haematologica
Journal of the Ferrata Storti Foundation

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Received: October 26, 2026.
Accepted: November 2, 2026.

Citation: Tae-Hoon Chung, Jia Geng Chang, Tze King Tan and Wee Joo Chng.
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Haematologica. 2026 Nov 12. doi: 10.3324/haematol.2026.302249 [Epub ahead of print]

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Response to Comment on: "Risk factors and their contributions to prognosis in multiple myeloma"

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T.-H.C. drafted the response; W.J.C. revised the response; and all authors approved the response.

The authors declare no competing interests.

As the commentators indicated[1], the main message we wanted to deliver through our study[2] was that, while a practical and good platform and points to a future direction of using technological developments such as sequencing-based information for prognosis, the current IMS/IMWG criteria has some limitation that should be recognized and we should look at how best to build on this. As we showed, incorporation of other genomics or transcriptomics signatures can add to the IMS/IMWG model. Importantly, if we use only the IMW/IMWG criteria, about 20% of high risk (HR) patients will have similar outcomes as standard risk patients despite their label as HR. We would argue further that we may also need to look for overlaps with other clinical and blood-based signatures such as the extramedullary disease, circulating tumor cells and even changes to the tumor microenvironment and immune profiles in the future.

They highlighted some gaps in our analysis and challenges to clinical utility of our work which we fully agree with and acknowledge. Since our exposition was based on a single cohort of patients in an observational study complicated by uncontrolled variabilities inherent in clinical information especially regarding therapies, our study should be considered mainly as exploratory, and many of specific details such as the determination of HR phenotype cutoffs for continuous valued signatures or the actual SKY92 scores instead of EMC92 need careful further validations as the comment noted. However, our claim that we should still continue to supplement IMS/IMWG recommendations with novel signatures utilizing technological developments or clinical phenotypes like the functional high risk (FHR) group would remain steadfast since there are still ample group of patients that could not have been recognized as HR with the help of risk factors as shown for the case of FHR group in our study. We regard the commentators' mention of gene expression signatures as a potential pool for expanding prognostic markers quite intriguing considering their wide possibility of capturing diverse facets of myeloma biology.[3]

One shortcoming in many of the current studies and approaches regarding prognostic markers is that they look at new markers or specific prognostic markers in isolation. In doing so, we cannot grasp the overlap with different factors. One valuable aspect of the CoMMpass dataset is that many genomics-related risk information beyond the IMS/IMWG criteria is accessible, so we can see how they overlap and add value directly although we are missing important emerging

information such as imaging, circulating tumor cells and extramedullary disease status for example. In the future, to better understand the role and utility of laboratory and clinical features comprehensively, we need to build datasets where all the relevant information is encompassed and collectively scrutinized. This may better inform us what are truly informative risk factors and how to apply them in the clinic.

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