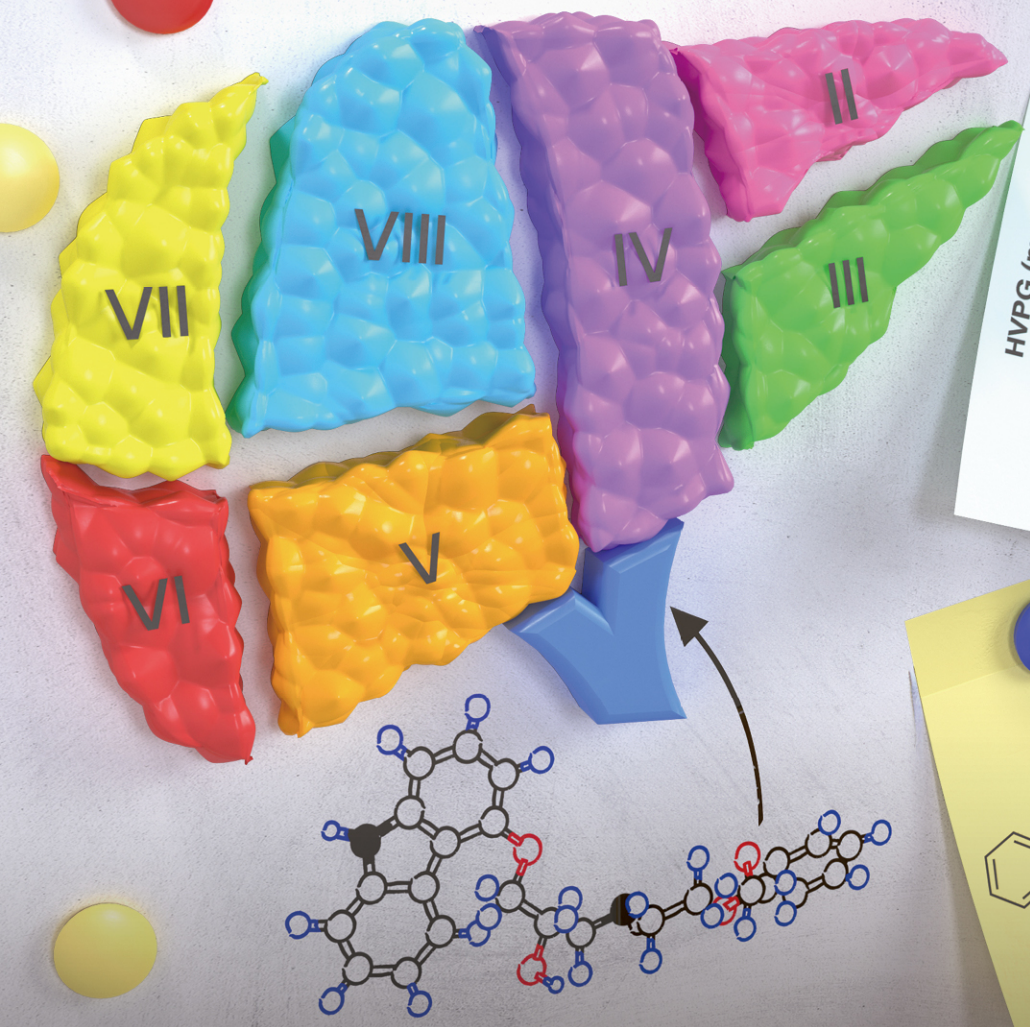
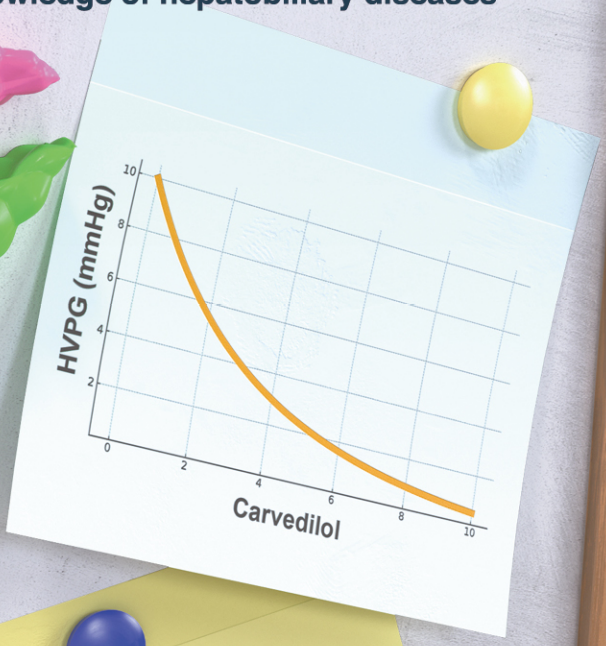
VOLUME 31 NUMBER 1 January 2025

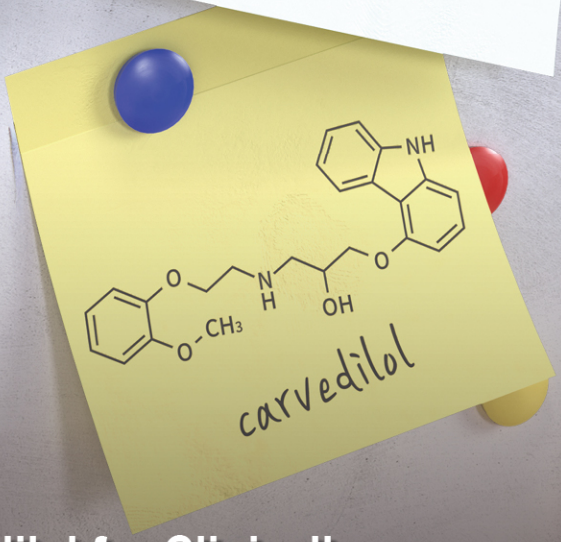
pISSN 2287-2728
eISSN 2387-285X

# CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases




## Non-invasive Model guiding Carvedilol for Clinically Significant Portal HTN

Intrapatient variability of tacrolimus on CKD in LT
HCV self-testing and disease burden reduction
MASLD and microbiota
Bariatric surgery for metabolic cirrhosis

