

We thank all reviewers for taking the time for a thorough review and for showing interest in our work. We acknowledge the points raised and have tried our best to address them in the reviewed manuscript. Below are specific responses to the points raised with the reviewer comments in black and responses in blue.

Reviewer #1:

Non-invasive assessment of NASH is increasing in desirability due to the invasive nature and costs associated with the liver biopsy. (mpMRI) to measure liver fat as well as elastography techniques VCTE-LSM), MRE and SWE to measure stiffness and fat are emerging alternatives which could be used as a safe surrogate to liver biopsy. In this study, the author evaluate the agreement of non-invasive imaging modalities with liver biopsy, and their subsequent diagnostic accuracy for identifying NASH patients. The result shows that quantitative mpMRI is an effective alternative to liver biopsy for diagnosing NASH and NAFL, and thus may offer clinical utility in patient management. . The manuscript well, concisely and coherently organized and presented, the style, language and grammar accurate and appropriate.

Reviewer #2:

Imajo et al. evaluated the agreement of non-invasive imaging modalities with liver biopsy, and their subsequent diagnostic accuracy for identifying NASH patients. The study is interesting and well written. My comments are listed below.

1. It would be better to verify the results in different cohorts.

Thanks for your important point relating to validation in an independent cohort. Whilst this was not possible in this analysis, these results have been reported elsewhere in the literature and addressed with the citations in the introduction

2. Does BMI or other metabolic parameters impact the diagnostic accuracy?

Thanks for the remarks on BMI and other metabolic parameters, is it important to be aware of all confounding factors in such measures. BMI and metabolic risk factors are inherently linked to fatty liver disease, which means they are considered a contributor to the signal rather than confounders. However the effect of BMI on measurement error is an important point. There is a clear effect of BMI on LSM-VCTE ^[1-4]. There are limited data on the effect of BMI on rate of failure and unreliable results with the other ultrasound techniques, but the studies that have conducted such analysis for LSM-ARFI and LSM-2DSWE have shown that BMI has an independent effect ^[5,6]. In contrast BMI has not been shown to affect the accuracy of MRE ^[7] or of mpMRI ^[8,9], except for the very unusual conditions when a participant is simply too large to fit into the scanner. This has been addressed in the discussion on page 13.

3. The total number of participants enrolled for analysis is 145, but the number of individuals with histology scores in Table 3 is 144.

Apologies for this inconsistency, this was a result one of the slides being unquantifiable for fibrosis and as such that patient was excluded for this analysis. This has been clarified in the legend of table 3

Reviewer #3:

Dr Imajo and colleagues evaluated the accuracy of mpMRI on NASH and NAFL diagnosis in the prospective cohort and proved a fairly good performance for the non-invasive diagnosis. However, I have some concerns about this paper.

1. First, as current mainstay of non-invasive method, limited number of cases were actually analyzed while not all included patients received VCTE and 2D SWE and nearly 50% missing data for 2D SWE and 20% missing data for VCTE, which may greatly weaken the statistical power and conclusion reliability.

Since no hypothesis testing was conducted in this analysis, we are not limited with statistical power. In terms of the conclusion, AUCs are obviously driven by the correct proportion of patients identified and thus if the missing data resulted in a bias this does limit the interpretation. This however is a finding in itself, in that is a measure if frequently missing because it could not be collected this questions its usefulness more generally.

2. Second, there's no clear definition for NASH and NAFL stated in the manuscript, although the study population were classified by the two disease categories in Table 1. The two major studied diseases need to be further stressed in the paper.

We apologise if this was not clear in the manuscript. NAFL and NASH define diseases states along a continuum of the disease spectrum and are not entirely different diseases. This has been addressed in the introduction on page 5.

