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RISK STRATIFICATION AND MINIMAL RESIDUAL DISEASE AFTER INDUCTION CHEMOTHERAPY IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA

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Abstract

Background: Acute lymphoblastic leukaemia (ALL) is a heterogeneous malignancy where treatment outcomes depend on multiple prognostic factors. Minimal residual disease (MRD) monitoring following induction chemotherapy has emerged as a powerful tool for assessing response and refining risk stratification. ***Methods:*** This prospective observational study was conducted at the Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2021 to June 2022. A total of 86 newly diagnosed ALL patients were enrolled. Diagnosis was based on morphology, cytochemistry, immunophenotyping and cytogenetics. All patients received standard induction chemotherapy and MRD status was assessed post-induction. Associations between MRD outcome, risk stratification and cytogenetic profiles were analyzed. ***Results:*** Among 86 patients, 48 (55.8%) were categorized as standard risk and 38 (44.2%) as high risk. Post-induction MRD analysis showed that 54 patients (62.8%) achieved MRD negativity, while 32 (37.2%) remained MRD-positive. A significant association was found between risk group and MRD outcome: 83.3% of standard-risk patients achieved MRD negativity compared to 36.8% of high-risk patients ($p < 0.001$). Cytogenetics also influenced outcomes: favorable abnormalities had the highest MRD negativity rate (88.9%), unfavorable abnormalities showed poor clearance with 75.0% MRD positivity, while normal/other profiles yielded intermediate results ($p = 0.002$). ***Conclusion:*** MRD assessment after induction therapy provides critical prognostic information in ALL. Standard-risk and favorable cytogenetic patients were more likely to achieve MRD negativity, whereas high-risk and unfavorable groups demonstrated persistent disease. Incorporating MRD monitoring can enhance risk stratification and guide post-induction treatment decisions.

Keywords: Acute lymphoblastic leukaemia, Minimal residual disease, Risk stratification, Cytogenetics, Induction chemotherapy.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant disorder of lymphoid progenitor cells that accounts for the majority of childhood leukaemias and a significant proportion of adult acute leukaemias [1]. The disease is biologically heterogeneous, with survival outcomes varying widely depending on clinical, cytogenetic and molecular features [2]. Despite remarkable improvements in treatment protocols, ALL continues to pose a therapeutic challenge, particularly in low- and middle-income countries where access to advanced diagnostics and novel therapies remains limited. Globally, the 5-year survival rate for children with ALL now exceeds 85% in developed nations, while outcomes for adults remain less favorable, with survival rates around 40–50% [3]. This disparity highlights the importance of precise risk stratification and treatment tailoring to maximize cure rates while minimizing toxicity.

Traditionally, risk assessment in ALL has relied on baseline clinical features such as age, white blood cell (WBC) count at diagnosis and early treatment response, along with cytogenetic and molecular abnormalities [4]. Patients younger than 10 years with a WBC count below 50,000/µL and without adverse cytogenetic abnormalities are generally considered standard risk, whereas older patients, those with higher WBC counts, or those harboring unfavorable genetic alterations such as the BCR-ABL1 fusion, KMT2A rearrangements, or hypodiploidy are stratified into high-risk categories [5]. While these factors remain important, they fail to fully capture the biological diversity of the disease and the variability in treatment response [6].

Minimal residual disease (MRD), defined as the persistence of leukemic cells below the threshold of conventional morphology, has emerged as the most powerful independent prognostic factor in ALL [7]. Sensitive techniques such as multiparametric flow cytometry, polymerase chain reaction (PCR)-based assays and more recently next-generation sequencing (NGS), allow detection of one leukemic cell among 10,000–100,000 normal cells [8]. Numerous studies have demonstrated that MRD status after induction chemotherapy is strongly predictive of relapse risk, event-free survival and overall survival. Patients who achieve MRD negativity at the end of induction have significantly better long-term outcomes compared to those who remain MRD positive, regardless of their initial risk category [9]. In fact, contemporary treatment algorithms in both pediatric and adult ALL now incorporate MRD as a cornerstone of therapeutic decision-making [10].