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pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0726
Clinical and Molecular Hepatology 2025;31:308-310

**Editorial**

# Transcriptomic signature in advanced hepatocellular carcinoma tissue to predict combination immunotherapy response: Editorial on "Genomic biomarkers to predict response to atezolizumab plus bevacizumab immunotherapy in hepatocellular carcinoma: Insights from the IMbrave150 trial"

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**Keywords:** Hepatocellular carcinoma; Immunotherapy; Predictive biomarker; Molecular signatures

See Article on https://doi.org/10.3350/cmh.2024.0333

Combination immunotherapies have been introduced as the standard care in the treatment of patients with unresectable advanced hepatocellular carcinoma (HCC).[1] However, the limited objective response rates to immune checkpoint inhibitor (ICI)-based regimens (approximately up to 30%) highlight the need to identify predictive biomarkers of response to avoid their application to patients who will not benefit from the therapies. Recent clinical and translational studies have suggested various types of molecular features as candidate predictive biomarkers associated with objective response and/or post-treatment survival, including intrinsic features of HCC cells (e.g., expression of suppressive immune checkpoints, transcriptomic signatures, somatic DNA mutations, and genetic instability), tumor immune microenvironmental features (e.g., tumor-infiltrating immune cell subsets and their functional status), and peripheral immune features (e.g., neutrophil-to-lymphocyte ratio and cytokine profiles).[2] Clinical and biochemical features (e.g., alpha-fetoprotein, Child-Pugh score, and albumin-bilirubin score) and their longitudinal changes, imaging-based features (e.g., gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic acid-enhanced magnetic resonance imaging and positron emission tomography/computed tomography), gut dysbiosis and metabolites, and immunologic adverse events have also been correlated with treatment responses. More recently, single-cell and spatial omics technologies have been utilized to identify specific effector immune cell subpopulations (e.g., PD-1-negative CD45RA-positive effector-memory CD8 T cells

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**Editor:** Han Ah Lee, Chung-Ang University College of Medicine, Korea

**Received :** Aug. 28, 2024 / **Accepted :** Aug. 29, 2024

and CXCL10-positive macrophages) associated with the response to combination immunotherapy in HCC.[3,4] Despite these extensive efforts, none of these features have been established as predictive biomarkers for combination immunotherapies in advanced HCC to date.

To address this urgent unmet need, in this issue of *Clinical and Molecular Hepatology*, Yim et al. tested a 105-gene tissue-based transcriptomic signature, immune signature score (ISS), from their prior study[5] to predict prognosis after receiving combination therapy in patients with unresectable advanced HCC.[6] The ISS was originally identified for its association with favorable response to anti-CTLA-4 therapy by utilizing The Cancer Genome Atlas datasets.[5] The authors extended the evaluation to atezolizumab and bevacizumab combination therapy for patients with unresectable HCC by analyzing data from the international multi-center GO30140 phase Ib and IMbrave150 phase III trials. As expected, patients with high-ISS showed better objective response rates as well as overall and progression-free survival compared to sorafenib-treated patients when treated with the combination therapy, whereas such a difference was not observed in ISS-low patients. The authors further refined ISS by reducing the number of genes, maintaining the prognostic association, and defined a 10-gene ISS10, which will lower the bar for its clinical translation. In an independent cohort of Taiwanese patients with advanced HCC treated with nivolumab and ipilimumab combination therapy, high-ISS10 patients showed a higher rate of objective response (i.e., partial response and stable disease) and prolonged overall survival than low-ISS10 patients. These findings collectively support the utility of ISS and ISS10 for the prediction of survival benefits for major combination therapy regimens.

Studies have suggested that response to ICI-based and other medical therapies can be affected by heterogeneities in patient characteristics, such as liver disease etiology, which may influence tumor immune microenvironmental features involved in their mechanisms of action.[7] Therefore, validation across diverse patient populations is critical to ensure the validity and generalizability of candidate predictive biomarkers. The successful validation of ISS/ISS10 in the multi-regional/ethnic cohorts is encouraging. However, the dominance of Asian patients (approximately 40%) and viral etiologies (50% hepatitis B virus- and 20% hepatitis C virus-infected patients) as well as the small sample size are limitations, and warrant further validation in larger cohorts, representing more non-Asian patients and metabolic etiologies such as metabolic dysfunction-associated steatotic liver disease. The requirement for tumor tissue may also limit the application of ISS/ISS10 in the setting of systemic therapies for advanced HCC. On the other hand, it may not be an issue in the setting of adjuvant therapy, where tissue acquisition is not a logistical hurdle. In summary, ISS/ISS10 represent another set of promising predictive biomarkers to guide the indication of emerging combination immunotherapies and refine the management of patients with advanced-stage and possibly early-stage HCC.

## Authors' contribution

HK drafted the manuscript. YH reviewed and finalized the manuscript.

## Conflicts of Interest

HK served as a consultant on advisory boards from Takeda and Bayer. YH is shareholder for Alentis Therapeutics and Espervita Therapeutics, advisory for Helio Genomics, Espervita Therapeutics, Elevar Therapeutics, and Roche Diagnostics.

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**Abbreviations:**

HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; ISS, immune signature score; MASLD, metabolic dysfunction-associated steatotic liver disease

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