

The Relationship between Early Clinical Presentation, Laboratory Data, and Minimal Residual Disease of Acute Lymphoblastic Leukemia with Cytogenetic Findings in Children

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ABSTRACT

Background and Objective: Eighty percent of childhood leukemia cases are classified as acute lymphocytic leukemia (ALL), with genetic abnormalities identified in the majority of instances. We conducted an examination of the early clinical manifestations of pediatric ALL and the minimal residual disease (MRD) following treatment with standard cytogenetic testing in children.

Methods: This descriptive and analytical study involved patients diagnosed with ALL who were admitted to three hospitals in Tehran, Iran, from 2020 to 2021. The clinical features assessed included splenomegaly, hepatomegaly, and lymphadenopathy. Laboratory tests conducted comprised complete blood count, lactate dehydrogenase levels, tumor lysis tests, bone marrow aspiration, MRD assessment, and cytogenetic analysis, with a p-value<0.05 considered statistically significant.

Findings: A total of eighty-four patients participated in the study. No significant associations were identified between early splenomegaly, lymphadenopathy, limping, tumor lysis, mediastinal mass, and cytogenetics or MRD. Hepatomegaly was found to correlate with the absence of unfavorable structural mutations, whereas anemia was associated with the presence of mutations. A white blood cell (WBC) count of less than 50,000/ μ l was linked to lower MRD levels, and a platelet count of less than 50,000/ μ l was associated with the del9p21 mutation and unidentified structural mutations ($P<0.05$). Additionally, lactate dehydrogenase (LDH) levels of less than 1000 IU/L were related to unfavorable numerical mutations.

Conclusion: This study found that anemia, a platelet count below 50,000, and LDH levels under 1,000 are significantly associated with mutations and cytogenetic abnormalities. Further controlled studies in this area could be beneficial.

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Introduction

Leukemias account for approximately 30% of childhood cancers, with acute lymphocytic leukemia (ALL) representing a significant 80% of these cases [1]. The World Health Organization (WHO) employs various classification methods for leukemia, one of which is cytogenetic classification [2]. Notably, gene abnormalities can be detected in over 75% of ALL cases, underscoring the genetic complexity of this disease [3]. The cytogenetic findings are crucial, as they significantly influence the prognosis of patients diagnosed with ALL [4].

Numerous researchers have investigated the correlation between various types of leukemia and their associated clinical symptoms, signs, and laboratory findings. However, the specific relationship between early clinical manifestations and cytogenetic factors has not been extensively explored. In this context, the term "early" refers to symptoms that present before the formal diagnosis and the initial circumstances under which the patient seeks medical attention. Understanding this potential relationship could enhance our comprehension of the pathophysiology related to gene abnormalities and the implications of specific mutations. Such insights could ultimately lead to improved diagnostic strategies and more effective treatment options for these patients.

Methods

Study design and participant

This study is descriptive and analytical, conducted on patients diagnosed with ALL who were admitted to the oncology ward of the affiliated hospitals of Tehran University of Medical Sciences, specifically Bahrami Hospital, Valiasr Hospital, and the Children's Medical Center, from 2020 to 2021.

Sampling

All patients admitted with ALL to the oncology ward of the specified centers from 2020 to 2021 who met the inclusion criteria were incorporated into this study. The inclusion criteria are defined as

individuals under the age of 16 years with a confirmed diagnosis established through bone marrow aspiration and flow cytometry. The exclusion criteria include patients with incomplete records, such as early clinical examinations and tests, as well as those for whom cytogenetic diagnostic testing was not conducted.

Data collection

Data from this study, encompassing demographic and medical history information, examination findings, and laboratory parameters, were collected from medical reports by sampling all eligible patient reports from 2020 to 2021.

Demographic and medical history information included age, sex, limb pain, occurrence of seizures, oliguria, and cardiac symptoms. Examination findings included splenomegaly, hepatomegaly, and lymphadenopathy, with hepatomegaly and splenomegaly confirmed by ultrasound. Laboratory parameters encompassed complete blood count (CBC), LDH levels, biochemical tests for tumor lysis syndrome (TLS), bone marrow aspiration, minimal residual disease assessment on the 33rd day of treatment (MRD-33), and cytogenetic results obtained through the conventional cytogenetic G-banding method. Hemoglobin levels below 11 mg/dL were classified as anemia.

