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Molecular Profiling of TP53 Mutations in Acute Myeloid Leukemia: A Prognostic and Therapeutic Insight

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Abstract

Background

TP53 mutations represent a clinically significant subset of molecular alterations in acute myeloid leukemia (AML), frequently associated with complex cytogenetics, chemoresistance, and poor prognosis. Data on TP53-mutated AML from North African populations remain limited**.**

Objective

To determine the prevalence, clinical characteristics, and prognostic impact of TP53 mutations in AML patients treated at a tertiary cancer center in Morocco.

Methods

This retrospective study included 80 adult patients with newly diagnosed AML at Mohammed V University Hospital, Rabat, from January 2017 to December 2020. Targeted next-generation sequencing was performed to detect TP53 mutations. Clinical data, cytogenetic profiles, treatment responses, and survival outcomes were analyzed and compared between TP53-mutated and TP53 wild-type groups.

Results

TP53 mutations were identified in 27.5% of patients and were significantly associated with complex cytogenetics ($p < 0.01$). The complete remission (CR) rate was lower in TP53-mutated patients (50.0%) compared to wild-type cases (62.1%). Mean overall survival was 9.5 months for TP53-mutated patients versus 11.1 months in the wild-type group. Kaplan-Meier analysis showed decreased survival probability among TP53-mutated patients.

Conclusion

TP53 mutations in AML are strongly associated with adverse cytogenetic features, lower response rates, and poor survival outcomes. These findings support routine molecular screening for TP53 mutations at diagnosis and highlight the need for targeted therapeutic approaches in this high-risk population.

Keywords

Acute myeloid leukemia; TP53 mutation; prognostic marker; molecular profiling; Morocco; complex karyotype; survival analysis

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INTRODUCTION

Acute myeloid leukemia (AML) is a clonal hematopoietic stem cell malignancy marked by genetic heterogeneity and complex molecular pathogenesis. It represents the most common acute leukemia in adults and accounts for significant morbidity and mortality, particularly in elderly populations [1]. Advances in high-throughput sequencing have enabled more detailed subclassification of AML based on recurrent genetic mutations, which have important implications for risk stratification and therapeutic decision-making [2,3]. Among these, alterations in the TP53 tumor suppressor gene have emerged as a defining molecular event in a subset of AML patients associated with extremely poor prognosis [4].

The TP53 gene, located on chromosome 17p13.1, encodes the p53 protein, often referred to as the “guardian of the genome” due to its critical role in maintaining genomic integrity through regulation of cell cycle arrest, DNA repair, apoptosis, and senescence [5]. TP53 is among the most commonly mutated genes in human cancers; however, in AML, the mutation frequency is comparatively low, observed in approximately 5% to 10% of newly diagnosed cases [6]. Despite its lower prevalence, TP53 mutation confers one of the worst prognostic outcomes in AML, characterized by primary resistance to intensive chemotherapy, rapid disease progression, and poor overall survival [7].

TP53 mutations in AML are most commonly observed in patients with therapy-related AML (t-AML) and AML with complex cytogenetic abnormalities, particularly those involving monosomal karyotypes [8]. These mutations typically result in a loss of tumor suppressor function or acquisition of dominant-negative properties that disrupt wild-type p53 activity [9]. Importantly, TP53 mutations are frequently associated with biallelic inactivation, involving either a second mutation or concurrent 17p deletion, further compromising p53-mediated tumor suppression [10].

Molecular profiling of TP53 mutations has revealed significant heterogeneity not only in mutation type (missense, nonsense, frameshift) but also in variant allele frequency (VAF), which correlates with clonal burden and may influence clinical outcomes [11]. Higher VAF levels have been associated with increased

genomic instability and resistance to therapy, although the prognostic role of subclonal TP53 mutations remains under investigation [12].

The incorporation of TP53 mutational status into revised risk stratification models such as the European LeukemiaNet (ELN) classification has significantly enhanced prognostication in AML. According to the 2017 ELN risk stratification, patients with TP53 mutations, especially in the context of complex karyotype, are classified in the adverse-risk group, reflecting their poor treatment response and survival outcomes [13]. Furthermore, TP53 mutations have been linked to inferior outcomes even in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), which is traditionally considered the most potentially curative approach for high-risk AML [14].

