Correspondence on Editorial regarding “Unveiling etiology-specific blood biomarkers in hepatocellular carcinoma: a gateway to personalized medicine”

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Dear Editor,

We extend our appreciation to Ahn and Yang for their valuable insights (1) provided on our study (2). Their commentary offers a thorough evaluation of the effectiveness of multiomics methodologies in discovering new blood-based biomarkers specific to the etiology of hepatocellular carcinoma (HCC). Divergent transcriptomic and immune profiles distinguish HBV-associated HCC (HBV-HCC), marked by upregulation of immune response-related genes, from nonviral HCC (NV-HCC), characterized by heightened expression of metabolic genes (2). These distinctions underscore the importance of delineating etiology-specific mechanisms in HCC to advance tailored diagnostic and therapeutic interventions.

Ahn and Yang note that in cases of HBV-HCC, where biomarkers are associated with immune response pathways, patients could potentially benefit from emerging immunotherapies or targeted treatments aimed at altering the immune milieu (1). Notably, findings from phase II and III trials (KEYNOTE-224(3) and KEYNOTE-394(4)) consistently demonstrate favorable responses to pembrolizumab, a PD-1-targeting monoclonal antibody, among a significant proportion of HBV+ HCC patients. The enhanced sensitivity of HBV+ HCC to immune checkpoint inhibitors (ICI) may be attributed to elevated expression levels of immune checkpoint genes, such as PD-1, CTLA-4, TIGIT, and HAVCR2, as well as the presence of more abundant regulatory T cells (Tregs), exhausted CD8+ T cells, and M1-like macrophages expressing MM9, thus contributing to a more immunosuppressive and exhausted tumor microenvironment in HBV+ HCC compared to HBV-HCC (5). Furthermore, in a mouse model of chronic HBV infection, it has been demonstrated that HBV infection leads to simultaneous increases in PD-L1 levels on liver-resident NK cells and PD-L1 expression on intrahepatic T cells (6). These findings highlight the impact of HBV on shaping tumor immunity, laying the groundwork for the development of improved immunotherapeutic approaches for HCC originating from various causes.

As Ahn and Yang pointed out, the non-invasive and scalable nature of liquid biopsy, which offers clinically relevant insights into tumor biology (7), could facilitate the incorporation of the identified
biomarkers into routine blood tests, particularly in areas with high HBV prevalence (1). In our investigation, SH3PXD2B and CD70 exhibited notable diagnostic efficacy in distinguishing early-stage HBV-HCC and NV-HCC, respectively, from at-risk patients with NASH or cirrhosis. To facilitate their clinical utility, it is crucial to assess their discriminatory capacity for early detection of HCC through randomized clinical trials conducted on larger and more diverse patient cohorts. Moreover, the establishment of a ‘universal’ cutoff defining high expression levels and stratifying patients warrants attention. While the universal cutoff, established at the intersection of sensitivity and specificity, serves as a standard metric, its applicability in clinical practice may not always align with optimal diagnostic outcomes (8). In the pursuit of enhancing diagnostic efficacy, the emphasis leans toward elevating sensitivity, even if this entails a trade-off with specificity, thereby increasing the likelihood of false-positive results. The rationale behind prioritizing sensitivity stems from the profound impact of early cancer detection on treatment efficacy and patient survival rates. Achieving this delicate balance is critical to ensure that diagnostic tests effectively identify HBV- or NV-HCC cases at an early stage while minimizing the risks associated with false-positive results, thereby optimizing patient outcomes in clinical practice. Lastly, the integration and standardization of various platforms for measuring gene expression, along with diverse bioinformatics pipelines, are imperative for advancing the development of clinically relevant gene expression-based assays within the clinical setting.

We acknowledge the necessity of further investigation into the mechanistic pathways by which newly discovered biomarkers impact HCC development. Although SH3PXD2B, an adapter protein implicated in the formation of invadopodia and podosomes, as well as extracellular matrix degradation, has been demonstrated to facilitate intravascular and extravascular invasion and metastasis in human colon cancer, breast cancer, and melanoma cells, its role in regulating HCC remains unexplored (9). Interestingly, suppression of SH3PXD2B impedes both the formation and functionality of invadopodia, as well as the invasive properties of Hep3B cells (9), which harbor an integrated HBV genome. These findings suggest a potential role in facilitating the invasion and metastasis of HCC. Moreover, the expression of SH3PXD2B correlates with a higher rate of HBV infection and shorter overall survival and recurrence-free survival in patients with HCC (9). These
associations underscore its potential as a prognostic biomarker for HCC, rather than solely as a diagnostic biomarker for HBV-HCC, as revealed by our study.

The immune checkpoint molecule CD70, a potent blood-based biomarker for NV-HCC diagnosis revealed by our study, is a ligand of CD27, where the involvement of the CD70-CD27 axis is increasingly being investigated in hematological and solid malignances (10). In HCC, while exact mechanism of CD70 expression in tumor cells remains unknown, recent evidence implicates the epigenetic dysregulation of this gene as evidenced by the hypomethylation of CD70 promoter and dominant CD70 expression in the tumor areas compared with the adjacent nontumor areas of HCC patients (11). Interestingly, depletion of MEF2D, which binds to the promoter region of the CD70 gene and promotes its transcription, in HCC cells injected into immunocompetent mice, along with the use of a CD70 blocking antibody, resulted in diminished immunosuppressive function of Tregs and heightened T cell-mediated anti-tumor immune responses (12). Taken together, these findings indicate that modulation of the CD70-CD27 signaling axis could enhance the effectiveness of immune therapies for HCC.

Given the urgent need to detect early-stage tumors and refine patient stratification for HCC surveillance (13), the utilization of multiomics approaches, which are increasingly employed (14, 15), to identify biomarkers linked to both HBV and non-viral causes of HCC, would not only enhance our comprehension of the disease's pathogenesis but also enable the development of improved personalized diagnostic and therapeutic strategies.

**Authors' contributions**

S.B.L. and H.J.C. drafted and approved the manuscript.

**Acknowledgments**

We acknowledge support provided by the National Research Foundation (NRF) of Korea (2020M3A9D8037604, 2020R1A6A1A03043539, 2022R1A2C1008793, 2022R1C1C1004756, and 2021R1C1C1009619, RS-2024-0039997) and the Korea Health Technology R&D Project of...
the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HR22C1734).

Conflicts of interest

The authors have no conflicts to disclose.
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hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease”.
