

Peer Review File

Article information: <https://dx.doi.org/10.21037/hbsn-23-393>

Reviewer A:

This is a prospective cohort study of 602 patients with MASLD. MRI-PDFF and LSM by 2D-SWE were evaluated at weeks 0, 24, and 48. The analysis was comprehensive and carefully performed. Here are my comments.

Major

Comment 1: Please update the sentences: “This was a prospective study derived from a well-characterized cohort with MRI-PDFF-proven MASLD in the XXX University” and “The study protocol was approved by the Institutional Review Board of XXX”.

Reply 1: Thank you very much for your positive feedback and interest in our study. The sentences have been rewritten as follows: “This was a prospective cohort study of MASLD patients diagnosed with MRI-PDFF at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). For this study, the baseline survey was conducted from January 2015 to February 2022 and followed up until April 2023.” (see Page 8, lines 138-141), and “This prospective study was approved by the Ethics Committee of the First Affiliated Hospital, Sun Yat-sen university {[2014]112}.” (see Page 8, lines 144-145).

Changes in the text: Page 8, lines 138-141; and Page 8, lines 144-145.

Comment 2: It would be good to present a table comparing the baseline characteristics of patients who stayed in the cohort and patients who were lost to follow-up.

Reply 2: Thank you for your suggestion. We have added a table comparing the baseline characteristics of patients who stayed in the cohort and patients who were lost to follow-up (see Supplementary Table 3).

Changes in the text: Page 16, lines 346-348; and Supplementary Table 3.

Comment 3: Besides subgroup analysis, the amount of weight loss at 24 weeks should be a factor in the multivariable logistic regression for steatosis response and fibrosis response. In fact, weight loss should be the most important factor affecting the steatosis response.

Reply 3: Thanks for the enlightening suggestion. As you suggested, we included the amount of weight loss at 24 weeks as a potential confounder in the multivariable logistic regression for steatosis response and fibrosis response (see Table 2). Notably, the relative decline in BMI was excluded from Table 2 because the relative changes in weight and BMI are identical. We have also updated the results of the logistic regression analyses (see Page 3, line 70, Page 17, lines 389-393, Page 19, lines 442-444, and Page 21, line 502). Furthermore, we added weight values to all tables (Table 1-2, and Supplementary Table 1-8).

Changes in the text: Page 3, line 70; Page 17, lines 389-393; Page 19, lines 442-444; Page 21, line 502; Table 1-2; and Supplementary Table 1-8.

Comment 4: In the discussion, the authors mentioned that “our findings suggested that residual insulin resistance might induce subsequent steatosis progression”. To verify this statement, the

information on baseline insulin resistance and insulin resistance at week 24 should both be included in the multivariable logistic regression model to study the effect of residual/sustained insulin resistance.

Reply 4: Thank you for your kind reminding. We have included both baseline insulin resistance and 24-week insulin resistance in multivariable logistic regression model (see Table 2). And we have updated the results of the logistic regression analyses (see Page 3, line 70, Page 17, lines 389-393, Page 19, lines 442-444, and Page 21, line 502). It's important to note that the statistical significance of insulin resistance remained unchanged.

Changes in the text: Page 3, line 70; Page 17, lines 389-393; Page 19, lines 442-444; Page 21, line 502; Table 2.

Minor

Comment 5: Please change the word multivariate logistic regression/multivariate analysis to multivariable logistic regression/multivariable analysis.

Reply 5: We are so sorry for the error. We have changed the word “multivariate” to “multivariable”.
Changes in the text: Lines 68, 72, 389, 405, 407, 417, 442, 450, 462, 480, and 836.

Comment 6: [Figures 3A and 3B] The Sankey diagram may be a bit too busy to convey a clear message. Let's see if some smaller groups can be combined to improve the readability.

Reply 6: Thank you for your suggestion. We have revised the Sankey diagram with smaller groups. In the revised Figure 3A, we combined moderate and severe steatosis into a single category labeled “moderate-severe steatosis”. In the revised Figure 3B, we grouped F1 and F2 into “F1-2” and F3 and F4 into “F3-4”.

Changes in the text: Revised Figure 3A and 3B.

Reviewer B:

This is an interesting study that adds evidence of factors associated with weight loss response. Although the results are not necessarily novel, the imaging analysis on intervention is convincing.

Comment 1: However, there are some aspects that need more clarification, for example, some details regarding the intervention program would help to understand the results. Specifically, is there any dietary information that the authors may add?

Reply 1: Thanks for your important suggestion. We have added more details regarding the intervention program, especially dietary information (see Pages 11-12, lines 226-238, and Supplementary Figure 1).

Changes in the text: Pages 11-12, lines 226-238; and Supplementary Figure 1.

Comment 2: Second, please clarify the cutoff used for insulin resistance. HOMA IR higher than 2.69 has any reference? Please add.

