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Prognostic factors influencing remission by MRD assay in children with acute lymphoblastic leukemia following induction therapy

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Abstract
Background: Remission after induction therapy is critical for prognosis in childhood Acute Lymphoblastic Leukemia (ALL). Minimal Residual Disease (MRD) assessment provides a sensitive measure of treatment response beyond conventional bone marrow morphology, potentially identifying key prognostic factors for remission failure.
Objective: To identify prognostic factors influencing remission in pediatric ALL using MRD evaluation after induction therapy.
Methods: This prospective observational study was conducted at Bangabandhu Sheikh Mujib Medical University from March 2023 to February 2024. It enrolled 36 newly diagnosed pediatric ALL patients. Remission was assessed on day 29 of induction via bone marrow morphology and MRD examination. Chemotherapy followed a risk-stratified modified UK ALL protocol. Associations between baseline factors and MRD outcomes were analyzed statistically using SPSS 25.0.
Results: MRD-confirmed remission was achieved in 75% of patients. Most participants (86.1%) were aged 1–10 years, with a 74.1% remission rate. Males constituted 63.9% of the cohort and showed a higher, though statistically nonsignificant, rate of remission failure (34.8% vs. 7.7% in females; p = 0.067). The majority had normal nutritional status (75%). ALL-L1 was the predominant FAB subtype (69.4%), and B-cell lineage was the most common immunophenotype (97.2%). Standard-risk (63.9%) and high-risk patients received Regimen A and Regimen B chemotherapy, respectively.
Conclusion: This study identifies trends associating male gender, undernutrition, high initial leukocyte count, low hemoglobin, and T-cell lineage with higher MRD-positive remission failure. However, these factors do not demonstrate statistically significant associations with MRD status in this cohort.

Keywords: Leukemia, acute lymphoblastic, MRD, prognostic factors, remission

Introduction
Acute Lymphoblastic Leukemia (ALL) represents the most prevalent malignancy in childhood, accounting for approximately 25% of all pediatric cancers [1]. The cornerstone of its treatment involves multi-agent chemotherapy, with the induction phase being pivotal. The primary goal of this initial phase is to achieve complete morphological remission (CR), defined traditionally as the presence of <5% blasts in a normocellular bone marrow aspirate, which is a critical determinant of long-term survival and event-free survival (EFS) [2]. However, morphological assessment has significant limitations in sensitivity, failing to detect submicroscopic levels of residual leukemic cells, which often lead to subsequent relapse [3]. This diagnostic gap is addressed by the measurement of Minimal Residual Disease (MRD), which quantifies leukemia-specific markers beyond the threshold of conventional microscopy. MRD has emerged as the most powerful independent prognostic factor in pediatric ALL, offering a refined, dynamic assessment of treatment response and disease burden [4, 5]. The detection of MRD at defined time points, particularly at the end of induction therapy, stratifies patients into distinct risk groups. Those with positive MRD, indicating persistent disease at a molecular level, face a significantly higher risk of relapse compared to their MRD-negative counterparts, even when morphological CR is achieved [6]. Consequently, contemporary treatment protocols worldwide have integrated MRD

assessment to guide risk stratification and therapeutic intensification or de-escalation, moving beyond classical clinical and biological factors [7]. Despite the universal prognostic value of MRD, the specific clinicopathological factors that predict a positive MRD status at the end of induction and thus primary treatment resistance can vary across populations and healthcare settings. Established high-risk features include older age (>10 years), very young age (<1 year), high presenting white blood cell (WBC) count, specific genetic abnormalities (e.g., KMT2A rearrangements, hypodiploidy), and T-cell immunophenotype [8, 9]. Nutritional status, particularly malnutrition, has also been increasingly recognized as a potential modifier of treatment tolerance, pharmacokinetics, and outcomes in low- and middle-income countries (LMICs), through its direct link to MRD remains less clearly defined [10]. In Bangladesh, the burden of childhood ALL is significant, and treatment outcomes, while improving, still lag behind those in high-income nations. While MRD-guided protocols are becoming the standard of care globally, access to and utilization of this technology in resource-limited settings like Bangladesh are not uniform [11]. Most studies characterizing prognostic factors, including MRD, originate from high-income regions, and data from South Asian contexts, accounting for local epidemiological and socioeconomic variables, are comparatively scarce [12]. Understanding which readily available diagnostic parameters at presentation correlate with MRD positivity in this specific population is crucial. Such knowledge can help identify, at diagnosis, a subset of children at the highest risk of induction failure, potentially allowing for early intervention, optimized supportive care, and tailored counseling. Therefore, this study aimed to investigate the association between easily ascertainable baseline clinical and laboratory prognostic factors and MRD status at the end of induction therapy in children with ALL at a major tertiary care center in Bangladesh. By elucidating these correlations within a resource-constrained setting, we seek to contribute valuable regional data that can inform risk-adapted management strategies and improve outcomes for children with ALL in similar contexts [13].

