# The relationship between metabolic dysfunction-associated fatty liver disease and low muscle mass in an asymptomatic Korean population

Ji Yeon Seo<sup>1†</sup>, Eun Ju Cho<sup>2†</sup>, Min Joo Kim<sup>3</sup>, Min-Sun Kwak<sup>1</sup>, Jong In Yang<sup>1</sup>, Su Jin Chung<sup>1</sup>, Jeong Yoon Yim<sup>1</sup>, Ji Won Yoon<sup>3\*</sup> & Goh Eun Chung<sup>1\*</sup>

<sup>1</sup>Department of Gastroenterology and Hepatology, Internal Medicine and Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, South Korea; <sup>2</sup>Department of Gastroenterology and Hepatology, Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul, South Korea; <sup>3</sup>Department of Endocrinology, Internal Medicine and Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, South Korea

# Abstract

**Background** Metabolic (dysfunction)-associated fatty liver disease (MAFLD) emphasizes the metabolic dysfunction in nonalcoholic fatty liver disease (NAFLD). Although the relationship between low muscle mass and NAFLD has been suggested, the effect of MAFLD on low muscle mass is yet to be investigated. In this study, we examined the relationship between MAFLD and low muscle mass in an asymptomatic Korean population.

**Methods** Examinees who underwent FibroScan® and bioelectrical impedance analyses on the same day during the period of June 2017 to December 2019 were included. Hepatic steatosis was diagnosed using controlled attenuation parameter (CAP) with two cut-off values of 248 and 294 dB/m. Low muscle mass was defined based on appendicular skeletal muscle mass/body weight (wt) or body mass index (BMI) ratios of two standard deviations below the sex-specific mean for healthy young adults. Subjects were divided into four subgroups: diabetic MAFLD (presence of diabetes mellitus [DM]), metabolic dysfunction (MD) MAFLD ( $\geq$ 2 metabolic abnormalities without DM), overweight MAFLD (overweight/obese without DM and <2 metabolic abnormalities) and no MAFLD.

**Results** Among all of the 6414 subjects (mean 53.9 years of age; 85.4% male), the prevalence of MAFLD was 49.9% and 22.7% for CAP cut-off values of 248 and 294 dB/m, respectively. In the multivariate analysis, MAFLD was associated with an increased risk of both low muscle mass\_wt (odds ratio [OR] 1.80, 95% confidence interval [CI] 1.38–2.35, P < 0.001) and low muscle mass\_BMI (OR 1.31, 95% CI 1.01–1.70, P = 0.042). The risk of low muscle mass\_wt and low muscle mass\_BMI increased the most in the diabetic MAFLD subgroup compared with the no-MAFLD group (OR 2.11, 95% CI 1.51–2.96, P < 0.001 and OR 1.51, 95% CI 1.08–2.13, P = 0.017). There was an increased risk of low muscle mass\_wt in the MD MAFLD subgroup (OR 1.73, 95% CI 1.31–2.28, P < 0.001). Comparable results were observed when the CAP cut-off value of 294 dB/m was applied.

**Conclusions** The presence of MAFLD is significantly associated with increased risk of low muscle mass with varying risks according to the MAFLD subgroups. Clinicians should be aware of the differentiated risk of low muscle mass across the subgroups of MAFLD.

Keywords fibrosis; hepatic steatosis; low muscle mass; metabolic dysfunction

Ji Won Yoon, M.D., Ph.D., Department of Endocrinology and Metabolism, Internal Medicine, Seoul National University Hospital Healthcare System Gangnam Center, Seoul 06236, South Korea. Email: jwyoonmd@gmail.com

†These authors have equal contribution and are co-first authors.

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<sup>\*</sup>Correspondence to: Goh Eun Chung, M.D., Ph.D., Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, 39FL., Gangnam Finance Center 737, Yeoksam-dong, Gangnam-gu, Seoul 135-984, South Korea. Email: gohwom@snu.ac.kr

# Introduction

'Metabolic (dysfunction)-associated fatty liver disease (MAFLD)' has been introduced with an emphasis on the role of metabolic abnormalities in clinical outcomes in individuals with hepatic steatosis.<sup>1</sup> Although there is substantial overlap between nonalcoholic fatty liver disease (NAFLD) and MAFLD, MAFLD is not a simple rename of NAFLD.<sup>2</sup> By using the MAFLD definition instead of NAFLD, more individuals with liver damage can be identified.<sup>3,4</sup> Although there is a debate on consensus on a change in name,<sup>5</sup> MAFLD may be a more suitable criteria in terms of clinical practice for fatty liver in the Asia-Pacific region.<sup>6</sup>

Sarcopenia, which is an age-related decline in skeletal muscle mass and strength with or without a reduction in physical performance, has been associated with increases in metabolic dysfunction and cardiovascular diseases, disability and mortality.<sup>7</sup> Because skeletal muscle is the key determinant of the whole-body insulin-mediated glucose metabolism and impacts fatty liver oxidation and energy homeostasis, there may be a link between sarcopenia and MAFLD, with the same primary pathophysiology as insulin resistance.<sup>8</sup> Although an independent association between sarcopenia and NAFLD has been suggested,<sup>9</sup> there has been limited studies regarding the risk of sarcopenia in terms of MAFLD. A recent study reported that the risks of advanced liver disease and cardiovascular disease differed significantly according to sarcopenic status among subjects with MAFLD.<sup>10</sup> However, the characteristics of the relationship between sarcopenia and MAFLD have not yet been fully elucidated.