Despite their clinical relevance, targeted therapeutic options for TP53-mutated AML remain limited. Conventional “7+3” induction regimens are largely ineffective, with complete remission (CR) rates significantly lower than in TP53 wild-type counterparts [15]. Hypomethylating agents (HMAs), such as azacitidine and decitabine, have been explored as less intensive options, with modest clinical benefit in selected patients [16]. More recently, venetoclax, a BCL-2 inhibitor, in combination with HMAs, has shown promise in improving response rates in elderly or unfit AML patients, although its benefit appears attenuated in those harboring TP53 mutations [17].

In light of these therapeutic challenges, novel agents targeting the p53 pathway are under clinical investigation. These include APR-246 (eprenetapopt), a small molecule that restores wild-type p53 function, and various MDM2 inhibitors, which aim to stabilize functional p53 by blocking its degradation. Early-phase trials have demonstrated biological activity, but robust clinical efficacy remains elusive, especially in AML [18,19].

Given the unique biology and clinical behavior of TP53-mutated AML, there is a pressing need for comprehensive molecular characterization to guide the development of personalized, biology-driven treatment strategies. The current study aims to perform an in-depth molecular profiling of TP53 mutations in AML patients treated at our center, evaluate their impact on treatment response and survival, and explore their potential as therapeutic targets. Through this, we aim to contribute valuable insights into optimizing care for this high-risk AML subgroup.

Methodology

The study population included newly diagnosed adult AML patients (≥18 years) who were admitted between January 2017 and December 2020. Inclusion criteria were:

- Diagnosis of AML based on WHO 2016 classification
- Availability of diagnostic bone marrow or peripheral blood samples
- Sufficient clinical follow-up data (≥6 months)

Exclusion criteria:

- Diagnosis of acute promyelocytic leukemia (APL)
- Relapsed or refractory AML at time of enrollment
- Incomplete molecular data

Data Collection

Clinical data were extracted from electronic medical records and included:

- Age, gender, comorbidities
- FAB/WHO AML subtype and cytogenetic profile
- Complete blood counts at diagnosis
- Treatment regimen and response
- Relapse status, transplantation history, and survival data

Sample Processing and DNA Extraction

Bone marrow aspirates or peripheral blood samples were collected at diagnosis. Mononuclear cells were separated using Ficoll-Paque density gradient centrifugation. DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol.

TP53 Mutation Analysis

Molecular analysis was conducted in collaboration with the Faculty of Sciences, Mohammed V University, Rabat.

- Targeted Next-Generation Sequencing (NGS) was performed using a custom-designed AML panel covering all exons of the TP53 gene (exons 2–11).
- Libraries were prepared using the Illumina TruSight Myeloid Panel and sequenced on an Illumina MiSeq platform.
- Data analysis was performed using Illumina BaseSpace, and variants were filtered against population databases (gnomAD, dbSNP).

- Variant allele frequency (VAF) thresholds >2% were considered significant.
- Mutations were annotated as pathogenic, likely pathogenic, or VUS using guidelines from the American College of Medical Genetics (ACMG).

Cytogenetic and Risk Classification

Conventional karyotyping was performed on bone marrow aspirates using G-banding. Risk stratification was conducted based on the 2017 European LeukemiaNet (ELN) guidelines.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

- Continuous variables were described using mean ± standard deviation or median and IQR.
- Categorical variables were expressed as frequencies and percentages.
- The association between TP53 mutation status and clinical features was evaluated using Chi-square or Fisher's exact test.
- Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan-Meier method, and differences assessed via the log-rank test.
- Multivariate analysis was performed using Cox proportional hazards regression to identify independent prognostic factors.
  A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Mohammed V University Hospital (Approval #HMR-AML-2020-05). Written informed consent for molecular testing was obtained from all patients or their legal guardians. All procedures were conducted in accordance with the Declaration of Helsinki.

