Original Article

Integrated Immunophenotyping and Gene Fusion Analysis in Pediatric Acute Lymphoblastic Leukemia: A Tertiary Care Hospital Study

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Abstract

Background: Pediatric Acute Lymphoblastic Leukemia (ALL) is a complex hematologic malignancy characterized by the uncontrolled proliferation of immature lymphoid cells. Early diagnosis and precise classification are crucial for effective treatment and prognosis. This study aims to evaluate the utility of integrated immunophenotyping and gene fusion analysis in the diagnosis and stratification of pediatric ALL at a tertiary care hospital.

Methods: We analyzed clinical and laboratory data from a cohort of 50 pediatric ALL patients, applying immunophenotyping techniques to characterize cell surface markers and identifying relevant gene fusions associated with various subtypes of the disease. All statistical analysis was performed using SPSS v30, incorporating both parametric and non-parametric variables.

Result: Immunophenotyping of the 50 patients revealed that 90% had B-ALL, while the remaining 10% had T-ALL or mixed lineage phenotypes. Q-PCR analysis detected gene fusion positivity in 58% of cases, including key fusions associated with high-risk subtypes. These findings underscore the value of integrating immunophenotyping and molecular diagnostics for accurate classification and risk stratification in pediatric ALL. Our results highlight the role of these diagnostic tools in improving the accuracy of ALL classification, identifying high-risk genetic alterations, and guiding therapeutic decisions.

Conclusion: This study emphasizes the importance of combining immunophenotyping with molecular techniques for comprehensive diagnostic and prognostic assessments in pediatric ALL, offering a deeper understanding of the disease's pathogenesis and supporting personalized treatment approaches.

Keywords: Acute lymphoblastic leukemia; Childhood; Diagnostic; Gene-fusion; Immunophenotyping; Prognostic

Introduction

Acute lymphoblastic leukemia (ALL) is the most common leukemia in children, accounting for 25% of all childhood malignancies. It most often affects children and adolescents. ALL is a condition in which normal hematopoiesis is suppressed, and the bone marrow is replaced by leukemic blasts [1]. The main clinical features arise due to a lack of red blood cells, white blood cells, and platelets, leading to anemia, neutropenia, and thrombocytopenia. Consequently, patients present with pallor and dyspnea [1]. These children are more susceptible to infections, and bleeding episodes occur due to thrombocytopenia. Other manifestations include organomegaly caused by the infiltration of organs by lymphoblasts. Bone pain and tenderness are also common manifestations of the disease [2].

ALL is broadly classified into B-cell and T-cell types based on immunophenotyping performed by flow cytometry. The immunological classification of ALL holds significant therapeutic and prognostic relevance. B-ALL accounts for 80% of all

cases of ALL, while T-ALL accounts for 15-20% of cases. B-ALL is further classified into Pro-B ALL, Common ALL (CALLA), and Pre-B ALL. Among these, CALLA-positive ALL has the best prognosis. T-ALL is further divided into Pro-T ALL, Pre-T ALL, Cortical T-ALL, and Mature T-ALL [3, 4].

In cases where immunophenotyping fails to conclusively identify the lineage of leukemic cells, molecular genetic studies, including Real-Time Polymerase Chain Reaction (RT-PCR)/Quantitative PCR (Q-PCR), are employed. The integration of immunophenotyping and gene fusion analysis provides a comprehensive approach to the characterization of ALL, enabling personalized medicine strategies. Molecular abnormalities such as TEL/AML1, PBX/E2A, BCR/ABL, MLL/AF4, and MYC/IGH can be identified using this method, which is of therapeutic and prognostic significance [5, 6]. This facilitates the identification of specific leukemia subtypes, guiding targeted treatment options. Q-PCR and flow cytometry are complementary techniques. This study aims to investigate the immunophenotypic and gene fusion profiles of pediatric ALL patients in a tertiary care hospital setting. By combining these approaches, comprehensive diagnostic and prognostic assessments, as well as optimal patient management, can be achieved.

