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Original article

Survival Outcomes and Toxicity Profile of Pediatric Acute Lymphoblastic Leukemia Treated with Modified BFM Protocol in a Resource-Limited Tertiary Care Center in India

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ABSTRACT

Background- Acute Lymphoblastic Leukemia (ALL) is the most common pediatric malignancy worldwide. In developing countries, management of pediatric ALL is challenged by delayed diagnosis, treatment interruptions, infections, malnutrition, and limited access to hematopoietic stem cell transplantation. Modified Berlin-Frankfurt-Münster (BFM) protocols are commonly adapted in Indian tertiary care centers to improve affordability and tolerability while maintaining acceptable survival outcomes.

Aim- To evaluate survival outcomes and treatment-related toxicity in pediatric ALL patients treated with a modified BFM protocol in a resource-limited tertiary care center in India.

Materials and Methods This retrospective observational study included 72 pediatric ALL patients treated between January 2019 and December 2024 at a tertiary cancer center. Demographic details, hematological parameters, risk stratification, treatment response, toxicities, relapse patterns, and survival outcomes were analyzed. Overall survival (OS), event-free survival (EFS), and treatment-related complications were assessed using descriptive and inferential statistics.

Results- The mean age of patients was 7.9 ± 3.6 years, with male predominance (61.1%). B-cell ALL constituted 83.3% of cases. High-risk disease was observed in 38.9% of patients. Complete remission after induction was achieved in 88.9% of patients. Febrile neutropenia was the most common toxicity (55.6%), followed by anemia requiring transfusion (48.6%) and hepatotoxicity (23.6%). Treatment-related mortality was 8.3%. The 3-year overall survival and event-free survival rates were 72.2% and 64.8%, respectively.

Conclusion- Modified BFM protocol demonstrated acceptable survival outcomes with manageable toxicity in pediatric ALL patients treated in a resource-constrained setting. Early diagnosis, improved supportive care, infection control, and treatment adherence are essential for optimizing outcomes in developing countries.

Keywords- Acute lymphoblastic leukemia; Modified BFM protocol; Pediatric oncology; Survival outcome; Toxicity profile.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy, accounting for approximately 25–30% of all pediatric cancers worldwide. Significant advances in chemotherapy protocols, supportive care, risk stratification, and minimal residual disease monitoring have improved survival rates in developed countries to over 85%. However, outcomes in developing countries remain inferior due to socioeconomic limitations, delayed presentation, malnutrition, treatment abandonment, and infectious complications.

The Berlin-Frankfurt-Münster (BFM) protocol is one of the most widely used treatment regimens for pediatric ALL. It incorporates risk-adapted intensive chemotherapy aimed at maximizing remission and preventing relapse. In low- and middle-income countries like India, modified BFM protocols are frequently utilized to reduce treatment-related toxicity and improve affordability without substantially compromising therapeutic efficacy.

Resource-limited settings face multiple challenges during pediatric ALL treatment. Inadequate nutritional support, poor sanitation, limited intensive care facilities, and financial burden contribute significantly to morbidity and mortality. Treatment interruptions caused by infections and socioeconomic constraints adversely affect survival outcomes. Therefore, evaluation of locally adapted treatment protocols becomes essential for optimizing management strategies.

Toxicity associated with chemotherapy remains a major concern during ALL treatment. Febrile neutropenia, sepsis, mucositis, hepatotoxicity, and hematological suppression are common complications requiring hospitalization and supportive interventions. Understanding the toxicity profile of modified BFM regimens in Indian settings may help clinicians develop strategies for better supportive care and risk reduction.

The present study was conducted to evaluate survival outcomes and treatment-related toxicities among pediatric ALL patients treated with a modified BFM protocol in a tertiary care center in India. The study also aimed to identify patterns of relapse, treatment-related mortality, and factors influencing outcomes in a resource-constrained environment.

