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Febrile Neutropenia In Pediatric Patients with Acute Leukemia During Induction Chemotherapy in Hiwa Hospital at Sulaimaniyah City, Kurdistan Region of Iraq

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ABSTRACT

Background: Febrile neutropenia (FN) is common in pediatric oncology patients, and the majority of patients with FN do not have a microbiologically defined infection, but those who do are at risk for overwhelming complications, including severe infection and death.
Objectives: To determine the risk factors and treatment outcomes of FN pediatric patients with acute leukaemia during induction of chemotherapy.
Patients and methods: This cross-sectional, retrospective, observational, hospital-based study was conducted on 10 years of recorded data (January 01, 2015, to January 01, 2025) of pediatric acute leukaemia patients (n=115) who developed FN during induction of chemotherapy from the Pediatric Department at Hiwa Hematology/Oncology Hospital, Sulaimaniyah, Iraq.
Results: The patients' mean age was 8.02 ± 4.65 years with a mean body mass index (BMI) of 16.56 ± 4.46 kg/m². Most patients were aged 1.0 – 6.0 years (41.7%, n=48), males (56.5%, n=65), underweight (76.5%, n=88), had blood group A+ (43.5%, n=50), had ALL (58.3%, n=67), experienced immunosuppression (87%, n=100), had no fatigue or anxiety (59.1%, n=68), and had a body temperature of >38.5° C (58.3%, n=67). Also, majority of patients had profound neutropenia (62.6%, n=72), fever (46.1%, n=53), negative microbial cultures/identified infection (82.6%, n=95), had positive C-Reactive Protein (63.5%, n=73), received prophylactic antimicrobial (73.0%, n=84), had no abnormality on imaging (87.8%, n=101), not admitted to Intensive Care Unit (ICU) (84.3%, n=97), and were recovered (89.6%, n=103). Consequently, no significant differences were observed in age, gender, BMI, or culture-related findings ($p \geq 0.05$).
Conclusions: A chemotherapy-induced FN is a crucial life-threatening complication of the cytotoxic drugs used in the management of pediatric acute leukaemias.

INTRODUCTION

Acute leukaemias represent approximately 30% of all malignancies diagnosed in children younger than 15 years and 25% of all malignancies in children and adolescents younger than 20 years. Approximately 3250 new cases of leukaemia are diagnosed annually in the United States [1].

Acute lymphoblastic leukaemia (ALL) is a neoplastic genetic disease characterized by the clonal expansion of leukemic cells in the bone marrow, lymph nodes, thymus, or spleen. It accounts for approximately 2500 (80%) cases per year. Approximately 20% of cases (800-900 cases per year) are acute myeloid leukaemia (AML), and a small fraction (1.0%) is chronic myeloid leukaemia (CML). There is a sharp peak in ALL incidence among 2- to 3-year-olds, which decreases by ages 8 to 10 years [2].

There are few established risk factors for childhood leukaemia, including sex, age, race, exposure to ionizing radiation, and congenital diseases (e.g., Down syndrome, neurofibromatosis); however, these risk factors account for only 10% of childhood leukaemia cases [3]. The incidence of ALL among 2- and 3-year-olds is approximately four times greater than that for infants and is nearly ten times greater than that for 19-year-olds. In contrast, AML rates are highest in the first 2 years of life, decrease with a nadir at approximately 9 years of age, and slowly increase again during adolescence [2].

The disease-free survival rates have increased markedly in children with advances in cancer treatment, intensification of chemotherapy protocols and stem cell transplant therapies [4]. A life-threatening and significant complication of intensive chemotherapy in children with cancer, particularly acute leukaemias, is febrile neutropenia (FN), which is a serious consequence of chemotherapy that usually results in hospitalization and the need for intravenous antibiotics. Febrile neutropenia may result in dose reductions, delays, or even discontinuation of chemotherapy, which, in turn, may compromise patient outcomes [5].

Neutropenic fever occurs when there is a single oral temperature of ≥ 102°F (38.5 °C) or a temperature of ≥ 100.4°F (38 °C) for at least an hour, with an absolute neutrophil count (ANC) of < 1,500 cells/mL. Chemotherapy regimens have been classified as having a high, intermediate, or low risk of developing FN based on prospective clinical trials of selected patients with variable capture of treatment-related toxicities, including neutropenia and FN. Current guidelines state that chemotherapy regimens with >20% FN rate in clinical trials of chemotherapy-naïve patients are considered high risk [6]. This study aimed to assess the risk factors, treatment outcomes, and survival rates of febrile neutropenia in pediatric patients with acute leukaemia during induction chemotherapy at Hiwa Haematology/Oncology Hospital.

MATERIALS AND METHODS

Study design and setting

This is a cross-sectional, retrospective, observational, hospital-based study conducted on the recorded data of pediatric acute leukaemia patients (n=115) who developed fever neutropenia (FN) during induction chemotherapy at Hiwa Haematology/Oncology Hospital,

Sulaimaniyah, Iraq, from January 1, 2015, to January 1, 2025 (10 years).

