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Antiviral therapy, HBsAg seroclearance and late recurrence of hepatitis B-related hepatocellular carcinoma

To the Editor:

We read with great enthusiasm the recent article *in the Journal of Hepatology* by Yoo *et al.*[1] To investigate the association between HBsAg seroclearance and late recurrence (2 years) after curative-intention liver resection for patients with HBV-related hepatocellular carcinoma (HCC), a total of 2,520 patients were enrolled into this retrospective cohort study. Among them, 172 (6.8%) patients achieved HBsAg seroclearance on nucleos(t)ide analogues (NUCs) during the follow-up after surgery. Compared with persistent HBsAg positivity, patients with HBsAg seroclearance had a lower risk of HCC recurrence in the 2-, 5-, and 8-year landmark analyses. Using the time-dependent multivariable Cox model, this study demonstrated that HBsAg seroclearance was independently associated with late recurrence after resection for HBV-related HCC. Although innovative and inspiring, several points warrant further clarification.

First, it is clear that the decreased risk of late recurrence and HBsAg seroclearance were related to postoperative antiviral therapy. In numerous previous studies on surgery for HBV-related HCC, the presence or absence of antiviral therapy was an important prognostic variable associated with recurrence and survival after liver resection for HBV-related HCC.[2–4] In Yoo *et al.*'s study, the authors divided all analytic patients into 3 groups: no NUC group, NUC at operation group, and NUC after operation group. However, it is surprising that such an important variable was not included in the univariate and multivariate analysis of late recurrence (Table 3 of Yoo *et al.*'s study). Did the authors intentionally exclude this variable out of concern for collinearity between antiviral therapy and HBsAg seroclearance? Would the inclusion of "antiviral therapy" cause the loss of independent significance for "HBsAg seroclearance"? We are seriously concerned about this possibility.

Second, in previous similar studies, other HBV-related variables potentially associated with postoperative recurrence and survival were often included in the prognostic analysis, such as HBV reactivation, viral resistance, irregular use or withdrawal of antiviral therapy, *etc.*[5–8] Did some patients with HBsAg seroclearance in this cohort return to HBsAg positivity during follow-up? What about the incidence of late recurrence for these cases? It's a pity that these potentially important variables were missing in Yoo *et al.*'s study. Fortunately, the information on HBV DNA levels at 2 years after surgery was available in most patients (85.45%, 2,152/2,520) of the analytic cohort. However, why did the authors not include this critical variable of "HBV DNA level at 2 years after surgery" in the univariate and multivariate analysis, given that it is theoretically more significant than "HBV DNA level at surgery" for predicting late recurrence (>2 years after surgery)?

Third, it should be pointed out that in Table 1 of Yoo *et al.*'s study, the expression of HBV DNA (log_{10}IU/ml) in terms of mean ± standard deviation did not meet the statistical norm (*e.g.* 2.0 ± 2.3 for the overall cohort). If the standard deviation is greater than the mean, this variable does not conform to the normal distribution. It should be changed to median with range or interquartile range.

Fourth, the occurrence of HBsAg seroclearance in Yoo *et al.*'s cohort was relatively high (6.8%, 172/2,520), which seems better than that reported with NUC monotherapy in the literature. It has been reported that the addition of pegylated alfa-2a interferon to NUCs can increase the occurrence of HBsAg seroclearance.[9,10] We wonder if any patients in Yoo *et al.*'s cohort received pegylated alfa-2a interferon?

In conclusion, an amendment regarding the aforementioned omissions would immensely solidify this study's findings.

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Conflict of interest

All authors declared no conflict of interest.

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Authors' contributions

Conception: Xiang-Min Tong; Manuscript preparation: Si-Yu Liu, Chen Yuan; Critical revision: Xiang-Min Tong. Si-Yu Liu and Chen Yuan contribute equally to this work. All authors reviewed the paper and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.07.005.

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Author names in bold designate shared co-first authorship

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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

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