Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Clinical Characteristics, Co-Mutations, and Prognostic Factors of TP53 Mutations in Acute Myeloid Leukemia and Myelodysplastic Syndrome

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ABSTRACT

Background: **TP53 mutations confer poor prognosis and heterogeneous clinical features in myeloid neoplasms, but distinguishing factors between AML and MDS and independent prognostic markers within this high-risk group remain unclear.**
Methods: **This retrospective study evaluated 45 adult patients with TP53-mutated acute myeloid leukemia (AML; n = 22) or myelodysplastic syndromes (MDS; n = 23) treated at Ganzhou People's Hospital between 2018 and 2023. Clinical, laboratory, cytogenetic, and targeted next-generation sequencing data were collected at diagnosis. Sixteen genes frequently mutated in myeloid malignancies were assessed for co-mutation patterns. Progression-free survival (PFS) and overall survival (OS) were analyzed by Kaplan-Meier and Cox regression; variables with univariate p < 0.10 entered multivariate models.**
Results: **MDS patients were older than AML patients (65.5 ± 9.0 vs. 56.0 ± 15.1 years; p = 0.013), and exhibited lower bone marrow blast percentages (5.6% vs. 49.5%; p < 0.001), while AML cases had higher peripheral WBC counts (8.6 × 10^9 vs. 2.9 × 10^9/L; p = 0.002). DNMT3A and TET2 co-mutations were most frequent (15.6% each); FLT3-ITD was enriched in AML (18.2% vs. 0%; p = 0.049). In multivariate analysis, allogeneic HSCT (HR = 0.08; p = 0.022), higher RBC count (HR = 0.39; p = 0.011), hemoglobin (HR = 0.98; p = 0.043), and albumin (HR = 0.91; p = 0.010) independently predicted superior PFS, whereas RUNX1 co-mutation (HR = 18.15; p = 0.028) and lower ALT (HR = 0.97; p = 0.018) were independently associated with OS.**
Conclusions: **Distinct clinical and molecular features differentiate TP53-mutated AML from MDS. Allogeneic HSCT confers marked survival benefit, and RUNX1 co-mutation identifies an ultra-high-risk subset. Early transplant evaluation combined with comprehensive genomic profiling is recommended to guide personalized treatment in this high-risk population.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250835)

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Manuscript accepted October 1, 2025

KEYWORDS

TP53, co-mutations, prognostic factors, acute myeloid leukemia, myelodysplastic syndromes

INTRODUCTION

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic malignancies arising from clonal stem cell defects that cause abnormal hematopoiesis [1,2]. The TP53 gene, a tumor suppressor gene located on chromo-

some 17p13, plays an important role in genome maintenance by cell cycle arrest, DNA repair, and inducing apoptosis when cells are stressed [3,4]. TP53 mutation is one of the most frequently mutated genes in human cancer, and it has been reported that the prognosis in hematologic malignancies was very poor in TP53 mutant tumors [5,6]. It has been shown that TP53 mutations accounted for ~ 5 - 15% of de novo AML cases, but they occurred more commonly (50% - 70%) in therapy-related acute myeloid leukemia (t-AML), or acute myeloid leukemia with complex karyotype [7,8]. Approximately 10% - 20% of MDS patients also harbored TP53 mutation, especially in higher risk or complex cytogenetics, and these patients were known to have chemotherapy resistant phenotype, shorter overall survival time, and a greater chance of transforming into acute myeloid leukemia [9,10].

However, although these clinical observations are important, little information exists about the specific co-mutation patterns and clinical/laboratory features distinguishing TP53-mutated AML from MDS, and we do not know the independent prognostic factors within this high-risk group of patients. Moreover, there remains considerable debate over what is the best therapeutic approach for treating these individuals, although new studies demonstrate benefits using novel therapies such as hypomethylating agents, venetoclax-based combination regimens, and allogeneic HSCT [11,12].

