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Review Article

Frequency of prognostically important acute myeloid leukemia mutations in the Iranian population: A systematic review and meta-analysis

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Abstract

Background: The geographic diversity of molecular genetic abnormalities in AML can help understand the genetic and environmental factors involved in the development of leukemia. In addition, high-risk groups can be recognized by identifying common mutations in AML patients, and appropriate treatment based on the type of mutation can be adopted. This systematic study and meta-analysis analyzed the common mutations in AML patients in Iran.

Methods: In this systematic study, common mutations in Iranian AML patients were comprehensively examined across four databases: PubMed, Scopus, Web of Science, and Magiran, from 1980 to 2024, following the PRISMA guidelines. Meta-Analysis Version 2 (CMA2 was used for data analysis, and I^2-test values greater than 50% were considered to indicate high heterogeneity among the studies.

Results: By reviewing 40 articles, it was found that the prevalence of FLT3-ITD mutation was 21.9% (CI: 19.19 - 24.1) in 34 studies (3,152 AML cases), FLT3-TKD mutation 6.6% (CI: 4.7 - 9.3) in 19 studies, NPM1 mutation 19% (CI: 15.9-22.6) in 18 studies DNMT3A mutation 13.9% (CI: 11.1 - 17.2) in 5 studies, CEBPA mutation was 18.5% (CI: 10.3 - 31) in 5 studies, and WT-1 mutation prevalence was 8.2% (CI: 5.6-11.8) in 4 studies. Other mutations investigated in the studies included NRAS, IDH1, IDH2, TET2, c-kit, ASXL1, and RUNX1.

Conclusions: Studies have shown that the FLT3-ITD mutation is the most prevalent mutation among Iranian AML patients. Following this, the most common mutations identified were NPM1, CEBPA, DNMT3A, and WT1, in that order.

Keywords: AML, Mutation, Iran, FLT3, NPM1, DNMT3A.

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Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy characterized by an increase in myeloid blasts in the bone marrow or peripheral blood (1, 2). AML primarily affects older adults, with a mean age of diagnosis around 68 years (3). The disease is driven by numerous gene mutations and cytogenetic abnormalities that play crucial roles in its pathogenesis. The most commonly observed AML chromosomal abnormalities include t(8;21)(q22;q22), inv(16)(p13;q22), t(15;17)(q22;q11-12), and t(6;9)(p23;q34) (2, 4, 5). The most recent categorization of hematologic malignancies has enlisted more genetically defined subgroups of AML, and this list is expected to expand in the future. The most important application of the genetic categorization of AML may fall in its prognostic value, where well-defined abnormalities at the chromosomal and molecular levels fairly predict disease behavior. The European Leukemia Net (ELN) 2017 guidelines classify AML prognosis into three risk groups: favorable, intermediate, and adverse, based on these cytogenetic abnormalities (6-8).

The advent of next-generation sequencing (NGS) technology has revealed additional mutational profiles in the AML genome, including genes encoding DNA methyltransferase 3A (DNMT3A), Tet oncogene family member 2 (TET2), and isocitrate dehydrogenase 1 and 2 (IDH1/2) (9). The most prevalent mutations include FLT3-ITD, observed in 20-30% of newly diagnosed patients, and NPM1 mutations, which is found in about 30% of cases. Other common mutations include CEBPA, ASXL1, RUNX1, and TET2 (7, 10). Clinical practice guidelines recommend testing for FLT3 and NPM1 mutations in AML patients, as they serve as crucial reference indicators for treatment decisions and risk stratification (11, 12).

A recent review shows that leukemia burden and mortality have increased in Iran in the recent three decades (13). The increase in mortality despite the advent of new treatments signifies in part the inaccessibility of novel therapeutics in Iran due to unjust sanctions; however, it also shows the lack of appropriate prognostic categorization of patients based on their genetic signatures. There are numerous studies investigating the frequencies of various mutations with well-known and under-question prognostic values among Iranian patients diagnosed with AML. Despite the high importance of common mutations in the prognosis and progression of AML disease, no systematic study has yet been conducted regarding the prevalence of common mutations in AML patients in the Iranian population. Thus, it is essential to perform a systematic review and meta-analysis to elucidate the significance of frequent mutations in AML patients in Iran. This systematic review and meta-analysis aimed to highlight the role of frequent mutations in AML in the Iranian population by using existing studies in this field.

Methods

Data source and search strategy: A methodical exploration was conducted across three electronic medical repositories, namely PubMed, Scopus, and Web of Science, as well as an Iranian database (Magiran), to assemble pertinent studies delving into mutations among Iranian AML patients from 1980 to 2024.

The search strategy in each repository encompassed keywords such as “AML” OR “Acute Myeloblastic Leukemia” OR “Acute myeloid leukemia” AND “Iran” OR “Persian” OR “Islamic republic of Iran” OR “IRI”. On March 17, 2024, two independent researchers (MN K and MM) carried out the quest, collated all identified articles using EndNote X7 reference manager software for assessment, and eliminated any duplicate publications.

Study selection and eligibility criteria: After elimination of duplicate articles, the remaining items underwent a screening process utilizing predetermined inclusion and exclusion criteria. Inclusion criterion encompassed focusing on the prevalence of common mutations among AML patients in Iran. Exclusion criteria entailed publication in languages other than English or Persian, review articles, studies on non-Iranian AML patients, and reporting inadequate data.

Data extraction and quality assessment: Two reviewers (MN K and MM) independently screened articles and extracted data. Discrepancies were resolved by discussion and, when necessary, by consulting a third reviewer (MR). The extracted data included the first author’s name, year of publication, country, number of patients, age, and gender distribution of patients, as well as the prevalence of selected mutations, and subtype of AML (if reported). To assess the quality of the included studies, the Joanna Briggs Institute (JBI) Appraisal Tool was utilized.

Data synthesis and analysis: Meta-analysis was performed using the comprehensive meta-analysis version 2 (CMA2) software and STATA software (version 18). The pooled incidence of each outcome was assessed utilizing either a random-effects model or fixed-effect model, depending on the heterogeneity observed among the studies. Heterogeneity between studies was evaluated using the I^2-test; an I^2 value greater than 50% was indicative of high heterogeneity. Results were presented as pooled prevalence along with 95% confidence intervals (CIs). Statistical significance was determined by a 2-tailed P value of less than 0.05. Continuous data were displayed as either means (standard deviations) or medians with interquartile ranges (IQRs). All descriptive analyses were conducted using GraphPad Prism version 10 (version 10, GraphPad Inc.).

Results

Selection and characterization of articles: We found 542 articles based on the for mentioned search strategy, including 108 articles from PubMed, 206 from Scopus, 90 from Web of Science, and 138 from Magiran. After removing duplicate articles, 382 articles remained. Subsequently, the articles were screened by reading titles and abstracts, and 96 papers were finally kept after reviewing their texts and qualification based on eligibility criteria. Finally, 40 (table 1) articles were included in the study (14-53). Figure 1 demonstrates the flow diagram of the study selection and screening steps. The studies included in our analysis focused on the occurrence and implications of various genetic mutations associated with

AML among Iranian patients. Notably, the most prevalent mutations identified were as follows: FLT3-ITD, NPM1, CEBPA, DNMT3A, WT1, and FLT3-TKD (table 2). A comprehensive review of 34 studies, involving a total of 3,152 AML patients, revealed that 678 individuals (21.9% (CI: 19.19 - 24.1); I2 72.2%) harbored the FLT3-ITD mutation, establishing it as the most frequently identified mutation in Iranians with AML (figure 2).

