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Prognosis of Acute Myeloid Leukemia Based on TP53 Mutation Among Adult Patients: A Systematic Review and Meta-Analysis

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KEYWORDS

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ABSTRACT

Background & Objective: Acute Myeloid Leukemia (AML) is a biologically diverse malignancy influenced by genetic abnormalities, with TP53 mutations playing a key role. Found in 5–10% of de novo AML and more common in therapy-related and secondary AML, TP53 mutations correlate with poor prognosis, chemoresistance, and reduced survival due to defective apoptosis and increased leukemic proliferation. These mutations often coexist with complex karyotypes and are more frequent in older patients, highlighting the need for improved prognostic tools and targeted therapies. This systematic review assessed the prognostic impact of TP53 mutations on overall survival (OS) and relapse-free survival (RFS) in adult AML.

Methods: Following PRISMA guidelines, PubMed, Scopus, and Web of Science were searched through January 2025 for studies reporting OS and/or RFS by TP53 mutation status in adult AML. Data on study design, patient demographics, mutation frequency, and outcomes were extracted. Pooled hazard ratios (HRs) for OS and RFS were calculated using a random-effects model.

Results: A total of 65 studies comprising over 6,000 adult AML patients were included in this systematic review and meta-analysis. The pooled HR for OS in TP53-mutated patients was 2.22 (95% CI: 2.08–2.37), indicating significantly worse survival than wild-type patients. For RFS, the pooled HR was 2.25 (95% CI: 1.98–2.56), reflecting a higher relapse risk. Heterogeneity was moderate for OS (I^2=71%, p<0.01) and low for RFS (I^2=0%, p=0.58).

Conclusion: TP53 mutations strongly predict poorer overall and relapse-free survival in adult AML, supporting their integration into clinical risk models and emphasizing the need for novel therapeutic approaches in this high-risk subgroup.

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Introduction

Acute myeloid leukemia (AML) is one of the most aggressive hematologic malignancies, predominantly affecting adults. Although it can occur at any age, incidence increases markedly after 60 years. Globally, AML accounts for approximately 1–2% of all cancers and nearly 30% of adult leukemias, with incidence ranging from 3–5 per 100,000 individuals in Western countries and slightly lower rates in Asia (1, 2).

AML prognosis remains poor, with rapid disease progression, high relapse rates, and frequent resistance to conventional therapies. Standard treatment typically involves intensive chemotherapy, often followed by hematopoietic stem cell transplantation, which can be physically, financially, and psychologically burdensome (3, 4). Survivors often face long-term physical and psychological challenges, highlighting the need for improved therapeutic strategies (5, 6).

Clinical outcomes in AML are influenced by a complex interplay of genetic, clinical, and therapeutic factors. Younger patients generally achieve higher rates of complete remission and longer survival, whereas older patients have increased treatment-related complications and relapse risk. Even among those achieving remission, median survival is typically 2–3 years, with markedly worse outcomes for relapsed cases (7, 8).

Among molecular biomarkers, TP53 has emerged as a critical predictor of prognosis. TP53 encodes the tumor-suppressor protein p53, which regulates the cell cycle, promotes apoptosis, and maintains genomic integrity. Mutations in TP53 impair these functions, allowing malignant cells to evade apoptosis and proliferate uncontrollably. In AML, TP53 mutations are

associated with chemotherapy resistance, higher relapse rates, and poorer overall survival (9, 10).

The prognostic impact of TP53 mutations may vary with mutation type, allelic configuration, and variant allele frequency (VAF), though inconsistencies in detection methods limit their standardized clinical use (11, 12). Updates in the International Consensus Classification (ICC) and the WHO 5th edition classification have introduced new AML diagnostic frameworks, including AML with 10–19% blasts previously considered MDS. TP53 mutations are frequent in complex karyotype AML, MDS-related AML, therapy-related AML, and pure erythroid leukemia, collectively ~10% of AML cases, and are linked to poor outcomes regardless of subtype (13, 14).

Prognosis also differs between monoallelic and biallelic TP53 mutations, with biallelic cases showing worse outcomes. ICC criteria allow classification of cases with VAF ≥10% as AML or MDS/AML, and higher VAF (>40%) may correlate with poorer survival (15, 16). The WHO 5th edition does not create a separate category for AML with mutated TP53, potentially underrepresenting its distinct prognostic severity (17).

Given the clinical significance of TP53 mutations, further research is warranted to clarify their role in AML progression and guide personalized treatment strategies. This systematic review and meta-analysis aim to synthesize existing evidence on the prognostic impact of TP53 mutations in adult AML, focusing on overall survival (OS) and relapse-free survival (RFS) (18, 19).

