

Original Article

## Survival Outcomes and Prognostic Indicators in Pediatric Acute Lymphoblastic Leukemia: A Study in a Tertiary Care Setting from Bangladesh

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### Abstract

**Background:** Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Survival outcomes are significantly higher in high-thiess to diagnostics and standardized therapy contributes to poor prognosis. This study evaluated survival patterns and prognostic indicators in pediatric ALL patients treated at a tertiary care center in Bangladesh.

**Materials and Methods:** A retrospective cohort of 36 pediatric ALL patients treated between March 2016 and March 2024 was analyzed. Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method. Prognostic indicators included age, white blood cell count, minimal residual disease (MRD) status, CD20 expression, risk classification, and Day 8 steroid response. Associations with MRD clearance were tested using Fisher’s exact and Mann–Whitney U tests. Risk differences with 95% confidence intervals were calculated for subgroup comparisons.

**Results:** MRD clearance (<0.01%) at the predefined analytic endpoint was achieved in 66.7% of patients. Clearance was more frequent in standard-risk than high-risk patients (85.71% vs. 40.00%; risk difference: 45.71%, 95% CI: 7.60–83.80; p = 0.032) and in CD20-negative compared to CD20-positive patients (86.67% vs. 52.38%; risk difference: 34.33%, 95% CI: 8.60–60.00; p = 0.040). No significant associations were found with initial blast count or steroid response. The 3- and 5-year Kaplan–Meier–adjusted OS and EFS were both 96.55% (95% CI: 77.95–99.51%). One non-relapse death due to infection was recorded.

**Conclusion:** This study demonstrates favorable survival outcomes among ALL patients at Evercare Hospital pediatric in Bangladesh who completed standardized therapy. MRD clearance was significantly associated with risk classification and CD20 expression, underscoring its utility in risk stratification. Larger, prospective multicenter studies are required to validate these findings and guide treatment strategies in resource-limited settings.

**Keywords:** Acute lymphoblastic leukemia, Minimal residual disease, Pediatric, Prognosis, Survival



## Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, comprising approximately 25% of all childhood cancers and nearly 75% of childhood leukemia cases in population-based data from the United States (1). The incidence and survival of pediatric ALL vary widely by geographic region, with high-income countries (HICs) reporting 5-year overall survival (OS) rates exceeding 90% (2,3). In contrast, outcomes in low- and middle-income countries (LMICs), including Bangladesh, remain significantly lower due to limited access to diagnostics, treatment infrastructure, and adherence to therapy (4–6).

Over recent decades, risk-adapted chemotherapy, hematopoietic stem cell transplantation (HSCT), and molecular-targeted therapies have significantly improved prognosis in pediatric ALL, particularly in well-resourced settings (7). However, these therapeutic gains are less evident in LMICs, where delayed diagnosis, financial constraints, and lack of uniform treatment protocols often compromise care (4,8). Understanding treatment response and survival outcomes in such settings is essential for identifying barriers and informing local strategies.

Established prognostic factors for pediatric ALL include age at diagnosis and initial white blood cell (WBC) count, immunophenotype, selected genetic abnormalities, and early treatment response (9). According to National Cancer Institute (NCI) criteria, children aged 1–9 years with WBC  $<50,000/\mu\text{L}$  are classified as standard risk, whereas those aged  $\geq 10$  years or with WBC  $\geq 50,000/\mu\text{L}$  are considered high risk, with higher relapse rates and poorer survival (10). Among available response-based markers, minimal residual disease (MRD) status after induction therapy is one of the strongest predictors of relapse and survival and plays a central role in modern risk-adapted treatment strategies (10–13). Although these tools have improved outcomes in high-resource settings, their implementation remains limited across many LMICs settings.

In Bangladesh, the use of established

prognostic tools is limited by restricted access to flow cytometry, molecular diagnostics, and standardized treatment protocols. Among the potential prognostic tools, minimal residual disease (MRD) clearance and CD20 expression are increasingly recognized as valuable markers for risk stratification in pediatric ALL. However, their application remains limited due to constraints in diagnostic infrastructure and standardized care protocols. This underscores the need for context-specific prognostic tools adapted to local diagnostic and treatment capacities. Despite the global burden of ALL, few studies from LMICs, particularly in South Asia, offer context-specific survival data that reflect local clinical realities. Most prognostic models are derived from high-income countries and may not be generalizable to populations with distinct healthcare limitations and genetic variability. This study aimed to evaluate survival patterns and prognostic indicators among pediatric ALL patients treated at a tertiary care center in Bangladesh, with particular emphasis on OS and event-free survival (EFS), MRD response, and risk stratification.

