

# Specific metabolic impairments indicate loss of sustained liver improvements in metabolic dysfunction-associated steatotic liver disease treatment

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**Background:** High liver fat content (LFC) induces increased risks of both hepatic and extrahepatic progression in metabolic dysfunction-associated steatotic liver disease (MASLD), while maintaining a significant decline in magnetic resonance imaging-based proton density fat fraction (MRI-PDFF) ( $\geq 30\%$  decline relative to baseline) without worsening fibrosis results in improved histological severity and prognosis. However, the factors associated with the loss of sustained responses to treatment remain unclear, and we aim to identify them.

**Methods:** Consecutive treatment-naïve MASLD patients between January 2015 and February 2022, with follow-up until April 2023, were included in this prospective cohort study. LFC quantified by MRI-PDFF and liver stiffness measurements (LSM) determined by two-dimensional shear wave elastography (2D-SWE) were evaluated at weeks 0, 24 and 48. MRI-PDFF response was defined as a  $\geq 30\%$  relative decline in PDFF values, and LSM response was defined as a  $\geq 1$  stage decline from baseline.

**Results:** A total of 602 MASLD patients were enrolled. Of the 303 patients with a 24-week MRI-PDFF response and complete follow-up of 48 weeks, the rate of loss of MRI-PDFF response was 29.4%, and multivariable logistic regression analyses showed that 24-week insulin resistance (IR), still regular exercise and caloric restriction after 24 weeks, and the relative decline in LFC were risk factors for loss of MRI-PDFF response. Loss of LSM response at 48 weeks occurred in 15.9% of patients, and multivariable analysis confirmed 24-week serum total bile acid (TBA) levels and the relative decline in TBA from baseline as independent predictors. No significant association was found at 48 weeks between loss of MRI-PDFF response and loss of LSM response.

**Conclusions:** MASLD patients with IR and high TBA levels are at higher risks of subsequent diminished sustained improvements of steatosis and fibrosis, respectively.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease (MASLD); loss of response; magnetic

resonance imaging-based proton density fat fraction response (MRI-PDFF response); liver stiffness measurements response (LSM response)

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## Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), renamed from nonalcoholic fatty liver disease (NAFLD), is the most prevalent etiology of chronic liver disease, impacting almost one-third of the general population worldwide (1,2). Unexpectedly, MASLD is rising in prevalence (increase of 29.1% up to 2030 compared to 2016), and the clinical burden of this unexpected increase is of great concern (3). Through its direct and indirect effect on disrupting glucose and lipid metabolism homeostasis by liver steatosis and subsequent liver injuries, MASLD not only induces deterioration from liver inflammation to fibrosis, liver decompensation and cancer, but also is a risk factor for the development of cardiovascular diseases, diabetes and stroke. As there remains no approval of a pharmacotherapy specific to MASLD, weight management to target is widely established as a first-line treatment (4-7).

For efficacy monitoring in MASLD, the gold standard of liver biopsy combined with histology scoring is limited by invasive procedures, related complications and sampling variations. Therefore, magnetic resonance imaging-based proton density fat fraction (MRI-PDFF), which quantifies the mobile proton density signal of triglycerides (TGs) and water noninvasively, has been accepted as an accurate alternative tool for repeated measurements of fat content within the liver. A meta-analysis of 1,100 patients derived from 13 cross-sectional studies demonstrated that its diagnostic value using liver biopsy as a reference can achieve an area under the summary receiver operating characteristic curve (AUC) of 0.91–0.98 for detecting steatosis grades of S1 to S3 (8). There is mounting evidence supporting that a  $\geq 30\%$  relative decline in MRI-PDFF is an imaging marker of disease activity resolution. One recent meta-analysis containing 346 subjects of clinical trials for MASLD found that MRI-PDFF response correlates positively with histologic remission response [pooled odds ratio (OR): 5.45; 95% confidence interval (CI): 1.53–19.46,  $P=0.009$ ] during treatment (9). However, most studies in the aforementioned meta-analysis utilized a 24-week follow-up time point in the study design, and these studies did not incorporate information regarding the loss of sustained MRI-PDFF response when extended follow-up was performed.

Liver fibrosis estimation is another aspect of great clinical importance in MASLD management. Achieving fibrosis regression [fibrosis stages decrease 1 stage or more in the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) the steatosis, activity and fibrosis (SAF) scoring systems] or at least no worsening was proposed as a treatment endpoint in clinical trials. Shear wave elastography (SWE) is one of several noninvasive modalities for diagnosing liver fibrosis. A meta-analysis comprising 64 studies with 13,045 MASLD patients demonstrated that the pooled AUC of SWE could be 0.95 for advanced fibrosis, which is superior to other noninvasive indices or vibration-controlled transient elastography (VCTE) but comparable to magnetic resonance elastography (MRE) (10).

Understanding the association between the loss of MRI-

### Highlight box

#### Key findings

- Metabolic dysfunction-associated steatotic liver disease (MASLD) patients with insulin resistance (IR) and high total bile acid (TBA) levels are at higher risks of subsequent diminished sustained improvements of steatosis and fibrosis, respectively.

#### What is known and what is new?

- Progression and reversal of hepatic steatosis and fibrosis are critical to the prognosis of MASLD.
- This is the first cohort study to explore factors associated with loss of sustained liver improvement in MASLD treatment. IR at 24 weeks indicates subsequent diminished sustained hepatic steatosis improvements. High TBA level at 24 weeks might predict loss of sustained improvements in hepatic fibrosis. However, loss of hepatic steatosis response is not parallel to vanished hepatic fibrosis response.

#### What is the implication, and what should change now?

- MASLD patients who achieve a magnetic resonance imaging-based proton density fat fraction response but with IR should undergo intensive lifestyle interventions, as monitoring TBA levels and lowering it may benefit from delaying fibrosis progression.

PDFF response [no longer maintaining a 30% decline in liver fat content (LFC)] or the worsening of fibrosis compared to baseline and potential influencing factors in the subjects receiving therapy would help design more efficacious management strategies for MASLD, thus reducing the burden of disease progression. We conducted a large, prospective cohort study evaluating 48 weeks of weight loss treatment in patients with MASLD. Our primary aim was to assess the incidence of loss of response and identify potential predictors. We present this article in accordance with the STROBE reporting checklist (available at <https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-393/rc>).

## Methods

### *Study design and population*

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. Of note, individuals with metabolic and alcohol-related/associated liver disease (MetALD) were not included in this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided signed informed consent prior to enrollment. This prospective study was approved by the Ethics Committee of The First Affiliated Hospital, Sun Yat-sen University [2014]112.

Subjects were included if they could be diagnosed with MASLD according to a multi-society Delphi consensus statement (1). The criteria include evidence of hepatic steatosis (hereby MRI-PDFF) in addition to at least one cardiometabolic risk factor. We excluded patients with any of the following exclusion criteria: (I) age <18 years; (II) other causes of liver disease, such as excessive alcohol intake (>210/140 g weekly in men/women), virus hepatitis, autoimmune liver disease and drug-induced liver injury; (III) decompensated cirrhosis; (IV) history or signs of malignancy, lung disease, heart disease or kidney disease; (V) glycated haemoglobin >9.0% or insulin usage; (VI) pregnancy or breastfeeding status; and (VII) incomplete information.

### *Clinical evaluation*

A standard proforma questionnaire was conducted through face-to-face interviews to obtain the following information

(supplementary file available at <https://cdn.amegroups.com/static/public/hbsn-23-393-1.pdf>): demographic data, medical history, physical activity, alcohol intake and dietary habits. For the average daily diet composition, the daily diet information (such as meat, seafood, eggs, vegetables, fruit and nuts) was recorded and further calculated according to the Chinese Food Composition Tables (11,12). All participants also underwent physical examinations to determine their body height, weight, body mass index (BMI), waist circumference (WC), and blood pressure.

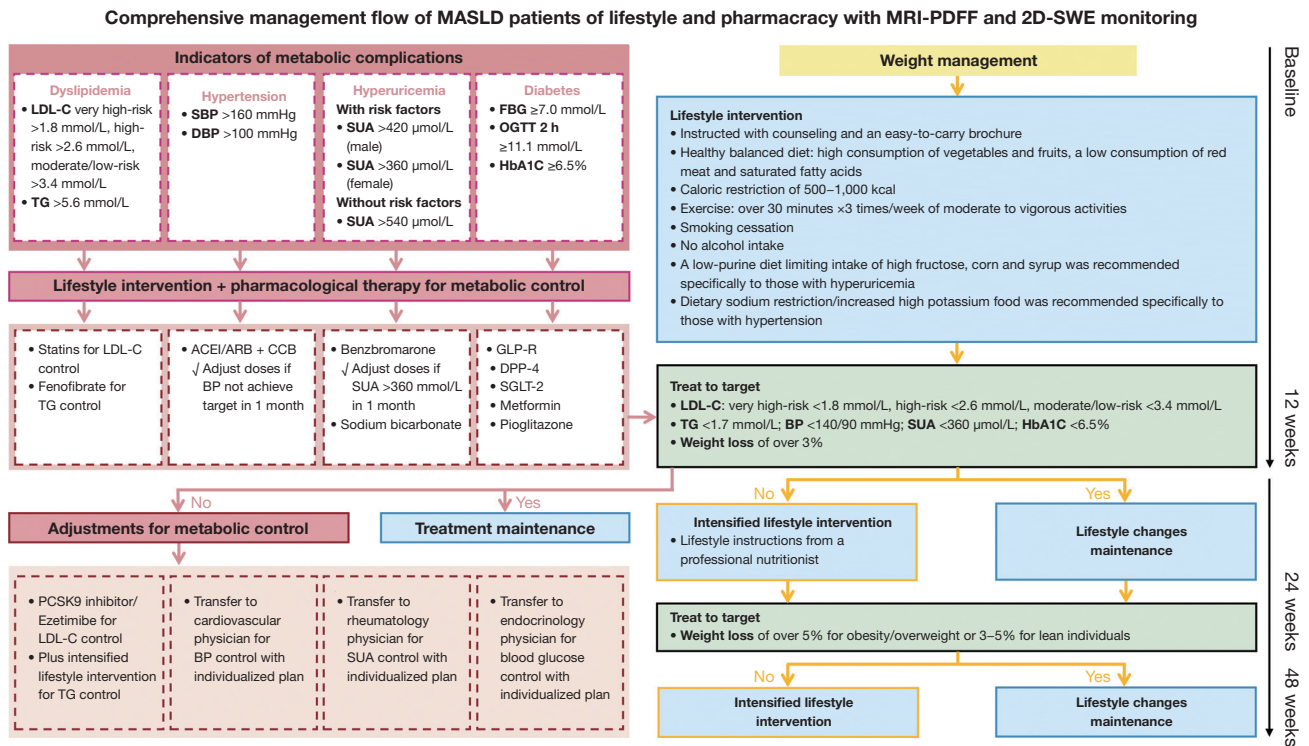
After fasting for a minimum of 8 hours, venous blood samples were collected to measure the following laboratory parameters using the Abbott c8000 Automatic Biochemistry Analyzer (Abbott, Abbott Park, IL, USA): liver biochemistry, lipid profiles, free fatty acid (FFA), uric acid (UA), fasting blood glucose (FBG) and insulin [fasting insulin (FINS)]. The levels of serum total bile acid (TBA) were measured by the enzyme circulation method (AU5800, Beckman Coulter, Brea, CA, USA). Hypertension was defined as high resting blood pressure levels  $\geq 140/90$  mmHg or the use of antihypertensive drugs (13). Hyperuricemia was defined as serum UA  $>420$   $\mu\text{mol/L}$  for males and  $>360$   $\mu\text{mol/L}$  for females. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as  $[\text{FINS} (\mu\text{U/mL}) \times \text{FBG} (\text{mmol/L})]/22.5$ . Its cutoff value was 2.69 (14,15), which was utilized to identify insulin resistance (IR) in similar populations based on our previous study. Diabetes mellitus was defined as an FBG  $\geq 7.0$  mmol/L or a self-reported history (16).

### *Hepatic steatosis assessment*

All participants underwent MRI-PDFF to diagnose fatty liver and evaluate average LFC using a 3.0-Tesla MRI scanner (Siemens 3.0 T Magnetom Verio; Siemens, Munchen, Germany). The fixed image analysts were blinded to all clinical data. The details of the MRI-PDFF protocol have been described previously and are briefly described as follows: time of echo 1 (TE1) 2.5 ms; TE2 3.7 ms; repetition time 5.47 ms; flip angle of  $5^\circ$ ;  $\pm 504.0$  kHz per pixel receiver bandwidth; and slice thickness, 3.0 mm (17). The cutoff values of hepatic fat accumulation were defined as LFC  $\geq 5\%$ , and its severity was classified as mild ( $<16.3\%$ ), moderate (16.3% to 21.7%) and severe ( $>21.7\%$ ) (18).

### *Liver stiffness measurements (LSM)*

Two-dimensional SWE (2D-SWE) (Aix-en-Provence,



**Figure 1** Comprehensive management flow of MASLD patients. The cardiovascular risk and LDL-C targets of MASLD patients were determined according to the American Heart Association blood cholesterol clinical practice guideline. MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; 2D-SWE, two-dimensional shear wave elastography; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; SUA, serum uric acid; FBG, fasting blood glucose; OGTT, oral glucose tolerance test; HbA1C, hemoglobin A1c; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; CCB, calcium channel blockers; GLP-1R, glucagon-like peptide 1 receptor; DPP-4, dipeptidyl peptidase 4; SGLT-2, sodium-dependent glucose transporters 2; PCSK9, proprotein convertase subtilisin/kexin type 9; BP, blood pressure.

France) was utilized to obtain liver stiffness measurements (LSM) by two fixed physicians who were blinded to the clinical information and had >5 years of experience with 2D-SWE measurements. The static SWE image was measured in a rectangular region of interest that was approximately 4 cm × 3 cm × 3 cm and set 1–2 cm below the surface of the liver, where a circular region of interest (the diameter set about 2.0 cm) without any focal lesion, biliary tracts, blood vessels, or artifacts from nearby lung gas or cardiac movement was selected. The means, minimum, maximum, and standard deviation (SD) of liver stiffness were obtained. The calculation of the average value of each participant was performed according to five consecutive 2D-SWE images, which were regarded as representative of the LSM (19). The cutoff values for discriminating different severities of liver fibrosis were defined as follows: F0

≤6.3 kPa, F1 6.4–7.5 kPa, F2 7.6–8.8 kPa, F3 8.9–9.8 kPa, and F4 ≥9.9 kPa (20).

### Follow-up and outcomes

During the follow-up, all subjects received surveillance and treatments from a multidisciplinary team, which included a hepatologist physician (B.Z.), a nutritional specialist (S.Z.), a cardiovascular physician (W.M.), an endocrinologist physician (X.C.) and a rheumatologist physician (L. Liang). Comprehensive management flow of MASLD patients of lifestyle and pharmacotherapy with MRI-PDFF and 2D-SWE monitoring in this study was summarised in *Figure 1*. All patients were instructed by a nutritionist (S.Z.) to restrict carbohydrate and fat intake and to exercise with an easy-to-carry brochure recording personalized prescriptions

(Figure S1A) according to the Dietary Reference Intakes and World Health Organization Global Strategy on Diet, Physical Activity and Health (21,22). Caloric restriction was defined as a reduction in daily energy (caloric) intake of 500–1,000 kcal/d from baseline (23). The nutritionist (S.Z.) estimated the patient's daily caloric requirements based on their weight and level of physical activity, and then provided a dietary program that reduced patient's daily energy intake by 500–1,000 kcal from the estimated caloric requirements (Figure S1B). The prescribed diets consisted of 60% carbohydrates, 15% protein, and 25% fat. 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 file available at <https://cdn.amegroups.cn/static/public/hbsn-23-393-1.pdf>), 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). For individuals with indications for pharmacological therapy for lipid profiles, blood glucose or UAs, drug therapy was administered by supervising physicians based on the guidelines (13,27-29). Namely, this therapy comprised a statin for low-density lipoprotein cholesterol (LDL-C) control, a fenofibrate for TG control, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB) or calcium channel blockers (CCB) for blood pressure control, glucagon-like peptide 1 receptor (GLP-1R), dipeptidyl peptidase 4 (DPP-4), sodium-dependent glucose transporters 2 (SGLT-2), metformin or pioglitazone for blood glucose control, and benzbromarone for UA control.

