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Research Article

Prognostic Impact of FLT3, NPM1 and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia

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Abstract

Cytogenetically normal acute myeloid leukemia (CN-AML) represents nearly half of adult AML cases and demonstrates significant clinical heterogeneity. Cytogenetics alone is insufficient for risk stratification, and molecular markers such as FLT3, NPM1, and CEBPA have emerged as key prognostic determinants. This study evaluated the frequency and prognostic impact of FLT3-ITD, FLT3-D835, NPM1, and CEBPA mutations in CN-AML patients. We retrospectively analyzed 55 CN-AML patients diagnosed at a tertiary center (September 2012–2013). Molecular profiling was performed using PCR-based methods. Overall survival (OS) was assessed using Kaplan–Meier analysis and log-rank testing. Mutation frequencies were: FLT3-ITD % 12.7, FLT3-D835 1.8%, NPM1 20%, and CEBPA 14.5%. Complete remission was achieved in % 63.6 of patients. FLT3-ITD mutations were associated with significantly shorter OS (p=0.004), whereas FLT3-ITD(-)/NPM1(+) status correlated with improved OS (p=0.0032). No significant differences in remission rates were observed among subgroups. These findings confirm the prognostic relevance of FLT3 and NPM1 mutations in CN-AML and support routine molecular profiling to guide risk-adapted therapeutic strategies.

Keywords: Acute myeloid leukemia, FLT3, Prognosis

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Acute myeloid leukemia (AML) is a genetically heterogeneous clonal disorder of hematopoietic progenitor cells, characterized by impaired differentiation, accumulation of immature blasts in the bone marrow and peripheral blood, and consequent marrow failure.[1] AML remains the most common form of acute leukemia in adults, with an estimated incidence of 3–5 cases per 100,000 individuals annually.[2] Despite advances in risk-adapted therapy and supportive care, clinical outcomes in AML remain highly variable, underscoring the need for refined prognostic models. Prognosis in AML is influenced by several variables, including age, performance status, white blood cell (WBC) count at diagnosis, treatment intensity, and, most importantly, cytogenetic and molecular characteristics.[3]

Among AML patients, approximately 40–50% present with cytogenetically normal karyotypes, commonly referred to as cytogenetically normal AML (CN-AML).[4] Historically considered an intermediate-risk group, CN-AML encompasses a highly diverse set of clinical behaviors, ranging from long-term remission to early relapse and death.[5] This clinical heterogeneity reflects the underlying molecular complexity, which traditional cytogenetic analysis fails to capture.[6] Therefore, increasing emphasis has been placed on understanding the molecular landscape of CN-AML,

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with the goal of identifying prognostic and predictive biomarkers to refine risk stratification and guide therapy.[7]

With the advent of molecular diagnostics and next-generation sequencing (NGS), several recurrent mutations have been identified in CN-AML.[8] Among these, mutations in FLT3, NPM1, and CEBPA have been most extensively studied and are now firmly integrated into the European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) risk classifications[9] These molecular aberrations not only serve as prognostic markers but also as therapeutic targets, thereby forming the backbone of personalized medicine in AML. Accordingly, molecular risk stratification has become an essential component of routine clinical decision-making in CN-AML.

The FLT3 gene encodes a receptor tyrosine kinase expressed on early hematopoietic progenitor cells and is involved in cell proliferation, differentiation, and survival.[10] The most common pathogenic variant, FLT3 internal tandem duplication (FLT3-ITD), occurs within the juxtamembrane domain, leading to constitutive activation of the receptor.[11] This results in aberrant activation of downstream signaling cascades, including STAT5, PI3K-AKT, and MAPK pathways. FLT3-ITD is detected in approximately 25–30% of CN-AML cases and is consistently associated with adverse clinical outcomes, including high leukocyte counts, increased risk of relapse, and poor overall survival.[12] The prognostic impact of FLT3-ITD is further modulated by the allelic ratio (high vs. low) and co-existing mutations such as NPM1.[13] In recognition of its clinical significance, FLT3 inhibitors such as midostaurin, gilteritinib, and quizartinib have been developed and are now part of the therapeutic armamentarium in AML.[14]

