Reviewer's report

Title: Quick assessment with controlled attenuation parameter for hepatic steatosis in children based on MRI-PDFF as the gold standard

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Reviewer: David Petroff

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Shin et al. present retrospective data comparing hepatic steatosis assessment in children between the Controlled Attenuation Parameter (CAP) and a gold standard, chosen here to be MRI-PDFF. They note the increasing need for non-invasive characterization in paediatric populations and that ultrasound-based CAP is simpler, faster and cheaper than MRI. There is a scarcity of data in children and their article provides a useful contribution.

Background

1. Line 63: I do not believe that citation [1] supports the claim in the first sentence. Perhaps "NAFLD is the most prevalent liver disease in children" would be more appropriate.

2. Lines 70-72: The authors mention that PDFF correlates "well" with histologic grades and cite [4, 5]. In citation [4] regarding adults, Fig. 1 shows strong overlap in PDFF signals between S1, S2 and S3. In the paediatric context, Fig. 2 in [5] looks somewhat better, but overlap is still common. The statement could be toned down.

Methods

3. Line 95: It is not clear to me if all patients with attempted or with successful MRI-PDFF and CAP were included. It would be useful to know if/when one of the techniques was invalid. It would also be helpful to know what patient criteria led to use of both techniques in this retrospective context - there may be a selection bias.

4. Line 101: Please add "...using the age and sex dependent 95th percentile..."  

Statistical Analyses

5. Post-hoc tests were probably used in the analyses associated with Figure 2A (Lines 178-180). The authors could state which they were. On a related note, the ROC curve comparisons (Lines 189-191) should be corrected for multiple testing, e.g. with a Bonferroni-Holm procedure.
6. The authors should add confidence intervals for the sensitivities and specificities at the Youden-optimized point and, ideally, for the value of the optimized point (241 dB/m) itself. This is an important point I return to below in point 10. There are a number of techniques for doing the latter (e.g. Bantis, Nakas, Reiser, 2018, Construction of confidence intervals for the maximum of the Youden index and the corresponding cut-off point of a continuous biomarker, Biometrical Journal) and the authors may wish to contact a statistician.

7. Some blood parameters, most notably ALT and AST, should be treated on a logarithmic scale. Large differences between mean and median values or large SD compared to the mean of a positive variable can indicate the need for this transformation (see also point 8).

Results

8. Lines 162-164 and Table 1: These results may change qualitatively after considering a logarithmic scale. Moreover, age should be included as a covariate when comparing blood parameters between the groups in Table 1. This may also affect the Discussion (lines 267-269).

9. Lines 166-167: The null-hypothesis that the correlation is zero is not meaningful here, hence the p-value is not meaningful and could be removed. A confidence interval would be informative however.

10. Lines 181-189: Here is where the confidence intervals are essential. There are only 10 patients with S0, meaning that estimates cannot be accurate. The "optimal" value of 241 dB/m will be very uncertain as a confidence interval will show. It is essential to understand this point for the discussion.

11. Lines 206-208: A formal statistical test with n=4 vs n=13 is extremely underpowered and should not be performed. Only median values should be provided. This then will change the statement completely. The difference between 326 dB/m (M probe) and 370 dB/m (XL probe) is not so small. It is incorrect to say they "were not different", even if the difference cannot be assessed so easily.

Discussion

12. Lines 239-240: Please tone down the statement "...demonstrated the ability...to...differentiate between histopathologic grades", since this was not very successful in citation [12], which had a small number of patients with steatosis and fairly large overlap (see Figure 1 in that paper).

13. Lines 270-277: The authors could add that histology measures percentage surface area covered by fat cells, MRI-PDFF measures a proportion of fat molecules and CAP
measures physical properties of the liver. These are essentially different (see e.g. your citation [11]). Particularly in children, this could explain the expected correlation between CAP and AWT, but surprising lack of correlation between PDFF and AWT.

14. Lines 284-294: The authors should point out explicitly that n=10 for S0 is a limitation and state that the estimate for the optimal cut-point is uncertain. They should also acknowledge more clearly the uncertainty in the gold-standard (lines 288-289). Again I refer to Fig. 1 in Permutt et al., i.e. reference [4]

Minor language issues

15. The level of English is excellent. Here are a few minor suggestions for improvement

a. Lines 42-43: "...(NAFLD) who were assessed for PDFF and CAP…"

b. Line 49: Delete "For steatosis grades"

c. Line 77: add "s" to "clinics due to…"

d. Line 78: add "n" in "is an ultrasound-based…"

e. Line 81: "TE, shows good correlation…"

f. Lines 88-89: "based on PDFF with subgroup analyses based on body mass index (BMI)."

g. Line 224: "but is probably limited during…high BMI, though longitudinal data are lacking."

h. Line 251: "The portion examined with the XL probe…"

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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