Study protocol

A standard validated questionnaire has been constructed, and patients' sociodemographic data, including age at diagnosis, gender, height and weight to determine body mass index (BMI; kg/m2), and ABO blood group were collected, together with their clinical data, such as leukaemia type/subtype, the severity of neutropenia, duration of neutropenia, highest recorded body temperature, acute complications, and associated symptoms. Additionally, patients' culture results were obtained in conjunction with prophylactic antimicrobial use during chemotherapy induction, identification of infections, and C-reactive protein (CRP) levels. Moreover, the patients' radiological modality and findings were collected, including chest X-ray (CXR), CT scan, MRI, and echocardiograph, together with radiological evidence of fungal infection. Additionally, data on chemotherapy completion, delays, and modifications due to FN, including clinical presentation, ICU admission, and response to treatment, were also collected. Finally, the correlation between patients' sociodemographic data, clinical/treatment characteristics, and their outcomes (recovery or death) was determined, along with the correlation between survival rate and time with leukaemia type.

Inclusion criteria

Pediatric patients aged <18 years old, regardless of gender, nationality, and residency, were diagnosed with initial acute leukaemia and developed FN during the induction of chemotherapy.

Exclusion criteria

Patients with chronic leukaemias had relapsed or refractory leukaemia, and those who developed either fever or neutropenia alone during induction of chemotherapy.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Review Board of Hiwa Haematology/Oncology Hospital and the Ethics Committee of the College of Medicine, University of Sulaimani, Sulaimaniyah, Iraq (No. 01/01, dated January 8, 2025). The study adhered to the ethical guidelines of the Declaration of Helsinki, 2008. The Hospital authority waived patient informed consent due to the nature of the study (retrospective).

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, USA, version 26). The Chi-square test was applied to assess the relationship between categorical variables. For continuous variables, the Kolmogorov-Smirnov test was used to check normality. Categorical variables were presented as numbers and percentages, while numerical variables were presented as mean ± standard deviation (SD). A p-value of <0.05 was considered significant, while $p<0.001$ was set as highly important.

RESULTS

The patients' ages ranged from 1.0 to 17 years, with a mean age of 8.02 ± 4.65 years. The BMI of the patients ranged from 10 to 32 kg/m², with a mean of 16.56 ± 4.46 kg/m². Most patients were aged 1.0–6.0 years (41.7%, n = 48), males (56.5%, n = 65), underweight (76.5%, n =

88), and had blood group A+ (43.5%, n = 50) (Table 1).

The majority of the patients had ALL (58.3%, n=67); among whom, 71.6% (n=48) were diagnosed with B-cell ALL (B-ALL), while 28.4% (n=19) had T-cell ALL (T-ALL). Additionally, 41.7% (n = 48) had AML, among whom 8.3% (n = 4) had APL. In terms of acute complications, 87.0% (n = 100) of patients experienced immunosuppression, while 13.0% (n = 15) did not. For physical and psychological well-being, 59.1% (n = 68) of the patients reported no fatigue or anxiety, whereas 40.9% (n = 47) experienced these symptoms. About 41.7% (n = 48) of patients had a body temperature of 38-38.5 °C, and 58.3% (n = 67) had a temperature greater than 38.5 °C. In terms of the degree of neutropenia, 7.8% (n = 9) of patients had mild neutropenia, 16.5% (n = 19) had moderate, 13.0% (n = 15) had severe, and 62.6% (n = 72) had profound neutropenia (Table 2).

Blood cultures were obtained in the majority of patients (77.4%, n = 89), while 22.6% (n = 26) had no blood cultures. Regarding culture results, 77.5% (n = 69) were negative, while 22.5% (n = 20) were positive. The most commonly identified microorganisms were Pseudomonas spp. (4.3%, n = 5), then E. coli and Streptococcus spp. (3.5%, n=4 each), Klebsiella spp. (2.6%, n=3), Staphylococcus spp. (1.7%, n=2), and Enterococcus faecium with Candida spp. (0.9%, n=1 each). The majority of patients (82.6%, n = 95) had no identified infection. However, infections were identified, including cellulitis (0.9%, n = 1), chest infections (9.6%, n = 11), gastrointestinal tract infections (5.2%, n = 6), and port-catheter-relatedport-catheter-related infections (1.7%, n = 2). A large proportion of patients (73.0%, n=84) received prophylactic antimicrobial treatment, and 36.5% (n=42) of the patients had negative CRP results, while 63.5% (n=73) tested positive (Table 3).

The most commonly used imaging modality was CXR (58.3%, n=67), followed by CT scan (14.8%, n=17), CXR + abdominal ultrasound (13.9%, n=16), then CXR + CT scan (7.0%, n=8), CXR + MRI (6.1%, n=7), and echocardiography (2.6%, n=3). Most patients (87.8%, n = 101) had no abnormalities, while 12 (12.2%) exhibited abnormalities. Regarding fungal infection, 73.9% (n=85) had no evidence, while 26.1% (n=30) showed evidence of fungal infection (Table 4).

