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RESEARCH ARTICLE

Genetic, Cytogenetic and Hematological Features in Newly Diagnosed Acute Lymphoid Leukemia Patients under Eighteen Years Age Rreferred to Ali Asghar Hospital of Tehran, Iran, from 2013 to 2023

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Abstract: ***Introduction*:** Acute lymphoblastic leukemia (ALL), a hematopoietic cancer of T or B lymphoblasts, is the most prevalent cancer in children. Ongoing research aims to better understand the factors contributing to ALL and create more successful treatment options. Therefore, the current study presented cytogenetic, genetic, and hematologic features from 318 ALL patients under eighteen years of age who were referred to Ali Asghar Hospital of Tehran, Iran, from 2013 to 2023.

***Methods*:** This study was designed as a retrospective cross-sectional analysis, focusing on 318 children in Tehran, Iran, who had been newly diagnosed with ALL. All data were extracted from the patient case files that included additional information, such as clinical data, and demographic information. The Flow cytometry technique was employed to perform immunophenotyping for various markers. Moreover, the standardized protocol was carried out for conventional cytogenetic analysis.

***Results*:** Out of 318, 179 (56.3%) and 139 (43.7%) were males and females, respectively. The most common subtype of ALL was Common B Cell ALL, accounting for 182 cases (57.23%), followed by Pre B cell ALL with 74 cases (23.27%) and T cell ALL with 27 cases (8.49%). Out of 222 patients, 17 (7.7%) had genetic abnormalities, with the highest incidence of abnormalities being associated with Runx 1 (four cases). Additionally, out of 228 patients, 143 (62.7%) were identified as having cytogenetic abnormalities, with the most prevalent abnormalities being hyperdiploidy (54 cases) and t (12;21) (28 cases).

***Conclusion*:** Our findings showed that some cytogenetic abnormalities, such as t (9;22) and hyperdiploidy, were consistent with previous studies. These results offer valuable foundational insights that can help direct future research on ALL patients and inform potential treatment strategies.

ARTICLE HISTORY

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1. INTRODUCTION

Acute lymphoblastic leukemia (ALL), a hematopoietic cancer of T or B lymphoblasts, is the most prevalent cancer in children [1]. Indeed, ALL represents about 75% of leukemia cases in individuals under the age of 20 and around 25% of all childhood cancers [2]. The majority of cases have been found in children between the ages of 2 and 5, being the most affected age group. In 2021, the United States recorded around 5,690 new cases of ALL, with more than half (53.5%) of these cases occurring in patients under the age of 20 [1, 3]. It has been shown that B-cell ALL was the most prevalent type, making up 85-90% of pediatric ALL cases and around 75% of adult ALL cases, while T-ALL was less prevalent [1, 4]. People with specific genetic conditions are

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recognized to have a higher likelihood of developing leukemia and genetic abnormalities significantly contribute to the development of leukemia, particularly in ALL [2].

Recent research has extensively explored the link between genetic factors involved in normal blood cell production and the advancement to acute leukemias, as well as the underlying mechanisms driving leukemia development [2]. The significance of genetics became apparent through concordance studies involving identical twins who had leukemia [5, 6]. Variations in the genes CEPBE, CDKN2A, ARID5B and IKZF1 have been demonstrated to be linked to a higher likelihood of developing ALL [7]. In B-cell ALL, there are specific genetic changes associated with each type of ALL immunophenotype. These include hypodiploidy, hyperdiploidy, BCR-ABL1, ETV6-RUNX1 or TCF3-PBX1 fusions, ETV6 or PAX5 mutations, intrachromosomal amplification of chromosome 21 (iAMP21) and MLL rearrangements which are specific to B-ALL. On the other hand, alterations in LMO2, TLX1, TLX2, TAL1, TAL2, or HOXA are characteristics of T-cell ALL [2, 8, 9].

On the other hand, cytogenetic abnormalities in ALL are categorized into three risk subgroups: (1) favorable, (2) intermediate, and (3) unfavorable prognosis groups. High hyperdiploidy with 51–65 chromosomes and t(12;21)(p13;q22) is placed in the favorable risk subgroup and is mainly seen in children. On the other hand, t(9;22)(q34;q11), a typical karyotype in the unfavorable-risk subgroup, is predominantly found in adults [10]. The occurrence of chromosomal abnormalities varies among different populations, possibly due to ethnic and geographic factors. It is widely recognized that cytogenetic information plays a crucial role in the diagnosis, treatment, and prognosis estimation of ALL, particularly in pediatric patients [11, 12]. However, there are limited reports from Iran regarding the frequency of these abnormalities [13].