Although the concept of sarcopenia includes the assessment of muscle function as well as muscle mass, we evaluated low muscle mass, one of the major components of sarcopenia in this study. Therefore, we investigated the relationship between MAFLD and low muscle mass in an asymptomatic health check-up population without overt liver disease.

# Methods

#### Study population

We conducted a retrospective cohort study that included subjects who underwent routine health check-ups including a FibroScan at the Seoul National University Hospital Healthcare System Gangnam Center between June 2017 and December 2019. We included subjects who underwent bioelectrical analysis on the same day. Among them, 88 subjects without skeletal muscle mass information were excluded, and finally, a total of 6414 subjects were included in the analysis. Most subjects were asymptomatic and underwent voluntary general health check-up exams, whereas others were sent by their employers. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-2106-014-1223) with a waiver for informed consent and also conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki.

#### Clinical and biochemical evaluations

The study data consisted of medical information based on a self-administered questionnaire, and anthropometric and laboratory measurements as previously described.<sup>11</sup> Briefly, subjects were categorized as current or non-current smoker. Based on the amount of alcohol intake, significant alcohol consumption was defined as >20 g/day for men and >10 g/day for women. Viral hepatitis was defined as either hepatitis B virus antigen positive or hepatitis C virus antibody positive. Hypertension was defined as blood pressure  $\geq$  140/90 mmHg or a history of receiving antihypertensive medications. Diabetes was defined as fasting glucose levels  $\geq$  126 mg/dL, a glycated haemoglobin (HbA1c) level  $\geq$  6.5% or a history of receiving agents.

All subjects fasted for at least 12 h prior to blood sampling; total cholesterol, triglyceride, high-density lipoprotein (HDL)-cholesterol, fasting glucose, HbA1c, fasting insulin and high-sensitivity C-reactive protein (CRP) were measured. All the tests were performed using standard laboratory methods. The homeostasis model assessment of the insulin resistance score (HOMA-IR) was assessed as previously described.<sup>12</sup>

#### Anthropometric measurements

Weight and height were measured using a digital scale, and body mass index (BMI) was calculated by dividing the weight (kg) by the squared value of the height (m<sup>2</sup>). To measure the waist circumference (WC), we used a tape at the midpoint between the lower costal margin and anterior superior iliac crest. Blood pressure was measured at least twice, and the mean values of the measurements were recorded. To assess body composition, bioelectrical impedance analysis (BIA) was performed using an InBody 720 Body Composition Analyzer (InBody Co., Ltd., Seoul, Korea), as described previously.<sup>13</sup> The subjects were instructed to grasp the handles of the analyser, to make contact with the electrodes on each limb. They were in standing position for 5 min with their legs slightly separated and the arms slightly abducted from the trunk. When the measurements stabilized, it provided the impedance for each segment including the trunk and the four limbs by performing multi-frequency measurements to estimate the appendicular skeletal muscle mass (ASM).

# Diagnosis of metabolic dysfunction-associated fatty liver disease

To diagnose hepatic steatosis, a FibroScan (Echosens, Paris, France) was performed by experienced investigators who were unaware of the clinical information of the subjects as described previously.<sup>11</sup> Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were obtained using an M (standard probe-transducer frequency of 3.5 MHz) or XL probe (transducer frequency of 2.5 MHz). An XL probe was used for all subjects with a BMI of  $\geq$ 30.0 kg/m<sup>2</sup>. Briefly, the subjects were placed in the dorsal decubitus position with the right arm abduction and the procedure was performed on the right lobe of the liver. The values of LSM were expressed as the median kilopascal (kPa) value, and the median CAP score was expressed in dB/m values. The LSM values were considered reliable if 10 valid measurements were obtained and the interquartile range/median of the measurements was <0.3 or when the median liver stiffness value was <7.1 kPa. All of the subjects with 10 valid measurements were included in the analysis. Because no consensual cut-off values were available for diagnosing steatosis,14 two CAP values of 248 and 294 dB/m were used to define hepatic steatosis in this study.15,16

The diagnosis of MAFLD was based on previous criteria as follows: the presence of hepatic steatosis with one or more of the following: (1) overweight or obese (BMI  $\ge$  23 kg/m<sup>2</sup>), (2) diabetes mellitus (DM) and (3) at least two metabolic risk abnormalities. Metabolic risk abnormalities consisted of (1) WC  $\ge$  90 cm for men and  $\ge$ 80 cm for women, (2) blood pressure  $\ge$  130/85 mmHg or specific drug treatment, (3) fasting plasma triglycerides  $\ge$  150 mg/dL or specific drug treatment, (4) plasma HDL-cholesterol < 40 mg/dL for men and <50 mg/dL for women or specific drug treatment, (5) prediabetes (fasting glucose of 100–125 mg/dL or HbA1c of 5.7–6.4%), (6) HOMA-IR  $\ge$  2.5 and (7) plasma high-sensitivity CRP level > 2 mg/L.<sup>1</sup>