## Material and Methods

### *Study design and setting*

This study was a retrospective cohort analysis conducted at Evercare Hospital, a tertiary care center in Bangladesh, and included pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) between March 2016 and March 2024.

BFM refers to the Berlin–Frankfurt–Münster regimen, an internationally established risk-adapted protocol. Variants used in this cohort included BFM-95, BFM-2002, and BFM-2009, reflecting protocol updates over time. A minority of patients received UK ALL-based protocols or Hyper-CVAD in selected circumstances.

The hospital provides specialized pediatric oncology care with access to essential diagnostic and supportive treatment facilities.

### *Study population and data collection*

Patients aged 0–18 years with a confirmed diagnosis of ALL, established based on morphological, immunophenotypic, and molecular

criteria following the World Health Organization (WHO) classification, were included. Patients with incomplete medical records, prior malignancy, or loss to follow-up were excluded.

Clinical and laboratory data—including demographic characteristics, baseline white blood cell (WBC) count, and minimal residual disease (MRD) results—were extracted from hospital records and electronic databases.

During the study period, 70 patients were identified. Of these, 34 were excluded due to treatment discontinuation or insufficient follow-up, leaving 36 evaluable patients for final analysis. A comparative assessment for baseline characteristics was conducted between the included and excluded cases to evaluate potential selection bias. Due to the retrospective design, no a priori sample size calculation was performed; all eligible patients were included in the descriptive and survival analyses.

### Outcome measures

The primary outcomes were overall survival (OS) and event-free survival (EFS). OS was defined as the time from diagnosis to death or last follow-up, while EFS was defined as the time from diagnosis to relapse, disease progression, death, or last follow-up without an event. MRD clearance was defined as MRD < 0.01% at the end of induction.

Clinical and laboratory data were extracted from medical records. Key prognostic indicators assessed in the present study included age, sex, baseline WBC count, risk group classification, Day 8 steroid response, CD20 expression, and MRD conversion status at predefined milestones.

MRD was assessed by multiparameter flow cytometry with a sensitivity threshold of 0.01% ( $10^{-4}$ ) using bone marrow samples collected on Days 15, 33, and 78, and during subsequent follow-up. All analyses were conducted at the Molecular Laboratory, Evercare Hospital, Dhaka, following EuroFlow standard protocols (14), using a FACSCanto II cytometer (BD Biosciences, USA).

### Statistical analysis

Continuous variables were assessed for

normality using the Shapiro–Wilk test. Normally distributed variables (age and hemoglobin) were summarized as mean  $\pm$  standard deviation (SD) and compared using the independent samples t-test. Non-normally distributed variables were summarized as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using Fisher's exact test. Kaplan–Meier survival curves were constructed to estimate OS and EFS, and survival probabilities at 36 and 60 months were reported. The median follow-up duration was estimated using the centile Kaplan–Meier method to account for censored observations. A p-value < 0.05 was considered statistically significant.

MRD clearance was defined as MRD < 0.01% at the end of induction. Differences in MRD clearance between subgroups were presented as risk differences with 95% confidence intervals (CIs), computed using the two-sample z-test for proportions. Statistical significance was set at p < 0.05. All analyses were performed using Stata version 17.0 (StataCorp, College Station, TX, USA).

## Results

### Patient inclusion and baseline characteristics

A total of 70 pediatric patients diagnosed with acute lymphoblastic leukemia (ALL) were identified during the study period. Of these, 36 were included in the analysis, while 34 were excluded due to treatment discontinuation or insufficient follow-up data. Excluded patients demonstrated significantly lower treatment adherence (p < 0.001), reflecting challenges in maintaining continuity of care within this population. Excluded patients were also older (mean age  $10.56 \pm 5.22$  years vs.  $7.24 \pm 3.51$  years; p = 0.012) and had a higher frequency of complications (p = 0.005). However, gender distribution (p = 0.285) and leukemia subtype (p = 0.087) did not differ significantly between groups (Table I).