Materials and Methods

Patients and sample collection: A total of 50 pediatric patients with acute lymphoblastic leukemia treated at our hospital from a period of April 2024 to till now were included in the study. After peripheral smear examination and bone marrow study confirmation during diagnosis, 2-3 ml of peripheral blood or bone marrow aspirate were sent to the recently established molecular pathology department to determine the immunophenotypic distribution using multi-parametric flow cytometry analysis and to detect chromosomal gene fusions using QPCR analysis. All the patients received the chemotherapy treatment plan of the ICiCLe (The Indian Collaborative Childhood Leukemia) protocol. Minimal residual disease (MRD) testing was performed using flow cytometry on the 4th week and 8th week of starting treatment. The study was approved by the Institutional Ethics Committee [IEC-MMC/Approval/15092024].

Inclusion criteria: Age between 0-14 years at the time of diagnosis. Diagnosed ALL cases by peripheral blood smear or bone marrow aspiration and flow cytometry.

Exclusion criteria: ALL cases on treatment. Cases with insufficient or inadequate blood sample.

Flow Cytometry analysis: Flow cytometry measures the properties of cells as they flow in a fluid suspension across an illuminated light source. The samples are labeled with fluorescent markers, and as they pass through, the focused light source emits light, which is converted into digital signals and stored in a file for analysis. The samples for flow cytometry in the leukemia panel are either peripheral blood or bone marrow aspirates collected in sodium heparin vacutainers. Five tubes are used, namely the B tube, T tube, CD64 tube, AML tube, and MPO tube, and markers conjugated with different fluorochromes, such as FITC (fluorescein isothiocyanate), PC5 (phycoerythrin cyanine 5 conjugate), and PE (phycoerythrin), are added.

The markers added in the B tube are CD19 FITC, CD10 PE, and CD20 PC5. In the T tube, CD7 PE and CD3 PC5 are added. CD64 FITC, CD13 PE, and anti-HLADR PC5 are added to the CD64 tube. In the AML tube, CD34 FITC, CD117 PC5, and CD33 PE are added. In the MPO tube, cytoplasmic markers, cyto-CD3, MPO, and cyto-CD79a, are added. The antibody clones used for these markers are listed in Table 1.

100 μL of sample is added to all test tubes. After 20 minutes, 2 mL of lysing solution is added to all test tubes except the MPO tube. After 15 minutes, all the test tubes are centrifuged. The supernatant is discarded. Two milliliters of phosphate-buffered saline is added to all test tubes and centrifuged two or three times until a clear pellet forms. After a clear pellet forms, 2 mL of phosphate-buffered saline is added, and the acquisition process is completed.

In the MPO tube, since it contains a cytoplasmic marker, intra-prep permeabilization is performed, and the other steps are similar to those followed for the other tubes, as described above. After acquisition, the stored data are analyzed, and immunophenotyping is performed. In acute lymphoblastic leukemia, flow cytometry uses a gating strategy to isolate and identify leukemic blasts by analyzing their unique antigen expression. The initial gating focuses on CD45 dim cells using a side scatter plot. Further gating involves specific markers such as CD19 (for B-cell precursor ALL) or T-cell markers such as cyto-CD3 (for T-cell ALL), to differentiate between subtypes. The initial gating identifies the lymphoid population, including blasts, by plotting CD45 expression against side scatter. Blasts are typically found in the CD45 dim region. Then, lineage-specific gating is performed. For B-ALL, CD19 is the primary marker. Additional markers such as CD10, CD22, and cyto-CD79a are used to further refine the B-cell blast population.

The diagnostic criteria for B-ALL include strong CD19 expression with at least one of the following markers strongly expressed, or weak CD19 expression with at least two of the following strongly expressed: CD79a, cytoplasmic CD22, and CD10. For T-ALL, T-cell markers such as cCD3, sCD3, CD5, CD99, and TdT are used to identify T-cell blasts. Among these markers, cytoplasmic CD3 or surface CD3 expression is most significant. The percentage of blasts is calculated, and a final impression is provided.

RNA extraction: Total RNA was extracted from the isolated lymphocyte cell pellet from peripheral blood or bone marrow aspirated blood sample using the Total RNA isolation system according to the manufacturer's instruction (Promega Corporation, USA). The quantity of the extracted RNA was measured using a Nanodrop spectrophotometer (Thermo Fischer Scientific Inc, USA). The purity of the RNA was assessed by measuring the absorbance ratio at 260/280 nm. Approximately 1 microgram of RNA was reverse transcribed into cDNA using the TRUPCR reverse transcriptase enzyme.

