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# Correlation of sarcopenia with progression of liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease: a study from two cohorts in China and the United States

Fan Zhang[1,2,5], Longgen Liu[3,5] and Wenjian Li[4,5*]

## Abstract

**Objective** The objective of this study was to investigate the association between sarcopenia and liver fibrosis in patients aged 18–59 years with metabolic dysfunction-associated steatotic liver disease (MASLD) and to assess the potential of sarcopenia as a risk factor for the progression of liver fibrosis.

**Methods** The study included 821 patients with MASLD in the US cohort and 3,405 patients with MASLD in the Chinese cohort. Liver controlled attenuation parameters (CAP) and liver stiffness measurements (LSM) were assessed by vibration-controlled transient elastography (VCTE) to evaluate the extent of hepatic steatosis and fibrosis. Sarcopenia was assessed by measuring appendicular skeletal muscle mass (ASM) and calculating ASMI. To analyze the relationship between sarcopenia, ASMI, and liver fibrosis, logistic regression models, multivariate-adjusted models, and restricted cubic spline (RCS) models were employed, with stratification and interaction analyses.

**Results** The results demonstrated that patients with sarcopenia exhibited a markedly elevated risk of significant liver fibrosis, advanced liver fibrosis, and cirrhosis compared to those without sarcopenia in both cohorts. After adjusting for confounding variables, sarcopenia was identified as an independent risk factor for the progression of liver fibrosis in patients with MASLD. A significant negative correlation was observed between ASMI and the severity of liver fibrosis, with a progressive reduction in the risk of liver fibrosis associated with increasing ASMI. Additionally, a non-linear feature was evident in some liver fibrosis indicators. Subgroup analysis further corroborated the finding that the harmful effect of sarcopenia on liver fibrosis was consistent across all identified subgroups.

**Conclusion** Sarcopenia may be associated with the progression of liver fibrosis in patients with MASLD. Monitoring ASMI may assist in identifying individuals at an elevated risk of liver fibrosis in MASLD patients.

**Keywords** Metabolic dysfunction-associated steatotic liver disease, Liver fibrosis, Sarcopenia, Appendicular skeletal muscle mass index, Multinational cohort study

*Correspondence:
Wenjian Li
760020240117@xzhmu.edu.cn
Full list of author information is available at the end of the article

## Introduction

The rising incidence of metabolic dysfunction-associated steatosis liver disease (MASLD) worldwide has elevated this condition to a prominent public health concern [1–3]. MASLD is not only characterized by localized damage to the liver but also by extensive systemic effects, including the development of comorbidities such as cardiovascular disease, type 2 diabetes mellitus, and chronic kidney disease. These comorbidities significantly adversely impact patients' quality of life and contribute to an increased healthcare burden [1, 4–7]. Liver fibrosis, as a crucial phase in the progression of MASLD, indicates a significant risk of disease advancement to cirrhosis or even hepatocellular carcinoma. The severity of the condition is closely correlated with the long-term prognosis of patients [3, 4, 8–10]. Therefore, It is imperative to conduct a comprehensive investigation into the etiology of liver fibrosis and its contributory factors in patients with MASLD to facilitate the early identification, intervention, and management of the disease.

In recent years, sarcopenia, a syndrome of decreased muscle mass and reduced muscle function that occurs with aging, its role in the pathologic process of MASLD, has been the subject of increasing academic attention [11–13]. Some studies have demonstrated a correlation between sarcopenia and the severity, as well as the poor prognosis, of liver disease, including non-alcoholic fatty liver disease (NAFLD) and chronic liver disease [12, 14]. Sarcopenia affects not only an individual's exercise capacity and daily functioning but may also contribute to the process of hepatic fibrosis in patients with liver disease through a variety of mechanisms, including increasing insulin resistance and promoting inflammatory responses [11]. The available evidence indicates that sarcopenia is not only a risk factor for the development of NAFLD but is also associated with the progression of significant fibrosis associated with NAFLD [15, 16]. However, studies on the relationship between sarcopenia and hepatic fibrosis in patients with MASLD are still insufficient, and the specific manifestations and mechanisms in different populations have not been fully described.

In addition to sarcopenia, the onset and progression of liver fibrosis are influenced by a variety of other factors, including lifestyle factors and genetics. Lifestyle factors, including poor dietary habits, lack of physical activity, and excessive alcohol consumption, have been demonstrated to be associated with an elevated risk of liver fibrosis [17–19]. Genetic factors, such as variations in specific genes, may also influence an individual's susceptibility to liver fibrosis [20]. Consequently, these factors should be considered collectively in studies to gain a more comprehensive understanding of the intricate mechanisms of liver fibrosis in patients with MASLD.

This study selected patients aged 18–59 in alignment with the epidemiologic characteristics of MASLD and the onset of sarcopenia. Although sarcopenia is more prevalent in the elderly, studying this age group may provide insights into the early relationship between sarcopenia and liver fibrosis, which is crucial for early identification and intervention. Furthermore, patients in this age group are more susceptible to lifestyle factors, which presents an opportunity to examine the influence of lifestyle modifications on MASLD and sarcopenia.

To gain a more comprehensive understanding of this complex relationship, this study employed cohort data from two distinct countries: the National Health and Nutrition Examination Survey (NHANES) 2017–2018 cohort in the United States and the Third People's Hospital Cohort in Changzhou City, China. The integration of data from disparate geographical regions confers several advantages. Primarily, this approach enhances the generalizability and representativeness of the study results while simultaneously reducing the impact of geographic and ethnic factors on the findings. Secondly, by comparing the characteristics of MASLD patients in different countries and cultures, we can investigate the potential heterogeneity of the relationship between sarcopenia and liver fibrosis in greater depth. Ultimately, this cross-cultural perspective enables the identification of novel research pathways and intervention strategies, thereby providing more comprehensive and scientific guidance for managing MASLD patients globally.

