

# Cytogenetics and Molecular Abnormalities in Pediatric Patients with Acute Myeloid Leukemia in a Referral Center in Tehran, Iran

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## Abstract

**Background:** Acute myeloid leukemia (AML) accounts for 15%-20% of childhood leukemia. A variety of cytogenetic abnormalities have been reported in AML, but it is still debated how these alterations affect patient survival and outcome. We aimed to evaluate the cytogenetic abnormalities of pediatric AML in association with prognosis.

**Method:** In this retrospective cross-sectional study, 46 cases of pediatric AML, diagnosed using French-American-British (FAB) criteria, admitted to a referral center during 2018-2023, who had not yet received chemotherapy, were included. Patients were evaluated for cytogenetic alterations by bone marrow karyotyping and polymerase chain reaction molecular methods. Patients were followed up to evaluate overall survival and recurrence-free survival. Data were analyzed using SPSS software version 23 and chi-square, Mann-Whitney, t-test and Kaplan-Meier tests.  $P < 0.05$  was considered significant.

**Results:** Totally, 19 of 46 (41.3%) patients showed cytogenetic abnormalities. The prevalence of numerical and structural abnormalities was 23.9% and 28.3%, respectively. The most common numerical changes included monosomy 7, loss of chromosome Y, and trisomy 21, as order. The most common structural variants included  $t(v;11)$ ,  $t(15;17)$ ,  $t(8;21)$  and  $del(7q)$ . Those with  $t(8;21)$  and  $t(15;17)$  or absence of cytogenetic abnormalities had a lower recurrence and death rate as compared with those with unfavorable cytogenetic abnormalities ( $P = 0.007$  and  $P = 0.002$  respectively). White blood cell count was significantly lower in patients with numerical cytogenetic abnormalities than those without.

**Conclusion:** Cytogenetic abnormalities were rather common in pediatric AML. Monosomy 7/ $del(7q)$  and chromosome 11 alteration were the most common cytogenetic abnormalities. Presence of abnormalities, other than those known as favorable, were associated with worse survival.

**Keywords:** Acute myeloid leukemia, Cytogenetics, Survival, Prognosis, Pediatrics

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## Introduction

Acute myeloid leukemia (AML), both clinically and genetically, exhibits a diverse range of characteristics, rendering it a multifaceted condition that encompasses 15%-20% of all forms of pediatric leukemia. It can either occur de novo or originate from a pre-existing myelodysplastic syndrome within the pediatric population.<sup>1</sup> Recently, the overall five-year survival of AML patients has been increased (from 30% to about 65%).<sup>2,3</sup> Various factors, including the classification of high-risk groups of patients based on cytogenetic characteristics and targeted therapies, have been responsible for this improvement in the disease prognosis.<sup>4, 5</sup> However, about half of the patients still face disease recurrence and sometimes death, which is due to various reasons or related to some cytogenetic characteristics in these patients.<sup>6</sup> Therefore, it seems that accurate identification of prognostic markers is necessary for early detection of high-risk groups prone to relapse, and determining an effective and safe treatment approach. Several prognostic factors have been identified in previous studies, including factors related to the host, or the treatment response, the characteristics of the disease itself and the cytogenetic characteristics of the disease.<sup>7</sup> Today, the cytogenetic analysis is widely regarded as an important component of prognostic investigations in leukemia, particularly AML.

Genomic studies have highlighted the molecular alterations of pediatric AML, including those that activate oncogenes or inhibit tumor suppressor genes. Certain gene rearrangements, such as PML-RARA, RUNX1-RUNX1T1, CBFB-MYH11 A and ETV6-RUNX1 fusion are frequently observed in AML and contribute to its tumorigenesis.<sup>8</sup> These mutations can either interfere with normal bone marrow cell differentiation or promote uncontrolled cell proliferation. The PML-RARA fusion prevents the activation of the P53 tumor suppressor pathway, which normally induces cell senescence in response to stress, thus inhibits cell death and blocks myeloid differentiation at early stages.<sup>9</sup> The RUNX1/RUNX1T1 oncogene fusion encodes