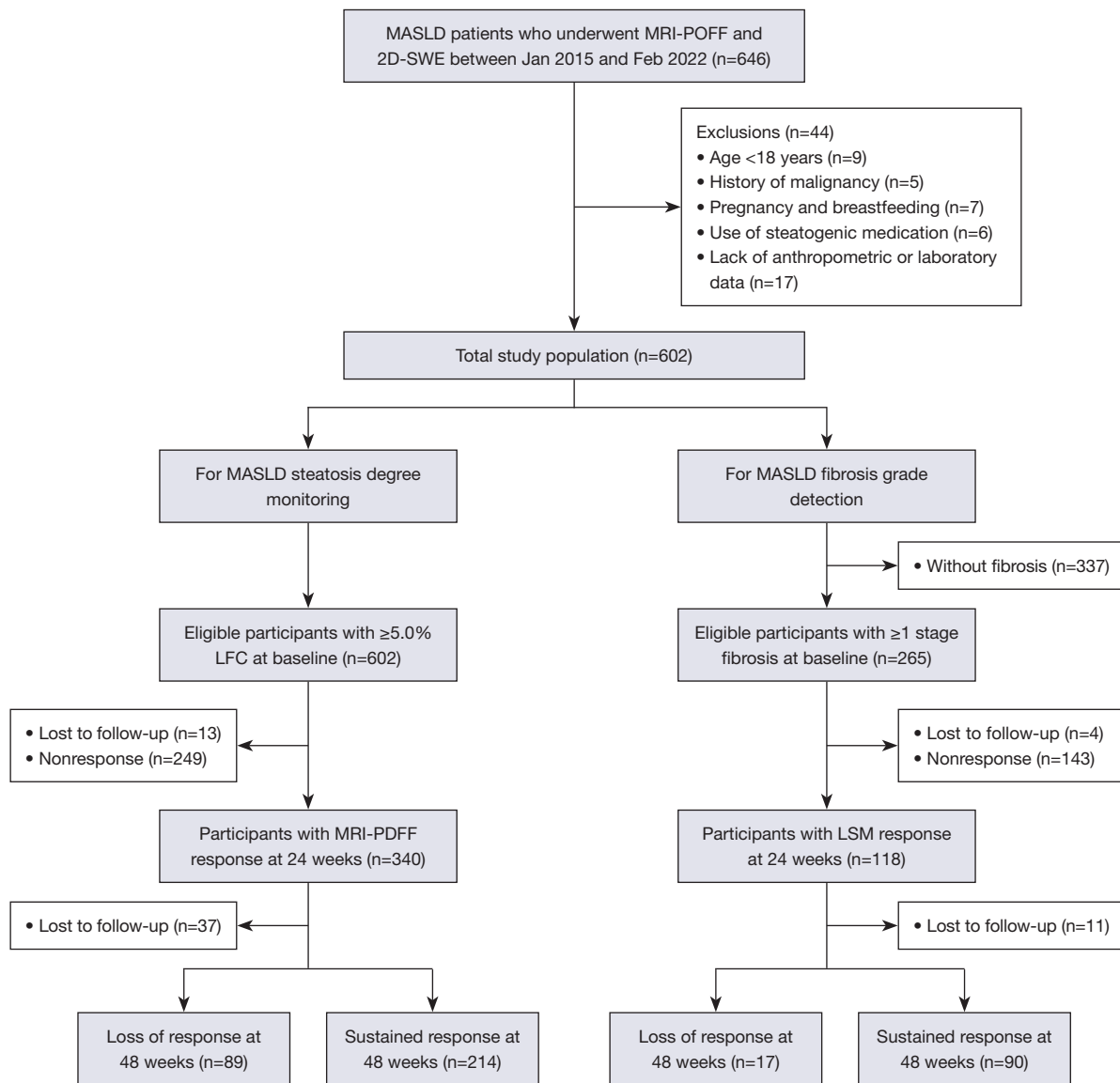
At weeks 0, 12, 24 and 48, all participants were scheduled for face-to-face visits at our center. During each visit, a structured lifestyle questionnaire, anthropometric parameters measurements and biochemical tests were conducted. If metabolic abnormalities remained uncontrolled or weight loss was less than 3% within 12 weeks, the multidisciplinary team would adjust medication prescriptions and provide intensified lifestyle intervention guidance. Intensified lifestyle interventions, implemented under the supervision of a clinical nutritionist (S.Z.), included individualized meal plans and longer durations of physical activity increased from 150 to

240 minutes of training per week (both aerobic and resistance training), the principles of which was detailed in Table S1.

At weeks 0, 24 and 48, MRI-PDFF and 2D-SWE were arranged to estimate the changes in LFC and LSM, respectively. MRI-PDFF response was defined as  $\geq 30\%$  relative decline of LFC values from baseline (8). For fibrosis regression evaluation, individuals with fibrosis stage 0 at baseline were removed from the analysis. LSM response was defined as  $\geq 1$  stage decline from baseline. The primary outcomes of the study were set as the loss of MRI-PDFF or LSM response at 48 weeks. Loss of MRI-PDFF response was determined as the absence of sustained MRI-PDFF response from week 24 to week 48, while loss of LSM response was defined as the absence of sustained LSM response from week 24 to week 48. Secondary outcomes included the changes from baseline in anthropological and biochemistry indicators, LFC quantified by MRI-PDFF and LSM determined by 2D-SWE at 24 and 48 weeks. The dynamic monitoring of these indicators was evaluated by absolute ( $\Delta$ ) and relative ( $\Delta\%$ ) changes. For example,  $\Delta\text{LFC}_{\text{baseline-24w}} = \text{LFC at baseline} - \text{LFC at 24 weeks}$ ;  $\Delta\text{LFC}_{\text{baseline-48w}} = \text{LFC at baseline} - \text{LFC at 48 weeks}$ ;  $\Delta\%\text{LFC}_{\text{baseline-24w}} = (\text{LFC at baseline} - \text{LFC at 24 weeks}) / \text{LFC at baseline} \times 100\%$ . All endpoints were collected at both 24 and 48 weeks of follow-up.

### Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (IBM, Chicago, USA). Continuous variables are expressed as the mean  $\pm$  SD or median [interquartile range (IQR)] and were compared using the independent samples *t*-test or the Wilcoxon-Mann-Whitney *U* test. Categorical variables are presented as frequencies (percentages) and were compared using the Chi-square test or Fisher's exact test. The dynamic changes in outcome measures were investigated by repeated-measures analysis of variance. Notably, the normal upper limited value of TBA was set at a concentration of 4.1  $\mu\text{mol/L}$ , which corresponded to the highest quartile concentration of TBA in our entire cohort. Univariable and multivariable logistic regression analyses were conducted to examine the risk factors for the loss of response in hepatic steatosis or fibrosis, and the multivariable adjustments included variables that were identified with statistic difference and potential confounders such as weight loss and IR status. Statistical significance was defined as two-sided *P* values  $< 0.05$ .



**Figure 2** Flowchart showing the flow of participants through the study. MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; 2D-SWE, two-dimensional shear wave elastography; LFC, liver fat content; LSM, liver stiffness measurement.

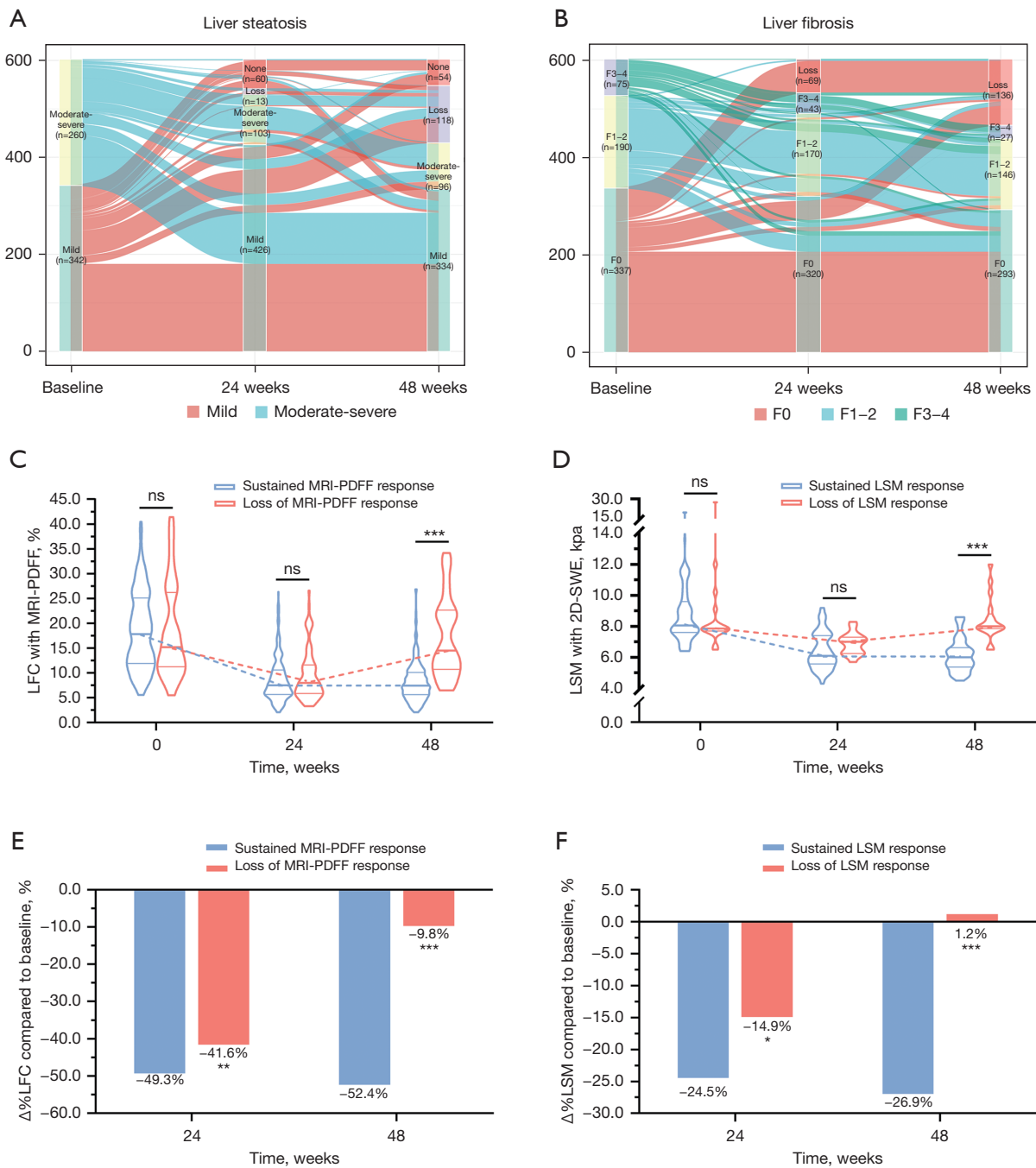
## Results

### Patient characteristics

As shown in *Figure 2*, a total of 602 consecutive MASLD patients who underwent MRI-PDFF and 2D-SWE assessments were enrolled in this prospective analysis. The majority of the patients were male (73.3%), with a mean age of  $41.1 \pm 13.6$  years old. Of these patients, 201 received lipid-lowering drugs, 76 received uric-acid-lowering drugs, 47

received hypoglycemic drugs, 470 exercised regularly, 164 received intensified lifestyle intervention, and 319 achieved caloric restrictions (*Table S2*).

The dynamic changes in hepatic steatosis and fibrosis in every participant are outlined in *Figure 3A, 3B*. After 24 weeks of follow-up, 57.7% (340/589) of MASLD patients presented MRI-PDFF response, 45.2% (118/261) of whom had LSM response concurrently. Regarding baseline clinical characteristics, subjects with MRI-PDFF response at 24



**Figure 3** Dynamic changes in LFC measured by MRI-PDFF and LSM measured by 2D-SWE in MASLD patients without or with loss response status. Evolution of hepatic steatosis (A) and fibrosis (B) from study enrollment to 48-week follow-up in the whole cohort. Violin plots showing the change trends of LFC (C) or LSM (D) in the two groups at 0, 24 and 48 weeks. Boxplots showing the relative decline ratio of LFC (E) or LSM (F) in the two groups at both 24 and 48 weeks. Nonparametric tests were employed for comparisons at each time point. \*, P<0.05; \*\*, P<0.01; \*\*\*, P<0.001. F0, liver fibrosis stage 0; F1-2, liver fibrosis stages 1 to 2; F3-4, liver fibrosis stages 3 to 4. ns, not significant; LFC, liver fat content; LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; 2D-SWE, two-dimensional shear wave elastography; MASLD, metabolic dysfunction-associated steatotic liver disease.

weeks exhibited significantly higher levels of FFA, HOMA-IR, alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transpeptidase (GGT), LFC and LSM but a higher proportion of regular exercise, caloric restriction than those with MRI-PDFF nonresponse (all  $P < 0.05$ , Table S2). Compared with the patients without 24-week LSM response, those with 24-week LSM response tended to have higher baseline LDL-C, FINS, HOMA-IR and LFC levels but lower age, baseline FFA levels and the proportion of caloric restriction (all  $P < 0.05$ , Table S2). Moreover, a lower prevalence of diabetes mellitus appeared in the LSM response group than in the LSM nonresponse (11.9% vs. 30.8%,  $P < 0.001$ ).

### *Clinical characteristic patterns of loss-response in steatosis and fibrosis*

In patients with improved hepatic steatosis or fibrosis at 24 weeks, we followed up for an additional 24 weeks and divided them according to whether they maintained the response status of steatosis and fibrosis, respectively. Baseline characteristics of MASLD patients who stayed in the cohort and those who were lost to follow-up are presented in Table S3. For hepatic steatosis, 37 patients were lost to follow-up, and the rate of loss of MRI-PDFF response was 29.4% (89/303). Patients who experienced a loss of MRI-PDFF response and those who maintained a sustained MRI-PDFF response exhibited similar baseline in anthropometrical parameters, liver biochemistry, metabolic indicators, LFC, LSM, and lifestyle status at 0–24 weeks (Table 1). Regarding liver fibrosis, 11 subjects were lost to follow-up, and the rate of loss of LSM response was 15.9% (17/107). Compared with the sustained LSM response group, higher baseline WC and FBG levels were observed in the loss of LSM response group (all  $P < 0.05$ , Table 1).

The absolute changes in clinical indicators are detailed in Tables S4,S5. Among the loss of MRI-PDFF response group, 24-week changes in weight, BMI, WC, FFA, FBG, UA, ALT, AST, GGT, and LFC were higher than 48-week changes (all  $P < 0.05$ , Table S4). Among the loss of LSM response group, changes in LSM were higher at 24 weeks than at 48 weeks [1.00 (IQR, 0.55, 2.30) vs. -0.10 (IQR, -0.35, 0.08) kpa,  $P < 0.001$ , Table S5]. Notably, when comparing 24-week changes between patients without and with sustained MRI-PDFF response at 48 weeks, significant differences were not observed (all  $P > 0.05$ , Table S4). However, individuals with loss of LSM response tended to have a larger decrease in total bilirubin but not in alkaline phosphatase, TBA and LSM (all  $P < 0.05$ , Table S5).

Furthermore, we analyzed the dynamic changes in LFC and LSM (Figure 3). The median LFC values in patients with loss of MRI-PDFF response status were 15.2%, 8.0% and 14.5% at 0, 24 and 48 weeks, respectively. On the other hand, patients with sustained MRI-PDFF response status contained median LFC values of 17.8%, 7.5% and 7.4% at each corresponding follow-up point, respectively. At 24 weeks, the median LFC levels between the two groups did not reach a significant difference (Figure 3C), while the relative decline ratio of LFC was lower in the loss of MRI-PDFF response group than in the sustained MRI-PDFF response group at 24 weeks (-41.6% vs. -49.3%,  $P = 0.001$ , Figure 3E). At 48 weeks, both the median LFC and relative decline ratio between the two groups showed significant differences (all  $P < 0.001$ , Figure 3C,3E). A similar trend was also shown in the median LSM values and corresponding relative decline ratios (Figure 3D,3F).

