Peer Review File

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Reviewer Comments

Responses to the Reviewers.

Dear Editorial Office,

Thank you very much for the opportunity to revise our manuscript. We thank the reviewers for their important remarks. Please find our Point-by-point answers below.

Kind regards
On behalf of all authors

Maximilian Joseph Brol

Reviewer A

Comment 1: This review paper overall read well.
I cannot say I am familiar with all aspects of this paper, I only comment parts I have some experiences.

Response 1: We thank the reviewer for her/his kind consideration of our work.

Comment 2: I feel the abstract can be more informative. Currently it looks more like an introduction, rather than abstract.

Response 2: Thank you very much for this remark. We redrafted the abstract in order to make it more informative and concrete with respect to the context.

Comment 3: This review says: Thus far, there is no FDA-approved antifibrotic agent, so prevention is the key strategy. It is not clear how to prevent? How can an early diagnosis help the patients? Authors may want to discuss these aspects.

Response 3: We thank the reviewer for this comment. We clarified this statement by including this explanation: “Prevention of liver fibrosis is mostly achieved by an early diagnosis and treatment of the underlying liver disease. When patients are aware of their chronic liver disease, it can either be treated (e.g. metabolic or cholestatic liver disease) or halted by lifestyle changes which mainly applies for alcoholic liver disease.” (ll. 94 – 97)

Comment 4: B-mode abdominal ultrasound can also be useful for advanced stage of liver fibrosis and cirrhosis.

Response 4: Thank you for this important point. We adjusted this statement in the

current version. “B-mode abdominal ultrasound is a widely-available frequently used diagnostic tool, which can be used for detection of advanced liver fibrosis or cirrhosis but it fails in detection of liver fibrosis.” (ll. 246 – 248)

Comment 5: < dual-energy CT derived normalized iodine concentration of the right liver lobe achieved an AUC of 0.86- 0.96 to differentiate F1-F4 fibrosis [67]. // differentiate between F1-F4 stages range from 0.77 to 0.96> These sentences are not easy to understand. differentiate F1-F4 fibrosis from healthy livers? differentiate F1-F4 fibrosis from F2-F4 fibrosis ?

Response 5: We apologize for this misunderstanding. The AUC range indicates the different comparisons of fibrosis stages. In order to clarify we changed these statements to: “dual-energy CT derived normalized iodine concentration of the right liver lobe achieved an AUC of 0.86 to differentiate F0 from F1-3 and 0.96 to differentiate F0-3 from F4 fibrosis.” (ll. 305-307)
And “Reported AUC values of different CNNs to differentiate between F0 and F1-F4 stages range from 0.77 to 0.96, depending on applied imaging modality and technique [70]”. (ll. 311-313).

Comment 6: Recently, some promising results have been published with diffusion MRI technique, authors may like to expand discussion on this topic.
Gender-specific liver aging and magnetic resonance imaging. Quant Imaging Med Surg. 2021 Jul;11(7):2893-2904. doi: 10.21037/qims-21-227. PMID: 34249621; PMCID: PMC8250034.
Diffusion-weighted MRI of the liver: challenges and some solutions for the quantification of apparent diffusion coefficient and intravoxel incoherent motion. Am J Nucl Med Mol Imaging. 2021 Apr 15;11(2):107-142. PMID: 34079640; PMCID: PMC8165724.
Another technique worthy to be mentioned is T1rho: Evaluation of fibrotic liver disease with whole-liver T1ρ MR imaging: a feasibility study at 1.5 T. Radiology. 2014 May;271(2):408-15. doi: 10.1148/radiol.13130342. Epub 2013 Dec 13. PMID: 24475807.

Response 6: We are very grateful for your suggestions. We included the suggested literature in the MRI paragraph. We expanded the paragraphs as follows:

“T1rho elongation was demonstrated to be an effective biomarker for collagen deposition and therefore liver fibrosis in animal models [76]. Significant differences of T1rho values were demonstrated between Child-Pugh cirrhosis stages, with AUCs of 0.95-0.98, indicating the ability of MRI techniques in differentiating different stages of cirrhosis [77]. However, it should be noted that women show a physiologically decrease of liver T1rho value with increasing age [78].” (ll. 329-334)

“As mentioned above, standard cross-sectional imaging techniques have low accuracy

in fibrosis determination. Diffusion weighed MRI can detect liver cirrhosis due to its association with the apparent diffusion coefficient, which is lower in cirrhosis, but fails in differentiating individual stages of fibrosis [86]. This can be improved via novel techniques as MRE and diffusion-weighted MRI. (ll. 356-360)"

Comment 7: Can authors discuss the relative strengths of sNIT vs iNIT?

Response 7: We thank the reviewer for this important point. Indeed, strengths of sNITs are the easy accessability, cheap acquisition for publicly available sNITs, no risk or adverse effects compared to liver biopsy and possibility of repetitive determination. These features are discussed throughout the manuscript. Here, we enlarged the introduction section: "Serum biomarker-based non-invasive liver fibrosis tests (sNITs) are calculated based on serum biomarker levels which are correlating with the degree of fibrosis. Due to its easy and low risk access, many studies investigated the ability in fibrosis assessment. Since many sNITs are based on standard laboratory values, they can be assessed repetitively in fibrosis assessment, if necessary. Therefore, sNITs are well accepted and widely used in the especially those with high accuracy." (ll.186-189).

Comment 8: And how they can complement each other? -considering both sNIT and iNIT have AUROC of around 0.8 for early stage liver fibrosis.

Response 9: Thank you for this important remark. sNITs and iNITs can be used alongside each other in order to increase the diagnostic accuracy for early stage liver fibrosis. As suggested by you, AUROC values can be increased when combining both test (e.g. https://doi.org/10.7863/ultra.16.01069). This has now been included in the discussion.

Reviewer B

Comment 1: This is a well-written and objective narrative review addressing both the more recent and classic literature on liver fibrosis and its assessment. It can be useful for clinicians, hepatologists and other specialists in related fields dealing with the subject. I congratulate the authors for the work and have no suggestions to add.

Response 1: We are very grateful for your kind acknowledgement.