1 Peer-review report

- Reviewer #1: Dear author(s) I read your letter on "Viral hepatitis and hepatocellular carcinoma: From molecular pathways to the role of clinical surveillance and antiviral treatment in World J Gastroenterol 2022; 28(21): 2251-2281 [DOI: 10.3748/wjg.v28.i21.2251] As I can not approve the presented risk stratification for PLC in above mentioned paper, because they did not do any quantitative pooled analysis, my mean is meta analysis, this approach could provide a reliable evidence based on pooling ORs in different published studies, they presented a risk stratification only based on a review on 4 studies as they presented in table 1, that are not so reliable. From this view point I am agree with you; however I am not agree also with your suggestions you presented in your letter; because it is based on guideline that it also is not based on pooled quantitative data analysis, nowadays the results of meta analysis is an essential part for preparing a comprehensive guideline. Also, in a part of your letter you mentioned the presented ORs in above published paper are not from a same study, this point is not correct and it is not needed to be from a same study! In many area of clinical subjects there a different guidelines or risk scores all have their own value such a developed guideline for PCL in china and you mentioned it however a strict decision about it superiority to other ones needs comprehensive comparative studies.

A： Thank you very much for your comments and suggestions. I agree with you very much. a single study or a small number of studies cannot comprehensively summarize the risk factors of PLA. Perhaps a meta-analysis is more reasonable. A meta-analysis of chronic hepatitis B hepatocellular carcinoma (HCC) from China included 3,165 cases and 10,896 controls from 27 studies. The results showed that for each factor investigated, the pooled odds ratio (OR) with 95% CI were: non antiviral treatment 2.70 (2.01, 3.62), high HBV DNA level 2.61 (1.73, 3.94), alcohol consumption 2.19 (1.53, 3.13), a family history of HCC 3.58 (2.53, 5.06) and men 2.14 (1.68, 2.73), respectively. Their meta-analysis supports that, from the currently available evidence, Chinese people with high HBV DNA levels, non antiviral treatment, alcohol consumption, family history of HCC and male chronic HBV infection are at

risk of hepatocellular carcinoma. In another meta-analysis of risk factors for nonalcoholic fatty liver disease (NAFLD) and HCC, 18 studies involving 470,404 patients were included. In NAFLD patients before cirrhosis, the incidence of HCC was 0.03/100 person years. In patients with liver cirrhosis, the incidence rate was 3.78/100 person years. However, it still needs to be noted that the risk factors of PLA that can be seen at present are for a specific disease, and there is still a lack of meta-analysis on the risk factors of all PLA.

Risk prediction models have a long history in predicting HCC incidence rate in CHB patients. Currently, approved models are as follows: CU-HCC, GAG-HCC, Page-B, mPAGE-B, REACH-B and mREACH-B. A meta-analysis used six models to perform AUC validation on 22 studies published between 2011 and 2020 The AUC values of the six models ranged from 0.715 to 0.778. In the antiviral treatment subgroup, the AUC values of mREACH-B, GAG-HCC and mPAGE-B were 0.785, 0.760 and 0.778, respectively. In the subgroup of liver cirrhosis, the recognition performance of all models is very poor (AUC < 0.7). The clinical application of these models can improve patients' prognosis and aid them in making informed decisions about treatment. However, these models are developed in different environments, such as untreated patients, patients receiving antiviral therapy, and mixed patients. Therefore, published guidelines rarely provide standard methods for evaluating HCC risk prediction in CHB patients .

We believe that the stratified analysis of risk factors and screening recommendations for PLA in China can be successfully implemented by doctors to aid the early diagnosis and treatment of PLA. Of course, large sample verification and observation are required.

We have revised the original text again according to the above contents.

Reviewer #2: Thanks for recommending me as a reviewer. In this Letter to the Editor, author have read an article with title: "Viral hepatitis and hepatocellular carcinoma: From molecular pathways to the role of clinical surveillance and antiviral treatment". According to the author,

the term "risk factors for the development of PLA" in this article could lead to misunderstandings by readers. First, not all odds ratio (OR) values were obtained from the same study. Second, among the risk factors, there was no family history of PLA. Third, untreated chronic hepatitis D virus infection was classified as a moderate risk factor in the analysis of HCC risk factors, with an OR of 3.9. This letter is well written. If minor revisions are made, the quality of the study will be further improved. 1. Please uniform the line spacing of the first row of Table 1. 2. In Table 1, it would be better to write the footnote as "ALT=alanine aminotransferase".

A：Thank you for your recommendation. We have modified it.