As the exact cause of ALL is still not fully understood, ongoing research aims to gain a better understanding of the underlying factors contributing to ALL as well as to create more successful treatment options. Hence, this research presented the cytogenetic, genetic, and hematologic disorders from ALL patients under eighteen years old who were referred to Ali Asghar Hospital of Tehran, Iran, from 2013 to 2023. The findings of this study regarding the prevalence of these abnormalities in ALL patients can aid in prognosis assessment, treatment planning, and research.

2. MATERIALS AND METHODS

2.1. Study Design and Participants

The current investigation was a retrospective cross-sectional study. The target population included children under eighteen years of age who were lately diagnosed with ALL in Tehran, Iran, and referred to Ali Asghar Hospital from 2013 to 2023. In this period, 1297 individuals were referred to the hospital, out of which 318 children were newly diagnosed with ALL. These criteria included having access to the patients' information, being recently diagnosed with ALL, and having developed the disease between birth and 17 years of age. The diagnosis of ALL was confirmed through comprehensive blood tests, physical examination, analysis of bone marrow samples, and immunophenotyping.

2.2. Cell Counting and Flow Cytometry

At first, three milliliters of venous blood were obtained and put into an Ethylenediaminetetraacetic acid (EDTA) tube. The Sysmex KX-2 automated hematology analyzer was used to obtain complete blood counts (CBC), following proper quality assurance procedures. Subsequently, flow cytometry was employed to perform immunophenotyping for various markers using the PARTEC Calibur instrument, following the protocols provided by the manufacturers for the respective kits.

2.3. Cytogenetic Analysis

The standardized protocol for conventional cytogenetic analysis involved culturing bone marrow samples in Rosewell Park Memorial Institute (RPMI) 1640 basal medium with 10% fetal calf serum for 24 hours at 37 °C. Subsequently, the samples were treated with 0.1 µg/ml of colcemid to halt cell division at the metaphase stage of mitosis. After harvesting and fixing the cells, the chromosomes were stained and analyzed using the standard Giemsa trypsin banding technique. A minimum of 20 metaphases were examined and the karyotypes were characterized following the guidelines of the International System for Human Cytogenetic Nomenclature (ISCN 2009). Structural abnormalities were noted when at least two metaphases displayed the same type of aberration. For numerical abnormalities to be documented, at least three metaphases had to exhibit the same aberration. The IKAROS chromosomal karyotyping software from Metasystem company was utilized for capturing and analyzing the chromosome images with a microscope [14].

2.4. Statistical Analysis

This study utilized descriptive statistics to present the mean and standard deviation (SD) for normally distributed data, and the median and interquartile range (IQR) for non-normally distributed data. Furthermore, nominal data comparisons were performed using the Pearson chi-square test, and comparisons between two groups were conducted using the t-test for normally distributed data and the Mann-Whitney test for non-normally distributed data, with a significance level set at $p < 0.05$. The analysis was conducted using SPSS software (version 21).

3. RESULTS

From 2013 to 2023, 1297 individuals were included in the current study and were referred to Ali Asghar Hospital. Of these individuals, 318 were children who were newly diagnosed with ALL. Table **1** demonstrates the demographic and hematological characteristics of 318 ALL patients under eighteen years old. The average age and BMI were 5.38 ±3.83 (SD) years and 15.84 ± 3.49 kg/m^2, respectively. The youngest individual was 4 days old, while the oldest patient was 17 years old.

Out of 318 patients, 179 (56.3%) and 139 (43.7%) were males and females, respectively. The median hematological indices like WBC and PLT were determined 13.10 ± 32.85 (IQR) × 10^9/L and 55.00 ± 102.50 × 10^9/L, respectively. Moreover, the mean Hb was found to be 8.24 ± 2.54 g/dl.

Table **2** and Fig. (**1**) show the subtype of ALL in 318 patients. The most common subtype of ALL was Common B

Cell ALL, accounting for 182 cases (57.23%), followed by Pre B cell ALL with 74 cases (23.27%) and T cell ALL with 27 cases (8.49%).

Table **3** shows the percentage of various clusters of differentiation (CD) markers in ALL patients under eighteen years old in Tehran, Iran. As indicated in Table **3**, the percentage of CD markers associated with ALL disorders was assessed based on the clinical symptoms of patients and/or other diagnostic tests. Therefore, not all patients were tested for all CD markers.