Additionally, an analysis of 19 studies encompassing 1,639 patients indicated that 101 patients (6.6% (CI: 4.7 - 9.3); I2 59.6%) presented with the FLT3-TKD mutation (figure 3). The NPM1 mutation, across 18 articles involving 1590 patients, was detected in a total of 291 cases (19% (CI: 15.9 – 22.6); I2 66.6%) (figure 4). The DNMT3A mutation emerged as another notable molecular defect, with 69 out of 505 patients (13.9% (CI: 11.1 – 17.2); I2 0%) exhibiting this mutation across 5 articles (figure 5). Additionally, an analysis of 5 studies, including 343 patients, indicated that 60 patients (18.5% (CI: 10.3 - 31); I2 80.6%) presented with the CEBPA mutation (figure 6).

Table 1. Summary of the studies included in meta-analysis.

First Author	Publication Date	Patients (N)	Gender (F/M)	Age (years)	Location	Study Population	Mutation Detection Method	Q. Score	Ref
MH. Sadeghian	2019	88	43/45	28.58±20.21	Mashhad	De novo AML	Not mentioned	8/10	(39)
A. Alavianmehr	2020	167	68/99	48.12±17.41	Shiraz	De novo AML	PCR-RFLP	8/10	(15)
Z. Zafari	2023	70	30/40	25.6	Mashhad	De novo AML	Not mentioned	5/8	(47)
MM. Kanesbi	2021	73	41/32	30.86	Mashhad	APL	PCR	6/8	(26)
F. Mirzaeyan	2021	188	90/98	45	Tehran	De novo non-M3 AML	Fragment Analysis and Sanger Sequencing	7/8	(28)
N. Nasiri	2014	100	45/55	5.5±1.6	Tehran	Child AML	PCR-RFLP and Sequencing	4/8	(31)
F. Zaker	2010	212	86/126	47±12	Tehran	De novo AML	PCR-RFLP	4/8	(50)
Z. Chehreghani	2022	51	22/29	33.8	Mashhad	De novo AML	Sanger sequencing and real-time PCR	6/8	(22)
M. Parsa-kondelaji	2022	40	20/20	33.22±20.91	Mashhad	De novo AML and secondary AML	Sequencing	5/8	(32)
E. Yazdandoust	2022	80	36/44	38	Mashhad	De novo AML	PCR	7/10	(46)

First Author	Publication Date	Patients (N)	Gender (F/M)	Age (years)	Location	Study Population	Mutation Detection Method	Q. Score	Ref
J. Naghinezhad	2023	30	11/19	64.57±13.8	Mashhad	De novo AML	Not mentioned	6/8	(30)
AH. Emami	2009	40	18/22	37/8±11.9	Tehran	De novo AML	PCR-RFLP	7/8	(17)
N. Rezaei	2017	70	21/49	47.73±18.64	Shiraz	De novo AML	Sequencing	6/8	(35)
A. Allahyari	2016	100	48/52	28.5	Mashhad	De novo AML	PCR-RFLP	5/8	(16)
M.Gholami	2020	58	27/31	40.88±18.52	Tehran & Shiraz	De novo AML	Sanger Sequencing	6/8	(24)
G. Toogeh	2016	88	33/55	44.62	Shiraz	De novo CN-AML	Sequencing	7/8	(45)
S. Rostami	2021	130	49/81	42	Tehran	De novo AML	Sequencing	8/11	(37)
S. Abbasis	2013	100	47/53	36	Tehran	De novo AML	PCR-RFLP	4/8	(14)
Y. Mortazavi	2007	60	25/35	14-57	Tehran	De novo AML	PCR-RFLP	6/8	(29)
Y. Mortazavi	2006	70	30/40	15-73	Tehran	De novo AML	PCR-RFLP	5/8	(53)
S. Shakeri	2021	80	36/44	29.53	Mashhad	De novo AML	PCR	6/8	(42)
P. Bagheri	2020	22	12--10	17.8±15.2	Mashhad	De novo AML	Direct Sequencing	6/8	(21)
S. Zaka Khosravi	2022	50	22/28	42.8±22.9	Tehran	De novo AML	HRM Analysis	5/8	(48)
M.Gholami	2017	91	45/46	41.88±17.73	Tehran	De novo AML	PCR-RFLP	7/11	(25)
H. Ayatollahi	2023	24	11/13	45.45±15.45	Mashhad	De novo AML	Not mentioned	6/8	(20)
D. Zare-Abdollahi	2016	128	55/73	44	Tehran	De novo AML	Direct Sequencing	7/8	(51)

First Author	Publication Date	Patients (N)	Gender (F/M)	Age (years)	Location	Study Population	Mutation Detection Method	Q. Score	Ref
A. Safaei	2018	76	29/47	44.5	Shiraz	De novo AML	PCR-RFLP	6/8	(40)
M. Teremmahi Ardestani	2018	220	58/162	32.79	Tehran	De novo non-M3 AML	PCR-RFLP	8/11	(19)
H. Pashaiefar	2018	65	34/31	43	Tehran	De novo non-M3 AML	HRM Analysis	6/8	(33)
T. Sohrabi	2018	80	36/44	29±18.7	Mashhad	De novo AML	PCR	7/8	(44)
D. Zare-Abdollahi	2015	96	43/53	42	Tehran	De novo AML	Direct Sequencing	6/8	(52)
M. Teremmahi Ardestani	2018	128	44/84	34	Tehran	De novo non-M3 AML	HRM Analysis and Bidirectional sequencing	6/11	(18)
M. Iravani Saadi	2018	39	8--31	51.24±18.7	Shiraz	De novo CN-AML	Direct Sequencing	7/8	(38)
A. Mahmoudi	2021	58	N/A	N/A	Tehran	De novo AML	HRM Analysis and Direct Sequencing	4/8	(27)
Z. Sanaat	2014	40	16/24	38.3±14.5	Tabriz	De novo AML	real-time PCR	7/8	(41)
G.Zidanloo	2021	83	38/45	28.2±18.61	Mashhad	De novo CN-AML	PCR-RFLP	6/8	(23)
F.Zaker	2008	101	N/A	N/A	Tehran	De novo AML	PCR-RFLP	4/8	(49)
V. Pazhakh	2009	131	N/A	N/A	Tehran	De novo AML	Sequencing	6/8	(34)
S. Rostami	2012	115	62/53	31	Tehran	APL	Multiplex-PCR and Sequencing	6/8	(36)
M. Sheikhi	2017	91	N/A	N/A	Tehran	child AML	PCR-RFLP	6/8	(43)

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism, RT-PCR: real-time PCR, HRM: High Resolution Melting,

