Response to reviewers

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Column: Retrospective Study

Title: The use of Aspartate Aminotransferase to Platelet Ratio (APRI) to reduce the need for FibroScan in the evaluation of liver fibrosis

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Reviewer 1 comments:

The submitted manuscript by Wong et al. is a retrospective study evaluating the use of APRI in the assessment of liver fibrosis. The Authors propose a APRI cut-off value of 0.5 to select patient for further evaluation with Fibroscan. The study emphasizes the possible use of an economical score in the evaluation of patients. However, some issues need to be addressed before coming to final conclusions.

1.The Authors propose a new cut-off value for APRI score based on a retrospective study. This aspect should be underlined in the discussion of the manuscript.

The proposed new cut-off and the retrospective study design has been highlighted in the abstract and conclusion as recommended by the reviewer.

2.The new cut-off value of 0.5 misses a substantial proportion of patients with significant fibrosis (F2 patients). How the Authors envision the stadiation (staging) of these patients? This is an important aspect and needs to be discussed by the Authors.

We agree with the reviewer that patients with F2 fibrosis may be missed with the proposed new cut-off. A discussion regarding the staging of patients with F2 fibrosis has been addressed.

The implication of fibrosis staging on clinical management of viral liver disease has changed recently. The availability of direct acting anti-virals with its high efficacy, tolerability and safety, has completely changed the treatment of hepatitis C. Current recommendations is for universal treatment of all patients with hepatitis C irrespective of fibrosis stage. The role of fibrosis staging is now mostly for identification of patients who will require long-term surveillance for potential complications of portal hypertension and hepatocellular cancer.

In regards to HBV, the decision to initiate treatment is based on the disease phase (immune tolerant, immune active, immune control or immune escape) and risk of disease progression or liver related complications. This is mostly guided by ALT and HBV DNA level.

3. In Figure 1 the Authors should specify if the evaluations refers to advanced fibrosis (as stated in the text) or cirrhosis (as presented in the figure) - Please provide the unit of each parameter of Table 1.

The figure legend and units have been corrected/ added.

Reviewer 2 comments:

Good work...

Reviewer 3 comments

The manuscript entitled "Using APRI to reduce the need for FibroScan in liver fibrosis evaluation" is a retrospective study evaluated the performance of APRI score against FibroScan in predicting the presence of fibrosis and proposed a new-cut off score of APRI as a screening tool. This study provides a good concept and enhances utilization of APRI score.

Major Comments

1. Methods: There are some differences in the population of chronic hepatitis B and chronic hepatitis C. Some cases with chronic hepatitis C might have HCV-associated immune thrombocytopenia. These might affect the APRI score in the subgroup of CHC. Authors should also discuss this issue.

We agree with the reviewer that there are differences between patients with hepatitis B and hepatitis C that might affect the APRI score. This has now been addressed in the discussion.

2. Methods: The number of cases (cases with biopsy assessment) is quite low. To conclude the new-cut off score of APRI, the authors should demonstrate in the method about the statistical analysis that this number is enough to conclude.

We acknowledge that the number of liver biopsies in this study is quite small. This has now been addressed in the discussion as a limitation of the study. With the wider availability of FibroScan, the volume of liver biopsies performed in our centre and across most centres has fallen dramatically. Non-invasive assessment for fibrosis is now standard of care. Due to ethical and expense reasons, only a small proportion of patients undergo the historic "gold standard" liver biopsy. Given that the primary outcome is not a hypothesis test but rather an assessment of accuracy, power calculation for inference was not applicable. Instead sensitivity and specificity were used as the relevant test performance measures.

The proposed new cut-off APRI score of 0.5 for the exclusion of advanced fibrosis would need to be confirmed with further prospective validation studies. This statement has been added to the conclusion.

3. Results: The new-cut off score of APRI as a screening tool at the level of 0.5 seem to be useful to discriminate the advance fibrosis cases (≥F3). However, this new-cut off level might miss some cases with significant fibrosis (≥F2) which treatment might be indicated. The authors should address on this point.

We agree with the reviewer that patients with F2 fibrosis may be missed with the proposed new cut-off; however a cut-off for the identification of advanced fibrosis (F3-F4) has greater clinical significance in the decision to initiate treatment in patients with viral hepatitis.

With the recent evolution in the treatment of hepatitis C, sustained virological response is achievable in the vast majority of patients. Given this, anti-viral therapy is recommended for all patients except those with limited life expectancy or clear contraindications. The decision for treatment initiation is no longer guided by fibrosis stage except in situations where there are limitations to universal treatment of all patients. In this setting, fibrosis staging may aid in prioritising patients with advanced fibrosis, in addition to guiding the duration of treatment in patients with cirrhosis.

Fibrosis staging, however, remains relevant for prognostication. While the new suggested cut-off may miss patients with F2 fibrosis, it is more critical to separate patients with F3 and F4 patients who require ongoing hepatocellular cancer surveillance and screening/ surveillance for varices. Current guidelines do not recommend routine follow- up of patients with F0-F2 fibrosis following successful treatment of hepatitis C, although this decision would be dependent on clinical judgement especially in patients with confounding risk factors for fibrosis progression (obesity, alcohol etc).

4. Conclusions: "More importantly, the use of APRI score of 0.5 or more as a screening tool for FibroScan can reduce the need for FibroScan in 43%." This sentence might lead to overlook significant fibrosis (≥F2).

This statement has been revised to clarify that the cut-off applies to identification of patients with advanced fibrosis (F3, F4).

Minor Comments 1.

Table 1 and 2: There is lack of unit in each row, eg. kPa, U/L.

The units have now been added to the Tables