### *Predictors of loss of response in hepatic steatosis*

The univariate analysis in patients with MRI-PDFF response at 24 weeks revealed that 24-week IR, still regular exercise and caloric restriction after 24 weeks,  $\Delta\%LDL-C_{\text{baseline-24w}}$  10% category and  $\Delta\%LFC_{\text{baseline-24w}}$  10% category were associated with the loss of response of hepatic steatosis. After multivariable adjustments, 24-week IR (OR: 2.97, 95% CI: 1.37–6.41,  $P = 0.006$ ), regular exercise (OR: 0.36, 95% CI: 0.16–0.80,  $P = 0.01$ ) and caloric restriction (OR: 0.29, 95% CI: 0.15–0.55,  $P < 0.001$ ) after 24 weeks, and  $\Delta\%LFC_{\text{baseline-24w}}$  10% category (OR: 0.75, 95% CI: 0.58–0.96,  $P = 0.02$ ) remained significantly and independently associated with the loss of response in hepatic steatosis (Table 2). As shown in Figure 4, different longitudinal IR patterns exhibited different dynamic changes in LFC measured by MRI-PDFF. Individuals with IR at baseline had more severe hepatic steatosis, while those with IR at 24 weeks tended to have a subsequent diminished sustained response in hepatic steatosis (Figure 4A).

To further explore the association of weight change, IR status, and gender with the sustained efficacy of hepatic steatosis, the participants who exhibited MRI-PDFF response at 24 weeks were subgrouped and analyzed by multivariable analysis. Subgroup clinical characteristics are provided in Tables S6–S8. Multivariable logistic regression model confirmed that 24-week IR (OR: 3.33, 95% CI: 1.40–7.90,  $P = 0.006$ ), regular exercise after 24 weeks (OR: 0.22, 95% CI: 0.08–0.62,  $P = 0.004$ ) and  $\Delta\%LFC_{\text{baseline-24w}}$  10% category (OR: 0.63, 95% CI: 0.43–0.94,  $P = 0.02$ ) were



**Table 1** Baseline characteristics of MASLD patients stratified by MRI-PDFF response or LSM response status at 48 weeks

Characteristics	Liver steatosis				Liver fibrosis			
	Total† (n=303)	Sustained MRI-PDFF response at 48 weeks (n=214)	Loss of MRI-PDFF response at 48 weeks (n=89)	P	Total† (n=107)	Sustained LSM response at 48 weeks (n=90)	Loss of LSM response at 48 weeks (n=17)	P
Age (years)	42.0±13.9	42.9±13.9	39.8±13.9	0.08	42.1±11.3	42.4±11.6	40.7±10.1	0.56
Male	221 (72.9)	157 (73.4)	64 (71.9)	0.80	77 (72.0)	62 (68.9)	15 (88.2)	0.18
Weight (kg)	76.7±11.6	76.4±11.3	77.5±12.4	0.43	77.1±11.2	76.5±11.4	80.7±9.5	0.15
BMI (kg/m <sup>2</sup> )	27.7±3.3	27.6±3.2	27.8±3.6	0.61	28.2±3.2	27.9±3.1	29.42± 3.5	0.08
WC (cm)	91.7±8.0	91.6±7.9	92.0±8.3	0.69	92.8±7.6	92.1±7.2	96.2±8.7	0.04
Waist-hip ratio	0.90±0.05	0.90±0.05	0.91±0.05	0.68	0.91±0.05	0.91±0.05	0.93±0.06	0.15
CHOL (mmol/L)	5.08±1.08	5.09±1.05	5.06±1.16	0.84	5.04±0.91	5.08±0.93	4.84±0.78	0.33
TG (mmol/L)	1.68 (1.18, 2.27)	1.74 (1.29, 2.36)	1.50 (1.14, 2.12)	0.06	1.69 (1.32, 2.20)	1.71 (1.34, 2.23)	1.30 (1.01, 2.00)	0.15
HDL-C (mmol/L)	1.14±0.27	1.14±0.25	1.14±0.32	0.78	1.10±0.23	1.10±0.23	1.08±0.21	0.66
LDL-C (mmol/L)	3.20±0.80	3.22±0.77	3.17±0.86	0.62	3.25±0.70	3.28±0.71	3.12±0.63	0.39
FFA (mmol/L)	541 (438, 739)	521 (437, 739)	551 (446, 738)	0.42	508 (424, 691)	497 (413, 660)	599 (476, 827)	0.06
FBG (mmol/L)	5.0 (4.6, 5.7)	5.0 (4.6, 5.7)	4.9 (4.6, 5.9)	0.89	5.0 (4.6, 6.0)	5.0 (4.6, 5.7)	6.0 (4.9, 6.7)	0.02
FINS (μU/mL)	11.0 (8.5, 14.9)	11.0 (8.5, 14.6)	11.7 (8.5, 15.6)	0.41	12.8 (9.7, 19.9)	12.8 (9.6, 20.8)	10.1 (9.2, 14.7)	0.14
HOMA-IR	2.65 (1.85, 3.70)	2.65 (1.91, 3.62)	2.69 (1.79, 3.93)	0.50	2.80 (2.20, 4.40)	2.89 (2.17, 4.89)	2.75 (2.09, 4.01)	0.78
UA (μmol/L)	433.2±100.9	428.7±97.9	444.2±107.6	0.22	404.4±95.1	401.5±101.2	419.8±51.3	0.27
ALT (U/L)	50.0 (32.0, 83.0)	50.0 (32.0, 81.5)	54.0 (31.0, 88.5)	0.78	38.0 (30.0, 72.0)	38.0 (30.0, 72.0)	38.0 (29.0, 96.0)	0.88
AST (U/L)	36.0 (26.0, 56.0)	36.0 (26.8, 55.0)	35.0 (24.5, 59.0)	0.51	34.0 (22.0, 51.0)	36.5 (22.0, 50.3)	27.0 (22.0, 57.0)	0.43
GGT (U/L)	47.0 (30.0, 72.0)	50.0 (29.0, 72.0)	44.0 (32.0, 59.8)	0.52	40.5 (29.8, 61.0)	40.0 (29.0, 59.5)	43.0 (29.5, 76.5)	0.76
ALP (U/L)	78.0 (67.0, 91.0)	78.0 (64.8, 93.0)	78.0 (68.0, 87.8)	0.86	78.0 (67.0, 90.0)	78.0 (67.0, 94.3)	74.0 (67.0, 81.0)	0.26
Albumin (g/L)	45.9±3.2	45.9±3.1	46.0±3.3	0.85	45.6±2.9	45.6±3.1	45.7±1.9	0.83
TB (μmol/L)	12.7 (10.2, 16.2)	12.6 (10.2, 16.1)	13.0 (10.1, 16.8)	0.35	12.3 (10.0, 17.0)	12.2 (10.0, 16.5)	16.3 (10.0, 24.2)	0.09
TBA (μmol/L)	2.6 (1.8, 4.1)	2.6 (1.8, 3.9)	2.6 (1.8, 4.8)	0.89	2.7 (2.0, 4.1)	2.7 (2.0, 4.0)	2.6 (1.6, 5.5)	0.89
LFC (%)	17.5 (11.7, 25.5)	17.8 (11.9, 25.1)	15.2 (11.2, 26.2)	0.51	18.3 (11.3, 24.3)	18.9 (11.1, 24.3)	14.7 (11.7, 27.5)	0.94
LSM (kpa)	6.7 (5.6, 8.0)	6.7 (5.6, 8.0)	6.7 (5.5, 8.4)	0.69	8.0 (7.6, 9.6)	8.1 (7.6, 9.6)	7.9 (7.7, 8.6)	0.63
Hypertension	84 (27.7)	54 (25.2)	30 (33.7)	0.12	28 (26.2)	23 (25.6)	5 (29.4)	0.98
Diabetes mellitus	57 (18.8)	37 (17.3)	20 (22.5)	0.30	14 (13.1)	12 (13.3)	2 (11.8)	1.00
Smoking	26 (8.6)	21 (9.8)	5 (5.6)	0.27	4 (3.7)	3 (3.3)	1 (5.9)	0.51
Regular exercise <sup>§</sup>	265 (87.5)	190 (88.8)	75 (84.3)	0.36	87 (81.3)	74 (82.2)	13 (76.5)	1.00
Caloric restriction <sup>§</sup>	196 (64.7)	142 (66.4)	54 (60.7)	0.40	53 (49.5)	48 (53.3)	5 (29.4)	0.09
Lipid-lowering drug	102 (33.7)	69 (32.2)	33 (37.1)	0.43	40 (37.4)	34 (37.8)	6 (35.3)	0.82
Hypoglycemic drug	30 (9.9)	19 (8.9)	11 (12.4)	0.33	6 (5.6)	6 (6.7)	0 (0.0)	0.59
Uric-acid-lowering drug	45 (14.9)	26 (12.1)	19 (21.3)	0.06	14 (13.1)	10 (11.1)	4 (23.5)	0.33
Intensified lifestyle intervention	86 (28.4)	60 (28.0)	26 (29.2)	0.87	33 (30.8)	31 (34.4)	2 (11.8)	0.06

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). †, 303 MASLD patients who showed MRI-PDFF response at 24 weeks and continued to complete a further 24-week follow-up; ‡, 107 MASLD patients who showed LSM response at 24 weeks and continued to complete a further 24-week follow-up; §, the lifestyle status at 0–24 weeks after enrollment. Caloric restriction was defined as a reduction in energy (caloric) intake of 500–1,000 kcal/day from baseline; regular exercise was defined as moderate-to-vigorous physical activity at least once a week. MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.

**Table 2** Factors associated with the loss of response in liver steatosis and fibrosis at 48 weeks among MASLD patients

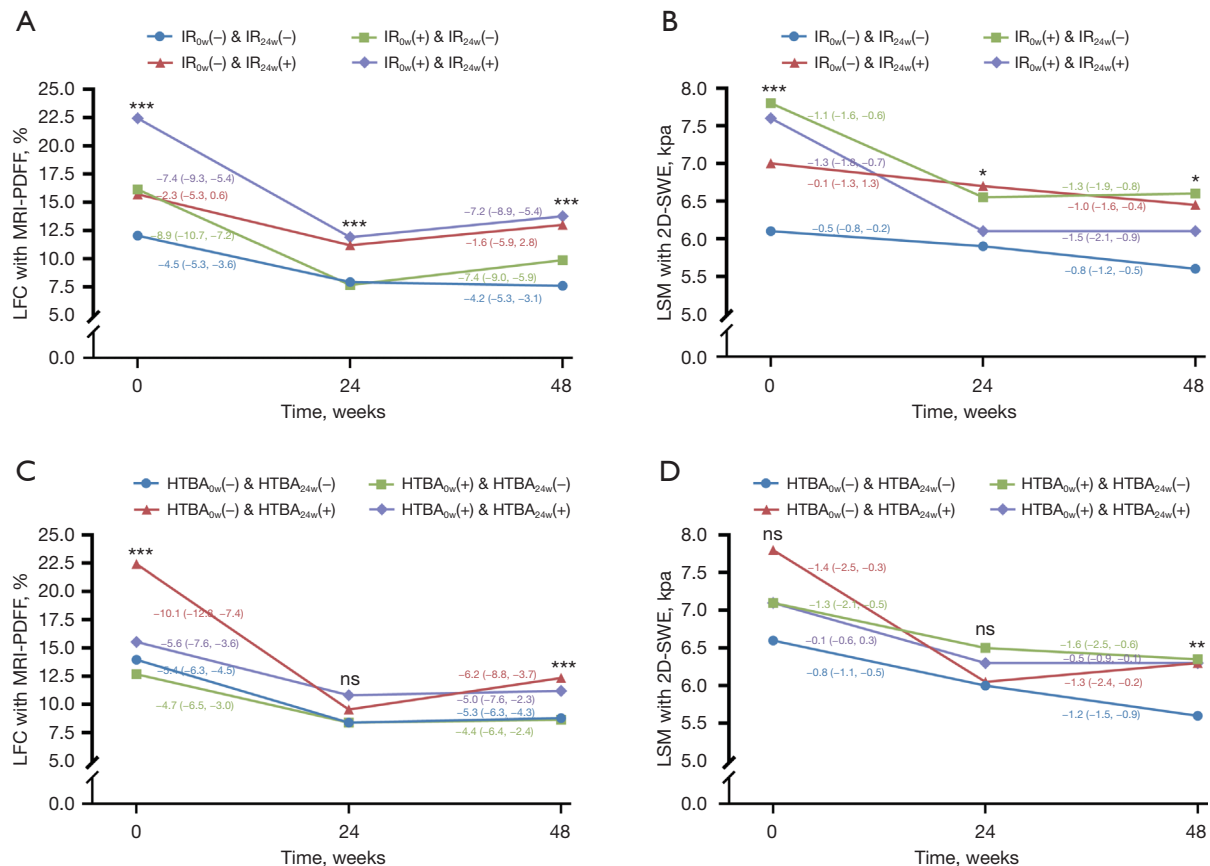
Predictors	Loss of steatosis response with MRI-PDFF (n=303)				Loss of fibrosis response with 2D-SWE (n=107)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age 10-year category	0.85 (0.71–1.02)	0.08	–	–	0.87 (0.55–1.38)	0.56	–	–
Sex (male)	0.93 (0.54–1.62)	0.80	–	–	3.39 (0.73–15.82)	0.12	–	–
Hypertension <sup>†</sup> (yes)	1.53 (0.90–2.63)	0.12	–	–	1.21 (0.39–3.82)	0.74	–	–
Diabetes mellitus (yes)	1.38 (0.75–2.54)	0.30	–	–	0.86 (0.17–4.22)	0.85	–	–
Smoking (yes)	0.57 (0.21–1.57)	0.28	–	–	1.81 (0.18–18.54)	0.62	–	–
Indicators at baseline								
Weight (kg)	1.01 (0.99–1.03)	0.43	–	–	1.03 (0.99–1.08)	0.15	–	–
BMI (kg/m <sup>2</sup> )	1.02 (0.95–1.10)	0.61	–	–	1.16 (0.98–1.37)	0.08	–	–
WC (cm)	1.01 (0.98–1.04)	0.69	–	–	1.08 (1.002–1.17)	0.04	0.94 (0.83–1.06)	0.32
TG (mmol/L)	0.89 (0.70–1.14)	0.35	–	–	0.94 (0.52–1.73)	0.85	–	–
HDL-C (mmol/L)	0.88 (0.35–2.21)	0.78	–	–	0.59 (0.06–6.14)	0.66	–	–
LDL-C (mmol/L)	0.92 (0.68–1.26)	0.62	–	–	0.70 (0.32–1.55)	0.38	–	–
FFA 100 mmol/L category	1.06 (0.93–1.20)	0.41	–	–	1.36 (1.01–1.82)	0.04	1.06 (0.65–1.75)	0.81
FBG (mmol/L)	1.19 (0.97–1.46)	0.09	–	–	1.38 (0.93–2.07)	0.11	–	–
FINS (μU/mL)	1.00 (0.97–1.04)	0.78	–	–	0.93 (0.85–1.02)	0.12	–	–
Insulin resistance <sup>†</sup>	1.34 (0.81–2.20)	0.25	1.04 (0.50–2.17)	0.91	1.68 (0.54–5.16)	0.37	3.66 (0.50–26.58)	0.20
Hyperuricemia <sup>†</sup>	1.67 (0.98–2.82)	0.06	–	–	1.41 (0.50–3.98)	0.52	–	–
TBA (μmol/L)	0.97 (0.88–1.07)	0.49	–	–	1.00 (0.89–1.13)	0.94	–	–
ALT 10 IU/L category	1.00 (0.95–1.06)	0.91	–	–	0.98 (0.85–1.13)	0.77	–	–
GGT 10 IU/L category	0.98 (0.94–1.02)	0.34	–	–	0.99 (0.89–1.10)	0.87	–	–
ALP 10 IU/L category	0.95 (0.88–1.01)	0.12	–	–	0.79 (0.58–1.08)	0.14	–	–
LFC 5.0% category	1.00 (0.86–1.16)	0.98	–	–	0.99 (0.73–1.35)	0.96	–	–
LSM (kpa)	0.95 (0.86–1.04)	0.27	–	–	1.03 (0.89–1.21)	0.68	–	–
Regular exercise at 0–24 weeks	0.69 (0.31–1.54)	0.37	–	–	0.78 (0.19–3.16)	0.73	–	–
Caloric restriction at 0–24 weeks	0.78 (0.44–1.39)	0.40	–	–	0.35 (0.10–1.22)	0.10	–	–
Indicators at 24 weeks								
Weight (kg)	1.01 (0.97–1.03)	0.47	–	–	1.03 (0.98–1.08)	0.28	–	–
BMI (kg/m <sup>2</sup> )	1.02 (0.94–1.10)	0.70	–	–	1.14 (0.94–1.37)	0.18	–	–
WC (cm)	0.99 (0.96–1.03)	0.61	–	–	1.05 (0.97–1.14)	0.20	–	–
TG (mmol/L)	0.82 (0.57–1.19)	0.29	–	–	0.79 (0.31–2.03)	0.63	–	–
HDL-C (mmol/L)	0.99 (0.43–2.28)	0.98	–	–	0.98 (0.10–9.77)	0.99	–	–
LDL-C (mmol/L)	1.45 (0.95–2.20)	0.08	–	–	1.20 (0.53–2.73)	0.67	–	–
FFA 100 mmol/L category	0.93 (0.81–1.07)	0.31	–	–	1.29 (0.98–1.69)	0.07	–	–
FBG (mmol/L)	1.10 (0.82–1.47)	0.54	–	–	1.31 (0.76–2.25)	0.33	–	–