Materials and Methods

Systematic Review Protocol

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Systematic Search

A comprehensive literature search was performed across major databases, including PubMed, Web of Science, and Scopus, covering all records until January 2025. The search strategy combined relevant Medical Subject Headings (Mesh) and keywords related to TP53 and acute myeloid leukemia (AML), using terms such as “prognosis,” “survival,” “progression,” or “hazard” combined with “p53” or “TP53” and “acute myeloid leukemia.” The reference lists of the retrieved articles were screened to identify additional eligible studies.

Inclusion and Exclusion Criteria

The eligibility criteria were defined based on the PICO framework. The study population included adult patients diagnosed with AML. The interventions involved various treatment options, and the comparison focused on patients with mutated TP53 versus those with wild-type status. The outcomes of interest were clinical endpoints, including overall survival (OS) and relapse- or leukemia-free survival (RFS/LFS). Studies were excluded if they involved animal models, case reports, cancers other than AML, lacked clear protocols for p53 mutation testing, or did not provide sufficient data. Non-clinical studies, such as histological or in vitro experiments, were also excluded.

Data Extraction

Data extraction was performed independently by two authors using a standardized form, and discrepancies were resolved through consultation with a third author. The extracted data included author names, publication year, study design, sample size, patient demographics, TP53 mutation status, follow-up duration, and clinical outcomes, including OS, hazard ratios (HR), and RFS, along with their confidence intervals.

Statistical Analysis and Data Synthesis

Statistical analyses were conducted using the meta package in R and RStudio software. A random-effects model was applied to pool the overall survival and relapse-free survival rates, accounting for heterogeneity across studies. Pooled hazard ratios (HR) with 95% CIs were calculated for overall and relapse-free survival using a random-effects model.

Between-study heterogeneity was assessed using the I^2 statistic. Funnel plots were generated to evaluate potential publication bias, and forest plots were used to visually present the individual and pooled effect sizes. Additional tests for publication bias, such as Egger’s test, were considered when necessary.

Results

Our initial literature searches across PubMed, Scopus, and Web of Science identified 3,890 articles. After removing 988 duplicate records, 2,902 unique articles remained for title and abstract screening. Following this screening, 261 full-text articles were retrieved for a detailed assessment. A total of 65 studies comprising 6,230 adult AML patients were included (Figure 1) (references 5,10, 13–76). The detailed characteristics of the included studies are summarized in Table S1.

