## Ethical statement

The study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of West China Hospital.

## Data availability statement

The data used to conduct the research are available from the corresponding author upon request.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.05.032

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Yongquan Tang[1,2,*]
Yan Chen[2]
Hai-Ning Chen[3,*]
[1]*Department of Pediatric Surgery, West China Hospital, Sichuan University, Chengdu, China*
[2]*State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China*
[3]*Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China*
[*]Corresponding authors. Address: No. 37 of Guoxue Xiang, Chengdu, 610041, China. Tel.: +86 18980606468 (H.-N. Chen). Tel.:+86 15882004495 (Y. Tang).
*E-mail addresses:* yqtang@scu.edu.cn (Y. Tang), hnchen@scu.edu.cn (H.-N. Chen)


# Reply to: "A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance: Considerations"

*To the Editor:*

We thank Tang and colleagues for their strong interest in our work which develops and validates a risk prediction model for hepatocellular carcinoma (HCC) after hepatitis B surface antigen (HBsAg) seroclearance.[1] Tang *et al.* have raised several considerations about the risk factors we used in our model.[2]

Our study identified age at HBsAg seroclearance (*i.e.*, exposure time to HBV in endemic regions) as an independent risk factor for HCC after seroclearance. Tang *et al.* contend that age itself is a potent factor for most cancers and the age at HCC diagnosis or last follow-up should be included as a potential risk factor in the analysis to confirm the true effect of age on HCC development. However, their claim is for the purpose of verifying its association in all hepatitis B patients and is not specific to HBsAg-cleared patients. We aimed to estimate the risk of HCC based on the clinical parameters at HBsAg seroclearance, particularly focusing on HBsAg-cleared patients. While their argument appears relevant for certain contexts, it is not useful when calculating future HCC risk in HBsAg-cleared patients, since it is only possible after the diagnosis of HCC. Alternatively, when analyzed within the 40 patients developing HCC, the time to HCC from seroclearance was not different among the age groups (4.73, 4.65, and 3.70 years in individuals aged <50, 50–59, and ≥60 years at HBsAg seroclearance, respectively; $p = 0.217$). It is presumed that if age itself rather than age at seroclearance is a risk factor for HCC, the time taken from HBsAg seroclearance to the onset of HCC would be shorter with advancing age. Despite the lack of significance in this simple analysis, the points raised by Tang *et al.* regarding age merit careful evaluation in larger studies.

We agree that the GGT level alone does not necessarily identify alcohol abuse. In our cohort, 12 (22.6%), 7 (13.2%), and 34 (64.2%) of those with a GGT ≥100 U/L (n = 53) were classified as non-drinkers, moderate drinkers, and more-than-moderate drinkers, respectively, as defined elsewhere.[3,4] On multivariable analysis, the GGT level was not an independent predictor of HCC (hazard ratio [HR] 1.002; 95% CI 0.999–1.006; $p = 0.232$). Thus, our findings are generally consistent with the results of Tang *et al.*, indicating that GGT alone is incomplete in


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identifying heavy drinkers. Furthermore, there were only seven drinkers whose GGT levels were ≥100 U/L in our cohort. When those individuals were classified as more-than-moderate drinkers as defined in our study, our model yielded the best performance in predicting HCC, compared to when they were excluded or classified as none-to-moderate drinkers (0.799, 0.794 and 0.790 for 5-year; 0.835, 0.831 and 0.829 for 10-year HCC prediction with the time-dependent AUROC). As mentioned in our article, we used GGT levels only to supplement self-reported drinking estimates; no cases of drinking estimates herein were assessed solely based on GGT levels.

Lastly, in response to Tang and colleagues' inquiry, we evaluated whether the risk of HCC would increase in moderate drinkers *vs.* non-drinkers among HBsAg-cleared patients. In the Cox proportional-hazard model, moderate drinking (n = 156) did not significantly increase the risk of HCC (HR 1.644, 95% CI, 0.719-3.759; $p$ = 0.239), but more-than-moderate drinking (n = 102) remained significant as an independent predictor of HCC after seroclearance (HR 5.050; 95% CI, 2.492–10.356; $p$ <0.001) compared to non-drinking (n = 573). Nevertheless, our findings do support the need for alcohol abstinence in patients with chronic HBV infection regardless of HBsAg status[5,6] in light of the non-negligible risk of HCC in moderate drinkers *vs.* non-drinkers as well as a linear association between alcohol consumption and HCC risk in our cohort.

In summary, we thank Tang and colleagues for giving us the opportunity to clarify these important points. Our prediction model is expected to enable reliable risk estimation of HCC and be a useful reference for decision-making in HCC surveillance and management of HBsAg-cleared patients. Further external validation is needed.

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## Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions
Hyun Yang (Conceptualization: Equal; Data curation: Lead; Formal analysis: Lead; Investigation: Lead; Methodology: Lead; Projection administration: Equal; Resources: Lead; Software: Lead; Writing – original draft: Lead; Writing – review & editing: Lead); Si Hyun Bae (Conceptualization: Supporting; Resources: Supporting; Projection administration: Supporting); Jeong Won Jang (Conceptualization: Lead; Data curation: Lead; Formal analysis: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Projection administration: Lead; Resources: Lead; Software: Equal; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead).

## Data availability statement
The data used to conduct the research are available from the corresponding author upon request.

## Ethical statement
This study was approved by the Institutional Review Board of The Catholic University of Korea (XC21RIDI0026).

## Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.026.

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Hyun Yang[1,2]
Si Hyun Bae[1,2]
Jeong Won Jang[1,2,*]
[1]*Division of Hepatology, Department of Internal Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[2]*The Catholic University Liver Research Center, Seoul, Republic of Korea*
[*]Corresponding author. Address: Division of Hepatology, Department of Internal Medicine, The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea, 222, Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea. Tel.: +82-2-2258-6015, fax. +82-2-3481-4025.
*E-mail address:* garden@catholic.ac.kr (J.W. Jang)