QPCR analysis: 4.0 μL of the cDNA was used as the input sample to detect chromosomal gene fusions using the TRUPCR Acute Leukemia Panel kit version 3.0 by QPCR analysis (3B Blackbio Biotech India Ltd). The reaction set up and thermal conditions for the qPCR were followed as per the kit insert. The list of detectable gene fusions in the panel is provided in Table 2. For each qPCR run, positive and negative controls are included as part of the quality control procedure. For all markers, the detection channel uses FAM as the reporter in the assay. The recommended cycle threshold fluorescence (ΔRn) (Ct) value for all markers, as specified by the kit, ranges from 0.02 to 0.05. A primer-probe that shows amplification at the set threshold value is considered positive for gene fusion.

Statistical analysis: Clinical and laboratory parameters were correlated with immunophenotyping and gene fusion profiles to assess prognostic implications. All statistical analyses were performed using SPSS software version 30. The parameters used for the statistical analysis were listed under Patient characteristics in Table 3. Differences in parametric variables were analyzed using the multivariate analysis and t-test, while non-parametric variables were analyzed using the chi-square test. A one-way ANOVA test was performed on the immunophenotyping data of the patients who showed expression markers. A p-value of < 0.05 was considered statistically significant unless indicated otherwise.

Results

Immunophenotype patterns: Based on the expression of B-cell and T-cell markers, the flow cytometry analysis found that around 90% of patients had B-ALL and 4% had T-ALL. We also found that 6% of patients had mixed lineage (Figure 1). Of the 34 male pediatric patients, 31 exhibited a B-ALL phenotype, while among the 16 female pediatric patients, 14 exhibited a B-ALL phenotype. All the 45 B-ALL cases expressed CD19, CD10, CD34, CD45 and so on (Figure 2A & B). Of the 50 pediatric patients, four samples were analyzed for Minimal Residual Disease (MRD) status monitoring using flow cytometry.

Gene fusion Identified: The real-time PCR analysis for the acute leukemia panel revealed 58% (29/50) gene fusion positivity within the study group. Among the positive cases, the majority of the gene fusions were E2A-PBX, seen in 13/29 positive cases, and the rest include MLL gene rearrangement, BCR-ABL, and TEL-AML1 fusion genes (Figure 3). In the study cohort, 67% male and 37% female pediatric patients were found to be positive for gene fusions. All patients with positive gene fusion results exhibited a B-ALL immunophenotype. Two patients had co-occurring gene fusion positivity in CBFB-MYH11: BCR-ABL and E2A-PBX: BCR-ABL fusion genes (Figure 4). Another patient with MLL gene rearrangement had a FLT3 gene Tyrosine kinase domain (TKD) mutation. All the patients with a T-ALL immunophenotype were found to be negative for gene fusions.

Of the four patients for whom MRD monitoring was performed using flow cytometry, three tested positive for gene fusions, one of whom had a co-occurring fusion gene. All patients with gene fusions were offered a standard chemotherapy regimen; the patient who was Philadelphia chromosome-positive received a tyrosine kinase inhibitor (TKI) as targeted therapy, and the patient with an MLL gene rearrangement received intensified chemotherapy along with CNS prophylaxis (Table 4).

Clinical correlations: The statistical analysis using multivariate analysis with parametric variables did not show any significant correlation between the clinical characteristics of patients, immunophenotyping, and gene fusion results. Given the lack of significance in the multivariate model, we proceeded with targeted univariate analyses to explore potential pairwise relationships that may have been masked in the multivariate approach. Specifically, Student's t-tests (one-sample, independent sample, and paired sample analyses) were conducted to examine associations between individual continuous variables. A statistically significant difference (p-value < 0.05) was identified in the paired sample t-test for the variables: patient age versus gene fusion result (p-value - <0.001) and blast cell percentage at diagnosis versus gene fusion result (p-value - 0.008). For non-parametric variables, the Chi-square test was performed; however, no statistically significant associations were observed between the variables. A one-way ANOVA test was performed for immunophenotyping data based on the expression of markers. We found an F-value of 23 suggests that the differences between group means are substantial compared to the variability within the groups, and the P-value of <0.0001 indicates that the group means are statistically significantly different.