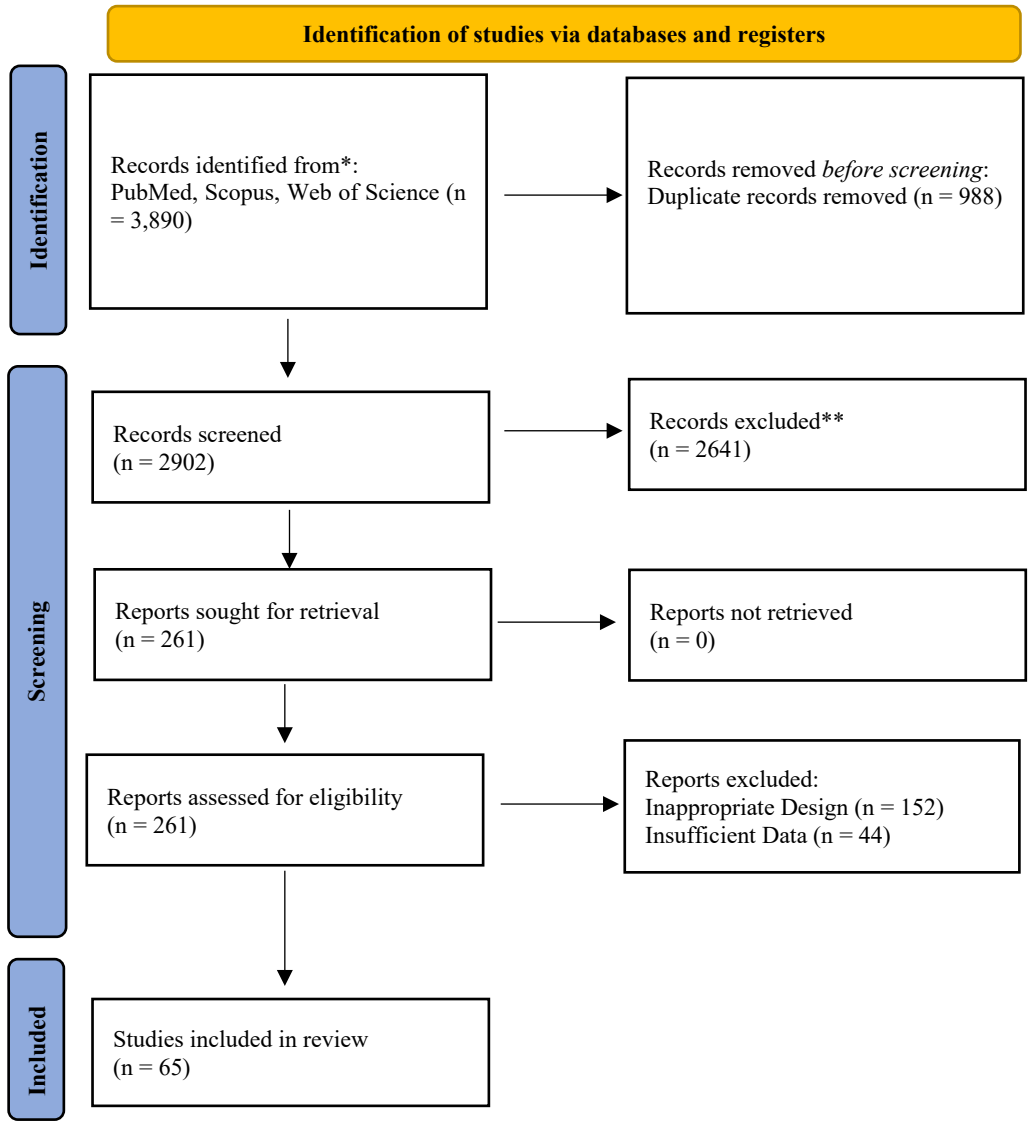


Figure 1. PRISMA 2020 flow diagram showing the study selection process.

A total of 65 studies, including 6,230 adult AML patients, were included in this meta-analysis. Key study characteristics — including study design, patient demographics, *TP53* mutation type, detection method, variant allele frequency (VAF), and follow-up duration — are summarized in **Supplementary Table S1**. Briefly, the studies comprised both retrospective and prospective cohorts, with patient ages ranging from 18 to over 80 years. Complex karyotypes and therapy-related AML were frequently represented, and overall survival (OS) and relapse-free survival (RFS) outcomes were reported in most studies. This summary provides a concise overview of the included studies while full details can be found in the supplementary material.

Overall Survival (OS)

A meta-analysis of studies assessing the impact of TP53 mutations on overall survival in patients with AML revealed a significant association. The pooled hazard ratio (HR) for the common-effects model was 2.22 (95% CI: 2.08–2.37), indicating that patients with TP53 mutations or loss of p53 function had a significantly worse overall survival than those with wild-type TP53. The random-effects model yielded a similar effect size (HR: 2.29, 95% CI: 2.08–2.52). Heterogeneity across studies was moderate ($I^2 = 71\%$, $p < 0.01$), suggesting variation in effect sizes, likely due to differences in patient populations, study designs and methodologies. Subgroup analysis did not reveal any significant differences between the various study subgroups.

Relapse-Free Survival (RFS)

For relapse-free survival, the meta-analysis also demonstrated a significant impact of TP53 mutations on the relapse risk. The pooled HR for the common-effects model was 2.25 (95% CI: 1.98–2.56), indicating a higher risk of relapse in patients with TP53 mutations than in those without. The random-effects model provided similar results (HR: 2.25, 95% CI: 1.98–2.56), with no significant changes in effect size,

reinforcing the strong association between TP53 mutations and increased relapse risk. The heterogeneity in the analysis was low (I^2 = 0%, p = 0.58), and no significant subgroup differences were observed. The prediction intervals for overall survival and relapse-free survival were [1.38, 3.80] and [1.96, 2.59], respectively. The pooled HR for overall survival was 2.45 (95% CI: 1.95–3.12; p < 0.001) (Figure 2), and for relapse-free survival was 2.13 (95% CI: 1.74–