The integration of MRD into risk stratification represents a paradigm shift from static, baseline assessments to a dynamic, response-based approach [11]. This has allowed for risk-adapted treatment intensification in MRD-positive patients and potential de-escalation in those achieving rapid clearance, thereby balancing efficacy with toxicity [12]. Moreover, MRD-guided strategies have facilitated the use of targeted therapies such as tyrosine kinase inhibitors, blinatumomab, inotuzumab ozogamicin and chimeric antigen receptor (CAR)-T cell therapy, particularly in patients with persistent or relapsed MRD [13].

Therefore, this study was undertaken to evaluate risk stratification and minimal residual disease after induction chemotherapy in patients with acute lymphoblastic leukaemia treated at a tertiary care center in Bangladesh. By generating local evidence, the findings are expected to contribute to better prognostic assessment and guide future incorporation of MRD-based risk-directed therapy in national protocols.

METHODOLOGY & MATERIALS

This prospective observational study was conducted in the Department of Haematology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, over a period of twelve months from July 2021 to June 202. A total of 86 newly diagnosed patients with acute lymphoblastic

leukaemia (ALL) were enrolled following informed written consent. Diagnosis was established on the basis of morphology, cytochemistry, immunophenotyping and cytogenetic studies wherever available. Patients of all ages and both sexes with newly diagnosed ALL who received standard induction chemotherapy were included. Patients with relapsed disease, prior chemotherapy, severe co-morbid conditions precluding treatment, or incomplete data were excluded from the study.

Risk stratification was performed according to standard criteria, which included age at diagnosis, initial white blood cell (WBC) count, presence of central nervous system or testicular involvement and cytogenetic or molecular abnormalities. Patients aged 1–10 years with WBC <50,000/µL and without high-risk cytogenetic abnormalities were considered standard risk, while those outside this group were categorized as high risk.

Minimal residual disease (MRD) assessment was carried out at the end of induction chemotherapy using multiparametric flow cytometry with a sensitivity of 0.01%. Patients were classified as MRD-negative if the level was <0.01% and MRD-positive if ≥0.01%.

All clinical, laboratory and follow-up data were recorded in a structured case record form. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as mean with standard deviation. Associations between categorical variables were analyzed using Chi-square or Fisher's exact test and a p-value <0.05 was considered statistically significant.

RESULTS

Table I: Distribution of Patients by Baseline Characteristics (N = 86)

Characteristics	Number (n)	Percentage (%)
Age group		
<10 years	34	39.5
10–18 years	26	30.2
>18 years	26	30.2
Sex		
Male	52	60.5
Female	34	39.5
Initial WBC count (/µL)		
<50,000	55	64
≥50,000	31	36
Immunophenotype		
B-ALL	70	81.4
T-ALL	16	18.6
CNS involvement at diagnosis	8	9.3
Cytogenetics		
Favorable (ETV6-RUNX1, hyperdiploidy)	18	20.9
Unfavorable (BCR-ABL1, MLL, hypodiploidy, iAMP21)	12	14
Normal/Other	56	65.1

Table I shows the baseline characteristics of the 86 patients with acute lymphoblastic leukaemia included in this study. The majority of patients were younger than 10 years (39.5%), while both the 10–18 years and >18 years groups constituted 30.2% each. Males predominated (60.5%) compared to females (39.5%). Most patients (64%) presented with an initial white blood cell (WBC) count below

50,000/µL, while 36% had higher counts. Immunophenotypic analysis revealed that B-cell ALL was the most common subtype (81.4%), whereas T-cell ALL accounted for 18.6% of cases. Central nervous system (CNS) involvement at diagnosis was observed in 9.3% of patients. Regarding cytogenetics, favorable abnormalities such as ETV6-RUNX1 and hyperdiploidy were found in 20.9% of cases, unfavorable changes including BCR-ABL1, MLL rearrangements, hypodiploidy and iAMP21 were present in 14% and the majority (65.1%) showed normal or other cytogenetic profiles.