**Table 2** (continued)

Table 2 (continued)

Predictors	Loss of steatosis response with MRI-PDFF (n=303)				Loss of fibrosis response with 2D-SWE (n=107)			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
FINS (μU/mL)	1.01 (0.98–1.04)	0.46	–	–	0.89 (0.78–1.03)	0.12	–	–
Insulin resistance <sup>†</sup>	2.37 (1.40–4.00)	0.001	2.97 (1.37–6.41)	0.006	0.43 (0.11–1.61)	0.21	0.38 (0.06–2.51)	0.32
Hyperuricemia <sup>†</sup>	1.03 (0.63–1.69)	0.91	–	–	0.92 (0.32–2.62)	0.87	–	–
TBA (μmol/L)	0.98 (0.93–1.04)	0.56	–	–	1.60 (1.25–2.06)	<0.001	1.41 (1.04–1.92)	0.03
ALT 10 IU/L category	0.88 (0.75–1.04)	0.12	–	–	0.81 (0.54–1.23)	0.33	–	–
GGT 10 IU/L category	0.97 (0.92–1.03)	0.33	–	–	1.04 (0.91–1.20)	0.54	–	–
ALP 10 IU/L category	0.93 (0.85–1.01)	0.10	–	–	0.94 (0.68–1.29)	0.69	–	–
LFC 5.0% category	1.25 (0.96–1.63)	0.10	–	–	0.92 (0.57–1.49)	0.73	–	–
LSM (kpa)	0.92 (0.79–1.08)	0.30	–	–	1.44 (0.91–2.29)	0.12	–	–
Regular exercise after 24 weeks	0.32 (0.16–0.65)	0.002	0.36 (0.16–0.80)	0.01	0.65 (0.12–3.52)	0.62	–	–
Caloric restriction after 24 weeks	0.33 (0.19–0.60)	<0.001	0.29 (0.15–0.55)	<0.001	0.24 (0.05–1.19)	0.08	–	–
Changes of indicators <sup>‡</sup>								
Δ%Weight <sub>baseline-24w</sub> 10% category	1.06 (0.61–1.83)	0.84	1.98 (0.89–4.41)	0.10	1.36 (0.53–3.49)	0.53	0.35 (0.08–1.55)	0.17
Δ%WC <sub>baseline-24w</sub> 10% category	1.48 (0.87–2.53)	0.15	–	–	1.91 (0.63–5.77)	0.25	–	–
Δ%TG <sub>baseline-24w</sub> 10% category	0.99 (0.93–1.05)	0.69	–	–	0.92 (0.79–1.06)	0.23	–	–
Δ%HDL-C <sub>baseline-24w</sub> 10% category	0.93 (0.81–1.06)	0.25	–	–	0.92 (0.65–1.31)	0.65	–	–
Δ%LDL-C <sub>baseline-24w</sub> 10% category	0.91 (0.83–0.99)	0.04	0.90 (0.81–1.002)	0.053	0.87 (0.68–1.11)	0.26	–	–
Δ%FFA <sub>baseline-24w</sub> 10% category	1.06 (0.98–1.13)	0.15	–	–	0.99 (0.90–1.09)	0.83	–	–
Δ%FBG <sub>baseline-24w</sub> 10% category	1.13 (0.93–1.37)	0.21	–	–	1.33 (0.92–1.92)	0.13	–	–
Δ%FINS <sub>baseline-24w</sub> 10% category	0.97 (0.91–1.05)	0.46	–	–	1.04 (0.88–1.23)	0.63	–	–
Δ%HOMA-IR <sub>baseline-24w</sub> 10% category	0.99 (0.93–1.06)	0.77	–	–	1.08 (0.93–1.26)	0.33	–	–
Δ%UA <sub>baseline-24w</sub> 10% category	0.97 (0.87–1.09)	0.61	–	–	1.06 (0.83–1.35)	0.66	–	–
Δ%TBA <sub>baseline-24w</sub> 10% category	0.99 (0.96–1.01)	0.31	–	–	0.87 (0.81–0.93)	<0.001	0.84 (0.75–0.95)	0.006
Δ%ALT <sub>baseline-24w</sub> 10% category	1.03 (0.97–1.10)	0.33	–	–	0.98 (0.88–1.09)	0.70	–	–
Δ%GGT <sub>baseline-24w</sub> 10% category	0.98 (0.91–1.06)	0.68	–	–	0.93 (0.81–1.08)	0.35	–	–
Δ%ALP <sub>baseline-24w</sub> 10% category	1.06 (0.93–1.19)	0.40	–	–	0.72 (0.50–1.03)	0.07	–	–
Δ%LFC <sub>baseline-24w</sub> 10% category	0.76 (0.64–0.92)	0.004	0.75 (0.58–0.96)	0.02	0.90 (0.78–1.04)	0.15	–	–
Δ%LSM <sub>baseline-24w</sub> 10% category	1.07 (0.91–1.25)	0.41	–	–	0.69 (0.46–1.04)	0.08	–	–
Loss of MRI-PDFF response	–	–	–	–	1.20 (0.28–5.05)	0.81	–	–

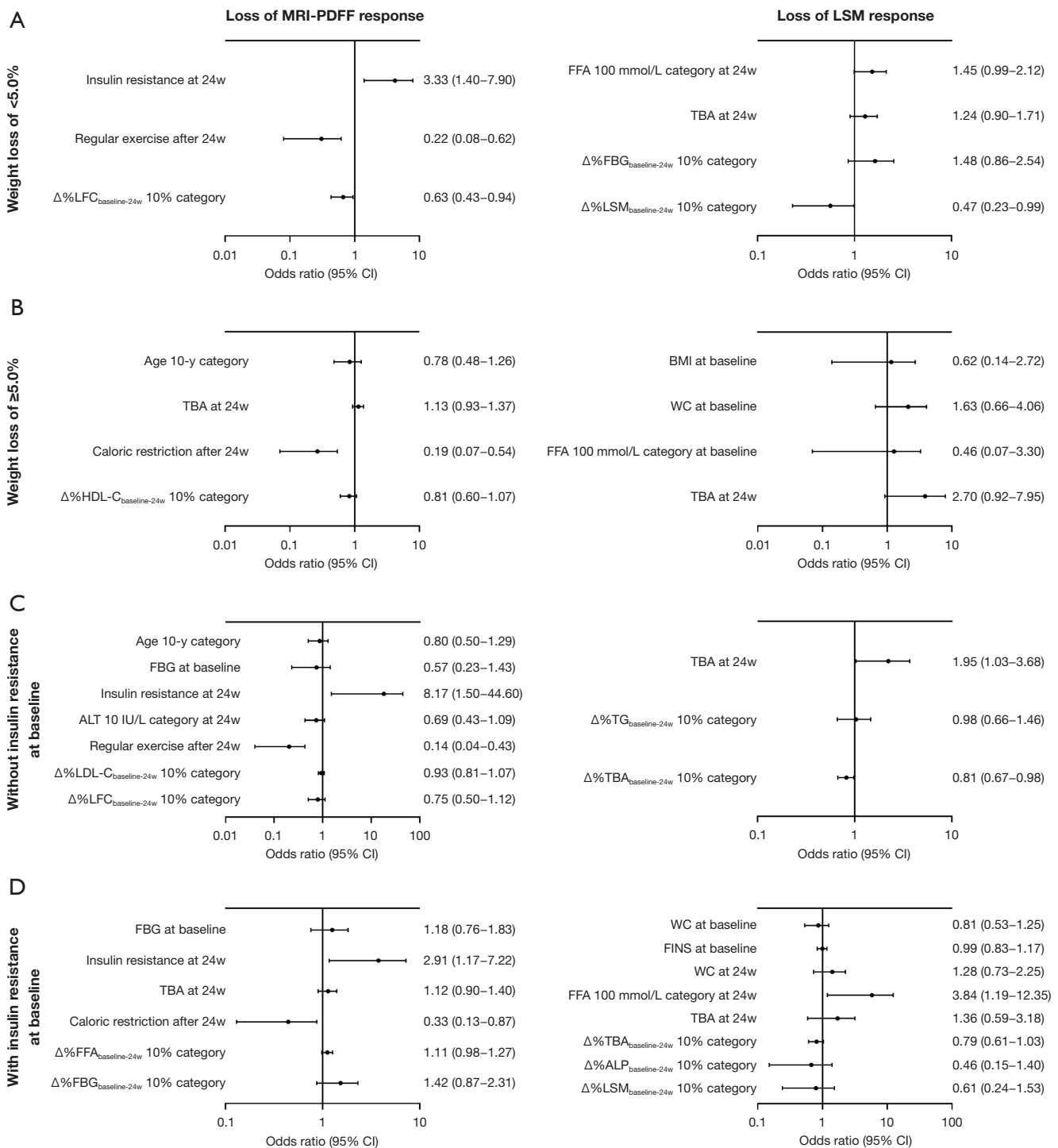
<sup>†</sup>, hypertension was defined as average blood pressure levels ≥140/90mmHg or use of hypertensive medication; insulin resistance was HOMA-IR >2.69. Hyperuricemia was defined as serum uric acid >420 μmol/L for male and >360 μmol/L for female; caloric restriction was defined as a reduction in energy (caloric) intake of 500–1,000 kcal/day from baseline; regular exercise was defined as moderate-to-vigorous physical activity at least once a week; <sup>‡</sup>, Δ%BMI<sub>baseline-24w</sub> 10% category was not included in this table because the relative changes in weight and BMI are identical. MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; 2D-SWE, two-dimensional shear wave elastography; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; WC, waist circumference; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting glucose; FINS, fasting insulin; TBA, total bile acid; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LFC, liver fat content; LSM, liver stiffness measurement; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; Δ%, relative change from baseline.



**Figure 4** Dynamic changes in LFC measured by MRI-PDFF and LSM measured by 2D-SWE in MASLD patients who completed a 48-week follow-up, stratified by insulin resistance (A,B) or total bile acid levels (C,D). The changes (95% CI) from baseline were noted, and comparisons at each time point were performed using nonparametric tests. \*,  $P < 0.05$ ; \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ . IR<sub>0w</sub>(-), without insulin resistance at baseline; IR<sub>0w</sub>(+), with insulin resistance at baseline; IR<sub>24w</sub>(-), without 24-week insulin resistance; IR<sub>24w</sub>(+), with 24-week insulin resistance; HTBA<sub>0w</sub>(-), without high total bile acid levels ( $\geq 4.1$   $\mu\text{mol/L}$ ) at baseline; HTBA<sub>0w</sub>(+), with high total bile acid levels ( $\geq 4.1$   $\mu\text{mol/L}$ ) at baseline; HTBA<sub>24w</sub>(-), without high total bile acid levels ( $\geq 4.1$   $\mu\text{mol/L}$ ) at 24 weeks; HTBA<sub>24w</sub>(+), with high total bile acid levels ( $\geq 4.1$   $\mu\text{mol/L}$ ) at 24 weeks. ns, not significant; LFC, liver fat content; MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; LSM, liver stiffness measurement; 2D-SWE, two-dimensional shear wave elastography.

risk factors for the loss of MRI-PDFF response at 48 weeks in the subgroup whose weight loss was  $< 5\%$  from baseline to 24 weeks (Figure 5A), while only caloric restriction after 24 weeks (OR: 0.19, 95% CI: 0.07–0.54,  $P = 0.002$ ) was a risk factor in those with weight loss of  $\geq 5\%$  (Figure 5B). A sub-analysis of the subjects without IR at baseline showed that 24-week IR (OR: 8.17, 95% CI: 1.50–44.60,  $P = 0.02$ ) and regular exercise after 24 weeks (OR: 0.14, 95% CI: 0.04–0.43,  $P = 0.001$ ) remained significant factors (Figure 5C). Among the subjects with IR at baseline, multivariable analysis showed that 24-week IR (OR: 2.91, 95% CI: 1.17–7.22,  $P = 0.02$ ) and caloric restriction after 24 weeks

(OR: 0.33, 95% CI: 0.13–0.87,  $P = 0.02$ ) were independent predictors of hepatic steatosis fluctuations (Figure 5D). In male patients, significant predictors of the loss of MRI-PDFF response included hypertension (OR: 3.25, 95% CI: 1.30–8.17,  $P = 0.01$ ), ALT 10-IU/L category (OR: 0.75, 95% CI: 0.57–0.99,  $P = 0.04$ ), and still regular exercise (OR: 0.23, 95% CI: 0.09–0.58,  $P = 0.002$ ) and caloric restriction after 24 weeks (OR: 0.43, 95% CI: 0.20–0.93,  $P = 0.03$ ) (Figure S2A). For female patients, significant predictors were caloric restriction after 24 weeks (OR: 0.07, 95% CI: 0.01–0.65,  $P = 0.02$ ) and  $\Delta\% \text{LFC}_{\text{baseline-24w}} 10\%$  category (OR: 0.39, 95% CI: 0.20–0.80,  $P = 0.01$ ) (Figure S2B).



**Figure 5** Multivariable logistic regression analysis for the loss of response in hepatic steatosis and fibrosis at 48 weeks among MASLD patients without (A) or with (B) weight loss of  $\geq 5.0\%$  at 0–24 weeks and among those without (C) or with (D) insulin resistance at baseline, respectively. MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; LFC, liver fat content; 24w, 24 weeks; 95% CI, 95% confidence interval; FFA, free fatty acid; TBA, total bile acid; FBG, fasting blood glucose; LSM, liver stiffness measurement; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WC, waist circumference; ALT, alanine aminotransferase; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; FINS, fasting insulin; ALP, alkaline phosphatase.

### Predictors of loss of response in hepatic fibrosis

Univariate analysis of patients with 24-week LSM response showed that the baseline WC and FFA, 24-week TBA and  $\Delta\%TBA_{\text{baseline-24w}}$  were significantly associated with the loss of LSM response. Further multivariable analysis demonstrated that 24-week serum TBA levels (OR: 1.41, 95% CI: 1.04–1.92,  $P=0.03$ ) and  $\Delta\%TBA_{\text{baseline-24w}}$  10% category (OR: 0.84, 95% CI: 0.75–0.95,  $P=0.006$ ) were the independent risk factors for the loss of response in hepatic fibrosis (Table 2). As presented in Figure 4D, different longitudinal TBA patterns affected the evolution of LSM, and subjects with high TBA levels at 24 weeks ( $\geq 4.1 \mu\text{mol/L}$ ) tended to lose response to liver fibrosis.

