March 22, 2022

Dear editors and reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "A novel index for the prediction of significant liver fibrosis and cirrhosis in chronic hepatitis B patients in China" (Manuscript NO.: 75476, Retrospective Study).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewers' comments are described as follows.

I'm very sorry to trouble you so much.

Thank you very much again for your consideration.

Sincerely,

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Responds to the reviewer's comments:

Reviewer #1: 1. This manuscript try to develop new parameter to predict the liver fibrosis and cirrhosis in chronic hepatitis B patients in China. 2. The overall results were acceptable for this new parameter (AGPR) and may be useful for clinical practicing. 3. The drawback was a very long time of cases collection which will impact the results. 4. There are some mistaken words, e.g. hepatitis Be antigen (HbeAg) --> hepatitis B e-antigen (HBeAg). Please rechecked through your manuscript. 5. The references format were not the corrected one.

Comment 1: The drawback was a very long time of cases collection which will impact the results.

Response: Thanks for your comments. As analyzed in the discussion section, this is a limitation of our study. This is because liver biopsy carries some risks that many patients do not accept it or are not suitable for the test. Therefore, the number of patients undergoing liver biopsy is small, and the time span of case collection is long. The long period of case collection may reduce the accuracy of our study. In our subsequent research, a prospective study is further performed to analyze the accuracy of AGPR index in predicting liver fibrosis and cirrhosis in multi-centre.

Comment 2: There are some mistaken words, e.g. hepatitis Be antigen (HbeAg) --> hepatitis B e-antigen (HBeAg). Please rechecked through your manuscript.

Response: We deeply apologized for our carelessness. We have corrected those errors.

Comment 3: The references format was not the corrected one.

Response: Thanks for your careful work. We have corrected the references format.

Reviewer #2: This manuscript focus on ALP, γ-GT and PLT, which are closely related to the characteristics of liver fibrosis / cirrhosis and the clinical evaluation of decompensation, explore a new index for predicting significant liver fibrosis /cirrhosis in patients with chronic hepatitis B - AGPR, and carry out a meaningful work in the field of noninvasive diagnosis for liver fibrosis/cirrhosis in CHB patients in China. However, there are still some limitations. First, it is a non multicenter retrospective study, which is not representative. Second, the specific data of liver fibrosis stage (F0, F1, F2, F3, F4) based on liver biopsy are incomplete. Third, the impact of treatment interventions on the serum biochemical indexes (ALP, γ-GT, etc.) were not specifically explained. These questions need to be further supplemented or explained by the authors.

Comment 1: First, it is a non multicenter retrospective study, which is not representative.

Response: As the reviewer stated, this is a non-multicenter retrospective study and is not representative. Whether the AGPR index can be generalized to different geographical areas remains to be determined. It needs to test the model in multi-centre study with a large sample size. In our subsequent research, a prospective study is further performed to analyze the discriminatory ability of AGPR in the prediction of liver fibrosis and cirrhosis by expanding the sample size in multi-centre.

Comment 2: Second, the specific data of liver fibrosis stage (F0, F1, F2, F3, F4) based on liver biopsy are incomplete.

Response: The specific data of liver fibrosis stage (F0, F1, F2, F3, F4) based on liver biopsy have been shown in table 1.

Comment 3: Third, the impact of treatment interventions on the serum biochemical indexes (ALP, γ-GT, etc.) were not specifically explained. These questions need to be further supplemented or explained by the authors.

Response: This suggestion is very valuable. As analyzed in the discussion section,

this is a limitation of our study. Indeed, there are many factors involved in liver fibrosis/cirrhosis. Some treatment interventions may affect the serum biochemical indexes and the accuracy of AGPR for predicting fibrosis/cirrhosis. The antiviral treatment, anti-inflammatory and hepatoprotective treatment have a greater impact on serum levels of aminotransferases, such as aspartate transaminase (AST) and alanine aminotransferase (ALT). However, according to clinical observation, ALP and γ-GT are regarded as less specific for liver injury than AST and ALT. The effects of antiviral therapy, anti-inflammatory therapy and hepatoprotective therapy on ALP and γ-GT are not as obvious as on AST and ALT. In fact, elevated serum γ-GT levels are strongly associated with alcohol consumption. However, the researchers have reported that a high relative risk of liver disease mortality with elevated γ-GT was not influenced by alcohol consumption[1]. These explanations have been added to the discussion section of the article as well. According to your suggestion, we will further stratify the AGPR index before and after patients received treatment in our subsequent prospective research. At the same time, we will further explore the influence of changes on predictive performance of AGPR index before and after treatment.

Once again, thank you very much for your comments and suggestions.

References

1. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. *Gastroenterology* 2009;136:477-85.e11.