an aberrant transcriptional factor involved in the regulation of alternative RNA splicing, which mediates the leukemogenesis.<sup>10</sup> Identification of cytogenetic abnormalities in children with AML is essential, because about 70 to 85% of patients have some degrees of clonal chromosomal abnormalities.<sup>11,12</sup> These abnormalities involve the number of chromosomes, the structure of chromosomes (including types of translocations, chromosomal deletion or inversions) or both categories. Specific cytogenetic rearrangements related to certain morphological subtypes are now acknowledged as significant parameters for diagnostic, prognostic, and follow-up purposes.<sup>13</sup> The identification of prognostic chromosomal rearrangements plays a great role in the accurate categorization of pediatric patients with AML into French-American-British (FAB) or World Health Organization (WHO) subgroups. This categorization enables grouping based on favorable, intermediate, or unfavorable risk groups, as well as the application of appropriate treatment protocols. Patients with cytogenetic features t(8;21), t(15;17) and inv(16) are considered as low risk level 12 and patients in high risk classification can include patients with cytogenetic features del(5q), del(7q), patients with complex karyotype (presence of  $\geq 3$  independent chromosomal abnormalities).<sup>14</sup> Recently, it has been demonstrated that in addition to background factors, cytogenetic factors can also serve as predictive indicators for the limited lifespan of patients. Patients' pretreatment karyotype (chromosomal rearrangements with known or unknown prognosis) is an independent prognostic factor, while additional chromosomal abnormalities can indicate the prognosis of the disease during the course. The study of chromosomal abnormalities also provides the possibility of classifying the severity of the disease. Therefore, it is possible to predict adverse events in the leukemogenesis process.<sup>15, 16</sup> In most cases, investigation of molecular alterations and study of genes located at chromosomal breakpoints facilitates the recognition of proteins implicated in the molecular pathogenesis of leukemia.<sup>17</sup>

Understanding the role of these proteins is

**Table 1.** Demographic, clinical and laboratory characteristics of the study participants

Variable	Mean ± SD	No. (%)	Variable	Mean ± SD	No. (%)
Age (Years)	8.29 ± 5.11		WBC count	32.08 ± 47.18	
Sex			Hemoglobin level	8.55 ± 1.68	
Male		28 (60.9)	Platelet count	55.56 ± 41.91	
Female		18 (39.1)	PB blasts (%)	36.37 ± 31.07	
Clinical symptoms			BM blasts (%)	60.57 ± 25.10	
Fever		23 (50)	AML subtypes*		
Weight loss		22 (47.8)	AML without maturation		3 (6.5)
Bone pain		18 (39.1)	AML with maturation		14 (30.4)
Organomegaly		10 (21.7)	APML ± PML:: RARA fusion		10 (21.7)
Skin and lip bruises		10 (21.7)	AMML		4 (8.7)
Bleeding gum		4 (8.7)	Acute monocytic leukemia		3 (6.5)
Headache		4 (8.7)	Acute erythroid leukemia		2 (4.3)
Vomiting		1 (2.2)	Acute megakaryoblastic leukemia		10 (21.7)
Recurrence			Survival		
Yes		18 (40)	Dead		21 (46.7)
No		27 (60)	Alive		24 (53.3)

\* According to the 5<sup>th</sup> edition of the World Health Organization Classification of Hematolymphoid Tumors; WBC: White blood cells; PB: Peripheral blood; BM: Bone marrow; APML: Acute promyelocytic leukemia; RARA: Retinoic acid receptor alpha; AMML: Acute myelomonocytic leukemia; AML: Acute myeloid leukemia; No.: Number

crucial to explore novel therapeutic approaches that are more specific and have fewer side-effects. The significance of cytogenetic observations played a significant role in the update of the WHO classification of AML in 2008 (primarily relying on cytogenetics), resulting in the inclusion of a subgroup of AML characterized by recurring genetic abnormalities. In addition, some specific molecular cytogenetic abnormalities recurrent in this subgroup of AML are employed for the diagnosis of AML, irrespective of the percentage of peripheral blood or bone marrow blasts.<sup>16</sup> Furthermore, cytogenetic methodologies have also been recently used for this purpose. Fluorescence in situ hybridization (FISH) may be used as a complementary method to detect subtler chromosomal abnormalities such as *inv(16)*, *t(11q23)*. Interphase FISH is also a valuable diagnostic tool in certain conditions. Comparative genomic hybridization (CGH) technique is also considered in situations to follow up the patient's genomic disorder. The classification of cytogenetic characteristics of children's AML includes various chromosomal numerical and structural changes to normal karyotype.