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Baseline hematologic parameters, including initial WBC count ( $p = 0.854$ ), hemoglobin ( $p = 0.467$ ), and platelet count ( $p = 0.785$ ), were comparable between included and excluded patients. Shapiro–Wilk testing showed that age ( $p = 0.118$ ) and hemoglobin ( $p = 0.225$ ) were approximately normally distributed, whereas baseline WBC count ( $p < 0.001$ ) and platelet count ( $p < 0.001$ ) were non-normally distributed. Among patients with available data, risk classification did not differ significantly between groups ( $p = 0.540$ ). Among the patients included in the study, 14 (38.89%) were standard risk, 16 (44.44%) intermediate risk, and 6 (16.67%) high risk (Table I).

#### *Treatment initiation among excluded patients*

Among the 34 excluded patients, 17 (50.0%) had a recorded treatment protocol, indicating that they initiated therapy but did not complete it. The most commonly initiated regimens were BFM-2009 ( $n = 11$ ), followed by BFM-95 ( $n = 3$ ), Hyper-CVAD ( $n = 2$ ), and BFM-2002 ( $n = 1$ ). The remaining 17 patients (50.0%) had no treatment protocol recorded, suggesting discontinuation immediately after diagnosis or loss to follow-up before therapy initiation. These findings highlight a high rate of early attrition following diagnosis, likely influenced by financial, logistical, and psychosocial barriers (Figure IA).

#### *Treatment protocol distribution among included patients*

Treatment regimens in the included cohort

primarily followed BFM-based or UK ALL-based protocols, with BFM regimens accounting for the majority. Among BFM regimens, BFM-2009 was the most frequently used, [ $n = 21$  (58.3%)], followed by BFM-95 in [ $n = 11$  (30.6%)] and BFM-2002 in [ $n = 3$  (8.3%)]. A UK ALL-based protocol was used in one patient [ $n = 1$  (2.8%)].

All 36 included patients completed therapy, whereas none of the excluded patients did ( $p < 0.001$ ). Among excluded patients, half [ $n = 17$  (50.00%)] received partial treatment, while the remaining half [ $n = 17$  (50.00%)] discontinued before therapy initiation (Figure IB).

#### *Association between prognostic factors and MRD clearance*

Among the 36 patients analyzed, MRD clearance differed across risk groups, with 85.71% of standard-risk patients achieving clearance compared to 40.00% of high-risk patients (risk difference: 45.71%; 95% CI: 7.60%–83.80%;  $p = 0.032$ ). CD20-negative patients were more likely to achieve MRD clearance than CD20-positive patients (86.67% vs. 52.38%; risk difference: 34.33%; 95% CI: 8.60%–60.00%;  $p = 0.040$ ). No significant association was observed between Day 8 steroid response and MRD clearance (risk difference: 45.00%; 95% CI: –26.60% to 94.00%;  $p = 1.000$ ), likely reflecting the small sample size. Risk difference represents the absolute difference in MRD clearance proportions between comparison groups, expressed as percentage points with 95% confidence intervals (Table II).

#### *MRD conversion trends*

MRD response was evaluated longitudinally across predefined treatment milestones. Among the 36 patients evaluated, 19/36 (52.78%) were MRD-positive on Day 15 and achieved MRD negativity by Day 33. Additionally, 11/36 (30.56%) remained MRD-negative from Day 15 onwards and remained negative during subsequent assessments. Although a smaller proportion, 4/36 (11.11%), remained MRD-positive on Day 33, they achieved MRD-negativity by Day 78. Only 2/36 (5.56%) remained MRD-positive through Day 78; although both subsequently achieved MRD negativity during follow-up (Figure II).

### *Survival status and outcomes*

At the last follow-up, 35 of 36 patients were alive, corresponding to a crude survival proportion of 97.22%, while one patient (2.78%) had died. No deaths were attributed to treatment-related toxicity or disease progression. The single fatality represented non-relapse mortality secondary to varicella infection.

### *Kaplan-Meier survival estimates (combined OS & EFS)*

The Kaplan–Meier–adjusted overall survival (OS) and event-free survival (EFS) rates at both 3 and 5 years were 96.55% (95% CI: 77.95%–

99.51%), with 21 and 6 patients remaining at risk at each respective time point (Table III). Only one event—a non-relapse death—occurred at 26 months and 24 days post-diagnosis, and no relapses or disease progressions were observed during follow-up. Accordingly, both OS and EFS

curves exhibited a single drop at approximately 26 months, remaining flat thereafter through 5 years. This plateau reflects the absence of additional events rather than confirmed long-term stability.