Laboratory tumor lysis syndrome (L-TLS) was recorded with the following criteria: serum uric acid levels exceeding normal or a 25% increase compared to baseline, serum phosphorus levels above 6 mg/dl, serum potassium levels exceeding 5 mEq/L, serum calcium levels below 7 mg/dl, and elevated serum urea and creatinine levels above normal. Clinical tumor lysis syndrome (C-TLS) was documented in the presence of oliguria, anuria, arrhythmia, or seizures during admission.

For enhanced analysis, cytogenetic data were categorized into five groups (Table 1) based on prognosis and type of mutations. Regarding the category of "Unspecified-structural mutations (SM)," no association was identified between this mutation and disease prognosis [5].

Statistical analysis

The data were analyzed using SPSS 22. Chi-square tests and independent sample t-tests were employed to compare data between groups. Additionally, the Mann-Whitney test, Pearson correlation test, Spearman correlation test, and Multiple Linear Regression (MLR) were utilized during the analysis. A p-value <0.05 was considered statistically significant.

Table 1. Cytogenetic groups based on prognosis and type of mutations

Mutation Groups	Full names of abbreviations	Mutations found in patients
Unspecified-SM	Unspecified structural mutations	Deletion9p21,T(2,5),Duplication14
Favorable-SM	favorable structural mutations	T(12,21)
Unfavorable-SM	Unfavorable structural mutations	T(9,16), T(10,11), T(1,19), T(17,19), T(4,11), T(6,11), T(6, 9), T(9,22)
Favorable-NM	favorable numerical mutations	Hyperdiploidy,Tetrasomy 21, Trisomy4
Unfavorable-NM	Unfavorable numerical mutations	Trisomy21, Monosomy7

Results

During the study, 99 patients were admitted, of whom 84 underwent cytogenetic testing and were included in the analysis. MRD-33 was not assessed for 8 patients, resulting in their exclusion from the MRD-33-related analyses.

The mean age of the participants was 6.66 ± 3.71 years, ranging from 13 months to 16 years. The cohort consisted of 43 (51.2%) boys and 41 (48.8%) girls. Flow cytometry results indicated that 84.5% of the patients were classified as B cell lineage, while 15.5% were classified as T cell lineage.

Cytogenetic results revealed that approximately 66.7% of the patients exhibited no chromosomal abnormalities (normal cytogenetics). The most

prevalent mutations identified were translocation (12;21) and deletion 9p21, with frequencies of 10.7% and 9.5%, respectively (see Figure 1). The mutation t(12;21) was the most common, occurring with a frequency of 14% in girls, while deletion 9p21 was observed with a frequency of 7.8% in boys.

Findings with no significant relationship indicate that approximately 62% and 12% of the patients presented with splenomegaly and lymphadenopathy, respectively. Additionally, 33%, 25%, 26%, and 10% of the patients exhibited limping, L-TLS, C-TLS, and mediastinal widening on chest X-ray, respectively. There was no significant association identified between early lymphadenopathy, limping, L-TLS, C-TLS, mediastinal mass, and any specific mutation, group of mutations, or MRD-33.

Regarding hepatomegaly, 20% of the patients were diagnosed with this condition. No significant association was found between early hepatomegaly and any specific mutation or MRD-33. However, a significant relationship was observed between unfavorable structural mutations (Unfavorable-SM) and hepatomegaly (Table 2). Approximately 76% of the patients with hepatomegaly did not possess these mutations ($p = 0.028$). Conversely, for other mutations, the relationship was not significant.

Anemia: Approximately 90% of the patients presented with anemia. No significant correlation was found between early anemia and any specific mutation or MRD-33. However, anemia was significantly more prevalent in patients with mutations compared to those with normal cytogenetics (100% versus 84%, respectively; $P=0.025$) (Table 2).

