric Inpatient Ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia - a level-IV national referral center. Data were collected from January 2023 to July 2025. A total sampling approach was used. During the study period, 291 inpatient episodes of children (aged 0–18 years) with ALL and

neutropenia were identified from the electronic medical records. The unit of analysis was the FN episode rather than the individual patient, as a single patient could experience multiple FN episodes during treatment. Inclusion criteria were (1) children aged 0–18 years with a confirmed diagnosis of ALL who fulfilled the diagnostic criteria for FN during hospitalization at Dr. Soetomo General Academic Hospital and (2) complete medical records containing hematological parameters and clinical outcome data. Episodes were excluded if the patient had a history of chronic infection (tuberculosis, hepatitis B/C, or HIV), syndromic conditions (e.g., Down syndrome), or hematologic malignancies other than ALL, including acute myeloid leukemia (AML). One episode of an ALL patient with Down syndrome and eighty-four episodes that did not meet the diagnostic criteria for FN were excluded. After applying the eligibility criteria, 206 FN episodes were included in the final analysis. Because the study population consisted of hospitalized children with ALL and FN during active treatment, all episodes fulfilled the criteria for high-risk FN according to current pediatric guidelines. The following data extracted were: age, sex, chemotherapy phase at FN onset (pre-treatment, induction, consolidation, re-induction, maintenance, relapse), ALL risk classification protocol (standard or high-risk per the Indonesian Childhood ALL Guideline), degree of neutropenia (severe: ANC ≤500 cells/mm^3; profound: ANC <100 cells/mm^3), microbiological culture results, and clinical outcomes (survival vs. death). Clinical and laboratory parameters at FN onset were also recorded, including hemoglobin, platelet count, leukocyte count, ANC, duration of fever, duration of hospitalization, duration of antibiotic therapy, and time to ANC recovery. The diagnosis and classification of ALL were primarily established based on bone marrow aspiration morphology according to the French-American-British (FAB) classification criteria. Cytogenetic and molecular analyses were not available during the study period because of resource limitations. Likewise, flow cytometry-based immunophenotyping was performed only in selected cases and was therefore not included in the analysis (5,6). All patients were treated according to the Indonesian Childhood ALL Guideline (2018), which classifies patients into standard-risk (SR) and high-risk (HR) groups. Patients were classified as HR if they presented at diagnosis with any of the following: age <1 year or ≥10 years, white blood cell count ≥50,000 cells/mm^3, mediastinal mass, central nervous system involvement, testicular involvement, T-lineage ALL, or mixed-lineage leukemia. Patients who did not meet any HR criteria were classified as SR. Treatment consisted of four phases: induction, consolidation, intensification (re-induction), and maintenance. Both SR and HR patients received induction, consolidation, and maintenance therapy; however, HR patients received additional cyclophosphamide during consolidation and underwent an intensification phase consisting of vincristine, dexamethasone, daunorubicin, cytarabine, and intrathecal methotrexate. Consequently, HR patients were exposed to more intensive chemotherapy regimens than SR patients. Trimethoprim-sulfamethoxazole prophylaxis against Pneumocystis jirovecii pneumonia was routinely administered during the consolidation and maintenance phases (7). At our institution, FN is managed according to the institutional Antimicrobial Resistance Control Program (PPRA) guidelines. All patients undergo prompt clinical assessment, blood culture collection before antibiotic administration, and initiation of empirical broad-spectrum intravenous antibiotic therapy targeting both gram-positive and gram-negative organisms, with ampicillin-sulbactam as the first-line regimen. Patients are reassessed after 48 hours, and gentamicin may be added if fever persists. Antifungal therapy is considered after 96 hours in patients with persistent fever or suspected fungal infection. Supportive care, including blood component transfusion, fluid therapy, and intensive care referral when indicated, is provided according to the patient's clinical condition. Antimicrobial therapy is subsequently adjusted based on microbiological findings and clinical response. Filgrastim (granulocyte colony-stimulating factor, G-CSF) was not part of the institutional standard management protocol for pediatric ALL; therefore, none of the patients included in this study received G-CSF therapy (8). Descriptive statistics were used to characterize the study population. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD); non-normally distributed variables were presented as median with interquartile range (IQR).

Categorical variables were expressed as frequency and percentage. Bivariate analysis was performed to assess associations between clinical/laboratory characteristics and mortality: the chi-square test was used for categorical variables, Mann-Whitney U test for non-normally distributed continuous variables, and independent samples t-test for normally distributed variables. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.

