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Heidelberg, May 15th 2023

Dear Prof. Hu,

we would like to thank you for being granted the opportunity to re-submit a revised version of our original manuscript entitled

‘Liver stiffness in pregnant women with intrahepatic cholestasis of pregnancy: a case control study’

We would like to thank your and the very helpful comments from both reviewers in order to further improve our manuscript. A detailed point-by-point response is given below. In summary, we have drastically shortened our manuscript by removing text paragraphs both in introduction and discussion sections that elaborated on the genetic background of cholestasis. We also have taken up all other suggestions by both reviewers.

Sincerely yours and thanks again for your consideration,

Sebastian Mueller

Point-by-point response:

1. **Reviewer #1:** The control group, that was taken from a previous published study, is not matched for gestational age, and this may have led to an overestimation of the value of liver stiffness in ICP. In fact, as reported in the results, “When performing ROC analysis only for women (control vs ICP) in the 3rd trimester, AUROC for LS decreased to 0.65 (0.58-0.72, $P=0.033$) with a cutoff value of 6.5 kPa”. This AUROC value clearly indicates that liver stiffness assessment has little value in this setting.

Response: We would like to thank for this helpful comment. We now only mention the data matched for the third trimester. Although we agree that the diagnostic discrimination remains modest. However, it still remains significant and, therefore, deserves to be addressed.

2. **Reviewer #1:** Introduction The introduction is lengthy and not related to the specific aims of the study. Be aware that this is an original article and not a review. Therefore, it must be shortened considering that this section is the background of the study. The statement that TE has a “10 times lower sampling error compared to the biopsy” is not sound and must be deleted.

Response: Thanks for these helpful comments. The introduction section has been drastically shortened and the genetic part has been removed. We now also state that “TE has a lower sampling error”.

3. **Reviewer #1:** Results The control group must be a matched group, therefore only pregnant women in third trimester must be included.

Response: As already mentioned above, we totally agree. We now only mention the data matched for the third trimester.

4. **Reviewer #1:** Discussion This section is lengthy and unfocused. The lengthy discussion about genetic factors is out of context: this study didn't explore genetic factors. Both the title and the aims of this study indicate that stiffness, by means of TE, is the parameter being explored. Please discuss the results and not unrelated findings. Otherwise, change the title and the aims of the study also using a different methodology for a different purpose.

Response: We thank reviewer #1 for this comment. Like the introduction section, we have also drastically shortened the discussion section and removed lengthy passages on genetics and enzymology.

5. **Reviewer #1:** Table 1 reference must be given for the CAP cutoff of 230 dB/m. To the best of my knowledge, recent studies have reported that the cutoff of CAP for diagnosing NAFLD is around 290 dB/m (Petroff D et al. Assessment of hepatic steatosis by controlled attenuation parameter using the M and XL probes: an individual patient data meta-analysis. *Lancet Gastroenterol Hepatol* 2021; Eddowes PJ et al. Accuracy of fibroscan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. *Gastroenterology* 2019).

Response: We now quote this important CAP metaanalysis and have corrected the cut-off values.

1. **Reviewer #2:** It is a well designed prospective study, well written, including a large cohort of pregnant women, offering very interesting new data regarding the early, non-invasive diagnostic of intrahepatic cholestasis in pregnancy. I only have minor comments: 1.Methods: Liver Stiffness and controlled attenuation parameter (CAP). Which were the criteria upon steatosis severity was graded 2. minor English language polishing is needed

Response: Many thanks for the encouraging comments and suggestions. In line with reviewer 1, we have now corrected the cut-off values for CAP and provide the reference. English has been proof-read by a professional lecturer.

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript.

Response: We have double-checked and re-performed English language editing (both style and grammar) by one of us (SM) who has served for many years and serves as editor for Springer Nature. All changes have been tracked. Please let us know if further actions should be taken.

Company editor-in-chief: To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>. Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...".

Response: We have applied the AI tool ("contains" method) with the key words "liver stiffness ICP", "liver stiffness intrahepatic cholestasis" and "liver stiffness pregnancy". No results were found.

Company editor-in-chief: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response: We now provide the figures with moveable and editable objects in a PowerPoint file.

Company editor-in-chief: Please provide a brief justification of self-citations.

Response: The unusual number of self-citations may be justified and explained by the following facts: The last author (SM) has published seminal original work on liver stiffness and elastography over the course of the last 15 years and he is the editor of the first book on liver elastography published by Springer Nature in 2020 with more than 800 pages. His group has also been the first to study liver elastography in pregnancy. Since reviewer 1 asked for quotation of the paper by Petroff et al in Lancet Gastroenterol., number of self-citations has further increased since SM is also co-author on this paper.