The frequency of cytogenetic and genetic abnormalities in ALL patients is shown in Table **4**. The abnormalities were assessed according to the clinical symptoms of the patients and/or other diagnostic tests used. As a result, not all patients underwent testing for every cytogenetic and genetic abnormality. Out of 222 patients, 17 (7.7%) were found to have genetic abnormalities, with the highest incidence of abnormalities being associated with Runx 1 (four cases, Table **5** and Fig. **2**), while 205 (92.3%) did not exhibit any abnormalities. There were no significant differences in the expression of CD markers between individuals with normal genetic profiles and those with abnormal genetic abnormalities (p >0.05).

On the other hand, the karyotype of ALL patients with some abnormalities is shown in Figs. (**3** and **4**). Out of 228 patients who were examined for cytogenetic abnormalities, 85 (37.3%) were found to have normal cytogenetic results. However, according to Table **6** and Fig. (**3**), 143 (62.7%) were identified as having cytogenetic abnormalities, with the most prevalent abnormalities being Hyperdiploidy (54 cases) and t (12;21) (28 cases). No significant differences (p >0.05) were observed in all CD markers between normal and abnormal cytogenetic groups, with the exception of CD13 and CD45. CD13 expression was significantly elevated in abnormal cytogenetic patients compared to normal patients (p =0.004), while CD45 expression was higher in normal cytogenetic patients than in abnormal patients (p =0.040).

Table 1. Demographic and hematological characteristics of 318 ALL patients under eighteen years old in Tehran, Iran. *Data presented as median ± IQR.

Variables	Mean ± SD *Median ± IQR	Minimum	Maximum
Age (Years)	5.38 ±3.83	0.01	17.00
BMI (kg/m^2)	15.84 ± 3.49	7.90	29.60
WBC* ($\times 10^9$/L)	13.10 ± 32.85	0.40	750.00
Hb (g/dl)	8.24 ± 2.54	1.90	16.00
Plt* ($\times 10^9$/L)	55.00 ± 102.50	7.00	637.00

Table 2. Subtype of ALL in 318 patients under eighteen years old in Tehran, Iran.

Subtype of ALL	No. of Subtype	% of Subtype
Pre B cell ALL	74	23.27
Common B Cell ALL	182	57.23
T cell ALL	27	8.49
Pre B cell /T Cell ALL	3	0.94
Mature B Cell ALL	5	1.57
Pro B cell ALL	16	5.03
Pre T cell ALL	4	1.25
TLBL	4	1.25
ETP T-ALL (Early T Cell Pre ALL)	3	0.94

Table 3. Percentage determination of various cluster of differentiation (CD) markers in ALL patients under eighteen years old in Tehran, Iran. The evaluation of CD markers was guided by the clinical symptoms of the patients and/or other diagnostic tests performed. As a result, not all patients were tested for every CD marker. *Data presented as median ± IQR.

Variables	No. of Patients Evaluated	Mean ± SD (%) *Median ± IQR (%)	Minimum (%)	Maximum (%)
CD2*	46	61.50 ± 47.00	12.00	99.00
CD3	42	59.35 ± 28.34	4.00	99.00
CD4*	20	26.00 ± 51.25	3.00	94.00
CD5*	43	70.02 ± 43.00	24.00	99.00
CD7*	53	82.00 ± 45.50	22.00	98.00
CD8	17	50.58 ± 28.63	1.00	98.00
CD10*	277	80.00 ± 34.00	.01	99.00
CD13	22	53.36 ± 20.63	24.00	95.00
CD19*	277	82.00 ± 36.00	1.00	99.00
CD20*	213	22.00 ± 39.00	0.40	99.00
CD22*	249	78.00 ± 42.00	0.01	99.00
CD33	23	49.43 ± 21.60	14.00	86.00
CD34*	269	59.00 ± 61.50	0.05	99.00
CD38*	15	86.00 ± 33.00	20.00	97.00
CD45*	285	75.00 ± 46.50	0.20	100.00
CD58*	50	91.00 ± 22.50	20.00	100.00
CD66c*	36	68.50 ± 54.75	1.00	98.00
CD123*	37	77.00 ± 38.50	1.00	97.00
HLADR*	272	81.00 ± 28.00	1.00	99.00
iCD3*	30	66.00 ± 47.75	4.00	99.00
TdT*	171	54.00 ± 55.00	0.50	98.00
iCD79a*	119	88.00 ± 15.00	0.20	98.00
Blast*	269	82.00 ± 20.00	10.00	97.00

