RISK STRATIFICATION OF PATIENTS TREATED FOR *NPM1*-MUTATED ACUTE MYELOID LEUKEMIA: A SINGLE-CENTER RETROSPECTIVE STUDY

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INTRODUCTION

Acute myeloid leukemia (AML) is an aggressive neoplasm that encompasses diverse molecular subtypes with unique clinical characteristics [1]. Overall, recent advances in incorporating targeted therapies and the accessibility of allogeneic hematopoietic cell transplantation (AlloHCT) due to variable stem cell sources, along with accustomed conditioning regimens, continue to reshape survival outcomes of AML [2, 3]. Nucleophosmin 1 (*NPM1*) mutation accounts for more than 30% of cases [4]. However, its potentially favorable outcome is contingent on co-mutational profiles. The occurrence of FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutation has well-established worse outcomes, which can be mitigated by the addition of *FLT3* inhibitors and consideration of AlloHCT in first remission (CR1) [1].

AIM

To risk stratify our treated *NPM1*-mutated AML patients and evaluate the effect of cooperative high-risk mutations (HRMs) on outcomes.

METHOD

We conducted a comprehensive retrospective study at our center across 3 cities. Treated *NPM1*-mutated AML patients were included from inception through February 28, 2026. Median leukemia-free survival (mLFS) and overall survival (mOS) were calculated using the Kaplan–Meier method. All survival analyses were performed in R© 4.5, 2025, Vienna, Austria, with median survival defined as the time point at which the estimated survival probability reached 50%.

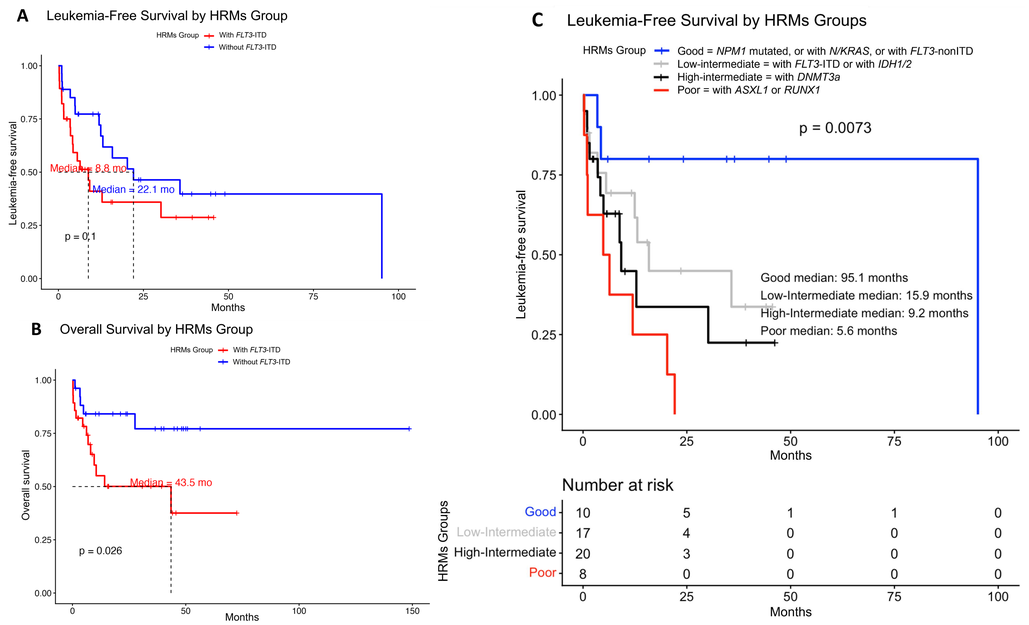
CONCLUSIONS

Evidence continues to point out substantial heterogeneity in *NPM1*-mutated AML outcomes, which we observed even in FIM cases. Deciphering these outcomes by identifying unique biological attributes like cooperative HRMs will need to be abrogated by further advances in therapy, like involvement of targeted therapy against *NPM1* that can suppress the driving clone, and the inclusion of AlloHCT in CR1 in potentially higher-risk cases.

RESULTS

We identified 55 patients who met our criteria. Mean age was 51.4 (range, 34.7–68.1) years. Twenty-eight patients (51%) were *FLT3*-ITD mutated (FIM). Thirty-eight patients (69%) received intensive chemotherapy. Thirteen patients (24%) received AlloHCT in CR1 (12 were FIM). Disease relapse or refractory status was observed in 27 patients (49%), including six who received AlloHCT in CR1. Fifteen relapse/refractory cases occurred in FIM (56%). Deaths occurred in 18 patients (33%). mLFS and mOS for FIM vs *NPM1* with unmutated *FLT3*-ITD were 8.8 (0.2–45.6) and 43.5 (0.2–72.5) months vs 22.1 (1.0–95.1) and not reached (1.1–148.6) months (P=0.1 and P=0.026, respectively) (Figure 1A and B). Thirteen of 15 FIM (87%) harbored additional HRMs, commonly DNA methyltransferase 3 alpha (*DNMT3A*). mLFS for FIM patients without HRMs was nearly doubled with significant mOS. mLFS for the remaining *NPM1* patients was also significant (P=0.0073) (Figure 1C).

Figure 1. Clinical outcomes of NPM1-mutated AML cases. (A) LFS and (B) OS for mutated vs unmutated FLT3-ITD. (C) LFS by HRMs groups.



ASXL1, additional sex combs-like 1; AML, acute myeloid leukemia; DNMT3A, DNA methyltransferase 3 alpha; FLT3-ITD, FMS-like tyrosine kinase 3 internal tandem duplication; HRMs, high risk mutations; IDH1/2, isocitrate dehydrogenase 1 and 2; mLFS, median leukemia-free survival; mOS, median overall survival; N/KRAS, Neuroblastoma/Kirsten rat sarcoma viral oncogene homolog; NPM1, Nucleophosmin 1; RUNX1, runt-related transcription factor 1.

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