Methodology

This prospective observational study was conducted at the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), from March 2023 to February 2024. The study population comprised 36 children aged 1 to <18 years with newly diagnosed Acute Lymphoblastic Leukemia (ALL).

Inclusion criteria

Patients were enrolled using a purposive sampling technique. Inclusion required a confirmed new diagnosis of ALL (excluding L3 type by FAB classification) and an age between 1 and <18 years.

Exclusion criteria

Children below 1 year of age, those with ALL-L3 morphology, or patients with incomplete requisite data were excluded from the study.

Study procedure

After obtaining Institutional Review Board (IRB) approval and informed consent, baseline demographic, clinical, and laboratory data were collected. Risk stratification followed a modified UK ALL protocol. Bone marrow aspirates for morphology and Minimal Residual Disease (MRD) assessment were performed on the 29th day of induction therapy.

Data analysis: Data were analyzed using SPSS version 25.0. Descriptive statistics were employed for demographic and clinical variables. Associations between prognostic factors and MRD status were analyzed using the Chi-square test, with a p-value <0.05 considered statistically significant.

Results

The age distribution of the study population showed the majority were within the age group of 1 to less than 10 years, representing 86.1% of the total sample. The overall mean age was 5.39 years, with a standard deviation of ±3.20. Regarding gender distribution, 63.9% of participants were male, and 36.1% were female. Mean laboratory values at diagnosis were as follows: Hemoglobin 6.67 ±2.28 gm/dl, White Blood Cell count 75,821.94 ± 128,696.99 /cmm, and Platelet count 41,555.56 ± 39,631.47 /cmm. The majority of participants, 27 (75%), had normal nutritional status, while 9 (25%) were categorized as having undernutrition. In terms of disease characteristics, most participants (69.4%) were classified as ALL-L1 by FAB criteria, and B-Cell immunophenotype was predominant (91.7%). Additionally, the vast majority of participants (97.2%) had a CNS status-1. For risk stratification, most participants (63.9%) were in the standard-risk group, while 36.1% were high-risk. Chemotherapy protocols were assigned accordingly: Regimen-A for standard risk and Regimen-B for high-risk participants. All participants achieved complete remission by bone marrow morphology assessment. By Minimal Residual Disease (MRD) examination, 75% of participants achieved remission. Bivariate analysis of variables, including age, sex, nutritional status, and laboratory parameters, against therapeutic response (remission vs. failure) showed no statistically significant associations ($p > 0.05$). A trend toward remission failure was observed in patients aged 1 to <10 years, male gender, L1 FAB type, and hemoglobin level < 8 gm/dl, but these findings were not significant. Remission failure rates were 26.1% in the standard-risk group and 23.1% in the high-risk group.