Most patients (87%, n=100) completed their chemotherapy, did not experience any delays, and had delayed chemotherapy due to FN (87%, n=100), while 13% (n=15) had their treatment stopped (Table 5). The most common signs/symptoms in patients were fever alone (46.1%, n=53), followed by fever with mucositis (29.6%, n=34), fever with cough (13%, n=15), fever with abdominal pain (5.2%, n=6), fever with jaundice (3.5%, n=4), and fever with headache (2.6%, n=3). Most patients (84.3%, n = 97) were not admitted to the ICU. The duration of ICU admission ranged from 3 to 31 days, with a mean duration of 9.17 ± 5.99 days. In terms of response to initial treatment, 89.6% (n = 103) of patients experienced recovery, while 10.4% (n = 12) did not respond (died) (Table 6).

Regarding age, the majority of patients who experienced resolution were aged 1 - 6 years (42.7%, n=44), followed by 7 - 12 years (38.8%, n=40), and then 13 - 17 years (18.4%, n=19). Among those who

died, 33.3% (n = 4) were in each age group (p = 0.472). In terms of gender, 45.6% (n = 47) of females experienced resolution, and 25.0% (n = 3) of them died, while 54.4% (n = 56) of males had a resolution, and 75.0% (n = 9) of them died (p = 0.172). Regarding BMI, the majority of patients (76.7%, n = 79) were underweight, with 15.5% (n = 16) having a normal weight, 5.8% (n = 6) being overweight, and 1.9% (n = 2) being obese. Among those who died, 75% (n=9) were underweight, and 8.3% (n=1) were overweight (p=0.949) (Table 7).

Mild neutropenia occurred in 23.3% (n = 24) of patients who experienced resolution. For moderate neutropenia, 18.4% (n = 19) of patients experienced resolution with no deaths. However, severe neutropenia was observed in 58.3% (n = 60) of the patients who recovered, while all 12 patients who died had severe neutropenia (p = 0.018). In terms of the type of leukaemia, 62.1% (n=64) of patients with ALL had a resolution, while 25% (n=3) of them died. In contrast, 75% (n=9) of patients with AML died, and 37.9% (n=39) of them had a resolution (p=0.014). Regarding culture findings, 84.5% (n = 87) of patients who experienced resolution had negative cultures, and 15.5% (n = 16) had positive cultures. In contrast, 66.7% (n = 8) of patients who died had negative cultures, and 33.3% (n = 4) had positive cultures (p = 0.124). For the highest recorded body temperature, 46.4% (n = 48) of patients who recovered had a body temperature of 38-38.5 °C, while 53.4% (n = 55) had a body temperature greater than 38.5 °C (p = 0.002). Regarding prophylactic antimicrobial use, 30.1% (n = 31) of patients who achieved resolution did not receive prophylactic antimicrobials, while 69.9% (n = 72) did. All patients who died (n = 12) received prophylactic antimicrobials (p = 0.026). In terms of chemotherapy completion as scheduled, 96.1% (n = 99) of patients who recovered completed chemotherapy, whereas only 3.9% (n = 4) did not. Among those who died, 91.7% (n=11) did not complete chemotherapy as scheduled (p<0.001). Regarding ICU admission, 94.2% (n = 97) of patients who recovered were not admitted to the ICU, while 5.8% (n = 6) were accepted. In contrast, 100% (n = 12) of the patients who died required ICU admission (p < 0.001) (Table 8).

The Kaplan-Meier survival analysis did not demonstrate a significant difference in survival rate between ALL and AML, as indicated by the Log-Rank test ($\chi^2 = 1.581$, p = 0.209). This suggests that the survival distributions of the leukaemia types are not significantly different during the observed period (Figure 1). The mean survival time for ALL was 24.75 days (95% CI: 20.03–29.47), whereas for AML, it was 22.21 days (95% CI: 17.65–26.76). The difference of approximately 2.5 days in average survival time is not meaningful, as reflected in the overlapping confidence intervals. The median survival time for both groups was 21 days. While the survival curve of AML shows a slightly earlier decline than that of ALL, the visual differences are not supported by statistically significant data.

The chemotherapy regimens administered to the patients included UKALL 2019 (57.4%, n = 66), then DA3+10 (32.2%, n = 37), LDAC (4.3%, n = 5), PETHEMA 2005 (3.5%, n = 4), FLAG-IDA (1.7%, n = 2), and Infantile (0.9%, n = 1). The majority of patients received either UKALL 2019 or DA3+10, which together accounted for 89.6% of all chemotherapy

regimens used in the study. The remaining 10.4% of patients were treated with less standard protocols, including LDAC, PETHEMA2005, FLAG-IDA, and Infantile regimens.

DISCUSSION

A significant life-threatening complication of intensive chemotherapy administered in children with leukaemia is FN. Thus, in this study, we aimed to evaluate the clinical features, risk factors, and consequences of FN attacks in children treated for acute leukaemia at the time of initial diagnosis of leukaemia retrospectively (2015-2025).