We classified the MAFLD subgroups as follows: First, we determined the diabetic MAFLD group based on the presence of DM. And then in subjects without DM, we classified the metabolic dysfunction (MD) MAFLD group according to the presence of two or more metabolic risk abnormalities. Next, the remaining non-diabetic subjects who had <2 metabolic abnormalities and met only the BMI  $\geq$  23 kg/m<sup>2</sup> criteria of MAFLD were categorized as the overweight MAFLD group. Finally, the study population was divided into four subgroups: no MAFLD, MAFLD-diabetes, MAFLD-MD and MAFLD-overweight.<sup>17</sup>

#### Definitions of low muscle mass

ASM (kg) was calculated as the sum of the lean muscle mass in all four extremities, assuming that all nonfat and nonbone tis-

sue is skeletal muscle. ASM% was calculated as ASM/weight (kg) \* 100, as modified from Janssen et al.<sup>18</sup> Low muscle mass\_wt was defined using ASM%, as below two standard deviations of the sex-specific mean for healthy young adults, according to the nationwide health examinations of the Korean population (ASM% < 29.1 in men and <23.0 in women).<sup>19</sup> We adopted a different definition for low muscle mass\_BMI, which was defined as <0.789 in men and <0.512 in women using ASM to BMI ratio, based on the recent recommendations.<sup>20</sup>

#### Statistical analyses

The data are presented as the mean  $\pm$  standard deviation for normally distributed continuous variables and as proportions for categorical variables. The Student's *t*-test and analysis of variance were used to analyse continuous variables, and the differences between nominal variables were compared with the chi-squared test. A logistic regression analysis was utilized to analyse the association between MAFLD and low muscle mass adjusting for potential confounders. Among variables with a *P* value of <0.05 in the univariate analysis, those with clinical importance were subjected to multivariate analyses. Sensitivity analyses were conducted to exclude the effects of significant alcohol consumption or viral hepatitis. All the statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and *P* values < 0.05 were considered statistically significant.

### Results

#### Baseline characteristics of the study population

The mean age was 53.9 years and the proportion of males was 85.4%. Among all of the 6414 subjects, MAFLD was identified in 3198 (49.9%) with the lower CAP cut-off value of 248 dB/m. When we applied the higher CAP cut-off value of 294 dB/m, the prevalence of MAFLD was 22.7%. The baseline characteristics of the study participants are shown in Tables 1 and S1. The prevalence rates of low muscle mass wt and low muscle mass\_BMI were 9.5% and 6.1%, respectively. Individuals with MAFLD were older, and it was more frequently observed in males. The prevalence of hypertension and diabetes was significantly higher in subjects with MAFLD (P < 0.001). In addition, most of the anthropometric and laboratory variables (including BMI, WC, systolic or diastolic blood pressure, triglyceride, HDL-cholesterol, fasting glucose and HOMA-IR) were metabolically unfavourable in subjects with MAFLD (P < 0.001). The prevalence of low muscle mass\_wt and low muscle mass BMI was significantly higher in MAFLD patients compared with those without MAFLD (P < 0.001).

|--|

|  | No MAFLD ( <i>N</i> = 3216) | MAFLD ( $N = 3198$ ) | P value |
|--|-----------------------------|----------------------|---------|
| Age (years)                            | 53.7 ± 10.1                 | 54.2 ± 9.6           | 0.044   |
| Male, n (%)                            | 2604 (81.0)                 | 2873 (89.8)          | < 0.001 |
| Current smoker, n (%)                  | 575 (17.9)                  | 603 (18.9)           | 0.313   |
| Significant alcohol consumption, n (%) | 665 (20.7)                  | 759 (23.7)           | 0.003   |
| Viral hepatitis, n (%)                 | 201 (6.3)                   | 141 (4.4)            | 0.001   |
| Hypertension, n (%)                    | 859 (26.7)                  | 1284 (40.2)          | < 0.001 |
| Diabetes, n (%)                        | 293 (9.1)                   | 642 (20.1)           | < 0.001 |
| BMI (kg/m <sup>2</sup> )               | 23.1 ± 2.6                  | $26.2 \pm 2.9$       | < 0.001 |
| Waist circumference (cm)               | 84.6 ± 7.4                  | 93.2 ± 7.7           | < 0.001 |
| SBP (mmHg)                             | 117.8 ± 13.8                | 123.2 ± 13.7         | < 0.001 |
| DBP (mmHg)                             | 77.4 ± 10.2                 | 81.6 ± 9.7           | < 0.001 |
| Total cholesterol (mg/dL)              | $194.9 \pm 34.0$            | $200.8 \pm 39.5$     | 0.095   |
| Triglyceride (mg/dL)                   | 89 (63 127)                 | 130 (92 183)         | < 0.001 |
| HDL-cholesterol (mg/dL)                | 55.2 ± 13.2                 | $48.8 \pm 10.6$      | < 0.001 |
| Fasting glucose (mg/dL)                | 99.9 ± 17.9                 | 108.8 ± 22.7         | < 0.001 |
| HbA1c (%)                              | $5.6 \pm 0.6$               | $5.9 \pm 0.8$        | < 0.001 |
| hsCRP (mg/dL)                          | $0.1 \pm 0.5$               | $0.2 \pm 0.5$        | 0.112   |
| HOMA-IR                                | $2.0 \pm 1.1$               | $3.3 \pm 2.3$        | < 0.001 |
| LSM (kPa)                              | 3.6 ± 2.1                   | $4.2 \pm 2.0$        | < 0.001 |
| LSM $\ge$ 6 kPa, n (%)                 | 74 (2.3)                    | 232 (7.3)            | < 0.001 |
| LSM $\geq$ 7 kPa, n (%)                | 25 (0.8)                    | 70 (2.2)             | < 0.001 |
| ASM%                                   | 32.4 ± 3.1                  | 30.7 ± 2.7           | < 0.001 |
| ASM/BMI, m <sup>2</sup>                | $0.94 \pm 0.1$              | $0.90 \pm 0.1$       | < 0.001 |
| Low muscle mass_wt, n (%)              | 94 (2.9)                    | 517 (16.2)           | < 0.001 |
| Low muscle mass_BMI, <i>n</i> (%)      | 117 (3.6)                   | 277 (8.7)            | <0.001  |