3. Third, as MRI is a useful meaning to diagnose NAFLD, what's its value in disease progression? When the patients progressed to fibrosis or cirrhosis, is the MRI test still useful? You may consider to include your data in the discussion. –

We thank the reviewer for this important remark regarding disease progression. The utility of the biomarkers is in the ability to track when a patient has transitioned from simple fatty liver disease to steatohepatitis and steatohepatitis with fibrosis. The biomarkers are able to detect this transition which is where their value lies. In terms of advanced fibrosis, our research and others ^[10,11] have reported negative association between PDFF and advanced fibrosis, a pattern that is not observed with elastography or corrected T1, this has been addressed on page 14 in the discussion. For NASH this serves to make the combination of information from the biomarkers even more useful as the divergence will be a strong indicator of advanced fibrosis.

EDITORIAL OFFICE'S COMMENTS

Registration Statement.

- The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement and fill out the CONSORT checklist with page numbers.

Apologies for the oversight. Please find all three forms completed and uploaded to the file destination

- Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

A power-point version of figures has uploaded to the file destination

- Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

References have been amended throughout

- Please write the “article highlights” section at the end of the main text

Apologies for the oversight. This section has been added after the conclusion in the main text (page 16)

- The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

References have been amended throughout

References cited in reviewer’s response

1. Attia D, Bantel H, Lenzen H, Manns M, Gebel M, Potthoff A. Liver stiffness measurement using acoustic radiation force impulse elastography in overweight and obese patients. *Aliment Pharmacol Ther.* 2016;44(4):366–79.
2. Ooi G, Earnest A, Kemp W, Burton P, Laurie C, Majeed A. Evaluating feasibility and accuracy of non-invasive tests for nonalcoholic fatty liver disease in severe and morbid obesity. *Int J Obesity.* 2018;42(11):1900–11.
3. Oeda S, Takahashi H, Imajo K, Seko Y, Ogawa Y, Moriguchi M. Accuracy of liver stiffness measurement and controlled attenuation parameter using FibroScan \textregistered M/XL probes to diagnose liver fibrosis and steatosis in patients with nonalcoholic fatty liver disease: a multicenter prospective study. *J Gastroenterol.* 2020;5540(4):428–40.
4. Vuppalanchi R, Siddiqui M, van Natta M, Hallinan E, Brandman D, Kowdley K. Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. *Hepatology*. 2018;67(1):134–44.
5. Cassinotto C, Boursier J, de Lédinghen V, Lebigot J, Lapuyade B, Cales P, Hiriart J.B, Michalak S, Bail B.L, Cartier V, Mouries A, Oberti F, Fouchard-Hubert I, Vergniol J AC. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy.
6. Trout AT, Sheridan RM, Serai SD, Xanthakos SA, Su W, Zhang B, et al. Diagnostic performance of MR elastography for liver fibrosis in children and young adults with a spectrum of liver diseases. *Radiology.* 2018 Feb;287(3):824–32.
7. Singh S, Venkatesh SK, Wang Z, Miller FH, Motosugi U, Low RN, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. *Clin Gastroenterol Hepatol [Internet].* 2015;13(3):440--451.e6. Available from: <https://pubmed.ncbi.nlm.nih.gov/25305349/>
8. Mojtahed A, Kelly CJ, Herlihy AH, Kin S, Wilman HR, McKay A, et al. Reference range of liver corrected T1 values in a population at low risk for fatty liver disease — a UK Biobank sub-study , with an appendix of interesting cases. *Abdom Radiol [Internet].* 2019;44(1):72–84. Available from: <https://doi.org/10.1007/s00261-018-1701-2>

9. Wilman HR, Kelly M, Garratt S, Matthews PM, Milanese M, Herlihy A, et al. Characterisation of liver fat in the UK Biobank cohort. *PLoS One*. 2017;
10. Permutt Z, Le T, Peterson M, Seki E, Brenner D, Sirlin C, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease – MRI accurately quantifies hepatic steatosis in NAFLD. *Aliment Pharmacol Ther*. 2012;36(1):22–9.
11. Wildman-Tobriner B, Middleton MM, Moylan CA, Rossi S, Flores O, Chang ZA, et al. Association Between Magnetic Resonance Imaging–Proton Density Fat Fraction and Liver Histology Features in Patients With Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis. *Gastroenterology* [Internet]. 2018;155(5):1428-1435.e2. Available from: <http://dx.doi.org/10.1053/j.gastro.2018.07.018>