[6] **Huang L**, **Li J**, Lau WY, Yan J, Zhou F, Liu C, et al. Perioperative reactivation of hepatitis B virus replication in patients undergoing partial hepatectomy for hepatocellular carcinoma. J Gastroenterol Hepatol 2012;27:158–164.
[7] **Wu CY**, **Chen YJ**, Ho HJ, Hsu YC, Kuo KN, Wu MS, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906–1914.
[8] Sohn W, Paik YH, Kim JM, Kwon CH, Joh JW, Cho JY, et al. HBV DNA and HBsAg levels as risk predictors of early and late recurrence after curative resection of HBV-related hepatocellular carcinoma. Ann Surg Oncol 2014;21:2429–2435.
[9] Bourlière M, Rabiega P, Ganne-Carrie N, Serfaty L, Marcellin P, Barthe Y, et al. Effect on HBs antigen clearance of addition of pegylated interferon alfa-2a to nucleos(t)ide analogue therapy versus nucleos(t)ide analogue therapy alone in patients with HBe antigen-negative chronic hepatitis B and sustained undetectable plasma hepatitis B virus DNA: a randomised, controlled, open-label trial. Lancet Gastroenterol Hepatol 2017;2:177–188.
[10] Brouwer WP, Xie Q, Sonneveld MJ, Zhang N, Zhang Q, Tabak F, et al. Adding pegylated interferon to entecavir for hepatitis B e antigen-positive chronic hepatitis B: a multicenter randomized trial (ARES study). Hepatology 2015;61:1512–1522.

Si-Yu Liu[1,2]
Chen Yuan[1]
Xiang-Min Tong[1,2,*]
[1]*Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Cancer Center, Affiliated People's Hospital of Hangzhou Medical College, Zhejiang Provincial People's Hospital, Zhejiang, China*
[2]*The Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Zhejiang University Lishui Hospital, Zhejiang, China*
[*]Corresponding author. Address: Key Laboratory of Tumor Molecular Diagnosis and Individualized Medicine of Zhejiang Province, Cancer Center, Affiliated People's Hospital of Hangzhou Medical College, Zhejiang Provincial People's Hospital, Zhejiang, China; or the Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Zhejiang University Lishui Hospital, Zhejiang, China.
E-mail address: tongxiangminzry@outlook.com (X.-M. Tong)

Reply to: Correspondence on "Impact of HBsAg seroclearance on late recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection"

To the Editor:

In reply to the concern from Diao *et al.*,[1] regardless of HBsAg seroclearance, all patients in our study were followed until HCC recurrence, transplantation, death from any cause, or last follow-up date.[2] A patient was censored at the time of HCC recurrence whether or not HBsAg seroclearance occurred subsequently. No patient with HBsAg seroclearance following HCC recurrence was included in the HBsAg seroclearance group in our analysis. Diao *et al.* demonstrated that both HBsAg seroclearance and the risk reduction in late recurrence of HCC were the consequences of antiviral therapy, and these coexisted in patients with antiviral therapy during follow-up. We partly agree with their viewpoint. However, 467 (18.5%) patients in the present study did not receive antiviral therapy and these patients were devoid of any potential antiviral therapy-related effects. Antiviral therapy is reported to reduce the incidence of HCC recurrence. Longer use of antiviral therapy was associated with a reduction of HCC recurrence but was not independently associated with HBsAg seroclearance as indicated in the Discussion (Table S7). This may be due to the fact that HBsAg seroclearance is very uncommon with current antiviral therapy.

Jin *et al.* addressed significant baseline differences between the HBsAg seroclearance and HBsAg-persistent-positive groups.[3] Despite our efforts in adjusting possible confounders, we concur with their assessment that potential bias and residual confounders cannot be completely eliminated from the observational study. However, differences in baseline characteristics between the 2 groups were already incorporated into our time-dependent Cox model, as shown in Table 3. We also agree that preoperative AFP level is highly associated with HCC recurrence. The preoperative median AFP level did not significantly differ between the 2 groups (19.6 and 14.8 in the HBsAg-positive and HBsAg seroclearance groups, respectively; $p = 0.308$). In addition, previous studies reported that tumor-related factors tended to be more strongly associated with early recurrence, whereas characteristics of the underlying liver diseases tended to be more significantly associated with later recurrence.[4,5] The role of transarterial chemoembolization as an adjuvant therapy after curative liver resection remains debatable and is not routinely recommended by the international guidelines for HCC.[6–8] Regarding the lengthy period investigated in our study, HBsAg seroclearance occurs naturally or as a result of therapy relatively infrequently. Moreover, only 172 (6.8%) of 2,520 patients in our study achieved HBsAg seroclearance during the nearly 7 years of follow-up after liver resection. To achieve sufficient statistical power by analyzing the impact of HBsAg seroclearance on the HCC outcomes following surgery, many patients should be enrolled with extended follow-up. Finally, more patients have been included in recent years based on the timing of liver resection. Indeed, undergoing liver resection in 2009–2012 and 2013–2017, relative to 2000–2004, was associated with a reduced risk of HCC recurrence based on our data, possibly owing to advances in surgical technique. However, even after including this variable in multivariable analysis, HBsAg seroclearance remained independently associated

Received 26 July 2022; accepted 29 July 2022; available online 18 August 2022
https://doi.org/10.1016/j.jhep.2022.07.032

with a reduced risk of late HCC recurrence (adjusted hazard ratio: 0.67; p = 0.01).