Leukocytosis: About 21% of the patients exhibited a WBC count exceeding 50,000/ μ l, while 79% had a WBC count below this threshold. There was no significant relationship between early WBC count and any specific mutation or group of mutations. A significant correlation was observed between early WBC count and MRD-33 (Table 3). Patients with a WBC count below 50,000/ μ l were associated with lower MRD-33 values ($p=0.037$). Approximately 66% of patients with a WBC count below 50,000/ μ l had MRD-33 <0.01, in contrast to

about 35% of patients with a WBC count exceeding 50,000/ μ l who had MRD-33 <0.01.

Thrombocytopenia was observed in approximately 55% of patients, who exhibited a platelet count greater than 50,000/ μ l, while 38 patients (45%) had a platelet count below 50,000/ μ l. The deletion of the 9p21 mutation was significantly correlated with a platelet count of less than 50,000/ μ l (Table 4). Notably, all patients with the deletion of 9p21 had platelet counts below 50,000/ μ l, in contrast to 48% of patients without this deletion ($p=0.006$). Furthermore, a significant association was identified between early platelet counts below 50,000/ μ l and unspecified structural mutations (Table 2), with 90% of patients exhibiting these mutations having platelet counts below 50,000/ μ l ($p=0.025$). However, no significant association was found between early thrombocytopenia and the group of mutations or MRD-33.

Serum LDH levels were observed, with approximately 21%, 46%, and 32% of patients exhibiting LDH levels of <500 IU/L, between 500-1000 IU/L, and >1000 IU/L, respectively. No significant correlation was found between LDH

levels and any specific mutation or MRD-33. However, a relationship was noted between early LDH levels and unfavorable NM (Table 2). All patients with these mutations had LDH levels <1000 IU/L, whereas 64% of patients without these mutations had LDH levels <1000 IU/L ($p=0.018$). Furthermore, 72% of patients with LDH levels >1000 IU/L did not present with any mutations ($p=0.044$).

Regarding MRD-33, we investigated the relationship between cytogenetics and MRD-33. A correlation was identified between the group of mutations and MRD-33 (see Table 2). Specifically, 71% and 80% of patients with Unspecified-SM and Unfavorable-SM, respectively, had MRD-33 >0.01 ($p=0.007$ and $p=0.001$, respectively). Additionally, 77% of patients without mutations (normal cytogenetics) had MRD-33 ≤ 0.01 , while 62% of patients with any mutations had MRD-33 ≤ 0.01 . Notably, 74% of patients with MRD-33 ≤ 0.01 had normal cytogenetics, in contrast to 57% of patients with MRD-33 ≥ 0.01 who also had normal cytogenetics ($p=0.048$).