Our current work aimed to determine whether specific factors could be used to identify TP53-mutated AML and MDS patients who would respond successfully to different therapeutic strategies compared to those employed for their more favorable-risk counterparts. We therefore performed a retrospective analysis of clinical characteristics, co-mutation profiles, and the presence of prognostic factors in our large cohort of adult TP53-mutated AML and MDS patients. Our data provide some insights into how these individual differences may help guide therapeutic decision-making for this challenging patient population.

MATERIALS AND METHODS

Patient selection and study design

Forty-five patients with mutated TP53 who were diagnosed as AML (n = 22) or MDS (n = 23) at Ganzhou People's Hospital from 2018 to 2023 participated in this retrospective study. The patients of AML and MDS were diagnosed according to WHO criteria [13]. Bone marrow or peripheral blood showed that more than 20% blasts were acute myeloid leukemia, dysplasia occurring in hematopoietic cells was myelodysplastic syndrome and less than 20% of the blast percentage. This experiment follows the Declaration of Helsinki. It was approved by our ethics committee.

Mutation analysis

Genomic DNA was extracted from bone marrow or peripheral blood at diagnosis. A targeted next generation sequencing using a comprehensive myeloid panel of genes that are frequently mutated in myeloid malignancies was performed. TP53 mutations were identified and confirmed as described above. Mutations occurring together with mutant P53 were analyzed for DNMT3A, TET2, WT1, ASXL1, NPM1, FLT3-ITD, IDH1, IDH2, CEBPA, PHF6, NF1, NARS, BCOR, KMT2D, RUNX1, and CSMD1.

Clinical and laboratory data collection

Clinical data included age, gender, performance status, disease history, and treatment situation; diagnosis laboratory parameters included white blood cell differential count, bone marrow blast percentage, cytogenetics, biochemistry tests (LDH, bilirubin, albumin, ALT, uric acid). Cytogenetic testing was performed by standard G-banding methods. Karyotype results were classified into normal and abnormal groups.

Treatment and follow-up

Treatment was decided on an institutional basis and on a patient-specific basis. Allogeneic HSCT was given, if possible, in case of suitable patients. CNSL was done according to CSF examination procedure,if needed clinically. Regular follow-up visits for response evaluation, relapse, and survival assessment were done for the patients.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means ± standard deviation or medians with interquartile ranges, as appropriate. Comparisons between AML and MDS groups were performed using chi-squared test or Fisher's exact test for categorical variables, and Student's *t*-test or Mann-Whitney U test for continuous variables.

Survival analyses were conducted using the Kaplan-Meier method for progression-free survival (PFS) and overall survival (OS). Univariate Cox regression analysis was performed to identify potential prognostic factors. Variables with p-values < 0.1 in univariate analysis were included in multivariate Cox regression models using backward stepwise selection. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. A receiver operating characteristic curve (ROC) analysis was conducted to evaluate the accuracy of ALT levels in predicting TP53 mutation status in AML/MDS patients with implications for overall survival outcomes. All statistical analyses were performed using appropriate software, and p-values < 0.05 were considered statistically significant.

Table 1. Clinical characteristics of patients with TP53 mutations in acute myeloid leukemia and myelodysplastic syndrome.