In addition to the various cytogenetic abnormalities, in some cases, we are also faced with the occurrence of complex karyotypes, which are associated with a bad prognosis of the disease.

The frequency of such karyotypes in children's AML is far less than that of single mutation cases, and these karyotypes are far more common than adults.<sup>18</sup> Most of these karyotype abnormalities have been observed in children under three years of age.

Currently, cytogenetic analysis has a promising predictive role in the prognosis of pediatric AML. Given the prognostic role of cytogenetic abnormalities in pediatric AML and the lack of research in Iranian pediatric population, the present study aimed to investigate cytogenetics alterations, and determine its prognostic role in Iranian pediatric AML.

## Materials and Methods

This was a retrospective cross-sectional study, conducted on 46 children with AML referred to Children's Medical Center Hospital, Tehran, Iran, between 2018 and 2023. The participants included patients whose diagnosis was confirmed based on FAB diagnostic criteria, morphologic and immunophenotype examination, not undergoing chemotherapy up to the time of testing. This study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences (No.: IR.TUMS.CHMC.REC.1400.074).

Demographic characteristics of the patients, including age, sex, and clinical symptoms, were collected by reviewing the patients' records.

**Table 2.** Frequency of numerical and structural chromosomal abnormalities in the studied patients

Numerical abnormalities	No. (%)	Structural abnormalities	No. (%)
45,XX,-7/45,XY,-7 (monosomy 7)	3 (6.5)	t(15;17)(q24;q21)	2 (4.3)
45,X (loss of chromosome 7)	2 (4.3)	t(8;21)(q22;q22)	2 (4.3)
47,XX,+21 (trisomy 21)	2 (4.3)	del(7)(q22)	2 (4.3)
45,XY,-5 (monosomy 5)	1 (2.2)	t(1;11)(q32;q13)	1 (2.2)
47,XX,+22 (trisomy 22)	1 (2.2)	t(7;17)(p10;p10)	1 (2.2)
47,XY,+11 (trisomy 11)	1 (2.2)	t(12;17)(p13;12)	1 (2.2)
48,XX,+6,+19 (trisomy 6 and 19)	1 (2.2)	t(9;11)(p22;q23)	1 (2.2)
		t(2;11)(p21;q14)	1 (2.2)
		t(1;22)(q10;q10)	1 (2.2)
		t(3.8)(q26;q24)	1 (2.2)

No.: Number

Laboratory information including the number of white cells, hemoglobin level, platelet count, percentage of peripheral blood and bone marrow blasts, and occurrence of relapse in the course of the disease were checked from the Hospital information system (HIS). The survival rate was investigated by reviewing patients' clinical records and phone follow-up, if necessary. Numerical chromosomal abnormalities were determined according to results of bone marrow karyotype. Structural abnormalities including chromosomal translocations, inversions, deletions, etc. were determined using cytogenetics and/or real-time polymerase chain reaction (PCR) molecular method.

#### *Karyotyping*

For cytogenetic analysis of bone marrow, based on bone marrow aspirate (BMA) white blood cell (WBC) count, appropriate amount (0.25-1 ml) of heparinized BMA was added to 10 cc of RPMI (to contain about  $10^6$  hematopoietic cells/cc). After 4 hours of incubation at 37°C, uridine and 5-fluorodeoxyuridine were added for synchronization.<sup>19</sup> After 17 hours of incubation, 100 µL thymidine was added and incubated for 5 hours. Then, 70 µL colcemid was added for harvest.<sup>20</sup> Finally, the fixed slides were stained by Giemsa banding method and 20 metaphases were photographed and analyzed and reported according to an International System for Human Cytogenomic Nomenclature 2020 (ISCN).