Age at diagnosis is a key factor for predicting the prognosis of pediatric leukaemia, especially regarding survivorship assessment [7]. In the current study, the patients' ages ranged from 1.0 to 17 years, with a mean age of 8.02 ± 4.65 years. Most patients were aged 1.0 to 6.0 years (41.7%). In this regard, Özdemir et al. [8] found that pediatric leukemic patients with FN were aged 1.0-18 years, with a mean age of 5.9 ± 3.7 years, and most of them were aged 1.0-6.0 years (64.5%). These slight variations among conducted studies may be related to factors such as sample size, environmental conditions, risk factors, genetic predispositions, and patient immune status.

In terms of response to initial treatment, 89.6% of patients had recovered, while 10.4% did not respond (i.e., they died). This outcome is impressive and aligns with international data [9,10]; however, it is correlated with the patients' sociodemographic characteristics, clinical data, risk factors, type of treatment, and response to treatment. Regarding the correlation between patients' age and survival rate, the majority of patients who experienced resolution were aged 1-6 years (42.7%; expected to be long-term survivors), while the least were among those aged 13-17 years (18.4%). Among those who died, 33.3% were non significantly died from each age group (p=0.472). Similarly, another study stated that older age (≥10 years) is associated with poorer survival in pediatric acute leukaemias [11]. However, the potential interaction of age and survival rate in pediatric leukaemia remains unaddressed.

Multiple studies demonstrated that a higher BMI at diagnosis is associated with a poorer survival rate in children with pediatric ALL or AML. On the other hand, being underweight has been associated with higher treatment-related toxicity [11]. The BMI of the patients in this study ranged from 10 to 32 kg/m², with a mean BMI of 16.56 ± 4.46 kg/m², and most of them were underweight (76.5%). Regarding the correlation between patients' BMI and fatality rate, among those who died, 75% were malnourished, and the least were overweight (8.3%); however, BMI-related outcomes were not significant (p=0.949). These findings indicate that low body weight is a considerable risk factor for chemotherapy response and survival rates.

In contrast to these outcomes, several studies mentioned that high BMI at diagnosis is associated with a low survival rate in children with pediatric ALL or AML [11-13]. However, a systematic review and meta-analysis by Galati et al., 2022 [14] indicates that overweight/obesity negatively affects the prognosis of children with ALL, while AML does not. These variations might be related to the sample size, unequal distribution of patients among groups,

patients' race and ethnicity, as well as publication bias.

Additionally, in the current study, males predominantly developed acute leukaemia with FN (56.5%), which is consistent with another study that observed a 52.1% male predominance among pediatric leukemic patients with FN [8]. Thus, in this study, regarding the correlation between patients' gender and survival rate, 54.4% of males and 45.6% of females experienced resolution, while 75% of males and 25% of females died non-significantly (p=0.172). These findings may be related to the fact that more male patients were involved in the study than female patients. On the contrary, Ansarian et al. 2025 [15] found inferior outcomes in males, while females exhibit superior survival despite experiencing greater treatment-related toxicities. At the same time, Williams et al. ((2019)) [16] found no significant difference ($p \geq 0.05$) between the genders in 5-year survival for ALL (85% for males and 88% for females). However, in an extensive population-based pediatric leukaemia study, Holmes et al. [17] found that males had poorer survival than females, which was not entirely explained by treatment received, tumour prognostic factors, or sociodemographic factors. The disparities between studies may be associated with sex hormones, X-chromosome loss, sex-specific patterns in distinct mutational profiles, differences in immune system function, and sex-based pharmacokinetic variations, collectively suggesting the necessity for sex-differentiated treatment approaches [15].

There is evidence suggesting potential associations between ABO blood groups and the development of cancer, particularly leukaemias [18]. In the current study, most pediatric patients with acute leukaemias had blood group A+ (43.5%). At the same time, the least common was blood group AB- (0.9%), indicating that blood group A is a risk factor for the development of acute leukaemia in this locality. In this respect, Alavi et al. found that in the ALL group, more patients had the O blood group (56.5%), followed by the A group (35.8%), and then the B group (26.9%). In the AML group, there were 28.8% more patients with A blood group [19]. On the other hand, a study in Sulaimaniyah, Iraq, by Hama et al. (2022) [20] suggested that blood groups A, AB, and O were positively and significantly related to acute leukaemias, with the O group being more vulnerable to ALL and AML, as indicated by beta coefficients of 0.444 and 0.445, respectively. ABO antigens are not limited to red blood cells. They are widely expressed in several human cells and tissues, which can cause a temporary discrepancy in the blood group and may return to the actual blood group after remission from leukaemia leukaemia [21].

In this study, the majority of pediatric patients had ALL (58.3%), with the majority of these cases being B-ALL (71.6%). While 41.7% of the patients had AML, among them, 8.3% had APL, a subtype of AML that requires distinct treatment approaches. The Institute of Medicine, National Research Council and National Cancer Policy Board in the USA also mentioned that ALL is the most prevalent type of cancer among children [22]. Similarly, Abdulkareem et al. [23] stated that ALL was the most prevalent type of cancer observed among pediatric patients. Siegel (2021) also reported that ALL is the most predominant type of childhood malignancy [24]. In regards to the correlation between the type of

leukaemia and patients' outcome, 62.1% of patients with ALL and 37.9% with AML had resolutions, while 25% of those with ALL and 75% with AML died. These correlations were significantly associated ($p = 0.014$) with ALL, showing a better prognosis than AML. Similarly, for children under 15, it was found that ALL has the highest survival rate (92%), with children being free of the disease 5 years after diagnosis, while AML has a survival rate of 69%. These outcomes may be related to the child's age, leukaemia characteristics, leukaemia risk groups, leukaemia subtype, genetic factors, treatment modality, and patient follow-up [25].