Variables	Total (n = 45)	AML (n = 22)	MDS (n = 23)	p value
Gender, n (%)				
Female	19 (42.2)	12 (54.5)	7 (30.4)	0.102
Male	26 (57.8)	10 (45.5)	16 (69.6)	
Age, years	60.8 ± 13.1	56.0 ± 15.1	65.5 ± 9.0	0.013
Karyotype, n (%)				
Normal	15 (33.3)	6 (27.3)	9 (39.1)	0.817
Complex	26 (57.8)	14 (63.6)	12 (52.2)	
Abnormal	4 (8.9)	2 (9.1)	2 (8.7)	
Fusion gene, n (%)				
No	44 (97.8)	21 (95.5)	23 (100)	0.489
Yes	1 (2.2)	1 (4.5)	0 (0)	
HSCT, n (%)				
No	43 (95.6)	21 (95.5)	22 (95.7)	1.000
Yes	2 (4.4)	1 (4.5)	1 (4.3)	
CNSL, n (%)				
No	41 (91.1)	18 (81.8)	23 (100)	0.049
Yes	4 (8.9)	4 (18.2)	0 (0)	
Blast, %	15.5 (5.6, 48.0)	49.5 (32.0, 74.8)	5.6 (2.7, 12.9)	< 0.001
WBC, × 10^9/L	3.6 (2.3, 9.2)	8.6 (3.4, 52.1)	2.9 (1.9, 3.8)	0.002
RBC, × 10^{12}/L	2.5 ± 0.7	2.7 ± 0.7	2.2 ± 0.5	0.009
Hemoglobin, g/L	73.0 (56.0, 84.0)	76.5 (64.2, 93.8)	72.0 (52.0, 78.5)	0.048
Platelet, × 10^9/L	35.0 (23.0, 64.0)	35.5 (23.5, 56.2)	35.0 (24.0, 103.0)	0.683
LDH, U/L	281.6 (202.4, 406.9)	312.5 (219.4, 592.1)	241.0 (196.3, 335.9)	0.074
total bilirubin, umol/L	12.5 (8.9, 20.2)	9.5 (8.2, 16.6)	14.4 (12.2, 27.9)	0.025
Serum UA, umol/L	329.9 (231.0, 434.0)	399.9 (244.2, 531.0)	300.0 (218.5, 381.0)	0.051
PFS, months	5.0 (4.0, 12.0)	5.0 (3.0, 12.0)	5.0 (4.0, 11.0)	0.828
OS, months	12.0 (6.0, 16.0)	6.0 (4.5, 14.0)	13.0 (6.0, 16.5)	0.272

HSCT: allogeneic hematopoietic stem cell transplantation, CNSL: central nervous system leukemia, WBC: white blood cell count, RBC: red blood cell count, LDH: lactic dehydrogenase, UA: uric acid, PFS: progression-free survival time, OS: overall survival time.

RESULTS

Patient characteristics

Of the 45 patients harboring TP53 mutations, 23 (51.1%) were MDS while 22 (48.9%) were AML. The total number of samples showed slight male predominance in our series (57.8% males vs. 42.2% females); however, this difference was not statistically significant between disease subgroups (p = 0.102). Age was significantly increased in the MDS group compared with the AML group (65.5 ± 9.0 years old vs 56.0 ± 15.1 years old; p = 0.013). Most of them (57.8%) exhibited complex karyotypes, and there was no difference between groups (52.2% vs 63.6%; p = 0.817); 19% demonstrated a normal karyotype, and others had various abnormalities (~ 62%). One AML sample revealed fusion gene (Table 1).

Laboratory features

There were significant differences in most hematologic parameters between AML and MDS: bone marrow blast percentage was remarkably elevated among the AML group compared with the MDS group (49.5% vs 5.6%, p < 0.001). The WBC count was higher in AML patients than in MDS patients (median 8.6 × 10^9/L vs. 2.9 × 10^9/L, p = 0.002). RBC counts were decreased in the MDS group (2.2 ± 0.5 × 10^{12}/L vs. 2.7 ± 0.7 × 10^{12}/L, p = 0.009), but hemoglobin levels showed no difference between the two groups (72.0 g/L vs. 76.5 g/L, p = 0.048); however, platelet counts demonstrated a non-significant increase in both (p = 0.683). Biochemistry parameter results indicated that total bilirubin levels tended to be higher among the MDS group than those of the AMLgroup (14.4 μmol/L vs 9.5 μmol/L, p = 0.025), while LDH was increased among AML patients (p =

Table 2. Comparison of co-mutations in AML and MDS with TP53 mutation.