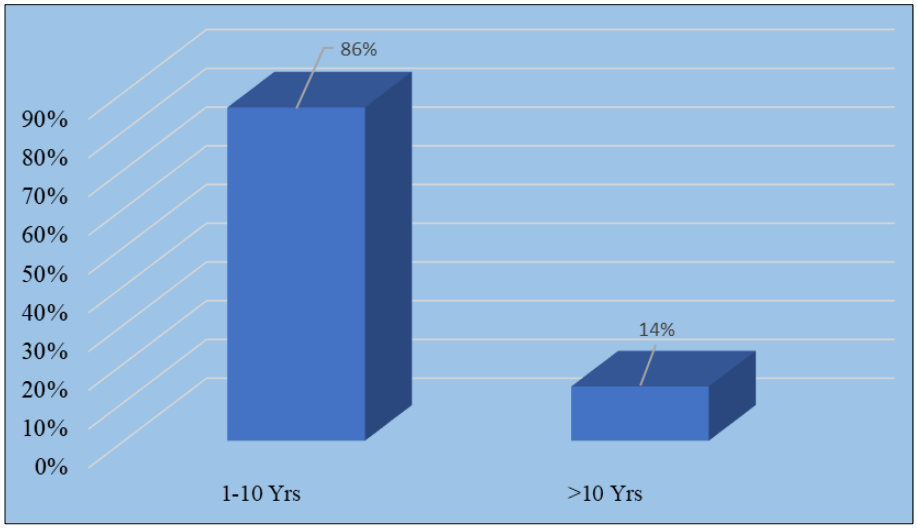

Fig 1: Age distribution of participants

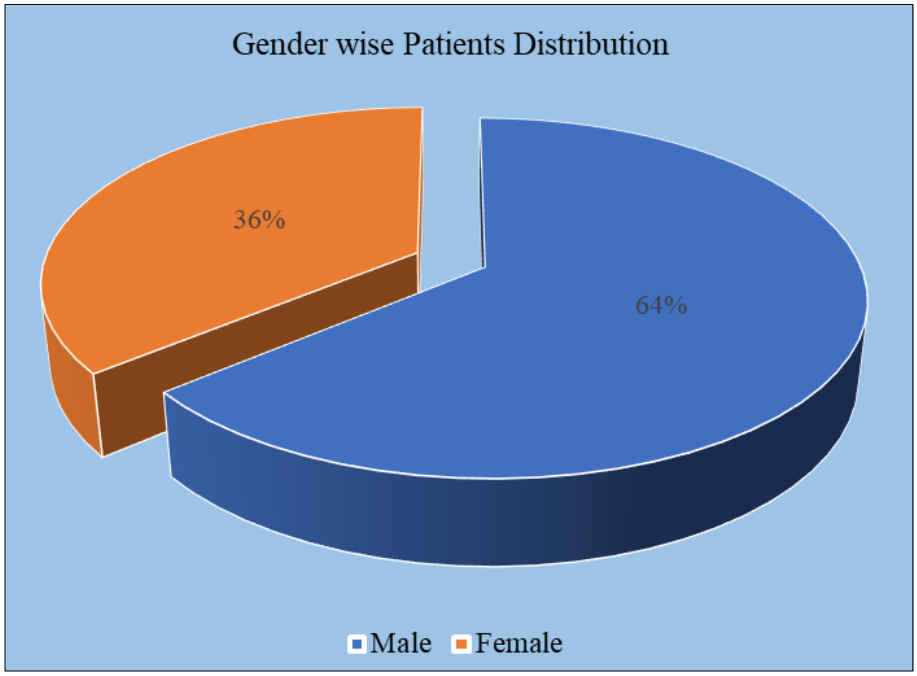

Fig 2: Gender distribution of participants

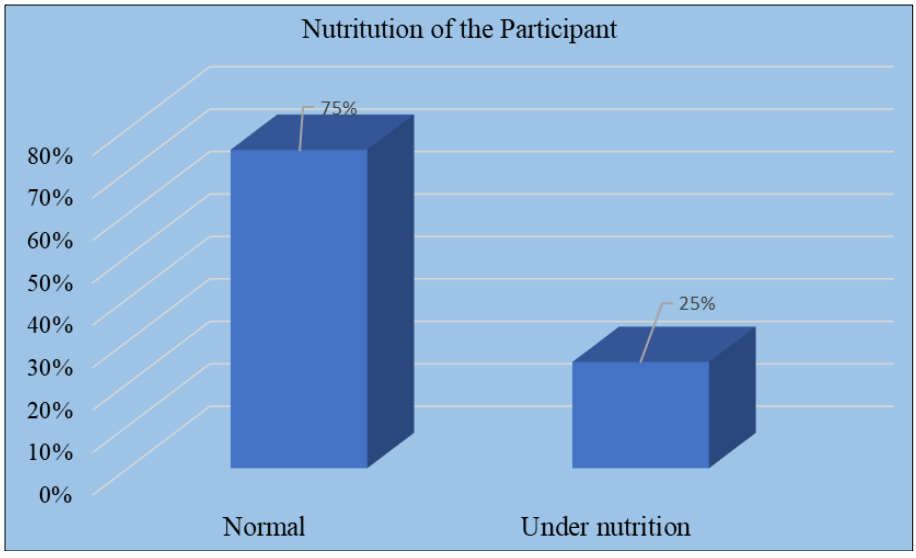

Fig 3: Nutritional status of the participants

Table 1: FAB classification, immunophenotype, and CNS status of the participants.