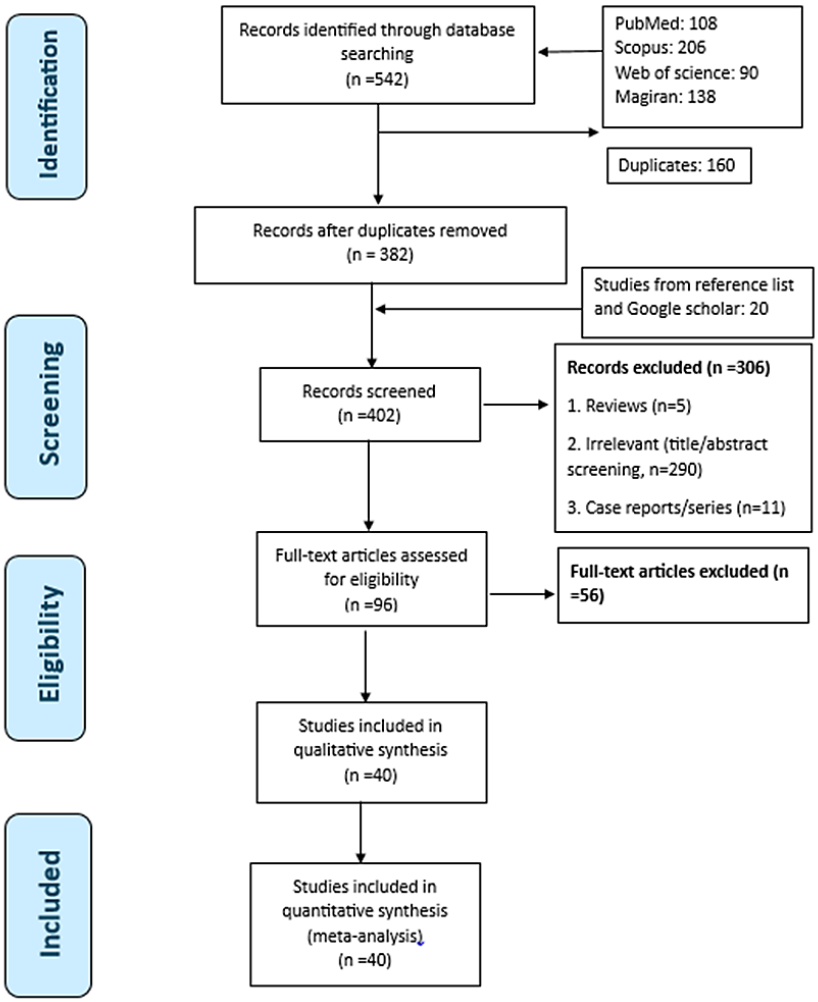

Figure 1. Flowchart describing the process of study selection

Gathering the data of 4 studies, the prevalence of mutated WT1 was 25 out of 327 patients (8.2% (CI: 5.6 – 11.8); I2 21.2%) (figure 7). The above review also noted other mutations, such as NRAS, IDH1, IDH2, TET2, c-kit, ASXL1, and RUNX1 among Iranian AML patients. Using PCR, Mortazavi et al. identified N-RAS mutations in 20% of 60 patients, predominantly in men over 40 years and those with FAB-M4 subtype (29). Zaka Khosravi et al. (48) found N-RAS mutations in 14% of 50 Iranian AML patients using the HRM method. Iravani Saadi et al. in yet another report from Iran, detected IDH1 and IDH2 mutations in 12.8% and 13.2% of 39 cytogenetically normal (CN)-AML patients, respectively, using PCR and direct sequencing (38). Chehreghani et al. reported TET2 mutations in 15.6% of 51 patients using PCR and direct sequencing (22), and another study on 212 AML patients found c-KIT mutations in 1.4% and 4.7% of the patients in exon 8 and D816, respectively, using PCR-RFLP (50). In a study on 40 AML patients in northeastern Iran, ASXL1 mutations were found in 10% and RUNX1 mutations in 2.5% of the patients (32).

Subgroup analysis: The frequency of genetic mutations, categorized by geographic distribution, was examined throughout four major areas of Iran. In the Western area (Tabriz), the predominant mutations identified among patients were FLT3-ITD (60.00%; 95% CI: 40.00 to 79.00), FLT3-TKD (38.00%; 95% CI: 15.00 to 63.00), and NPM1 (36.00%; 95% CI: 18.00 to 56.00). In contrast, the Eastern area (Mashhad) had the highest frequencies of mutations: CEBPA (22.00%; 95% CI: 11.00 to 35.00), FLT3-ITD (19.00%; 95% CI: 16.00 to 22.00), and NPM1 (17.00%; 95% CI: 8.00 to 27.00).

In the Central area (Tehran), the predominant mutations were FLT3-ITD (20.00%; 95% CI: 16.00 to 25.00), NPM1 (19.00%; 95% CI: 16.00 to 21.00), and DNMT3A (14.00%; 95% CI: 11.00 to 17.00), respectively. In the Southern area (Shiraz), the most often seen mutations were FLT3-ITD (23.00%; 95% CI: 18.00 to 29.00), NPM1 (18.00%; 95% CI: 11.00 to 26.00), and DNMT3A (13.00%; 95% CI: 4.00 to 25.00), respectively (figure 8).

Table 2. Meta-analysis of the prevalence of prognostically important mutations among Iranian AML patients. 9is not mentond in the text

Group	No. studies	No. patients	Heterogeneity		Model	Meta-analysis
			I^2	*P*		Prevalence (95%CI)
FLT3-ITD	34	3152	72.2	.000	Random	21.9 (19.19 -24.1)
FLT3-TKD	19	1639	59.6	0.00	Random	6.6 (4.7-9.3)
NPM1	18	1590	66.6	0.00	Random	19 (15.9 – 22.6)
DNMT3A	5	505	0	0.57	Fixed	13.9 (11.1 – 17.2)
CEBPA	5	343	80.6	0.00	Random	18.5 (10.3 – 31)
WT1	4	327	21.2	0.28	Fixed	8.2 (5.6 – 11.8)

FLT3-ITD: FMS like Tyrosine Kinase 3 receptor- internal tandem duplication, FLT3-TKD: FLT3- tyrosine kinase domain, NPM1; Nucleophosmin, DNMT3A: DNA methyltransferase 3 alpha, CEBPA: CCAAT enhancer binding protein alpha, WT1: Wilms' tumor 1

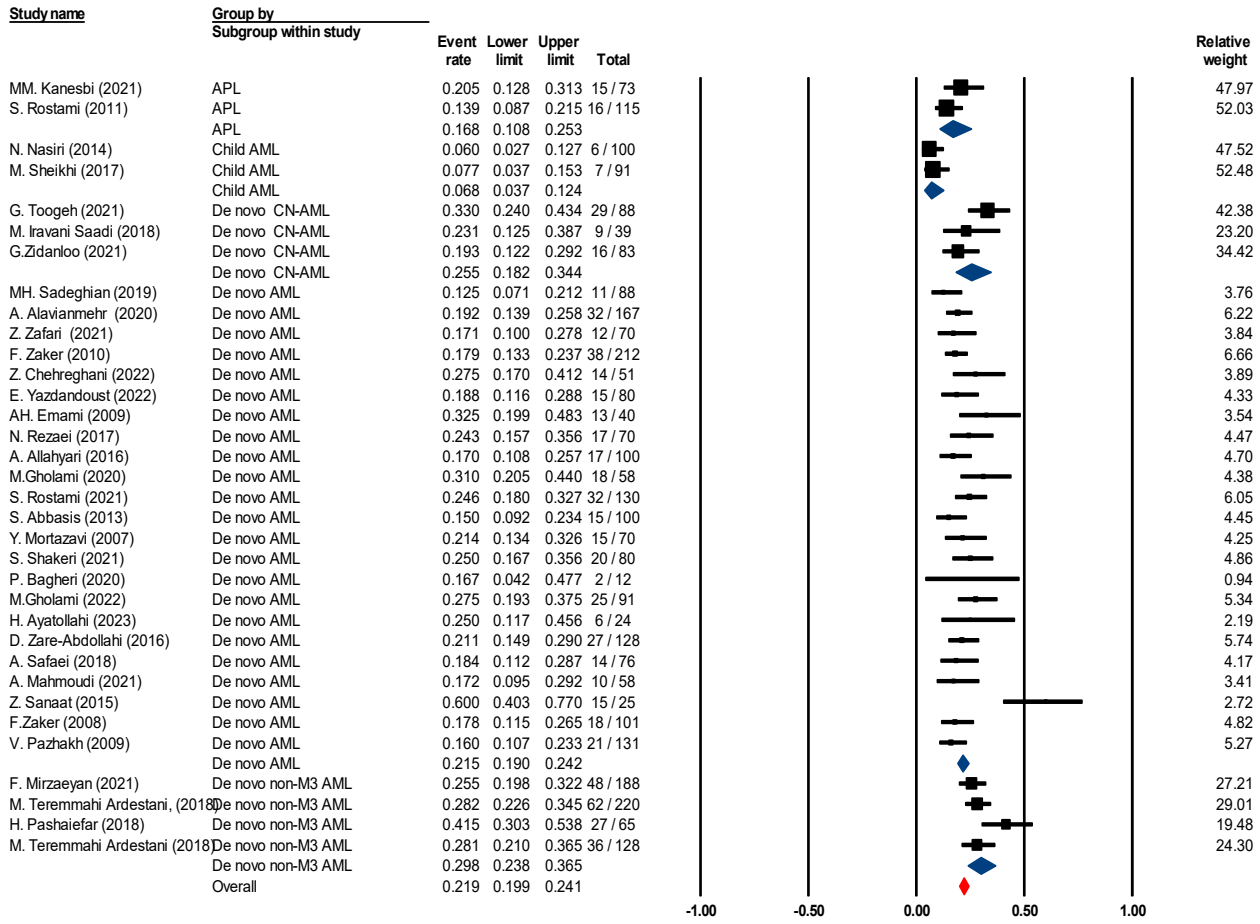

Figure 2. The forest plot of the FLT3.ITD mutation prevalence in Iranian AML patients.