Variables	Total (n = 45)	AML (n = 22)	MDS (n = 23)	p-value
TP53, n (%)	45 (100)	22 (100)	23 (100)	1.000
DNMT3A, n (%)	7 (15.6)	3 (13.6)	4 (17.4)	1
TET2, n (%)	7 (15.6)	3 (13.6)	4 (17.4)	1
WT1, n (%)	5 (11.1)	3 (13.6)	2 (8.7)	0.665
ASXL1, n (%)	4 (8.9)	3 (13.6)	1 (4.3)	0.346
NPM1, n (%)	4 (8.9)	2 (9.1)	2 (8.7)	1
FLT3.ITD, n (%)	4 (8.9)	4 (18.2)	0 (0)	0.049
IDH-1, n (%)	4 (8.9)	3 (13.6)	1 (4.3)	0.346
IDH2, n (%)	2 (4.4)	1 (4.5)	1 (4.3)	1
CEBPA, n (%)	2 (4.4)	1 (4.5)	1 (4.3)	1
PHF6, n (%)	2 (4.4)	2 (9.1)	0 (0)	0.233
NF1, n (%)	2 (4.4)	1 (4.5)	1 (4.3)	1
NARS, n (%)	1 (2.2)	1 (4.5)	0 (0)	0.489
BCOR, n (%)	1 (2.2)	0 (0)	1 (4.3)	1
KMT2D, n (%)	1 (2.2)	0 (0)	1 (4.3)	1
RUNX1, n (%)	1 (2.2)	1 (4.5)	0 (0)	0.489

Table 3. Univariate and multivariate Cox regression analysis was used to analyze the influencing factors of PFS in AML/MDS patients with TP53 gene mutation.

Variables	Univariate regression analysis		Multivariate regression analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (1,1.06)	0.044		
Gender, male vs. female	0.74 (0.37,1.47)	0.387		
Karyotype, ab vs. no	1.91 (0.88, 4.14)	0.086	2.09 (0.88,4.98)	0.095
Blast	0.99 (0.98,1.00)	0.274		
WBC	0.99 (0.99,1.00)	0.336		
Monocyte percentage	1.02 (1,1.04)	0.055	1.02 (1, 1.05)	0.06
BASO percentage	0.89 (0.56,1.4)	0.605		
RBC count	0.63 (0.38,1.05)	0.074	0.39 (0.19, 0.81)	0.011
Hemoglobin	0.98 (0.97,1)	0.046	0.98 (0.96, 1)	0.043
Blood platelet count	0.99 (0.99,1)	0.068	1 (0.99, 1)	0.18
HSCT, yes vs. no	0.08 (0.01,0.61)	< 0.001	0.08 (0.01,0.69)	0.022
CNSL, yes vs. no	0.13 (0.02,1)	0.002	0.15 (0.02,1.21)	0.075
INR	12.28 (0.86,176.43)	0.065	10.41 (0.5,218.63)	0.132
Serum albumin	0.91 (0.85,0.97)	0.004	0.91 (0.84, 0.98)	0.01
Serum ALT	0.99 (0.97,1)	0.0084	0.99 (0.97, 1.01)	0.465
LDH	1.0 (1.00,1.00)	0.029	1.0 (1.00,1.00)	0.029

BASO: basophil cell, WBC: white blood cell count, RBC: red blood cell count, LDH: lactic dehydrogenase, CNSL: central nervous system leukemia, HSCT: allogeneic hematopoietic stem cell transplantation, ALT: alanine aminotransferase, PFS: progression-free survival time.

Table 4. Univariate and multivariate Cox regression analysis was used to analyze the influencing factors of OS in AML/MDS patients with TP53 gene mutation.

Variables	Univariate regression analysis		Multivariate regression analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.03 (0.99, 1.07)	0.19		
Gender, male vs. female	1.07 (0.47, 2.45)	0.872		
Karyotype, ab vs. no	1.91 (0.75, 4.86)	0.173		
Blast	1.0 (0.99, 1.0)	0.814		
WBC	0.99 (0.99, 1.00)	0.514		
RBC count	0.66 (0.36, 1.19)	0.168		
Hemoglobin	0.99 (0.97, 1)	0.143		
Blood platelet count	0.99 (0.99, 1.00)	0.675		
HSCT, yes vs. no	0.1 (0.01, 0.82)	0.032	0.08 (0.01,0.74)	0.026
CNS-L	0.17 (0.02, 1.32)	0.09	0.15 (0.02,1.36)	0.092
LDH	1.00 (1.00, 1.00)	0.044	1.00 (1.00,1.00)	0.127
Serum albumin	0.97 (0.9, 1.04)	0.343		
ALT	0.97 (0.95, 1.00)	0.05	0.97 (0.94, 0.99)	0.018
RUNX1	34.58 (2.99, 400.29)	0.005	18.15 (1.37, 239.77)	0.028
TET2	2.64 (0.96, 7.24)	0.06	1.96 (0.68, 5.7)	0.214
CSMD1	7.33 (0.89, 60.37)	0.064	4.46 (0.46, 42.98)	0.196