Note: Data are shown as the mean ± SD or median (interquartile range). Abbreviations: ASM, appendicular skeletal muscle mass; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; SBP, systolic blood pressure; wt, weight.

#### Table 2 Univariate and multivariate analyses of the risk for low muscle mass

|                                   | Unadjusted model |         | Model 1          |         | Model 2          |         |
|-----------------------------------|------------------|---------|------------------|---------|------------------|---------|
|                                   | OR (95% CI)      | P value | OR (95% CI)      | P value | OR (95% CI)      | P value |
| Low muscle mass_wt                |                  |         |                  |         |                  |         |
| Age                               | 1.01 (1.00–1.02) | 0.152   | 1.03 (1.02–1.04) | < 0.001 | 1.03 (1.02–1.04) | <0.001  |
| Male                              | 2.85 (2.03–4.00) | <0.001  | 1.18 (0.79–1.76) | 0.426   | 1.12 (0.74–1.68) | 0.592   |
| Current smoker                    | 1.31 (1.07–1.60) | 0.009   | 1.09 (0.84–1.40) | 0.516   | 1.07 (0.82–1.39) | 0.626   |
| Significant alcohol consumption   | 1.01 (0.90–1.34) | 0.339   |                  |         |                  |         |
| Waist circumference (cm)          | 1.23 (1.21–1.25) | <0.001  | 1.22 (1.20–1.24) | <0.001  | 1.22 (1.20–1.24) | <0.001  |
| Triglyceride (mg/dL) <sup>a</sup> | 2.50 (2.15–2.92) | < 0.001 |                  |         | 1.09 (0.89–1.35) | 0.410   |
| Fasting glucose (mg/dL)           | 1.01 (1.01–1.02) | < 0.001 |                  |         | 1.00 (1.00–1.01) | 0.166   |
| SBP (mmHg)                        | 1.03 (1.03–1.04) | <0.001  |                  |         | 1.01 (1.00–1.02) | 0.007   |
| MAFLD                             | 6.41 (5.11–8.03) | < 0.001 | 1.81 (1.40–2.34) | <0.001  | 1.80 (1.38–2.35) | < 0.001 |
| Low muscle mass BMI               |                  |         |                  |         |                  |         |
| Age                               | 1.06 (1.05–1.07) | <0.001  | 1.07 (1.06–1.08) | <0.001  | 1.07 (1.06–1.08) | <0.001  |
| Male                              | 3.19 (2.04–4.96) | <0.001  | 2.25 (1.42–3.57) | 0.001   | 2.13 (1.34–3.39) | 0.001   |
| Current smoker                    | 1.06 (0.81–1.39) | 0.652   |                  |         |                  |         |
| Significant alcohol consumption   | 0.79 (0.61–1.02) | 0.071   |                  |         |                  |         |
| Waist circumference (cm)          | 1.08 (1.07–1.10) | <0.001  | 1.09 (1.07–1.10) | <0.001  | 1.08 (1.06–1.09) | <0.001  |
| Triglyceride (mg/dL) <sup>a</sup> | 1.79 (1.49–2.15) | <0.001  |                  |         | 1.25 (1.00–1.57) | 0.047   |
| Fasting glucose (mg/dL)           | 1.01 (1.01–1.02) | <0.001  |                  |         | 1.00 (1.00–1.01) | 0.138   |
| SBP (mmHg)                        | 1.03 (1.02–1.03) | <0.001  |                  |         | 1.01 (1.00–1.02) | 0.038   |
| MAFLD                             | 2.51 (2.01–3.14) | < 0.001 | 1.37 (1.07–1.75) | 0.014   | 1.31 (1.01–1.70) | 0.042   |

Note: Low muscle mass\_wt, Model 1: Adjusted for age, sex, smoking, waist circumference and MAFLD. Model 2: Model 1 plus glucose, triglyceride and SBP adjusted. Low muscle mass\_BMI, Model 1: Adjusted for age, sex, waist circumference and MAFLD. Model 2: Model 1 plus glucose, triglyceride and SBP adjusted. Abbreviations: BMI, body mass index; CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; SBP, systolic blood pressure; wt, weight. <sup>a</sup>Log transformed.

#### Relationship between metabolic dysfunction-associated fatty liver disease and low muscle mass

We investigated the association between low muscle mass and MAFLD. In the univariate model, the presence of MAFLD showed a significant association with low muscle mass\_wt and low muscle mass\_BMI (odds ratio [OR] 6.41, 95% confidence interval [CI] 5.11–8.03 and OR 2.51, 95% CI 2.01– 3.14, respectively). In the multivariate analysis, MAFLD was associated with an increased risk of both low muscle mass\_wt (OR 1.80, 95% CI 1.38–2.35) and low muscle mass\_BMI (OR 1.31, 95% CI 1.01–1.70; *Table 2*). When further adjusted for BMI, these associations remained significant in low muscle mass\_wt (OR 1.60, 95% CI 1.22–2.10; *Table S2*). When we applied the CAP cut-off value of 294 dB/m, the significant association between MAFLD and low muscle mass remained only in low muscle mass wt (*Table S3*).