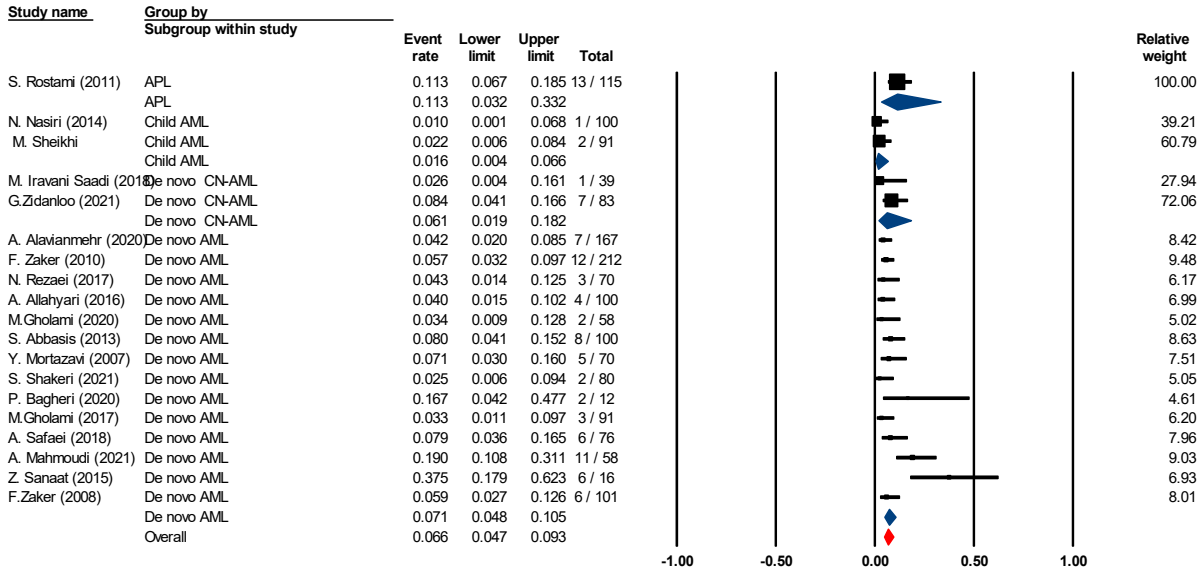

Figure 3. The forest plot of the FLT3-TKD mutation prevalence in Iranian AML patients.

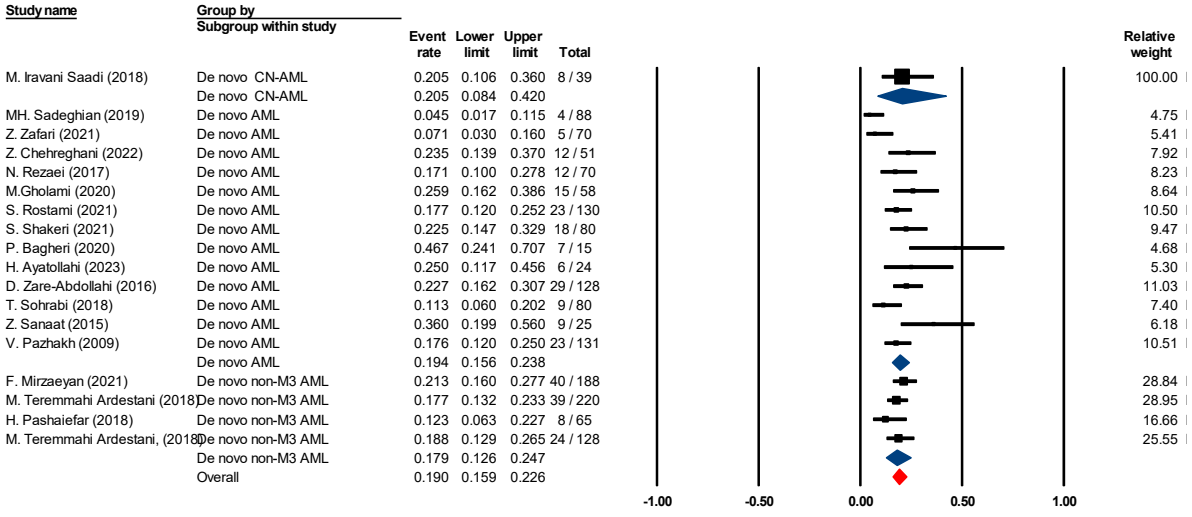

Figure 4. The forest plot of the NPM1 mutation prevalence in Iranian AML patients.

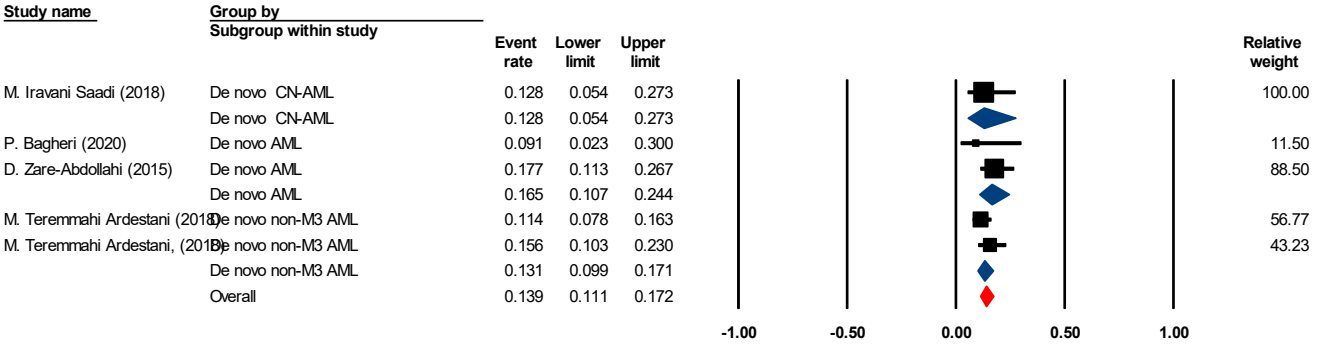

Figure 5. The forest plot of the DNMT3A mutation prevalence in Iranian AML patients.