WBC: white blood cell count, RBC: red blood cell count, LDH: lactic dehydrogenase, CNSL: central nervous system leukemia, HSCT: allogeneic hematopoietic stem cell transplantation, ALT: alanine aminotransferase, OS: overall survival time.

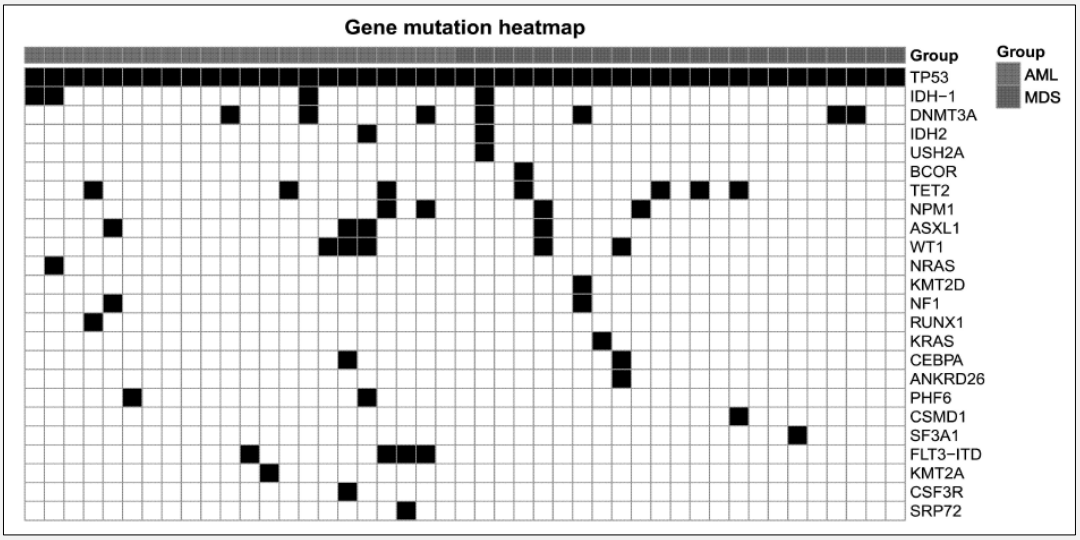

Figure 1. Heatmap of the most frequent mutations divided by AML (light gray) and MDS (dark gray) status. TP53 mutation and all other mutations are indicated by black (present) and white (absent) blocks.