Chemotherapy protocols for pediatric acute leukaemias are complex and typically involve multiple phases, including induction, consolidation, and maintenance. These protocols are tailored to the specific type of leukaemia, its risk factors, and the individual child's response to treatment. The most commonly used chemotherapy regimens in this study were UKALL 2019 (57.4%), then DA3+10 (32.2%), LDAC (4.3%), PETHEMA2005 (3.5%), FLAG-IDA (1.7%), and Infantile (0.9%). Another study mentioned that all pediatric patients with leukaemia were treated using the Berlin-Frankfurt-Münster protocol [26]. Additionally, treatment protocols have been shown to significantly correlate with improved survival rates, as evidenced by a 5-year overall survival rate of 88% in pediatric patients with acute leukaemias when the standardized AIEOP-BFM-2009 protocol was used [27].

In terms of acute complications, most patients experienced immunosuppression (87%), while 13% did not. Hence, immunosuppression might be the typical case of developing FN among patients, reflecting the ongoing health challenges faced by many patients who received chemotherapy. Bacterial infections (especially E. coli and P. aeruginosa) often reflect profound immunosuppression among patients even before chemotherapy is initiated. Thus, Carbapenem-sparing antimicrobial regimes for patients with community-acquired infections seem a reasonable choice when hemodynamically stable and without other risk factors. Cennamoet al. stated that [28] severe infection complications in patients with chemotherapy-induced FN were associated with bone marrow involvement, diagnosis of pre–B-cell leukaemia, viral infection, CRP values, haemoglobin and leukocyte counts, and presence of the central venous catheter. Furthermore, in this study, 59.1% of the patients reported no fatigue or anxiety, whereas 40.9% had both symptoms. These findings might be directly related to the patient's quality of life and high survival rate.

Long-term neutropenia is a leading cause of infectious mortality for oncological children receiving cytotoxic chemotherapies, although the data from available studies are controversial. Thus, the degree of neutropenia was significantly associated with patient outcomes. In this study, most patients (62.6%) had severe neutropenia, of which 58.3% of them recovered, while the rest died, and none of the patients who died had mild/moderate neutropenia. Consequently, the degree of neutropenia is a critical risk factor for infection and other complications during induction chemotherapy. These outcomes highlight a significant association between severe neutropenia and adverse outcomes ($p = 0.018$).

On the other hand, most patients (58.3%) had a body temperature of >38.5° C, and

all of those who died were among this group (12 patients). The vast majority of patients who recovered (46.4%) had a body temperature of 38 °C to 38.5 °C. The variations in recorded body temperatures were significant (p = 0.002).

Moreover, a high body temperature among patients results in fever alone in most patients (46.1%) or a combination of fever together with mucositis (29.6%), cough (13%), abdominal pain (5.2%), jaundice (3.5%), and finally fever with headache (2.6%). Thus, all acute leukemic leukemic pediatric patients in this study (100%) had a fever (FN). Approximately 1/3 of children treated for cancer or who underwent HSCT experienced FN during the neutropenic period [28], while another study stated that 59% of all FN attacks were fever of unknown origin [8]. While FN is a condition affecting both adult and pediatric patients, there are several differences between the two age groups. An important consideration is that children have a higher risk chance of developing bacterial infections from an unknown source [29]. Several factors, including an increased number of patients, altered hospital flora, and structural changes in inpatient care, may impact the frequency of FN [8].

It's well-established that microbial infections are a primary cause of febrile neutropenia (FN), and infections in patients with chemotherapy-induced neutropenia have been described since the introduction of these therapies in the mid-20th century [26]. However, in the current study, most cultured samples (82.6%) were negative for microbial agents, while 17.4% were positive, even under the best laboratory conditions and techniques for bacterial and fungal identification. Hence, we were unable to perform viral culture and identification due to the lack of availability of a specific facility for this purpose. Consequently, our results suggest that the majority of febrile episodes were not associated with detectable microbial growth. Among the positive cultures, Pseudomonas spp. was the most commonly found microorganism (4.3%), followed by E. coli and Streptococcus spp. (3.5% each), Klebsiella spp. (2.6%), Staphylococcus spp. (1.7%), and Enterococcus faecium with Candida spp. (0.9% each). In this aspect, Özdemir et al. [8] isolated 18 microorganisms in pediatric cultured samples during FN throughout treatment in 75 patients, of which 86% were bacterial, 8.0% were viral, and 6.0% were fungal. They also found that coagulase-negative staphylococcus and E. coli (n = 17 each) were the most frequent Gram-positive and Gram-negative pathogens, respectively.