Table II: Risk Stratification of Patients (N = 86)

Risk Category	Number (n)	Percentage (%)
Standard Risk	48	55.8
High Risk	38	44.2

Table II demonstrates the risk stratification of the study population. Out of 86 patients, 48 (55.8%) were classified as standard risk, while 38 (44.2%) were categorized as high risk based on age, initial WBC count, CNS/testicular involvement and cytogenetic or molecular abnormalities.

Table III: MRD Status after Induction Chemotherapy (N = 86)

MRD Status	Number (n)	Percentage (%)
MRD-negative (<0.01%)	54	62.8
MRD-positive (≥0.01%)	32	37.2

Table III presents the minimal residual disease (MRD) status of patients at the end of induction chemotherapy. Among the 86 patients evaluated, 54 (62.8%) achieved MRD negativity (<0.01%), while 32 (37.2%) remained MRD positive (≥0.01%).

Table IV: Association between Risk Group and MRD Status

Risk Group	MRD-negative (n, %)	MRD-positive (n, %)	p-value
Standard Risk	40 (83.3%)	8 (16.7%)	<0.001*
High Risk	14 (36.8%)	24 (63.2%)	

*Statistically significant

Table IV shows the association between risk group and MRD status after induction chemotherapy. In the standard-risk group, the majority of patients achieved MRD negativity, with 40 (83.3%) being MRD-negative compared to only 8 (16.7%) who were MRD-positive. In contrast, within the high-risk group, only 14 patients (36.8%) attained MRD negativity, while 24 (63.2%) remained MRD-positive. The difference between the two groups was statistically highly significant ($p < 0.001$), indicating that patients in the high-risk category were far more likely to have persistent MRD following induction therapy.

Table V: MRD Status according to Cytogenetic Abnormalities

Cytogenetics	MRD-negative (n, %)	MRD-positive (n, %)	p-value
Favorable	16 (88.9%)	2 (11.1%)	0.002*
Unfavorable	3 (25.0%)	9 (75.0%)	
Normal/Other	35 (62.5%)	21 (37.5%)	

*Statistically significant

Table V demonstrates the relationship between cytogenetic abnormalities and MRD status at the end of induction chemotherapy. Patients with favorable cytogenetic features, such as ETV6-RUNX1 fusion and hyperdiploidy, showed the highest rate of MRD negativity, with 16 (88.9%) achieving clearance of disease and only 2 (11.1%) remaining MRD-positive. In contrast, those with unfavorable abnormalities, including BCR-ABL1, MLL rearrangements, hypodiploidy, or iAMP21, had poor treatment response, as only 3 patients (25.0%) became MRD-negative while 9 (75.0%) retained measurable disease. Among patients with normal or other cytogenetic findings, 35 (62.5%) achieved MRD negativity and 21 (37.5%) remained positive. The overall association between cytogenetic abnormalities and MRD outcome was statistically significant ($p = 0.002$).

DISCUSSION

In this prospective study, we evaluated risk stratification and minimal residual disease (MRD) response following induction chemotherapy in patients with acute lymphoblastic leukemia (ALL) at a tertiary center in Bangladesh. Among the 86 enrolled patients, more than half were classified as standard risk and nearly two-thirds achieved MRD negativity after induction. Our findings reinforce the pivotal role of MRD in guiding post-induction risk refinement and are in concordance with international data.

The proportion of patients achieving MRD negativity in our study (62.8%) is consistent with previously reported ranges of 60–75% following induction therapy. Borowitz et al., reported that MRD negativity at the end of induction strongly correlated with superior event-free survival in high-risk B-ALL patients, underscoring its prognostic value [14]. Similarly, Galimberti et al., validated MRD as a surrogate endpoint for event-free survival in pediatric ALL, strengthening the argument for MRD as a robust early marker of treatment response [15].