The median follow-up duration was 40.90 months (95% CI: 30.69–48.37 months), calculated using the centile Kaplan–Meier method (Figure III).

Table I: Baseline differences between included and excluded pediatric ALL patients

Characteristic	Included (n = 36)	Excluded (n = 34)	p-value
Age (mean ± SD), years, mean ± SD	7.24 ± 3.51	10.56 ± 5.22	<b>0.012<sup>a</sup></b>
Gender, n (%)			<b>0.285</b>
Male	21 (58.33)	24 (70.59)	
Female	15 (41.67)	10 (29.41)	
Complications (e.g., infections), n (%)	21 (58.33)	30 (88.24)	<b>0.005</b>
Treatment adherence, n (%)			<b>&lt;0.001</b>
Completed treatment	36 (100.00)	0 (0.00)	
Incomplete treatment received	0 (0.00)	17 (50.00)	
Discontinue before treatment	0 (0.00)	17 (50.00)	
WBC ( $\times 10^9/L$ ), median (IQR)	8.14 (3.05–31.53)	8.09 (3.60–30.11)	<b>0.938<sup>b</sup></b>
Hemoglobin (g/dL), mean ± SD	7.44 ± 2.98	8.28 ± 3.12	<b>0.467<sup>a</sup></b>
Platelet count ( $\times 10^9/L$ ), median (IQR)	74 (25–152.5)	55 (25–110)	<b>0.716<sup>b</sup></b>
CNS involvement at diagnosis, n (%)			<b>0.548</b>
CNS1	32 (94.12)	9 (90.00)	
CNS2	1 (2.94)	0 (0.00)	
CNS3	1 (2.94)	1 (10.00)	
Risk group classification, n (%)			<b>0.540</b>
Standard risk	14 (38.89)	5 (38.46)	
Intermediate risk	16 (44.44)	4 (30.77)	
High risk	6 (16.67)	4 (30.77)	
Leukemia subtype, n (%)			<b>0.087</b>
B-cell (%)	33 (91.67)	21 (75.00)	
T-cell (%)	3 (8.33)	4 (14.29)	
ETP-ALL	0 (0.00)	3 (10.71)	

p-values were obtained using Fisher's exact test for categorical variables; <sup>a</sup>independent samples t-test for normally distributed continuous variables; and <sup>b</sup>Mann–Whitney U test for non-normally distributed continuous variables; p<0.05 considered statistically significant. Risk classification was unavailable

for most excluded patients because treatment was discontinued before completion of baseline diagnostic workup or staging.

Abbreviations: WBC = white blood cell; SD = standard deviation; IQR = interquartile range; CNS = central nervous system; CNS1 = no blasts in cerebrospinal fluid; CNS2 = blasts present below critical threshold; CNS3 = high blast count; B-cell = B-lymphoblastic leukemia; T-cell = T-lymphoblastic leukemia; ETP-ALL = early T-cell precursor acute lymphoblastic leukemia

Table II. Association between prognostic factors and MRD clearance at the end of induction (N = 36)

Characteristic	MRD cleared (n = 24)	MRD not cleared (n = 12)	Risk difference (95% CI)	p-value
<b>Risk group, n (%)</b>				
Standard risk	12 (85.71)	2 (14.29)	45.71 (7.60–83.80)	0.032
Intermediate risk	8 (66.67)	4 (33.33)	—	
High risk	4 (40.00)	6 (60.00)	—	
<b>CD20 expression, n (%)</b>				
Negative	13 (86.67)	2 (13.33)	34.33 (8.60–60.00)	0.040
Positive	11 (52.38)	10 (47.62)	—	
<b>Day 8 steroid response, n (%)</b>				
<1000/ $\mu$ L	19 (63.33)	11 (36.67)	45.00 (–26.60–94.00)	1.000
>1000/ $\mu$ L	1 (50.00)	1 (50.00)	—	
<b>Initial blast count (BM), median (IQR)</b>	1100.50 (1.00–40740.00)	2990.00 (150.75–11742.50)	—	0.890 <sup>b</sup>

Note: Values are presented as n (%) for categorical variables and median (IQR) for non-normally distributed continuous variables. p-values were calculated using Fisher's exact test for categorical variables and the Mann-Whitney U test for non-normally distributed continuous variables. Risk differences and 95% confidence intervals (CIs) were calculated using the two-sample z-test for proportions. "—" indicates not applicable (risk difference not calculated for continuous variables). p < 0.05 was considered statistically significant. Day 8 steroid response data were available for 20 patients with complete documented peripheral blast counts.

