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From prognostic discrimination to clinical utility in high-risk myeloma. Comment on: "Risk factors and their contributions to prognosis in multiple myeloma"

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Chung and colleagues provide further evidence that adverse biology in multiple myeloma extends beyond the abnormalities captured by the recent IMS/IMWG consensus definition of high-risk disease.[1,2] Using the Multiple Myeloma Research Foundation CoMMpass dataset, they evaluated whether four additional genomic and transcriptomic features, namely the EMC92 gene expression signature, proliferation index, APOBEC mutational activity, and chromothripsis, add prognostic information to the IMS/IMWG criteria. Among patients with complete data for all five factors, 63% had at least one adverse feature, and increasing numbers of features were associated with progressively worse survival. Adding all five factors increased the C-statistic for overall survival from 0.63 in the age- and sex-based model to 0.72, with EMC92 included in each of the models with the highest discrimination. These findings support the potential value of broader molecular profiling, but they also highlight a central challenge. The goal is not simply to identify more adverse features, but to determine which add reproducible information beyond existing systems and meaningfully inform clinical decisions.

The study is particularly valuable in showing how frequently adverse features co-occur. Cytogenetic and genomic abnormalities, gene expression patterns, proliferative activity, APOBEC mutational signatures, and chromothripsis may reflect distinct but interconnected aspects of aggressive disease. Evaluating them together may therefore capture more of the biology associated with poor outcomes, although their overlap also makes a simple count of adverse “hits” difficult to interpret. Discrimination generally improved as factors were added, but the magnitude of improvement varied. Proliferation, for example, was strongly associated with overall survival in univariate analysis, with a hazard ratio of 2.22. However, adding it to the model containing EMC92 increased the C-statistic by only 0.006. This small incremental gain despite a strong univariate association is consistent with partly overlapping prognostic information. Future models may need to weight features according to their incremental contribution rather than treat each as an equivalent additional hit.

The reported improvement in discrimination is encouraging but remains exploratory. Thresholds for several continuous measures were selected within CoMMpass according to their association with outcome, and performance was then assessed in the same cohort. This is reasonable for identifying candidate markers, but when cutoffs are chosen and tested in the same

dataset, performance generally appears better than it will in a new population.[3] Independent validation using thresholds specified in advance will therefore be essential.

The reconstructed EMC92 score should also be distinguished from the validated SKY92 assay. EMC92 was originally developed using microarray data and subsequently implemented as SKY92 using an algorithm and classification threshold fixed in advance.[4-6] Chung and colleagues instead reconstructed the signature from CoMMpass RNA sequencing data and selected a cutoff within CoMMpass that classified approximately 33% of evaluable patients as high risk. This is informative as a research analysis, but the resulting classification should not be considered equivalent to that generated by SKY92. The findings support the prognostic importance of gene expression profiling but do not directly establish that SKY92 should be routinely incorporated into the IMS/IMWG framework.

A related consideration is what should qualify as clinically high risk. With four of five measures each classifying approximately 25–35% of patients as adverse, the cumulative high-risk group was broad and included 63% of patients with complete data. This does not diminish the prognostic relevance of the associations, but a clinical classification should identify a group with outcomes sufficiently distinct to justify different monitoring, trial eligibility, or treatment. The proposed factors should therefore be tested for added value beyond contemporary staging systems such as the R2-ISS and the IMS/IMWG definition.[2,7] Identifying prognostic markers is an important first step, but the clinically relevant issue is whether reclassification changes what we recommend for the patient. The authors also found that approximately one-quarter of patients with functional high-risk disease lacked all five baseline features, reinforcing the need to integrate baseline molecular risk with treatment response.

Emerging studies illustrate how this work can be taken forward. Beer and colleagues combined IMS/IMWG criteria with the validated SKY92 assay in patients enrolled in Myeloma XI, while OPTIMUM/MUKnine incorporated SKY92 prospectively to select patients for an intensified strategy.[8,9] Neither study establishes that treatment intensification guided by risk improves outcomes, but together they show how genomic and transcriptomic information can be evaluated using a standardized assay, fixed risk definitions, and defined treatment settings.

Chung and colleagues have shown that current consensus definitions capture only part of adverse myeloma biology and that EMC92 contributed most consistently to the models with the highest discrimination. Their work strengthens the rationale for integrating gene expression profiling with genomic risk assessment. With prespecified thresholds, independent validation, and prospective evaluation, the prognostic signals identified by Chung and colleagues may ultimately translate into clinically useful risk stratification.

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