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Authors' contributions

JBW drafted the response and DS and TRM edited. All authors read, critically reviewed and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.08.024.

References

[1] Johansen S, Thiele M, Juel HB, Hansen T, Krag A. External validation of a genetic risk score that predicts development of alcohol-related cirrhosis. J Hepatol 2022;77:1720–1721. https://doi.org/10.1016/j.jhep.2022.06.006.

[2] Whitfield JB, Schwantes-An TH, Darlay R, Aithal GP, Atkinson SR, Bataller R, et al. A genetic risk score and diabetes predict development of alcohol-related cirrhosis in drinkers. J Hepatol 2022;76:275–282.

[3] Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet 2018;50:1219–1224.

[4] Mars N, Koskela JT, Ripatti P, Kiiskinen TTJ, Havulinna AS, Lindbohm JV, et al. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers. Nat Med 2020;26:549–557.

[5] Hao L, Kraft P, Berriz GF, Hynes ED, Koch C, Koratagere VKP, et al. Development of a clinical polygenic risk score assay and reporting workflow. Nat Med 2022;28:1006–1013.

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A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance: Considerations

To the Editor:

We read with great interest the article by Yang *et al.* reporting a risk prediction model for hepatocellular carcinoma (HCC) after hepatitis B surface antigen (HBsAg) seroclearance.[1] Currently, the optimal treatment endpoint of chronic hepatitis B (CHB) is seroclearance of HBsAg, which has been well-documented to significantly decrease the risk of developing HCC in patients with CHB.[2] However, some patients who achieve HBsAg seroclearance still develop HCC.[3,4] In previous studies, several risk factors were identified, including cirrhosis or diabetes mellitus, male sex, and old age at HBsAg seroclearance. However, most of these studies were limited by insufficient population size and/or follow-up period. In this study, a total of 831 patients were enrolled, among whom 40 patients developed HCC during follow-up. Through univariate and multivariate Cox regression analyses, age at HBsAg seroclearance, cirrhosis, family history of HCC, and more-than moderate drinking were identified as independent factors associated with HCC development. Based on these independent risk factors, a prediction model for HCC development after HBsAg seroclearance was established. We appreciate that the authors provided a promising model to predict HCC after HBsAg seroclearance. Despite the strengths of this study, several important issues warrant further discussion.

In this study, the authors identified age at HBsAg seroclearance as an independent risk factor of HCC, which may be interpreted as exposure time to HBV in endemic regions as they stated. However, it should be noted that age itself is a potent factor for the development of most cancers, including HCC.[5] In spite of the different etiological characteristics, the incidence of HCC has been shown to increase with age in epidemiological studies (Fig. 1A-C).[6] Moreover, separate cohort studies have shown that despite HBV infections, most HCC cases develop in patients over 60 years old (Fig. 1D,E).[7] Given the large deviation of patients' age and long-term period of follow-up in this cohort, the onset of HCC is likely to be attributed in large part to advancing age despite the HBsAg seroclearance. Therefore, the age at HCC diagnosis or last follow-up should be categorized (*e.g.*, >60 or not) and included as another potential risk factor in the analysis, which may further justify the effect of age at HBsAg seroclearance (*i.e.*, exposure time to HBV) on HCC development.

In terms of alcohol consumption, in addition to self-reported alcohol use (two and one standard drink of alcohol per day for males and females, respectively), drinkers with serum gamma-glutamyltransferase (GGT) levels over 100 U/L and no evidence of obesity or cholestatic liver disease were also classified as having more-than-moderate alcohol consumption. Accurate estimation of alcohol consumption from questionnaires