Discussion

The study aimed to evaluate the immunophenotypic patterns, gene fusion characteristics, and their clinical correlations in pediatric acute leukemia patients using flow cytometry and QPCR methods. The findings provide valuable insights into the distribution of immunophenotypes, the prevalence of gene fusions, and their potential clinical implications. Our patients'

Table 1: List of Antibody clones used for flow cytometry analysis

Marker	Fluorochrome	Antibody clone
B Tube:		
CD19	FITC	HIB19
CD10	PE	HI10a
CD20	PC5	B9E9
T Tube:		
CD7	PE	M-T701
CD3	PC5	UCHT1
CD64 Tube:		
CD64	FITC	10.1
CD13	PE	WM15
HLA-DR	PC5	IMMU-357
AML Tube:		
CD34	FITC	581
CD117	PC5	104D2
CD33	PE	D3HL60.251
MPO Tube:		
Cyto-CD3	Intracellular	UCHT1
MPO	Intracellular	CLB-MPO1
Cyto-CD79a	Intracellular	HM47

Table 2: List of detectable gene fusions

S.No	Gene	Variant
1	BCR-ABL	e13a2 & e14a2 (p210), e1a2 (p190), e19a2 (p230)
2	E2A-PBX1	TCF3-PBX1
3	TEL-AML1	BCL2L14-RUNX1
4	MLL-AF4	e10-e4, e9-e4, e9-e5, e11-e4, e9-e6
5	MLL-ENL	e9-e2, e10-e2
6	ABL1 (Reference gene)	Internal control gene
7	FLT3-TKD	Codon 835
8	CBFB-MYH11	CBFB-MYH11 (Inv 16)

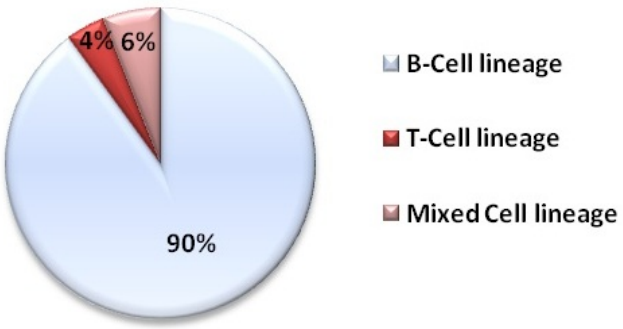


Figure 1: Immunophenotype analysis

clinical and biological features align with previously reported findings. The highest incidence of pediatric ALL was observed in the 1-4 year age group, with the mean age of a pediatric patient being 5 years [7, 8].

The immunophenotype analysis revealed that the majority of patients exhibited B-ALL, while a smaller proportion presented with T-ALL. Additionally, 6% of patients exhibited a mixed lineage immunophenotype. Our findings align with previous reports, where B-ALL is the predominant subtype in pediatric acute leukemia cases [9, 10]. Mixed lineage immunophenotypes, though less common, highlight the heterogeneity of acute leukemia and emphasize the need for comprehensive diagnostic approaches to appropriately classify these cases [11, 12].

QPCR acute leukemia panel analysis identified E2A-PBX as the most frequent fusion event, observed in 13 of the 29 positive cases. This was followed by MLL gene rearrangements, BCR-ABL, and TEL-AML1 fusion genes. The predominance of E2A-PBX among fusion-positive cases is consistent with its known association with B-ALL, further emphasizing the relationship between specific genetic abnormalities and immunophenotypic subtypes [13]. Patients with this gene fusion achieved complete remission by day 35, except for two individuals who experienced relapse during follow-up and are

Table 3: Patient Clinical characteristics

S.NO	PARAMETERS	NO. OF PATIENTS (%) [N = 50]
1.	**Age**	
	0-10 years	44 (88)
	11-14 years	6 (12)
2.	**Sex**	
	Male	34 (68)
	Female	16 (32)
3.	**Enlarged organ at diagnosis**	
	Yes	27 (54)
	No	23 (46)
4.	**WBC at diagnosis**	
	Normal	10 (20)
	Abnormal	40 (80)
5.	**Hemoglobin level at diagnosis**	
	Normal	8 (16)
	Abnormal	42 (84)
6.	**Platelet at diagnosis**	
	Normal	7 (14)
	Abnormal	43 (86)
7.	**Blasts at diagnosis**	
	0-50%	24 (48)
	51-90%	26 (52)
8.	**Immunophenotype distribution**	
	B-Lineage	45 (90)
	T-Lineage	2 (4)
	Mixed Lineage	3 (6)
9.	**Molecular analysis**	
	Positive for gene fusion	29 (58)
	Negative for gene fusion	21 (42)