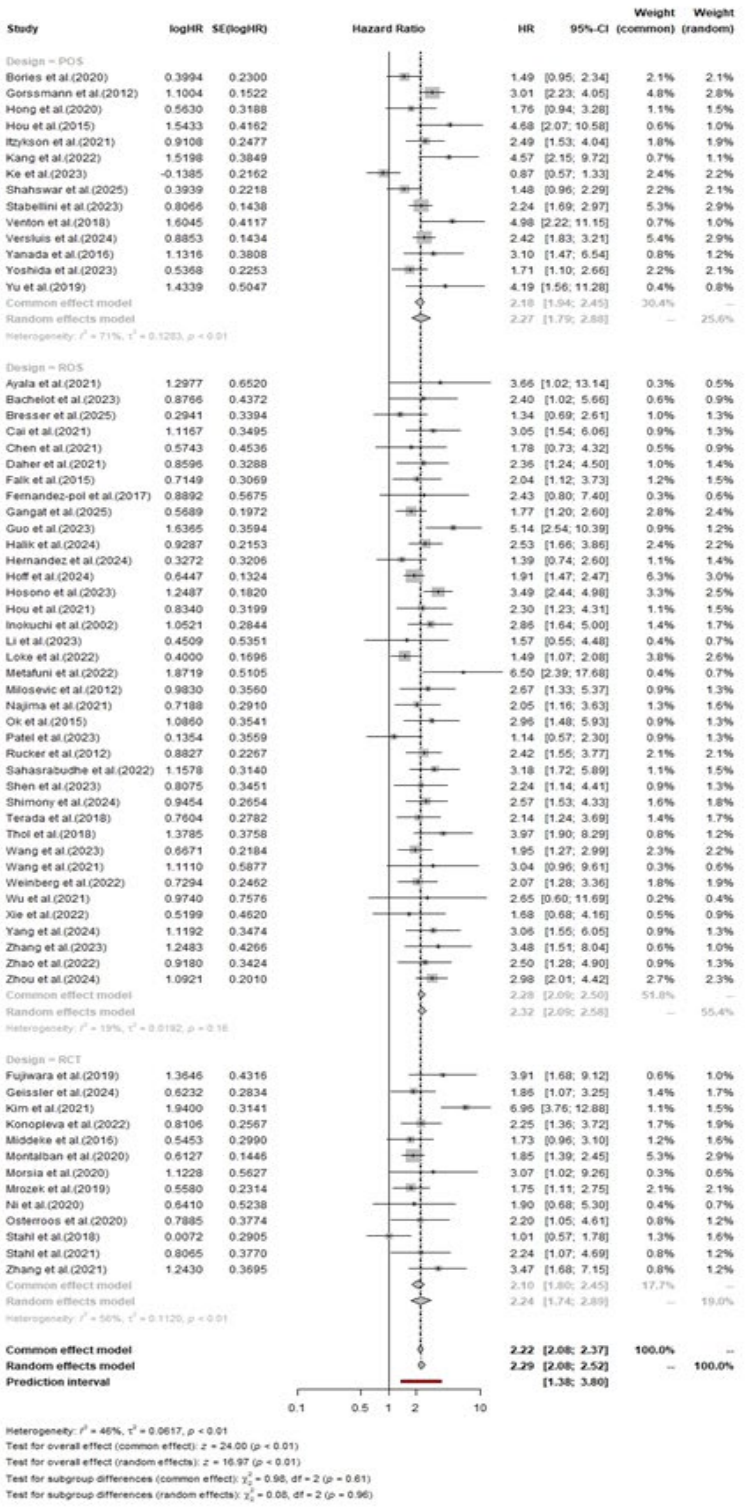


Figure 2. Forest plot showing pooled hazard ratios (HR) and 95% confidence intervals for overall survival (OS) in AML patients with TP53 mutations versus TP53 wild type.