This study received ethical exemption approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital (Letter of Exemption No. 2109/LOE/301.4.2/IX/2025, dated September 8, 2025). Patient identities were anonymized and kept confidential throughout the research process.

Results

Patient characteristics

A total of 135 patients with 206 FN episodes were included in the analysis, yielding a mean of 1.52 episodes per patient. Of the 135 patients, 41 experienced more than one FN episode (ranging from 2 to 6 episodes per patient), while 94 patients experienced only one episode. Repeated FN episodes were not significantly associated with mortality (p=0.107). The characteristics of all study subjects are presented in Table 1. More than half of all FN episodes (51.9%) occurred in children younger than 5 years, and males predominated (58.3%). The induction phase of chemotherapy was the most frequent phase at FN onset (42.2%), followed by pre-treatment (23.8%) and maintenance (18.9%). High-risk ALL protocol was documented in 52.9% of episodes. Most episodes involved severe neutropenia (63.1%), while profound neutropenia was present in 36.9%.

Microbiological profile

Of 206 FN episodes, 59 (28.6%) yielded positive culture results: 51 blood cultures, 7 urine cultures, and 1 stool culture. The detailed microbiological profile is presented in Table 2. Among blood culture isolates (n=51 episodes), gram-negative bacteria predominated (54.9%), with Pseudomonas aeruginosa being the most frequently identified pathogen (15.69%), followed by Escherichia coli and Klebsiella pneumoniae (9.80% each). Gram-positive bacteria accounted for 45.1% of blood culture isolates, with Staphylococcus aureus being most common (15.69%).

Clinical outcomes and mortality

Overall, 34 out of 206 FN episodes (16.5%) resulted in death. On a per-patient basis, 34 of 135

Table 1. Clinical Characteristics of Study Subjects and Mortality Distribution

Characteristic	All Episodes n = 206 (%)
Age	
< 5 years	107 (51.9)
≥ 5 years	99 (48.1)
Sex	
Male	120 (58.3)
Female	86 (41.7)
Chemotherapy Phase	
Pre-treatment	49 (23.8)
Induction	87 (42.2)
Consolidation	23 (11.2)
Re-induction	7 (3.4)
Maintenance	39 (18.9)
Relapse after remission	1 (5)
Chemotherapy Protocol	
High-risk	109 (52.9)
Standard-risk	97 (47.1)
Degree of Neutropenia	
Severe (ANC ≤500 cells/mm^3)	130 (63.1)
Profound (ANC <100 cells/mm^3)	76 (36.9)
Blood Culture Result	
Positive	59 (28.6)
Negative	147 (71.4)
Clinical Outcome	
Survived	172 (83.5)
Died	34 (16.5)

Abbreviation: ANC = absolute neutrophil count

Table 2. Microbiological Profile of Identified Pathogens

Microorganism	n (%)
Blood Culture (n = 51 episodes)	
Gram-Negative Bacteria	28 (54.9)
Pseudomonas aeruginosa	8 (15.69)
Escherichia coli	5 (9.80)
Klebsiella pneumoniae	5 (9.80)
Salmonella enterica serovar Paratyphi B	4 (7.84)
Salmonella species	2 (3.92)
Aeromonas veronii	2 (3.92)
Moraxella species	1 (1.96)
Acinetobacter baumannii	1 (1.96)
Gram-Positive Bacteria	23 (45.1)
Staphylococcus aureus	8 (15.69)
Staphylococcus hominis	4 (7.84)
Staphylococcus epidermidis	2 (3.92)
Staphylococcus haemolyticus	1 (1.96%)
Staphylococcus kloosii	1 (1.96%)
Staphylococcus equorum	1 (1.96%)
Streptococcus mitis / Streptococcus oralis	1 (1.96%)
Streptococcus dysgalactiae subsp. equisimilis	1 (1.96%)
Bacillus spp	1 (1.96%)
Corynebacterium species	1 (1.96%)
Urine Culture (n = 7 episodes)	
Gram-Negative Bacteria	4 (57.14)
Aeromonas veronii	1 (14.29)
Pseudomonas aeruginosa	1 (14.29)
Klebsiella pneumoniae	1 (14.29)
Citrobacter amalonaticus	1 (14.29)
Gram-Positive Bacteria	2 (28.57)
Enterococcus faecium	2 (28.57)
Fungi	1 (14.29)
Candida albicans	1 (14.29)
Stool Culture (n = 1 episode)	
Gram-Negative Bacteria	1 (100)
Escherichia coli	1 (100)

patients (25.2%) died. Among the factors evaluated, the following were statistically significantly associated with mortality: high-risk chemotherapy protocol (p=0.024), profound neutropenia (p=0.034), positive culture results (p<0.001), prolonged hospitalization (p=0.015), prolonged fever duration (p=0.004), delayed ANC recovery time (p=0.032), lower hemoglobin at presentation (p=0.002), lower platelet count (p=0.016), and lower ANC (p=0.002). Age, sex, time from last chemotherapy to FN onset, time from symptom onset to admission, duration of antibiotic therapy, and leukocyte count were not significantly associated with mortality. The full comparative analysis is presented in Table 3.

