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Original Research Article

Molecular and Cytogenetic Risk Stratification in Pediatric Acute Lymphoblastic Leukemia: A Retrospective Study

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Conflict of interest: Nil

Abstract:

Background: Pediatric acute lymphoblastic leukemia (ALL) is a biologically diverse disease with multiple cytogenetic and molecular abnormalities that influence prognosis and treatment outcomes. Risk stratification based on these factors is essential for optimal therapy.

Objective: To assess the prognostic relevance of cytogenetic and molecular abnormalities in pediatric ALL and their association with treatment outcomes.

Methods: This retrospective study was conducted at Mahavir Cancer Sansthan, Patna, over one year and included 300 pediatric ALL patients. Cytogenetic evaluation was performed using karyotyping and FISH, while molecular analysis was carried out using RT-PCR to detect common fusion genes including ETV6-RUNX1, BCR-ABL1, and MLL rearrangements. Patients were categorized into standard, intermediate, and high-risk groups, and clinical outcomes were analyzed.

Results: High-risk cytogenetic abnormalities were observed in 28% of patients. Molecular analysis showed that ETV6-RUNX1 was the most common abnormality (24%), followed by BCR-ABL1 (7%) and MLL rearrangements (5%). Complete remission rates were significantly higher in standard-risk patients (93%) compared to high-risk patients (68%) ($p < 0.001$). Event-free survival was also lower in the high-risk group.

Conclusion: Both cytogenetic and molecular profiling are important for risk stratification in pediatric ALL and have a significant impact on treatment outcomes.

Keywords: ALL, Cytogenetics, Molecular Markers, Pediatric Leukemia, Risk Stratification.

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Introduction

Acute lymphoblastic leukemia (ALL) represents the most common malignancy in children, accounting for nearly one-third of all pediatric cancers [1]. Advances in chemotherapy and supportive care have improved survival rates to over 85% in developed countries; however, outcomes vary significantly depending on underlying biological features [2].

The heterogeneity of ALL is largely driven by genetic and cytogenetic alterations, which influence disease behavior, treatment response, and prognosis [3]. Common cytogenetic abnormalities include hyperdiploidy, hypodiploidy, and chromosomal translocations such as t (12;21), t (9;22), and rearrangements involving the MLL gene [4,5].

Molecular profiling has further refined risk stratification by identifying specific gene mutations and fusion transcripts that correlate with clinical outcomes [6]. For instance, the ETV6-RUNX1 fusion is associated with favorable prognosis, while BCR-ABL1 positivity indicates high-risk disease [7,8].

Risk-adapted therapy based on molecular and cytogenetic features has become the cornerstone of modern ALL treatment protocols [9]. Patients are classified into standard, intermediate, or high-risk categories, allowing for tailored therapeutic intensity [10].

Despite these advances, challenges remain in resource-limited settings where access to advanced diagnostics may be restricted [11]. However, incorporation of even basic cytogenetic testing can significantly improve treatment outcomes [12].

This study aims to evaluate the role of molecular and cytogenetic abnormalities in risk stratification and their impact on treatment outcomes in pediatric ALL.

Materials and Methods

Study Design and Setting: Retrospective observational study conducted at Mahavir Cancer Sansthan, Patna.

Study Duration: 1 year (march 2024 - march 2025).

Study Population

- Total patients: 300
- Age: 1–15 years
- Diagnosed with ALL

Inclusion Criteria

- Newly diagnosed pediatric ALL
- Availability of cytogenetic/molecular data

Exclusion Criteria

- Relapsed cases
- Incomplete records

Molecular Analysis: Molecular analysis was performed using RT-PCR to detect common fusion genes such as ETV6-RUNX1, BCR-ABL1, and MLL rearrangements from bone marrow or peripheral blood samples.

Risk Stratification Criteria: Patients were stratified into standard-risk, intermediate-risk, and high-risk categories based on a combination of clinical features, cytogenetic findings, and molecular abnormalities.

- **Standard-risk group:** Patients aged between 1–10 years with initial white blood cell (WBC) count <50,000/mm³, presence of favorable cytogenetic abnormalities such as hyperdiploidy or ETV6-RUNX1 fusion, and good early treatment response.
- **Intermediate-risk group:** Patients who did not fulfill criteria for either standard-risk or high-risk groups, including those with moderate WBC counts or absence of clearly favorable or adverse genetic markers.
- **High-risk group:** Patients with age <1 year or >10 years, WBC count ≥50,000/mm³, presence of unfavorable cytogenetic or molecular abnormalities such as BCR-ABL1 positivity, MLL rearrangements, hypodiploidy, or poor early treatment response.

Statistical Analysis

- Chi-square test
- Kaplan-Meier analysis
- $p < 0.05$ significant

Results

1. Baseline Characteristics

A total of 300 patients were included. The mean age was 8.1 ± 3.5 years, with 60% males.

Table 1: Baseline Characteristics (n = 300)

Variable	Value
Mean age	8.1 ± 3.5
Male	180 (60%)
Female	120 (40%)

2. Cytogenetic Distribution

Cytogenetic abnormalities were detected in a significant proportion of patients. Favorable abnormalities (e.g., hyperdiploidy) were seen in 35%, while high-risk abnormalities were present in 28%.