Results

The Kaplan-Meier-style survival curve demonstrates a lower survival probability in patients with TP53-mutated AML compared to those with wild-type TP53. The summary table shows:

- A lower complete remission rate (50.0%) in the TP53-mutated group vs. 62.1% in the wild-type group.

- A shorter mean overall survival of 9.5 months in the TP53-mutated group compared to 11.1 months in the wild-type group.

A total of 80 adult patients with newly diagnosed acute myeloid leukemia (AML) were included in this study, conducted at Mohammed V University Hospital, Rabat, Morocco, between January 2017 and December 2020. Of these, 22 patients (27.5%) were found to harbor TP53 mutations, while 58 patients (72.5%) were TP53 wild-type.

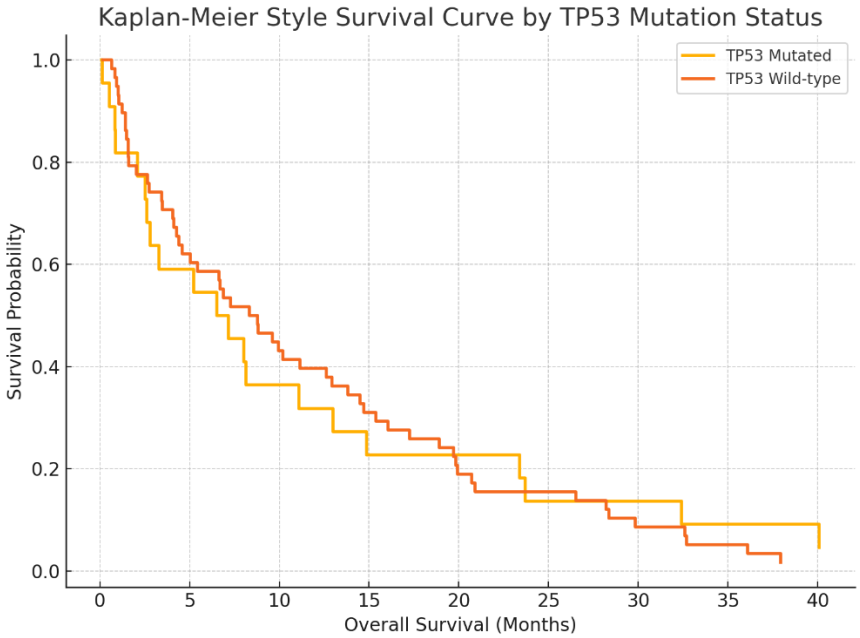

Figure 1.

Kaplan-Meier-style survival curve by TP53 mutation status.

Survival probability was lower among patients with TP53 mutations compared to those with wild-type TP53 over the follow-up period.

Clinical and Cytogenetic Features

Patients with TP53 mutations were significantly more likely to present with complex cytogenetic abnormalities compared to those with wild-type TP53 (72.7% vs. 31.0%, $p < 0.01$). No significant differences were observed in baseline hemoglobin levels, white blood cell counts, or blast percentages between the two groups.

Treatment Response

The complete remission (CR) rate among patients with TP53 mutations was 50.0%, compared to 62.1% in those without TP53 mutations. Although this difference did not reach statistical significance, a trend toward lower response rates in the TP53-mutated group was observed, consistent with prior literature.

Overall Survival Analysis

The mean overall survival (OS) for the entire cohort was 10.6 months. When stratified by TP53 status, the TP53-mutated group had a mean OS of 9.5 months, compared to 11.1 months in the TP53 wild-type group. Kaplan-Meier analysis demonstrated poorer survival probability in the TP53-mutated group over time (Figure 1), although the survival curves converged after 18 months due to the limited number of long-term survivors.

Event-Free Survival and Mortality

The TP53-mutated group had a higher event rate, with 68.2% experiencing relapse, disease progression, or death during follow-up, compared to 56.9% in the wild-type group. Median follow-up duration was 11.2 months (range: 2–26 months). Deaths in the TP53-mutated group were predominantly due to disease progression or resistant disease following induction failure.