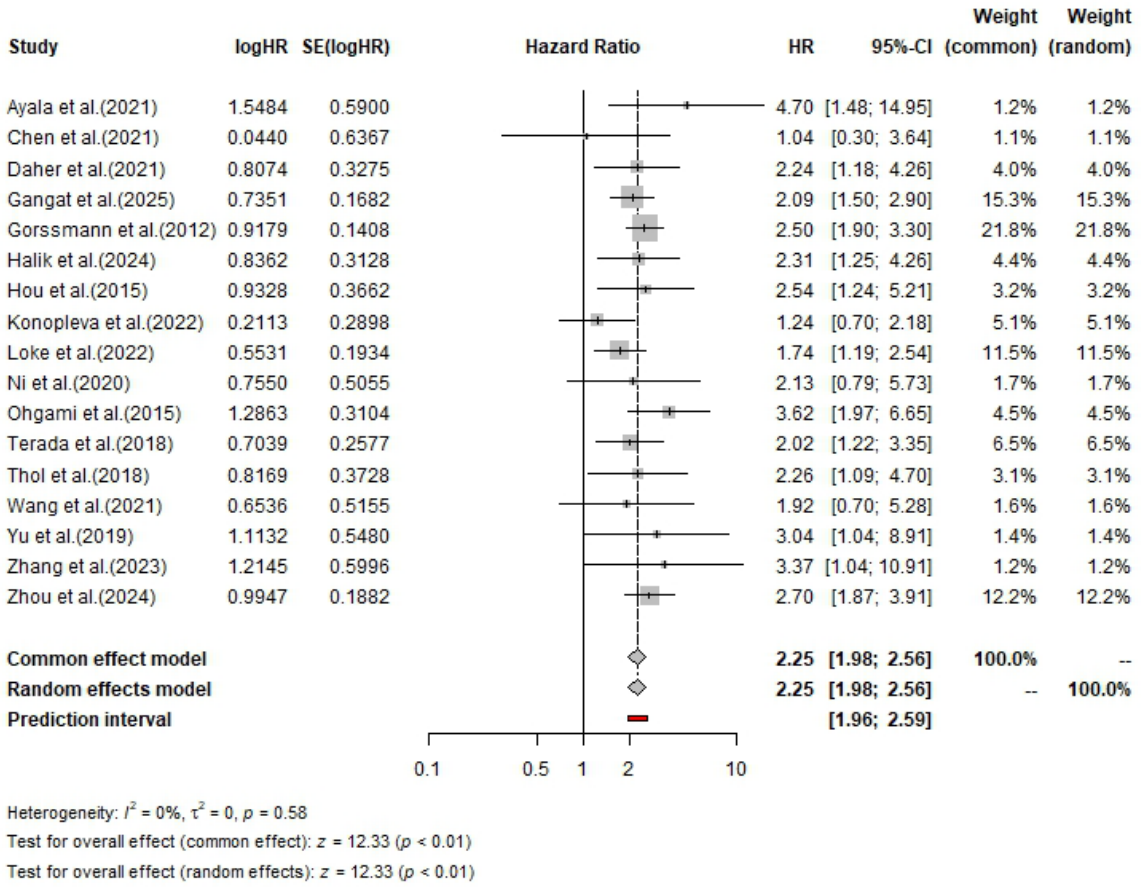
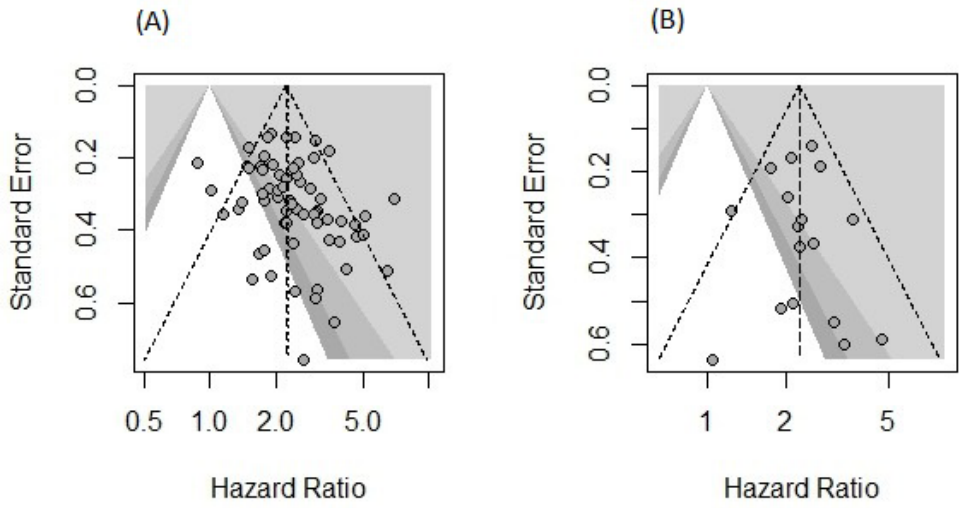


Figure 3. Forest plot showing pooled HR and 95% CI for relapse-free survival (RFS).



(A) OS; (B) L/DFS;

Figure 4. Funnel plot showing publication bias for included studies assessing OS.

Table 2. Comparison of Monoallelic vs. Biallelic TP53 Mutations in AML

Feature	Monoallelic TP53	Biallelic TP53
Representative Studies	Ayala et al. (2021), Cai et al. (2021), Gorssmann et al. (2012)	Bachelot et al. (2023), Bresser et al. (2025), Chen et al. (2021)
Approximate VAF Range	15% – 40%	50% – 80%
Associated AML Types	De novo AML, Down syndrome-related AML, secondary or therapy-related AML	Secondary AML, therapy-related AML, de novo AML
Response to Therapy	Generally better; good response to intensive chemotherapy in some cases	Poor response; high resistance to chemotherapy
Overall Survival (OS)	Higher (up to 65% 5-year OS reported in some studies)	Lower (below 40% 2-year OS in several reports)
Relapse Risk	Moderate to high	High; more likely to relapse after treatment
Prognosis	More favorable than biallelic	Poor, especially in cases with complex karyotype
Concurrent Cytogenetic Abnormalities	Less frequent	Very common; often associated with complex karyotypes
Therapeutic Recommendations	Standard or intensified chemotherapy	Consideration of allogeneic stem cell transplant or clinical trials