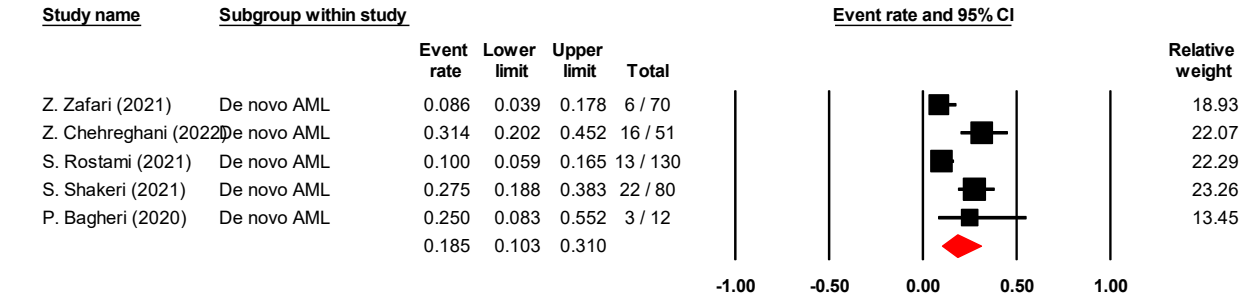

Figure 6. The forest plot of the CEBPA mutation prevalence in Iranian AML patients.

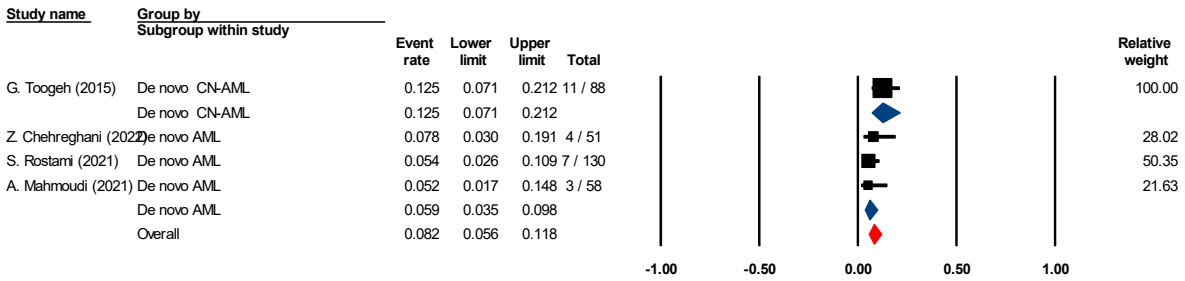

Figure 7. The forest plot of the WT1 mutation prevalence in Iranian AML patients.

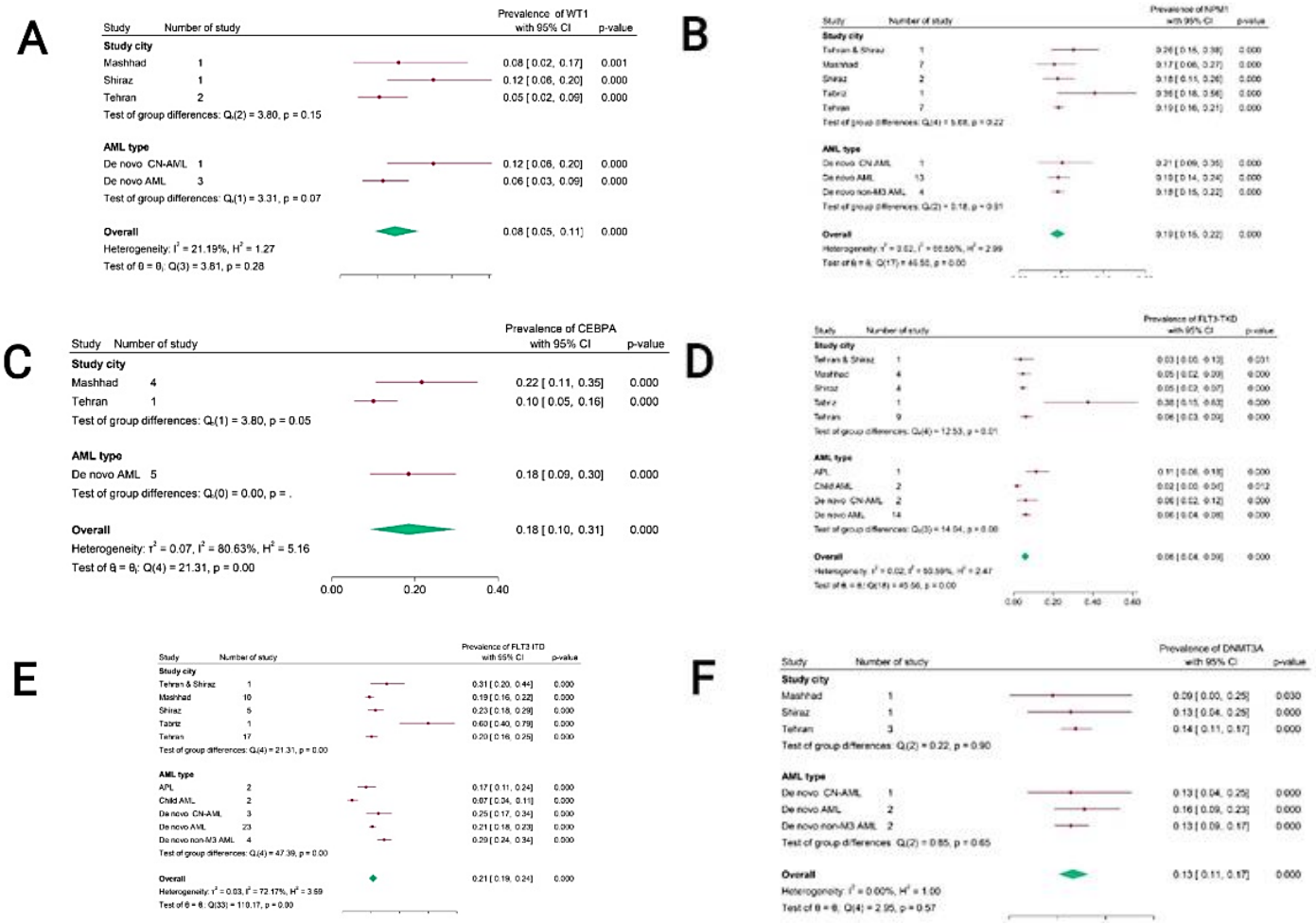

Figure 8. The forest plot of pooled prevalence of gene mutation in Iranian AML patients based on study location and AML subtype. (A) WT1; (B) NPM1; (C) CEBPA; (D) FLT3-TKD; (E) FLT3-ITD; and (F) DNMT3A.

Discussion

AML development is believed to involve multiple pathogenic stages that requires a minimum of two types of genetic changes. In 2001, Gilliland and Griffin introduced the two-hit mutation model and categorized primary oncogenic mutations (54). The theory suggests that AML results from the interaction of at least two types of mutations: class I mutations provide proliferation and survival advantages, while class II mutations affect cell differentiation and apoptosis. This theory; however, fails to explain many cases where no known mutations are found. Besides, some mutations, particularly epigenetic modifiers, do not fall into these two categories (55). The finding of these mutations has greatly enhanced our comprehension of leukemogenesis. AML exhibits high heterogeneity manifested through intricate cytogenetic alterations and molecular genetic abnormalities (56, 57). Reports that provide detailed information about the geographical variation of molecular genetic abnormalities in AML can help understand the genetic and environmental factors that play a role in the development of leukemia; however, more data from different regions of the world are necessary. Thus, we conducted this research to analyze the epidemiological data on the common AML-associated mutations among 3,340 Iranian patients. This review stands as a part of a consecutive series reported on AML mutations in a West Asian population, and it is the first nationwide study on this subject in Iran. Our comprehensive research indicated that the FLT3-ITD gene mutation was the most prevalent, followed by NPM1, CEBPA, DNMT3A, and WT1. The results of this study align with Japanese studies, notably on the elevated prevalence of FLT3, NPM1, and CEBPA mutations (58).

