2. NEWLY DIAGNOSED MULTIPLE MYELOMA

# INTEGRATED P53 ISOFORM EXPRESSION DEFINES NOVEL PROGNOSTIC SUBGROUPS IN MULTIPLE MYELOMA

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**Introduction.** In multiple myeloma (MM), TP53 abnormalities, including deletions and mutations, are well-established drivers of high-risk disease. Beyond full-length p53 (p53FL), alternative p53 isoforms modulate p53 transcriptional activity, cellular stress responses, and tumor behavior. However, the expression patterns, interactions, and clinical relevance of p53 isoforms in MM remain largely unexplored. A deeper understanding of isoform-specific biology may refine current risk stratification and support precision medicine approaches.

**Aim.** To improve MM risk stratification by integrating p53 isoform expression profiles, identify novel molecular subgroups, and enhance prognostic accuracy beyond conventional TP53 assessment.

**Patients and Methods.** RNA-sequencing data from 659 newly diagnosed MM patients enrolled in the CoMMpass study were analyzed for major p53 isoforms. Expression levels were categorized as absent, low, or high using median-based cut-offs. Associations with genomic features, treatment response, progression-free survival (PFS), and overall survival (OS) were evaluated. Isoform expression profiles were integrated with cytogenetic risk factors to define novel prognostic categories.

**Results.** p53FL and p53β were widely expressed (95% and 99% of patients, respectively), whereas p53γ, Δ40p53α, and Δ133p53α/β showed heterogeneous expression patterns. High p53FL frequently co-occurred with high p53β and Δ133p53α, while absence of Δ133p53β was enriched in patients with high p53FL/p53β expression, suggesting functional interactions among isoforms. Del(17p) was detected in 10.8% of patients and was associated with significantly lower p53FL and p53β expression ($p<0.0001$); notably, Δ133p53β expression was absent in del(17p)-positive patients ($p<0.0001$). Absence of p53FL (4.9% of patients) correlated with elevated LDH levels, inferior treatment response, and markedly reduced survival (median PFS: 7.0 vs 32.8 vs 20.6 months; median OS: 7.0 vs 60.3 vs 36.7 months for absent, high, and low expression, respectively; $p<0.001$). p53β expression was associated with favorable biological features, whereas Δ133p53β identified a small subset of patients with particularly poor prognosis ($p<0.001$). Integration of p53 isoform profiles with key cytogenetic abnormalities stratified patients into favorable, intermediate, and poor-risk groups. Poor-risk patients showed significantly higher hazards for PFS (HR 2.74, 95% CI 1.50–4.99, $p=0.001$) and OS (HR 3.79, 95% CI 1.91–7.51, $p<0.001$) compared with favorable-risk patients. When combined with ISS, poor-risk patients within ISS stage III exhibited markedly shorter median PFS (11.5 months) and OS (21.1 months) than favorable-risk patients (PFS 46–50 months; OS 102 months). Isoform-based risk retained independent prognostic significance in multivariate models (interaction $p=0.002$), improving overall prognostic accuracy.

**Conclusion.** p53 isoform profiling captures clinically relevant MM heterogeneity and identifies high-risk patients beyond conventional TP53 assessment. An isoform-based risk classifier robustly stratifies PFS and OS, particularly when combined with ISS, supporting its potential as a prognostic tool for personalized MM management. Prospective validation is warranted prior to clinical implementation. *Acknowledgments. AIRC19-IG22059, BolognAIL OdV, RC2025-2797269.*

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