Table 4: Treatment response of patient with fusion genes in the study

Gene Fusions identified (N=29)	**E2A-PBX1 (N=13)**	**BCR-ABL (N=5)**	**TEL-AML1 (N=4)**	**MLL rearrangement (N=7)**
Treatment Offered	Standard treatment regimen	Intensive combination of systemic therapy (TKIs)	Standard treatment regimen	Intensified Chemotherapy & CNS prophylaxis
Response to treatment	MRD (2) Response (11)	MRD (1) Response (4)	Response (4)	MRD (1) Response (6)

currently undergoing MRD monitoring. Minimal Residual Disease (MRD) analysis was performed in only 4 out of the 50 patients included in this study. This limited scope was due to the unavailability of follow-up samples for the majority of patients, which restricted the ability to assess MRD status across the full cohort. While MRD is a valuable prognostic tool in pediatric ALL and can guide risk-adapted treatment decisions, our study could not systematically evaluate its impact due to this sample constraint. Patients with TEL-AML1 fusion generally have a favorable prognosis and response to standard chemotherapy regimens. Even in our study, all the patients achieved complete remission and remained responsive to treatment [14, 15]. Patients with gene fusions are not routinely given targeted therapy unless they relapse or show resistance. Immunotherapy is highly effective in the B-ALL subtype. Our study cohort requires long-term follow-up to evaluate the potential use of targeted therapy or immunotherapy. Importantly, no gene fusions were detected in T-ALL patients, suggesting distinct genetic pathways in the pathogenesis of T-ALL compared to B-ALL [16].

Interestingly, two patients exhibited co-occurring gene fusions, a rare observation in pediatric leukemia. These cases involved CBFB-MYH11: BCR-ABL and E2A-PBX: BCR-ABL fusion genes, suggesting potential synergistic or overlapping pathways in leukemogenesis. The CBFB-MYH11: BCR-ABL co-occurring gene fusion was seen in a patient with Mixed Lineage Leukemia (MLL) sharing the biphenotypic characteristics of lymphoid and myeloid phenotypes. The presence of CBFB-MYH11, a fusion more commonly associated with core-binding factor AML, in conjunction with BCR-ABL, typically seen in both CML and Ph+ ALL, suggests an aggressive disease biology with potential lineage plasticity [17, 18]. Clinically, mixed phenotype leukemia (MPAL) patients are known to have poorer outcomes compared to those with lineage-specific leukemias, often due to resistance to conventional therapies and higher relapse rates. The dual presence of AML- and ALL-associated fusions in this case suggests the need for a hybrid therapeutic approach, incorporating both myeloid- and lymphoid-directed regimens, and possibly early consideration for allogeneic hematopoietic stem cell transplantation (HSCT)

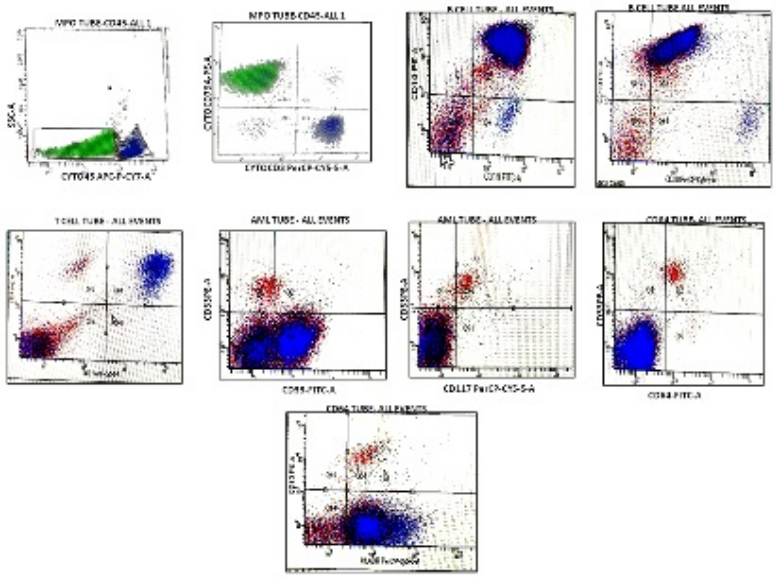


Figure 2: Representative flow cytometry analysis for patient with. B-cell lineage showing CD10/CD19, CD10/CD20, CD79A and HLADR moderate positivity