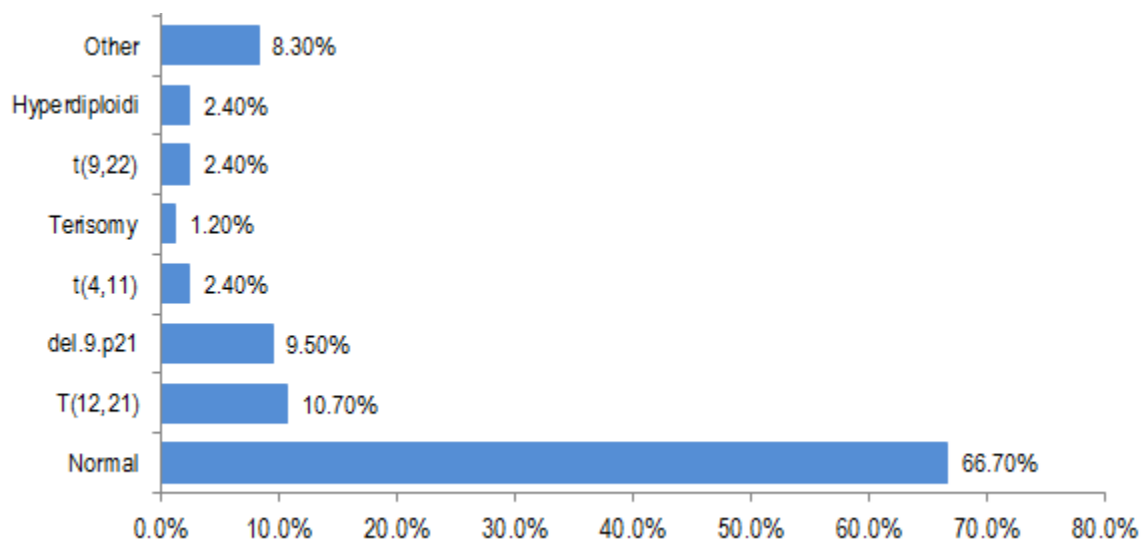


Figure 1. Mutations frequency of this study

Table 2. Frequency of early hepatomegaly, anemia, thrombocytopenia, serum LDH levels, and MRD-33 in patients with ALL, categorized according to the classification of mutations

Mutations groups			Normal		Favorable-SM*		Unfavorable-SM		Unspecified-SM		Favorable-NM**		Unfavorable-NM	
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Hepatomegaly	Yes	N(%)	11(18)	6(21.4)	1(11.1)	16(21.3)	4(50)	13(17.1)	1(11.1)	16(21.3)	0	17(21.0)	1(25)	16(20)
	No	N(%)	45(80.4)	22(78.6)	8(88.9)	59(78.7)	4(50)	63(82.9)	8(88.9)	59(78.7)	3(100)	64(79.0)	3(75)	64(80)
	p-value		0.84		0.47		0.028		0.47		0.37		0.8	
anemia	Yes	N(%)	47(83.9)	28(100)	9(100)	66(88)	8(100)	67(88.2)	9(100)	66(88)	3(100)	72(88.9)	4(100)	71(88.8)
	No	N(%)	9(16.1)	0	0	9(12)	0	9(11.8)	0	9(12)	0	9(11.1)	0	9(11.3)
	p-value		0.025		0.27		0.3		0.27		0.54		0.47	
platelet	<50000	N(%)	5(44.6)	20(71.4)	6(66.7)	39(52.0)	4(50)	41(53.9)	8(88.9)	37(49.3)	2(66.7)	43(53.1)	3(75)	42(52.5)
	>50000	N(%)	31(55.4)	8(28.6)	3(33.3)	36(43.0)	4(50)	35(46.1)	1(11.1)	38(50.7)	1(33.3)	38(46.9)	1(25)	38(47.5)
	p-value		0.02		0.4		0.83		0.025		0.64		0.37	
LDH	<500	N(%)	7(12.5)	10(35.7)	2(22.2)	15(20)	3(37.5)	14(18.4)	4(44.4)	13(17.3)	1(33.3)	16(19.3)	3(75)	14(17.5)
	500-1000	N(%)	28(50)	10(35.7)	5(55.6)	33(44)	2(25)	36(47.4)	2(22.2)	36(48)	2(66.7)	36(44.4)	2(25)	37(46.3)
	>1000	N(%)	21(37.5)	8(28.6)	2(22.2)	27(36)	3(37.5)	26(34.2)	3(33.3)	26(34.7)	0	29(38.8)	0	29(36.3)
	p-value		0.044		0.7		0.34		0.12		0.43		0.018	
MRD-33	0-0.01	N(%)	35(66)	11(47.8)	8(88.9)	38(56.7)	1(20)	45(63.4)	0	46(66.7)	1(33.3)	45(61.6)	2(100)	44(59.5)
	0.01	N(%)	6(11.3)	3(13.7)	1(11.1)	8(11.9)	0	9(12.7)	2(28.6)	7(10.1)	1(33.3)	8(11.0)	0	9(12.2)
	0.01-1	N(%)	12(22.6)	6(26.1)	0	18(26.9)	2(40)	16(22.5)	4(57.1)	14(20.3)	1(33.3)	17(23.3)	0	18(24.3)
	>1	N(%)	0	3(13)	0	3(4.5)	2(40)	1(1.4)	1(14.3)	2(2.9)	0	3(4.1)	0	3(4.1)
	p-value		0.048		0.24		<0.001		0.007		0.6		0.72	

* Structural mutations

** Numerical mutations

Table 3. Frequency of early leukocytosis groups in patients with ALL is assessed according to the MRD-33.