This geographic study offers a detailed picture of the mutational landscape of AML across four significant geographical regions of Iran. The results highlight the persistent prevalence of FLT3-ITD and NPM1 mutations across all regions, with significant geographical variations, including a higher incidence of CEBPA mutations in the Eastern area and FLT3-TKD mutations in the Western region. The occurrence of DNMT3A mutations in both central and Southern areas underscores the heterogeneous genetic landscape of AML within the Iranian population.

This study reports a prevalence of FLT3-ITD mutations in AML patients at 21.9% (95% CI, 19.19 - 24.1), consistent with other findings (58-61). The results of this study differ from some research conducted in Saudi Arabia and India, especially regarding the elevated occurrence of FLT3-ITD mutations (9%, 14.4%, and 15.3%, respectively) (62-64). In addition, a research conducted in Turkey found that FLT3-ITD was present in around 25% of individuals (65). The potential reasons for the variability in FLT3-ITD frequency across different research include discrepancies in sample size, variations in the selected patient populations, or age variances. Research by Sabir et al. (66), including 180 Pakistani AML patients aged 15-60, revealed a FLT3-ITD prevalence of 18.9%. The investigation revealed no statistically significant correlation with age, sex, socioeconomic status, total leukocyte count, or blast cell count, consistent with the findings of Allahyari et al (67). Adult AML patients have a prevalence of 25-30% for FLT3-ITD, whereas pediatric patients have a prevalence of 10-21% (63, 67). Additionally, FAB-classified M2 and M4 AML subsets had a higher frequency of the FLT3-ITD mutation (16, 68). The median age of the research participants may explain why the prevalence of FLT3-ITD is different in Iran compared to neighboring countries. In studies conducted in Saudi Arabia and India, the median age of the patients was relatively low. Furthermore, the Turkish study included participants who were 18 years of age and older. However, variations in the occurrence of FLT3 mutation may be influenced by changes in ethnicity and geographical location.

Although we applied consistent inclusion criteria, notable variation remained in the reported frequencies of mutations, especially CEBPA and FLT3-TKD. These discrepancies likely reflect differences in patient populations, geographic backgrounds, and the diagnostic methods employed. Due to inconsistent reporting, subgroup and meta-regression analysis for other variables could not be conducted. This highlights the importance of more transparent and standardized reporting in future research.

NPM1 was the second most common mutation, with an overall frequency of about 19.2% (95% CI, 15.9 – 22.6). Vemprala et al. (64) detected NPM1 mutations in 16.02% of AML patients (n=896). In a larger group of 2668 AML patients, Sargas et al. (69) identified mutated NPM1 in 22.4% of cases. A research by Yatsenko et al. (70) in Russia involving 186 pediatric de novo AML patients (with median age of 8) revealed an NPM1 prevalence of 8% (95% CI, 5.2%, 2.2-8.3). Research indicates that NPM1 mutations have a higher prevalence with getting older. Rau et al. (71) showed that among over 4,300 adult patients, the overall frequency of NPM1 mutations was 31.4% (ranging from 25.4% to 41%), whereas among over 900 pediatric AML patients, the frequency of NPM1 mutations was 7.5%. In the Pakistani population (n=108), the frequency of the NPM1 mutation was 34.3% (72). The results of our study, gathered from three prominent AML investigation centers in Iran (Tehran, Mashhad, and Shiraz), represent various ethnic

groups, while the majority of cohorts in other countries originate from single centers and do not accurately represent the conditions of their respective nations. In our research, we also discovered CEBPA and DNMT3A mutations as the third and fourth most common genetic abnormalities, respectively. Taubo et al. (73) examined 4708 newly diagnosed AML adult patients for CEBPA defects and reported a prevalence of 5.1%. The significant difference compared to our report might be due to ethnic and sample size variations. In line with our data, Hou et al. (74), in a study in Taiwan, found DNMT3A mutations in 14% of AML patients. Research conducted in China by Dou et al. (56) showed a high prevalence of epigenetic gene mutations, particularly in male patients and the elderly, in genes including TET2 (47.2%), ASXL1 (22.6%), and DNMT3A. Due to the high frequency of recurrent AML-associated somatic mutations in epigenetic regulators and the fact that leukemic epigenetic states may be reversible, these mechanisms are attractive therapeutic targets (75). Despite the importance of mutant epigenetic genes, little research has been done in Iran with small sample sizes, which calls for more study in this field. The results of these studies reveal significant differences in the occurrence of prognostically significant AML mutations, potentially influenced by genetic variability arising from ethnic diversity among Iranian provinces, along with regional variations in population genetics and environmental exposures. Limited access to molecular diagnostics in underdeveloped regions may result in underreporting or misclassification of mutations, hence impacting the quality and generalizability of prevalence statistics. These complexities highlight the urgent need to establish national protocols for detecting and predicting AML mutations to enhance treatment efficacy and prolong patient life.

This review has a few limitations worth mentioning. To start, we relied on published data which could have led to publication bias because studies with positive or unique results are more likely to be published than those with neutral or negative findings. In addition, a high I^2 value was indicative of significant variability among the studies. This variability may have compromised the reliability of our results. The lack of association between age, sex, and various FAB subtypes with AML mutations hinders a comprehensive understanding of patient conditions in Iran. Also, some of the included studies lacked information about the baseline characteristics of their patients. Finally, the studies analyzed employed different techniques for detecting mutations, such as DNA sequencing and PCR, which offer varying sensitivities. PCR assays (ARMS-PCR, allele-specific PCR) limit detection to specific, well-characterized mutations or hotspots, which can lead to an underestimation of mutation prevalence in cases where rare or novel mutations are present. In contrast, NGS panels cover multiple genes and mutation types simultaneously, capturing a wider range of mutations and multiple concurrent mutations. Ultimately, NGS often report a higher overall mutation prevalence. NGS typically shows a higher overall mutation prevalence, and methodological variations may impact the accuracy of mutation detection (76). Besides, some studies did not specify the techniques they utilized.

Another significant limitation of this review is the lack of consistent reporting on clinical outcomes such as survival, treatment response, or remission. As a result, we could not evaluate the correlation between specific mutations and clinical outcomes. We recommend that future studies in Iran include detailed clinical follow-up data to enable a more comprehensive understanding of the prognostic value of these mutations. This meta-analysis offers valuable insights into prognostically significant genetic mutations in Iranian AML patients, which may assist the Ministry of Health of Iran in understanding the current patient landscape and informing their decision-making processes. Finding FLT3-ITD, NPM1, and DNMT3A as three of the most common mutations in Iranian AML patients highlights the need to develop efficient molecular testing techniques that prioritize these variations based on their frequency and prognosis. Targeted PCR-based screening for these mutations, as opposed to costly broad-panel NGS, facilitates risk classification and access to customized medicines (like FLT3 inhibitors and IDH1/2 inhibitors) within financial limitations. Policymakers should prioritize investment in accessible PCR technology and domestic research to develop treatment regimens that fit the unique Iranian genetic profile, thereby achieving results despite budget constraints.