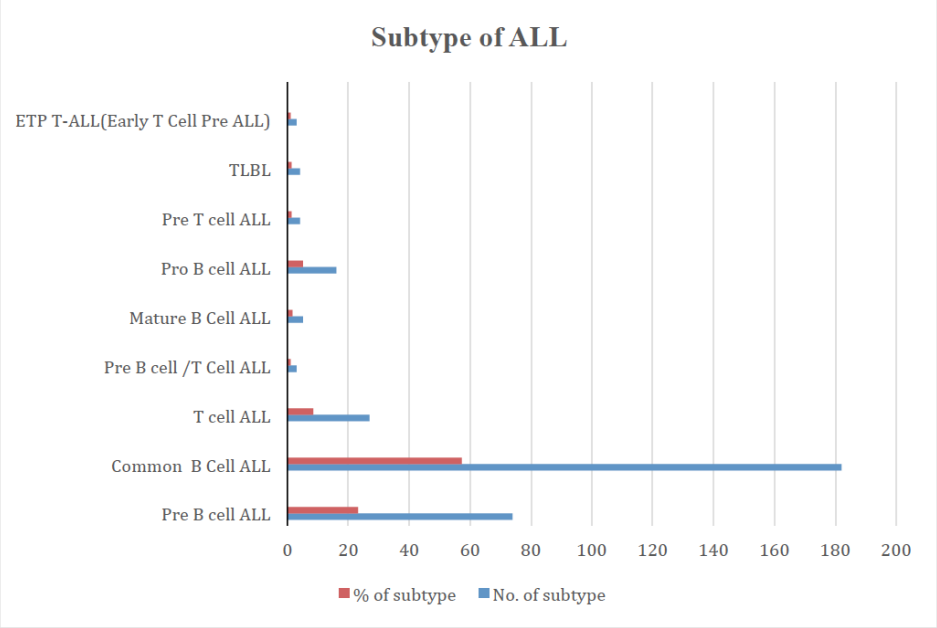


Fig. (1). Subtype of ALL in 318 patients under eighteen years old in Tehran, Iran. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 4. The frequency of cytogenetic and genetic abnormalities in ALL patients under eighteen years old in Tehran, Iran. The abnormalities were assessed according to the clinical symptoms of the patients and/or other diagnostic tests used. As a result, not all patients underwent testing for every cytogenetic and genetic abnormality.

Variables	No. of Patients Evaluated	Normal N (%)	Abnormal N (%)
Cytogenetic abnormality	228	85 (37.3)	143 (62.7)
Genetic abnormality	222	205 (92.3)	17 (7.7)

Table 5. The frequency of genetic abnormalities observed in 222 ALL patients under the age of eighteen in Tehran, Iran. Out of all the cases, 17 patients were positive for abnormalities, with the most common mutation linked to the Runx1 gene, found in four cases.

Genetic Abnormalities	No. of Abnormalities
TCF3-PBX1 (E2A-PBX1)	2
del ATM	1
5 KMT2-3MLLT3	1
ABL kinase	1
CDKN2A	1
del 3	1
IgH Chain	1
IgH-MYC	1
MLL	2
Runx 1	4
TEL-AML1	2