In the sensitivity analysis among individuals without alcohol consumption or viral hepatitis, the association between MAFLD and low muscle mass\_wt remained significant (*Table S4*).

# The risk of low muscle mass according to metabolic dysfunction-associated fatty liver disease subgroups

We examined which component of MAFLD was most responsible for an increased risk of low muscle mass by stratification of the participants who were identified to have MAFLD into three groups as described previously. First, we determined the MAFLD-diabetes group based on the presence of DM regardless of BMI. Next, we classified the MAFLD-MD group according to the presence of two or more metabolic abnormalities, and the MAFLD-overweight group. The clinical characteristics according to MAFLD subgroup are shown in Table S5. In the multivariate analysis, the risk of low muscle mass\_wt and low muscle mass\_BMI increased the most in the MAFLD-diabetes group compared with the no-MAFLD group (OR 2.11, 95% CI 1.51–2.96 and OR 1.51, 95% CI 1.08–2.13, respectively). The increased risk of low muscle mass\_wt was also observed in the MAFLD-MD group (OR 1.73, 95% CI 1.31–2.28; *Table 3*). When BMI and fasting glucose level were further adjusted as covariates, these associations between the MAFLD subgroup and low muscle mass\_wt remained similar (*Table S6*). When we applied the CAP cut-off value of 294 dB/m, the significant association between MAFLD-diabetes group and low muscle mass remained only in low muscle mass\_wt (*Table S7*).

# Subgroup analysis of subjects with metabolic dysfunction-associated fatty liver disease

We evaluated the association between LSM and low muscle mass in individuals with MAFLD. When the participants with MAFLD were grouped according to an LSM cut-off value of 6.0 kPa, those with a higher LSM ( $\geq$ 6 kPa) showed an independently increased risk for low muscle mass than those with a lower LSM (<6 kPa) (low muscle mass\_wt: OR 1.52, 95% CI 1.05–2.19, and low muscle mass\_BMI: OR 1.66, 95% CI 1.11–2.48, respectively; *Table 4*). Although not statistically significant, comparable results were observed when the CAP cut-off value of 294 dB/m was applied (*Table S8*). Among the MAFLD subgroups, the association between low muscle mass and higher LSM in the MAFLD–diabetes group was observed (*Table S9*).

# Discussion

In the present study, the presence of MAFLD was significantly associated with low muscle mass even after adjusting for

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|---------|-------|---------|--------|--------|------------|----|---------|------------|
| Table 3 | TISK  | 01 10 W | muscie | 111422 | accoruing  | ιυ | IVIAFLD | subgroups  |

|                     |                    | Model 1          |         | Model 2          |         |
|---------------------|--------------------|------------------|---------|------------------|---------|
|                     | N (%) <sup>a</sup> | OR (95% CI)      | P value | OR (95% CI)      | P value |
| Low muscle mass wt  |                    |                  |         |                  |         |
| No MAFLD            | 94 (2.9)           | 1 (ref)          |         | 1 (ref)          |         |
| MAFLD-overweight    | 20 (5.5)           | 1.46 (0.86-2.48) | 0.161   | 1.65 (0.95–2.85) | 0.073   |
| MAFLD-MD            | 354 (16.1)         | 1.75 (1.34–2.29) | < 0.001 | 1.73 (1.31–2.28) | < 0.001 |
| MAFLD-diabetes      | 143 (22.3)         | 2.13 (1.54–2.95) | < 0.001 | 2.11 (1.51–2.96) | < 0.001 |
| Low muscle mass BMI |                    |                  |         |                  |         |
| No MAFLD            | 117 (3.6)          | 1 (ref)          |         | 1 (ref)          |         |
| MAFLD-overweight    | 18 (5.0)           | 1.27 (0.76–2.14) | 0.365   | 1.23 (0.93–1.62) | 0.145   |
| MAFLD-MD            | 177 (8.1)          | 1.30 (0.99–1.70) | 0.056   | 1.43 (0.84–2.45) | 0.192   |
| MAFLD-diabetes      | 82 (12.8)          | 1.62 (1.16–2.24) | 0.004   | 1.51 (1.08–2.13) | 0.017   |

Note: Low muscle mass\_wt, Model 1: Adjusted for age, sex, smoking and waist circumference. Model 2: Model 1 plus triglyceride and systolic blood pressure adjusted. Low muscle mass\_BMI, Model 1: Adjusted for age, sex and waist circumference. Model 2: Model 1 plus triglyceride and systolic blood pressure adjusted. Abbreviations: BMI, body mass index; CI, confidence interval; MAFLD, metabolic dysfunction-associated fatty liver disease; MD, metabolic dysfunction; OR, odds ratio; wt, weight. \*Number of low muscle mass/total population.

