pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2021.0130
Clinical and Molecular Hepatology 2021;27:448-450

Editorial

Risk of hepatocellular carcinoma in untreated patients with chronic hepatitis B: Independent of HBeAg status?

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Keywords: Hepatitis B, Chronic; Carcinoma, Hepatocellular; Hepatitis B e antigens; Immune tolerance

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There are two aspects of "untreated status" in the natural course of chronic hepatitis B (CHB) such as "immune-tolerant" and "immune-inactive" phases according to the definition from Korean Association for the study of the Liver.[1] It indicates that the "immune-tolerant phase" is defined by positive hepatitis B e antigen (HBeAg), very high serum hepatitis B virus (HBV) DNA levels of $\geq 10^7$ IU/mL, persistently normal alanine aminotransferase (ALT; ≤34 IU/L in males and ≤30 IU/L in females), and no significant fibrosis or inflammation. Meanwhile, the "immune-inactive phase" is defined by negative HBeAg and positive hepatitis B e antibody (HBeAb), low serum HBV DNA levels of <2,000 IU/mL, normal ALT, and no significant fibrosis or inflammation.[1] There have been some efforts to extend the treatment criteria in "untreated" patients with CHB, regardless of the serum ALT levels and HBeAg status, to treat early or to just observe the progression of the two phases. A recent study by Kim et al.[2] suggested the use of antiviral therapy in untreated HBeAg-positive patients with CHB and with high HBV DNA levels (≥20,000 IU/mL) due to a higher risk of hepatocellular carcinoma (HCC) compared to treated immune-active phase patients. Additionally, Sinn et al.[3] suggested the use of antiviral therapy in patients with compensated cirrhotic CHB and low viral load (<2,000 IU/mL) because of higher HCC risk compared to that in individuals with undetectable HBV DNA levels. To answer this question more clearly, accurate assessment of the HCC incidence is very crucial, particularly for cost-effective analysis of antiviral therapy.

A recent study reported that CHB patients with HBV DNA levels of 4.0–8.0 $\log_{10}$ IU/mL (moderate replication phase) had a high risk of HCC development irrespective of HBeAg status.[4] In the aforementioned study, among 4,868 HBeAg-negative patients who had no cirrhosis and had serum ALT levels <2×upper limit of normal at baseline (a mean age of 47 years, a median HBV DNA levels of 3.1 $\log_{10}$ IU/mL), 4.5% of patients developed HCC during 8 years of median follow-up duration. This study concluded that moderate replication phase (HBV DNA levels of 4.0–8.0 $\log_{10}$ IU/mL) was associated with the highest HCC risk, which may require immediate antiviral treatment irrespective of the patient's

Abbreviations:

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma

Editor: Chang Wook Kim, College of Medicine, The Catholic University of Korea, Korea

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Received : May 7, 2021 / **Revised :** Jun. 18, 2021 / **Accepted :** Jun. 23, 2021

HBeAg status and serum ALT levels. In another study that focused on CHB patients who were all HBeAg-negative (a mean age of 47 years, a median HBV DNA levels of 5.4 $\log_{10}$ IU/mL without cirrhosis at baseline), the estimated annual incidence of HCC per 100 patient-years was 0.96 (approximately 4.8% for 5 years).[5] The incidence of HCC was marginally different between untreated patients with mildly active phase and patients treated with antivirals (P=0.04).[5]

In contrast to the results from the two aforementioned studies, Liang et al.'s study[6] from this issue of *Clinical and Molecular Hepatology* reported a low risk of HCC development in a large cohort of untreated CHB patients, of whom 84% were HBeAg-negative, and suggested a prediction model for HCC development. In this study, 15,187 patients who had a median age of 51.9 years, had a median HBV DNA levels of 4.4 $\log_{10}$ IU/mL, and of whom 5.4% had cirrhosis, only 1.2% developed HCC during a mean follow-up of 52 months. Although baseline characteristics in this study,[6] such as old age, higher cirrhosis rates, and similar serum HBV DNA levels, showed a higher risk of HCC development compared with those in previous studies,[4,5] the risk of HCC development was quite lower than that in previous studies. The 5-year risk of HCC development was only 0.19% in the low-risk group and 1.12% in the high-risk group according to the Liang scores.[6] Even in the high-risk group, the HCC risk in this study was still lower than that mentioned in the previous studies.[4,5]

Regarding the much lower incidence of HCC in the study by Liang et al.[6] compared to the two previous studies, it will be helpful for readers to understand how HCC risk can be significantly different within HBeAg-negative status when HBV DNA levels and serum ALT levels (i.e., inactive, replicative, and mildly active phases) in CHB patients HBeAg-negative are taken into consideration. Although HBeAg status was not an independent factor for HCC development in a previous study,[4] HCC incidence in HBeAg-negative CHB patients was still lower than in those who are HBeAg-positive.[4] The study by Liang et al.[6] also reported a low incidence of HCC in a large cohort mainly composed of HBeAg-negative patients. Overall, in the three studies,[4-6] the HCC incidence appears to be relatively lower in CHB patients who are HBeAg-negative than those who are HBeAg-positive.

In the Liang score, fibrosis-4 index was included as one of significant variables to predict HCC, which could more objectively estimate cirrhosis status compared to a variable of "cirrhosis" in previous models of CU-HCC score[7] and GAG-HCC score.[8] Particularly, negative predictive value for development of HCC within 5 years was 99.9% based on the Liang score, which was higher than that of the models such as CU-HCC score, GAG-HCC score, and REACH-B score.[9] Thus, Liang score can be useful to identify very-low-risk patients who would not need HCC surveillance.

In the changing process from an HBeAg-positive to an HBeAg-negative status, the HCC risk can also vary according to the fluctuation of the HBV DNA levels between HBeAg-negative early and late phase. Because of the heterogeneity within the "HBeAg status", such as different HBV DNA levels or fibrotic burden suggested by the Liang scores, prospective observational studies for accurate assessment of clinical outcomes in various conditions of CHB are required to determine "early treatment" or "observation" for CHB patients who do not meet the current treatment criteria.

Authors' contribution

All authors were responsible for the interpretation of data, the drafting, and critical revision of the manuscript for important intellectual content.

Conflicts of Interest

The authors have no conflicts to disclose.

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