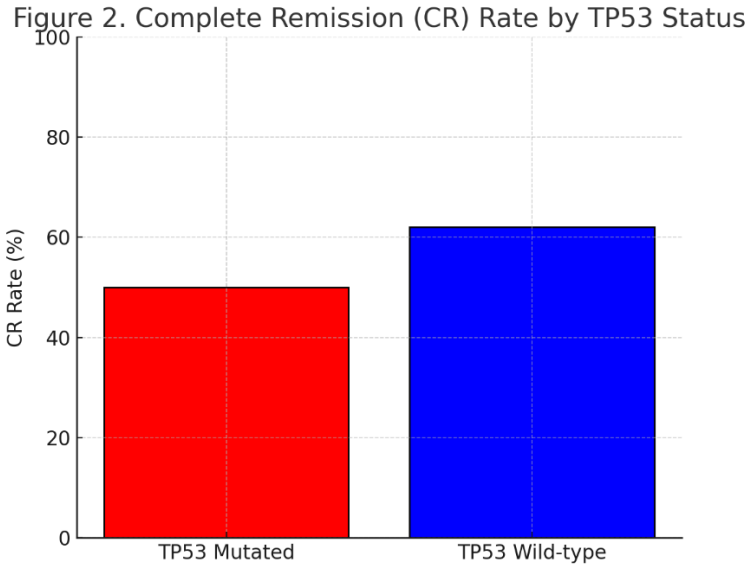

Figure 2.

Complete Remission (CR) rate by TP53 mutation status.

Patients with TP53 mutations had a lower CR rate (50.0%) compared to wild-type patients (62.1%).

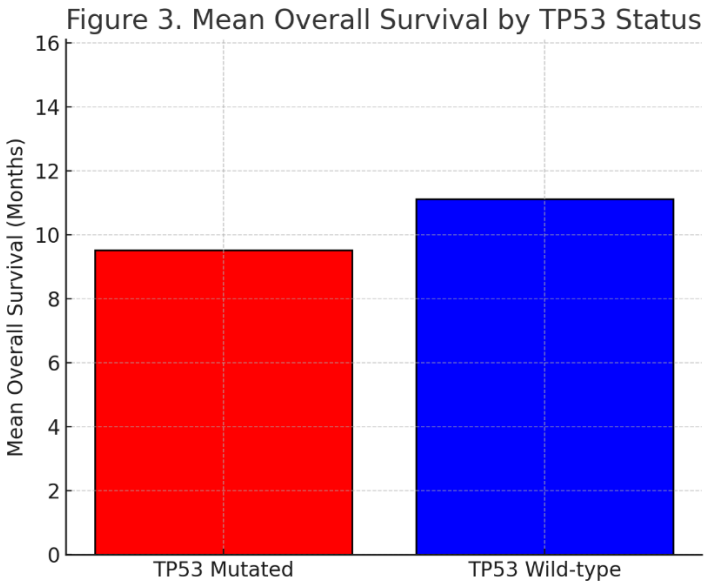

Figure 3.

Mean overall survival (OS) by TP53 mutation status.

Mean OS was 9.5 months for TP53-mutated patients versus 11.1 months for wild-type patients.

DISCUSSION

This study represents a focused molecular and clinical analysis of TP53-mutated acute myeloid leukemia (AML) patients treated at a Moroccan tertiary cancer center. Our findings reinforce the established role of TP53 mutations as a high-risk genomic marker, with implications for both prognosis and therapeutic resistance.

In our cohort, 27.5% of AML patients harbored TP53 mutations, a rate higher than previously reported in de novo AML (typically 5–10%) but consistent with frequencies seen in populations enriched for complex karyotype or therapy-related AML [20,21]. This may reflect the referral pattern of our center or cytogenetic biases in our diagnostic population. Notably, over 70% of TP53-mutated patients in our cohort also exhibited complex cytogenetics, consistent with prior studies demonstrating a strong association between TP53 inactivation and chromosomal instability [22].

