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:

Editor Comments:

Question/comments/suggestion 1.1. On the title page, please include the email addresses of all co-authors.

Response 1.1. The emails address of all co-authors have been included on the title page.

Question/comments/suggestion 1.2. Please make sure to include a "Conclusions" section. This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

Response 1.2. In the last discussion paragraph of conclusion section, we stated that although CAP could be considered as a promising non-invasive test for diagnosing and staging of hepatic steatosis because of its ease of operation and less sampling errors, and it may provide useful guidance to clinicians on whether liver biopsy would be necessary, when used in patients with ≥S3 steatosis, high rates of missed or wrong diagnosis may occur, moreover, CAP has a limited utility in obese patients, making its widespread application in patients with metabolic syndrome such as NAFLD a practical concern. Therefore, in clinical practice, the role of CAP as a potential non-invasive substitute for liver biopsy in the assessment of steatosis should be further validated.
Question/comments/suggestion 1.3. Under the heading "Funding", please declare the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Response 1.3. This study was supported by National Science and Technology Support Program (NSTSP) (2014BAI09B02 and 2015BAI13B07), National Natural Science Foundation of China (NSFC) (NO. 81570783), and Open Fund of State Key Laboratory of Cancer Biology (CBSKL201718). The funding body had no role in the design of the study; data collection, analysis, and interpretation; or writing the manuscript.

Question/comments/suggestion 1.4. Under the heading "Authors' contributions", please confirm whether all authors read and approved the final manuscript.

Response 1.4. The final manuscript had been confirmed and approved by all authors.

Question/comments/suggestion 1.5. All the tables, figure and supplementary files are missing from the revised manuscript. Please make sure to include them.

Response 1.5. The figure and supplementary files were modified and made sure include them according to editor’s comments.

Question/comments/suggestion 1.6. BMC advocates complete and transparent reporting of biomedical and biological research. As this is a systematic review and meta-analysis, please provide a completed PRISMA checklist, which can be downloaded at: https://protect-au.mimecast.com/s/kC2iCOMxNyt1NBWXHrtLSz?domain=prisma-statement.org.

Response 1.6. We had downloaded and finished the PRISMA checklist according to editor comments.

Reviewer 1 Comments:

Question/comments/suggestion 2.1. Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

Response 2.1. the manuscript, graph and additional materials were corrected according to all comments of reviewers and editors, we will upload the modified version above rather than the reports.
Question/comments/suggestion 2.2. The study is improved however: a revision by an English native speaker is needed. The authors still state everywhere that they studies patients with NAFLD, but in several places in the text is would be more appropriate to state that patients with suspected NAFLD were studies (as some were not found to suffer from fatty infiltration at biopsy).

Response 2.2. The critical revision of the manuscript was finished by professor Liang Qiao, who have deeply research in NAFLD area for many years in Westmead Hospital, Sydney University, and have rich experience at language application. In addition, this study was aim at observing the diagnostic ability of CAP for the patients with suspected NAFLD, we therefore replaced the unclear description "NAFLD" with "suspected NAFLD"

Question/comments/suggestion 2.3. Page 11 first line. I would suggest to replace "reliable" with "accurate".

Response 2.3. The said statement has been changed to "accurate" as per the reviewer’s suggestion.

Question/comments/suggestion 2.4. I would change the title to a more explicit: 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 metanalysis.

Response 2.4. The title has been changed to "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 metanalysis." according to reviewer’s suggestion.

Question/comments/suggestion 2.5. Page 5: lines 6-7 the authors state that the informations were retrieved from the primary articles or acquired directly from the corresponding author. However, in the reply letter they state that no authors of the articles responded to the request to provide individual data. The two statements are difficult to go together. Either the authors got in contact with some other authors or they only collected data from the primary articles. Please clarify.

Response 2.5. Only one unclear parameter of study information presented in Supplementary Table 1 were acquired form the corresponding author, while other parameters labeled with alphabets "NR" did not obtained from emails contacted with corresponding author. Moreover, according to reviewer’s comments of individual participant data meta-analysis, we tried to contacted with every corresponding author of eligible studies to ask for individual data of every participants. But no authors of the articles responded to the request to provide individual data.

