

LETTER TO EDITOR

Critical appraisal of “Transient receptor potential channel-related biomarkers for prognostic assessment in hepatocellular carcinoma”

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Dear Editor,

Chen *et al.*¹ report a four-gene “TRP channel-related” prognostic signature comprising *CYP2C9*, *KIF20A*, *SPP1*, and *TRNP1* for hepatocellular carcinoma (HCC), developed using The Cancer Genome Atlas (TCGA) cohort and validated in the International Cancer Genome Consortium (ICGC), with functional emphasis on *TRNP1*. The work is timely given growing interest in transient receptor potential (TRP) channels in liver cancer and the need for robust, biologically grounded prognostic tools.^{2,3} However, several interconnected issues warrant caution before the signature is interpreted as TRP-dependent or clinically actionable. In particular, its mechanistic relationship to TRP-channel activity remains unestablished, clinical validation is limited to retrospective public datasets, functional evidence is restricted largely to *TRNP1* phenotypes in a single cell line, and the proposed immune and therapeutic implications remain computational rather than clinically validated.¹⁻³

The authors define “TRP-related genes” broadly, drawing 107 genes from Reactome and KEGG TRP-channel gene sets, and explicitly note that these genes need not encode TRP proteins.¹ Yet the title and narrative position the biomarkers as “TRP channel-related,” which may imply a stronger mechanistic relationship than has been demonstrated. None of the four final genes in the final signature—*CYP2C9*, *KIF20A*, *SPP1*, and *TRNP1*—encode canonical TRP channels, and the study does not demonstrate that their expression or manipulation alters TRP-channel abundance, activity, or calcium flux, or downstream TRP-dependent signaling in HCC.¹ No measurements of intracellular Ca²⁺, TRP currents, or downstream calcium-dependent pathways (e.g., calcineurin/NFAT, CAMK, or TRP-linked PI3K/AKT/MAPK signaling) are presented.⁴ In TRP biology, such functional linkage is central: TRP channels shape oncogenic phenotypes via Ca²⁺-dependent signaling, and causal claims typically require showing that perturbing the candidate gene changes TRP-mediated flux or signaling.^{4,5} In the absence of such evidence, the signature may represent a computationally derived, TRP-pathway-associated gene set rather than a mechanistically validated TRP-channel signature.¹

Protein-level validation is also incomplete. Protein validation was reported for *KIF20A*, *SPP1*, and *TRNP1*, whereas *CYP2C9* was not confirmed by western blotting. This incomplete protein validation underscores the need for direct mechanistic and protein-level assessment in larger, well-characterized cohorts.¹

The model’s validation is confined to retrospective public datasets, with TCGA used for model development and ICGC for external validation. Although such validation is valuable, it does not substitute for independent clinical cohorts with standardized

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information on treatment and etiology data.¹⁻³ HCC is etiologically heterogeneous, encompassing viral, alcohol-associated, and metabolic causes, and prognosis varies substantially.⁶ The study does not report stratified model performance according to etiology, liver function measures (e.g., Child–Pugh class or albumin–bilirubin [ALBI] grade), or treatment modality, all of which strongly influence outcomes.⁶ Protein-level assessment was limited to a small patient sample and was reported for only three of the four candidate genes; CYP2C9 was not verified by western blotting. Accordingly, the discrepancy between the bioinformatic result and the available protein-level findings should be interpreted cautiously rather than attributed definitively to sample size or heterogeneity. Larger, better-characterized cohorts are needed to clarify the finding.¹ For a biomarker intended to inform prognosis and potentially treatment selection, this level of tissue-level confirmation is insufficient.⁶ Prospective or multicenter validation, with harmonized clinical variables and etiologic stratification, would be needed to establish generalizability and clinical utility.⁶

Functional characterization focuses primarily on *TRNP1* knockdown and overexpression in HuH-7 cells, with corresponding changes in migration, viability, and invasion.¹ Although these findings support a role for *TRNP1* in malignant cellular phenotypes, they do not establish the underlying mechanism. No rescue experiments are reported to confirm the specificity of the observed effects, and no pathway-level analyses link *TRNP1* to TRP-channel signaling or to canonical oncogenic pathways (e.g., epithelial–mesenchymal transition, cell-cycle regulation, apoptosis, PI3K/AKT signaling, or MAPK/ERK signaling).¹ Given the TRP-centered framing of the study, direct assessment of TRP dependence (e.g., via Ca^{2+} -flux assays, pharmacological or genetic inhibition of relevant TRP channels, or downstream signaling measurements) would materially strengthen the claim that *TRNP1* acts within a TRP-related axis.^{4,5} Moreover, reliance on a single cell line limits functional generalizability because HCC cell lines differ markedly in genetic background, differentiation status, and signaling activity. TRP-channel expression profiles also vary across models.⁴ Validation in additional lines (e.g., HepG2 and Hep3B) or patient-derived models would mitigate the risk of cell-line-specific artifacts.⁴ Recent work indicating that *TRNP1* can promote HCC through c-Kit/STAT3 signaling, rather than TRP channels, and influence responsiveness to PD-1 blockade further raises the possibility that its tumor-promoting effects may occur through mechanisms independent of TRP channels.⁷ Notably, because TRPC channels (a major TRP subfamily) are well-established modulators of cancer-cell migration

and invasion across multiple cancers, reinforcing the expectation that a truly TRP-dependent signature should show direct effects on TRP-mediated calcium signaling and motility pathways.⁸

The study reports differences in 13 immune-cell populations and suggests relevance to immune checkpoint inhibitor (ICI) response, based on computational estimates (eg, ESTIMATE, ssGSEA) and drug-sensitivity analyses.¹ These approaches infer immune infiltration from bulk RNA sequencing rather than directly measuring immune-cell populations.¹ More importantly, no ICI-treated cohort is analyzed to determine whether patients classified as high or low risk differ in objective response, progression-free survival, or overall survival during immunotherapy.^{1,5} Without such data, the signature should be regarded as prognostic—associated with outcome—rather than predictive of benefit from a specific therapy.¹ This distinction is critical for clinical translation, particularly in HCC where multiple first-line systemic options exist.⁶

The study further reports that the risk score is an independent prognostic factor alongside pathological T stage but does not benchmark the model against established HCC staging systems (e.g., Barcelona Clinic Liver Cancer stage, tumor–node–metastasis, Child–Pugh class, and ALBI grade) using measures of discrimination, calibration, clinical utility, or reclassification.^{1,6} Statistical independence does not guarantee improved patient-level decision-making.¹ Additionally, dichotomization by the median risk score is cohort-dependent and may not reproduce across populations; this limitation should be addressed through external validation and prespecified thresholds.¹

We commend the authors for a thoughtful bioinformatic and initial functional exploration. Direct TRP-channel and calcium-signaling assays would clarify the biological basis of the signature.^{4,5,8} Larger, etiologically stratified cohorts and comparisons with established clinical prognostic factors are also required.^{1,6} Expanded functional studies should include additional HCC models, rescue experiments, and pathway dissection.^{1,7} Finally, analysis of ICI-treated cohorts is needed to assess predictive rather than merely prognostic value.^{1,6} Until such data are available, the signature should be interpreted as a promising, TRP-pathway-associated prognostic model rather than a mechanistically validated TRP-channel biomarker panel.^{1,5}

Conflict of interest

The author declares no competing interests.

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