Abbreviations: MRD = minimal residual disease; CI = confidence interval; IQR = interquartile range.

Table III: Kaplan-Meier survival estimates (combined OS & EFS)

Time (years)	Survival rate (%)	95% CI	Patients at risk
3 Years	96.55	77.95 – 99.51	21
5 Years	96.55	77.95 – 99.51	6

Note: Survival probabilities were estimated using the Kaplan–Meier method. Confidence intervals are wide due to the limited number of events ( $n = 1$ ); therefore, survival estimates beyond 3 years should be interpreted with caution.

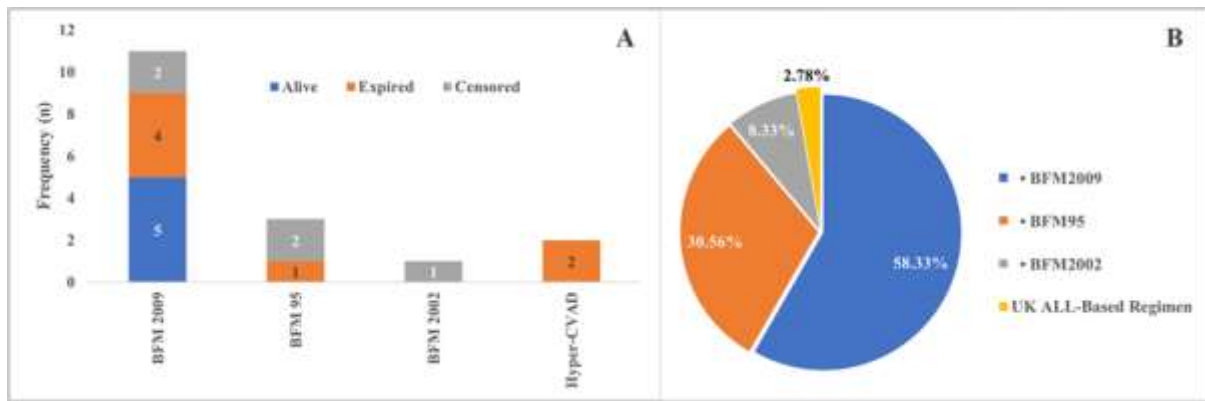


Figure I. Distribution of treatment protocol initiation and completion among pediatric ALL patients. (A) Treatment initiation among excluded patients ( $n = 34$ ). (B) Distribution of treatment protocols among included patients ( $n = 36$ ).