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References

1. Pelcovits A, Niroula R. Acute myeloid leukemia: a review. R I Med J 2020; 103: 38-40.
2. Motyckova G, Stone RM. The role of molecular tests in acute myelogenous leukemia treatment decisions. Curr Hematol Malig Rep 2010; 5: 109-17.
3. Dang L, Jin S, Su SM. IDH mutations in glioma and acute myeloid leukemia. Trends Mol Med 2010; 16: 387-97.
4. Cairoli R, Beghini A, Grillo G, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood 2006; 107: 3463-8.
5. Riera L, Marmont F, Toppino D, et al. Core binding factor acute myeloid leukaemia and c-KIT mutations. Oncol Rep 2013; 29: 1867-72.
6. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017; 129: 424-47.
7. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. N Engl J Med 2005; 352: 254-66.
8. Mrózek K, Marcucci G, Paschka P, Whitman SP, Bloomfield CD. Clinical relevance of mutations and gene-expression changes in adult acute myeloid leukemia with normal cytogenetics: are we ready for a prognostically prioritized molecular classification? Blood 2007; 109: 431-48.
9. Ilyas AM, Ahmad S, Faheem M, et al. Next generation sequencing of acute myeloid leukemia: influencing prognosis. BMC Genomics 2015; 16: 1-12.
10. Network CGAR. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 2013; 368: 2059-74.
11. Ley TJ, Mardis ER, Ding L, et al. DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome. Nature 2008; 456: 66-72.
12. Patel SS, Pinkus GS, Ritterhouse LL, et al. High NPM1 mutant allele burden at diagnosis correlates with minimal residual disease at first remission in de novo acute myeloid leukemia. Am J Hematol 2019; 94: 921-8.
13. Poopak A, Saeedi Moghaddam S, Esfahani Z, et al. National and subnational burden of leukemia and its risk factors, 1990–2019: Results from the Global Burden of Disease study 2019. Plos One 2023; 18: e0287917.
14. Abbasi S, Ajdari A, Mohammadi S. The relationship between FLT3 mutations and complete remission of AML patients referring to Shariati hospital. Payavard Salamat 2013; 7: 177-87.
15. Alavianmehr A, Mansouri M, Ramzi M, et al. Association of killer-cell immunoglobulin-like receptor genes with acute myelogenous leukaemia. Int J Immunogenet 2020; 47: 512-21.
16. Allahyari A, Sadeghi M, Ayatollahi H, Yazdi HN, Tavakol M. Frequency of FLT3 (ITD, D835) gene mutations in acute myelogenous leukemia: A report from northeastern Iran. Asian Pac J Cancer Prev 2016; 17: 4319-22.
17. Amir Hossein E, Ramin S, Meysamie A, et al. fms like tyrosine kinase3- internal tandem duplication (FLT3-ITD) in acute myeloid leukemia, mutation frequency and its relation with complete remission, 2007- 2008. Int J Hematol Oncol Stem Cell Res 2009; 3: 14-20.
18. Ardestani MT, Kazemi A, Chahardouli B, et al. FLT3-ITD compared with DNMT3A R882 mutation is a more powerful independent inferior prognostic factor in adult acute myeloid leukemia patients after allogeneic hematopoietic stem cell transplantation: A retrospective cohort study. Turk J Haematol 2018; 35: 158-67.
19. Ardestani MT, Chahardouli B, Mohammadi S, et al. Detection of R882 mutations in DNMT3A gene in acute myeloid leukemia: A method comparison study. Iran J Ped Hematol Oncol 2018; 8: 172-9.
20. Ayatollahi H, Boroumand-Noughabi S, Ferns G, et al. Evaluation of the expression of LC3-II and BECLIN1 genes of autophagy pathway in patients with hematological malignancies. Caspian J Intern Med 2023; 14: 694-702.
21. Bagheri P, Zaker F, Sadeghian MH, et al. Frequency of DNMT3A Mutations in Patients with Acute Leukemia in Mashhad. Intern J Med Lab 2020; 7: 258-66.
22. Chehreghani Z, Sadeghian MH, Ayatollahi H, et al. Detection of TET2 mutation in patients with de novo acute myeloid leukemia: a mutation analysis of 51 Iranian patients. Asian Pac J Cancer Prev 2022; 23: 803-6.

23. Ghazaey S, Amini N. Prevalence analysis of FLT3 mutations in patients with acute myeloid leukemia with normal karyotype in Northeastern Iran. Cell Mol Res (Iran J Biol) 2022; 34: 524-33.
24. Gholami M, Bayat S, Pashaiefar H, et al. Mutational screening of RTK-BRAF genes in de novo adult acute myeloid leukemia. Gene Rep 2020; 21: 100904.
25. Gholami M, Pashaiefar H, Ebrahimpour MR, et al. Mutational analysis of FLT3 internal tandem duplication and D835 in de novo adult acute myeloid leukemia. J Adv Med Med Res 2017; 24: 1-9.
26. Kanesbi MM, Jarahi L, Ayatollahi H, Sheikhi M. Comparison of differences in blood laboratory results between acute promyelocytic leukemia and acute promyelocytic leukemia+ FLT3-internal tandem duplication patients. Iraqi J Hematol 2021; 10: 34-40.
27. Mahmoudi A, Moradabadi A, Noroozi-Aghideh A. Comparison of high-resolution melting analysis with direct sequencing for detection of FLT3-TKD, FLT3-ITD and WT1 mutations in acute myeloid leukemia. Cancer Treat Res Commun 2021; 28: 100432.
28. Mirzaeyan F, Chahardouli B, Mirzaeian A, et al. Concurrent evaluation of the expression and methylation of secreted frizzled-related protein 2 along with beta-catenin expression in patients with non-M3 acute myeloid leukemia. Iran J Med Sci 2021; 46: 180-8.
29. Mortazavi Y, Behzadi Fard M, Pourfathollah AA, Kaviani S, Feizi AA. Detection of N-RAS gene mutations in codons 12, 13 and 61 in patients with acute myeloid leukemia. Sci J Iranian Blood Transfus Organ 2007; 4: 11-7. [in Persian]
30. Naghinezhad J, Alenabi A, Ayatollahi H, et al. Expression of DR4, DR5, FAS, caspase-8 and, DDIAS genes in AML patients. Med J Islam Repub Iran 2023; 37: 68.
31. Nasiri N, Shaikhy M, Zaker F, et al. Detection and biological characteristic of FLT3 gene mutations in children with acute leukemia. Arch Iran Med 2014; 17: 258-61.
32. Parsa-Kondelaji M, Ayatollahi H, Rostami M, et al. Evaluating the frequency, prognosis and survival of RUNX1 and ASXL1 mutations in patients with acute myeloid leukaemia in northeastern Iran. J Cell Mol Med 2022; 26: 3797-801.
33. Pashaiefar H, Yaghmaie M, Tavakkoly-Bazzaz J, et al. PARP-1 overexpression as an independent prognostic factor in adult non-M3 acute myeloid leukemia. Genet Test Mol Biomarkers 2018; 22: 343-9.
34. Pazhakh V, Zaker F, Ali Moghadam K, Atashrazm F. Detection and assessment of the frequency of NPM1 and FLT3 ITD mutations in acute myeloid leukemia patients. Sci J Iran Blood Transfus Organ 2009; 6: 199-207.
35. Rezaei N, Arandi N, Valibeigi B, et al. FMS-Like tyrosine kinase 3 (FLT3) and nucleophosmin 1 (NPM1) in Iranian adult acute myeloid leukemia patients with normal karyotypes: Mutation status and clinical and laboratory characteristics. Turk J Haematol 2017; 34: 300-6.
36. Rostami S, Abroun S, Noruzinia M, Ghavamzadeh A, Alimoghaddam K. Impact of FLT-3 mutations on clinical features and response to the therapy in acute promyelocytic leukemia patients. Sci J Iran Blood Transfus Organ 2012; 8: 242-50.
37. Rostami S, Kazemi A, Chahardouli B, et al. The Prognostic impact of WT1 expression levels, mutations, and SNP rs16754 in AML patients: A retrospective cohort study. J Adv Med Biomed Res 2021; 29: 109-17.
38. Saadi MI, Zarei T, Ramzi M, Arandi N. Mutation of the DNMT3A and IDH1/2 genes in Iranian acute myeloid leukemia patients with normal karyotype (CN-AML): association with other gene mutation and clinical and laboratory characteristics. J Hematopathol 2018; 11: 29-36.
39. Sadeghian M-H, Ayatollahi H, Shams S-F, Rezaei Dezaki Z. Analysis of EVI1 gene expression in acute myeloid leukemia patients in the Northeast of Iran. Middle East J Cancer 2019; 10: 305-13.
40. Safaei A, Monabati A, Mokhtari M, Safavi M, Solhjoo F. Evaluation of the CD123 expression and FLT3 gene mutations in patients with acute myeloid leukemia. Iran J Pathol 2018; 13: 438-46.
41. Sanaat Z, Shams K, Nejati B, et al. NPM1 and FLT3-(ITD) gene mutations and laboratory findings in patients with acute myeloid leukemia in Northwest of Iran. J Gorgan Uni Med Sci 2014; 16: 80-6. [in Persian]
42. Shakeri S, Javan M, Ayatollahi H, et al. Conventional cytogenetic and molecular analysis in acute myeloid leukemia (AML) and their association with overall survival. Acta Medica Bulgarica2021; XLVIII: 15-22.
43. Sheikhi M, Zaker F, Javadi G, et al. Surveying mutation of FLT3 genes in children with acute leukemia. Asian Pacific J Cancer Care 2017; 2: 7-7.
44. Sohrabi T, Ayatollahi H, Rokni M, et al. Correlation of BCRP expression to NPM1 mutations in acute myeloid Leukemia. Intern J Hematol Onco 2018; 34: 186-186.