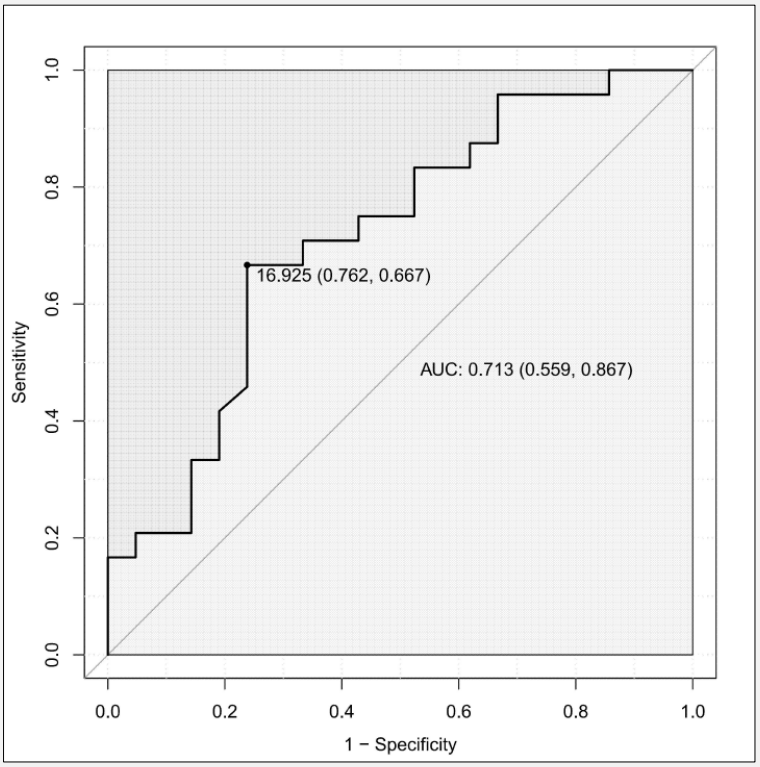

Figure 2. A receiver operating characteristic curve (ROC) analysis was conducted to evaluate the accuracy of ALT levels in predicting TP53 mutation status in AML/MDS patients with implications for overall survival outcomes.

0.074), and serum uric acid also showed a trend toward elevation in AML patients although it did not reach statistical significance (p = 0.051) (Table 1). Allogeneic HSCT was performed in 2/45 patients (4.4%), with similar proportions in the AML and MDS groups (AML 4.5% vs. MDS 4.3%, p = 1), as presented in Table 1. Central nervous system involvement was reported only in the AML subset.

Co-mutation analysis

Most commonly co-occurring with TP53 in this patient group were DNMT3A and TET2 at 15.6% each, with similar frequencies between the two groups. WT1 occurred in 11.1% of the patients and was slightly more frequent in AML than MDS (13.6% vs. 8.7%). ASXL1 occurred in 8.9% of the cases and was also more frequent in AML than MDS (13.6% vs. 4.3%, p = 0.346), whereas NPM1 was similar between AML and MDS (9.1% vs. 8.7%). FLT3-ITD occurred only in the AML group and was more frequent in AML than MDS (18.2% vs. 0%, p = 0.049). IDH1 was also more frequent in AML than MDS (13.6% vs. 4.3%). IDH2 and CEBPA were infrequent, with one case in each diagnostic group. PHF6 occurred only in AML; NARS and RUNX1 were also observed only in AML, whereas BCOR and KMT2D were observed only in MDS. NF1 occurred in one patient in each group (Table 2).

Mutation pattern analysis

Using heatmap analyses, distinct mutational patterns were observed between AML and MDS patients with TP53 mutation; although TP53 mutation was present in both groups by study design, the corresponding co-mutation frequencies differed between the two diagnoses, which may reflect biological differences in clonal evolution. FLT3-ITD, ASXL1, and IDH1 were more frequent in AML patients (Figure 1).

Prognostic factor analysis

Univariate Cox regression analysis for PFS revealed several possible predictive factors. Age showed shorter PFS (HR: 1.03, 95% CI: 1.00 - 1.06, p = 0.044); among the lab parameters, RBC tended to improve PFS (HR: 0.63, 95% CI: 0.38 - 1.05, p = 0.074), but lower hemoglobin levels were related to worse results (HR: 0.98, 95% CI: 0.97 - 1.00, p = 0.046) (Table 3).

Clinical interferences also had prognostic impact. Allogeneic HSCT had strong beneficial effect on PFS (HR:

0.08, 95% CI: 0.01 - 0.61, p < 0.001), and CNSL was favorable as well (HR: 0.13, 95% CI: 0.02 - 1.00, p = 0.002). Serum albumin presented a protective effect (HR: 0.91, 95% CI: 0.85 - 0.97, p = 0.004), while LDH elevation was linked with worse PFS (HR: 1.00, 95% CI: 1.00 - 1.00, p = 0.029) (Table 3).

