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by Hamza Sajid

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Comment on: Clinical interrogation of TP53 aberrations and its impact on survival in patients with myeloid neoplasms

Hamza Sajid
Allama Iqbal Medical College, Lahore

E-mail: hamzasajid490@gmail.com
ORCID: 0009-0000-1032-9297
Address: Hostel no 3 Allama Iqbal Medical College, Lahore

Correspondence:

Name: Hamza Sajid

Institute: Allama Iqbal Medical College, Lahore

Email: hamzasajid490@gmail.com

ORCID: 0009-0000-1032-9297

Address: Hostel no 3 Allama Iqbal Medical College, Lahore

The study by Senapati et al. provides a comprehensive retrospective analysis of the impact of TP53 aberrations on outcomes in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), highlighting the prognostic significance of TP53 mutational burden, disease subtype, and the role of allogeneic hematopoietic stem cell transplantation (HSCT).[1] While the authors present valuable insights into the clinical relevance of TP53 allelic status and treatment outcomes, several aspects warrant further discussion, including the implications of TP53 heterogeneity, the limitations of retrospective design, and the need for prospective validation of risk stratification models.

The classification of TP53 aberrations into high-risk (TP53HR) and low-risk (TP53LR) groups based on variant allele frequency (VAF), allelic loss, or multiple mutations is a pragmatic approach. However, the biological heterogeneity of TP53 mutations—such as missense versus truncating mutations—may further influence outcomes. For instance, missense mutations often exhibit dominant-negative effects or gain-of-function properties, which could exacerbate disease aggressiveness.[2] The study briefly mentions the prevalence of missense mutations (87%) but does not explore their differential impact on survival. Future analyses could stratify outcomes by mutation type to refine prognostic models.

The study's retrospective nature and the predominance of patients treated at a single tertiary center may introduce selection bias. Patients enrolled in clinical trials (75% of the cohort) often have better performance status and access to novel therapies, potentially skewing survival estimates. Additionally, the exclusion of patients with missing cytogenetic data or low blast counts (<5%) may underrepresent the true diversity of TP53-mutated myeloid neoplasms. Prospective, multicenter studies are needed to validate these findings in broader populations.[3]

The study reaffirms HSCT as a critical intervention for TP53-mutated MDS/AML, with transplanted patients achieving superior survival (median OS: 14 months in AML, 17.3 months in MDS). However, the benefit was most pronounced in patients achieving MRD-negative remission pre-HSCT (median OS: 29.5 months). This underscores the importance of MRD assessment, yet the study does not detail MRD monitoring methods or its consistency across patients. Standardized MRD protocols, such as next-generation sequencing (NGS) or multiparameter flow cytometry, could enhance predictive accuracy.[4]

While venetoclax-based regimens improved response rates (OR: 66% vs. 48%), they did not translate into survival benefits, contrasting with prior reports.[5] This discrepancy may reflect the high prevalence of TP53HR (87%) in the cohort, a subgroup known for venetoclax resistance.[6] The lack of survival advantage also questions whether venetoclax merely selects for less aggressive clones without altering disease biology.

Conversely, the equivalence of intensive and low-intensity therapy in younger patients (<60 years) challenges the dogma that TP53-mutated AML universally benefits from reduced-intensity approaches.[7]

The study notes superior survival in MDS (median OS: 10.8 months) versus AML (5.9 months), even within TP53HR subgroups. This aligns with recent debates about the arbitrary 20% blast cutoff for AML/MDS classification.[8] However, the absence of survival differences between MDS patients with 5–10% versus >10% blasts suggests that TP53 aberrations may override traditional blast-based prognostication. This supports calls for integrating molecular profiling into diagnostic criteria.[9]

The study's validation of a 40% VAF cutoff for TP53HR (corroborated by machine learning) is clinically actionable, but dynamic monitoring of TP53 clones during therapy could refine risk assessment. Emerging therapies targeting p53 stabilization (e.g., eprenetapopt) or immune-based strategies may benefit TP53HR patients, particularly in combination with HSCT.[10]

In conclusion, Senapati et al. provide a robust framework for TP53 risk stratification, but prospective studies addressing mutation heterogeneity, MRD, and novel therapies are needed to optimize outcomes in this high-risk population.

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