MATERIALS AND METHODS

Study Design

This was a retrospective observational study.

Study Setting

The study was conducted at the Department of Medical Oncology and Pediatric Hemato-Oncology of a tertiary care cancer center in India.

Study Duration

Patients treated between January 2019 and December 2024 were included in the study.

Study Population

Children diagnosed with Acute Lymphoblastic Leukemia and treated using the modified BFM protocol were enrolled.

Sample Size

A total of 72 pediatric ALL patients were included in the study.

Inclusion Criteria

1. Age less than 18 years.
2. Newly diagnosed ALL confirmed by bone marrow examination and immunophenotyping.
3. Patients treated with modified BFM chemotherapy protocol.
4. Patients with complete treatment and follow-up records.

Exclusion Criteria

1. Patients with relapsed ALL at presentation.
2. Patients who received treatment elsewhere before referral.

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3. Incomplete medical records.
4. Patients lost to follow-up immediately after diagnosis.

Data Collection

Clinical records were reviewed from hospital medical record archives. Data collected included:

- Age and gender
- Nutritional status
- Immunophenotypic subtype
- Initial white blood cell count
- Risk stratification
- CNS involvement
- Treatment response
- Toxicity profile
- Relapse patterns
- Survival outcomes

Treatment Protocol

All patients received modified BFM chemotherapy consisting of:

- Induction phase
- Consolidation phase
- Re-induction phase
- Maintenance therapy

Supportive care included:

- Blood product transfusions
- Broad-spectrum antibiotics
- Antifungal therapy
- Nutritional supplementation
- Growth factor support when indicated

Outcome Measures

Primary outcomes:

- Overall Survival (OS)
- Event-Free Survival (EFS)

Secondary outcomes:

- Treatment-related toxicity
- Remission rates
- Relapse rates
- Treatment-related mortality

Statistical Analysis

Data were analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Kaplan-Meier survival analysis was

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used to determine OS and EFS. Chi-square test and Student's t-test were used for comparison where appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Clinical Characteristics

Variable	Frequency	Percentage
Age <5 years	22	30.6%
Age 5–10 years	31	43.1%
Age >10 years	19	26.4%
Male	44	61.1%
Female	28	38.9%
B-cell ALL	60	83.3%
T-cell ALL	12	16.7%
Standard risk	24	33.3%
Intermediate risk	20	27.8%
High risk	28	38.9%
CNS involvement	8	11.1%
Severe malnutrition	18	25.0%

The majority of patients belonged to the 5–10 years age group. Male predominance was observed. B-cell ALL was the most common subtype. High-risk disease was identified in 38.9% of patients.

Table 2: Treatment Response and Survival Outcomes

Parameter	Frequency	Percentage
Complete remission after induction	64	88.9%
Induction failure	5	6.9%
Early death during induction	3	4.2%
Relapse	14	19.4%
CNS relapse	4	5.6%
Bone marrow relapse	10	13.9%
Treatment-related mortality	6	8.3%
Alive at last follow-up	52	72.2%

Complete remission was achieved in most patients. Bone marrow relapse was more common than CNS relapse. Treatment-related mortality was mainly associated with severe infections and sepsis.

Table 3: Toxicity Profile During Treatment

Toxicity	Frequency	Percentage
Febrile neutropenia	40	55.6%
Severe anemia	35	48.6%
Thrombocytopenia requiring transfusion	30	41.7%

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Mucositis	20	27.8%
Hepatotoxicity	17	23.6%
Sepsis	15	20.8%
Fungal infections	8	11.1%
Pancreatitis	3	4.2%
Chemotherapy delay >2 weeks	18	25.0%

Febrile neutropenia was the most common treatment-related complication. Infectious complications significantly contributed to treatment delays and mortality.

Survival Analysis

The 3-year overall survival (OS) rate was 72.2%, while the event-free survival (EFS) rate was 64.8%. Patients with standard-risk ALL demonstrated significantly better survival compared to high-risk patients ($p<0.05$). Severe malnutrition and prolonged treatment interruptions were associated with poorer outcomes.