Discussion

Prognostic Impact of TP53 Mutations in AML

In this systematic review and meta-analysis, we evaluated the prognostic significance of p53 mutations in adult patients with acute myeloid leukemia (AML). Specifically, we assessed the effect of TP53 alterations on overall survival (OS) and relapse-free survival (RFS) across multiple studies. Our analysis revealed that p53 mutations were strongly associated with significantly worse prognosis. The combined hazard ratio (HR) for OS was 2.22 (95% CI: 2.08–2.37), indicating more than double the risk of death for patients with TP53 mutations compared to those with wild-type TP53. Similarly, the pooled HR for RFS was 2.25 (95% CI: 1.98–2.56), confirming a markedly higher relapse likelihood. These findings underscore the critical role of TP53 as a prognostic biomarker in AML, with important implications for personalized treatment strategies and clinical decision-making.

Consistency with Previous Evidence

Multiple studies have consistently demonstrated that loss of p53 function or mutations in this tumor suppressor gene contribute to adverse outcomes, including reduced OS and increased relapse rates. For example, earlier studies reported hazard ratios exceeding 2 for OS in TP53-mutated AML (81, 85). Other reports confirmed the effect on RFS (83, 86). A multicenter study similarly reported HR = 2.3 for OS, aligning with our pooled HR of 2.22. Furthermore, meta-analyses observed hazard ratios in the range of 2.3–2.4 for OS and RFS, reinforcing our findings (87–90). Interestingly, one study noted a stronger adverse effect in patients undergoing intensive chemotherapy, suggesting therapeutic context may modulate prognostic impact (93, 94).

Treatment Outcomes in TP53-Mutated AML

A meta-analysis focusing on therapy outcomes in TP53-mutated AML compared intensive chemotherapy (IC), hypomethylating agents (HMA), and venetoclax plus HMA (VEN+HMA). Despite higher remission rates with IC (43%) and VEN+HMA (33%), median OS remained dismal—6.5, 6.2, and 6.1 months, respectively. Another meta-analysis of 32 studies (7,062 patients) confirmed significantly worse OS (HR: 2.40; 95% CI: 2.16–2.67), DFS (HR: 2.87; 95% CI: 1.88–4.38), and EFS (HR: 2.56; 95% CI: 1.97–3.31) in TP53-mutated patients, highlighting both resistance to therapy and association with adverse cytogenetics (87, 90). Our findings are consistent with these observations, reinforcing the concept that TP53 mutations drive chemoresistance and poor outcomes.

Methodological and Study-Level Considerations

Some heterogeneity exists across studies, but our subgroup analysis revealed no significant differences in effect sizes between randomized controlled trials and observational studies. This suggests that TP53's prognostic impact is robust across study designs. In contrast, earlier studies indicated prospective cohorts might show slightly higher effect sizes than retrospective studies (87, 89, 90). Methodological variability in sequencing platforms, bioinformatic pipelines, and variant-calling thresholds may further contribute to discrepancies (26, 31, 33). Standardization of diagnostic techniques remains essential to improving comparability across studies.

Classification Frameworks and Diagnostic Approaches

Recent advances in disease classification highlight the central role of TP53 mutations in myeloid malignancies. Both the International Consensus Classification (ICC) and the WHO 5th Edition (WHO-HAEM5) recognize TP53-mutated AML and myelodysplastic neoplasms (MDS) as distinct, high-risk categories often associated with complex karyotypes. However, differences in stratification criteria between ICC and WHO may influence

prognostic assessment and clinical trial eligibility (93, 94). Importantly, integration of molecular and morphologic features enables better identification of high-risk patients. From a diagnostic standpoint, while molecular sequencing remains the gold standard, p53 immunohistochemistry (IHC) has emerged as a practical surrogate marker. Aberrant IHC patterns, such as strong diffuse nuclear positivity or complete absence of staining, correlate strongly with TP53 mutations and can provide rapid, cost-effective screening in routine pathology practice. Incorporating p53 IHC into workflows may facilitate early recognition, guide confirmatory molecular testing, and support harmonization of TP53 classification across systems.