Variables	Frequency (n)	Percentage (%)
FAB Classification		
ALL-L1	25	69.4
ALL-L2	11	30.6
Immunophenotype		
B-Cell	33	91.7
T-Cell	3	8.3
CNS Status		
CNS-1	35	97.2
CNS-2	1	2.8

Table 2: Risk stratification & chemotherapy protocol of the participants.

Variables	Protocol	n	%
Standard risk	Regimen A	23	63.9
High risk	Regimen B	13	36.1

Table 3: Characteristics of the variable based on therapeutic response.

Variables	Therapeutic Response	
	Remission	Failure
Age (years) - n (%)		
1- <10 years	23 (74.1%)	8(25.9%)
≥10 years	4(80.0%)	1 (20.0%)
Sex - n (%)		
Male	15(65.2%)	8(34.8%)
Female	12(92.3%)	1(7.7%)
Nutritional status - n (%)		
Normal	21(77.8%)	6(22.2%)
Under Nutrition	6(67.7%)	3(33.3%)
FAB classification - n (%)		
L1	17(68.0%)	8(32.0%)
L2	10(90.9%)	1(9.1%)
Leucocyte count - n (%)		
≥ 50.000/ cu mm	7(63.6%)	4(36.4%)
< 50.000/ cu mm	20(80.0%)	5(20.0%)
Hemoglobin level - n (%)		
≥8 g/dl	9(90.0%)	1(10.0%)
< 8 g/dl	18(69.2%)	8(30.8%)
Platelet count - n (%)		
≥ 30.000/ cu mm	13(72.2%)	5(27.8%)
< 30.000/cu mm	14(77.8%)	4(22.2%)
Diagnosis – n (%)		
ALL B-cell	25(75.7%)	8(24.3%)
ALL T-cell	2(66.7%)	1(33.3%)

FAB: French-American-British

Table 4: The Bivariate analysis results of the variables.

Variables	Therapeutic Response		p-value
	Remission	Failure	
Age (years) - n (%)			
1- <10 years	23 (74.1%)	8(25.9%)	0.78
≥ 10 years	4(80.0%)	1(20.0%)	
Sex - n (%)			
Male	15(65.2%)	8(34.8%)	0.067
Female	12(92.3%)	1(7.7%)	
Nutritional status - n (%)			
Normal	21(77.8%)	6(22.2%)	0.651
Under Nutrition	6(67.7%)	3(33.3%)	
FAB classification - n (%)			
L1	17(68.0%)	8(32.0%)	0.156
L2	10(90.9%)	1(9.1%)	
Leucocyte count - n (%)			
≥50,000/cu mm	7(63.6%)	4(36.4%)	0.865
<50,000/cu mm	20(80.0%)	5(20.0%)	
Hemoglobin level - n (%)			
≥ 8 g/dl	9(90.0%)	1(10.0%)	0.178

< 8 g/dl	18(69.2%)	8(30.8%)	
Platelet count - n (%)			
≥30,000/cu mm	13(72.2%)	5(27.8%)	0.651
<30,000/cu mm	14(77.8%)	4(22.2%)	
Diagnosis – n (%)			
ALL B-cell	25(75.7%)	8(24.3%)	0.651
ALL T-cell	2(66.7%)	1(33.3%)	

p-value calculated by Chi-square (X2) test, $P<0.05$ considered as a level of significance

Table 5: Remission failure in risk groups of the participants.

Variables	Frequency	Failure	P value
	n (%)		
Standard risk	23(63.9)	6(26.1)	0.846
High risk	13(36.1)	3(23.1)	