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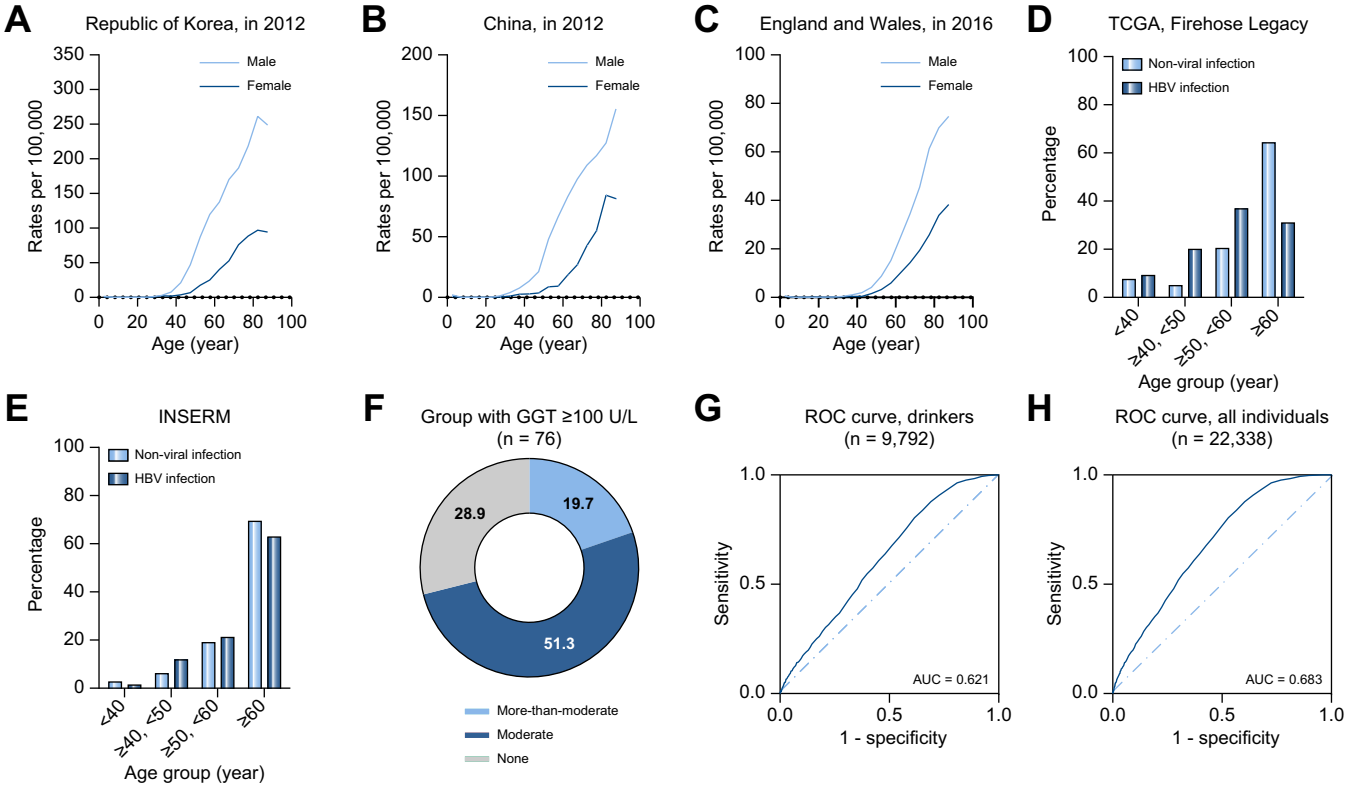

Fig. 1. HCC incidence and alcohol consumption. Age-specific incidence of HCC in Republic of Korea (A), China (B), and areas of the United Kingdom (C), provided by the International Agency for Research on Cancer, World Health Organization. Age-grouped percent of HCC patients, provided by TCGA, Firehose Legacy (D), and INSERM, Nat Genet 2015 (E). Reported alcohol consumption in patients with GGT ≥100 U/L without evidence of obesity or cholestatic liver disease (F). The AUC shows the performance of the GGT levels in identifying the heavy drinkers in only drinkers (G), or in the whole population (H). GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma.

