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Editorial

Decreasing performance of HCC prediction models during antiviral therapy for hepatitis B: what else to keep in mind: Editorial on "Hepatocellular carcinoma prediction model performance decreases with long-term antiviral therapy in chronic hepatitis B patients"

Beom Kyung Kim[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine; [2]Institute of Gastroenterology, Yonsei University College of Medicine; [3]Yonsei Liver Center, Severance Hospital, Seoul, Korea

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To date, the majority of hepatocellular carcinoma (HCC) has been caused by chronic hepatitis B virus (HBV) infection globally, with East Asian population being the most affected.[1] Potent oral nucleos(t)ide analogs (NUCs) used in long-term antiviral therapy (AVT) have the potential to significantly inhibit HBV-DNA replication, attenuate hepatic necroinflammation/fibrosis, and ultimately lower the risk of developing HCC.[2] However, in addition to detectable serum HBV-DNA, there are still a number of factors that can influence the development of HCC. For this reason, an accurate risk prediction model is still required for tailored HCC surveillance, which allows for the early diagnosis of HCC.[3]

Most HCC prediction models that included clinical factors within two years of AVT had satisfactory overall predictive results.[4] AVT, which is long-term and often lifelong, is now recognized as a major disease modulator since it can lower blood HBV-DNA levels, normalize serum aminotransferase levels, and, in certain situations, even partially restore liver function by reversing fibrosis. It is yet unknown, though, how the HCC prediction models' long-term predictive performances change as time goes on during prolonged AVT.

For such unmet need, Wu et al.[3] comprehensively validated and reassessed the predictive performance of 17 HCC models in a multicenter cohort including chronic HBV-infected patients receiving long-term AVT. When model scores were calculated using on-treatment values at 2.5, 3, 3.5, 4, 4.5, and 5 years of AVT to predict three-year risk of HCC occurrence, their performance decreased with the prolongation of AVT, with modest to poor AUROCs using on-treatment scores at years 2.5 to 5. Two possible hypotheses might explain this phenomenon. First of all, since

Corresponding author : **Beom Kyung Kim**
Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-1930, Fax: +82-2-393-6884, E-mail: beomkkim@yuhs.ac
https://orcid.org/0000-0002-5363-2496

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long-term AVT gradually improves the values of on-treatment key variables, i.e., serum HBV-DNA, alanine aminotransferase, aspartate transaminase, platelet counts, and liver stiffness values, compared to those at baseline, the prognostic significance of models based upon such key variables might be attenuated during long-term AVT, diminishing discriminatory ability by models. In addition, in contrast to the former variables which tend to improve during prolonged AVT, patient age, an independently strong risk factor for HCC development, simultaneously increases with the prolonged duration of AVT. Thus, without consideration of dynamic changes in other key predictors, the predictive performance of such models must be suboptimal than reported previously.

Unfortunately, there have been a few studies developing the HCC prediction model based upon on-treatment variables during long-term AVT.[5-7] However, they also had clinical unmet needs. First, their predictive performances might be higher than those of conventional ones in their own studies. However, the same results had not been consistently maintained for other cohorts with chronic HBV infection.[8] In addition, the predictive performances of such novel models based upon on-treatment variables during long-term AVT had been still at best around 0.85, which is only "acceptable" range. As a matter of fact, many HCC prediction models using only baseline variables also provided the predictive performance (assessed by c-index or area under the receiver-operating characteristic curve) of 0.80–0.85. Provided that models including on-treatment variables have no additional benefit compared to models including only baseline variables, the latter is more favored in the real-world practice than the former, given the good convenience. Last, the time-point to evaluate on-treatment variables might be somewhat arbitrary, so the delicate prognostication at short- or mid-term time point during prolonged AVT might not be feasible. Therefore, further studies are required to explore pathophysiology-based novel biomarkers beyond the easily available routine laboratory test.

