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Reply to Correspondence

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

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Dear Editor,

I am grateful to Wu et al. for providing additional new insight to my editorial regarding their research article entitled "Hepatocellular carcinoma prediction model performance decreases with long-term antiviral therapy in chronic hepatitis B patients".[1-3] Wu et al.[2] indicated several key points which will guide how to further improve hepatocellular carcinoma (HCC) prediction during long-term antiviral therapy (AVT) for chronic hepatitis B virus (HBV) infection. Herein, I would like to make some comments.

Firstly, even though using dynamic changes in serum biomarkers allows for the creation of a more thorough profile of each patient's HCC development over time, it is frequently the case that monitoring these changes during routine follow-up may not significantly improve diagnostic performance.[4,5] Based on repeated measurements of aMAP (age–male–albumin-bilirubin score–platelets) and alpha-fetoprotein, Fan et al.[6] demonstrated the promising prediction performance for HCC development, i.e., area under receiver-operating characteristic curves of roughly 0.85. However, we should be cautious, when adopting the findings of their study. As a matter of fact, previous HCC prediction models, such as PAGED-B,[7] have demonstrated comparable efficacy and consistent results in the validation cohort, even with a single assessment. This is most likely because the magnitude of improvement in critical parameters between time-points (often two time-points) during long-term AVT cannot be proportionately translated into the reduction in HCC risk. Furthermore, there is a higher chance of a non-linear pattern with changes in such important parameters. Therefore, constant collaboration and communication between clinicians and engineers should be necessary in order to create a more complex and optimized algorithm. Additionally, it can facilitate a thorough analysis of a variety of patients' other characteristics, such as co-morbidities (such as obesity, dyslipidemia, or metabolic associated fatty liver disease), lifestyle choic-

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es and habits, family medical history, and concurrent medications (such as aspirin, statins, anti-diabetic drugs, and so on), as well as total exposure to oral nucleos(t)ide analogs. An further concern pertains to the potential improvement in predictive ability of the HCC prediction model by incorporating data evaluated at several time points (>2) over the long-term AVT. Therefore, the development of novel analytical approaches designed for long-term longitudinal follow-up should be required simultaneously, given that clinicians eventually become reluctant to utilize HCC prediction models with very complex equations, but with only marginal or equivocal advantage.

Secondly, there must be an intrinsic constraint on the development of very accurate HCC prediction models that outperform earlier models based on the primary factors available in ordinary clinical practice. It is important to acknowledge that, based on their "background" knowledge, physicians recommend imaging or laboratory tests after seeing patients. Therefore, it might be challenging to construct the novel HCC prediction model in the absence of the novel knowledge. Therefore, the key to achieving this goal is to find multi-omics data, which includes genetic, metabolic, and proteomic information in addition to radiological imaging parameters. For instance, using artificial intelligence (AI) technology in conjunction with radiomics to evaluate steatosis, inflammation, and fibrosis may be a viable option,[8-10] as liver biopsy is not routinely available owing to its invasive nature. Concurrently, in line with such an advance, it is advisable to take into account the use of imaging modalities other than ultrasonography for HCC surveillance, such as computed tomography (CT) or magnetic resonance imaging (MRI). Furthermore, it should be necessary to conduct a prospective cohort research with serial sampling in order to determine individual genetic profile. We should keep in mind that HBV-related HCC might occur without fibrosis progression primary owing to the carcinogenic property of HBV itself.

Lastly, from the standpoint of the physicians, the main goals of HCC prediction models should be to identify the sub-groups for which bi-annual HCC surveillance can be waived and those for which more stringent surveillance should be necessary, in order to make HCC prediction models successfully applied in real-world practice. Since the adoption of CT and/or MRI,[11] as previously mentioned, may significantly overcome the suboptimal sensitivity of ultrasonography, which has historically been advised for periodic HCC surveillance, it should also be necessary to develop corresponding algorithms that are readily available in routine clinical practice. Ultimately, future research on the cost-effectiveness of this kind of risk stratification-based, customized HCC surveillance program is warranted.

In conclusion, I agree with Wu et al.'s future perspective regarding the necessity for AI technology and sophisticated longitudinal data analysis techniques, in addition to incorporation of not only novel and dynamic biomarkers linked to the HBV viral life cycle but also multi-omics. Then, the creation of a customized HCC surveillance program built on a dynamic risk assessment may help to lessen the socio-economic burden.

Conflicts of Interest

The author has no conflicts of interest to declare.

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Abbreviations:

AI, artificial intelligence; aMAP, age–male–albumin-bilirubin score–platelets; AVT, antiviral therapy; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging

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