#### *Real-time PCR molecular testing*

RNA was extracted from BMA specimen using QIAamp RNA Blood Mini Kit and complementary DNA (cDNA) was synthesized

using AmpliSens reverse transcription kit according to the manufacturer's instructions. Real-time PCR was performed to detect commonly occurring molecular alterations in AML including t(8;21) (RUNX1-RUNX1T1, inv(16) (CBFB-MYH11 A), t(15;17) (PML RARA-bcr1, bcr2, bcr3), t(9;22) (BCR ABL Mbc, mbc), t(12;21) (ETV6-RUNX1), t(1;19) (E2A-PBX1) and t(4;11) (MLL-AF4) using Qiagen real-time PCR Kits and light Cyclor 96 instrument for detection of these fusion gene transcripts in bone marrow leukemic cells. Control gene (ABL) expression was performed in parallel to ensure absence of PCR inhibitors.

#### *Statistical analysis*

According to the type of cytogenetics abnormalities, the patients were classified into favorable/normal and unfavorable groups, and were compared in terms of survival and recurrence. We considered t(v;11), -7, -5, del(7q) and other cytogenetic abnormalities not classified as favorable or adverse (intermediate cytogenetic abnormalities) as unfavorable, and t(8;21), t(15;17), inv(16) and cytogenetically normal cases as favorable/normal group according to Quessada et al.<sup>21</sup> The data were analyzed using SPSS software version 23. The categorical data were analyzed based on chi-square analysis and reported as frequency and percentages. Quantitative variables were analyzed either by t-test, if they followed a normal distribution or Mann-Whitney test, if they did not have a normal distribution. Kaplan-Meier curve analysis was used to evaluate the survival of patients. *P* value less than 0.05 was considered significant.

