Author’s response to reviews

Title: Diagnostic accuracy of controlled attenuation parameter (CAP) as a non-invasive test for steatosis in suspected non alcoholic fatty liver disease: a systematic review and meta-analysis

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Author’s response to reviews:

Reviewer 1:
Question/comments/suggestion 1.1. Page 13. Line 3 from bottom. Probably they would not like to state “is without bias”, but rather "may be imperfect" or something similar.

Response 1.1. The said statement has been changed to “may be imperfect” as per the reviewer’s suggestion.(Discussion, line 55, page13)

Question/comments/suggestion 1.2. For what concerns me, as a clinician, the analysis appears sound. However, the statistical analysis represent the core of this study, once the studies have been selected. I suggest the manuscript to be reviewed by a statistician as well.

Response 1.2. The statistical analysis of the manuscript has been thoroughly assessed by a statistician at the School of Public Health in Lanzhou University. The methodologies adopted, data analysis, data interpretation and presentation were confirmed to be appropriate.

Question/comments/suggestion 1.3. One major concern is how the CAP applies to the everyday patient, who would not have fitted into a study (no indication for biopsy). In fact, the findings of this study could only apply to patients who (even in a study) were considered to usefully undergo
a biopsy, which clearly does not represent the consecutive patients entering ultrasound labs or hepatology offices. Moreover, this study declare to be focused in patients with histology proven NAFLD. The Authors state "In this study, we analyzed the diagnostic accuracy of CAP in distinguishing different stages of hepatic steatosis in liver-biopsy proven NAFLD patients, and assessed the possible contributing factors affecting CAP values” However, a number of patients had no significant liver steatosis (S0). How could a diagnosis of histological NAFLD be achieved in patients in whom histology showed no steatosis? What sort of disease did these patients suffer from?

Response 1.3. In some of the included articles, patients with biopsy-proven NAFLD were included, while other articles used MRI or ultrasonography to screen the suspected NAFLD patients before liver biopsy validation. However, all included articles did not specify how histological assessment was done in patients with normal liver function or mild physical signs. In clinical setting, clinicians often do not advise their patients with mild steatosis and normal liver function to undergo liver biopsy. We speculate that in their study design, NAFLD participants with no indications for the liver biopsy might have been recruited as volunteers. Another important possibility is the possible discrepancy between the imaging studies and liver biopsy, and this is not uncommon in clinical practice.

Reviewer 2:

Question/comments/suggestion 2.1. Authors should specify more clearly in the title, the abstract and the conclusions that the reference standard for steatosis evaluation was histologically assessment by a pathologist of liver biopsy, which is subject to sampling variability, inter individual disagreement and is a qualitative/semi-quantitative approach. Studies are now also available for comparison with MRI-PDFF (it would be good to discuss them)

Response 2.1. The authors are grateful to these comments. The limitations of liver biopsy such as sampling variability, inter individual disagreement and being a qualitative/semi-quantitative approach have been included in the abstract and conclusion. Moreover, it should be noted that in this study we mainly focused on the diagnostic accuracy of CAP rather than to compare CAP to MRI-PDFF. MRI-PDFF has been shown to have a better diagnostic ability and accuracy in hepatic steatosis of NAFLD patients. However, only a few studies compared CAP and MRI-PDFF in detecting steatosis in patients with NAFLD. In a prospective cross-sectional study of NAFLD patients, Park CC et al reported that MRI-PDFF was more accurate than CAP in detecting all grades of steatosis. However, this was a single center study in a highly specialized setting, the reported data need to be validated in large scale prospective and multi-center cohort studies. Overall, there was inadequate evidence to permit comparison between MRI-PDFF and CAP.

Question/comments/suggestion 2.2. Another major limitation that needs to be discussed is related to the lack of availability of individual patient data, which might have allowed to discriminate better the sources of heterogeneity and to propose more robust thresholds for the
diagnosis and staging of steatosis, with adjustment for confounders (as proposed by Karlas et al. in liver diseases overall). Did the Authors contact Authors of the studies to check whether at least part of them was willing to share the data for such an analysis? Even if performed in a subgroup, this would increase the value of the manuscript.

Response 2.2. The authors have contacted the corresponding authors of the selected studies to request the individual patient data. Thus far, we have not yet received their responses.

Question/comments/suggestion 2.3. Authors should specify throughout the manuscript that studies were conducted in patients with "suspected NAFLD", as apparently histological steatosis was not detected in a fraction of evaluated individuals. Otherwise it would have been impossible to evaluate the performance in detecting the presence of NAFLD. In this regard, since this is a very selected population in which apparently other liver diseases were ruled out and pre-test probability of NAFLD was very high, we submit that the diagnostic accuracy of CAP for evaluation of steatosis presence is over-inflated. Authors should specify that this may be much lower in the general population.

Response 2.3. Authors thank this reviewer for this comment and suggestion. We have revised the manuscript to reflect the fact that only patient with "suspected NAFLD" were selected. (Discussion, line 57, page13)

Question/comments/suggestion 2.4. Sensitivity analyses: I would present an analysis by removing the two studies at high risk of bias.

Response 2.4. Based on the sensitivity analysis, two studies (de Ledinghen V and Park CC) likely contributed to the risk bias or heterogeneity as they influenced the DOR value (26.35 and 27.52). (Result, line 103, page11. Discussion, line 33, page13)

Question/comments/suggestion 2.5. Minor: it would be useful to stress the importance of the assessment of hepatic fat content as a possible driver of liver disease progression in patients with NAFLD, see e.g. Dongiovanni, J Inter Med 2018.

Response 2.5. This aspect has been discussed in the revised manuscript.