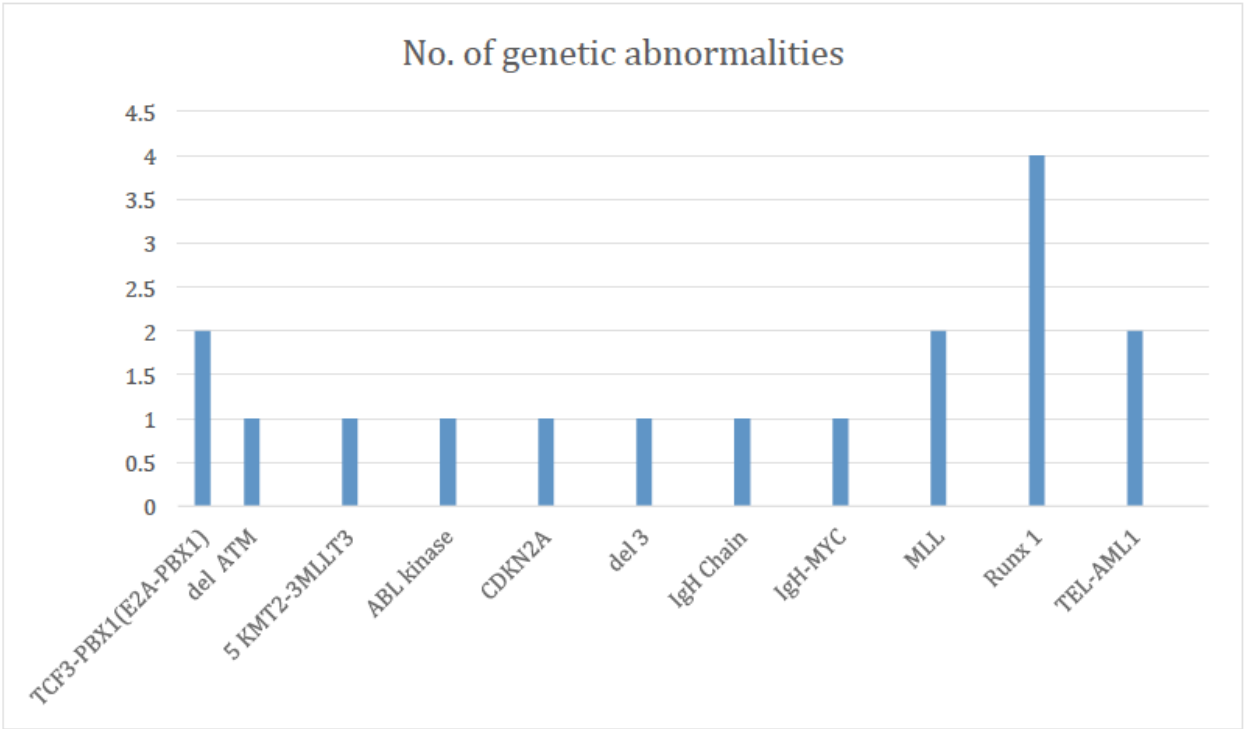


Fig. (2). The frequency of genetic abnormalities observed in 222 ALL patients under the age of eighteen in Tehran, Iran. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 6. The incidence of cytogenetic abnormalities found in 228 ALL patients under the age of eighteen in Tehran, Iran. Among the total number of patients, 143 subjects were observed positive, with the most common abnormalities being Hyperdiploidy (54 cases) and t(12;21) (28 cases). Note: Some patients had more than one cytogenetic abnormality. Others: t(x;10), t(9;12), t(9;11), t(x;9), t(5;11), t(8;14), t(5;9), t(3;20), t(2;7), t(2;12), t(21;21), t(14;19), t(1;12), t(1;22), t(1;7), del 4, add 1, add 7, del 11, add 19, add 1, add 3, inv 3, inv 9. Complex: more than 5 abnormalities per metaphase.

Cytogenetic Abnormalities	No. of Abnormalities
Hyperdiploidy	54
Hypodiploidy	13
t(12;21)	28
t(1;19)	12
t(9;22)	6
t(4;11)	4
del 6q	9
del 9p	8
Others	21
Complex	14