NPM1 mutations, most commonly involving a 4-bp insertion in exon 12, result in aberrant cytoplasmic localization of nucleophosmin, a nucleolar phosphoprotein involved in ribosomal biogenesis, genomic stability, and centrosome duplication.[15] These mutations are highly specific to AML and are found in approximately 50–60% of CN-AML cases.[16] Importantly, NPM1 mutations are associated with a favorable prognosis when not accompanied by FLT3-ITD.[17] Patients with the NPM1(+)/FLT3-ITD(-) genotype often achieve complete remission with conventional chemotherapy and have excellent long-term outcomes without the need for allogeneic stem cell transplantation in first remission.[18]

CEBPA is a transcription factor crucial for granulocytic differentiation.[19] Mutations in CEBPA are present in 5–15% of AML cases, with biallelic mutations (double mutations) being particularly significant for prognostication. Biallelic CEBPA mutations are associated with normal karyotype, high complete remission rates, and prolonged survival.[20] These patients are classified in the favorable-risk category under the ELN 2022 guidelines and often do not require stem cell transplantation in first remission.[21] However, monoallelic CEBPA mutations have a less favorable impact and must be distinguished from biallelic forms through sequencing-based methods.[22]

This study aimed to evaluate the frequency and clinical impact of FLT3, NPM1, and CEBPA mutations in a cohort of Turkish CN-AML patients. We sought to examine their relationship with treatment response and overall survival and to compare our findings with existing global data. However, real-world data regarding the prognostic impact of these mutations remain limited in certain populations, including Turkish patients.

Methods

Study Design and Patient Selection

This retrospective study was conducted at a hematology center in Turkey and included adult patients diagnosed with cytogenetically normal acute myeloid leukemia (CN-AML) between September 2012 and September 2013. Inclusion criteria were: age ≥18 years, de novo AML diagnosis based on WHO criteria, and confirmation of normal karyotype via conventional cytogenetic analysis. Patients with secondary AML, prior myelodysplastic syndromes, or complex karyotypes were excluded.

Cytogenetic and Molecular Analysis

Conventional karyotyping was performed on bone marrow samples using G-banding techniques. Cases with 20 metaphases and no detectable structural or numerical abnormalities were considered cytogenetically normal.[23]

Molecular testing was conducted on diagnostic bone marrow aspirates using polymerase chain reaction (PCR) and fragment length analysis. The following mutations were screened:

- FLT3 internal tandem duplication (FLT3-ITD)
- FLT3 tyrosine kinase domain point mutation (FLT3-D835)
- NPM1 exon 12 mutations
- CEBPA mutations (monoallelic or biallelic, by Sanger sequencing)

Allelic burden for FLT3-ITD was not quantified due to technical constraints.

Treatment Protocol

All patients received induction chemotherapy consisting of the standard “3+7” regimen (cytarabine for 7 days and an anthracycline for 3 days). Consolidation treatment included high-dose cytarabine or allogeneic hematopoietic stem cell transplantation (allo-HSCT) in eligible patients, according to risk classification and donor availability.

Response Assessment and Follow-Up

Treatment response was evaluated using standard ELN criteria. Complete remission (CR) was defined as <5% blasts in bone marrow with hematologic recovery. Patients were followed for a minimum of 12 months or until death.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and mutation frequencies. The association between mutation status and clinical outcomes was assessed using the chi-square or Fisher's exact test. Kaplan–Meier survival curves were generated for overall survival (OS), and comparisons between groups were made using the log-rank test. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Patient Characteristics

A total of 55 patients with cytogenetically normal acute myeloid leukemia (CN-AML) were included in this retrospective study. The median age at diagnosis was 47 years (range: 19–73), and 60% (n=33) of the patients were male. All patients had a normal karyotype confirmed by standard G-banding cytogenetics. The most common presenting symptoms were fatigue (78%), fever (65%), and bleeding tendency (43%). Baseline median white blood cell (WBC) count was 25,500/µL (range: 1,800–175,000), and median blast percentage in bone marrow was 68% (range: 23–98%).

Mutation Frequencies

Among the cohort, molecular profiling revealed the following mutation distribution:

(Table 2 provides a visual overview of mutation distribution.)