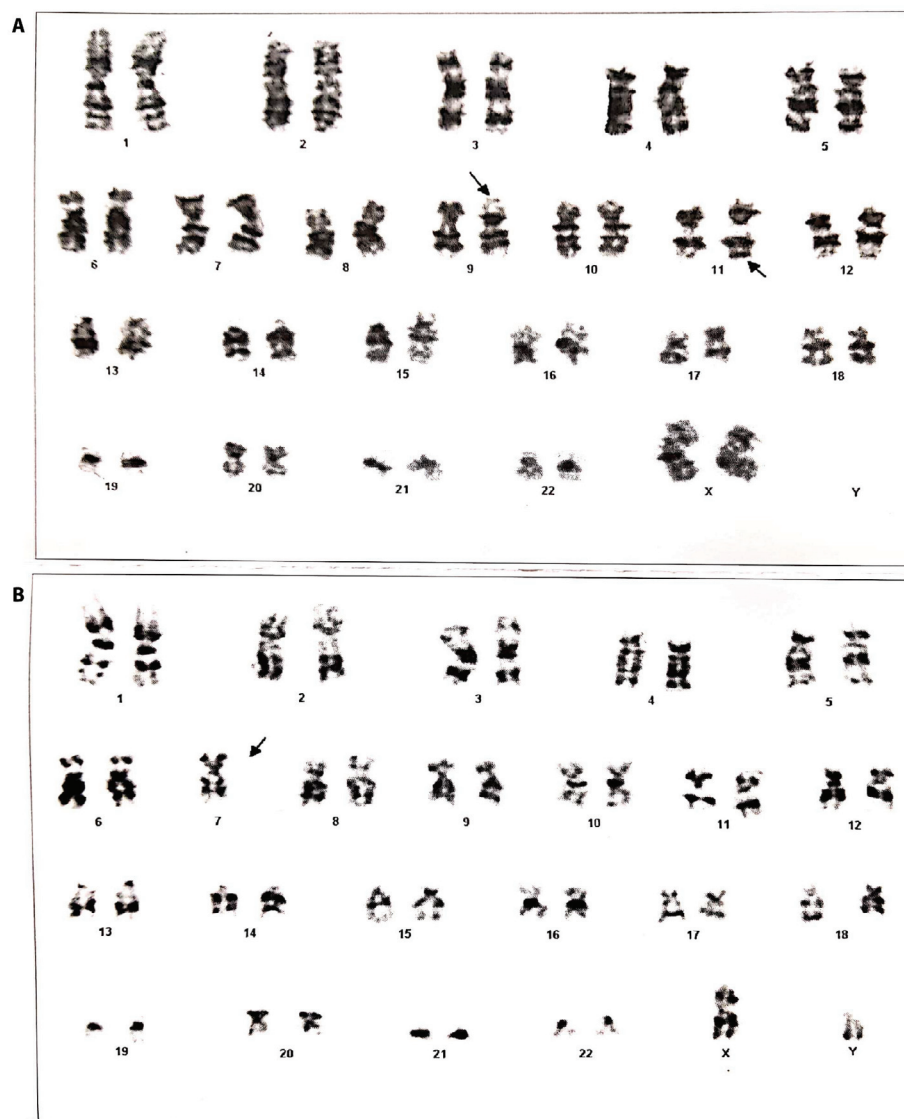


## Results

A total of 46 patients with AML were included in the study. The most common clinical manifestations included fever in 23 (50%), weight loss in 22 (47.8%), and bone pain in 18 (39.1%) cases. The most common AML subtypes according to the 5<sup>th</sup> edition of the WHO classification of hematolymphoid tumors<sup>22</sup> included AML with maturation in 14 cases (30.4%), acute promyelocytic leukemia in 10 cases (21.7%) and acute megakaryoblastic leukemia in 10 cases (21.7%). Table 1 shows the

clinical and laboratory findings of the patients.

Cytogenetic abnormalities were observed in 19 out of 46 (41.3%) cases, including 11 cases (23.9%) with numerical, and 13 cases (28.3%) with structural abnormalities. AML with maturation subtype showed the highest prevalence of numerical (54.5%) and structural (38.5%) cytogenetic abnormalities among all AML subtypes. About 13.9% of patients had both numerical and structural abnormalities on karyotype. Among those with numerical abnormalities, 6 cases (13.2%) showed loss of



**Figure 1.** Karyotype analysis of bone marrow specimen from two pediatric patients with acute myeloid leukemia is shown in metaphase spread of blastic cells; A. karyotyping from bone marrow metaphase cells shows structural abnormality, 46, XX, t(9;11)(p22;q23) (marked by arrows). B. Karyogram of the bone marrow leukemic cell in a patient with numerical chromosomal abnormality (monosomy 7) is shown (45, XY, -7).

**Table 3.** Comparison of clinicopathologic characteristics between patients with and without numerical chromosomal abnormalities

Variable	Without abnormality	With abnormality	P Value
Age (Mean ± SD)	7.61 ± 5.14	10.45 ± 4.61	0.109
<b>Gender</b>			0.296
Male	23 (82.1)	5 (17.9)	
Female	12 (66.7)	6 (33.3)	
<b>Clinical signs</b>			
Fever	17 (48.6)	6 (54.5)	0.730
Weight loss	17 (48.6)	5 (45.5)	0.999
Bone pain	13 (37.1)	5 (45.5)	0.622
Organomegaly	8 (22.9)	2 (18.2)	0.743
Bruising of skin and lips	6 (17.1)	4 (36.4)	0.220
Bleeding from gums	4 (11.4)	0 (0)	0.559
Vomiting	1 (2.9)	0 (0)	0.999
Headache	3 (8.6)	1 (9.1)	0.999
<b>WBC count</b>	40.19 ± 9.70	8.56 ± 2.77	0.004
<b>Hemoglobin level</b>	8.42 ± 1.84	8.94 ± 1.10	0.412
<b>Platelet count</b>	55.69 ± 46.10	55.20 ± 28.33	0.412
<b>PB blasts (%)</b>	36.80 ± 33.59	35.30 ± 25.22	0.900
<b>BM blasts (%)</b>	61.70 ± 26.06	57.18 ± 22.80	0.611
<b>AML subtypes, by differentiation*</b>			0.251
AML without maturation	3 (8.6)	0 (0)	
AML with maturation	8 (22.9)	6 (54.5)	
APML ± PML::RARA fusion	10 (28.6)	0 (0)	
AMML	3 (8.6)	1 (9.1)	
Acute monocytic leukemia	2 (5.7)	1 (9.1)	
Acute erythroid leukemia	2 (5.7)	0 (0)	
Acute megakaryoblastic leukemia	7 (20)	3 (27.3)	