Regarding the correlation between culture findings and patient outcomes, 84.5% of patients who recovered had negative cultures, while 15.5% had positive cultures. In contrast, 66.7% of patients who died had negative cultures, and 33.3% had positive cultures, without a significant association between the two groups (p = 0.124). These outcomes indicated that positive culture results were not directly related to the patient's response and treatment outcomes. In this regard, Viscoli et al. [30] observed that neutropenia was associated with bloodstream infections in 84% of patients with acute leukaemias, compared to 47% of patients with solid tumours and 55% of those who received bone marrow transplants. Simultaneously, Carlesse et al., 2024 [31] indicated that infection-related deaths in pediatric patients with acute leukaemias ranged

from 5.4 - 7.3% during chemotherapy, being more frequent in the intensive phase.

Additionally, they noted that invasive fungal infections were highly associated with mortality, especially those caused by Aspergillus spp. Variations between studies may be related to the patient's immune status, treatment protocol, risk factors, and leukaemia leukaemia type, as well as its associated risk group. Consequently, infections not only lead to increased mortality but also extend hospital stays, hinder the administration of chemotherapy, impact the quality of life, and raise healthcare resource utilization [31].

One of the strongest predictive factors of infectious complications in children with FN is CRP, which was confirmed by several studies. High CRP at first admission of pediatric patients with acute leukaemias was also found to be the most important independent risk factor for high mortality rate [32]. In this study, 36.5% of our patients had negative CRP results, while 63.5% tested positive, indicating an inflammatory response likely associated with the febrile episodes. In parallel to this outcome, Lima et al., 2023 [33] and Das et al., 2018 [34] showed that a CRP of >90 mg/L (acute phase) at the onset of a febrile episode was associated with a higher risk of infection and it could be helpful for the establishment of risk scores for infection in neutropenic children [33].

It is well established that a quantitative reduction in circulating immune cells makes the host more susceptible to invasive infections. Also, immature myeloid cells potentially inhibit the antigen-specific T-cell response. The humoral immune system is also affected by the disease and its treatment, so the majority of patients will have immunoglobulins deficiency that leads to the development of infection. Regarding the focus of infection in the current study, the majority of patients (82.6%) had no identified infection, indicating that febrile neutropenia episodes were not always associated with an underlying infectious source. However, infections were identified in some cases, including cellulitis (0.9%), chest infections (9.6%), gastrointestinal tract infections (5.2%), and port-catheter-related infections (1.7%). In the same manner, Özdemir et al. [8] found the focus of infection clinically in 22% of paediatrics with acute leukaemias, including infections in the pulmonary area (38%), gastrointestinal tract (29%), urinary tract (18%), otolaryngological/dental regions (9.0%), dermatological and soft tissue regions (4.5%), and meningitis (1.5%). The low rate of these infections among paediatrics with FN might be related to complete remission, neutropenia periods, and the use of prophylactic antimicrobials during chemotherapy induction.

Antibiotic prophylaxis is a crucial strategy for reducing bacterial infections and associated complications in pediatric patients with acute leukaemia [35]. In the present study, most patients (73%) received prophylactic antimicrobial treatment during induction of chemotherapy, while 27% did not. Regarding the correlation between prophylactic antimicrobial use during chemotherapy induction and patient outcomes, most surviving patients (69.9%) received prophylactic antimicrobials, while 30.1% did not ($p = 0.026$). At the same time, all patients who died were received prophylactic antimicrobials. These outcomes suggest that the use of

prophylactic antimicrobials may have affected patients' survival rates. Intensive chemotherapy for acute leukaemias, particularly during the induction phase, leads to prolonged neutropenia, making patients more susceptible to infections and needing prophylactic antimicrobials [36]. Thus, these medications can effectively reduce bloodstream infections and febrile episodes in acute leukaemia settings. However, conclusive evidence on the impact on mortality is lacking, warranting further research [36].

Diagnostic imaging is essential in the diagnosis and management, including surveillance, of known or suspected cancer in children. The chest radiograph aids in the diagnosis of pneumonia, empyema, and acute lung injury in pediatric patients with acute leukaemias [37]. Thus, the most commonly used imaging modality among our patients was chest X-ray (CXR) (58.3%), and the least was echocardiography (2.6%). The results revealed that most patients had no abnormality (87.8%). Among those with positive findings (12.2%), bilateral, left-side, and right-side lung involvement was observed (4.3%, 2.6%, and 1.7%, respectively). Regarding radiological evidence of fungal infection, 73.9% of patients had no evidence, while 26.1% showed evidence of fungal infection. Generally, for pediatric leukaemia, several imaging modalities are used, with MRI and PET/CT often playing key roles. MRI is functional for evaluating soft tissues and bone marrow, while PET/CT aids in staging and monitoring treatment response [37]. However, PET was not used for the patients of this study as it is not available at the hospital. Thus, pediatric patients mainly depend on chest X-rays and other modalities (abdominal ultrasound, CT, and MRI).