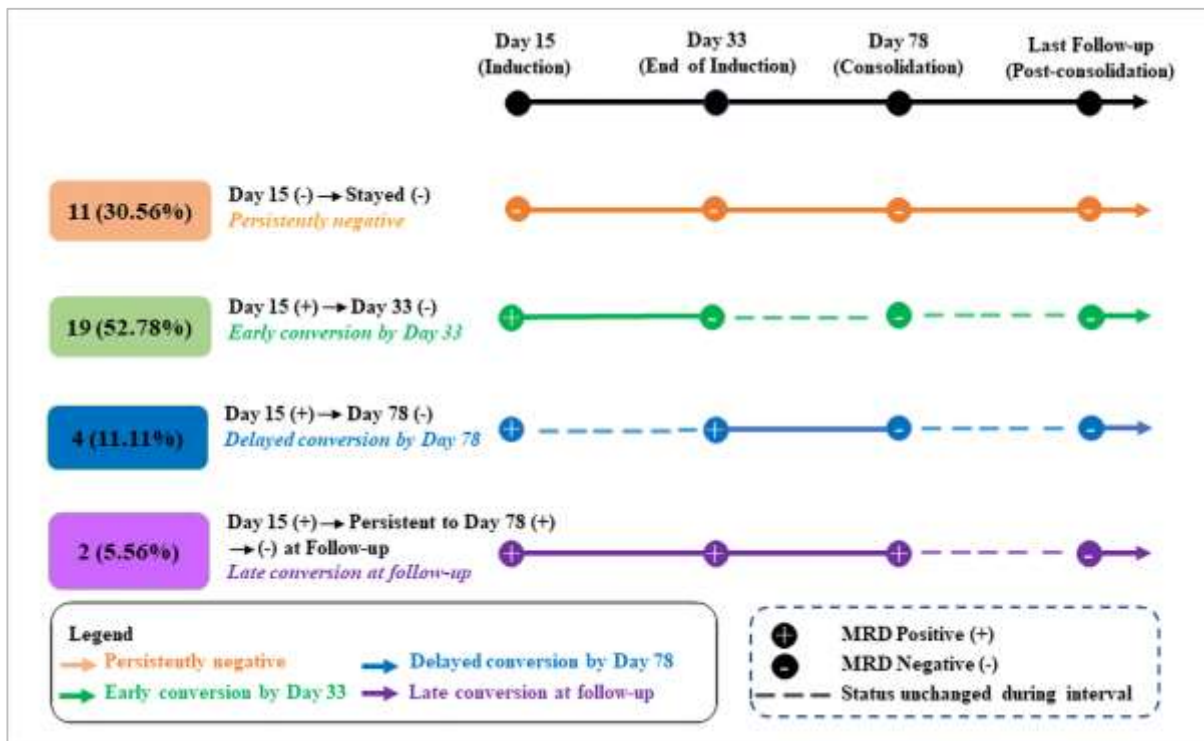


Figure II. Longitudinal MRD conversion trends across treatment milestones.

Among 36 patients, 11 (30.56%) were MRD-negative from Day 15 onward, while 19 (52.78%) converted from positive on Day 15 to negative by Day 33. Four (11.11%) converted by Day 78, and two (5.56%) achieved negativity at later follow-up.

## Discussion

This study provides a real-world evaluation of long-term survival and prognostic factors among pediatric patients with acute lymphoblastic leukemia (ALL) in a tertiary care center in Bangladesh. The findings demonstrate that favorable outcomes are achievable when standardized therapy, adherence, and supportive care are maintained, while also highlighting systemic challenges affecting broader patient retention and follow-up.

Of the 70 eligible pediatric ALL patients, 36 were included in the final analysis, while 34 were excluded due to treatment discontinuation or insufficient follow-up. Excluded patients showed poorer treatment continuity, older age, and greater complication burden, reflecting well-documented challenges in sustaining long-term treatment compliance in pediatric oncology—particularly in low-resource settings (15). Despite this, there were

no significant differences between included and excluded patients in terms of gender, leukemia subtype, WBC, hemoglobin, or platelet counts, suggesting that attrition was more likely influenced by systemic and socioeconomic barriers than by disease biology. A numerically higher proportion of high-risk patients was observed among excluded patients, although this difference was not statistically significant. Notably, 50% of excluded patients never initiated treatment, while the remainder discontinued therapy after partially completing induction or consolidation. This substantial early attrition highlights the vulnerability of patients to socioeconomic constraints, logistical challenges, and gaps in supportive care or counseling—underscoring the urgent need for targeted interventions to reduce treatment abandonment and improve retention in pediatric cancer care in low- and middle-income countries (16–18).

Treatment in the included cohort primarily

followed BFM-based protocols, with BFM-2009 being the most commonly implemented, reflecting adoption of contemporary risk-adapted treatment strategies (19). The use of multiple protocols, including BFM-95, BFM-2002, and one UK-based regimen, may reflect institutional preferences, protocol availability, and individual physician discretion. While this variation did not appear to affect survival outcomes in this cohort, it emphasizes the need for protocol harmonization and consistent application of risk-adapted regimens in resource-limited settings (16,20).