In response to Liu *et al.*'s letter,[9] examining the influence of 2 time-dependent factors (HBsAg seroclearance and antiviral therapy in our study) on outcomes is relatively challenging in an observational study. Given that not all patients began antiviral treatment simultaneously, the timing of HBsAg seroclearance varied for each patient. Consequently, further sophisticated statistical adjustment may be necessary. As we share the concerns expressed by Liu *et al.* regarding this issue, time-dependent sequential matching propensity score (PS) analysis was first used to exactly match the use and duration of antiviral therapy. Despite this adjustment, our PS analysis revealed that HBsAg seroclearance was associated with decreased risk of HCC recurrence (hazard ratio [HR] 0.65; 95% CI 0.43–0.98; p = 0.04). Furthermore, when antiviral treatment was included as a variable in our multivariable model, the adjusted HR of HBsAg seroclearance on the risk of HCC recurrence was statistically significant (adjusted HR 0.57; 95% CI 0.40–0.81; p = 0.002). Nonetheless, we engaged in extensive discussion with the reviewers and statisticians throughout the review process. Estimating the causal effect of factors (antiviral therapy in our study) other than the intervention (HBsAg seroclearance) using causal inference methods (PS, in particular) and more particularly in a time-dependent setting, remains controversial. Statistically, applying time-dependent sequential PS matching analysis and simultaneous inclusion of 2 time-dependent variables in a multivariable model may be premature in our study.[10] As a result, we excluded these analyses in the revised manuscript, although our results might be somewhat weakened from a causality aspect. However, to assess the late recurrence of HCC based on HBsAg seroclearance (Fig. 3), we used a multistate model using 3 potential transitions and then estimated cumulative HRs using Nelson–Aalen estimates.

In our study, almost all patients (97.2%) had undetectable HBV DNA. No statistical difference was observed in this rate between the 2 groups, and undetectable HBV DNA was not statistically significant even in univariate analysis. Once HBsAg seroclearance is achieved, its recurrence is known to be very rare and experienced only temporarily.[11,12] Based on previous studies, HBV reactivation, viral resistance, and adherence to antiviral therapy may also influence the likelihood of HCC recurrence. However, most of these characteristics are not easily quantifiable and they are extremely hard to combine with potential factors into a multivariable model in an observational study, making this a limitation that should be considered. Nonetheless, we assume that 2,174 (86.3%) of the included patients underwent liver resection after 2007 when entecavir became available. Therefore, antiviral resistance and inadequate viral suppression may not significantly affect the long-term outcomes of our study's population. In contrast to Liu *et al.*'s assertion, the incidence of HBsAg seroclearance in our study is not relatively high, considering the study period (median 7 years). A recent meta-analysis demonstrated that the pooled annual HBsAg seroclearance rate was 1.02% and that cumulative incidence rates were 4.03% and 8.16% at 5 and 10 years, respectively.[13] Lastly, in our database, only 13 (0.5%) patients (11 and 2 from the HBsAg positive and HBsAg seroclearance groups, respectively) received interferon treatment after liver resection, which would likely have had a negligible impact on our main finding.

In conclusion, our study showed that HBsAg seroclearance was independently associated with a reduced risk of HCC recurrence after curative liver resection. This observational study may not provide sufficient evidence of a causal relationship between the 2 outcomes because of its inherent limitations. Further study is required to corroborate these findings.

Financial support

This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Ministry of Science and ICT) (No. 2021R1G1A1009506).

Conflict of interest

No industry funded or supported this study.

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

Authors' contributions

J. Choi had full access to all data used in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis. J. Choi approved the final version of this letter.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.032.

References

Author names in bold designate shared co-first authorship.

[1] Diao YK, Kong QY, Yang T. HBsAg seroclearance and reduction in late recurrence of HBV-related HCC: causality or co-existence? J Hepatol 2022;77:1468–1469.
[2] **Yoo S**, **Kim JY**, Lim YS, Han S, Choi J. Impact of HBsAg seroclearance on late recurrence of hepatitis B virus-related hepatocellular carcinoma after surgical resection. J Hepatol 2022;77:939–946.
[3] Jin B, Du S, Yang H. HBsAg seroclearance reduces the risk of late recurrence in HBV-related HCC. J Hepatol 2022;77:1469–1470.
[4] Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200–207.
[5] Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500–507.
[6] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[7] Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358–380.
[8] Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317–370.
[9] Liu SY, Yuan C, Tong XM. Antiviral therapy, HBsAg seroclearance and late recurrence of hepatitis B-related hepatocellular carcinoma. J Hepatol 2022;77:1471–1472.
[10] Rubin DB. Comment: which ifs have causal answers. J Am Stat Assoc 1986;81:961–962.

[11] Yip TC, Wong GL, Wong VW, Tse YK, Lui GC, Lam KL, et al. Durability of hepatitis B surface antigen seroclearance in untreated and nucleos(t)ide analogue-treated patients. J Hepatol 2017.
[12] **Choi J**, **Yoo S**, Lim YS. Comparison of long-term clinical outcomes between spontaneous and therapy-induced HBsAg seroclearance. Hepatology 2021;73:2155–2166.
[13] Yeo YH, Ho HJ, Yang HI, Tseng TC, Hosaka T, Trinh HN, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019;156:635–646 e639.

Jonggi Choi*
Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Republic of Korea
*Corresponding author. Address: Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea; Tel.: +82-02-3010-1328, fax: +82-02-485-5782.
E-mail address: j.choi@amc.seoul.kr