Allogeneic HSCT emerged as the most powerful independent predictor in multivariate analysis of prognosis for PFS (HR: 0.08, 95% CI: 0.01 - 0.69, p = 0.022). Higher RBC count (HR: 0.39, 95% CI: 0.19 - 0.81, p = 0.011), hemoglobin level (HR: 0.98, 95% CI: 0.96 - 1.00, p = 0.043), serum albumin (HR: 0.91, 95% CI: 0.84 - 0.98, p = 0.010) and LDH (HR: 1.00, 95% CI: 1.00 - 1.00, p = 0.029) maintained independent prognostic significance (Table 3).

Fewer significant predicting factors are displayed in univariate Cox regression analysis for OS. Allogeneic HSCT showed a strong protecting effect (HR: 0.10, 95% CI: 0.01 - 0.82, p = 0.032), elevated LDH (HR: 1.00, 95% CI: 1.00 - 1.00, p = 0.044) and ALT (HR: 0.97, 95% CI: 0.95 - 1.00, p = 0.050) levels were adverse. Interestingly, RUNX1 co-mutation was strongly correlated with poor OS (HR: 34.58, 95% CI: 2.99 - 400.29, p = 0.005). Allogeneic HSCT remained benefitcial in multivariate analysis for OS (HR: 0.08, 95% CI: 0.01 - 0.74, p = 0.026), whereas RUNX1 co-mutation continued to be strongly adverse (HR: 18.15, 95% CI: 1.37 - 239.77, p = 0.028). Lower ALT levels exhibited an independent benefit for OS (HR: 0.97, 95% CI: 0.94 - 0.99, p = 0.018) (Table 4). Although allogeneic HSCT showed a significant association with improved survival in multivariate analysis, the statistical power was severely constrained by the event count (only 2 transplanted cases), raising the possibility of model overfitting.

The ROC analysis revealed an area under the curve (AUC) of 0.713 (95% confidence interval: 0.559 - 0.867), indicating moderate predictive accuracy for identifying TP53 mutations using ALT levels. At the optimal cutoff value of 16.925, the model achieved a sensitivity of 76.2% and specificity of 66.7% (Figure 2).

DISCUSSION

In summary, 45 patients with TP53-mutated AML or MDS were fully analyzed regarding the clinical features, molecular landscapes and prognostic determinants in a high-risk patient population. We identified major differences between TP53-mutated AML and MDS concerning their phenotypic and molecular characteristics that have considerable consequences for risk stratification and therapeutic decisions in current hematologic practice.

Interestingly, compared with MDS patients (65.5 ± 9.0 years), the mean age of AML patients (56.0 ± 15.1 years) was remarkably younger, which may be due to the small sample size of our research. It remains unclear whether such an age difference really exists and how TP53 dysfunction contributes to leukemogenesis at different ages. These results should be confirmed by larger studies.

Distinct but overlapping co-mutation patterns provide us clues about the clonal evolution and pathogenesis of TP53-mutated myeloid neoplasms. The equal proportion of DNMT3A/TET2 mutation frequency across two disease entities reflects the essential contribution of these epigenetic-related mutations to TP53-driven malignancies [14,15]. These mutations are likely early clonal events setting up the pre-leukemic state; subsequently, TP53 alterations can also act as progression events that might overcome p53-mediated tumor suppressive mechanisms [16].

The differential distribution patterns of some co-mutations between AML and MDS suggests the complex and heterogeneous molecular profiles of TP53-mutated diseases. In this cohort, ASXL1 and IDH1 mutations were numerically more frequent in AML than in MDS (13.6% vs. 4.3% for each), although these differences were not statistically significant. Given the small number of events, these subgroup patterns should be interpreted cautiously and require validation in larger cohorts [16,17].

These distinctive mutational spectra among samples reflect the accumulating knowledge that TP53-mutated myeloid malignancies represent molecularly defined diseases that require targeted therapeutic approaches. The identification of particular co-mutation combinations may help the design of new therapies targeting multiple pathways simultaneously in this challenging patient group, thus allowing better outcomes for patients historically treated ineffectively [18].

Our survival analysis identifies several clinically-actionable and independent predictors affecting patient outcome and therapy choice, including powerful protection from allogeneic HSCT (HR = 0.08 for both PFS and OS, p < 0.025) on the basis of which we can understand more clearly the critical role played by immunological interventions against TP53-dependent drug resistance [19]. This result is concordant with emerging clinical evidence indicating that HSCT is considered the best treatment option for TP53-mutated high-risk patients.

