Title: Baseline metabolites could predict the responders with HBV-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet. (Manuscript NO.: 86248)

Dear Editors and Reviewers:

Thanks for your letter and for reviewer comments concerning our manuscript entitled “Baseline metabolites could predict the responders with HBV-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet”. (Manuscript ID: 86248). 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 your comments are as follows:

#Comment 1 There is a lack of sensitive and specific objective method to determine the necroinflammation and fibrosis stages in CHB patients. Accurate and noninvasive diagnosis and staging of liver fibrosis are essential for effective clinical management of chronic hepatitis B.

Response: As far as we know, the objective methods commonly used to assess the sensitivity and specificity of necroinflammation in CHB include liver tissue histopathologic biopsy and serum markers. These methods aid doctors in evaluating the extent of liver inflammation and disease severity in patients.

Liver Tissue Histopathologic Biopsy: Liver tissue biopsy involves obtaining a liver tissue sample for microscopic examination to assess the degree of liver inflammation, necrosis, and fibrosis. While this method is reliable, it has limitations such as potential discomfort, risks, and the provision of localized information.

Serum Markers: Serum markers are specific molecules measured in the blood that can reflect liver function and inflammation levels. In the evaluation of chronic hepatitis B, the following serum markers are commonly used to assess sensitivity and specificity:

ALT (Alanine Aminotransferase): ALT is a commonly used liver function indicator, and its elevation may suggest liver inflammation and damage.

AST (Aspartate Aminotransferase): AST is another liver function indicator, and elevated levels may be associated with liver inflammation.

Liver Elastography: This non-invasive method measures liver stiffness to assess fibrosis levels, indirectly reflecting inflammation.

Liver Function Tests: Markers such as serum bilirubin, albumin, etc., provide information about liver function and help evaluate the extent of liver damage.

HBV DNA: The level of hepatitis B virus (HBV) DNA can indicate virus activity, indirectly reflecting the state of liver inflammation.

Despite the limitations of histopathological examination of liver tissue, including sampling errors and subjective judgment, it remains the gold standard for assessment. Liver fibrosis and inflammation levels are evaluated using scoring systems such as Ishak, Metavir, or Knodell RG, and the relevant assessment processes are described in the "Scoring System Guidelines" to

mitigate subjective influences. Furthermore, accurate non-invasive diagnostics represent a new trend in liver fibrosis assessment, including methods such as elastography, APRI, and FIB-4. Previous studies have also reported consistency between non-invasive methods and liver histopathological evaluation (PMID: 32572776).

The sentences of "In this study, the primary focus of research was on the progression of liver fibrosis. Liver histopathology was employed as the indicator for therapeutic assessment, with fibrosis severity evaluated according to the Ishak scoring system. Meanwhile, the primary outcome was the proportion of patients with a 1-point improvement of liver fibrosis stage using the Ishak score from baseline to week 48. Liver biopsies were performed before and 48 weeks after initiation of combination TCM and graded independently by 3 pathologists. A decrease in Ishak score of 1 or greater, was considered fibrosis regression [16]. The final fibrotic scores were obtained by consensus from 2 or more pathologists. If there was disagreement, liver biopsy samples were evaluated and decided by central pathologist. However, a detailed distinction of inflammation levels was not conducted. On the noninvasive diagnosis and staging of liver fibrosis, APRI and FIB-4 were predominantly used as adjunct diagnostic tools for assessing liver fibrosis severity." were added on our revised manuscript (p. 4, lines 22-29; p. 5, lines 1-4).

#Comment 2 4-metabolite panel has potential usefulness in clinical assessments of chronic liver disease progression in patients with chronic hepatitis B virus infection. The proposed metabolomic biosignature has the potential to be used as indicator for antiviral treatment for chronic hepatitis B management. There was no single FZHY groups. The selected differential metabolites and metabolism pathways of findings need to be further verified in terms of HBV-related liver fibrosis patients with response to FZHY treatment alone. Above mentioned factors should be referred to.

Response: As all participants included in this study were CHB patients, and the occurrence of liver fibrosis in these patients was directly or indirectly caused by HBV, antiviral therapy was the fundamental treatment. Treating HBV-related liver fibrosis patients solely with FZHY would be inconsistent with clinical ethical standards; therefore, the observation of the therapeutic effect of FZHY as a standalone treatment was lacking. As for the FZHY monotherapy group, in order to further validate the identified differential metabolites and metabolic pathways, it may be considered for future research to select other etiologies of liver fibrosis for validation, or to explore the differences between monotherapy and combination therapy in animal experiments. These sentences mentioned above were added on our revised manuscript (p. 13, lines 23-30; p. 14, line 1).

We appreciate for editors and the reviewers' warm work earnestly. According to your suggestions and comments, we have made revision in the paper. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help. We hope that our manuscript could be considered for publication in your journal. Thank you very much for your help.