Furthermore, subgroup analyses were conducted and baseline characteristics are detailed in Tables S6–S8. After subgrouping by weight loss  $\geq 5\%$  at 0–24 weeks, multivariable analysis only found that  $\Delta\%LSM_{\text{baseline-24w}}$  10% category (OR: 0.47, 95% CI: 0.23–0.99,  $P=0.04$ ) was significant in predicting the loss of LSM response among the individuals with weight loss of  $<5\%$  (Figure 5A). After stratifying by baseline IR status, multivariable logistic regression model showed that 24-week TBA (OR: 1.95, 95% CI: 1.03–3.68,  $P=0.04$ ) and  $\Delta\%TBA_{\text{baseline-24w}}$  10% category (OR: 0.81, 95% CI: 0.67–0.98,  $P=0.03$ ) were risk factors for the loss of LSM response in the individuals without IR at baseline (Figure 5C), while only 24-week FFA 100-mmol/L category (OR: 3.84, 95% CI: 1.19–12.35,  $P=0.02$ ) was a risk factor in those with IR at baseline (Figure 5D). A subgroup analysis of male patients showed that FBG at baseline (OR: 3.45, 95% CI: 1.20–9.91,  $P=0.02$ ) and  $\Delta\%TBA_{\text{baseline-24w}}$  10% category (OR: 0.86, 95% CI: 0.76–0.97,  $P<0.001$ ) were significant predictors of hepatic fibrosis fluctuations (Figure S2A). However, no statistically significant variables were identified in the univariate logistic regression analysis for female patients, and therefore multivariable analysis was not conducted.

### Association between MRI-PDFF response and LSM response

The relationship of MRI-PDFF response with LSM response was examined. At 24 weeks, individuals with MRI-PDFF response showed a higher proportion of LSM response compared to those with MRI-PDFF nonresponse (50.0% vs. 35.6%,  $P=0.03$ , Figure S3A). Additionally, a relative decline in LFC of  $\geq 30\%$  at 24 weeks was significantly associated with a decline in LSM of

$\geq 1$  stage in a multivariable logistic regression model controlling for age and gender, with an OR of 1.92 (95% CI: 1.11–3.31,  $P=0.02$ , Figure S3B). However, at 48 weeks, there was no difference in the rate of loss of LSM response between MASLD patients with and without loss of MRI-PDFF response (15.8% vs. 13.6%,  $P=0.81$ , Figure S3C). Furthermore, loss of MRI-PDFF response at 48 weeks was not found to be a risk factor for the loss of LSM response (OR: 1.20, 95% CI: 0.28–5.05,  $P=0.81$ , Table 2, Figure S3D).

### Discussion

Utilizing a large prospective longitudinal cohort of 602 MASLD patients receiving treatment with paired MRI-PDFF and 2D-SWE estimations, we observed that after another 24 weeks from the 24-week time point of baseline, the incidence of secondary loss of response to hepatic steatosis and fibrosis was 29.4% and 15.9%, respectively. Additionally, persistent IR, lack of regular exercise and caloric restriction after 24 weeks, and lower  $\Delta\%LFC_{\text{baseline-24w}}$  were noted for the incidences of loss of response in hepatic steatosis, while higher TBA levels and lower  $\Delta\%TBA_{\text{baseline-24w}}$  were associated with increasing failure of sustained response in hepatic fibrosis. Thus, our findings indicated that MASLD patients would experience sustained benefits to their liver improvements by lessening IR, lowering TBA levels and modifying lifestyle.

This is the first study to utilize the loss of sustained MRI-PDFF response as an end-point in MASLD. According to a review summarizing 52 weeks of line in MASLD, only approximately 9–12% of patients achieved weight loss over 5% to target and experienced histologic benefit (30). As a chronic disease, relying on long-term weight loss management has become the major obstacle in its therapy, mainly because there remains no specific pharmacology available. A few impactors of loss of response in steatosis were identified in our observations. Similar to correctional study demonstrating that IR was independently associated with steatosis grades (31), our findings suggested that residual IR might induce subsequent steatosis progression, especially in MASLD patients with unsuccessful weight loss. However, this conclusion should be interpreted with caution since the IR measurements did not adopt the gold standard of the glucose clamp technique in this study. Notably, IR is characterized by insensitively of target organs such as muscle, liver or adiposity to insulin and compensated high insulinemia, the latter of which could both directly activate *de novo* fatty acid generation and indirectly fat mass lipolysis, inducing overaccumulation of intrahepatic fat (31).

Altered enterohepatic circulation of bile acid has been recognized as a marker of liver damage. TBA levels and compositions can be affected by either one of the changes in the synthetic, transported, secretory or reabsorption abilities of the liver (32). Serum bile acids are derived from TBA pool that leak from the bile or intestinal tract into the circulation. High concentrations of TBA can bind to several receptors among hepatocytes, macrophages, ileal enterocytes, and hepatic stellate cells, such as farnesoid X receptor, protein-coupled receptor 5, vitamin D receptor and sphingosine 1-phosphate receptor 2 (S1PR2) (33). The binding of bile acid to S1PR2 can exacerbate liver fibrosis severity by activating the extracellular signal-regulated protein kinase 1/2 (ERK1/2) signaling pathway. Moreover, bile acids are directly involved in disrupting the cell membrane by activating the p38 MAPK, nuclear factor-kappaB (NF- $\kappa$ B), and phospholipase A2 pathways, generating much more toxic reactive oxygen species and therefore inducing liver fibrosis. In agreement with previous molecular mechanisms, elevated TBA has been found to be a marker of liver fibrosis progression among patients with chronic liver diseases (34). In a clinical study with 328 patients with chronic hepatitis B infection, TBA presented significant positive correlations with biopsy-proven significant fibrosis stage ( $r=0.38$ ,  $P<0.001$ ) (35). Similarly, a recent study also reported a dose-dependent relationship between lesions of steatosis-related fibrosis status confirmed by histology and serum TBA levels determined by liquid chromatograph-mass spectrometer (36). Our results additionally highlighted the potential role of monitoring dynamic changes in TBA for predicting fibrosis progression.

Regarding the association between changes in hepatic steatosis and fibrosis, the current study proved a significant association between steatosis improvement and fibrosis regression at 24 weeks in MASLD patients, which was in accordance with previous studies (37,38). Significantly, this study is the first to further explore the association between the loss of sustained steatosis response by MRI-PDFF and the loss of sustained fibrosis response by 2D-SWE. However, we were not able to identify significant association at 48 weeks. Although previously underappreciated, this phenomenon may be attributed to that resolution and progression of hepatic steatosis and fibrosis represent a complex interplay of genetic, environmental, and intrinsic microbial factors (39). Previous researches have revealed that the majority (approximately 80%) of MASLD patients experienced gradual fibrosis progression over time, and simple steatosis typically experienced 1 stage of fibrosis

progression over an average of 14.3 years (40). And the number of MASLD patients with LSM  $\geq 6.4$  kpa who completed the 48-week follow-up was too small in this study to draw meaningful conclusions regarding fibrosis regression. Therefore, further investigations are warranted to explore this relationship in studies with larger sample sizes and longer follow-up.

This study has several strengths. Our results were obtained from a well-established prospective cohort with MRI-PDFF and SWE regular monitoring, first exploring the phenomenon of loss of response in MASLD long-term management. To identify predictors of loss of response, we also documented data on daily dietary habits and exercise, which can further help to classify potential confounders. Several limitations also exist in the current research. Inflammatory mediators, including interleukin levels, lack measurements. The other liver injury lesions, such as ballooning, were not included in this analysis. Part of the natural regression of steatosis was not distinguished from the lost response. The relatively small sample size and limited number of events per variable constrain the statistical power of the logistic regression analysis and the robustness of the findings (41), particularly in the assessment of subgroup liver fibrosis efficacy. Moreover, the excellent AUC values are based on separation between mild, significant, advanced fibrosis, the relevance of change of SWE is not validated so any claims regarding this must be done with great caution and those with such a significant change in fibrosis stage based on SWE during a short study should be interpreted with the greatest of caution and need more validation. Although our subjects were included in the largest tertiary center in southern China, the generalizability would inevitably be attenuated.

## Conclusions

The gap between therapeutic needs and outcomes for MASLD continues to expand because no effective pharmacology interventions have been widely approved. Current guidelines/consensuses provide unmet instruction to clinicians for treating patients with loss of response. The current analysis indicates that patients who achieve an MRI-PDFF response but with IR should undergo intensive lifestyle interventions, as monitoring TBA levels and lowering it may benefit from delaying fibrosis progression. As MASLD comprises a heterogeneous pathology mechanism (42), precise treatment or treatment of multiple targets remains necessary.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://hbsn.amegroupp.com/article/view/10.21037/hbsn-23-393/rc>

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://hbsn.amegroupp.com/article/view/10.21037/hbsn-23-393/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of The First Affiliated Hospital, Sun Yat-sen University [[2014]112]. All participants provided signed informed consent prior to enrollment.

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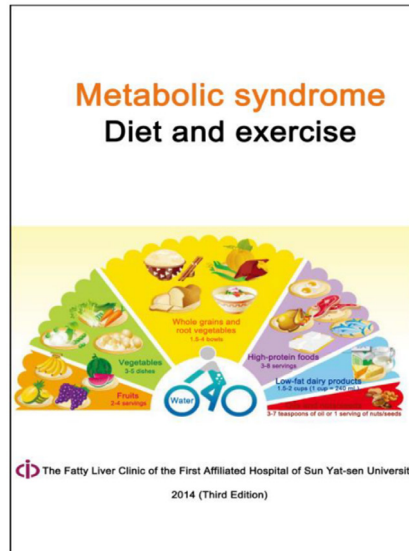
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A

An easy-to-carry brochure with personalized dietary and exercise advice



B

Recipes examples

**1200 kcal recipe:**

Suitable for those who need 1200-1300 kcal daily. Use 15 grams of cooking oil (1.5 tablespoons) and 6 grams of salt (3 grams for hypertensive patients, 2 grams for hypertensive patients with diabetes) throughout the day.

Breakfast (Choose any one)	
1	Low-fat milk/soy milk (1 cup/250ml), boiled egg (1) Soda cracker (5 pieces)
2	Low-fat milk/soy milk (1 cup/250ml), boiled egg (1) Steamed bun (1), fresh tomato (1)
3	Low-fat milk/soy milk (1 cup/250ml), boiled egg (1) Vegetable salad (1 small bowl), savory bread (2 pieces)
Lunch (Choose any one)	
1	Rice (1 small bowl/100g) Tir-fried shredded vegetables (100g green bell pepper, 100g jute stem, 50g pork) Mushroom and tofu soup (50g mushrooms, 50g tofu) Rice (1 small bowl/100g)
2	Stir-fried bottle gourd with scrambled eggs (80g bottle gourd, 50g eggs) Fish ball and cabbage soup (50g fish meat, 200g cabbage)
3	Noodles (1 small bowl/100g)
Afternoon snacks (Choose any one)	
	Cold mixed bitter melon (100g bitter melon) Radish stewed beef (50g carrots, 50g beef)
Dinner (Choose any one)	
1	Rice (1 small bowl / 100g) Stir-fried zucchini with shredded chicken (60g zucchini, 50g shredded chicken) Minced pork with mustard bean curd (lean pork 25g, mustard mustard 50g, tofu 100g)
2	Rice (1 small bowl / 100g) Cauliflower sliced Pork (100g cauliflower, 50g lean pork) Shredded kelp mixed (50g wet kelp)
3	Steamed bun (1) Spare ribs with Kelp (wet kelp 100g, spare ribs 50g) Stir-fried spinach (spinach 100g)
Dessert after dinner (Choose any one)	
	Pear (1 small), pomelo (2-3 slices), strawberries (4-5 pieces)

**1500 kcal recipe:**

Suitable for those who need 1500-1600 kcal daily. Use 15 grams of cooking oil (1.5 tablespoons) and 6 grams of salt (3 grams for hypertensive patients, 2 grams for hypertensive patients with diabetes) throughout the day.

Breakfast (Choose any one)	
1	Low-fat milk/soy milk (250ml), boiled egg (1), steamed twisted roll (1)
2	Low-fat milk/soy milk (250ml), boiled egg (1), steamed bun (1)
3	Low-fat milk/soy milk (250ml), boiled egg (1), Sugar-free rice cake (1)
Lunch (Choose any one)	
1	Rice (1 small bowl/100g) Stir-fried pork slices with zucchini (50g lean pork, 100g zucchini) Stir-fried baby bok choy with shiitake mushrooms (5g shiitake mushrooms, 150g baby bok choy) Dried shrimp and seaweed soup (5g dried shrimp, 2g seaweed, 25g cucumber)
2	Rice (1 small bowl/100g) Poached chicken (100g) Spinach soup (50g spinach, 2g seaweed)
3	Pastry (1 sheet) Kaiyang bean sprouts (Mung bean sprouts 100g, Kaiyang 5-6) Meatballs (Lean pork 100g) Tomato and egg soup (1 tomato, 1 egg)
Afternoon snacks (Choose any one)	
	Oranges (1), watermelon (1-2 pieces), strawberries (4-5 pieces)
Dinner (Choose any one)	
1	Rice (1 small bowl / 100g) Lettuce in onion oil (150g lettuce) Minced pork with tofu (lean pork 25g, tofu 50g)
2	Rice (1 small bowl / 100g) Mixed bitter melon (100g) Celery and shredded pork (150g celery, 50g lean pork) Green vegetable Soup (150g green vegetable)
3	Steamed bun (1) Fried White Melon with plain (White melon 150g) Shredded pork with salted vegetable (25g lean pork, 50g potherb mustard) Ham and winter melon soup (150g winter melon, several slices of ham)
Dessert after dinner (Choose any one)	
	Green apple (1), pear (1), strawberry (4-5)

**1700 kcal recipe**

Suitable for those who need 1700-1800 kcal daily. Use 25 grams of cooking oil (2.5 tablespoons) and 6 grams of salt (3 grams for hypertensive patients, 2 grams for hypertensive patients with diabetes) throughout the day.

Breakfast (Choose any one)	
1	Low-fat milk/soy milk (250ml), boiled egg (1), steamed twisted roll (1)
2	Low-fat milk/soy milk (1 cup /250ml), steamed bun (1 piece), meat floss (1 small dish)
3	Low fat milk/soy milk (1 cup /250ml), boiled egg (1), salted bread (2 slices), mixed cucumber (half)
Lunch (Choose any one)	
1	Rice (1 bowl / 150g) Seaweed salad (100g wet seaweed) Sliced cauliflower (50g lean pork, 100g cauliflower) Loofah Egg Soup (50g loofah, 50g egg)
2	Rice (1 bowl / 150g) Spare ribs with kelp (100g spare ribs, 100g wet kelp) Stir-fried cabbage with plain (cabbage 200g)
3	Scallion cake (standard flour 100g) Stir-fried three shreds (lean pork 50g, green pepper 100g, water stem 100g) Mixed radish and jellyfish (radish 100g, jellyfish 50g) Prawn skin and seaweed soup (50g prawn skin, 2g seaweed)
Afternoon snacks (Choose any one)	
	Peach (1), apple (1), pear (1)
Dinner (Choose any one)	
1	Rice (1 bowl / 150g) Ham and winter melon (slices of ham, 150g winter melon) Mushroom tofu (50g mushroom, 100g tofu)
2	Pastry (1 sheet) Fried pork slices with water gluten (100g water gluten, 50g lean pork) Mixed Mung bean sprouts (100g mung bean sprouts) Pickled mustard Soup (15g)
3	Steamed bun (1) Spinach balls (lean pork 100g, spinach 150g) Cowpea with garlic sauce (Cowpea 150g)
Dessert after dinner (Choose any one)	
	Strawberries (4-5), oranges (1), pears (1)

Figure S1 Dietary management.