In this cohort, MRD clearance at the end of induction was more frequently achieved among standard-risk patients compared to those classified as high-risk. This is biologically plausible, as higher-risk disease is often associated with greater leukemic burden and slower treatment response. This trend is consistent with prior studies showing that high-risk ALL patients are more likely to exhibit delayed MRD clearance and treatment resistance due to more aggressive disease biology and higher leukemic burden at diagnosis (21,22). Additionally, MRD clearance was significantly more common among CD20-negative patients, supporting evidence that CD20 expression may be associated with adverse prognosis and reduced chemosensitivity in pediatric ALL (23). This suggests that CD20 expression may have practical prognostic relevance. However, given the small cohort and wide confidence intervals, these associations should be interpreted cautiously and validated in larger, prospective studies.

MRD conversion trends further reinforced the importance of early treatment response. Most initially MRD-positive patients achieved clearance during induction or early consolidation, whereas a smaller subset demonstrated delayed conversion, suggesting preserved treatment sensitivity in a substantial proportion of cases. These patterns emphasize the prognostic utility of early MRD dynamics—particularly Day 33 clearance—as a surrogate for chemosensitivity and long-term survival in pediatric ALL (24,25). Although all

patients demonstrated favorable Day 8 steroid responses, no significant association was observed between steroid response and MRD status, diverging from earlier reports and possibly reflecting cohort size limitations or biological heterogeneity (26). Similarly, initial blast counts were not significantly associated with MRD clearance in this cohort. The findings affirm MRD as a robust biomarker for early risk stratification and support its incorporation into risk-adapted treatment planning.

Survival outcomes were highly favorable, with only one death during follow-up, caused by varicella infection, representing non-relapse, non-treatment-related mortality. This outcome highlights the effectiveness and safety of current pediatric ALL protocols when adherence is maintained. The absence of relapse or treatment-related mortality aligns with global data from well-managed settings (4,27). However, the fatal infection underscores the vulnerability of immunocompromised children to preventable illnesses such as varicella, emphasizing the need for targeted vaccination and prophylactic strategies in pediatric oncology populations. Kaplan–Meier estimates were similarly favorable, reflecting the absence of relapse or progression events.

The survival outcomes observed in this study appear higher than those reported in several neighboring LMIC cohorts (5,28,29). This discrepancy may reflect the specific treatment environment of the study center rather than broader national outcomes. Evercare Hospital offers comparatively advanced diagnostic infrastructure, serial MRD monitoring, specialist supportive care, antimicrobial access, and infection-control practices. These resources likely contributed to the favorable outcomes observed in this cohort. Selection effects may also be relevant, as survival analyses were limited to patients who remained in care and completed therapy. Therefore, the present results should be interpreted as demonstrating what may be achievable under well-resourced, protocol-adherent conditions rather than representing population-level survival in Bangladesh.

The absence of additional events beyond 3

years may reflect either durable remission among responders, although shorter follow-up in some patients may also have contributed, as suggested by the median follow-up duration of 40.90 months (95% CI: 30.69–48.37), estimated using the centile Kaplan–Meier method. These favorable outcomes align with results from high-resource settings, confirming that protocol-adherent therapy can achieve comparable results even in resource-limited environments (4). To our knowledge, this is one of the first studies from Bangladesh to examine ALL survival outcomes alongside MRD response and clinical prognostic indicators.

### Limitations

This relatively small sample size, single-center design, and incomplete follow-up for many patients may limit the generalizability of these findings to broader pediatric ALL populations, particularly in diverse LMIC settings. In addition, because the Kaplan–Meier curves are based on a single event, the resulting survival estimates and confidence intervals should be interpreted cautiously, as they may not fully capture long-term survival patterns or subgroup differences. Selection bias is also possible because patients who discontinued therapy early were excluded from the principal survival analyses.

### Conclusion

This study demonstrates that risk-adapted therapy for pediatric ALL, when supported by consistent adherence and follow-up, can yield survival outcomes approaching those reported in high-resource settings. Early MRD clearance emerged as an important indicator of treatment response. While these findings should be interpreted cautiously because of the small sample size and low event rate, they highlight the potential to improve pediatric ALL outcomes in resource-constrained settings through structured care delivery. Larger, prospective multicenter studies are needed to validate these outcomes and guide national pediatric oncology strategies.

### Availability of Data

Not applicable

### Ethical Considerations

This study was approved by EHD/R/res.ec\_app.01 (Evercare Hospital Dhaka Ethics Committee)

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None

### Authors' Contributions

AJMS: Designing and writing the study. OSH and TR, collecting data and analyzing. MUC. Editing manuscript

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None

### Conflict of Interest

None

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