Reply 2: We feel very sorry for our not clear expressions. Assessment of insulin resistance via the HOMA-IR is a key index for the primary prevention of MASLD/NAFLD or diabetes. However, the cut-off value of HOMA-IR varies by race, age, gender, disease, and complication (1). Due to the complexity of insulin resistance, determining specific cut-off values for HOMA-IR across various

ethnicities remains an important issue (2). The cutoff value in this study was utilized to identify insulin resistance in similar populations based on previous studies to lessen the potential bias (see Page 9, lines 184-185). And we have added the relevant references (3,4) to the paper (see Page 29, lines 675-680).

(1) Tang Q, Li X, Song P, Xu L. Optimal cut-off values for the homeostasis model assessment of insulin resistance (HOMA-IR) and pre-diabetes screening: Developments in research and prospects for the future. *Drug Discov Ther.* 2015;9:380-385.

(2) Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr.* 2022;16:102581.

(3) Shao C, Ye J, Li F, Lin Y, Wu T, Wang W, et al. Early Predictors of Cardiovascular Disease Risk in Nonalcoholic Fatty Liver Disease: Non-obese Versus Obese Patients. *Dig Dis Sci.* 2020;65:1850-1860.

(4) Li R, Liao XH, Ye JZ, Li MR, Wu YQ, Hu X, et al. Association of keratin 8/18 variants with non-alcoholic fatty liver disease and insulin resistance in Chinese patients: A case-control study. *World J Gastroenterol.* 2017;23:4047-4053.

Changes in the text: Page 9, lines 184-185; and Page 29, lines 675-680.

Comment 3: In addition, please add to all the tables values of fasting glucose and insulin levels.

Reply 3: Thank you for your valuable suggestion. As you suggested, we have included the values for fasting glucose and insulin levels in all tables (see Table 2). Furthermore, we have included these values into the subgroup logistic regression analyses (see Revised Figure 5). We have also updated the results (see Page 18, lines 413-419, and Page 19-20, lines 449-467).

Changes in the text: Page 18, lines 413-419; Page 19-20, lines 449-467); Table 2; and Revised Figure 5.

Comment 4: Please elaborate on the term regular exercise.

Reply 4: Thank you for your kind reminding. We have added more details about the definition of term regular exercise as follow: “Regular exercise was defined as participating in any kind of moderate-to-vigorous physical activity (MVPA) at least once a week (24,25). Total MVPA encompassed both recreational and occupational physical activity that lasted long enough to produce perspiration, such as bicycling, football, volleyball, carrying or lifting heavy loads, digging and construction work. On the structured questionnaires (Supplementary Appendix 1), participants provided information on the frequency, duration, and intensity of various physical activities. These activities were categorized into walking and MVPA based on the reported intensity (26)” (see Page 12, lines 238-245). Additionally, we have added the following three references to provide additional supporting information on regular exercise (see Page 30, lines 708-716):

Reference 24: Ryu S, Chang Y, Kim DI, Kim WS, Suh BS. gamma-Glutamyltransferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. *Clin Chem.* 2007;53:71-77.

Reference 25: Osaka T, Hashimoto Y, Hamaguchi M, Kojima T, Obora A, Fukui M. Nonalcoholic fatty liver disease remission in men through regular exercise. *J Clin Biochem Nutr.* 2018;62:242-246.

Reference 26: Wang J, Qi Y, Xin Z, Huo Y, Wan Q, Qin Y, et al. Isotemporal substitution of different

behaviour patterns with the presence of MAFLD in Chinese adults. *Liver Int.* 2022;42:2683-2695.
Changes in the text: Page 12, 238-245; and Page 30, lines 708-716.

Comment 5: Specifically, was exercise indicated that by a physician?

Reply 5: We feel very sorry for our not clear expressions. Lifestyle management in this study, including dietary restrictions and exercise, was conducted under the guidance of a professional nutritionist (SY Zhuo) (see Page 11, lines 226-230, and Page 13, line 281). And each participant received an easy-to-carry brochure with dietary and exercise advice (Supplementary Figure 1A).
Changes in the text: Page 11, lines 226-230; Page 13, line 281; and Supplementary Figure 1A.

Comment 6: Finally, despite tables indicate that there are no gender differences in intervention response, this reviewer considers that additional analysis stratified by sex would help to understand the results. Please perform the same analyses segregated by sex.

Reply 6: Thanks for the constructive suggestions. We have already supplemented subgroup analyses by gender (see Page 19, lines 430-437, Page 20, lines 467-472, and Supplementary Figure 2). Given the relatively small sample size of female patients, the statistical power of the logistic regression analysis was limited. We included 82 female patients in the analysis of hepatic steatosis efficacy, 25 of whom experienced loss of MRI-PDFF response, and only 30 female patients in the analysis of hepatic fibrosis efficacy, 2 of whom had loss of LSM response (see Supplementary Table 8). Therefore, we have noted and discussed this limitation in the Discussion section (see Page 24, lines 584-587).

Changes in the text: Page 19, lines 430-437; Page 20, lines 467-472; Page 24, lines 584-587; Supplementary Figure 2; and Supplementary Table 8.