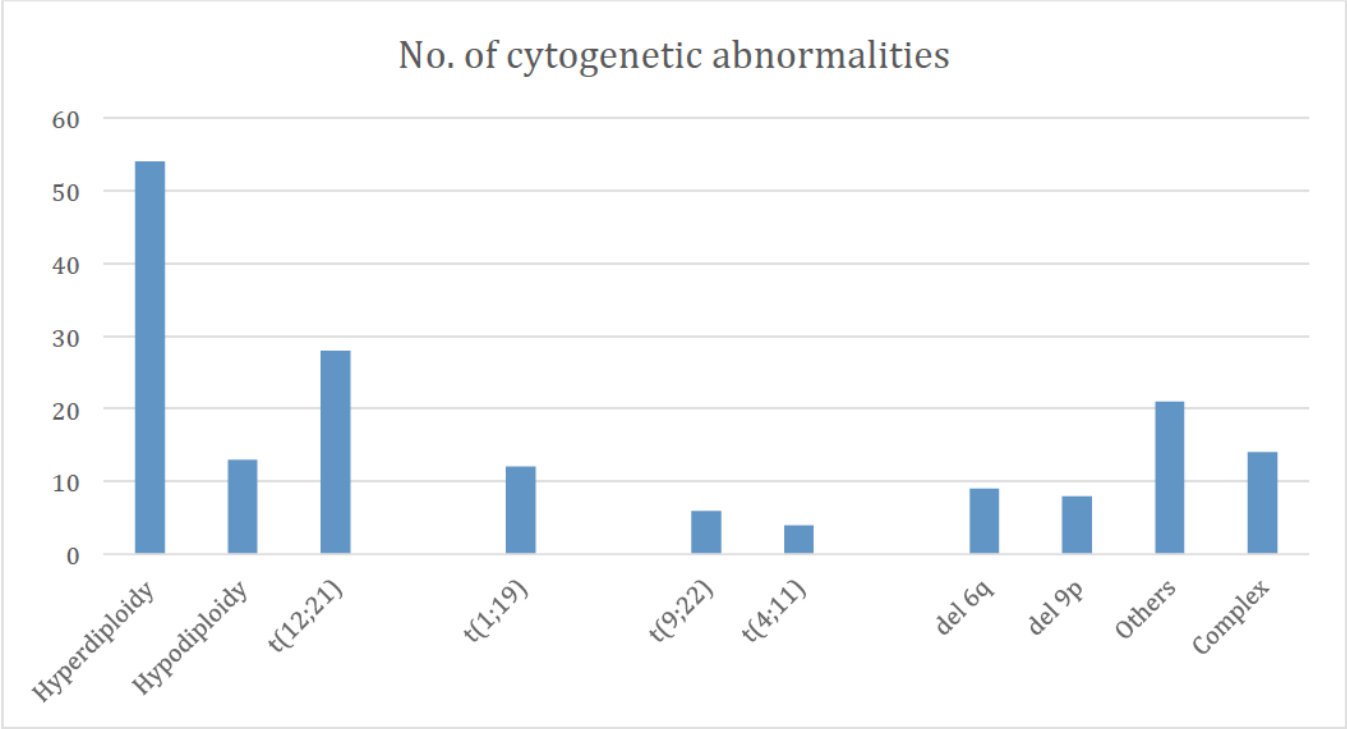
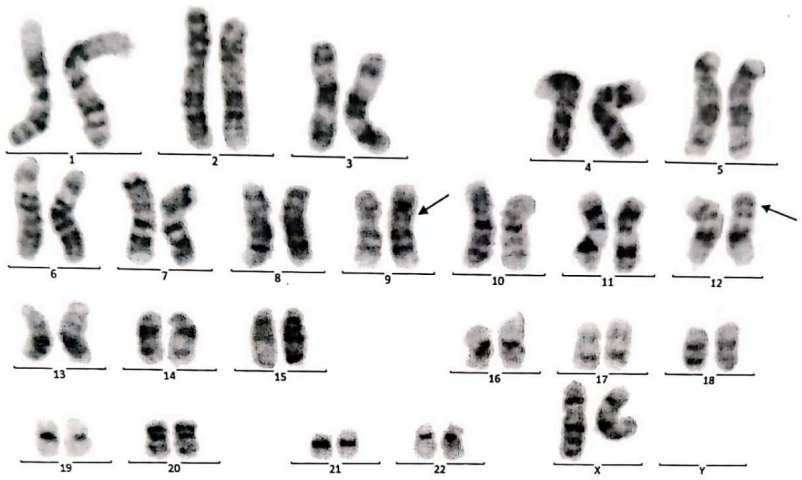


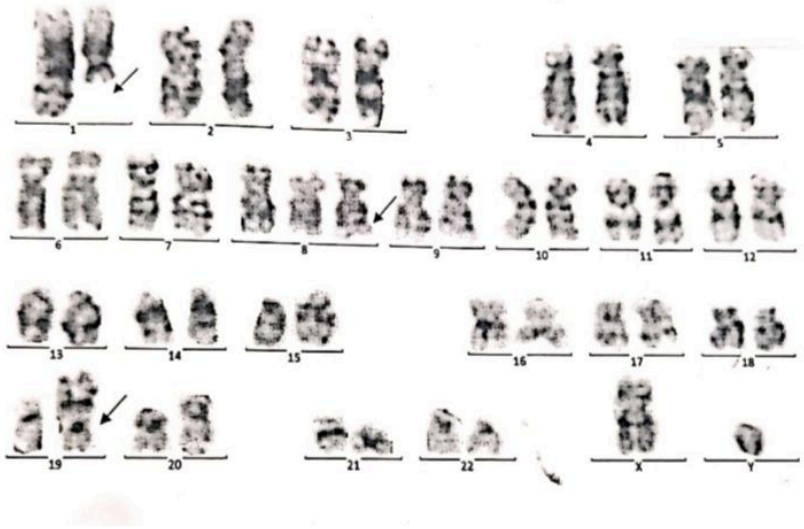
Fig. (3). The frequency of cytogenetic abnormalities observed in 228 ALL patients under the age of eighteen in Tehran, Iran. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