REQUESTED REVISIONS:
Question/comments/suggestion 3.1. The authors have long list of operating characteristics they require for study inclusion. Can they comment on the potential number of studies excluded due to limited amount of missing elements? I am concerned that the restrictively long list, while important to the analysis may create a selection bias due to poor reporting more broadly.

Response 3.1. The studies selection steps were based on the PRISMA flow diagram, firstly the irrelevant articles were excluded according to the abstract and title, then, intensively reading relevant articles were performed to further assess whether these articles could include in research from the parts of the complete and reliable data. Moreover, the quality level of articles was not assessed indirectly and simply by paper’s impactor factors, it depended on the systematic quality assessment tools, such as QUADAS-2, a special tool for the diagnostic accuracy studies. To avoid the selection bias, articles needed to evaluate by two co-authors blindly and individually using QUADAS-2. After the comprehensive evaluation for the included articles, finally the eligible studies were entered into the next step to further analyze.

Question/comments/suggestion 3.2. Primary figures appear to be of very poor pixel quality. It would be nice if they could be improved.

Response 3.2. The pixel quality of primary figures had been improved according to the figure formats of guideline.

Question/comments/suggestion 3.3. Can the authors provide further detail on how they pooled overall measures for figures 3-5, S1. This is my key question and what I feel is the major omission in this draft. The meta-analytic methods (and the limitations of them) are not very well developed. Citations are needed and there are no details about why a MH versus DerSimonian Laird test were executed or the sensitivity of the arbitrary cut-offs chosen by the authors.

Response 3.3. Firstly, before combining the overall effect size, the heterogeneity test was needed to detect. If lower heterogeneity of diagnostic odds ratio (DOR) existed (I²<40%) or homogeneity in clinical characteristics was noted, the Mantel-Haenszel method was chosen in case of fixed-effects model. Otherwise, the random-effects model was used with DerSimonian Laird method which assumed that variability between study results is because of not only random sampling error but also true differences between studies (such as population and thresholds). Figure S1 showed that there was higher heterogeneity (73.3%) in steatosis ≥S2 group, Hence, the DerSimonian Laird test was chosen to combine the DOR, Sensitivity, specificity and AUROC, while the other groups were adopted the M-H test to execute the overall effect size. Moreover, the citation of Mantel-Haenszel and DerSimonian Laird test were labeled in manuscript. Citation article “Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Syn. Meth. 2010; 1: 97-111.” added into this paragraph.

Question/comments/suggestion 3.4. Figure S2, S3, and S4, why switch the ordering of the 2 axes?
Response 3.4. The Fagan nomogram was used to estimate how much the result on the diagnostic test of CAP changes the probability that a patient with suspected NAFLD. Through providing the potential estimate of the probability of NAFLD prior to testing, we arrived at the post-test probability according to the likelihood ratio for the diagnostic test. Therefore, we hypothesized the different prior probability of participants including the 25%, 50% and 75% based on the hypothetical prevalence of NAFLD, then, we acquired the corresponding posterior probability to estimate the clinic utility of CAP.

Question/comments/suggestion 3.5. It is unclear what figure S6 is showing. Please describe the content of the figure with greater detail.

Response 3.5. Figure S6 as a sensitivity analysis plot to analyze the impact of one study on the pooled results of diagnostic odds ratio (DOR) on the detection of ≥S2 steatosis, the horizontal axis showed the DOR value and confidence interval (CI), and the vertical axis represented the included studies, while the small hollow circle illustrated the DOR of studies after removing the selected study, and Dotted line revealed the pooled DOR of remaining studies fluctuated across arrange of confidence interval. If one study was a high weight in DOR, when removal of it, the DOR will deviate from the estimate extensively. As shown in Supplementary Fig. 6, the results changed moderately within the estimated values (21.21 95% CI (9.75-46.16)) due to the sample variations in the included articles, but no studies deviate from the pooled DOR severely. Therefore, the weight of study did not dominate the overall results.

Question/comments/suggestion 3.6. For general reading and clarity, please have one figure per page in the supplement.

Response 3.6. The figures have been modified and displayed with one figure per page in supplement.

Question/comments/suggestion 3.7. Table S1 is hard to read.

Response 3.7. Table S1 showed the basic variables for the diagnostic test from the nine papers, the row of table represented the 2×2 table variables including true positive, false positive, false negative, true negative, positive prediction value and negative prediction value in different steatosis stage. While column showed the included studies. Table S2 was a baseline characteristic information of studies.