**Table S1** Principles of intensified lifestyle intervention plan

Principle	Amount
Dietary changes	
Limit calorie intake	
Energy (kJ/day)	1,067
Protein (34.3%) (g/day)	22.9
Fat (22.2%) (g/day)	6.6
Carbohydrate (38.1%) (g/day)	25.4
Increase intake of fiber-rich foods (g/day)	40–45
Include seasonal greens and fruits (g/day)	>600
Include sea fish (g/week)	200
Limit the amount of sodium (g/day)	<6.0
Limit processed food items	–
Ad libitum intake of water and tea is allowed	–
Alcohol is discouraged throughout the intervention period	–
Increase physical activity	
Increase duration of physical activity (minutes/weeks)	150–240
Training modality (aerobic and/or resistance training)	Decided by the trainers
Encourage 10,000 steps per day	–
Avoid sedentary behaviour	–
Increase sleep duration (hours/night)	7–8

**Table S2** Baseline characteristics of MASLD patients stratified by MRI-PDFF response or LSM response status at 24 weeks

Characteristics	Liver steatosis				Liver fibrosis			
	Total <sup>†</sup> (n=602)	MRI-PDFF response at 24 weeks (n=340)	MRI-PDFF nonresponse at 24 weeks (n=249)	P	Total <sup>‡</sup> (n=265)	LSM response at 24 weeks (n=118)	LSM nonresponse at 24 weeks (n=143)	P
Age (years)	41.1±13.6	41.6±13.9	40.1±13.2	0.19	44.7±13.1	41.7±11.9	47.1±13.6	0.001
Male	441 (73.3)	245 (72.1)	188 (75.5)	0.35	184 (69.4)	87 (73.7)	95 (66.4)	0.20
Weight (kg)	76.6±12.2	76.8±11.8	76.6±12.6	0.79	77.7±12.9	77.6±11.9	78.0±13.6	0.77
BMI (kg/m <sup>2</sup> )	27.4±3.4	27.7±3.4	27.2±3.5	0.17	28.5±3.5	28.2±3.3	28.7±3.5	0.22
WC (cm)	91.3±8.3	91.8±8.1	91.0±8.5	0.27	93.4±8.3	93.0±7.6	94.0±8.8	0.31
Waist-hip ratio	0.90±0.05	0.90±0.05	0.90±0.05	0.50	0.91±0.04	0.91±0.05	0.92±0.04	0.50
CHOL (mmol/L)	5.04±1.05	5.11±1.11	4.96±0.97	0.09	5.03±1.14	5.08±0.93	4.98±1.28	0.45
TG (mmol/L)	1.62 (1.14, 2.21)	1.66 (1.18, 2.27)	1.61 (1.07, 2.18)	0.14	1.65 (1.20, 2.27)	1.68 (1.33, 2.20)	1.63 (1.14, 2.38)	0.98
HDL-C (mmol/L)	1.16±0.29	1.15±0.29	1.18±0.30	0.14	1.12±0.26	1.10±0.23	1.13±0.29	0.26
LDL-C (mmol/L)	3.17±0.77	3.23±0.81	3.10±0.71	0.05	3.18±0.83	3.29±0.72	3.08±0.90	0.045
FFA (mmol/L)	521 (422, 681)	539 (438, 717)	497 (412, 618)	0.01	553 (440, 735)	520 (426, 671)	587 (469, 756)	0.005
FBG (mmol/L)	4.9 (4.6, 5.5)	5.0 (4.6, 5.7)	4.9 (4.5, 5.3)	0.09	5.0 (4.7, 6.0)	5.0 (4.7, 6.1)	5.1 (4.7, 6.0)	0.75
FINS (μU/mL)	10.8 (7.9, 14.8)	11.0 (8.5, 15.2)	10.4 (7.5, 14.7)	0.09	11.2 (8.9, 16.1)	12.6 (9.8, 20.1)	11.0 (8.0, 14.6)	0.009
HOMA-IR	2.46 (1.75, 3.60)	2.65 (1.81, 3.70)	2.30 (1.69, 3.50)	0.03	2.69 (1.93, 4.02)	2.78 (2.20, 4.65)	2.66 (1.77, 3.63)	0.03
UA (μmol/L)	427.7±102.4	432.5±103.0	420.8±100.8	0.18	418.7±94.5	410.3±98.6	424.4±90.4	0.23
ALT (U/L)	45.5 (28.0, 75.0)	50.0 (32.0, 82.0)	36.5 (25.0, 63.8)	<0.001	39.0 (27.0, 74.5)	40.0 (30.8, 81.8)	35.0 (24.0, 70.0)	0.08
AST (U/L)	33.0 (24.0, 48.0)	36.0 (26.0, 54.0)	30.0 (22.0, 42.0)	<0.001	33.0 (23.0, 50.5)	36.5 (23.0, 59.0)	29.0 (23.0, 47.0)	0.06
GGT (U/L)	44.0 (28.8, 72.0)	47.0 (30.0, 72.0)	40.0 (26.0, 62.5)	0.03	42.0 (27.0, 63.0)	42.0 (30.0, 61.0)	41.0 (23.0, 63.8)	0.41
ALP (U/L)	78.0 (67.0, 89.0)	78.0 (67.0, 91.0)	76.0 (64.8, 88.0)	0.17	78.0 (66.0, 90.0)	78.0 (67.0, 92.0)	76.0 (62.0, 89.0)	0.09
Albumin (g/L)	45.9±3.1	45.9±3.2	46.0±3.0	0.69	45.3±3.4	45.7±2.9	45.0±3.7	0.10
TB (μmol/L)	12.7 (10.1, 16.2)	12.7 (10.2, 16.3)	12.7 (10.0, 16.2)	0.64	12.8 (10.4, 16.1)	12.3 (10.3, 16.9)	13.2 (10.5, 15.7)	0.57
TBA (μmol/L)	2.7 (1.8, 4.2)	2.6 (1.8, 4.1)	3.0 (1.8, 4.3)	0.43	2.7 (2.0, 4.5)	2.7 (2.0, 4.1)	2.7 (1.8, 5.5)	0.95
LFC (%)	14.4 (10.0, 22.4)	17.1 (11.7, 25.0)	11.7 (8.0, 18.7)	<0.001	14.3 (9.5, 22.0)	18.9 (11.3, 24.3)	11.9 (9.0, 18.0)	<0.001
LSM (kpa)	6.3 (5.4, 7.9)	6.7 (5.6, 8.0)	6.0 (5.3, 7.8)	0.006	7.9 (7.2, 9.1)	8.0 (7.6, 9.6)	7.8 (6.9, 8.8)	0.06
Hypertension	158 (26.3)	95 (27.9)	62 (24.9)	0.43	82 (30.9)	34 (28.8)	47 (32.9)	0.46
Diabetes mellitus	95 (15.8)	63 (18.5)	32 (12.9)	0.09	58 (21.9)	14 (11.9)	44 (30.8)	<0.001
Smoking	63 (10.5)	30 (8.8)	31 (12.4)	0.16	17 (6.4)	7 (5.9)	9 (6.3)	0.86
Regular exercise <sup>§</sup>	470 (78.1)	297 (87.4)	162 (65.1)	<0.001	213 (80.4)	98 (83.1)	111 (77.6)	0.36
Caloric restriction <sup>§</sup>	319 (53.0)	220 (64.7)	95 (38.2)	<0.001	156 (58.9)	59 (50.0)	95 (66.4)	0.01
Lipid-lowering drug	201 (33.4)	113 (33.2)	86 (34.5)	0.76	110 (41.5)	46 (39.0)	63 (44.1)	0.45
Hypoglycemic drug	47 (7.8)	33 (9.7)	13 (5.22)	0.048	29 (10.9)	6 (5.1)	23 (16.1)	0.005
Uric-acid-lowering drug	76 (12.6)	50 (14.7)	24 (9.6)	0.07	39 (14.7)	19 (16.1)	19 (13.3)	0.53
Intensified lifestyle intervention	164 (27.2)	94 (27.6)	68 (27.3)	0.96	92 (34.7)	37 (31.4)	55 (38.5)	0.26

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). <sup>†</sup>, 602 MASLD patients included in the efficacy analysis for hepatic steatosis; <sup>‡</sup>, 265 MASLD patients who had fibrosis stage ≥1 at baseline included in the efficacy analysis for hepatic fibrosis; <sup>§</sup>, the lifestyle status at 0–24 weeks after enrollment. Caloric restriction was defined as a reduction in energy (caloric) intake of 500–1,000 kcal/day from baseline; Regular exercise was defined as moderate-to-vigorous physical activity at least once a week. MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.

**Table S3** Baseline characteristics of MASLD patients who stayed in the cohort and those who were lost to follow-up

Characteristics	Liver steatosis				Liver fibrosis			
	Analyzable participants (n=303)	Lost to follow-up at 0–24 weeks (n=13)	Lost to follow-up at 24–48 weeks (n=37)	P	Analyzable participants (n=107)	Lost to follow-up at 0–24 weeks (n=4)	Lost to follow-up at 24–48 weeks (n=11)	P
Age (years)	42.0±13.9	44.0±13.7	38.9±13.7	0.38	42.1±11.3	45.8±14.2	37.7±16.3	0.41
Male	221 (72.9)	8 (61.5)	24 (64.9)	0.43	77 (72.0)	2 (50.0)	10 (90.9)	0.20
Weight (kg)	76.7±11.6	70.1±12.1	78.4±14.0	0.10	77.1±11.2	68.0±14.6	81.6±17.5	0.41
BMI (kg/m <sup>2</sup> )	27.7±3.3	25.7±2.5	27.5±3.7	0.13	28.2±3.2	25.0±3.3	28.6±4.1	0.26
WC (cm)	91.7±8.0	85.4±6.6	92.0±8.7	0.02	92.8±7.6	85.3±7.5	94.8±7.9	0.10
Waist-hip ratio	0.90±0.05	0.87±0.04	0.90±0.04	0.05	0.91±0.05	0.88±0.04	0.90±0.03	0.28
CHOL (mmol/L)	5.08±1.08	4.84±1.09	5.42±1.33	0.19	5.04±0.91	5.30±1.57	5.50±1.05	0.29
TG (mmol/L)	1.68 (1.18, 2.27)	1.42 (0.92, 1.89)	1.39 (1.02, 2.41)	0.28	1.69 (1.32, 2.20)	1.69 (1.19, 2.11)	1.68 (1.50, 2.21)	0.88
HDL-C (mmol/L)	1.14±0.27	1.16±0.22	1.20±0.46	0.58	1.10±0.23	1.13±0.20	1.05±0.17	0.71
LDL-C (mmol/L)	3.20±0.80	3.08±0.76	3.48±0.92	0.17	3.25±0.70	3.49±1.05	3.60±0.83	0.28
FFA (mmol/L)	541 (438, 739)	605 (436, 857)	536 (456, 610)	0.53	508 (424, 691)	572 (416, 662)	542 (492, 544)	0.96
FBG (mmol/L)	5.0 (4.6, 5.7)	4.8 (4.7, 5.6)	4.7 (4.5, 5.5)	0.65	5.0 (4.6, 6.0)	4.8 (4.7, 6.3)	5.2 (5.0, 6.1)	0.60
FINS (μU/mL)	11.0 (8.5, 14.9)	9.3 (4.6, 13.1)	10.4 (6.0, 20.9)	0.08	12.8 (9.7, 19.9)	11.9 (6.0, 16.6)	10.4 (9.8, 30.2)	0.68
HOMA-IR	2.65 (1.85, 3.70)	1.89 (1.01, 3.14)	2.29 (1.41, 5.00)	0.15	2.80 (2.20, 4.40)	2.51 (1.27, 4.72)	2.65 (2.31, 5.64)	0.61
UA (μmol/L)	433.2±100.9	430.3±115.7	424.6±125.3	0.91	404.4±95.1	462.8±118.6	468.4±117.3	0.07
ALT (U/L)	50.0 (32.0, 83.0)	58.0 (42.0, 111.5)	57.5 (37.0, 77.0)	0.46	38.0 (30.0, 72.0)	111.5 (36.5, 125.8)	84.0 (62.0, 93.0)	0.04
AST (U/L)	36.0 (26.0, 56.0)	30.0 (25.0, 58.5)	37.0 (26.5, 42.5)	0.87	34.0 (22.0, 51.0)	58.5 (33.5, 82.8)	59.0 (36.0, 81.0)	0.049
GGT (U/L)	47.0 (30.0, 72.0)	51.0 (33.0, 185.5)	49.0 (28.0, 81.8)	0.55	40.5 (29.8, 61.0)	185.5 (60.0, 284.8)	48.0 (37.0, 58.0)	0.03
ALP (U/L)	78.0 (67.0, 91.0)	82.0 (74.0, 85.0)	80.0 (71.0, 89.0)	0.75	78.0 (67.0, 90.0)	84.0 (73.5, 126.0)	85.0 (76.8, 99.0)	0.28
Albumin (g/L)	45.9±3.2	45.9±3.2	44.9±4.3	0.17	45.6±2.9	45.7±2.9	47.1±2.5	0.15
TB (μmol/L)	12.7 (10.2, 16.2)	12.7 (10.0, 16.2)	12.9 (9.7, 19.2)	0.48	12.3 (10.0, 17.0)	12.9 (10.0, 16.0)	13.3 (11.1, 16.2)	0.45
TBA (μmol/L)	2.6 (1.8, 4.1)	3.0 (1.8, 4.3)	2.5 (2.0, 4.1)	0.96	2.7 (2.0, 4.1)	2.6 (1.8, 4.3)	4.1 (3.5, 4.5)	0.03
LFC (%)	17.5 (11.7, 25.5)	10.5 (7.2, 26.3)	16.1 (12.3, 22.0)	0.41	18.3 (11.3, 24.3)	14.3 (7.9, 28.6)	20.5 (12.4, 33.1)	0.40
LSM (kpa)	6.7 (5.6, 8.0)	5.5 (5.0, 7.4)	5.7 (4.8, 7.9)	0.03	8.0 (7.6, 9.6)	8.3 (7.1, 9.2)	8.0 (6.8, 10.3)	0.77
Hypertension	84 (27.7)	1 (7.7)	11 (29.7)	0.20	28 (26.2)	1 (25.0)	6 (54.5)	0.17
Diabetes mellitus	57 (18.8)	0 (0.0)	5 (13.5)	0.06	14 (13.1)	0 (0.0)	0 (0.0)	0.14
Smoking	26 (8.6)	2 (15.4)	4 (10.8)	0.73	4 (3.7)	1 (25.0)	3 (27.3)	0.02
Regular exercise <sup>†</sup>	265 (87.5)	–	31 (83.8)	0.71	87 (81.3)	–	9 (81.8)	1.00
Caloric restriction <sup>†</sup>	196 (64.8)	–	24 (64.9)	0.98	53 (49.5)	–	6 (54.5)	0.75
Lipid-lowering drug	102 (33.7)	2 (15.4)	10 (27.0)	0.28	40 (37.4)	1 (25.0)	6 (54.5)	0.47
Hypoglycemic drug	30 (9.9)	0 (0.0)	3 (8.1)	0.23	6 (5.6)	0 (0.0)	0 (0.0)	0.44
Uric-acid-lowering drug	45 (14.9)	2 (15.4)	5 (13.5)	0.99	14 (13.1)	1 (25.0)	5 (45.5)	0.047
Intensified lifestyle intervention	86 (28.4)	1 (7.7)	8 (21.6)	0.13	33 (30.8)	0 (0.0)	4 (36.4)	0.21

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). <sup>†</sup>, the lifestyle status at 0–24 weeks after enrollment. Caloric restriction was defined as a reduction in energy (caloric) intake of 500–1,000 kcal/day from baseline; regular exercise was defined as moderate-to-vigorous physical activity at least once a week. BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,  $\gamma$ -glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content; LSM, liver stiffness measurement.