45. Toogeh G, Ramzi M, Faranoush M, et al. Prevalence and prognostic impact of Wilms' tumor 1 (WT1) gene, including SNP rs16754 in cytogenetically normal acute myeloblastic leukemia (CN-AML): An Iranian experience. Clin Lymphoma Myeloma Leuk 2016; 16: e21-6.
46. Yazdandoust E, Sadeghian MH, Shams SF, et al. Evaluation of FLT3-ITD mutations and MDR1 gene expression in AML patients. Iran J Pathol 2022; 17: 419-26.
47. Zafari Z, Ayatollahi H, Sohrabi T, et al. BMI-1 Gene expression in patients with acute and chronic myeloid leukemia in the Northeast of Iran. Middle East J Cancer 2023; 14: 41-8.
48. Zaka Khosravi S, Moonesi M, Moradabadi A, et al. Rapid detection of N-RAS gene common mutations in acute myeloid leukemia (AML) using high resolution melting (HRM) method. Asian Pac J Cancer Prev 2022; 23: 125-30.
49. Zaker F, Mohammadi MH, Kazemi A, Bakhshayesh M. Diagnosis of FLT3 mutations including internal tandem duplication and D835 aspartic acid point mutation in patients with acute myeloid leukemia. Razi J 2009; 15: 79-86. [in Persian]
50. Zaker F, Mohammadzadeh M, Mohammadi M. Detection of KIT and FLT3 mutations in acute myeloid leukemia with different subtypes. Arch Iran Med 2010; 13: 21-5.
51. Zare-Abdollahi D, Safari S, Movafagh A, et al. Expression analysis of BECN1 in acute myeloid leukemia: association with distinct cytogenetic and molecular abnormalities. Int J Lab Hematol 2016; 38: 125-32.
52. Zare-Abdollahi D, Safari S, Movafagh A, et al. A mutational and expressional analysis of DNMT3A in acute myeloid leukemia cytogenetic subgroups. Hematology 2015; 20: 397-404.
53. Mortazavi Y, Niazpour M, Ghaffari H. FLT3 mutations in newly diagnosed AML patients. Daneshvar Med 2006; 14: 63-8. [in Persian]
54. Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood 2002; 100: 1532-42.
55. Makkar H, Majhi RK, Goel H, et al. Acute myeloid leukemia: novel mutations and their clinical implications. Am J Blood Res 2023; 13: 12-27.
56. Dou X, Dan C, Zhang D, et al. Genomic mutation patterns and prognostic value in de novo and secondary acute myeloid leukemia: A multicenter study from China. Int J Cancer 2024; 155: 2253-64.
57. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022; 36: 1703-19.
58. Kihara R, Nagata Y, Kiyoi H, et al. Comprehensive analysis of genetic alterations and their prognostic impacts in adult acute myeloid leukemia patients. Leukemia 2014; 28: 1586-95.
59. Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood 2002; 99: 4326-35.
60. Suzuki T, Kiyoi H, Ozeki K, et al. Clinical characteristics and prognostic implications of NPM1 mutations in acute myeloid leukemia. Blood 2005; 106: 2854-61.
61. Ghosh K, Swaminathan S, Madkaikar M, et al. FLT3 and NPM1 mutations in a cohort of AML patients and detection of a novel mutation in tyrosine kinase domain of FLT3 gene from Western India. Ann Hematol 2012; 91: 1703-12.
62. Alrajeh AI, Abalkhail H, Khalil SH. Cytogenetics and molecular markers of acute myeloid leukemia from a tertiary care center in Saudi Arabia. J Appl Hematol 2017; 8: 68-74.
63. Elyamany G, Awad M, Fadalla K, et al. Frequency and prognostic relevance of FLT3 mutations in Saudi Acute myeloid leukemia patients. Adv Hematol 2014; 2014: 141360.
64. Vemprala A, Gajendra S, Gupta R, et al. Clinico-hematological profile of acute myeloid leukemia: Experience from a tertiary care cancer center in North India. Cureus 2023; 15: e50869.
65. Merdin A, Dal MS, Kizil Çakar M, et al. Molecular evaluation of mutations in acute myeloid leukemia patients from Turkey: A single-center study. Medicine (Baltimore) 2021; 100: e27458.
66. Sabir K, Butt NI, Akram M, et al. Prevalence of FLT-3 mutation in acute myeloid leukaemia. J Ayub Med Coll Abbottabad 2021; 33: 399-402.
67. Czogała M, Czogała W, Pawińska-Wąsikowska K, et al. Characteristics and outcome of FLT3-ITD-positive pediatric acute myeloid leukemia—experience of polish pediatric leukemia and lymphoma study group from 2005 to 2022. Cancers 2023; 15: 4557.
68. Semary SF, Hammad M, Soliman S, et al. Outcome of childhood acute myeloid leukemia with FLT3-ITD mutation: The experience of children's cancer hospital

Egypt, 2007-17. Clin Lymphoma Myeloma Leuk 2020; 20: e529-41.

69. Sargas C, Ayala R, Larráyoz MJ, et al. Molecular landscape and validation of new genomic classification in 2668 adult AML patients: Real life data from the PETHEMA Registry. Cancers (Basel) 2023; 15: 438.
70. Yatsenko Y, Kalennik O, Maschan M, et al. NPM1, FLT3, and c-KIT mutations in pediatric acute myeloid leukemia in Russian population. J Pediatr Hematol Oncol 2013; 35: e100-8.
71. Rau R, Brown P. Nucleophosmin (NPM1) mutations in adult and childhood acute myeloid leukaemia: towards definition of a new leukaemia entity. Hemato Onco 2009; 27: 171-81.
72 Mahmood R, Altaf C, Malik HS, Khan SA. Clinico-Haematologic association and prognostic relevance of NPM1 and FLT3-ITD mutations in acute myeloid leukaemia. Pak J Med Sci 2019; 35: 23-8.
73. Taube F, Georgi JA, Kramer M, et al. CEBPA mutations in 4708 patients with acute myeloid leukemia: differential impact of bZIP and TAD mutations on outcome. Blood 2022; 139: 87-103.
74. Hou HA, Kuo YY, Liu CY, et al. DNMT3A mutations in acute myeloid leukemia: stability during disease evolution and clinical implications. Blood 2012; 119: 559-68.
77. Cai SF, Levine RL. Genetic and epigenetic determinants of AML pathogenesis. Semin Hematol 2019; 56: 84-9.
76. Severina N, Sidorova Y, Risinskaya N, et al. PB1792: NGS vs PCR for the detection of NPM1 gene mutations in acute myeloid leukemia. HemaSphere 2022; 6: 1672-3.