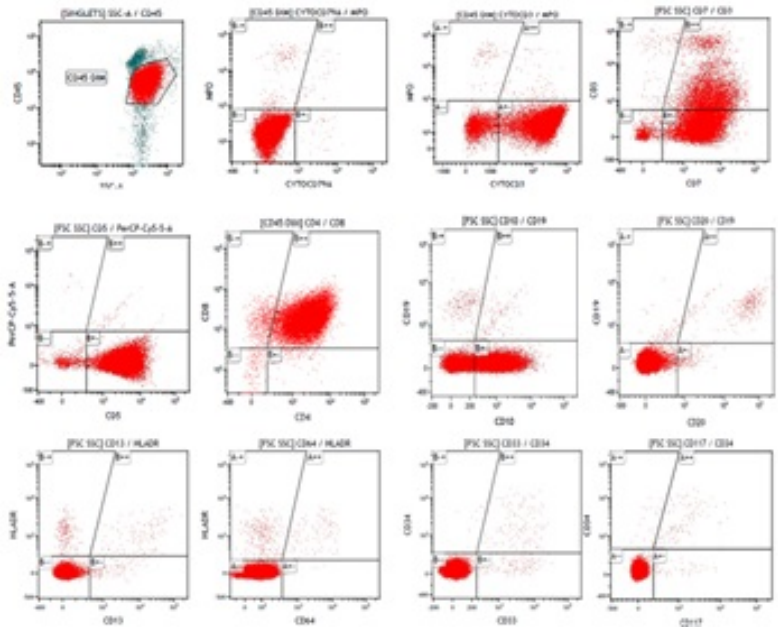


Figure 3: Representative flow cytometry analysis for patient with T-cell lineage acute lymphoblastic leukemia showing CD45DIM, CytoCD3, CD4/CD8, CD7/CD3 showing moderate positive blast cells.

[19]. Furthermore, the detection of BCR-ABL supports the use of tyrosine kinase inhibitors (TKIs), which may improve prognosis when integrated into the treatment plan [20]. This case highlights the importance of thorough immunophenotypic and molecular characterization in ambiguous presentations, such as MPAL, to enable accurate classification and to inform multidisciplinary treatment strategies tailored to complex genetic profiles. This co-occurring mutation has already been reported in AML cases and is found to be associated with an aggressive clinical outcome [17, 18].

Another co-occurring fusion gene, E2A-PBX: BCR-ABL, was seen in a patient with the B-ALL phenotype. Apart from CML, the BCR-ABL gene fusion was also seen in ALL patients, particularly those with the B-ALL subtype. A recent study by Sanjeev Khera reports a 15.8% prevalence of BCR-ABL gene fusion in pediatric B-ALL patients [21]. Additionally, a patient with an MLL gene rearrangement was found to harbor an FLT3 tyrosine kinase domain (TKD) mutation, which is often associated with a poor prognosis. These findings highlight the importance of detecting co-occurring mutations to enable personalized risk stratification and inform treatment planning.

To evaluate the relationship between gene fusion status and clinical parameters, multiple statistical methods were employed, each chosen for its specific analytical strengths. Chi-square tests and multivariate analyses were initially applied to identify

