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COMMENTS TO AUTHORS

The authors provide interesting data on the usefulness of ARFI singly and in combination with other indices for the assessment of fibrosis in chronic hepatitis B infection in this paper.

Some important concerns need addressing:

1. "Combined assessments of ARFI + APRI/ARFI +Forns index: A logistic regression analysis model for hepatic fibrosis ⩾ F2 has been established by using the ENTER method." How were the results of any two tests (e. g. ARFI in m/s and APRI as an absolute value) combined?

Answer: Thanks for the comment! In this manuscript, we set whether hepatic fibrosis ⩾ F2 as variable Y, values of ARFI and APRI as variable X, and then use the ENTER method to establish the analytical logistic regression model for combined ARFI+APRI diagnosis. In addition, predicted probability value is used for following ROC analysis.

2. The results section beginning with "From the result, it showed that the diagnostic performance of ARFI for predicting stages more than F2 was 91% ..." makes for confused reading – with "diagnostic performance", "general effectiveness" "sensitivity and specificity" or "accuracy" for individual stages (e. g. F4), for comparisons between stages (e. g. F1 vs F2), or for cut off of stages (e. g. =/> F2). While table can provide full data, the text to should be simplified to include the most essential information.

Answer: We thoroughly revised that paragraph as suggested.

3. The discussion is silent on the authors' results on ARFI in comparison with the results from the literature and why in light of this, we need to combine ARFI with APRI, if at all. In fact the authors refer to a single paper on ARFI to assess fibrosis in HBV infection, that too a passing mention in the introduction. No ref directly related to study results – no discussion on other studies on ARFI in HBV.

Answer: ARFI is a kind of physical approach which quantifies the hepatic biomechanical properties through measuring the shear wave velocity from ultrasound, to indicate the fibrotic level. However, a number of factors can influence the accuracy of ARFI, including BMI, fat content, subcutaneous soft tissue thickness and liver volume. That is why ARFI has to be combined with APRI. In the revised discussion section, we discussed its inherent limitations and compared our results with other studies on ARFI in HBV with more references.

4. Were the patients consecutively enrolled?

Answer: Yes the patients were consecutively enrolled. We indicated it in the revised version (A total of 246 subjects were consecutively enrolled in this study, including 206 CHB subjects and 40 healthy subjects).

4. What was the time interval between the liver biopsy and the noninvasive assessment of fibrosis?

Answer: All CHB patients were examined by ARFI and serological markers one day before or on the day of liver biopsy.

5. Our pilot study in healthy volunteers ... similar results with smaller standard deviation (1.08 ± 0.21 m/s vs. 1.11 ± 0.12 m/s). A statistical value should be provided for the comparison.
Answer: Sorry for the mistake. The statistical values are t = 0.6794, P > 0.05. We added this information in revised MM section.

5. "Inclusion criteria are ..... 18.5 < BMI < 31." – Needs correcting.
Answer: We corrected this error.

6. Supplementary Table 1 and the related text are redundant.
Answer: We deleted redundant Supplementary Table 1.

7. Table 1 Comparison of fibrosis stage with ARFI etc - p value for the post hoc analysis not shown in text or table).

Answer: We did not put P values for the post hoc analysis in Table 1 because there are more than 50 P values to be presented, which will make the table redundant. However, in the revised manuscript, we added necessary P values to the text as:

Basic information (e.g. age and gender) and assessment results of ARFI, APRI, and Forns index of all subjects were shown in Table 1. The average ages of subjects with significant or serious fibrosis (F2, F3 and F4) were significantly higher than subjects with mild fibrosis (F1) (P = 0.009 for F2 vs. F3， P < 0.001 for F2 vs. F4, and P < 0.001 for F3 vs. F4). Also, male patients showed higher incidence of hepatic fibrosis (from F1 to F4) than female patients. The differences of ARFI results among F0, F1, F2, F3 and F4 groups were significant (P < 0.001). For Forns index, except for F0 and F1 group, the differences among other groups were significant (P < 0.05). Results of APRI indicated that only F4 showed significant change from other groups (F0, F1, F2 and F3) (all P < 0.001), while the F1, F2, and F3 groups showed significantly higher values than the F0 group (all P < 0.001) (Table 1). "

8. Fig 1: Why should there be outliers beyond the range? Range should include all values, right
Answer: In this study, outliers are results with obvious error due to the change of patient position and breathing during measurements. Clinically, those results should be deleted because they are not the real data from the measurements.

9. Table 1: M ± Q should be expanded to full form.
Answer: We provided its full name in revised Table 1 (Mean ± Quartile).

10. My understanding is that a p value of < 0.05 is not acceptable after a Bonferroni test. The authors

should seriously look into this.

Answer: Thanks for the comment! In the revised Table 1, the significant level for gender, ARFI and APRI comparisons has been adjusted to a'= α/n =0.05/10= 0.005. We re-performed the analysis and found that our original conclusion was correct. SPSS software will automatically adjust the significant level (lower or higher than P = 0.05) when performing a multiple comparison. That is why we wrote P < 0.05 after a Bonferroni test.

11. The language needs a lot of polishing.

Answer: We thoroughly improved the language.

COMMENTS TO AUTHORS

This is a good attempt by Dong et al to compare ARF1, APR1 and Forns to determine fibrosis stage in chronic HBV patients. As these are not new techniques for fibrosis evaluation and they wanted to establish that combination of ARF1/ APRI and ARF1/ Forns as better non-invasive technique, they should consider transient elastography (TE) data of same patients.

Answer: Thank you for your professional review! Due to the time limit, we did not include the TE data in the current manuscript, which will be performed in our following studies.

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This paper is well written and addresses a very important point in the assessment of patients with chronic HBV hepatitis. My only comment is that the inclusion criteria specified a liver biopsy sample greater than 20 mm in length but the liver biopsy and staging section states that the samples were 15-20 mm in length. So many of the biopsies would not have been acceptable. This needs to be cleared up.

Answer: Thank you for your comment! The original standard we set was ≥ 20 mm in length. But during the performance of survey, we collected some samples had 15-20 mm in length. Our pathologists considered that those samples could reflect the accurate fibrotic grading. Thus, we modified the criteria as greater than 15 mm. We made a mistake in the original version of this manuscript, which has been corrected.