**Table S4** Comparison of changes in outcome values between MASLD patients with and without MRI-PDFF response at 48 weeks

Characteristics	Sustained MRI-PDFF response (n=214)		Loss of MRI-PDFF response (n=89)		P value			
	ΔBaseline-24w [1]	ΔBaseline-48w [2]	ΔBaseline-24w [3]	ΔBaseline-48w [4]	[1] vs. [2]	[3] vs. [4]	[1] vs. [3]	[2] vs. [4]
Weight (kg)	3.69±3.81	3.97± 4.97	3.95±3.48	1.78±3.37	0.52	<0.001	0.59	<0.001
BMI (kg/m <sup>2</sup> )	1.34±1.38	1.44±1.76	1.41±1.26	0.66±1.24	0.52	<0.001	0.69	<0.001
WC (cm)	3.32±4.50	3.39±5.24	4.16±4.79	1.80±5.27	0.88	0.003	0.16	0.02
Waist-hip ratio	0.01±0.04	0.01±0.04	0.02±0.04	0.01±0.04	0.46	0.48	0.12	0.28
CHOL (mmol/L)	0.53±1.02	0.41±1.11	0.37±1.03	0.04±1.24	0.23	0.052	0.23	0.01
TG (mmol/L)	0.23 (−0.08, 0.75)	0.20 (−0.16, 0.77)	0.09 (−0.13, 0.72)	0.12 (−0.26, 0.53)	0.60	0.19	0.37	0.07
HDL-C (mmol/L)	−0.03±0.22	−0.05±0.18	−0.04±0.22	−0.05±0.27	0.24	0.75	0.75	0.93
LDL-C (mmol/L)	0.41±0.78	0.31±0.86	0.23±0.82	0.01±0.93	0.20	0.09	0.07	0.007
FFA (mmol/L)	29.0 (−64.0, 189.5)	32.0 (−58.0, 192.3)	125.0 (−6.0, 207.0)	28.5 (−50.0, 153.3)	0.44	0.04	0.09	0.44
FBG (mmol/L)	0.20 (−0.23, 0.60)	0.00 (−0.40, 0.40)	0.10 (−0.10, 0.60)	0.00 (−0.59, 0.60)	0.03	0.03	0.51	0.70
FINS (μU/mL)	1.93 (−0.17, 4.72)	2.36 (0.00, 5.17)	1.54 (−0.61, 5.24)	0.19 (−1.85, 3.71)	0.35	0.11	0.55	0.001
HOMA-IR	0.50 (−0.09, 1.22)	0.56 (−0.08, 1.35)	0.48 (−0.21, 1.49)	0.11 (−0.64, 1.04)	0.68	0.06	0.96	0.01
UA (μmol/L)	34.58±104.84	21.49±103.39	33.84±124.92	−11.58±122.91	0.19	0.02	0.96	0.02
ALT (U/L)	15.50 (2.00, 45.25)	15.00 (2.00, 47.25)	21.00 (1.00, 59.00)	5.00 (−7.00, 29.00)	0.98	<0.001	0.47	<0.001
AST (U/L)	10.00 (1.00, 26.00)	9.00 (1.00, 28.00)	10.00 (1.00, 29.00)	3.00 (−2.00, 13.50)	0.67	0.004	0.59	0.002
GGT (U/L)	13.00 (3.00, 35.00)	12.50 (3.00, 37.75)	11.50 (1.25, 30.50)	6.50 (−2.25, 17.00)	0.90	0.009	0.53	0.001
ALP (U/L)	3.00 (−4.00, 10.00)	4.00 (−3.00, 13.00)	2.00 (−3.75, 9.75)	3.00 (−3.00, 7.75)	0.11	0.92	0.88	0.20
Albumin (g/L)	−0.03±2.74	0.28±2.81	−0.26±2.91	0.46±2.59	0.27	0.10	0.52	0.62
TB (μmol/L)	−0.30 (−2.30, 2.30)	−0.45 (−2.60, 2.48)	0.80 (−1.80, 3.00)	−0.10 (−2.10, 1.45)	0.68	0.06	0.09	0.84
TBA (μmol/L)	0.00 (−0.90, 1.10)	0.20 (−0.50, 1.18)	−0.05 (−1.00, 0.58)	0.20 (−0.55, 1.75)	0.30	0.07	0.35	0.52
LFC (%)	8.17 (5.02, 13.84)	9.28 (5.52, 13.04)	6.20 (4.63, 12.22)	1.23 (−0.69, 4.31)	0.40	<0.001	0.054	<0.001
LSM (kpa)	0.60 (0.10, 1.80)	1.00 (0.20, 2.60)	0.70 (0.10, 1.80)	0.70 (−0.50, 1.10)	0.03	0.10	0.58	0.001
Regular exercise	190 (88.8)	189 (88.3)	75 (84.3)	63 (70.8)	0.97	0.06	0.36	0.002
Caloric restriction	142 (66.4)	127 (59.3)	54 (60.7)	29 (32.6)	0.20	0.001	0.40	<0.001
Lipid-lowering drug	69 (32.2)	73 (34.1)	33 (37.1)	21 (23.6)	0.71	0.06	0.43	0.08
Hypoglycemic drug	19 (8.9)	23 (9.8)	11 (12.4)	8 (9.0)	0.56	0.43	0.33	0.67
Uric acid lowering drug	26 (12.1)	28 (13.1)	19 (21.3)	19 (21.3)	0.83	0.92	0.06	0.06
Intensified lifestyle intervention	60 (28.0)	69 (32.2)	26 (29.2)	29 (32.6)	0.35	0.58	0.87	0.90

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; 24w, 24 weeks; 48w, 48 weeks; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content; LSM, liver stiffness measurement.

**Table S5** Comparison of changes in outcome values between MASLD patients without and with LSM response at 48 weeks

Characteristics	Sustained LSM response (n=90)		Loss of LSM response (n=17)		P value			
	ΔBaseline-24w [1]	ΔBaseline-48w [2]	ΔBaseline-24w [3]	ΔBaseline-48w [4]	[1] vs. [2]	[3] vs. [4]	[1] vs. [3]	[2] vs. [4]
Weight (kg)	3.62±3.72	3.57±4.35	4.85±7.48	3.45±6.82	0.94	0.59	0.51	0.95
BMI (kg/m <sup>2</sup> )	1.35±1.39	1.31±1.53	1.79±2.78	1.39±2.58	0.86	0.68	0.53	0.91
WC (cm)	2.53±4.11	2.75±4.61	4.24±7.44	4.42±8.00	0.74	0.95	0.37	0.48
Waist-hip ratio	0.00±0.03	0.00±0.03	0.02±0.05	0.03±0.07	0.90	0.67	0.36	0.29
CHOL (mmol/L)	0.43±0.99	0.24±1.12	0.09±1.10	0.38±0.92	0.23	0.40	0.20	0.62
TG (mmol/L)	0.21 (-0.14, 0.61)	0.10 (-0.20, 0.58)	-0.12 (-0.30, 0.34)	0.10 (-0.28, 0.97)	0.47	0.47	0.20	0.78
HDL-C (mmol/L)	0.00±0.18	-0.00±0.18	-0.02±0.12	-0.00±0.17	0.75	0.71	0.57	0.96
LDL-C (mmol/L)	0.35±0.77	0.21±0.86	0.12±0.67	0.25±0.64	0.27	0.57	0.25	0.88
FFA (mmol/L)	70.5 (-59.8, 170.0)	16.0 (-65.0, 146.0)	141.0 (-322.0, 354.0)	186.0 (77.5, 414.0)	0.49	0.16	0.76	0.002
FBG (mmol/L)	0.20 (-0.30, 0.50)	0.00 (-0.60, 0.60)	0.20 (-0.10, 1.30)	0.30 (-0.23, 1.20)	0.42	0.74	0.36	0.33
FINS (μU/mL)	2.63 (-0.41, 7.40)	2.72 (-0.27, 6.85)	2.88 (-0.37, 4.82)	1.65 (-1.57, 5.88)	0.99	0.58	0.75	0.26
HOMA-IR	0.65 (-0.11, 1.95)	0.71 (-0.14, 2.02)	0.86 (0.23, 1.97)	0.33 (-0.37, 1.48)	0.99	0.17	0.71	0.28
UA (μmol/L)	13.00±97.39	-3.67±112.02	15.00±78.04	-11.25±147.96	0.29	0.53	0.94	0.81
ALT (U/L)	9.00 (1.00, 44.00)	10.00 (0.50, 33.00)	10.00 (4.25, 80.00)	2.00 (-9.25, 65.75)	0.60	0.33	0.71	0.54
AST (U/L)	7.50 (3.00, 20.75)	6.00 (1.00, 22.50)	4.00 (0.00, 40.00)	5.00 (-3.25, 35.00)	0.44	0.68	0.42	0.42
GGT (U/L)	9.00 (2.00, 26.00)	7.50 (-1.00, 25.75)	8.00 (-1.00, 39.00)	9.50 (-1.75, 44.75)	0.27	0.90	0.70	0.68
ALP (U/L)	6.00 (-2.25, 11.25)	6.00 (-3.50, 13.00)	-7.00 (-10.00, 7.00)	-0.50 (-2.75, 6.75)	0.82	0.31	0.03	0.22
Albumin (g/L)	-0.46±2.97	0.43±2.27	0.28±3.51	0.77±2.87	0.03	0.68	0.37	0.62
TB (μmol/L)	-0.40 (-2.33, 2.13)	-0.60 (-3.35, 2.03)	2.75 (-1.08, 4.08)	-0.10 (-5.10, 9.00)	0.37	0.45	0.04	0.51
TBA (μmol/L)	0.55 (-0.20, 1.40)	0.70 (-0.20, 1.50)	-1.30 (-3.90, 0.40)	0.00 (-7.20, 3.30)	0.57	0.58	0.002	0.40
LFC (%)	5.97 (2.90, 13.26)	6.32 (2.88, 11.91)	4.72 (-1.51, 14.59)	4.72 (-2.56, 17.56)	0.97	0.97	0.42	0.73
LSM (kpa)	2.00 (1.18, 3.20)	2.35 (1.10, 3.10)	1.00 (0.55, 2.30)	-0.10 (-0.35, 0.08)	0.31	<0.001	0.04	<0.001
Regular exercise	74 (82.2)	79 (87.8)	13 (76.5)	14 (82.4)	0.41	1.00	1.00	0.98
Caloric restriction	48 (53.3)	41 (45.6)	5 (29.4)	3 (17.6)	0.32	0.80	0.09	0.13
Lipid-lowering drug	34 (37.8)	30 (33.3)	6 (35.3)	5 (29.4)	0.50	0.71	0.82	0.75
Hypoglycemic drug	6 (6.7)	7 (7.8)	0 (0.0)	0 (0.0)	0.79	-	0.59	0.51
Uric acid lowering drug	10 (11.1)	11 (12.2)	4 (23.5)	4 (23.5)	0.84	1.00	0.33	0.40
Intensified lifestyle intervention	31 (34.4)	25 (27.8)	2 (11.8)	4 (23.5)	0.31	0.65	0.06	0.95

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). MASLD, metabolic dysfunction-associated steatotic liver disease; LSM, liver stiffness measurement; 24w, 24 weeks; 48w, 48 weeks; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.



**Table S6** Subgroup baseline characteristics of MASLD patients with treatment response at 24 weeks, stratified by weight loss status

Characteristics	With MRI-PDFF response at 24 weeks (n=303)			With LSM response at 24 weeks (n=107)		
	Weight loss of <5.0% (n=169)	Weight loss of ≥5.0% (n=134)	P	Weight loss of <5.0% (n=59)	Weight loss of ≥5.0% (n=48)	P
Age (years)	43.8±14.7	39.6±12.7	0.009	43.9±11.5	39.9±10.9	0.07
Male	122 (72.2)	99 (73.9)	0.73	46 (78.0)	31 (64.6)	0.13
Weight (kg)	75.4±11.3	78.4±11.8	0.03	75.9±9.9	78.7±12.5	0.19
BMI (kg/m <sup>2</sup> )	27.2±3.3	28.2±3.4	0.02	27.5±2.9	29.0±3.4	0.02
WC (cm)	91.1±7.5	92.5±8.6	0.14	92.3±6.4	93.4±8.8	0.46
Waist-hip ratio	0.90±0.04	0.90±0.05	0.54	0.91±0.04	0.91±0.06	0.97
CHOL (mmol/L)	4.92±1.02	5.31±1.10	0.002	5.08±0.99	4.99±0.81	0.61
TG (mmol/L)	1.66 (1.22, 2.23)	1.71 (1.18, 2.34)	0.77	1.83 (1.48, 2.27)	1.39 (1.18, 1.85)	0.005
HDL-C (mmol/L)	1.17±0.31	1.11±0.22	0.06	1.12±0.26	1.08±0.18	0.42
LDL-C (mmol/L)	3.05±0.78	3.42±0.76	<0.001	3.25±0.73	3.26±0.67	0.97
FFA (mmol/L)	500 (435, 655)	587 (449, 774)	0.008	495 (413, 599)	545 (441, 698)	0.35
FBG (mmol/L)	4.9 (4.6, 5.7)	5.0 (4.6, 5.8)	0.33	4.9 (4.7, 5.7)	5.2 (4.6, 6.1)	0.35
FINS (μU/mL)	11.2 (8.5, 14.5)	10.8 (8.6, 16.3)	0.83	12.8 (10.3, 16.2)	12.0 (8.5, 22.8)	0.91
HOMA-IR	2.65 (1.91, 3.70)	2.69 (1.79, 3.86)	0.69	2.83 (2.26, 3.98)	2.78 (1.78, 5.63)	0.57
UA (μmol/L)	422.9±82.6	445.5±119.9	0.07	408.7±91.3	399.0±100.2	0.60
ALT (U/L)	49.0 (28.5, 74.0)	56.0 (36.0, 93.0)	0.04	35.0 (28.0, 64.5)	43.0 (33.5, 101.0)	0.03
AST (U/L)	32.0 (25.0, 56.0)	37.5 (28.5, 55.0)	0.22	27.0 (22.0, 47.5)	39.5 (27.5, 63.0)	0.01
GGT (U/L)	46.0 (29.0, 70.0)	51.0 (32.0, 76.0)	0.14	36.0 (27.0, 54.5)	51.0 (31.0, 76.0)	0.1
ALP (U/L)	77.0 (62.0, 92.5)	78.5 (70.0, 88.5)	0.54	77.0 (64.5, 97.0)	78.0 (70.0, 85.0)	0.65
Albumin (g/L)	45.8±3.1	46.2±3.1	0.29	45.8±2.6	45.4±3.3	0.56
TB (μmol/L)	12.2 (9.5, 15.2)	13.8 (11.3, 18.1)	<0.001	12.1 (9.6, 14.7)	12.9 (11.1, 18.1)	0.02
TBA (μmol/L)	2.8 (1.8, 4.8)	2.4 (1.8, 3.3)	0.01	3.1 (2.1, 4.5)	2.6 (2.0, 3.2)	0.15
LFC (%)	16.1 (11.7, 22.4)	18.7 (11.9, 26.7)	0.053	14.6 (10.7, 19.3)	20.7 (11.5, 26.9)	0.01
LSM (kpa)	6.5 (5.6, 8.3)	7.2 (5.6, 7.9)	0.33	8.8 (7.8, 10.4)	7.8 (7.5, 8.4)	0.01
Hypertension	53 (31.4)	31 (23.1)	0.11	15 (25.4)	13 (27.1)	0.85
Diabetes mellitus	38 (22.5)	19 (14.2)	0.09	11 (18.6)	3 (6.3)	0.06
Smoking	17 (10.1)	9 (6.7)	0.29	3 (5.1)	1 (2.1)	0.76
Regular exercise	150 (88.8)	115 (85.8)	0.55	42 (71.2)	45 (93.8)	0.008
Caloric restriction	107 (63.3)	89 (66.4)	0.63	28 (47.5)	25 (52.1)	0.76
Lipid-lowering drug	62 (36.7)	40 (29.9)	0.22	27 (45.8)	13 (27.1)	0.04
Hypoglycemic drug	23 (13.6)	7 (5.2)	0.02	3 (5.1)	3 (6.3)	1.00
Uric acid lowering drug	28 (16.6)	17 (12.7)	0.31	7 (11.9)	7 (14.6)	0.70
Intensified lifestyle intervention	50 (29.6)	36 (26.9)	0.61	18 (30.5)	15 (31.3)	0.98

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.