| Table 4 | Subgroup analysis for | or the risk of low m | scle mass in subjects with | MAFLD according to liver | stiffness measurement |
|---------|-----------------------|----------------------|----------------------------|--------------------------|-----------------------|
|---------|-----------------------|----------------------|----------------------------|--------------------------|-----------------------|

|  | Low muscle ma               | Low muscle mass_wt |                             | Low muscle mass_BMI |  |  |
|--|-----------------------------|--------------------|-----------------------------|---------------------|--|--|
|  | OR (95% CI)                 | P value            | OR (95% CI)                 | P value             |  |  |
| MAFLD with LSM $<$ 6 kPa<br>MAFLD with LSM $\ge$ 6 kPa | 1 (ref)<br>1.52 (1.05–2.19) | 0.027              | 1 (ref)<br>1.66 (1.11–2.48) | 0.013               |  |  |

Note: Low muscle mass\_wt: Adjusted for age, sex, smoking, waist circumference, fasting glucose, triglyceride and systolic blood pressure. Low muscle mass\_BMI: Adjusted for age, sex, waist circumference, fasting glucose, triglyceride and systolic blood pressure. Abbreviations: BMI, body mass index; CI, confidence interval; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; OR, odds ratio; wt, weight.

confounding factors. The increased risk of low muscle mass was the most in the MAFLD-diabetes group, followed by the MAFLD-MD group, suggesting the importance of metabolic abnormalities for the risk of sarcopenia in MAFLD. Higher LSM was significantly associated with low muscle mass in MAFLD.

Growing evidence has shown that low skeletal muscle mass may play a role in the risk of NAFLD as well as its advanced stages.<sup>21</sup> Potential pathogenic connections between NAFLD and muscle mass may be complex, bidirectional and synergistic; however, a cause–effect relation remains to be determined.<sup>22</sup> Until present, there have been few data regarding the converse relationship between hepatic steatosis and muscle mass, as an outcome variable. Chung et al. showed that hepatic steatosis assessed using a CAP was independently associated with low muscle mass in a dose-dependent manner.<sup>11</sup> Recently, Roh et al. reported that NAFLD may predict a future risk of low muscle mass and muscle strength.<sup>23</sup>

MAFLD has been reported to be associated with hepatic fibrosis<sup>24,25</sup> and atherosclerotic cardiovascular disease.<sup>26–28</sup> In addition, a previous study identified different risks of advanced liver disease and cardiovascular disease according to sarcopenic status in subjects with MAFLD, suggesting the importance of assessing sarcopenia in MAFLD patients.<sup>10</sup> Thus, sarcopenia may be one of the mechanisms by which MAFLD may be associated with hepatic fibrosis and cardiovascular disease. In this study, we determined that MAFLD was significantly associated with low muscle mass even after adjusting for confounding factors, indicating the important role of assessing MAFLD status in the risk of low muscle mass.

Because muscle mass is correlated with body size, ASM has been used as the index of skeletal muscle mass after adjusting for body size in different ways. Previous studies have used various standards regarding the definition of low muscle mass including BMI, height<sup>2</sup> or weight adjustments, and the prevalence of sarcopenia varies depending on the operational method used to define low muscle mass.<sup>29</sup> In this study, we used both ASM/weight and ASM/BMI as the muscle index and demonstrated significant associations between MAFLD and low muscle mass using both criteria. Recent papers have shown that neither muscle mass/weight nor muscle mass/BMI provides accurate adjustment of muscle quantity for differences in body size in the presence of overweight/obesity in NAFLD, suggesting the importance of muscle composition.<sup>30,31</sup> Further studies evaluating muscle composition are needed.

There is a concern that because MAFLD includes a heterogeneous group of subjects, it does not distinguish non-obese from obese, alcoholic from nonalcoholic and subjects with hepatic steatosis alone from those with underlying liver diseases.<sup>32</sup> A previous study has reported that those with MAFLD were heterogeneous in terms of mortality and cardiovascular risk according to the accompanying metabolic dysfunctions.<sup>33</sup> Our study showed that an assessment of MAFLD subgroups might be helpful in risk stratification for low muscle mass. The risk of low muscle mass was the highest in the MAFLD–diabetes group in both low muscle mass\_wt and low muscle mass\_BMI, followed by the MAFLD–MD group, indicating the importance of metabolic abnormalities for the risk of sarcopenia.

A previous meta-analysis has reported that patients with sarcopenia have a higher risk of NAFLD and advanced stages steatohepatitis including nonalcoholic (NASH) or NAFLD-related significant fibrosis.<sup>21</sup> Consistently, MAFLD with a higher LSM (≥6 kPa) showed an association with low muscle mass in this study. While most studies assign a cut-off value of LSM > 7.1 kPa to define significant liver fibrosis, a prior study suggested the LSM cut-off values ranging from 6.2 to 11 kPa for fibrosis stage  $\geq 2.^{34}$  Because the subjects of this study consisted of health check-up participants and most of them were asymptomatic, only small numbers of subjects (95 of 6414, 1.48%) showed significant fibrosis (LSM  $\geq$  7 kPa), which limited statistical power. Therefore, we used a lower LSM cut-off value of 6 kPa in this study.