Regarding ICU admission, the majority of patients (84.3%) were not admitted, while 15.7% required admission. The duration of ICU admission ranged from 3 - 31 days, with a mean duration of 9.17 ± 5.99 days. Regarding ICU admission, 94.2% of patients who recovered were not admitted, while 5.8% were admitted to the ICU. In contrast, 100% of the patients who died required ICU, indicating a strong association between ICU admission and mortality ($p<0.001$). The need for intensive care in children with ALL, especially for children with T-cell acute lymphoblastic leukaemia and CNS leukaemia, is high, with most admissions occurring during early treatment.

In terms of chemotherapy completion as scheduled, 96.1% of patients who recovered completed chemotherapy, whereas only 3.9% did not. Among those who died, 91.7% did not complete chemotherapy as scheduled, highlighting a strong association between chemotherapy completion and survival ($p<0.001$). Survival analysis by Pasha et al. (2024) [27] showed that 55% and 40% of patients achieved 2-year and 5-year event-free survival rates, respectively, after completing chemotherapy. The completion rates can vary depending on factors such as age, subtype of acute leukaemias, patients' immune status, and overall health.

This study had some limitations, including its single-centred design and the fact that paediatric leukaemia subtypes pes were not investigated. Additionally, the inability to provide detailed treatment information, encompassing cumulative doses of chemotherapeutic drugs or radiation and studying secondary malignancies after

pediatric acute leukaemias, was not addressed.

CONCLUSIONS

The majority of febrile episodes were not associated with detectable microbial growth. The inflammatory response is likely associated with the febrile episodes. The survival rate was not directly correlated with patients' age, gender, BMI, and culture findings. The survival rate directly correlated to patients' neutropenia severity, leukaemia type, highest recorded body temperature, use of prophylactic antimicrobials, chemotherapy completion, and ICU admission. Survival rates for childhood leukaemia have improved, but the risk of infections remains a significant concern.

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TABLES

Table 1. Sociodemographic Characteristics of Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy at Hiwa Hospital.

Sociodemographic Characteristics		Number (Percentage)
Age (Years)	1 - 6	48 (41.7%)
	7 - 12	44 (38.3%)
	13 - 17	23 (20.0%)
Gender	Female	50 (43.5%)
	Male	65 (56.5%)
Body Mass Index (BMI) (kg/m²)	Underweight	88 (76.5%)
	Normal weight	18 (15.7%)
	Overweight	7 (6.1%)
	Obese	7 (6.8%)
ABO Blood Group	A+	50 (43.5%)
	A -	2 (1.7%)
	B +	24 (20.9%)
	B -	2 (1.7%)
	AB +	3 (2.6%)
	AB -	1 (0.9%)
	O +	31 (27.0%)
	O -	2 (1.7%)
Total		**105 (100%)**

Table 2. Clinical Characteristics of Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy.

Clinical characteristics		Number (Percentage)
Type of Leukemia	ALL	67 (58.3%)
	AML	48 (41.7%)
Duration of neutropenia (Days)	≤7	15 (13.0%)
	>7	100 (87.0%)
Acute complications	Yes	100 (87.0%)
	No	15 (13.0%)
Physical and psychological well-being (fatigue/anxiety)	No	68 (59.1%)
	Yes	47 (40.9%)
Highest recorded body temperature (°C)	38 - 38.5	48 (41.7%)
	>38.5	67 (58.3%)
Degree of neutropenia	Mild (1000-1500 cells/µL)	9 (7.8%)
	Moderate (500-1000 cells/µL)	19 (16.5%)
	Severe (200-500 cells/µL)	15 (13.0%)
	Profound (<200 cells/µL)	72 (62.6%)
Total		**115 (100%)**

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia

Table 3. Microbiological Findings, Infection Focus, and Prophylactic Treatment in Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy.

Variables			Number (%)
Having Blood Culture	Yes		89 (77.4%)
	No		26 (22.6%)
Culture and Sensitivity	Negative (No Growth)		69 (77.5%)
	Positive (Microbial Growth)		20 (22.5%)
Identified Microorganism	Candida spp.		1 (0.9%)
	Gram-positive	*Staphylococcus spp.*	2 (1.7%)
		Streptococcus spp.	4 (3.5%)
		Enterococcus faecium	1 (0.9%)
	Gram-negative	*Klebsiella spp.*	3 (2.6%)
		Pseudomonas spp.	5 (4.3%)
		Escherichia coli	4 (3.5%)
Prophylactic Antimicrobial Use during Chemotherapy Induction	No		31 (27.0%)
	Yes		84 (73.0%)
C-Reactive Protein	Negative		42 (36.5%)
	Positive		73 (63.5%)
Total			**115 (100%)**

Table 4. Radiological Findings in Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy.

Radiological Findings		Number (%)
Imaging Modality	CXR	67 (58.3%)
	CT scan	17 (14.8%)
	CXR + CT scan	8 (7.0%)
	CXR + MRI brain	7 (6.1%)
	CXR + Abdominal ultrasound	16 (13.9%)
Abnormality Findings	No	101 (87.8%)

	Yes	14 (12.1%)
Radiological Evidence of Fungal Infection	No	85 (73.9%)
	Yes	30 (26.1%)

CXR: Chest X-ray; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

Table 5. Chemotherapy Completion, Delays, and Modifications in Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy.