4. DISCUSSION

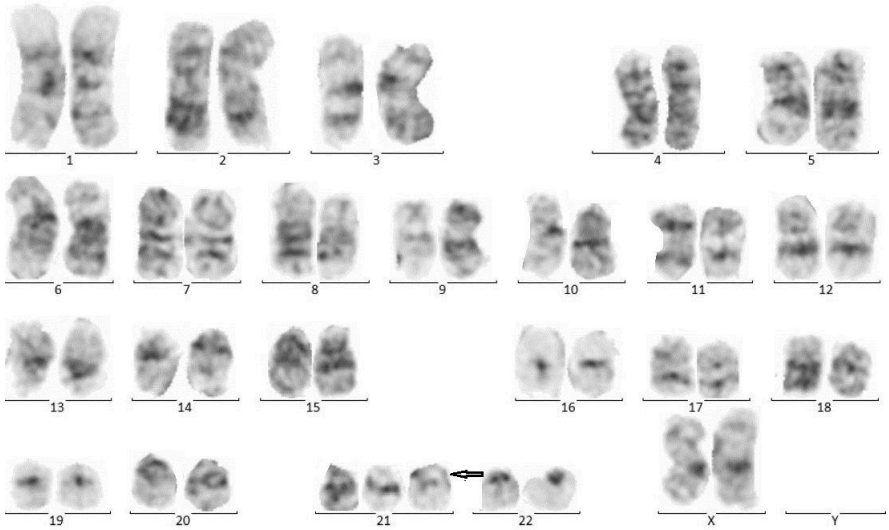
Cytogenetic abnormalities play an essential role in hematological malignancies and provide crucial insights into the diagnosis, classification and prognosis of these disorders [15]. These abnormalities include structural and numerical alterations and affect the genetic integrity of hematopoietic cells [16]. Diagnosing these abnormalities and understanding their importance plays a fundamental role in the management and treatment strategies of hematological malignancies [17]. Accordingly, the primary aim of current research was to gain a deeper understanding of the factors contributing to the development of ALL and to develop more effective treatment strategies, as the precise cause of the disease remains unclear. In line with this objective, the present study was conducted in Tehran, the capital of Iran, to examine hematologic, genetic,



(A)

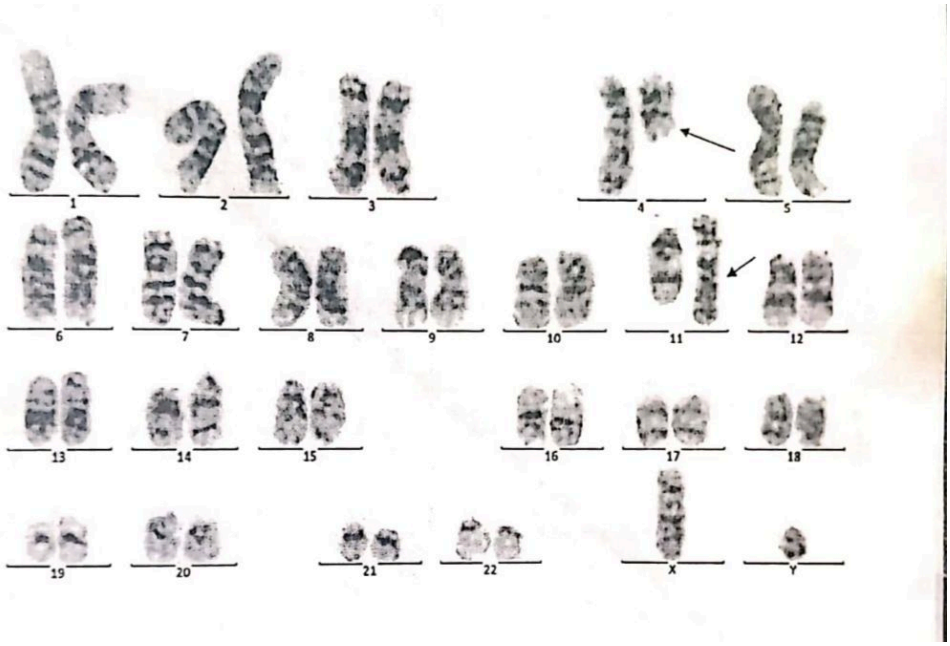


(B)



(C)

(Fig. 4) Contd…



(D)

Fig. (4). The karyotype of ALL patient with some abnormalities. A: t (9;12) (q34; p13), B: [t (1;19) (q23; q13.3), +8], C: t (12;21) (P13; q22), D: t (4;11) (q21; q23).

and cytogenetic abnormalities in 318 ALL patients under the age of eighteen. It has been reported that the average yearly incidence rate of ALL under the age of fifteen was 2.25 per 100,000 in Iranian children between 2006 and 2014 [18]; these children appeared to have a lower incidence of ALL than children in the developed nations. Hence, the incidence rate of ALL was between three and seven per 100,000 children in other countries [19-22]. However, it is very important to manage this disease effectively in Iran to ensure optimal outcomes for affected children and to address the healthcare challenges associated with ALL.