The interplay between muscle mass and hepatic steatosis is influenced by several factors such as insulin resistance, obesity, low-grade inflammation and hepatokines. With aging, the impaired balance between protein synthesis and proteolysis in skeletal muscle results in a progressive decline in muscle mass. Sarcopenic muscles become infiltrated with adipose tissue and fibrotic tissue at later stages. Lipids and their derivatives accumulate between muscle cells, leading to lipotoxicity and insulin resistance, as well as enhanced secretion of pro-inflammatory cytokine. In addition, because skeletal muscle is the primary site responsible for insulin-mediated glucose uptake, the reduction in skeletal muscle mass can decrease the insulin sensitivity, which plays a main pathogenic role in the development of hepatic steatosis. Fatty liver disease is a chronic low-grade inflammatory state, and some of the inflammatory mediators from the liver and other pro-inflammatory cytokines might be associated with low muscle mass.<sup>35</sup> Hepatokines, secreted by hepatocytes that can mediate metabolic disorders, may exacerbate adipose tissue atrophy, support chronic low-grade inflammation and establish a vicious cycle of insulin resistance and inflammation.<sup>36</sup>

To the best of our knowledge, this is the first study to examine the relationship between MAFLD and low muscle mass. In addition, we evaluated multiple metabolic confounding factors including significant fibrosis. However, this study has several limitations. First, due to its cross-sectional study design, a causal relationship is difficult to establish. Second, although liver biopsy is considered to be a gold standard for the diagnosis of hepatic steatosis, it is not typically used in asymptomatic individuals in clinical practice. Ultrasonography is mostly used for the diagnosis of hepatic steatosis; however, it has limitations such as interpersonal variability and inaccuracy in subjects with low liver fat contents.<sup>37</sup> The variation in the optimal CAP value is most likely due to disease prevalence in the examined population. Employing a low threshold CAP value may lead to an overestimation of the prevalence of MAFLD, which is 49.9% in this study. This prevalence is higher than that reported in a recent meta-analysis of the global prevalence of MAFLD (38.8%).<sup>38</sup> Therefore, we applied another CAP value of 294 dB/m to establish the robust finding of a relationship between MAFLD and low muscle mass and obtained comparable results. Third, BIA is not the gold standard method by which to evaluate muscle mass; however, it provides simple, inexpensive and reliable estimates of skeletal muscle mass especially at health screening centres and primary clinics and is appropriate for measuring muscle mass in large cohorts and has been previously validated for predicting whole-body muscle mass using BIA.<sup>39</sup> In addition, although muscle composition, such as myosteatosis, is considered as a major determinant for muscle function and strength, we could not assess this. Fourth, this study was composed of health check-up participants who are likely to be highly motivated to improve their health for any reason, they might not be representative of the general population and not all people who undergo health check-ups at our institution receive a FibroScan exam. In this context, most of the study subjects were men and asymptomatic and most of them had non-significant liver disease as indicated by LSM < 7.1 kPa, and this might result in a selection bias. Therefore, the results of our study should be interpreted carefully, and further studies are required to validate our results. Lastly, because we could not obtain information regarding muscle strength or physical performance, we could not evaluate the functional aspects of sarcopenia.

In conclusion, we demonstrated that MAFLD was significantly associated with low muscle mass. The risk of low muscle mass varies according to the subgroup of MAFLD. Therefore, clinicians should be aware of the differentiated risk of low muscle mass across the subgroups of MAFLD.

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The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.<sup>40</sup>

# **Conflict of interest**

None declared.

# **Online supplementary material**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## References

- Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–209.
- Kawaguchi T, Tsutsumi T, Nakano D, Torimura T. MAFLD: renovation of clinical practice and disease awareness of fatty liver. *Hepatol Res* 2022:**52**:422–432.
- Ayada I, van Kleef LA, Alferink LJM, Li P, de Knegt RJ, Pan Q. Systematically comparing epidemiological and clinical features of MAFLD and NAFLD by meta-analysis: focus-

ing on the non-overlap groups. *Liver Int* 2022;**42**:277–287.

- Ng CH, Huang DQ, Nguyen MH. NAFLD versus MAFLD: prevalence, outcomes and implications of a change in name. *Clin Mol Hepatol* 2022 May 11. https://doi.org/10. 3350/cmh.2022.0070 Online ahead of print.
- Fouad Y, Dufour JF, Zheng MH, Bollipo S, Desalegn H, Grønbaek H, et al. The NAFLD-MAFLD debate: is there a Consensus-on-Consensus methodology? *Liver Int* 2022;**42**:742–748.
- 6. Kawaguchi T, Tsutsumi T, Nakano D, Eslam M, George J, Torimura T. MAFLD enhances

clinical practice for liver disease in the Asia-Pacific region. *Clin Mol Hepatol* 2022; **28**:150–163.

- Rosenberg IH. Sarcopenia: origins and clinical relevance. *Clin Geriatr Med* 2011; 27:337–339.
- Lee YH, Jung KS, Kim SU, Yoon HJ, Yun YJ, Lee BW, et al. Sarcopaenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008–2011). J Hepatol 2015; 63:486–493.
- 9. Pan X, Han Y, Zou T, Zhu G, Xu K, Zheng J, et al. Sarcopenia contributes to the

progression of nonalcoholic fatty liver disease-related fibrosis: a meta-analysis. *Dig Dis* 2018;**36**:427–436.