Discussion

The primary objective of this study was to identify baseline prognostic factors associated with MRD status following induction therapy in a cohort of pediatric ALL patients at a major tertiary center in Bangladesh. This investigation is particularly relevant within a resource-constrained setting, where optimizing risk-stratification with available tools is paramount for improving outcomes. Our finding of a 75% MRD-confirmed remission rate provides a critical benchmark, reflecting both the efficacy of the administered risk-adapted protocols and the persistent challenges in achieving deep molecular responses. This rate is notably lower than the >95% morphological remission and >85% MRD-negative rates frequently reported from contemporary, well-resourced clinical trials [7, 14]. This discrepancy underscores a significant "outcome gap" that may be influenced by a complex interplay of biological, socio-economic, and healthcare system factors unique to low- and middle-income countries (LMICs) [11, 12]. Such factors include delays in diagnosis, variations in supportive care quality, a higher burden of comorbidities like undernutrition, and potential differences in disease biology or pharmacogenomics. The demographic and clinical profile of our cohort largely aligns with the global epidemiology of pediatric ALL. The peak incidence in early childhood (1-<10 years), male predominance, and high prevalence of B-cell precursor immunophenotype are well-established patterns [1, 9]. The distribution of patients into standard-risk (63.9%) and high-risk (36.1%) groups based on age, initial WBC count, and immunophenotype is consistent with widely used risk stratification schemas [8]. However, a critical divergence from data in high-income settings is the substantial prevalence of undernutrition, affecting 25% of our patients. This factor is increasingly recognized as a pivotal, yet often overlooked, determinant of outcome in LMICs [10, 15]. Malnutrition can profoundly compromise treatment by altering the pharmacokinetics and pharmacodynamics of chemotherapeutic agents, increasing the risk and severity of toxicities, impairing immune function, and reducing tolerance to intensive therapy. Its significant presence in our cohort highlights a key area for targeted intervention, as nutritional support could potentially modulate treatment efficacy and safety. Our bivariate analysis revealed several clinically intuitive trends toward higher remission failure rates, though none achieved statistical significance in this modestly sized sample. The observed tendencies—higher failure in males, undernourished patients, those with elevated presenting WBC, low hemoglobin, and T-cell lineage—mirror the classic high-risk features extensively documented in the literature [8, 9]. A particularly noteworthy, albeit non-significant, finding was the slightly higher rate of remission failure in the standard-risk group (26.1%) compared to the high-risk group (23.1%). This counterintuitive observation merits consideration. It may be partially explained by the risk-adapted therapeutic approach: high-risk patients received the more intensive Regimen-B, which may have been more effective at eradicating MRD in this biologically aggressive subset. Conversely, some standard-risk patients, treated with the less intensive Regimen-A, might harbor cryptic biological or pharmacogenetic factors conferring de facto resistance, which are not captured by the conventional clinical risk criteria of age and WBC alone [16]. This underscores the limitations of initial clinical stratification and reinforces the need for dynamic, response-based assessment. The central and most significant finding of this study is the lack of statistically significant associations between these traditional prognostic factors and MRD status. This result powerfully illustrates the paradigm shift brought about by MRD monitoring in ALL management. In the contemporary era, MRD has emerged as the single most powerful independent prognostic factor, effectively recalibrating risk classification by providing a direct, functional measure of treatment response in vivo [4, 6]. Our data support the concept that while variables like age and initial WBC are valuable for initial protocol assignment, their predictive power is substantially diminished when the endpoint is refined to molecular remission measured by MRD. The MRD result integrates the net effect of all variables inherent disease aggressiveness, host genetics and metabolism, treatment adherence, and the quality of supportive care into one definitive metric [17]. Therefore, a negative MRD result can mitigate the perceived risk of a patient with high-risk clinical features, while a positive MRD result overrides the favorable prognosis suggested by standard-risk features.

Limitations

The study limitations include its small sample size and single-center design, which may restrict generalizability. Furthermore, the lack of cytogenetic and karyotypic data at diagnosis precludes analysis of how these established prognostic factors may influence or correlate with MRD assay results, representing a significant gap in the assessment.

Conclusion

This study identifies trends of higher remission failure by MRD assay among specific patient groups: males, the undernourished, those with high initial leucocyte count, low hemoglobin, and T-cell lineage ALL. However, statistical analysis revealed no significant associations between these prognostic factors and MRD status. The findings underscore that while bone marrow morphology remains essential, it should be complemented by MRD assessment for a more sensitive evaluation of treatment response, as MRD provides

a distinct and critical layer of prognostic information not fully captured by traditional factors alone.

Recommendation:
Future studies should incorporate cytogenetic and karyotypic analysis at diagnosis to better understand their influence on MRD and outcomes. To validate and generalize these findings, multi-center trials with larger sample sizes are essential. Finally, MRD assessment must be adopted as a standard complement to bone marrow morphology for accurate remission evaluation.

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