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Response to Comment on: "Prognostic implications of myelodysplasia-related gene mutations in *NPM1*-mutated acute myeloid leukemia: a systematic review and meta-analysis"

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Author contributions

YS Chang and HA Hou conceptualize, wrote and approved the commentary.

Conflict of Interest Statement

The authors declare no conflicts of interest.

To the editor,

We thank Desai *et al.*[1] for their comments on our recent meta-analysis of myelodysplasia-related gene (MRG) mutations in *NPM1*-mutated acute myeloid leukemia (AML).[2] Our primary aim was to determine whether co-occurring MRG mutations affect survival in *NPM1*-mutated AML, which is generally classified as favorable risk in the absence of *FLT3*-ITD or adverse-risk cytogenetics.[3] We found that co-occurring MRG mutations were associated with inferior overall survival (pooled hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.11-1.51; $P<0.001$), event-free survival (pooled HR, 1.43; 95% CI, 1.11-1.85; $P=0.006$), and complete remission (CR) rates (risk ratio, 0.94; 95% CI, 0.90-0.99; $P=0.001$).[2]1 These findings remained consistent in subgroup analyses limited to intensively treated patients and those with ELN-2022 favorable-risk disease.

We agree that the key issue raised by our meta-analysis beyond whether MRG mutations carry prognostic value in *NPM1*-mutated AML, is how this information should be integrated into transplant decision-making. As Desai *et al.* noted,[1] our transplant-stratified subgroup analysis did not demonstrate a statistically significant differential survival effect according to transplantation status, and these analyses were constrained by limited sample size, inherent selection bias of study-level observational data and inability to adjust for important confounders, including co-occurring *FTL3*-ITD. Our meta-analysis was designed to clarify prognostic significance, not to establish the benefit of transplantation in first CR. Transplant decisions should remain individualized rather than dictated by MRG status alone. Moreover, whether the modest adverse prognostic impact associated with MRG mutations (HR, 1.3) is sufficient to justify transplantation, given its substantial potential morbidity and mortality, remains uncertain and warrants further study. Even among patients with ELN-2022 intermediate-risk AML, a group generally associated with HR of approximately 1.5 to 2.27,[4, 5] the decision to proceed to transplantation is often individualized and guided by factors such as age, comorbidities, treatment response, measurable residual disease (MRD) status, donor availability, and patient preference. As noted in our study limitations, our analysis was based on published aggregate data rather than individual participant data (IPD), which precluded evaluation of MRD effects. In a large cohort of *NPM1*-mutated AML, Othman *et al.* identified peripheral blood (PB) MRD negativity after two courses of chemotherapy (post-C2) as the strongest independent prognostic factor for survival.[6] In the updated 2025 ELN-DAVID MRD guideline, post-C2 MRD positivity in PB is designated as "warning" rather than "high risk for treatment failure" and whether to proceed to transplantation or to continue consolidation chemotherapy remains uncertain.[7]

We acknowledge that MRG mutations might not be regarded as a biologically uniform entity. In our gene-level meta-regression analyses, *ASXL1* was associated with significantly inferior survival (pooled HR=2.27, 95% CI: 1.44-3.59), whereas *SRSF2* and *STAG2* were not.[2] However, these subgroup analyses were again limited by the small number of included studies and modest sample size. These findings, along with the growing evidence from studies focusing on AML with MRG mutations,[8] support the view that aggregation of all MRG mutations into a single category may oversimplify clinical interpretation. Rather, the adverse effect of MRG mutations in *NPM1*-mutated AML is likely heterogeneous and partly driven by specific genes.

Taken together, we believe the comment is fundamentally valid. Our study shows that co-occurring MRG mutations identify a subgroup of *NPM1*-mutated AML with inferior outcomes; however it does not imply that all such patients should undergo transplantation in first CR. Rather, our findings support a more refined approach in which MRG status is considered as one component of risk assessment, interpreted alongside the specific mutated gene, treatment response, MRD status, and transplant-related risk. Future studies using IPD that integrate mutation-specific effects, standardized MRD assessment, and transplantation outcomes will be required to clarify how these factors should be incorporated into future treatment algorithms.

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