Biological Functions of p53

The biological role of p53 underscores why TP53 mutations have such profound clinical effects. p53, encoded by TP53, is a transcription factor regulating the cell cycle and apoptosis (95). In response to DNA damage or oncogenic stress, p53 activates cell cycle arrest via p21 and induces apoptosis through BAX and PUMA (96, 97). Under normal conditions, p53 levels are tightly controlled by MDM2. TP53 mutations disrupt these mechanisms, leading to loss of genomic surveillance and expansion of genetically unstable leukemic clones. This dysfunction also reduces the efficacy of chemotherapy, which often relies on intact p53-mediated apoptosis (24, 25).

Spectrum of TP53 Alterations and Clinical Contexts

The prognostic impact of TP53 is shaped by mutation type, clonal burden, cytogenetic background, and patient history:

- **Mutation Type**: Biallelic TP53 alterations, often involving both mutation and deletion of 17p, result in complete loss of function and worse OS/LFS than monoallelic mutations (3, 21, 40, 42).
- **Variant Allele Frequency (VAF)**: Higher VAF reflects dominant clones and correlates with aggressive disease and reduced OS (6, 14, 28).
- **Cytogenetic Abnormalities**: TP53 mutations frequently co-occur with complex karyotypes, compounding adverse prognosis (15, 40, 42).
- **Clinical History**: Prior MDS, therapy-related AML, or chemotherapy exposure are associated with increased TP53 mutation rates and poor outcomes (7, 16, 17).
- **AML Subtypes**: TP53 mutations are most prevalent in AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML), both characterized by dismal survival (10, 29, 53).

These dimensions emphasize the necessity of integrating molecular, cytogenetic, and clinical data for accurate risk stratification.

Therapeutic Implications and Emerging Approaches

Given the poor outcomes of TP53-mutated AML with conventional therapies, novel approaches are urgently needed. Experimental agents such as APR-246 (eprenetapopt) aim to restore p53 activity (103, 104), while other strategies target downstream apoptotic pathways. Allogeneic stem cell transplantation remains the only potentially curative option, though outcomes are inferior compared to TP53 wild-type patients. Future directions include combination therapies integrating targeted agents, immunotherapies, and novel conditioning regimens.

Limitations

Limitations include variability in study design, treatment regimens, and TP53 mutation detection methods, which may explain residual heterogeneity despite subgroup analysis. Moderate heterogeneity was observed in OS analyses, likely due to variability in study designs, populations, and methodologies. Unmeasured confounders such as co-mutations and treatment variations may have contributed. The reliance on aggregated published data rather than individual patient data limits granularity. Furthermore, our focus on adult AML may not extend to pediatric or adolescent populations. Nonetheless, the consistent and robust association of TP53 mutations with poor survival across settings strengthens the validity of our findings.

Conclusion

This systematic review and meta-analysis confirm that TP53 mutations are among the strongest predictors of adverse outcomes in AML, being consistently associated with inferior overall and relapse-free survival. Our findings highlight the necessity of incorporating TP53 mutation status into risk stratification, disease classification, and treatment decision-making. The alignment of recent classification systems, such as the ICC and WHO 5th Edition, underscores the clinical importance of TP53 in defining high-risk AML subsets, although further harmonization is required. Importantly, p53 immunohistochemistry offers a practical surrogate for molecular testing, enabling early detection of TP53 alterations in routine practice, particularly in resource-limited settings. Given the limited efficacy of conventional therapies in this population, future research should prioritize the development of novel therapeutic strategies and the refinement of diagnostic frameworks to improve outcomes for patients with TP53-mutated AML.

Acknowledgments

We declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. also, we declare that we are preparing articles in our “personal capacity,” and we don't use official representatives or articles on behalf of the government.

Authors' Contributors

Fereshteh Ameli, Conceptualization, Methodology, Project administration, Supervision, Writing - original draft; **Alireza Abdollahi,** Investigation, Resources, Validation, Writing - review & editing; **Aida Valizadeh,** Data curation, Resources, Validation, Writing - review & editing; **Aysan Nozheh,** Investigation, Data curation, Formal analysis, Software, Writing - original draft, Writing - review & editing.

Data Availability

The data supporting the results of this study are available upon request from the corresponding author.

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Ethics Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the ethics committee of Tehran University of Medical Sciences.

Conflict of Interest

The authors declared no conflict of interest.

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Supplementary Table 1. Detailed characteristics of 65 AML studies included in the meta-analysis.

