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TP53 VAF AS AN EASIER PROGNOSTIC INDICATOR IN MYELODYSPLASTIC NEOPLASMS IN COMPARISON WITH *TP53* ALLELIC STATUS

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INTRODUCTION

Biallelic *TP53* inactivation negatively affects overall survival (OS) and leukemia-free survival (LFS) of patients with myelodysplastic syndromes (MDS), whereas MDS patients with monoallelic *TP53* defects display outcomes similar to those of *TP53*wt patients[1]. Biallelic *TP53* inactivation is defined by WHO 2022 classification as the presence of multiple *TP53* mutations or evidence of *TP53* copy number loss, like del(17p) and copy neutral loss of heterozygosity (cnLOH). However, detection of del(17p) and cnLOH requires advanced cytogenetic evaluations, not routinely available in all centers. Both WHO and ICC 2022 classifications indicate variant allele frequency (VAF) ≥50% as a surrogate for definition of multi-hit status[2,3].

METHOD

MDS patients (n=2496) from the publicly available dataset of the IPSS-M study by E. Bernard et al.[4] were analyzed. A ROC curve was used to identify an optimal *TP53* VAF threshold to discriminate mono- from multi-hit status. Cox proportional hazards modeling with stepwise variable selection was adopted to correlate VAF threshold with OS and LFS and to compare it with the conventional 50% VAF.

CONTACT INFORMATION

The authors have no potential conflict of interest to disclose.

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RESULTS

Our analysis showed that a *TP53* VAF ≥24% adequately predicted multi-hit status (AUC=0.81, sensitivity=0.81, specificity=0.74) and the Cox proportional hazards model confirmed the 24% VAF threshold as a stronger predictor for OS and LFS than the 50% threshold.

Additionally, MDS patients with *TP53* VAF ≥24% had similar outcomes to MDS patients with confirmed *TP53* multi-hit status (median OS 0.77 and 0.76 years, LFS 0.65 and 0.64 years, respectively). Further supporting the threshold, patients with *TP53* VAF <24% and single-hit *TP53* displayed similar OS (2.52 vs 2.24) and LFS (2.2 vs 2.2 years).

Thus, the *TP53* 24% VAF threshold seem to exhibits the same prognostic power as *TP53* allelic status for OS and LFS across distinct IPSS-R categories, achieving statistical significance in all but low and high-risk categories.

Table 1. Summary of Clinical features for 2193 Patients by TP53 category

Characteristic		*TP53* wt	*TP53* VAF<24%	*TP53* VAF≥24%
Patient - No (%)		2193 (87,8)	114 (4,6)	189 (7,6)
Age		72	73,5	72
IPSS-M - No (%)	Very low	293 (14,3)	10 (9,2)	1 (0,6)
	Low	726 (35,4)	28 (25,7)	3 (1,7)
	Moderate low	252 (12,3)	8 (7,2)	4 (2,2)
	Moderate high	233 (11,3)	12 (11)	5 (2,8)
	High	300 (14,6)	19 (17,4)	11 (6,2)
	Very high	248 (12,1)	32 (29,4)	155 (86,6)
TP53 allelic. Status - No (%)	Single-hit	/	75 (65,8)	27 (14,3)
	Multi-hit	/	39 (34,2)	162 (85,7)
MDS type - No (%)	Primary	1989 (92,9)	95 (86,4)	139 (76,4)
	s/t MDS	152 (7,1)	15 (13,6)	43 (23,6)
Chromosome 17 status - No (%)	Normal	2177 (99,3)	98 (86)	81 (42,9)
	Abnormal (del, cnloh, iso17q)	16 (0,7)	16 (14)	108 (57,1)

Table 2. Summary of clinical outcomes by TP53 category according to mutational state and TP53 VAF24 category

Characteristic		*TP53* wt	*TP53* single hit	*TP53* VAF<24	*TP53* multi hit	*TP53* VAF≥24
Median OS (25–75% range) — yr		1,94 (0,82 - 3,85)	1,78 (0,71 - 3,35)	1,5 (0,62 - 3,09)	0,67 (0,23 - 1,26)	0,68 (0,23 - 1,28)
Median LFS (25–75% range) — yr		1,67 (0,72 - 3,6)	1,73 (0,76 - 3,22)	1,34 (0,59 - 2,61)	0,55 (0,2 - 1,08)	0,55 (0,18 - 3,6)
Odd ratio death - yr (95% CI)	by 1yr	0,15 (0,13 - 0,17)	1,23 (0,71 - 2,12)	1,85 (1,17 - 2,93)	8,13 (5,99 - 11,02)	7,72 (5,66 - 10,55)
	by 2yr	0,34 (0,31 - 0,38)	1,4 (0,92 - 2,15)	1,84 (1,25 - 2,72)	7,98 (5,76 - 11,05)	7,17 (5,25 - 9,78)
Odd ratio AML transformation - yr (95% CI)	by 1yr	0,2 (0,18 - 0,23)	1,13 (0,68 - 1,88)	1,84 (1,2 - 2,82)	7,93 (5,85 - 10,77)	7,17 (5,25 - 9,78)
	by 2yr	0,38 (0,35 - 0,42)	1,24 (0,81 - 1,9)	1,76 (1,2 -2,59)	8,29 (5,92 - 11,62)	7,43 (5,3 - 10,42)

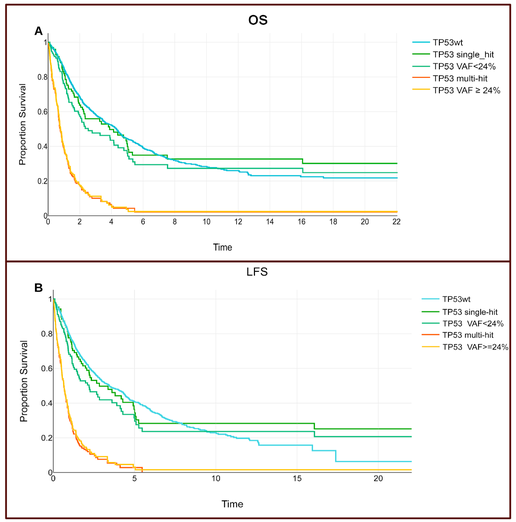


Figure 1.Kaplan–Meier probability estimates of (A) overall survival (OS) and (B) leukemia free survival (LFS) for TP53 allelic status and TP53 VAF category

CONCLUSIONS

Our results showed that a TP53 VAF threshold of 24% informs MDS prognosis equally to TP53 allelic status. This parameter offers a simpler and more feasible approach for clinical practice, potentially improving patient stratification and management.in centers where advanced diagnostics are not available.

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