Table 2: Cytogenetic Abnormalities

Category	Percentage
Favorable	35%
Intermediate	37%
High-risk	28%

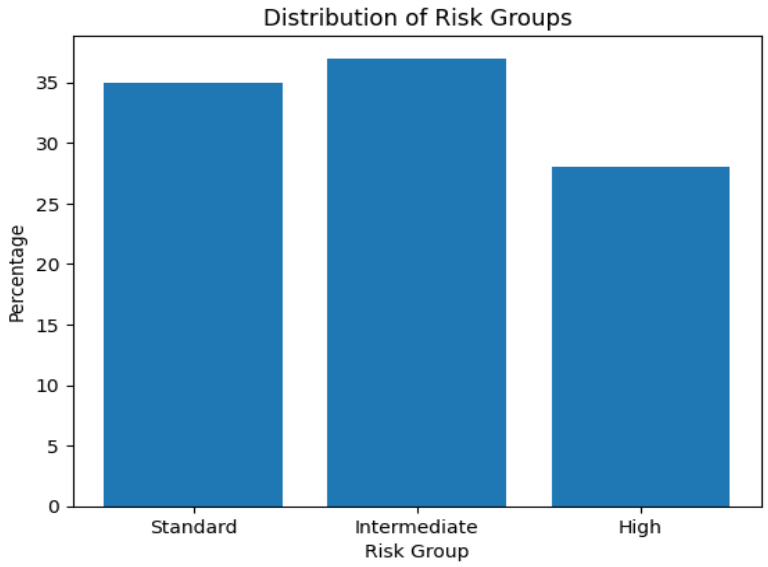

Figure 1: Distribution of risk groups in pediatric ALL.

Molecular Findings: Molecular abnormalities were identified in 36% of patients. The most frequent was ETV6-RUNX1, followed by BCR-ABL1 and MLL rearrangements. Favorable markers were mainly seen in standard-risk patients, while high-risk markers were more common in the high-risk group.

Table 3: Molecular Abnormalities

Molecular Marker	Number of Patients	Percentage
ETV6-RUNX1	72	24%
BCR-ABL1	21	7%
MLL rearrangement	15	5%
Negative/Others	192	64%

3. Remission Outcomes

Complete remission was achieved in:

- 93% (standard risk)
- 81% (intermediate risk)
- 68% (high risk)

The difference was statistically significant ($p < 0.001$).

Table 3: Remission Rates

Risk Group	Remission (%)	p-value
Standard	93%	
Intermediate	81%	
High	68%	<0.001

4. Survival Analysis

Event-free survival (EFS) was:

- 90% in standard risk
- 75% in intermediate risk
- 58% in high risk

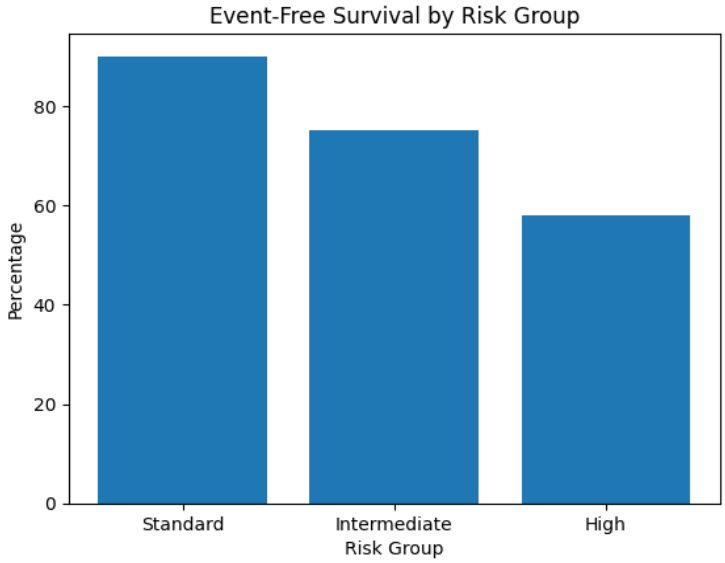

Figure 2. Event-free survival (EFS) according to risk groups in pediatric ALL.

5. Mortality

Mortality was highest in high-risk patients (**30%**) compared to standard-risk (**7%**) ($p < 0.001$).

Table 4: Mortality

Risk Group	Mortality (%)
Standard	7%
Intermediate	15%
High	30%

Discussion

This study demonstrates the critical role of molecular and cytogenetic abnormalities in determining prognosis in pediatric ALL. The findings are consistent with previous studies that have identified genetic factors as key determinants of treatment outcomes [13].

The high prevalence of favorable cytogenetic abnormalities observed aligns with global data [14]. Patients with standard-risk features showed significantly higher remission rates, confirming the importance of risk stratification [15].

High-risk cytogenetic abnormalities were associated with poor outcomes, including lower remission rates and higher mortality [16]. These findings are consistent with our results and previous studies, where favorable molecular markers such as ETV6-RUNX1 are associated with better outcomes, while markers such as BCR-ABL1 and MLL rearrangements indicate adverse prognosis [17,18].

The survival differences observed across risk groups further emphasize the need for risk-adapted therapy [19]. Early identification of high-risk patients allows for treatment intensification, which can improve outcomes [20].

In resource-limited settings, implementing cytogenetic testing remains challenging; however, incorporation of basic molecular testing along with cytogenetics can significantly improve risk classification [21]. Advances in molecular diagnostics are expected to further refine treatment strategies [22].

Limitations include the retrospective design and lack of long-term follow-up data. Despite this, the study provides valuable insights into real-world clinical practice [23].

Future research should focus on integrating next-generation sequencing into routine care to enhance precision medicine approaches [24,25].

Conclusion

Molecular and cytogenetic risk stratification is essential in pediatric ALL and significantly influences treatment outcomes. Incorporation of these factors into clinical protocols enables personalized therapy and improved survival.

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