

December 30<sup>th</sup>, 2020

Dear Prof. Ghosh and Tarnawski,

Thank you for your decision letter regarding our manuscript entitled “Effect of liver inflammation on accuracy of FibroScan device in assessing liver fibrosis stage in patients with chronic hepatitis B virus infection” (Manuscript Number ID: 60984). We also thank the reviewers for the recognition of the scientific merits of our study and the valuable comments. We have revised the manuscript according to the reviewer’s suggestion. Point-to-point responses to the reviewers’ comments are listed as follows:

**Reviewer #1:**

1. The golden standard for fibrosis stage was set to histological findings of the liver biopsy which was determined by two experienced pathologists. Diagnosis of fibrosis staging such as F0 to F4 and activity such as A0 to A3 is sometimes different by the pathologists. The authors should clearly show the difference of pathological diagnosis between the two pathologists.

**Response:** Thanks for your comment. The histopathological results of all the patients in our study were officially reported after discussion and review by at least two experienced pathologists. Therefore, in case of any disagreement, the final result should be determined and officially reported by a senior and more qualified pathologist.

2. As pointed out by the authors, hepatic steatosis in the liver may affect the diagnostic performance of FibroScan. The degree of steatosis evaluated by histology of liver biopsy should be evaluated in uni- and multivariate analysis in Table 3.

**Response:** Thank you for your careful review. We also considered that hepatic steatosis in the liver may affect the diagnostic performance of FibroScan. Therefore, we excluded patients with fatty liver disease and hepatic steatosis in our study, and investigated in detail the impact of liver inflammation on LSM values and the diagnostic performance of FibroScan in assessing the stage of fibrosis in patients with chronic HBV infection.

3. In the patients with activity score  $<A2$ , some patients showed overstaging and understaging. The authors should discuss on this point.

**Response:** Thanks for your comment. We have discussed this point in paragraph 2 and 3 of the Discussion section (page 13-14) in the manuscript.

Although LSM values measured by ultrasound elastography are related to the stage of fibrosis, they could be affected by some confounders which may reduce the diagnostic performance of FibroScan device in fibrosis staging. Therefore, we found that the rate of misdiagnosis of fibrosis stage using FibroScan was 34.1% (142/416 patients), with 19.5% of patients (81/416) over-staged and 14.7% of patients (61/416) under-staged in our study. Subsequently, we analyzed in detail the effect of liver inflammation on diagnostic accuracy of FibroScan staging. We found patients with inflammation activity  $\geq 2$  had higher rates of FibroScan mis-staging (55.8% vs. 20.2%,  $P < 0.001$ ), overstaging (36.8% vs. 8.3%,  $P < 0.001$ ), and understaging (19.0% vs. 11.9%,  $P = 0.044$ ), compared with patients with inflammation activity  $< 2$ . Therefore, patients with inflammation activity  $< 2$  also had the probability of FibroScan mis-staging, overstaging and understaging, which were relatively smaller compared to patients with inflammation activity  $\geq 2$ .

**Editorial Office's comments:**

1、 The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval

document(s).

**Response:** We will supplement the approval documents provided by the funding agencies with the file names Science and Technology Department of Fujian Province, China, No. 2019Y0015 and No. 2019J01432; and Quanzhou Science and Technology Project of Fujian Province, China, No. 2018Z074, respectively.

2、 The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Response:** We will provide the figures using PowerPoint.

3、 PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

**Response:** We carefully checked the reference list and added all the PMID and DOI in the reference list except reference 21 which was a book citation.

4、 The “Article Highlights” section is missing.

**Response:** We will add the “Article Highlights” section at the end of the main text.

5、 Re-Review: Required

**Response:** Thank you for your reminding, we have carefully checked and revised the language, tables, figures and references of our paper, hoping to better meet the requirements of your publication

We would once again like to thank you and the reviewers for evaluating of our manuscript. We believe that the quality of our manuscript has been significantly improved after revising it according to the comments and suggestions. We hope that the revised manuscript is now acceptable for publication in your prestigious journal *World Journal of Gastroenterology*. We look forward to hearing from you.

Best Regards,

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