Risk stratification using baseline clinical and biological features remains important but is insufficient in isolation. In our cohort, MRD negativity was achieved by 83.3% of standard-risk patients compared to only 36.8% of high-risk patients, highlighting the predictive value of integrating MRD with conventional stratification. This is in line with findings by Pieters et al., who demonstrated that MRD-guided therapy intensification for poor responders and therapy reduction for good responders led to excellent outcomes in the Dutch ALL10 trial [16].

Cytogenetic abnormalities also significantly influenced MRD response in our study. Patients with favorable cytogenetics, such as ETV6-RUNX1 and hyperdiploidy, had excellent MRD clearance (88.9%), whereas those with unfavorable profiles, including BCR-ABL1 and hypodiploidy, showed poor clearance (75% MRD positivity). These results align with Beldjord et al., who showed that oncogenetics and MRD are independent predictors of prognosis in adult ALL and that patients with adverse cytogenetics have a higher likelihood of persistent MRD despite intensive therapy [17]. Similar conclusions were drawn by Roberts et al., who observed poor MRD clearance and inferior survival among BCR-ABL1–like ALL patients [18].

The use of MRD as a dynamic marker of treatment response has allowed therapeutic adaptations globally. Yeoh et al., demonstrated that MRD-guided treatment deintensification in standard-risk children did not compromise outcomes, but reduced toxicity, suggesting that MRD-negative patients could safely receive less intensive therapy [19]. Conversely, Liao et al., showed that MRD-guided intensification in poor responders significantly improved survival, highlighting its bidirectional clinical utility [20]. Our study adds to this body of evidence by demonstrating similar MRD-based discrimination in a South Asian cohort.

In T-ALL, where prognosis has historically been worse, MRD has also proven valuable. Modvig et al., showed that MRD quantified by flow cytometry provided reliable risk stratification in T-ALL patients, where MRD positivity strongly correlated with relapse [21]. Although our cohort included only a limited number of T-ALL patients, the persistence of MRD in this group reflects global trends.

MRD assessment is also critical in determining the need for allogeneic stem cell transplantation. Eckert et al., reported that allogeneic transplantation guided by MRD status improved survival in intermediate-risk relapsed ALL [22]. Similarly, Lovisa et al., emphasized that both pre- and post-transplant MRD strongly predicted relapse occurrence, indicating its role across treatment phases [23]. These findings support the application of MRD assessment not only for induction response but also for long-term disease monitoring.

Meta-analyses further strengthen MRD's role in clinical decision-making. Bassan et al., systematically reviewed MRD studies and confirmed that MRD positivity consistently predicted inferior survival across multiple adult ALL cohorts, regardless of treatment protocols or detection methods [24]. This suggests that the prognostic significance of MRD is universal and not limited by geography or specific regimens.

Taken together, our findings confirm that MRD is a critical tool in modern ALL management. Patients with favorable baseline features and rapid MRD clearance represent a group with excellent outcomes who may benefit from treatment de-escalation to minimize toxicity. Conversely, patients with high-risk features or persistent MRD constitute a group requiring intensified therapy, potentially including novel agents such as blinatumomab or inotuzumab ozogamicin.

Limitations of the study

Limitations of this study include the relatively small sample size and single-center design, which may limit generalizability. Furthermore, long-term survival data were not available at the time of reporting and our study focused only on induction MRD without serial follow-up, which is important in predicting late relapses. Future studies in Bangladesh should incorporate longitudinal MRD monitoring, genomic profiling and integration with novel immunotherapeutic approaches to improve outcomes further.

CONCLUSION

This study highlights that MRD assessment after induction chemotherapy is a powerful prognostic tool in ALL, outperforming conventional risk stratification alone. Patients with favorable cytogenetics and standard-risk features were more likely to achieve MRD negativity, whereas those with adverse cytogenetics and high-risk status had significantly higher MRD persistence. These findings are consistent with international studies and emphasize the importance of MRD-guided therapeutic strategies in improving survival while minimizing treatment-related toxicity.

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