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Correspondence

Correspondence to editorial on "Hepatocellular carcinoma prediction model performance decreases with long-term antiviral therapy in chronic hepatitis B patients"

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Dear Editor,

We appreciate Prof. Kim's insightful comments[1] on our recent study of decreasing performance of hepatocellular carcinoma (HCC) prediction models during long-term antiviral therapy (AVT) in patients with chronic hepatitis B (CHB).[2] We concur with the suggestion that incorporating novel biomarkers related to the hepatitis B virus (HBV) viral life cycle, both static and dynamic, as well as using artificial intelligence (AI)-based algorithms, could enhance predictability of HCC in CHB patients with long-term AVT. As highlighted by Prof. Kim, key clinical and viral variables, such as serum HBV-DNA, alanine transaminase, aspartate transaminase, platelet counts, and liver stiffness values, tend to gradually normalize during long-term treatment.[1] However, antiviral therapy could decrease but not eradicate HBV DNA integration.[3] Novel markers reflecting viral integration activities with host genome show promise in augmenting existing predictive models.[4] Additionally, AI-based algorithms, including machine learning and deep learning, are advantageous in depicting the complex pictures between predictor variables and clinical outcomes, surpassing traditional statistical models in effectiveness.[5] Herein, we would like to add three additional points on the future research to further improve HCC prediction during long-term AVT.

Utilization of dynamic changes in serum biomarkers enables the construction of a more comprehensive profile of each patient's progression over time. Tracking of these changes with routinely collected serum samples during regular follow-up did not add additional logistical burden. However, this would require sophisticated statistical techniques. While several analytical methods for longitudinal data, such as joint modeling, landmarking, and functional principal component analysis are available, they are less capable of handling high-dimensional biomarker data-

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sets.[6] Traditional dynamic models mainly use biomarker information from only two timepoints, either as absolute values or percent changes, which fails to capture the dynamic trajectories over multiple timepoints.[7,8] Recent advancements in analyzing longitudinal data have been successfully applied in the field of hepatology. Fan et al.[9], for instance, by using repeatedly measured aMAP scores and alpha-fetoprotein with longitudinal discriminant analysis, developed and externally validated the aMAP-2 model using data from 13,728 patients in mainland China.[9] Their study showed that the aMAP-2 scores significantly outperformed existing HCC risk scores. One caveat is that applying complex computational algorithms needs the development of user-friendly applications or online calculators to enhance the generalizability and interpretability of risk scores in practical settings.

Multi-omics data, including genetic, metabolic and proteomic information, as well as radiological imaging parameters, are providing new insights into disease diagnosis, staging, prediction of disease onset and therapeutic response. Polygenic risk scores (PRS) have increasingly demonstrated their utility in predicting HCC in populations with non-alcohol fatty liver diseases or any chronic liver disease, irrespective of etiology.[10,11] For patients with CHB undergoing long-term AVT, leveraging PRS incorporated with HBV integration information could help to identify high-risk individuals susceptible to carcinogenesis, enabling more effective risk stratifications. Proteomic and metabolic panels have also shown high accuracy in predicting the progression to HCC.[12,13] In the field of radiomics, one study demonstrated that deep learning-based automatic measurements of spleen volume and body composition on computed tomography images could predict the comprehensive prognosis of patients with CHB.[14] Despite these advancements in multi-omics, it's important to note that the high cost of these techniques limits their widespread clinical use. A more rational use of these markers would be to further enrich high-risk individuals after primary screening, thereby directing limited resources to the right population and ensuring affordability, accessibility, and feasibility in surveillance.

In addition to the challenges posed by the need for new techniques and novel markers for accurate HCC prediction, we are now confronted with an aging population of CHB patients who have a growing prevalence of co-morbidities, such as diabetes mellitus, obesity, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease. A recent study demonstrated that the performance of HCC risk scores is lower in diabetic CHB patients compared to non-diabetic patients, with discriminations ranging between 0.67–0.71 versus 0.78–0.82, respectively.[15] Similarly, subgroup analysis in our study showed that the performances of 17 HCC prediction models declined more significantly in patients with pretreatment cirrhosis compared with the total cohort.[2] These findings raise concerns about the effectiveness of risk stratification within CHB patients with co-morbidities, a population that is expected to grow over time.

In conclusion, we agree that incorporating novel and dynamic biomarkers related to the HBV viral life cycle and multi-omics offers new opportunity to develop more accurate HCC risk prediction models, particularly for patients with CHB undergoing long-term treatment. AI technology and advanced longitudinal data analysis method must prioritize transparency, interpretability, practicality, and generalization of results. Special attention should also be given to patients with increasing co-morbidities. Finally, validation with real-world data and cost-effectiveness analyses are crucial for implementing these risk scores in routine clinical practice.

Authors' contributions

Yuanyuan Kong designed the correspondence. Xiaoqian Xu drafted the manuscript. Hong You, Jidong Jia, and Yuanyuan Kong revised the manuscript. All authors approved the final version of the correspondence.

Conflicts of Interest

The authors declare no conflicts of interest for this work.

Abbreviations:

AI, artificial intelligence; AVT, antiviral therapy; CHB, chronic hepatitis B; HBV, hepatitis B virus; PRS, polygenic risk scores

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