**Table S7** Subgroup baseline characteristics of MASLD patients with treatment response at 24 weeks, stratified by baseline insulin resistance status

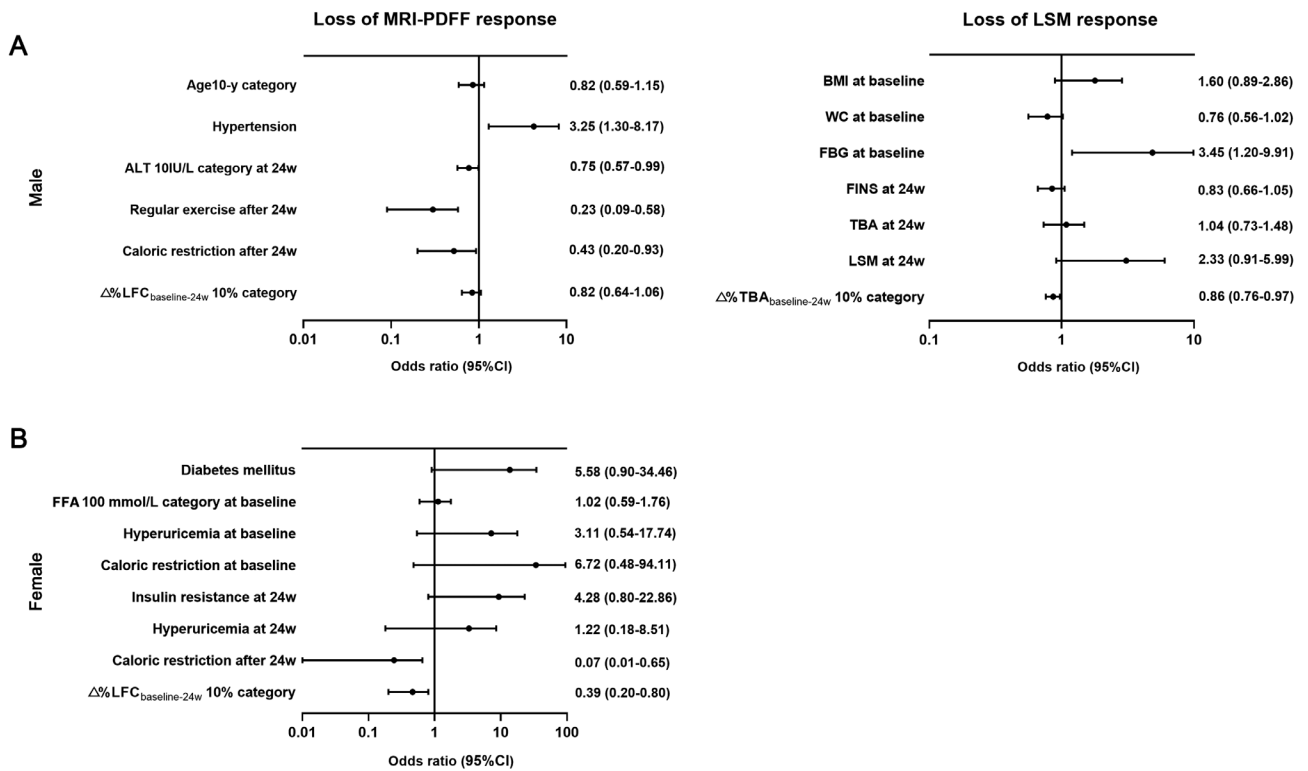
Characteristics	With MRI-PDFF response at 24 weeks (n=303)			With LSM response at 24 weeks (n=107)		
	Without insulin resistance (n=164)	With insulin resistance (n=139)	P	Without insulin resistance (n=42)	With insulin resistance (n=65)	P
Age (years)	42.9±13.2	40.8±14.7	0.18	42.2±10.4	42.1±12.0	0.97
Male	127 (77.4)	94 (67.6)	0.04	36 (85.7)	41 (63.9)	0.01
Weight (kg)	74.1±11.3	79.7±11.3	<0.001	75.1±9.8	78.5±11.8	0.12
BMI (kg/m <sup>2</sup> )	26.6±2.9	29.0±3.4	<0.001	26.7±2.9	29.1±3.0	<0.001
WC (cm)	89.6±7.5	94.2±7.9	<0.001	90.1±6.3	94.5±7.9	0.003
Waist-hip ratio	0.90±0.04	0.91±0.05	0.02	0.90±0.03	0.92±0.06	0.07
CHOL (mmol/L)	5.33±1.11	4.80±0.98	<0.001	5.25±0.90	4.91±0.90	0.06
TG (mmol/L)	1.82 (1.31, 2.37)	1.60 (1.18, 1.98)	0.02	1.70 (1.32, 2.20)	1.69 (1.33, 2.12)	0.79
HDL-C (mmol/L)	1.17±0.29	1.11±0.25	0.04	1.09±0.23	1.11±0.23	0.74
LDL-C (mmol/L)	3.33±0.83	3.05±0.74	0.002	3.44±0.67	3.13±0.70	0.03
FFA (mmol/L)	521 (390, 745)	565 (450, 704)	0.14	499 (364, 692)	517 (441, 660)	0.699
FBG (mmol/L)	4.8 (4.5, 5.2)	5.4 (4.8, 6.5)	<0.001	4.7 (4.5, 5.0)	5.2 (4.8, 6.1)	<0.001
FINS (μU/mL)	8.9 (7.0, 10.7)	15.6 (12.8, 23.5)	<0.001	8.6 (7.4, 10.4)	17.2 (13.2, 21.7)	<0.001
HOMA-IR	1.9 (1.5, 2.4)	3.9 (3.0, 6.1)	<0.001	1.79 (1.59, 2.30)	3.94 (3.00, 5.63)	<0.001
UA (μmol/L)	426.6±88.8	441.5±113.6	0.20	400.5±101.2	406.9±91.6	0.74
ALT (U/L)	46.0 (28.5, 72.0)	58.0 (33.5, 99.0)	0.003	37.5 (29.0, 71.0)	40.0 (31.0, 101.0)	0.43
AST (U/L)	31.0 (25.0, 43.0)	44.0 (27.0, 71.5)	<0.001	31.0 (22.0, 44.0)	37.0 (24.0, 62.0)	0.04
GGT (U/L)	42.0 (28.5, 62.0)	52.5 (35.0, 76.0)	0.009	36.0 (27.0, 46.0)	51.0 (31.0, 76.0)	0.01
ALP (U/L)	75.0 (64.0, 89.5)	80.0 (70.0, 93.0)	0.02	76.0 (64.0, 84.0)	78.0 (71.0, 97.0)	0.02
Albumin (g/L)	46.4±3.2	45.5±3.1	0.01	46.0±3.0	45.4±2.9	0.26
TB (μmol/L)	13.7 (11.4, 16.1)	12.1 (9.2, 16.1)	0.01	12.8 (11.4, 17.2)	12.10 (9.60, 16.40)	0.12
TBA (μmol/L)	2.45 (1.80, 4.70)	2.7 (2.0, 3.9)	0.47	2.7 (1.5, 3.3)	3.10 (2.20, 4.50)	0.06
LFC (%)	14.5 (11.2, 19.9)	20.8 (13.6, 26.7)	<0.001	13.0 (8.4, 19.9)	19.7 (14.3, 27.0)	<0.001
LSM (kpa)	6.3 (5.2, 7.4)	7.8 (5.7, 8.6)	<0.001	7.6 (7.0, 9.0)	8.4 (7.8, 9.6)	0.009
Hypertension	38 (23.2)	46 (33.1)	0.06	5 (11.9)	23 (35.4)	0.007
Diabetes mellitus	25 (15.2)	32 (23.2)	0.08	6 (14.3)	8 (12.3)	0.79
Smoking	18 (11.0)	8 (5.9)	0.11	2 (4.8)	2 (3.1)	1.00
Regular exercise	141 (86.0)	124 (89.2)	0.44	32 (76.2)	55 (84.6)	0.25
Caloric restriction	110 (67.1)	86 (61.9)	0.40	18 (42.9)	35 (53.8)	0.23
Lipid-lowering drug	59 (36.0)	43 (31.2)	0.37	18 (42.9)	22 (33.8)	0.30
Hypoglycemic drug	10 (6.1)	20 (14.5)	0.02	1 (2.4)	5 (7.7)	0.48
Uric acid lowering drug	27 (16.5)	18 (13.0)	0.41	7 (16.7)	7 (10.8)	0.35
Intensified lifestyle intervention	36 (22.0)	50 (36.2)	0.005	6 (14.3)	27 (41.5)	0.004

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.

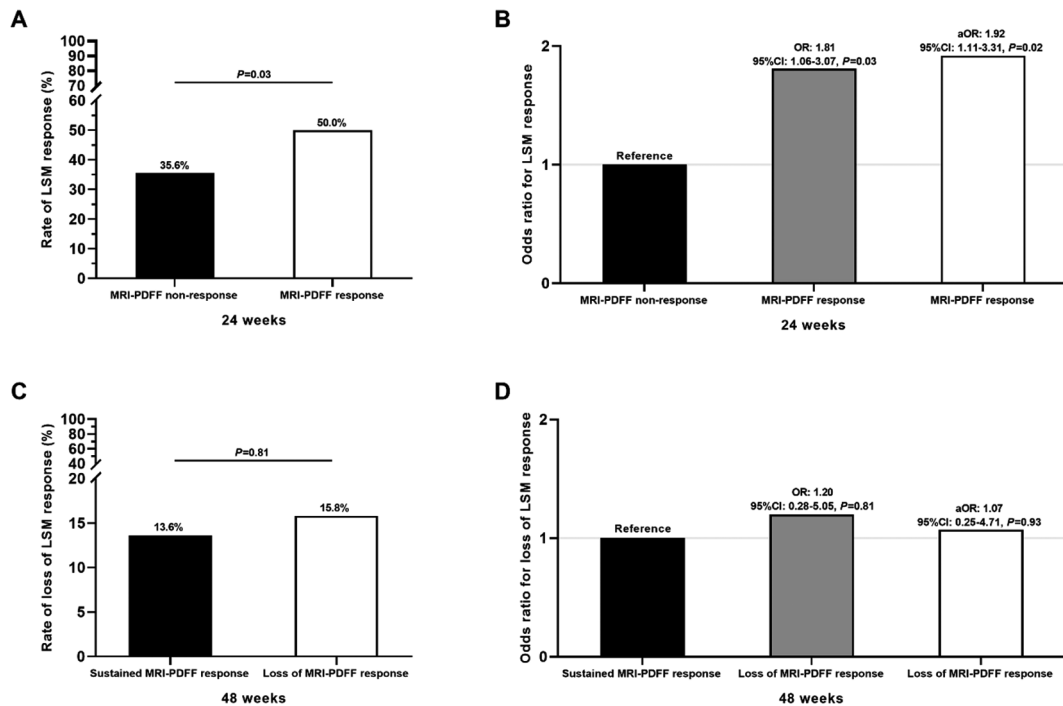
**Table S8** Subgroup baseline characteristics of MASLD patients with treatment response at 24 weeks, stratified by gender

Characteristics	With MRI-PDFF response at 24 weeks (n=303)			With LSM response at 24 weeks (n=107)		
	Male (n=221)	Female (n=82)	P	Male (n=77)	Female (n=30)	P
Age (years)	38.1±11.8	52.4±13.9	<0.001	40.5±10.5	46.4±12.6	0.02
Weight (kg)	79.9±9.9	67.9±11.5	<0.001	80.3±10.2	69.1±9.5	<0.001
BMI (kg/m <sup>2</sup> )	27.6±3.1	27.7±4.0	0.87	28.1±3.2	28.4±3.3	0.71
WC (cm)	92.8±7.2	88.8±9.2	0.001	94.2±6.9	89.0±7.9	0.001
Waist-hip ratio	0.91±0.05	0.89±0.05	<0.001	0.92±0.04	0.89±0.05	0.001
CHOL (mmol/L)	5.09±1.14	5.06±0.92	0.80	5.10±0.97	4.90±0.74	0.30
TG (mmol/L)	1.72 (1.18, 2.35)	1.56 (1.23, 1.99)	0.10	1.71 (1.18, 2.27)	1.62 (1.34, 1.85)	0.87
HDL-C (mmol/L)	1.07±0.21	1.33±0.33	<0.001	1.06±0.21	1.19±0.25	0.008
LDL-C (mmol/L)	3.24±0.82	3.11±0.73	0.22	3.32±0.72	3.10±0.63	0.14
FFA (mmol/L)	512 (437, 739)	587 (480, 738)	0.10	497 (424, 715)	521 (434, 587)	0.72
FBG (mmol/L)	4.9 (4.5, 5.6)	5.4 (4.8, 5.7)	0.004	5.0 (4.6, 6.1)	5.1 (4.8, 5.7)	0.52
FINS (μU/mL)	10.6 (8.5, 14.1)	12.8 (10.3, 20.8)	0.003	11.8 (9.5, 17.2)	14.7 (12.8, 21.7)	0.02
HOMA-IR	2.46 (1.79, 3.34)	2.98 (2.34, 4.92)	0.002	2.69 (2.04, 3.91)	3.86 (2.73, 6.06)	0.03
UA (μmol/L)	451.7±97.8	383.4±92.6	<0.001	420.8±91.8	362.2±91.6	0.004
ALT (U/L)	51.0 (36.0, 81.0)	36.0 (22.0, 95.0)	0.03	47.0 (33.0, 81.0)	32.5 (21.0, 41.0)	0.002
AST (U/L)	36.0 (27.0, 50.0)	36.0 (22.0, 75.0)	0.71	37.0 (24.0, 51.0)	27.0 (21.0, 48.0)	0.06
GGT (U/L)	52.0 (32.0, 76.0)	41.5 (23.5, 61.0)	0.002	43.5 (31.5, 73.5)	31.0 (25.0, 51.0)	0.02
ALP (U/L)	78.0 (67.0, 91.0)	78.0 (67.0, 87.0)	0.42	78.0 (66.0, 90.0)	78.0 (73.0, 89.0)	0.38
Albumin (g/L)	46.8±2.8	43.6±2.7	<0.001	46.4±2.5	43.6±3.0	<0.001
TB (μmol/L)	13.2 (11.0, 16.4)	11.1 (9.5, 15.2)	0.001	12.4 (10.4, 17.5)	11.2 (9.5, 13.7)	0.051
TBA (μmol/L)	2.5 (1.8, 4.1)	2.6 (1.7, 4.5)	0.42	2.7 (2.3, 4.4)	2.1 (1.6, 3.1)	0.04
LFC (%)	16.1 (11.4, 22.4)	18.9 (12.2, 27.1)	0.01	16.2 (11.1, 22.2)	20.0 (11.3, 26.7)	0.13
LSM (kpa)	6.5 (5.6, 7.8)	7.6 (5.7, 8.6)	0.006	8.0 (7.6, 9.2)	7.8 (7.6, 11.6)	0.94
Hypertension	44 (19.9)	40 (48.8)	<0.001	18 (23.4)	10 (33.3)	0.29
Diabetes mellitus	31 (14.0)	26 (31.7)	0.001	12 (15.6)	2 (6.7)	0.35
Smoking	26 (11.8)	0 (0.0)	0.001	4 (5.2)	0 (0.0)	0.48
Regular exercise	194 (87.8)	71 (86.6)	0.70	61 (79.2)	26 (86.7)	0.54
Caloric restriction	131 (59.3)	65 (79.3)	0.005	32 (41.6)	21 (70.0)	0.009
Lipid-lowering drug	76 (34.4)	26 (31.7)	0.64	32 (41.6)	8 (26.7)	0.19
Hypoglycemic drug	11 (5.0)	19 (23.2)	<0.001	4 (5.2)	2 (6.7)	1.00
Uric acid lowering drug	34 (15.4)	11 (13.4)	0.78	14 (18.2)	0 (0.0)	0.03
Intensified lifestyle intervention	43 (19.5)	43 (52.4)	<0.001	16 (20.8)	17 (56.7)	<0.001

Values are expressed as mean ± standard deviation, median (interquartile range) or n (%). MASLD, metabolic dysfunction-associated steatotic liver disease; MRI-PDFF, magnetic resonance imaging proton density fat fraction; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; CHOL, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FFA, free fatty acid; FBG, fasting blood glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; UA, uric acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TB, total bilirubin; TBA, total bile acid; LFC, liver fat content.



**Figure S2** Multivariable logistic regression analysis for the loss of response in hepatic steatosis and fibrosis at 48 weeks in male (A) or female (B) MASLD patients. MRI-PDFF, magnetic resonance imaging-based proton density fat fraction; ALT, alanine aminotransferase; LFC, liver fat content; 95% CI, 95% confidence interval; 24w, 24 weeks; LSM, liver stiffness measurement; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; FINS, fasting insulin; TBA, total bile acid; LSM, liver stiffness measurement; FFA, free fatty acid; MASLD, metabolic dysfunction-associated steatotic liver disease.



**Figure S3** Association of MRI-PDFF response with LSM response in MASLD patients. At 24 weeks, the rate of LSM response between MASLD patients with MRI-PDFF non-response and response (A), and odds ratio of MRI-PDFF response for LSM response (B). At 48 weeks, the rate of loss of LSM response between MASLD patients with sustained MRI-PDFF response and loss of MRI-PDFF response (C), and odds ratio of loss of MRI-PDFF response for loss of LSM response (D). MRI-PDFF response and non-response are defined as  $\geq 30\%$  relative decline and  $< 30\%$  relative decline in MRI-PDFF. LSM response and non-response are defined as no or  $\geq 1$  stage decline from baseline in 2D-SWE. LSM, liver stiffness measurement; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OR, odds ratio; 95% CI, 95% confidence interval; aOR, adjusted odds ratio (adjusted for sex and age); MASLD, metabolic dysfunction-associated steatotic liver disease.