MRD-33	WBC Count		P-Value
	>50000	<50000	
0-0.01	6(37.5%)	40(66.7%)	0.037
0.01	4(25.0%)	5(8.3%)	
0.01-1	4(25.0%)	14(23.3%)	
>1	2(12.5%)	1(1.7%)	

Table 4. Frequency of early thrombocytopenia groups in patients with ALL is analyzed based on cytogenetics and the classification of mutations

Cytogenetic		Platelet		P-Value
		<50000	>50000	
T(12,21)	Yes	6(66.7%)	3(33.3%)	0.4
	No	39(52%)	36(48%)	
Del.9p21	Yes	3(100%)	0	0.006
	No	37(48.7%)	39(51.3%)	
t(4.11)	Yes	1(50%)	1(50%)	0.91
	No	44(53.7%)	38(46.3%)	
Trisomy-21	Yes	1(100%)	0	0.34
	No	44(53%)	39(47%)	
t(9,22)	Yes	1(50%)	1(50%)	0.91
	No	44(53.7%)	33(46.3%)	
Hyperdiploidi	Yes	2(100%)	0	0.18
	No	43(52.4%)	39(47.6%)	
Other	Yes	3(42.9%)	4(57.14%)	0.55
	No	46(54.5%)	35(45.5%)	

Discussion

The primary objective of this study was to examine the relationship between the initial clinical presentation (signs and symptoms) and laboratory findings concerning the cytogenetics of patients diagnosed with ALL. The findings of the present study indicated that the mean age and sex distribution of patients, as well as the flow cytometry results (B/T cell type) of the disease, were consistent with those reported in other studies [6, 7]. However, regarding cytogenetics, 56 (66.7%) of patients exhibited normal cytogenetics, which was slightly higher than that reported in other studies [6-8]. Concerning clinical presentations, the current study revealed no significant differences in frequencies compared to previous research. Specifically, we report the frequencies of splenomegaly, hepatomegaly, limping, L-TLS, C-TLS, anemia (Hb<11 g/dl), hyperleukocytosis (WBC count>50,000/ μ l), thrombocytopenia (platelet count<50,000/ μ l), and elevated LDH levels (greater than 1000 IU/L) in the ongoing study, which were approximately 62%, 20%, 33%, 25%, 26%, 90%, 21%, 45%, and 32%, respectively. These findings were comparable to those in other studies: splenomegaly (58-73%) [9-11], hepatomegaly (20-78%) [9-11, 17], limping (21-59%) [10, 11], TLS (12-28%) [13, 14], anemia (83-88%) [9, 11], Hyperleucocytosis (20%) [9],

thrombocytopenia (33-87%) [9] and LDH level (41-66%) [23]. The only exception was lymphadenopathy; in the present study, 12% of patients had lymphadenopathy, which was lower than the incidence reported in other studies (41-83%) [9-11].

Settin et al. demonstrated that splenomegaly in leukemic patients has no relationship with treatment response, which aligns with the findings of the present indicating no relationship with MRD [12]. There was no significant relationship between early clinical/laboratory TLS and cytogenetics. Al-Bagshi and Naeem reported that the incidence of TLS before treatment is associated with late diagnosis and a poorer prognosis [13, 14]; however, in the current study, no significant relationship with MRD was observed. Ten percent of patients exhibited mediastinal widening on chest X-ray, which is consistent with findings from other studies (10-20%)(15). There was no significant relationship between mediastinal mass and cytogenetics. According to Attarbaschi, mediastinal mass is not necessarily associated with a poor prognosis [16], and in the present study, no relationship with MRD-33 was found.

Approximately 76% of patients exhibiting hepatomegaly did not present with Unfavorable-SM, indicating that these mutations are often not associated with hepatomegaly. Research on the cytogenetic relationship between these mutations and hepatomegaly is limited. Johnson noted that there was no significant relationship between the abnormality of chromosome 21 and the presence of hepatomegaly or lymphadenopathy in patients with ALL [18]. Similarly, Schlieben demonstrated a lack of correlation between the t (9;22) mutation and the occurrence of hepatomegaly and splenomegaly [19].

