

risk of late recurrence for patients with HBV-related HCC. Although interesting, we have the following concerns about the inherent relationship between HBsAg seroclearance and late recurrence.

First, in this study, Yoo *et al.* did not give the details regarding the sequence of HBsAg seroclearance and late recurrence. During the median follow-up of 6.9 years, among 172 patients with HBsAg seroclearance, 36 (20.9%) patients developed late recurrence. It is very possible that some patients first developed late recurrence of HCC and then achieved HBsAg seroclearance in the real world. If so, it is inappropriate for a cohort study to use variables that occurred after the occurrence of the endpoint event. In our opinion, the ambiguous sequentiality between HBsAg seroclearance and late recurrence suggests that the causal relationship between them is really very weak.

Second, by inhibiting viral replication, antiviral therapy has been widely recognized as being associated with reduced post-operative recurrence, especially late recurrence of HBV-related HCC.^{2,3} Actually, HBsAg seroclearance is also one of the results of antiviral therapy, although the probability of its occurrence is still very low nowadays.^{4,5} That is to say, both HBsAg seroclearance and the reduction in late recurrence are the consequences of antiviral therapy, and these outcomes co-exist in patients treated with regular antiviral therapy during follow-up.

In conclusion, HBsAg seroclearance and no recurrence are optimal outcome events for patients undergoing curative liver resection for HBV-related HCC who receive antiviral therapy during the follow-up period. However, the effect of HBsAg seroclearance on the reduction of recurrence is still worthy of further mechanistic research.

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Conflicts of interest

The authors disclose no conflicts.

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Authors' contributions

Study concepts: Yong-Kang Diao, Qing-Yu Kong, Tian Yang; Manuscript preparation and editing: Yong-Kang Diao, Qing-Yu

Kong; Manuscript review: Tian Yang. All the authors reviewed the paper and approved the final version. Yong-Kang Diao and Qing-Yu Kong contributed equally to this work.

Supplementary data

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Author names in bold designate shared co-first authorship

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HBsAg seroclearance reduces the risk of late recurrence in HBV-related HCC

To the Editor:

We read with great interest the article published in the *Journal of Hepatology* by Yoo *et al.* and colleagues.¹ This study found that HBsAg loss was associated with a 38% lower risk of late recurrence of hepatocellular carcinoma (HCC) after curative liver resection compared with persistent HBsAg positivity.

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We appreciate their efforts to provide new insights into the postoperative recurrence of HBV-related HCC. However, we believe that there are some issues that merit further discussion to ensure that the results of this study are more convincing.

First, there were significant differences in many baseline characteristics between the HBsAg-positive group and HBsAg serocleared group in this study, which may affect the interpretation of results. Although the authors used propensity scores and time-dependent covariate Cox models, which are general statistical analysis methods for reducing bias,^{2,3} potential bias and residual confounders cannot be completely eliminated. The authors used the absolute standardized difference (ASD) to compare the differences in baseline characteristics between the 2 groups, and the difference was generally considered small when ASD <0.10. In the HBsAg seroclearance group in this study, patients had lower aspartate aminotransferase, alanine aminotransferase, and HBV DNA levels, less satellite nodules, and a lower proportion had cirrhosis, as shown in Table 1.¹ Studies have shown that high viral load and hepatic inflammatory activity are associated with an increased risk of late recurrence of HBV-related HCC.^{4,5} Yao *et al.* reported that satellite nodules are also an independent risk factor for postoperative recurrence of HCC.⁶ The authors should use more stringent propensity score matching and other statistical methods to minimize the differences in baseline characteristics between the 2 groups.

Second, the authors did not report some other factors that may affect the recurrence of HCC in the 2 groups of patients, including preoperative alpha-fetoprotein level, surgical margin, intraoperative blood transfusion, and postoperative adjuvant therapy.⁶ Transarterial chemoembolization (TACE) is often recommended as an adjuvant therapy after surgery for patients with early-stage HCC combined with high-risk recurrence factors, such as multiple tumors and microvascular invasion. Studies have shown that TACE can reduce the risk of recurrence in patients with liver cancer after radical surgery.^{7,8} The findings of this study could be further strengthened if the authors could additionally provide details on these factors. In addition, patients were included in this study from 2000 to 2017, which is a very long time. Over time, advances in surgical techniques, including the concept of tumor-free resection and less invasive surgical procedures, may affect the recurrence of liver cancer. Subgroup analyses of different time periods may help to eliminate the potential effect of the long study period.

In conclusion, we agree with the main conclusion of the study and applaud the authors for this important study. This study found that, in patients with early-stage HBV-related HCC undergoing radical liver resection, HBsAg seroclearance was associated with a reduced risk of late recurrence. However, baseline differences must be excluded and more factors affecting recurrence must be reported to obtain more reliable conclusions.

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Conflict of interest

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Authors' contributions

B.J. and H.Y. conceived the manuscript. All authors wrote and reviewed the manuscript.

Supplementary data

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