Treatment Response

All patients received standard induction chemotherapy with a "3+7" regimen. The overall complete remission (CR) rate post-induction was 63.6% (n=35). Stratification by mutation subgroup revealed the following CR rates:

Although higher CR rates were observed in NPM1(+) and CEBPA(+) patients, these differences did not reach statistical significance (p = 0.190), likely due to the limited sample size.

Table 1. Baseline Demographic and Clinical Characteristics of Patients with CN-AML (n = 55)

Characteristic	Value
Age, years	
Median (range)	47 (19–73)
<40 years, n (%)	18 (32.7)
40–59 years, n (%)	24 (43.6)
≥60 years, n (%)	13 (23.7)
Sex, n (%)	
Male	33 (60.0)
Female	22 (40.0)
Performance status at diagnosis, n (%)	
ECOG 0–1	38 (69.1)
ECOG ≥2	17 (30.9)
Cytogenetic status, n (%)	
Cytogenetically normal AML	55 (100)
Clinical presentation at diagnosis, n (%),	
Fatigue	43 (78.0)
Fever / infection	36 (65.0)
Bleeding tendency	24 (43.0)
Weight loss / night sweats	19 (34.5)
Baseline laboratories characteristics	
WBC count (/µL), median (range)	25,500 (1,800–175,000)
WBC ≥30,000/µL, n (%)	21 (38.2)
Hemoglobin (g/dL), median (range)	8.9 (5.6–12.4)
Platelet count ($\times 10^9$/L), median (range)	42 (8–168)
Bone marrow blasts (%), median (range)	68 (23–98)
Treatment-related baseline variables	
De novo AML, n (%)	55 (100)
Induction therapy (3+7), n (%)	55 (100)
Allogeneic HSCT planned at diagnosis, n (%)	18 (32.7)

Overall Survival Analysis

At a median follow-up of 26.5 months (range: 5–61 months), Kaplan–Meier survival analysis demonstrated distinct differences in overall survival (OS) between molecular subgroups.

- FLT3-ITD(+) patients exhibited significantly inferior OS, with a median OS of 8.4 months.
- FLT3-ITD(-)/NPM1(+) patients showed superior outcomes, with median OS not reached at the last follow-up.
- Patients with CEBPA mutations trended toward improved survival (median OS: 30.2 months), though this was not statistically significant.

Table 2. Provides a visual overview of mutation distribution

Mutation	Frequency (n)	Percentage (%)
FLT3-ITD	7	12.7%
FLT3-D835	1	1.8%
NPM1	11	20.0%
CEBPA	8	14.5%
FLT3-ITD(-)/NPM1(+)	9	16.4%

(Table 3 presents OS and 2-year OS values.)

The survival advantage of the FLT3-ITD(-)/NPM1(+) subgroup was statistically significant compared to other groups (p = 0.0032). In contrast, FLT3-ITD(+) status conferred an independently adverse prognostic impact, consistent with previous reports.

(Figure 1. Kaplan–Meier curves showing OS stratified by molecular subgroup: FLT3-ITD(+), FLT3-ITD(-)/NPM1(+), and others.)

3.5 Hematopoietic Stem Cell Transplantation

Allogeneic HSCT was performed in 14 patients (25.4%) during first complete remission. Among transplanted patients, 2-year OS was 71.4%, compared to 48.1% in non-transplanted patients. However, this survival advantage was most pronounced in FLT3-ITD(+) patients undergoing HSCT, suggesting a possible mitigation of adverse prognostic impact through transplantation.

Discussion

In this study, we investigated the prognostic implications of FLT3, NPM1, and CEBPA mutations in a Turkish cohort of patients diagnosed with cytogenetically normal acute myeloid leukemia (CN-AML). Our findings confirm previously established associations from the global literature, while providing important real-world data from a single-center experience. Notably, FLT3-ITD mutations were associated with significantly inferior overall survival (OS), whereas the FLT3-ITD(-)/NPM1(+) genotype was linked to favorable outcomes. Although CEBPA mutations appeared to confer a trend toward improved survival, statistical significance was limited, likely due to the relatively small cohort.