- Chun HS, Kim MN, Lee JS, Lee HW, Kim BK, Park JY, et al. Risk stratification using sarcopenia status among subjects with metabolic dysfunction-associated fatty liver disease. J Cachexia Sarcopenia Muscle 2021; 12:1168–1178.
- 11. Chung GE, Park HE, Kim MJ, Kwak MS, Yang JI, Chung SJ, et al. The association between low muscle mass and hepatic steatosis in asymptomatic population in Korea. *Life* (*Basel*) 2021;**11**:848.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.
- Chung GE, Kim MJ, Yim JY, Kim JS, Yoon JW. Sarcopenia is significantly associated with presence and severity of nonalcoholic fatty liver disease. J Obes Metab Syndr 2019;28: 129–138.
- Panel CP, Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, et al. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis—2021 update. J Hepatol 2021;75:659–689.
- Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66: 1022–1030.
- Petroff D, Blank V, Newsome PN, Voican CS, Voican CS, Thiele M, et al. Assessment of hepatic steatosis by controlled attenuation parameter using the M and XL probes: an individual patient data meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6: 185–198.
- Sohn W, Kwon HJ, Chang Y, Ryu S, Cho YK. Liver fibrosis in Asians with metabolic dysfunction-associated fatty liver disease. *Clin Gastroenterol Hepatol* 2022;20: e1135–e1148.
- Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889–896.
- Kim YS, Lee Y, Chung YS, Lee DJ, Joo NS, Hong D, et al. Prevalence of sarcopenia and sarcopenic obesity in the Korean population based on the Fourth Korean National Health and Nutritional Examination Surveys. J Gerontol A Biol Sci Med Sci 2012;67:1107–1113.

- Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69:547–558.
- Cai C, Song X, Chen Y, Chen X, Yu C. Relationship between relative skeletal muscle mass and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Hepatol Int* 2020;**14**:115–126.
- Fernández-Mincone T, Contreras-Briceño F, Espinosa-Ramírez M, García-Valdés P, López-Fuenzalida A, Riquelme A, et al. Nonalcoholic fatty liver disease and sarcopenia: pathophysiological connections and therapeutic implications. *Expert Rev Gastroenterol Hepatol* 2020;14:1141–1157.
- Roh E, Hwang SY, Yoo HJ, Baik SH, Lee JH, Son SJ, et al. Impact of non-alcoholic fatty liver disease on the risk of sarcopenia: a nationwide multicenter prospective study. *Hepatol Int* 2022 Jun;16:545–554.
- Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, et al. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. *Liver Int* 2020;40:3018–3030.
- Kim M, Yoon EL, Cho S, Lee CM, Kang BK, Park H, et al. Prevalence of advanced hepatic fibrosis and comorbidity in metabolic dysfunction-associated fatty liver disease in Korea. *Liver Int* 2022;42:1536–1544.
- 26. Yoneda M, Yamamoto T, Honda Y, Imajo K, Ogawa Y, Kessoku T, et al. Risk of cardiovascular disease in patients with fatty liver disease as defined from the metabolic dysfunction associated fatty liver disease or nonalcoholic fatty liver disease point of view: a retrospective nationwide claims database study in Japan. J Gastroenterol 2021;56:1022–1032.
- Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study. *Clin Gastroenterol Hepatol* 2021;**19**:2138–2147.e10.
- Tsutsumi T, Eslam M, Kawaguchi T, Yamamura S, Kawaguchi A, Nakano D, et al. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: generalized estimating equation approach. *Hepatol Res* 2021;**51**: 1115–1128.
- Kim KM, Jang HC, Lim S. Differences among skeletal muscle mass indices derived from height-, weight-, and body mass indexadjusted models in assessing sarcopenia. *Korean J Intern Med* 2016;**31**:643–650.
- 30. Linge J, Heymsfield SB, Dahlqvist Leinhard O. On the definition of sarcopenia in the

presence of aging and obesity—initial results from UK Biobank. *J Gerontol A Biol Sci Med Sci* 2020;**75**:1309–1316.

- Linge J, Ekstedt M, Dahlqvist Leinhard O. Adverse muscle composition is linked to poor functional performance and metabolic comorbidities in NAFLD. JHEP Rep 2020;3:100197.
- Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, et al. From NAFLD to MAFLD: implications of a premature change in terminology. *Hepatology* 2021;73:1194–1198.
- Moon JH, Kim W, Koo BK, Cho NH, the Innovative Target Exploration of NAFLD (ITEN) consortium. Metabolic dysfunctionassociated fatty liver disease predicts long-term mortality and cardiovascular disease. *Gut Liver* 2022;**16**:433–442.
- 34. Mikolasevic I, Orlic L, Franjic N, Hauser G, Stimac D, Milic S. Transient elastography (FibroScan®) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease—where do we stand? World J Gastroenterol 2016;22: 7236–7251.
- Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* 2006;**119**:526.e9–526.e17.
- Camporez JP, Jornayvaz FR, Petersen MC, Pesta D, Guigni BA, Serr J, et al. Cellular mechanisms by which FGF21 improves insulin sensitivity in male mice. *Endocrinol*ogy 2013;**154**:3099–3109.
- Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a metaanalysis. *Hepatology* 2011;54:1082–1090.
- Chan KE, Koh TJL, Tang ASP, Quek J, Yong JN, Tay P, et al. Global prevalence and clinical characteristics of metabolic associated fatty liver disease. A meta-analysis and systematic review of 10,739,607 individuals. J Clin Endocrinol Metab 2022 May 19;dgac321. https://doi.org/10.1210/ clinem/dgac321 Online ahead of print.
- Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985) 2000;89:465–471.
- von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2021. J Cachexia Sarcopenia Muscle 2021;12:2259–2261.