Author’s response to reviews

Title: Diminished Accuracy of Biomarkers of Fibrosis in Low Replicative Chronic Hepatitis B

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Response to Reviewers

We thank the reviewers for their valuable comments to improve the quality of the manuscript. We are thrilled to be offered this opportunity to revise and resubmit our manuscript. We offer herein a point-by-point response to the comments raised by both reviewers. We trust that these modifications and response to the reviewers’ comments will make the manuscript acceptable for publication.
Reviewer 1:
This study is quite well designed. I thank to writers. But some sentences are not well understandable.
For example what do you mean?:
"The median number of ALT performed pre liver biopsy were 5 (interquartile range [IQR] 4-8) over a period of 21 months (IQR 8-46)."

Response to reviewer 1: We have taken pains to improve the quality of the English language, and have made changes that we believe improves the quality of the text.
To address the specific point mentioned by this reviewer (under Methods, study design), we have modified the text to better relay the meaning:
“The median number of ALT tests performed pre liver biopsy was 5 (interquartile range [IQR] 4–8), and these were sampled over a median period of 21 months (IQR 8–46).”

Reviewer 2:
Although this manuscript did not show any statistical errors and methodological pitfalls, the unmeasured bias is the most important barrier for the generalization of the results of this study. This kind of study is influenced by the spectrum bias (ex, how much significant fibrosis is included in the entire cohort). Therefore, sufficient number of participants and validation is needed.
Due to the retrospective nature of this study, I can only find statistical trend or association, not suitable for the generalization.

Response to reviewer 2: We thank the reviewer for the comments. We have mentioned in the Results section the prevalence of significant fibrosis in the overall HBV cohort, high-replicative state and the low-replicative state.
“In the overall cohort, F2-4 fibrosis was seen in 113 (30.9%) patients of whom 20 (5.5%) had F4 fibrosis. Of the low-replicative (HBV DNA <20,000 IU/mL) and high-replicative (≥20,000 IU/mL) patients, 40 (18.8%) and 73 (47.7%) had F2-4, respectively…”
In addition, we have clearly mentioned in the discussion section the limitations of potential inclusion bias. However, we would like to point out that the current study represents one of the largest cohorts of HBV patients towards analyzing the role of the commonly used biomarkers of fibrosis such as APRI and FIB-4. In addition, none of the previous studies have looked into the role of these biomarkers in the low-replicative disease specifically. While our high-replicative cohort validates the findings of previous studies, the role of these biomarkers in identifying fibrosis in the low-replicative state offers new insight. In order to address the comment of this reviewer, we have added the following statement in the Discussion section:

“Clearly, these results must be validated in larger, unselected and properly stratified HBV-infected populations before generalizing these results. Despite these limitations, our study with a substantially large number of patients with low viral replication, offers a leading insight into a poorly appreciated disease state.”

Reviewer 2 comment: Liver fibrosis is the dynamic process and arbitrarily dividing patients into low replicative state and high replicative state with DNA level 20000 IU/mL might not correctly reflect the low viremia level.

We accept this concern of the reviewer and do note that fluctuations of HBV DNA level may occur at this threshold level. However, fluctuations are more likely to occur at the lower HBV DNA threshold of 2000 IU/mL than at the 20,000 IU/mL level (Sanai et al. Clin Gastroenterol Hepatol 2013;11:1493-99.e2.) and hence the suitability of the 20,000 IU/mL threshold. We have pointed this out in the Discussion section of the manuscript as a limitation of the study. In addition, we have devoted an entire paragraph discussing the limitations of the study. In order to address this concern, we have added the following part to the Discussion section:

“In order to correct for such aberrations we categorized patients on the basis of the HBV DNA level recordings falling predominantly within the high or low replicative state. Overall, despite guideline-stratified thresholds, it remains a questionable approach to divide patients arbitrarily into low and high replicative states given the nature of HBV DNA fluctuations.”