The identification of RUNX1 co-mutation as a powerful independent adverse prognostic factor (OS HR 18.15, p = 0.028) is a new and clinically important finding with immediate impact for risk assessment and treatment planning. RUNX1 is a master switch regulating hematopoietic differentiation; this TP53 and RUNX1 double mutant may be creating an especially aggressive molecular profile with profound differentiation block and increased stem cell self-renewal [20,21]. The findings suggest that patients with double TP53/RUNX1 mutations represent an ultra-high-risk molecular subset requiring alternative therapy or investigation in their management [22].

These results support previous work describing red blood cell counts, hemoglobin levels, and serum albumin in clinical laboratories having the most significant

effects on patient outcome prognosis (OS HR 0.39, p = 0.011; hemoglobin HR 0.98, p = 0.043; albumin HR 0.91, p = 0.010) likely reflecting disease burden and physiological reserve. These observations support combining comprehensive clinical evaluation with genetic assessment to better define sophisticated prognostic models specifically for TP53-mutated patients.

These findings supporting the clear benefit of allogeneic HSCT in young and old highlight the paramount importance of upfront transplant evaluation for all TP53 mutated patients regardless of age or disease subtype [19]. These observations provide strong evidence for contemporary treatment algorithms supporting upfront transplant consideration in suitable candidates due to consistently poor responses to conventional intensive chemotherapy observed within this molecular subset.

That these specific diseases have different molecular features supports considering therapeutic selection using comprehensive mutational profiling could achieve improved outcomes through personalized treatments. Specific groups being enriched with epigenetic modifier mutations (DNMT3A, TET2, ASXL1) can support favoring the use of hypomethylating agents or other epigenetic therapies for bridging approaches prior to transplantation or for maintenance therapy in non-transplant patients [23,24].

There are several limitations to this analysis which should be noted. Retrospective single institution study designs coupled with smaller sample sizes do not lend themselves well to generalizing low frequency co-mutations across institutions with variable treatment programs. Referral patterns along with local treatment protocols within a certain institution's walls must also be considered while selecting potential participants for multi-center trials as bias exists regarding which cases were selected into our current analysis based upon institutional referral patterns.

Several research questions deserve attention in the future: first, confirming RUNX1 co-mutant as an independent unfavorable prognostic factor needs further validation in larger datasets and molecular mechanisms need to be characterized for the underlying enhancement of therapy resistance; secondly, prospective clinical trials stratifying patients by their molecular risks derived from TP53 co-mutation might permit individualized therapeutic choice and could lead to improved results through molecular medicine approaches; fourth, a rapidly changing therapeutical scenario with new TP53-targeted drugs, MDM2 inhibitors, and immunologic check-point modifications requires reconsideration of the prognosis according to recent regimens. Monitoring dynamic molecular information via measurable residual disease or serial mutational profile analysis may yield more substantial perspectives about evolving clonal features and resistance mechanisms against therapies.

In summary, this study's comprehensive molecular and clinical profiling of TP53-mutated AML/MDS uncovered key prognostic features with immediate clinical impact, including RUNX1 co-mutation as a novel ultra-high-risk marker that justifies more aggressive risk stratification and intensified therapy. Allogeneic HSCT was associated with improved progression-free and overall survival; however, this finding should be interpreted cautiously because only two patients underwent transplantation.

The study analyzed progression-free survival (PFS) and overall survival (OS), rather than relapse-free survival, and "was associated with" is more appropriate than causal wording for this retrospective study. Together, these findings establish a foundation for precision-medicine approaches in TP53-mutant myeloid neoplasms and warrant validation in larger cohorts to translate into better patient outcomes.

Given the relatively small sample size and limited number of events, these results should be interpreted as hypothesis-generating and require external validation.

Source of Funds:
Ganzhou City Guiding Science and Technology Planning Project (GZ2024ZSF061).

Declaration of Interest:
All authors declares no conflicts of interest.

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