Editorial Commentary

The antiviral treatment should be initiated before the development of cirrhosis

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Hepatitis B virus (HBV) infection increases the risk of liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (1). International guidelines recommend antiviral treatment for eligible patients to prevent the development of HCC and the progression of liver disease. However, there is discrepancy in these guidelines regarding treatment recommendations for patients with compensated cirrhosis and low-level viremia (LLV), defined as serum HBV-DNA level of 20–2,000 IU/mL (2-4). And data on the natural history of untreated compensated cirrhotic patients with LLV is limited.

Recently, Huang *et al.* performed a multi-ethnic, multi-center and retrospective study, enrolling 2,316 patients, explored the nature history of untreated compensated cirrhotic patients with LLV compared to spontaneous-maintained virological response (MVR) and antiviral therapy (AVT)-MVR (5). The annual HCC incidence was 2.7/100 person-years (PYs), 2.6/100 PYs, and 3.3/100 PYs for LLV (n=742), Spontaneous-MVR (n=333), and AVT-MVR (n=1,241) groups, respectively. No significant difference was found in the three groups, which indicated that LLV in HBV-infected compensated cirrhosis did not increase the risk of disease progression compared to spontaneous—MVR and AVT-MVR (5). Current guidelines by the American Association for the Study of the Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend AVT for cirrhotic patients with LLV, but the Asia-Pacific Association for the Study of the Liver (APASL) guidelines recommend AVT when HBV-DNA level is >2,000 IU/mL. Present study indicated a similar risk of HCC in cirrhotic patients with LLV compared to patients with spontaneous-MVR and AVT-MVR, which is different from our previous knowledge that LLV increases the risk of developing HCC (6). On the one hand, this may be due to the different study populations included in these studies. The LLV population in present study was the untreated cirrhotic population, whereas previous studies referred to patients with chronic hepatitis B (CHB) on treatment (including cirrhotic and non-cirrhotic patients). On the other hand, previous studies have shown no significant difference in the risk of HCC between non-cirrhotic patients with LLV and MVR, but higher risk of HCC in cirrhotic patients with LLV compared to cirrhotic patients with MVR (7). Moreover, REVEAL study indicated low risk of HCC in CHB patients with viral load between 300 and 9,999 copies/mL (including a small number of cirrhotic patients), and the annual HCC incidence was 0.11/100 PYs, which is lower than the HCC incidence in present study (1). The different prognosis of cirrhotic patients with LLV may suggest the potential virologic and immunologic differences, which need to be further explored.

First, LLV mentioned in present study occurred in CHB patients without treatment is not the same as the identified LLV definition [the definition of LLV in CHB was borrowed from the concept of LLV in human immunodeficiency virus (HIV)], which occurred in CHB patients received AVT more than 48 weeks, and might be associated with stability of covalently closed circular DNA (cccDNA) pool, drug resistance, proliferation of hepatocytes, host's immune function and genetic background (2,8). And LLV occurred after AVT is generally considered to increase the risk of cirrhosis and HCC. However, the LLV occurred in untreated patients suggests effective suppression of viral replication achieved by host's immune system and low risk of disease progression. Therefore, the untreated LLV is a new definition and we need to distinguish between untreated LLV and LLV occurred after AVT. The potential virologic and immune differences between untreated LLV and LLV occurred after AVT needed to be further explored.

Second, in present study, more than 40% of the LLV patients in present study received AVT and were terminated from follow-up, but the specific reasons for AVT were not mentioned. According to antiviral indications and clinical practice, patients receiving AVT are generally at high risk of disease progression. The authors artificially screened out the population at low risk of disease progression for follow-up, which may result in low risk of HCC in cirrhotic patients with LLV. On the other hand, HBV integration in these patients was ignored by authors, which occurred in all the phases of chronic infection and closely related to the occurrence of HCC (9). And viral integration has occurred in these patients prior to the occurrence of cirrhosis and may have partially initiated the oncogene pathway. Moreover, AVT did not directly target the integrated HBV DNA, so it did not reduce the pre-existing HBV integration before AVT (10) Therefore, the risk of HCC maybe comparable in three cirrhotic populations. It is worth noting that since AVT did not decrease the risk of HCC after patients developing cirrhosis, AVT should be initiated as early as possible (before the development of cirrhosis), not after the development of cirrhosis.

Third, the methods evaluating the risk of HCC may not be appropriate in present study, although multivariable Cox-regression analyses, as well as propensity score matching (PSM), stratified and sensitivity analyses were used to demonstrate the similar risk of HCC in patients with LLV, spontaneous MVR and AVT MVR (5). However, the occurrence of HCC is associated with many variables, the authors should use the risk model for screening for populations at high risk of developing HCC and then further compared the risk of developing HCC among the three populations. Moreover, AVT is an important disease modifier, the HCC risk models are different in patients without treatment and received AVT. The risk of occurrence of HCC should be evaluated by HCC risk models CU-HCC (The Chinese University HCC score) and GAG-HCC (The Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis), which are applicable to the patients without treatment, and PAGE-B (platelet age gender-B), which is applicable to the patients received treatment (11-13).

In summary, the current international guidelines are controversial about whether to initiate AVT in cirrhotic patients with LLV (2-4), but the Chinese guideline is more positive about initiating AVT in these patients (14). Because studies have shown that there are racial differences in the risk of HCC, and that Asian populations are at a higher risk of HCC and have a poorer prognosis than Western Europe and the United States populations (15). Therefore, more robust evidence is still needed to explore the prognosis of untreated cirrhotic patients with LLV. Based on the findings in this study that AVT does not decrease the risk of HCC in cirrhotic patients, and the viral integration occurred before the development of cirrhosis, the AVT should be initiated as early as possible (before the development of cirrhosis). Moreover, what we commonly think of as LLV (occurred after treatment) is different from the LLV that occurred during the course of natural history and the potential virologic and immunologic differences between them need to be further explored to better explain the different prognosis in cirrhotic patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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