Regarding anemia, the prevalence of anemia in patients with mutations was significantly higher than in those without mutations, indicating a meaningful association between anemia and mutations. However, studies examining the relationship between cytogenetics and anemia are limited. Teuffel reported that lower hemoglobin levels are associated with poorer prognosis [20]; however, no relationship was found between hemoglobin levels and MRD in the current study.

Reddy demonstrated that an early WBC count does not correlate with disease survival [8]. However, in the present study, patients with a WBC count of $<50,000/\mu\text{l}$ were associated with a lower MRD-33, indicating a better prognosis. Similar findings were reported in acute myeloid leukemia (AML) patients; Ghafoor noted that individuals with a WBC count of $<50,000/\mu\text{l}$ have a five-year survival rate that is twice as high [21].

The deletion of the 9p21 mutation was significantly associated with a platelet count of $<50,000/\mu\text{l}$. Similarly, Unspecified-SM were correlated with a platelet count of $<50,000/\mu\text{l}$, likely due to the presence of the deletion 9p21 mutation within this gene group. The current study indicated that this mutation did not exhibit a specific prognostic value, warranting further investigation. Gendi's research demonstrated that the deletion 9p21 mutation was not associated with platelet count; however, it was linked to a WBC count exceeding $50,000/\mu\text{l}$ and a poorer prognosis [22].

An LDH level of less than 1000 IU/L has been associated with Unfavorable-NM. Additionally, the present study revealed that the majority (72%) of patients with an LDH level exceeding 1000 IU/L exhibit normal cytogenetics ($p=0.044$). Several studies have indicated a correlation between elevated LDH levels and poor prognosis. Shaimaa demonstrated that a high LDH level is linked to high-risk disease, particularly in patients aged over 10 years or with a WBC count of $\geq 50,000/\mu\text{L}$ [24].

In the ongoing study; however, no significant relationship was observed between LDH levels and MRD-33. Unspecified-SM and Unfavorable-SM were associated with MRD-33 at a significance level greater than 0.01. This finding was anticipated within the unfavorable-SM group (characterized by unfavorable mutations correlating with higher MRD-33 levels). In contrast, the implications of Unspecified-SM (including deletion 9p21) require further investigation, as prior studies have not established a definitive relationship with the prognosis of these mutations. Additionally, a significant relationship was identified between

patients exhibiting normal cytogenetics and MRD-33 levels below 0.01, indicating a better prognosis.

These findings suggest that patient cytogenetics can be assessed based on the initial clinical presentation, which is valuable when cytogenetic testing is unavailable. We recommend further molecular cell studies to understand how these mutations affect the body, potentially leading to improved diagnostics and treatments.

Limitations

A limitation encountered in the present study was the refusal of numerous patients to undergo genetic testing due to the associated high costs, resulting in incomplete data files. Consequently, these patients were excluded from the study.

Conclusion

CBC test findings showed a correlation with cytogenetics. Anemia was associated with a mutation. A WBC count below $50,000/\mu\text{l}$ correlated with a lower MRD-33, suggesting a better prognosis. Unspecified-SM, including deletion 9p21, was linked to a platelet count below $50,000/\mu\text{l}$ and a higher MRD-33, indicating a worse prognosis. Decreased serum LDH levels were related to Unfavorable numerical mutations. Normal cytogenetics were associated with lower MRD-33 (better prognosis), reduced LDH levels, and a platelet count above $50,000/\mu\text{l}$.

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Ethical Consideration:

Patient information was collected anonymously from files. Participation in the study did not affect subsequent treatments, and no intervention was performed.

Ethics code: [IR.TUMS.CHMC.REC.1400.163](https://ir.tums.chmc.rec.1400.163)

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Conflict of Interest

All authors declare no competing interests related to this manuscript, ensuring the research is free from biases or conflicts that could influence the findings.

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