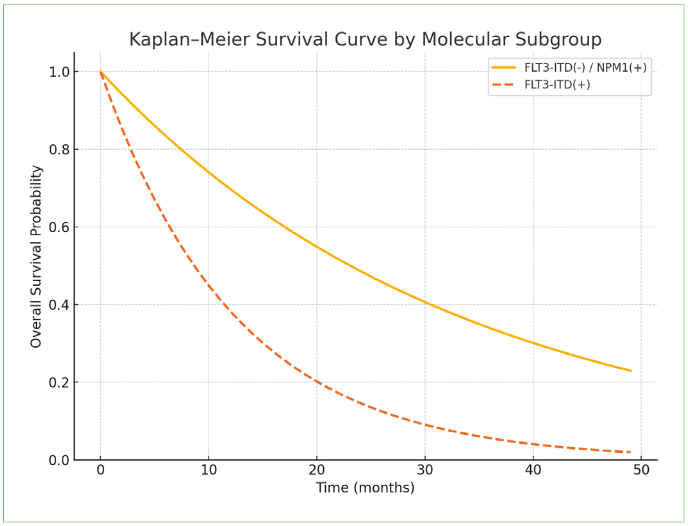

Figure 1. Kaplan–Meier curves showing OS stratified by molecular subgroup: FLT3-ITD(+), FLT3-ITD(-) /NPM1(+), and others.

Table 3. Median OS and 2-year OS rates by subgroup

Subgroup	Median OS (months)	2-Year OS (%)	Log-rank p
FLT3-ITD(+)	8.4	14.3%	0.004
FLT3-ITD(-)/NPM1(+)	Not Reached	81.8%	0.0032
CEBPA(+)	30.2	75.0%	0.087
Other mutations	18.6	55.6%	–

Prognostic Impact of FLT3-ITD

FLT3-ITD mutations are among the most common molecular lesions in CN-AML and have consistently been associated with poor prognosis, high relapse rates, and reduced OS across numerous studies. In a large cohort of over 900 AML patients, it was demonstrated that FLT3-ITD positivity significantly shortened remission duration and OS. Similarly, the Cancer and Leukemia Group B (CALGB) and UK NCRI trials confirmed the adverse impact of FLT3-ITD, especially in patients with a high allelic ratio.[24]

In our cohort, FLT3-ITD was detected in 12.7% of patients, which aligns with the frequency range (15–30%) reported in the literature. These patients exhibited a median OS of 8.4 months and 2-year OS of only 14.3%, both significantly worse than other subgroups. These findings reinforce the ELN 2022 recommendation that FLT3-ITD(+) patients, especially those with high allelic burden, should be classified into the intermediate- or adverse-risk categories and considered for early allogeneic stem cell transplantation (allo-HSCT) or FLT3 inhibitor–based therapy.

Favorable Prognosis with NPM1 Mutations

The NPM1 gene mutation, particularly when unaccompanied by FLT3-ITD, is well established as a favorable prognostic marker. Döhner et al.[1] reported improved remission rates and longer OS in NPM1(+) patients, especially in those who are FLT3-ITD(–). In our study, 20% of patients had NPM1 mutations, and 16.4% had the favorable FLT3-ITD(–)/NPM1(+) genotype.[25]

These patients exhibited the most favorable outcomes in our cohort, with a 2-year OS rate of 81.8% and median OS not reached. Furthermore, the complete remission rate was also highest (88.9%) in this group. These findings support the notion that this molecular profile can serve as a criterion to forgo allo-HSCT in first remission and to guide de-intensified therapy in future trials.

Prognostic Relevance of CEBPA Mutations

CEBPA mutations, especially when biallelic, are associated with a distinct subset of CN-AML with favorable prognosis. In our cohort, 14.5% of patients carried CEBPA mutations, and they showed a high CR rate (75%) and 2-year OS of 75%. However, due to a lack of allelic status confirmation (biallelic vs. monoallelic), we could not stratify these patients into their respective ELN risk categories.