\* According to the 5<sup>th</sup> edition of the World Health Organization Classification of Hematolymphoid Tumors; WBC: White blood cells; PB: Peripheral blood; BM: Bone marrow; APML: Acute promyelocytic leukemia; RARA: Retinoic acid receptor alpha; AMML: Acute myelomonocytic leukemia; AML: Acute myeloid leukemia

chromosome (monosomy) and 5 cases (10.7%) showed gain of chromosome (trisomy or polysomy). The most common types of numerical abnormalities included monosomy 7, loss of chromosome Y, and trisomy 21, respectively. The most common structural aberrations included translocations t(v;11), t(15;17)(q24,q21), t(8;21)(q22,q22) and del (7q). Overall, the most common cytogenetic abnormalities were chromosome 7 and chromosome 11 alterations (Figure 1). Five out of 46 patients (10.8%) had chromosome 7 abnormalities, including 3 patients with monosomy 7 and two patients with del(7q). Four cases (8.8%) showed chromosome 11 alterations, including three cases with t(v;11) and one case of trisomy 11. The observed structural and numerical cytogenetic abnormalities of the studied patients are listed, in order of prevalence, in table 2.

The average WBC count was significantly lower in the group with numerical cytogenetic abnormalities (8.56 ± 2.77 versus 40.19 ± 9.70, respectively,  $P = 0.004$ ). In patients with and

without structural abnormalities, the mean WBC count was not significantly different between the two groups ( $P = 0.246$ ). The mean age, sex distribution and the frequency of clinical symptoms did not show a significant difference in the patients with and without numerical or structural abnormalities. The mean hemoglobin level, average platelet count, and average blood and bone marrow blast percentage were not significantly different between patients with and without numerical or structural cytogenetic abnormalities. The relationship between cytogenetic abnormalities and the underlying characteristics of the patients and their clinical symptoms is shown in tables 3 and 4, respectively.

The frequency of mortality or recurrence did not show any significant difference in patients with and without numerical or structural cytogenetic abnormalities. The relationship between numerical and structural cytogenetic abnormalities with patient mortality and disease recurrence is shown in table 5. According to the prognostic classification, there was a significant

**Table 4.** Comparison of clinicopathologic characteristics between patients with and without structural chromosomal abnormalities

Variable	Without abnormality	With abnormality	P Value
Age (Mean ± SD)	7.86 ± 5.07	9.38 ± 5.26	0.370
<b>Gender</b>			0.540
Male	21 (75)	7 (25)	
Female	12 (66.7)	6 (33.3)	
<b>Clinical signs</b>			
Fever	18 (54.5)	5 (38.5)	0.326
Weight loss	17 (51.5)	5 (38.5)	0.425
Bone pain	13 (39.4)	5 (38.5)	0.953
Organomegaly	7 (21.2)	3 (23.1)	0.890
Bruising of skin and lips	6 (18.2)	4 (30.8)	0.435
Bleeding from gums	3 (9.1)	1 (7.7)	0.999
Vomiting	0 (0)	1 (7.7)	0.283
Headache	3 (9.1)	1 (7.7)	0.999
<b>WBC count</b>	37.99 ± 10.16	18.77 ± 8.23	0.246
<b>Hemoglobin level</b>	8.72 ± 1.65	8.17 ± 1.76	0.354
<b>Platelet count</b>	60.93 ± 47.55	43.50 ± 22.4	0.235
<b>PB blasts (%)</b>	34.87 ± 30.02	39.25 ± 34.19	0.698
<b>BM blasts (%)</b>	57.29 ± 25.55	68.38 ± 23.07	0.184
<b>AML subtypes, by differentiation*</b>			0.588
AML without maturation	2 (6.1)	1 (7.7)	
AML with maturation	9 (27.3)	5 (38.5)	
APML with PML:RARA fusion	6 (18.12)	4 (30.8)	
AMML	4 (12.1)	0 (0)	
Acute monocytic leukaemia	3 (9.1)	0 (0)	
Acute erythroid leukaemia	2 (6.1)	0 (0)	
Acute megakaryoblastic leukaemia	7 (21.2)	3 (23.1)	

\*According to the 5<sup>th</sup> edition of the World Health Organization Classification of Hematolymphoid Tumors; WBC: White blood cells; PB: Peripheral blood; BM: Bone marrow; APML: Acute promyelocytic leukemia; RARA: Retinoic acid receptor alpha; AMML: Acute myelomonocytic leukemia; AML: Acute myeloid leukemia

relationship between the recurrence in the two categories of normal/favorable and unfavorable cytogenetic abnormalities, as 18.8% had recurrence in the former, and 66.7% had relapses in the latter group ( $P = 0.007$ ). Also, there was a significant relationship between the death rate in the two categories of normal/favorable and unfavorable (18.8% vs. 73.3%, respectively,  $P = 0.002$ ) (Table 5). All of the patients with del(7q)/monosomy 7 had died during follow-up. Survival was lower in patients with monosomy 7 as compared with those showing del(7q), though not statistically significant (12.1 months versus 18.3 months,  $P = 0.36$ ).