DISCUSSION

Acute Lymphoblastic Leukemia remains a major pediatric oncology challenge in developing countries despite substantial advancements in chemotherapy protocols and supportive care. The present study evaluated outcomes of pediatric ALL patients treated with a modified BFM protocol in a resource-limited Indian tertiary care center and demonstrated encouraging remission and survival rates despite considerable treatment-related toxicities.

In the present study, the mean age at diagnosis was comparable to previous Indian and international studies, with the highest incidence occurring between 5 and 10 years of age. Male predominance observed in our study is consistent with the epidemiological distribution reported globally. B-cell ALL represented the majority of cases, similar to other pediatric leukemia studies from India.

Complete remission after induction therapy was achieved in 88.9% of patients. This finding is comparable to studies conducted by Advani et al. and Arora et al., who reported remission rates ranging from 85–92% using modified pediatric protocols. Improved remission rates in recent years may be attributed to better supportive care measures, early use of broad-spectrum antibiotics, and improved blood component availability.

The overall survival rate of 72.2% in the present study, although lower than developed countries, remains encouraging for a resource-constrained setting. Developed nations report survival rates exceeding 85–90%, while survival in many low-income settings remains below 60%. The difference is primarily due to socioeconomic disparities, delayed diagnosis, malnutrition, inadequate supportive care, and higher infection-related mortality.

High-risk ALL patients showed comparatively poorer survival outcomes in the present study. Similar observations have been reported in multiple international studies where high leukocyte count, T-cell phenotype, CNS involvement, and poor nutritional status were associated with inferior prognosis. Resource limitations further amplify these risks due to inability to intensify treatment safely.

Treatment-related toxicity remains a major obstacle during ALL therapy. Febrile neutropenia was the most common complication observed in the present study. Similar rates have been documented in Indian pediatric oncology centers where overcrowding, inadequate hygiene, and delayed access to antibiotics contribute to

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increased infection rates. Sepsis and invasive fungal infections were important contributors to mortality in our cohort.

Hepatotoxicity and mucositis were common non-hematological toxicities. These toxicities often resulted in chemotherapy interruption and prolonged hospitalization. Nutritional deficiency may have aggravated chemotherapy intolerance among children in the present study.

Treatment abandonment and delay continue to affect outcomes in developing countries. Approximately 25% of patients in our study experienced treatment delays exceeding two weeks. Financial constraints, travel difficulties, infection-related admissions, and parental anxiety were major contributing factors. Addressing these social determinants is critical for improving long-term survival.

The relapse rate observed in our study was 19.4%, with bone marrow relapse being more common than CNS relapse. Similar relapse patterns have been documented in pediatric ALL literature. Relapsed ALL remains difficult to manage in low-resource settings due to limited access to stem cell transplantation and novel targeted therapies.

Supportive care infrastructure plays a crucial role in improving pediatric ALL outcomes. Availability of isolation facilities, infection surveillance, nutritional rehabilitation, and trained pediatric oncology teams significantly influence treatment success. Strengthening these areas may further improve survival even without access to transplant facilities.

The present study highlights the feasibility of implementing modified BFM protocols in developing countries with acceptable outcomes. Careful risk stratification, early infection management, nutritional optimization, and psychosocial support are essential components of successful treatment strategies in such settings.

CONCLUSION

Modified BFM protocol provides acceptable remission and survival outcomes in pediatric ALL patients treated in a resource-limited tertiary care center. Despite significant chemotherapy-related toxicities, most complications were manageable with appropriate supportive care. Infection-related morbidity and treatment interruptions remain major challenges in developing countries. Strengthening supportive care infrastructure, nutritional support, early infection management, and improving treatment adherence may further enhance survival outcomes in pediatric ALL.

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