Variables		Number (%)
Chemotherapy completion as scheduled	No	15 (13.0%)
	Yes	100 (87.0%)
Febrile neutropenia episodes leading to delays in chemotherapy	No	94 (81.7%)
	Yes	21 (18.3%)
Chemotherapy regimen due to febrile neutropenia	Delayed	100 (87.0%)
	Stopped	15 (13.0%)

Table 6. Clinical Presentation, ICU Admission, and Response to Treatment in Febrile Neutropenic Pediatric Patients with Acute Leukemia During Induction of Chemotherapy.

Variables		Number (%)
Sign and Symptoms	Fever alone	53 (46.1%)
	Fever and cough	15 (13.0%)
	Fever and mucositis	34 (29.6%)
	Fever and abdominal pain	6 (5.2%)
	Fever and headache	3 (2.6%)
	Fever and Jaundice	4 (3.5%)
ICU Admission	No	97 (84.3%)
	Yes	18 (15.7%)
Response to Initial Treatment	Recovered (Resolution)	103 (89.6%)
	Did not respond (Died)	12 (10.4%)

ICU: Intensive Care Unit

Table 7. Association Between Patients' Sociodemographic Characteristics and Their Outcomes.

Variables		Resolution (n=103, 89.6%)	Death (n=12, 10.4%)	Total (n=115, 100.0%)	p-value
Age (Years)	1 -6	44 (42.7%)	4 (33.3%)	48 (41.7%)	0.472
	7 - 12	40 (38.8%)	4 (33.3%)	44 (38.3%)	
	13 - 17	19 (18.4%)	4 (33.3%)	23 (20.0%)	
Gender	Female	47 (45.6%)	3 (25.0%)	50 (43.5%)	0.172
	Male	56 (54.4%)	9 (75.0%)	65 (56.5%)	
Body Mass Index	Underweight	79 (76.7%)	9 (75.0%)	88 (76.5%)	0.949
	Normal weight	16 (15.5%)	2 (16.7%)	18 (15.7%)	
	Overweight	6 (5.8%)	1 (8.3%)	7 (6.1%)	
	Obese	2 (1.9%)	0 (0.0%)	2 (1.7%)	

Table 8. Association Between Patients' Clinical and Treatment Characteristics and Their Outcomes.

Variables		Resolution (n=103, 89.6%)	Death (n=12, 10.4%)	Total (n=115, 100%)	p-value
Degree of neutropenia	Mild	24 (23.3%)	0 (0.0%)	24 (23.3%)	0.018*
	Moderate	19 (18.4%)	0 (0.0%)	19 (18.4%)	
	Severe	60 (58.3%)	12 (100.0%)	72 (62.6%)	
Type of leukaemia	ALL	64 (62.1%)	3 (25.0%)	67 (58.3%)	0.014*
	AML	39 (37.9%)	9 (75.0%)	48 (41.7%)	
Duration of neutropenia (Days)	≤7	13 (12.6%)	2 (16.7%)	15 (13.0%)	0.694
	>7	90 (87.4%)	10 (83.3%)	100 (87.0%)	
Culture and sensitivity	Negative	87 (84.5%)	8 (66.7%)	95 (82.6%)	0.124
	Positive	16 (15.5%)	4 (33.3%)	20 (17.4%)	
Highest recorded body temperature (°C)	38 - 38.5	48 (46.4%)	0 (0.0%)	48 (41.7%)	0.002*
	>38.5	55 (53.4%)	12 (100.0%)	67 (58.3%)	
Prophylactic antimicrobial use during chemotherapy induction	No	31 (30.1%)	0 (0.0%)	31 (27.0%)	0.026*
	Yes	72 (69.9%)	12 (100.0%)	84 (73.0%)	
Chemotherapy completion as scheduled	No	4 (3.9%)	11 (91.7%)	15 (13.0%)	<0.001**
	Yes	99 (96.1%)	1 (8.3%)	100 (87.0%)	
ICU admission	No	97 (94.2%)	0 (0.0%)	97 (84.3%)	<0.001**
	Yes	6 (5.8%)	12 (100.0%)	18 (15.7%)	

ALL: Acute lymphocytic leukemia; AML: Acute myelocytic leukemia; ICU: Intensive Care Unit; *: Significant difference, **: Highly significant difference

FIGURES

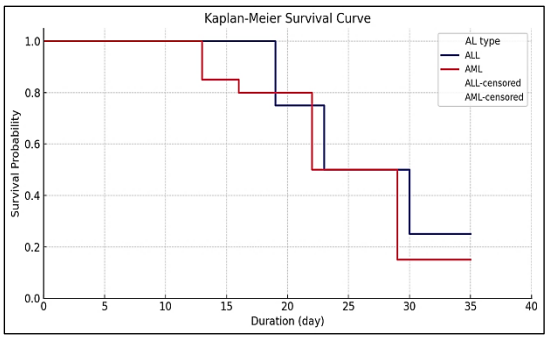

Figure 1. Survival Probability Among Different Types of Acute Leukemia.