Based on the calculation of survival of patients using Kaplan-Meier curve, the six-month and one-year overall survival (OS) of the patients with numerical chromosomal abnormalities was estimated 66.7% and 33.3%, respectively. Also, the six-month and one-year recurrence-free survival (RFS) of these patients were estimated as 60% and 40%, respectively. During the follow-

up of patients with structural abnormalities, the six-month and one-year OS and RFS of the patients was 71.4% and 42.9%, respectively. The six-month and one-year OS and RFS of the patients was estimated 100% and 33% in patients with favorable/normal cytogenetic abnormality and 75% and 67% in patients with unfavorable cytogenetics abnormalities, respectively.

## Discussion

This study evaluated the cytogenetic characteristics of children with AML in a selected sample of Iranian population. The prevalence of cytogenetic changes was 41.3% in pediatric AML in our study, including 23.9% numerical and 28.3% structural abnormalities. AML with maturation subtype showed the highest prevalence of cytogenetic abnormalities among all AML subtypes. The most common numerical abnormality was monosomy 7. The most common structural abnormalities were chromosomal translocations involving chromosome 11. We

**Table 5.** The relationship between cytogenetic abnormalities and the outcome of the studied patients

Outcome	Cytogenetic abnormality No. (%)		P	Numerical No. (%)		P	Structural No. (%)		P
	Favorable/NI	Unfavorable		Present	Absent		Present	Absent	
<b>Death</b>			0.002			0.476			0.344
Yes	3 (18.8)	11 (73.3)		6 (54.5)	15 (42.9)		7 (53.8)	14 (42.4)	
No	13 (81.2)	4 (26.7)		5 (45.5)	20 (57.1)		6 (46.2)	19 (57.6)	
<b>Recurrence</b>			0.007			0.464			0.130
Yes	3 (18.8)	10 (66.7)		5 (45.5)	13 (37.1)		7 (53.8)	11 (33.3)	
No	13 (81.2)	5 (33.3)		6 (54.5)	22 (62.9)		6 (46.2)	22 (66.7)	

No.: Number

found that chromosome 7 and chromosome 11 abnormalities (del(7q)/monosomy 7 and t(v;11)/trisomy 11) were rather frequent in pediatric AML, occurring in 10.9% and 8.7% of our cases, respectively. Patients with t(8;21) and t(15;17) or absence of cytogenetic abnormalities had a lower recurrence and death rate as compared with patients with unfavorable cytogenetic abnormalities. The average WBC count was significantly lower in patients with numerical cytogenetic abnormalities. According to the prognostic classification, there was a significant difference in ultimate outcome between the two categories of unfavorable and favorable/ normal cytogenetic abnormalities. According to our results, the occurrence of cytogenetic abnormalities, other than cytogenetic changes known as favorable, are associated with an inferior outcome and poor survival. There was a higher rate of recurrence and death in the former. The six-month and one-year OS of the patients were estimated 100% and 33% in patients with favorable cytogenetic abnormality and 75% and 67% in patients with unfavorable cytogenetics abnormalities.