The findings of the present study showed that the predominant subtype of ALL was Common B Cell ALL with 57.23%, while Pre B cell ALL accounted for 23.27% and T cell ALL for 8.49%. In line with our study, it has been reported that the prevalence of B cell ALL was higher than T cell ALL [23]. An updated classification of B-ALL emphasizes the diverse genetic characteristics of the disease, categorizing it into 23 subtypes based on chromosomal rearrangements, sequence mutations, or varied genomic alterations. The majority of these genetic changes are acquired rather than inherited [24]. There is also a suggestion of epigenetic priming in pediatric ALL [25].

Hyperdiploidy, which refers to having more than 50 chromosomes, is linked to a more favorable prognosis. This improved outcome is attributed to the increased sensitivity of hyperdiploid cells to certain chemotherapeutic drugs, particularly antimetabolite [26]. Our results showed that cytogenetic abnormalities were detected in 62.7% of the patients. Therefore, hyperdiploidy was the most commonly identified abnormality. In line with our results, the prevalence of hyperdiploidy in ALL in Western nations varies from 25–30% in children and 7 to 10% in adults [27]. Nonetheless, it was greater among Indian patients, comprising 44% of pediatric cases and 24% of adult cases [28].

After hyperdiploidy, t (12; 21) was the most prevalent abnormality in our study. In the study conducted by Xin Li *et al.* [10], it was found that the most common anomaly in children (21%) was the translocation of t(12; 21). However, the authors were able to identify this anomaly using the RT-PCR method. Identifying this anomaly requires sophisticated molecular methods such as Southern blot, RT-PCR, and FISH analysis, as it is difficult to detect [29]. As a result, Safaei *et al.* did not observe the translocation of (12;21) in their study population in Iran [13].

On the other hand, the present findings indicated that genetic abnormalities were discovered in 7.7% of patients, with Runx 1 showing the highest frequency of abnormalities. It has been demonstrated that RUNX1 plays a critical role in differentiation, and this involvement extends beyond myeloid differentiation [30, 31]. RUNX1 has been demonstrated to play a role in lymphoid development, particularly in T-cell differentiation, according to Wong *et al.* [32]. Furthermore, naïve CD4-positive T cells have RUNX1 proteins. These proteins inhibit the expression of GATA3 and IL4, which affects the development of these cells into Th2 T-helper cells [30, 31].

The present study has some limitations. Although our sample size was adequate, not all patients underwent testing for every CD marker. Furthermore, the assessment of cytogenetic and genetic abnormalities relied on the patients' clinical symptoms and/or other diagnostic tests, leading to not all patients being tested for each abnormality. It is recommended to future researchers to evaluate the abnormalities in large sample sizes. Finding out how frequently these abnormalities

occur in ALL patients is a useful tool for prognostic evaluation, therapy planning, and research advancement.

CONCLUSION

The current research focused on understanding cytogenetic, genetic, and blood-related disorders in children under 18 with ALL in Tehran, Iran. Our findings revealed the prevalence of some genetics, such as Runx 1 and cytogenetic anomalies like t (9;22) and hyperdiploidy that were in line with what has been reported in the literature. The results of this study, which was carried out in Tehran, can provide basic information and help guide future research on ALL patients as well as treatment options. Indeed, by exploring how common these abnormalities are in ALL patients, the findings offer important clues that can help doctors better predict outcomes, tailor treatments, and advance future research efforts. In order to successfully detect hidden chromosomal anomalies, we recommend using sophisticated molecular approaches in future research.

AUTHORS' CONTRIBUTIONS

ERL and NM conceived and designed the research. AE and SH conducted experiments. RAF, RAS and ZS drafted the manuscript. RAF and ERL revised the manuscript. All authors have reviewed and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol for the present study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran. (Approval No. IR.IUMS. REC.1402.551).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The datasets utilized and/or analyzed during the current study can be obtained from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

FUNDING

None.

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