individually is always difficult, especially with the risk of underestimating heavy consumption. However, as a sensitive enzymatic indicator of liver disease, GGT may be upregulated by numerous pathophysiological conditions (*e.g.*, latent infection, liver damage) with no signs of cholestatic liver disease via biological mechanisms such as oxidative stress, immunity, and metabolism,[8] making it questionable to use GGT as a surrogate marker to quantify alcohol intake. Consistently, several studies revealed that serum GGT level was poorly correlated with alcohol consumption, even in individuals without CHB.[9,10] Based on the health management database of our institution, we obtained a total of 22,338 consecutive patients with CHB after HBsAg seroclearance without evidence of obesity or cholestatic liver disease and found that only 19.7% of those with a GGT ≥100 U/L were heavy drinkers, while 28.9% reported no history of alcohol consumption (Fig. 1F). Furthermore, GGT proved ineffective in identifying heavy drinkers in the univariate regression model, neither in drinkers nor in the whole population (AUC 0.621 and 0.683, respectively, Fig. 1G,H). Thus, the GGT level is not necessarily dependent on alcohol consumption in patients with CHB who achieved HBsAg seroclearance and should be included in the regression analysis as an independent factor along with alcohol consumption. In any case, it would be helpful to know how many patients in this study were considered heavy drinkers based on their GGT scores.

Moreover, patients with CHB, particularly those with cirrhosis, were generally advised to abstain from alcohol to reduce disease-related deaths. This study found that patients with non or moderate alcohol consumption are at relatively low risk of developing HCC, which may lead to a potentially contentious conclusion. Therefore, it is necessary to clarify the effect of moderate alcohol consumption on HCC risk in comparison to those with no alcohol consumption. Even with limited event cases, data on this subgroup of moderate drinkers may benefit future research on the management of patients with CHB and alcohol dependence, allowing for a more practical recommendation.

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Conflict of interest

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

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Authors' contributions

Y.T. and Y.C. contributed equally as joint first author to this manuscript. Prof. H.C. provided original data, and contributed to supervision and manuscript revision.

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

References

Author names in bold designate shared co-first authorship.

[1] Yang H, Bae SH, Nam H, Lee HL, Lee SW, Yoo SH, et al. A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Hepatol 2022;77:632–641.

[2] Tout I, Loureiro D, Mansouri A, Soumelis V, Boyer N, Asselah T. Hepatitis B surface antigen seroclearance: immune mechanisms, clinical impact, importance for drug development. J Hepatol 2020;73:409–422.

[3] **Choi J**, **Yoo S**, Lim YS. Comparison of long-term clinical outcomes between spontaneous and therapy-induced HBsAg seroclearance. Hepatology (Baltimore, Md) 2021;73:2155–2166.

[4] Terrault NA, Wahed AS, Feld JJ, Cooper SL, Ghany MG, Lisker-Melman M, et al. Incidence and prediction of HBsAg seroclearance in a prospective multi-ethnic HBeAg-negative chronic hepatitis B cohort. Hepatology (Baltimore, Md) 2022;75:709–723.

[5] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a Cancer J clinicians 2022;72:7–33.

[6] International Agency for Research on Cancer WHO. Age-specific. Cancer over time 2022 [cited 2022 8 May]; Available from: https://gco.iarc.fr/overtime/en/dataviz.

[7] **Schulze K**, **Imbeaud S**, **Letouzé E**, Alexandrov LB, Calderaro J, Rebouissou S, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet 2015;47:505–511.

[8] Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol 2019;70:284–293.

[9] Stewart SH, Connors GJ, Hutson A. Ethnicity and gamma-glutamyltransferase in men and women with alcohol use disorders. Alcohol Alcohol (Oxford, Oxfordshire) 2007;42:24–27.

[10] Walther L, de Bejczy A, Löf E, Hansson T, Andersson A, Guterstam J, et al. Phosphatidylethanol is superior to carbohydrate-deficient transferrin and γ-glutamyltransferase as an alcohol marker and is a reliable estimate of alcohol consumption level. Alcohol Clin Exp Res 2015;39:2200–2208.

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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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