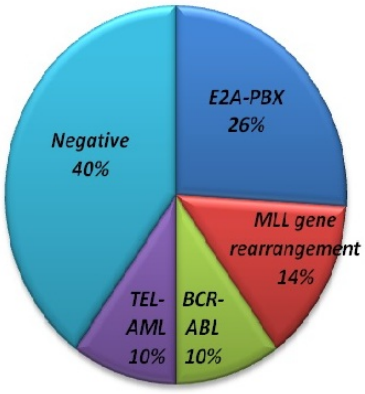
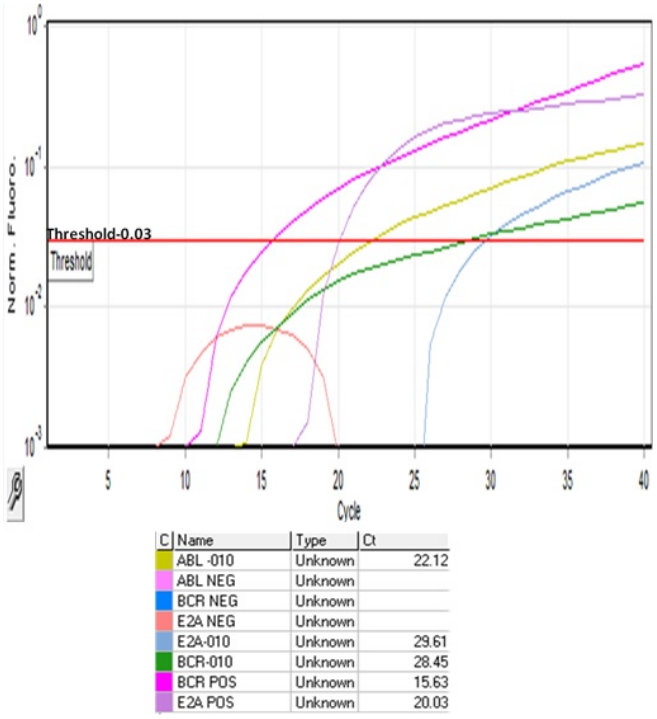


Figure 4: QPCR Acute Leukemia Panel Result showing prevalence of identified gene fusions.



C	Name	Type	Ct
	ABL -010	Unknown	22.12
	ABL NEG	Unknown	
	BCR NEG	Unknown	
	E2A NEG	Unknown	
	E2A-010	Unknown	29.61
	BCR-010	Unknown	28.45
	BCR POS	Unknown	15.63
	E2A POS	Unknown	20.03

Figure 5: QPCR amplification plot for patient with co-occurring BCR-ABL and E2A-PBX1 fusion genes.

broad associations between categorical clinical characteristics (e.g., gender, risk group) and gene fusion status. However, these analyses yielded limited statistically significant results, possibly reflecting the complexity and heterogeneity of the clinical variables.

In contrast, paired-sample t-tests were used to compare continuous variables between patients with and without gene fusions. This approach revealed significant correlations between gene fusion status and both patient age ($p < 0.001$) and blast cell percentage at diagnosis ($p = 0.008$). These findings suggest that patients with gene fusions tend to present at a younger age and with higher blast counts, both of which are clinically relevant markers in hematologic malignancies. Younger age at presentation may be indicative of distinct disease biology, while elevated blast percentages often correlate with more aggressive disease and can influence treatment urgency and risk stratification [19, 22].

Furthermore, a one-way ANOVA was conducted to assess differences in immunophenotypic marker expression across gene fusion groups. The significant result ($p < 0.0001$) indicates that marker expression profiles differ substantially depending on fusion status, underlining the potential for integrating immunophenotyping and molecular data to refine diagnostic and prognostic frameworks.

Despite these insights, the lack of significant associations in multivariate analysis may reflect the complexity of pediatric leukemia, where multiple genetic and environmental factors interact to influence clinical outcomes. The absence of significant correlations between non-parametric variables and gene fusion results suggests that gene fusions may not have a straightforward impact on some clinical parameters.

Conclusion

This study emphasizes the significance of comprehensive immunophenotypic and genetic profiling in pediatric acute leukemia to better understand disease heterogeneity and inform clinical decision-making. In clinical practice, we recommend incorporating routine gene fusion testing using QPCR panels at initial diagnosis to guide risk-adapted therapy, especially in B-ALL patients. Additionally, integrating immunophenotypic profiles with genetic data can support more personalized treatment decisions, such as the early use of targeted therapies or immunotherapy in high-risk or refractory cases. Future multicenter studies with extended follow-up are essential to validate these approaches and to explore the prognostic relevance of rare and co-occurring mutations in pediatric leukemia. Future studies with larger cohorts are warranted to explore the mechanistic roles of gene fusions and co-occurring mutations, and to validate their clinical relevance in pediatric leukemia.

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Conflicts of Interest: There are no conflicts of interest to declare.

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