Discussion

Incidence and epidemiological profile

This study presents a comprehensive clinical profile of FN in children with ALL at Eastern Indonesia's largest pediatric hematology-oncology referral center. The mean rate of 1.52 FN episodes per patient is consistent with international literature, which reports a similar average of 1.58–1.86 episodes per patient (3,9). A patient with acute leukemia may experience more than one episode of FN, and this was also revealed by other study, in which 69.3% of patients had experienced at least one previous episode of FN (10). The observation that 41 patients (30.4%) experienced recurrent FN underscores the cumulative infectious burden that children with ALL face across their entire treatment course. The predominance of episodes in children aged <5 years (51.9%) is in keeping with the known epidemiology of ALL, which peaks in early childhood, and reflects the findings of Rondinelli et al. (11), who identified age <5 years as an independent risk factor for severe infectious complications in FN. The male preponderance (58.3%, ratio 1.54:1) is consistent with prior reports across different settings (ratios ranging from 1.21:1 to 1.6:1) (3,12,13) and is reflective of the higher incidence of ALL in males.

Chemotherapy phase and risk classification

Neutropenic fever can occur at any time during the course of a malignant disease, particularly hematologic malignancies, ranging from diagnosis through the terminal stage. Most episodes of neutropenic fever are typically limited to the early diagnostic phase

Table 3. Factors Associated with Mortality in Febrile Neutropenia Episodes

Variable	Died (n=34)	Survived (n=172)	p
Age, years — mean (±SD)	7.47 (±4.67)	6.16 (±3.72)	0.074[a]
Sex, n (%)			
Male, n (%)	19 (55.9)	101 (58.7)	0.759[c]
Female, n (%)	15 (44.1)	71 (41.3)	
Chemotherapy protocol, n (%)			
High-risk protocol, n (%)	24 (70.6)	85 (49.4)	**0.024**[c]
Standard-risk protocol, n (%)	10 (29.4)	87 (50.6)	
Neutropenia degree, n (%)			
Severe neutropenia, n (%)	16 (47.1)	114 (66.3)	**0.034**[c]
Profound neutropenia, n (%)	18 (52.9)	76 (36.9)	
Culture result, n (%)			
Positive culture, n (%)	21 (61.8)	38 (22.1)	<**0.001**[c]
Negative culture, n (%)	13 (38.2)	134 (77.9)	
Duration from the last chemotherapy, days — median (range)	8 (0-92)	6 (0-653)	0.290[b]
Duration from symptoms to hospital, days — median (range)	2 (0 - 60)	1 (0 - 120)	0.771[b]
Length of stay, days — median (range)	13 (0–36)	8 (3–50)	**0.015**[b]
Length of fever, days — median (range)	8 (0–29)	4 (0–49)	**0.004**[b]
Antibiotic duration, days — median (range),	11 (0 - 36)	7 (1 - 49)	0.144[b]
Time to ANC recovery, days — median	10 (2–26)	7 (1–44)	**0.032**[b]
Hemoglobin, g/dL	8.3 (2.5–13.2)	9.25 (2.6–15.6)	**0.002**[b]
Platelet count, $\times 10^3/\mu L$	15 (1–81)	24 (0–386)	**0.016**[b]
Leukocyte count, $10^3/\mu L$	2.20 (0.11 – 319.13)	1.71 (0 – 73.25)	0.461[b]
ANC, $\times 10^3/\mu L$ — median	0.09 (0–0.44)	0.20 (0.01–0.55)	**0.002**[b]