Recently, cytogenetic alterations in various types of leukemia have received special attention, and various studies have shown the relationship of these underlying cytogenetic changes with the outcome and survival of pediatric patients. A wide range of cytogenetic changes as well as genomic mutations associated with AML have been reported. Due to the rarity of AML in children, the true prognostic importance of chromosomal abnormalities in this age group as well as the extent to which they affect patient survival and treatment outcomes remain a topic of ongoing debate. It seems that such a relationship can be

strongly influenced by demographic and genetic characteristics. In the present study, 41.3% exhibited chromosomal abnormalities and 58.7% of patients had no cytogenetic aberrations. A significant part of the patients may have a completely normal cytogenetic pattern. According to Nunes et al. 78.7% of adolescents and children with AML had cytogenetics and molecular abnormalities, the most common being t(15;17).<sup>16</sup> Sandahl et al. studied 596 cases of pediatric AML and reported abnormal karyotype in 76% of cases, including 40% numerical aberrations.<sup>23</sup>

Few studies have examined chromosome 7 abnormalities and their prognostic importance in pediatric AMLs. Chromosome 7 and chromosome 10 monosomy has been reported to be the most frequent chromosomes subject to losses in pediatric AML.<sup>24</sup> Chen et al. demonstrated that t(8;21) is the most common abnormal karyotypes in pediatric AML.<sup>15</sup> According to Harrison et al. 11q23 rearrangement was the most common abnormality found in approximately 16% of patients, of which 50% were infants.<sup>25</sup> Tarlock et al. reported an intermediate outcome for patients with 11q23 abnormalities.<sup>26</sup> Hasle et al. studied 258 pediatric patients with AML or refractory anemia with excess blasts in transformation (RAEB-T) and -7 or del(7q) and suggested that monosomy 7 was associated with a poorer prognosis than del(7q).<sup>27</sup> We observed a lower survival in patients with monosomy 7 compared with those with del(7q); however, this was not statistically significant due to the small number of cases. Like Adult AMLs, rearrangements of 11q23 are rather frequently seen in pediatric AML, and are linked with unfavorable prognosis. Some authors have claimed different outcomes within various subgroups of 11q23-rearranged pediatric



AML, depending on the chromosome partner involved in the translocation.<sup>28, 29</sup> 11q23 rearrangements and t(10;11) are shown to be associated with an unfavorable prognosis in pediatric AML.<sup>30</sup> Therefore, it seems that in some populations, the existence of some cytogenetic aberrations is considered an important prognostic factor and along with other background and clinical factors, they will be useful for predicting the survival of patients. Some pediatric cytogenetic abnormalities are stated to be in the same prognostic classification category as adults, like 11q23 rearrangements that are considered as unfavorable,<sup>21</sup> but some other cytogenetic abnormalities seem to differ between pediatric and adult AML regarding their prognostic category, due to different tumor biology and pathogenesis.<sup>25</sup> There is little evidence to support the prognostic significance of these cytogenetics abnormalities and accurate risk stratification of pediatric AML patients, and further studies are necessary.

OS reported for pediatric AML varies in different studies, depending on the follow-up interval period. Nunes et al. reported a five-year OS of about 50%.<sup>16</sup> Meena et al. found a 40-months OS of about 58%.<sup>31</sup>

The most important limitation of this study was the small sample size, resulting in low statistical power. This may have impacted the strength of the relationships being examined. To achieve a better understanding of the impact of different cytogenetic abnormalities on the prognosis of pediatric AML, it is necessary to evaluate a wide range of patients with different races and ethnicities in multicenter studies to investigate the effect of race and ethnicity, as the confounding factors, on the prognostic role of cytogenetic abnormalities.

## Conclusion

Cytogenetic abnormalities are rather common in pediatric patients. Numerical and structural chromosomal abnormalities occur in 23.9% and 28.3% of Iranian pediatric patients with AML, respectively. The alterations of chromosome

7/del(7q) and 11/del(11q) were shown to be the most common cytogenetic abnormalities observed in childhood AML in our study. Indeed, the average WBC count was significantly lower in the group with numerical cytogenetic abnormalities than those without numerical abnormalities. Unfavorable cytogenetic abnormalities were associated with lower survival, suggesting a prognostic value for such abnormalities in the pediatric population.

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## Authors' Contribution

M.H.S and M.M: Study design, data gathering, drafting the manuscript; M.V: Study design, interpretation of the data, and reviewing the manuscript; S.M: Study design, data gathering, statistical analysis, reviewing the manuscript; M.H: Data gathering, reviewing the manuscript; M.S: Study design, interpretation of the data, reviewing the manuscript. All authors have read and approved the final manuscript and agreed with all parts of the work in ensuring that any queries about the accuracy or integrity of any component of the work are appropriately investigated and handled.

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## Conflict of Interest

None declared.

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