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Letters to the editor

Enhancing the clinical utility of a ten-gene prognostic signature for HCC

Dear Editor,

We commend Zhang and Chen for their comprehensive study on a ten-gene prognostic signature for hepatocellular carcinoma (HCC) based on chronic liver disease, leveraging multi-omics data to stratify risk and explore molecular mechanisms [1]. The study's integration of LASSO and Cox regression to develop the DR5 signature, validated in TCGA-HCC (AUC=0.91) and GSE14520 datasets, is a robust contribution. However, several aspects warrant further consideration to enhance clinical applicability.

First, the prognostic model's reliance on retrospective datasets limits its generalizability. Validation in prospective, multi-ethnic cohorts, as recommended by recent HCC risk prediction studies [2], would strengthen its robustness. Second, the study identifies a negative correlation between DNA methylation and mRNA expression, yet the unexpected patterns in ESR1 and FCN3 suggest potential locus-specific variability. Targeted methylation sequencing could clarify these discrepancies and refine the molecular model [3]. Finally, the drug sensitivity analysis for TACE and sorafenib, based on GSE104580 (n = 66), lacks validation in clinically relevant systems. Incorporating patient-derived organoids [4] or real-world data (e.g., TriNetX) [5] could bridge the gap between computational predictions and therapeutic outcomes, addressing microenvironmental and pharmacokinetic factors.

Addressing these gaps through prospective validation, targeted sequencing, and functional assays would elevate the model's potential as a clinical tool for personalized HCC management.

Declaration of interests

None.

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