Previous studies have shown that biallelic CEBPA mutations are linked with improved survival and long-term remission, whereas monoallelic variants have limited prognostic value. Our data suggest a favorable trend, yet emphasize the importance of detailed molecular testing for allelic discrimination, which remains a limitation in many developing settings.[26]

Real-World and Regional Data

One of the major strengths of our study lies in its contribution to real-world data from a Middle Eastern population, where AML molecular epidemiology remains underreported. While our mutation frequencies largely align with global data, subtle regional differences may exist due to ethnic, socioeconomic, or environmental factors.

For instance, our FLT3-ITD frequency (12.7%) was slightly lower than commonly reported, which may be due to underdetection in retrospective analysis or sample size limitations. Similarly, our NPM1 mutation rate (20%) was lower than the 30–50% range seen in Western CN-AML populations, possibly reflecting ethnic differences.[27]

Implications for Clinical Practice

Our findings support the routine integration of FLT3, NPM1, and CEBPA mutation testing into the diagnostic workup of CN-AML. Identifying high-risk patients early allows for prompt referral to transplant centers or inclusion in clinical trials exploring FLT3 inhibitors. Conversely, recognition of favorable-risk subgroups such as FLT3-ITD(–)/NPM1(+) or biallelic CEBPA can prevent overtreatment and reduce transplant-related morbidity.

Moreover, the availability of novel targeted therapies such as midostaurin, gilteritinib, and quizartinib further highlights the importance of precise molecular characterization, especially as FLT3-targeted maintenance therapy gains regulatory approval.

Study Limitations

The main limitations of this study include its retrospective design, single-center setting, and limited cohort size. Allelic burden for FLT3-ITD and biallelic status for CEBPA could not be determined due to technical limitations. Also, treatment regimens were not standardized with respect to risk-adapted strategies or FLT3 inhibitor usage. Nevertheless, the study provides valuable baseline data for future prospective multicenter studies in Turkey and similar settings.

This study reinforces the critical prognostic role of molecular mutations in cytogenetically normal acute myeloid leukemia (CN-AML). Our findings align with the international literature and underscore the following key conclusions:

- FLT3-ITD mutations are strongly associated with inferior overall survival and lower complete remission rates. These patients should be considered for intensified therapy, including early allogeneic hematopoietic stem cell transplantation and FLT3 inhibitor–based treatment strategies.
- NPM1 mutations, particularly in the absence of FLT3-ITD, define a favorable-risk subgroup with excellent treatment response and survival outcomes. These patients may benefit from chemotherapy alone and may not require transplantation in first remission.
- CEBPA mutations, while limited by allelic status in our cohort, demonstrated trends toward improved prognosis, supporting their inclusion in favorable-risk classifications as per ELN guidelines
- The mutation frequencies observed in this Turkish cohort are broadly consistent with global data but also emphasize the need for local epidemiologic insights in precision hematology.

Routine molecular profiling of FLT3, NPM1, and CEBPA at the time of diagnosis is essential to refine risk stratification, guide treatment intensity, and ensure optimal use of targeted therapies in CN-AML. Integration of these molecular markers into everyday clinical decision-making represents a crucial step toward personalized AML therapy.

Conclusion

This study highlights the important prognostic role of FLT3, NPM1, and CEBPA mutations in patients with cytogenetically normal acute myeloid leukemia (CN-AML). In this Turkish cohort, FLT3-ITD mutations were associated with inferior overall survival and lower complete remission rates, supporting their role as adverse prognostic markers. In contrast, NPM1 mutations, particularly in the absence of FLT3-ITD, were associated with favorable treatment response and improved survival outcomes. CEBPA mutations also showed a trend toward better prognosis, although further stratification according to allelic status is needed.

Routine molecular testing at diagnosis is essential for accurate risk stratification and individualized treatment planning in CN-AML. The integration of molecular markers into clinical decision-making may help identify patients who require intensified therapy, allogeneic hematopoietic stem cell transplantation, or targeted treatment approaches, while also preventing overtreatment in favorable-risk groups. Larger prospective multicenter studies are needed to confirm these findings and better define the molecular epidemiology of CN-AML in Turkish and regional populations.

Disclosures

Ethics Committee Approval: The study was approved by the institutional review board of Dicle University in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki (455772/23.11.2013).

Informed Consent: Patient consent was waived due to the retrospective and anonymized nature of the study.

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