Dear reviewer:

Thank you for comments on our manuscript entitled “Long-term follow-up outcomes regarding the cumulative incidence of hepatocellular carcinoma among 362 patients with chronic hepatitis B without antiviral therapy” (Manuscript NO: 60420). Those comments we received are very helpful for revising and improving our paper. We have studied the comments carefully and made detailed corrections which we hope meet with approval. The main corrections are in the manuscript and the responds to the reviewers’ comments are as follows (the replies are highlighted in blue).

Replies to the reviewers’ comments:

Reviewer 1:The authors analyzed the effect of antiviral therapy on liver carcinogenesis in chronic liver disease patients related to hepatitis B virus, and concluded that early introduction of antiviral therapy should be cautious, because of lack of its decreasing effect on liver carcinogenesis in chronic hepatitis patients. Although I cannot point out any major problems with the observation results and their interpretation, I would like to request additional description or discussion of the following points: 1. reasons for inclusion and exclusion criteria 2. data on the methods and intervals of imaging tests for screening of liver cancer and whether there are differences between groups. In addition, information on the size of the liver cancer at the time of initial diagnosis. 3. discussion on the appropriate timing for initiation of antiviral drugs based on the results of this analysis.

1：reasons for inclusion and exclusion criteria.

Response：

Basic information including patients’ diagnostic criteria and age were set as inclusion and exclusion criteria. Notably, a large number of data reported that it generally took 6 to 12 months for HCC to be detected by B-ultrasound screening. In order to ensure the reliability and the objectivity of results, we set the inclusion criteria: HCC occurring within 1 years of follow-up will be excluded. Base on this, we restricted the follow-up period to at least 2 years, and patients who developed detectable liver cancer within 1 year after enrollment were excluded. Considering that the time of find of HCC event takes 1-2 years, the follow-up period was determined to at least 2 years. Our result showed no patient in the chronic hepatitis B group but 6 patients in the cirrhosis group developed HCC within 1 years and we subsequently excluded these patients in the following observation.

2. data on the methods and intervals of imaging tests for screening of liver cancer and whether there are differences between groups. In addition, information on the size of the liver cancer at the time of initial diagnosis.

Response：

Response：In addition to disease history, the guidelines call for alpha-fetoprotein level and B-ultrasound as screening tools for HCC. Once a liver mass is found, MRI or CT examination is performed to further confirm. Follow the instructions: if AFP is greater than 400ug/L, only one imaging diagnosis is required, while AFP is less than 400ug/L,

two or more imaging diagnoses are required. Follow-up data will be collected at least once every 6 months. Once HCC was found, the follow-up was terminated. And there were no differences between groups on the methods and intervals of imaging tests for screening of liver cancer. Because our research mainly studied the cumulative incidence of liver cancer, the occurrence of HCC was set as the ultimate goal. The size and stage of liver cancer were not included in our observation range. Tumor size varied from 2-7cm in our observed data.

3. Discussion on the appropriate timing for initiation of antiviral drugs based on the results of this analysis.

Response：Thanks for your valuable and thoughtful comments. The results of this study showed that patients with liver cirrhosis had a higher cumulative incidence of HCC, so it was very important to prevent patients from developing cirrhosis. Then, patients with cirrhosis must receive antiviral therapy. Of course, antiviral therapy can be implemented in the stage of progressive liver fibrosis to prevent the rapid occurrence of cirrhosis, which will be beneficial to the long-term prevention of HCC. According to your suggestion, we have added data that discussion on the appropriate timing for initiation of antiviral drugs based on the results of this analysis.

Once again, thank you very much for your constructive comments and suggestions which would help us in depth to improve the quality of the paper.

Kind regards,

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