Abbreviations: SD = standard deviation; ANC = absolute neutrophil count; a. Mean (+SD) using an independent samples t-test; a significant association is indicated when $p < 0.05$. b. Median (IQR) using the Mann-Whitney U test; a significant association is indicated when $p < 0.05$. c. Chi-square test; a significant association is indicated when $p < 0.05$

and active treatment. Often, fever is the sole sign of infection due to a suppressed inflammatory response (14). The induction phase accounted for the highest proportion of FN episodes (42.2%), consistent with the 52.4% reported by Erbas et al. (9). This finding is expected, as induction therapy involves the most intensive myelosuppressive treatment and is associated with profound and prolonged neutropenia. Mortality was significantly higher among patients treated under the high-risk protocol than the standard-risk protocol (70.6% vs. 29.4%; p=0.024), likely reflecting both more aggressive disease characteristics and greater treatment intensity. This observation is consistent with data from the Indonesian Pediatric Cancer Registry (IPCaR), which reported higher mortality among children receiving high-risk compared with standard-risk ALL protocols (17.7% vs. 7.75%) (7) Furthermore, previous studies have shown that more than half of FN episodes occur in children with high-risk ALL. The increased burden of FN and mortality in this population is likely attributable to intensified chemotherapy exposure, including additional consolidation agents and a

dedicated intensification phase, resulting in deeper and more prolonged immunosuppression (7,9).

Microbiological findings

The culture positivity rate of 28.6% in this study is slightly higher than what some international series report (approximately 20%), but falls within the range reported in resource-limited settings (4). The predominance of gram-negative organisms (54.9% of blood culture isolates), particularly Pseudomonas aeruginosa, is consistent with trends in pediatric oncology centers in Asia and developing countries (4,15). This finding has important implications for empirical antibiotic selection; current international guidelines recommend broad-spectrum anti-pseudomonal coverage as first-line empirical therapy for high-risk FN, which is appropriate given these local microbiological data. Gram-positive organisms, particularly Staphylococcus aureus (15.69%), represented a substantial proportion of isolates, likely attributable in part to central venous catheter use in this patient population. The significant association between positive culture results and mortality ($p<0.001$) in this cohort reinforces the principle that documented bacteremia markedly worsens outcomes in FN, particularly when caused by resistant organisms or when associated with septic shock (16).

Factors associated with mortality

The mortality rate of 16.5% per episode (25.2% per patient) in this study is higher than that reported in some high-income countries (2–5%) but is consistent with mortality rates reported from tertiary centers in lower-middle income countries (10–25%) (4). The relatively high mortality observed in our cohort underscores the ongoing challenges of managing FN in resource-constrained settings and supports the need for continuous refinement of management strategies through locally validated risk stratification tools, risk-adapted antimicrobial therapy, and optimized supportive care protocols. Profound neutropenia (ANC <100 cells/mm^3) was significantly associated with mortality ($p=0.034$), consistent with established literature demonstrating that the depth of neutropenia is a stronger predictor of infectious complications than the duration alone (9). Lower hemoglobin ($p=0.002$), lower platelet count ($p=0.016$), and lower ANC ($p=0.002$) at presentation all reflect a state of more severe bone marrow suppression, consistent with higher mortality risk. These hematological parameters are readily available at initial assessment, making them practical bedside prognostic markers. Prolonged fever duration ($p=0.004$) and delayed ANC recovery ($p=0.032$) in the mortality group likely reflect inadequate or delayed infectious source control, antibiotic failure, or refractory myelosuppression — all recognized contributors to poor FN outcomes. The significantly longer hospitalization in the mortality group (median 13 vs. 8 days; $p=0.015$) may partially reflect disease severity and the time required to manage complications prior to death. Importantly, age and sex were not significantly associated with mortality ($p=0.074$ and $p=0.759$, respectively), suggesting that while young age is a risk factor for the occurrence and severity of FN, it does not independently predict death in this cohort once other clinical factors are controlled for.

Limitations

This study has several limitations. The retrospective, single-center design may limit the generalizability of the findings to other institutions in Indonesia. In addition, cytogenetic, molecular, and immunophenotypic data were not available because of resource limitations. Consequently, the potential influence of favorable or unfavorable genetic abnormalities and ALL immunophenotypic subtypes on the occurrence of FN and mortality could not be assessed. Future prospective multicenter studies incorporating comprehensive molecular characterization and standardized data collection are warranted to validate and extend these findings.

Conclusion

This study provides a comprehensive clinical and microbiological profile of FN in Indonesian children with ALL. The induction phase, high-risk protocol, profound neutropenia, bacteremia, and impaired hematological parameters at onset are key factors

associated with mortality. Gram-negative bacteria, particularly Pseudomonas aeruginosa, predominate in this setting, supporting the need of anti-pseudomonal empirical antibiotic regimens. These findings can serve as a foundation for the development of locally validated clinical algorithms and clinical practice guidelines for FN management at Dr. Soetomo General Academic Hospital and similar tertiary centers in Indonesia.

Ethic Approval: Ethical exemption approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital (Letter of Exemption No. 2109/LOE/301.4.2/IX/2025, dated September 8, 2025).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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