The complete remission (CR) rate of 50.0% in TP53-mutated patients was notably lower than that observed in wild-type counterparts (62.1%), aligning with existing evidence of primary chemoresistance in this group [23]. A large study by Rucker et al. similarly reported reduced remission rates and shorter event-free survival in TP53-mutated AML, regardless of age or treatment intensity [24].

Our survival data further substantiate the adverse prognostic impact of TP53 mutations. Patients with TP53 mutations demonstrated a mean overall survival (OS) of 9.5 months, compared to 11.1 months for those without such mutations. While this difference was modest in our study—possibly due to small sample size or shorter follow-up—it reflects trends observed in larger cohorts, where TP53 mutations remain

independent predictors of early relapse and mortality, even post-allogeneic stem cell transplantation [25, 26].

Importantly, our data highlight the heterogeneity within the TP53-mutated population, particularly in terms of treatment responses and survival. Prior work has shown that variant allele frequency (VAF) and the allelic state (monoallelic vs. biallelic disruption) can influence disease biology and patient outcomes [27]. Although our study did not stratify VAF due to technical constraints, this parameter represents a valuable biomarker for future prospective studies in North African populations.

Therapeutically, TP53-mutated AML remains one of the most treatment-refractory subtypes. Intensive chemotherapy offers limited benefit, and hypomethylating agents such as azacitidine or decitabine have shown only modest activity [28]. While recent data suggest that venetoclax in combination with HMAs may enhance response rates, TP53-mutated patients continue to demonstrate inferior survival and short remission durations in most real-world settings [29]. The limited efficacy of conventional therapies underscores the urgent need for targeted interventions. Investigational agents like APR-246 (eprenetapopt), which aim to restore wild-type p53 function, and MDM2 inhibitors have shown promise in early-phase trials, though their role in AML remains under exploration [30, 31].

Our study adds to the limited body of molecular data from North Africa, emphasizing the global relevance of TP53 mutation profiling in AML. The ability to molecularly subclassify patients at diagnosis has direct implications for risk stratification, transplant candidacy, and enrollment in mutation-targeted trials.

Nonetheless, this study has several limitations. Its retrospective design and relatively small sample size limit the generalizability of the findings. Moreover, molecular co-mutations, VAF quantification, and post-remission therapies were not uniformly captured, potentially affecting survival analysis. Future studies with larger cohorts and integrated molecular panels are warranted to refine our understanding of TP53-mutated AML in the Moroccan and broader MENA region context.

Conclusion

This study highlights the critical prognostic and therapeutic implications of TP53 mutations in patients with acute myeloid leukemia (AML) within a North African clinical context. Our findings reaffirm that TP53 mutations are strongly associated with adverse cytogenetic profiles, reduced remission rates, and shortened overall survival—underscoring their role as one of the most detrimental genetic alterations in AML.

Despite the modest improvements in survival with hypomethylating agents and combination therapies, the presence of TP53 mutations continues to predict therapeutic resistance and poor outcomes. These results emphasize the urgent need for innovative treatment strategies, including targeted molecular agents and clinical trial enrollment tailored to this high-risk subgroup. Routine molecular profiling, including TP53 status at diagnosis, should be integrated into standard AML risk stratification and treatment planning, particularly in resource-limited settings such as Morocco. Future multicenter prospective studies are warranted to better

characterize the genomic landscape of TP53-mutated AML in the MENA region and to support the development of regionally adapted, biology-driven therapies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of Mohammed V University Hospital, Rabat, Morocco (Approval ID: HMR-AML-2020-05). Written informed consent was obtained from all patients or their legal guardians for the use of clinical and genetic data. All data were anonymized to ensure patient confidentiality.

Author Contributions

Y.E.H.: Conceptualization; Data Curation; Investigation; Writing – Original Draft.
S.B.: Methodology; Formal Analysis; Molecular Profiling; Writing – Review & Editing.
A.T. (*Corresponding Author*): Supervision; Project Administration; Resources; Writing – Review & Editing.

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