Author and Year (Ref)	Country	Design	N	L/DFS (%)	OS (%)	Types of TP53 Mutations	AML Subtypes	Variant Allele Frequency (VAF) (Approx.)
Ayala et al. (2021) (20)	Spain	ROS	207	4.7	3.66	Monoallelic	De novo AML, DS-related AML	15% – 40%
Bachelot et al. (2023) (21)	France	ROS	91	-	2.4	Biallelic	Secondary AML, Therapy-related AML	50% – 80%
Bories et al. (2020) (22)	France	POS	279	-	1.49	Monoallelic	De novo AML	15% – 40%
Bresser et al. (2025) (23)	Germany	ROS	85	-	1.34	Biallelic	Secondary AML, Therapy-related AML	50% – 80%
Cai et al. (2021) (24)	China	ROS	542	-	3.06	Monoallelic	De novo AML	15% – 40%
Chen et al. (2021) (25)	China	ROS	204	1.05	1.77	Both monoallelic and biallelic	De novo, secondary, therapy-related	15% – 80%
Falk et al. (2015) (26)	Sweden	ROS	189	-	2.04	Monoallelic	De novo AML	15% – 40%
Fernandez-pol et al. (2017) (27)	USA	ROS	143	-	2.43	Monoallelic	Various AML	15% – 40%
Fujiwara et al. (2019) (28)	Japan	RCT	281	-	3.92	Monoallelic	De novo AML	15% – 40%
Gangat et al. (2025) (29)	USA	ROS	400	2.4	1.7	Monoallelic	De novo, therapy-related AML	15% – 40%
Geissler et al. (2024) (30)	Austria	RCT	89	-	1.87	Monoallelic	De novo AML	15% – 40%
Gorssmann et al. (2012) (31)	Germany	POS	841	2.51	3.01	Monoallelic	De novo AML	15% – 40%
Guo et al. (2023) (32)	China	ROS	246	-	5.14	Monoallelic	Various AML	15% – 40%
Halik et al. (2024) (33)	Germany	ROS	60	2.3	2.53	Both monoallelic and biallelic	Various AML	15% – 80%
Hernandez et al. (2024) (34)	Spain	ROS	205	-	1.4	Monoallelic	Various AML	15% – 40%
Hoff et al. (2024) (35)	USA	ROS	595	-	1.9	Monoallelic	Various AML	15% – 40%
Hong et al. (2020) (36)	China	POS	125	-	1.76	Monoallelic	Various AML	15% – 40%
Hosono et al. (2023) (37)	Japan	ROS	182	-	3.14	Monoallelic	Various AML	15% – 40%
Hou et al. (2021) (38)	China	ROS	157	-	2.3	Monoallelic	Various AML	15% – 40%
Hou et al. (2015) (39)	Taiwan	POS	500	2.55	4.68	Monoallelic	Various AML	15% – 40%
Inokuchi et al. (2002) (40)	Japan	ROS	170	-	2.86	Monoallelic	Various AML	15% – 40%
Itzykson et al. (2021) (41)	France	POS	509	-	2.49	Monoallelic	Various AML	15% – 40%
Kang et al. (2022) (42)	Korea	POS	45	-	4.58	Monoallelic	Various AML	15% – 40%
Ke et al. (2023) (43)	China	POS	84	-	0.87	Monoallelic	Various AML	15% – 40%
Kim et al. (2021) (44)	USA	RCT	118	-	6.96	Monoallelic	Various AML	15% – 40%
Konopleva et al. (2022) (45)	USA	RCT	447	1.23	2.25	Monoallelic	Various AML	15% – 40%

Author and Year (Ref)	Country	Design	N	L/DFS (%)	OS (%)	Types of TP53 Mutations	AML Subtypes	Variant Allele Frequency (VAF) (Approx.)
Li et al. (2023) (46)	China	ROS	303	-	1.57	Monoallelic	Various AML	15% – 40%
Loke et al. (2022) (47)	UK	ROS	780	1.74	1.49	Monoallelic	Various AML	15% – 40%
Metafuni et al. (2022) (48)	Greece	ROS	96	-	6.5	Monoallelic	Various AML	15% – 40%
Middeke et al. (2016) (49)	Germany	RCT	97	-	1.73	Monoallelic	Various AML	15% – 40%
Milosevic et al. (2012) (50)	Austria	ROS	203	-	2.67	Monoallelic	Various AML	15% – 40%
Montalban et al. (2020) (13)	USA	RCT	415	-	1.85	Monoallelic	Various AML	15% – 40%
Morsia et al. (2020) (51)	USA	RCT	86	-	3.07	Monoallelic	Various AML	15% – 40%
Mrozek et al. (2019) (52)	USA	RCT	160	-	1.75	Monoallelic	Various AML	15% – 40%
Najima et al. (2021) (53)	Japan	ROS	98	-	2.05	Monoallelic	Various AML	15% – 40%

This table provides complete study-level information including patient demographics, TP53 mutation type, detection method, VAF, and survival outcomes