To date, there have been reports of some imaging- and laboratory-based biomarkers thus far.[9] When establishing an HCC risk prediction model with a better prognostic performance even with long-term AVT, novel biomarkers such as quantitative hepatitis B surface antigen, hepatitis B core related antigen, pre-genomic RNA, and pre-S1/S2 mutation might be viable candidates based on the well-elucidated HBV viral life-cycle.[10] On the other hand, as a fibrosis surrogate marker, the imaging biomarker other than liver stiffness might be proposed.[10,11] Furthermore, a variety of artificial intelligence (AI) algorithms may be useful in the investigation of imaging biomarkers from computed tomography (CT) and their integration into HCC risk prediction models. In this article by Wu et al.[3] HCC risk prediction models where "gross liver cirrhosis" as a dichotomized variable is incorporated as a model constituent tended to show the higher predictive performance at least numerically than those not including "gross liver cirrhosis". Such a finding indicates that the gross liver morphology shown on the ultrasound/CT still has a significant prognostic role, even though liver stiffness assessed by transient elastography, as a prognostic indicator in the microscopic milieu, could be improved through prolonged AVT. Accordingly, adding such a novel imaging biomarker will, at the very least, somewhat compensate for the present inadequate prediction performances observed during the long-term AVT. Finally, non-viral factors like co-morbidities (such as obesity, dyslipidemia, or metabolic associated fatty liver disease), lifestyle/habit, and medication other than oral NUCs (such as aspirin, statins, and metformin) might be taken into consideration as disease modifiers in this setting in order to design more delicate HCC risk prediction models with the sustained acceptable prognostic performance during long-term AVT.[12,13]

In conclusion, the prognostic performances of existing HCC prediction models in patients with chronic HBV infection decreased to modest or even poor levels during long-term AVT, even though they had acceptable performances at baseline. Investigating the novel biomarkers reflecting the pathophysiology of the HBV viral life cycle during extended AVT is necessary to close this knowledge gap. Furthermore, the development of HCC risk prediction models may be aided by the variety of new AI-based algorithms

Abbreviations:

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; NUCs, nucleos(t)ide analogs; AVT, antiviral therapy; AI, artificial intelligence; CT, computed tomography

that process dynamic changes of diverse variables during long-term AVT.

Conflicts of Interest

The author has no conflicts of interest to declare.

REFERENCES

1. Kao JH, Hu TH, Jia J, Kurosaki M, Lim YS, Lin HC, et al. East Asia expert opinion on treatment initiation for chronic hepatitis B. Aliment Pharmacol Ther 2020;52:1540-1550.
2. Su TH, Hu TH, Chen CY, Huang YH, Chuang WL, Lin CC, et al. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755-1764.
3. Wu X, Xu X, Zhou J, Sun Y, Ding H, Xie W, et al. Hepatocellular carcinoma prediction model performance decreases with long-term antiviral therapy in chronic hepatitis B patients. Clin Mol Hepatol 2023;29:747-762.
4. Wu S, Zhou J, Wu X, Sun Y, Wang B, Kong Y, et al. Comparative performance of 14 HCC prediction models in CHB: A dynamic validation at serial on-treatment timepoints. Am J Gastroenterol 2022;117:1444-1453.
5. Papatheodoridis GV, Sypsa V, Dalekos GN, Yurdaydin C, Van Boemmel F, Buti M, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. J Hepatol 2020;72:1088-1096.
6. Nam H, Lee SW, Kwon JH, Lee HL, Yoo SH, Kim HY, et al. Prediction of hepatocellular carcinoma by on-therapy response of noninvasive fibrosis markers in chronic hepatitis B. Am J Gastroenterol 2021;116:1657-1666.
7. Ha Y, Lim J, Chon YE, Kim MN, Lee JH, Kim KM, et al. Five-year on-treatment variables-based PPACS model predicts subsequent hepatocellular carcinoma in entecavir/tenofovir-treated patients. Int J Cancer 2023;153:2045-2054.
8. Lee JS, Lee HW, Lim TS, Min IK, Lee HW, Kim SU, et al. External validation of the FSAC model using on-therapy changes in noninvasive fibrosis markers in patients with chronic hepatitis B: A multicenter study. Cancers (Basel) 2022;14:711.
9. Mak LY, Hui RW, Fung J, Seto WK, Yuen MF. The role of different viral biomarkers on the management of chronic hepatitis B. Clin Mol Hepatol 2023;29:263-276.
10. Kim BK, Ahn SH. Prediction model of hepatitis B virus-related hepatocellular carcinoma in patients receiving antiviral therapy. J Formos Med Assoc 2023;122:1238-1246.
11. Yoo J, Cho H, Lee DH, Cho EJ, Joo I, Jeon SK. Prognostic role of computed tomography analysis using deep learning algorithm in patients with chronic hepatitis B viral infection. Clin Mol Hepatol 2023;29:1029-1042.
12. Yun B, Park H, Ahn SH, Oh J, Kim BK, Yoon JH. Liver cancer risk across metabolic dysfunction-associated steatotic liver disease and/or alcohol: A nationwide study. Am J Gastroenterol 2024 Jun 27. doi: 10.14309/ajg.0000000000002920.
13. Yun B, Oh J, Ahn SH, Yoon JH, Kim BK. Association of alcohol consumption with liver cancer and all-cause mortality in chronic hepatitis B patients without cirrhosis. Clin Gastroenterol Hepatol 2023;21:3191-3194.e3.