In light of the background above, this study aimed to examine the relationship between sarcopenia and liver fibrosis in MASLD patients aged 18–59 by analyzing data from MASLD patients in China and the United States. The objective of this study is to provide new epidemiological evidence on the relationship between sarcopenia and liver fibrosis in patients with MASLD through a cross-national cohort study. Moreover, the objective is to establish a scientific basis for developing individualized intervention strategies for patients with MASLD.

## Materials and methods

### Study population

The data for this study were derived from two distinct cohorts: the NHANES 2017-2018 cohort in the United States and the Third People's Hospital of Changzhou City, China cohort, which spanned May 2018 to July 2023. The NHANES database incorporates the findings of cross-sectional surveys conducted biennially by the Centers for Disease Control and Prevention (CDC) in the United States. The study protocol for the NHANES database has been approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants have provided informed consent to the relevant ethical

guidelines. Following pertinent NIH policies, the data in the NHANES database, which was not obtained through direct contact with participants, may be utilized directly for data analysis without further review by the institutional ethics committee. Accordingly, the Changzhou Third People's Hospital Ethics Committee has determined that no further ethical review approval is required to use NHANES data in this study. The Changzhou Third People's Hospital Ethics Committee granted approval for the Chinese cohort. This study was conducted by the ethical principles outlined in the Declaration of Helsinki. Before the commencement of the study, all participants were required to complete an informed consent form.

The U.S. cohort comprised 9,254 participants, informed by the 2017-2018 NHANES survey. As the NHANES survey only included dual-energy X-ray absorptiometry (DXA) testing for participants under the age of 60 in the sub-survey cycle, the Chinese cohort was initially constituted of participants younger than 60 years of age, amounting to a total of 7,436 individuals. The following participants were excluded from both cohorts during the study: Individuals under the age of 18 and pregnant women were excluded from the study. Additionally, participants with missing controlled attenuation parameters (CAP) or liver stiffness measurements (LSM) data, as well as those lacking appendicular skeletal muscle mass (ASM) data, were not included. Finally, those who consumed excessive alcohol, defined as more than an average of five drinks per day for males and more than four drinks per day for females in the 12 months preceding the survey, were also excluded. Individuals with a history of viral hepatitis B or C, autoimmune hepatitis, or hepatocellular carcinoma; those currently undergoing treatment with medications known to cause fatty liver, including amiodarone, methotrexate, or tamoxifen, for a minimum of three months before enrollment were excluded. Furthermore, participants with incomplete body mass index (BMI) data, those lacking chronic disease information, individuals with missing crucial biochemical indicators, and non-MASLD participants were excluded. Following a comprehensive screening process, 3,405 participants from the Chinese cohort and 821 from the US cohort were ultimately included in the data analysis (Fig. 1).

#### Assessment of MASLD and liver fibrosis

Vibration-controlled transient elastography (VCTE) was employed to assess the extent of hepatic steatosis, with CAP measurements utilized for this purpose. A CAP value of 269 dB/m or greater was observed in each participant, indicating the presence of hepatic steatosis [21]. Moreover, a diagnosis of MASLD was confirmed if any of the following five cardiometabolic criteria were met: (1) A BMI of 25 kg/m$^2$ or greater, or a waist circumference (WC) of 94 cm or greater for males and 80 cm or greater for females; (2) a fasting plasma glucose (FPG) level of 100 mg/dL or greater, or a two-hour post-load blood glucose level of 140 mg/dL or greater, or a glycated hemoglobin (HbA1C) level of 5.7% or more significant, or a diagnosis of diabetes mellitus (DM), or the receipt of glucose-lowering therapy for DM; (3) a blood pressure reading of ≥130/85 mmHg, or the use of antihypertensive medication. (4) A fasting plasma triglyceride (TG) level of 150 mg/dL or greater, or the use of lipid-lowering therapy; and (5) A high-density lipoprotein cholesterol (HDL-c) level of less than 40 mg/dL in men and less than 50 mg/dL in women, or the use of lipid-lowering therapy [4].

Liver fibrosis was assessed based on the values obtained from the LSM test. An LSM of ≥7.6 kPa was deemed indicative of significant liver fibrosis (F≥F2), whereas an LSM of ≥9.8 kPa was indicative of advanced liver fibrosis (F≥F3). An LSM of ≥12.9 kPa was indicative of cirrhosis (F4) [21].

#### Assessment of sarcopenia

The DXA was utilized to quantify ASM, which represents the total lean mass of the arms and legs. Individuals who were excluded from the DXA examination included those who were pregnant (as indicated by a positive urine pregnancy test and/or self-report at the time of the examination), had used a radiographic contrast agent (barium) within the past seven days, and had a body weight exceeding 450 lbs. or height exceeding 6 ft. 5 in. The ASMI is calculated by dividing the ASM by the BMI. By the criteria established by the Foundation for the National Institutes of Health (FNIH), an ASMI of less than 0.789 for males and 0.512 for females indicates sarcopenia [22].

#### Assessment of covariates

Multivariate adjustment models were constructed to investigate the effect of confounding variables on the relationship between ASMI, sarcopenia, and liver fibrosis in patients with MASLD. In this study, the covariates included gender (male/female), age (years), smoking status (yes/no), alcohol intake (yes/no), physical activity level, and history of chronic diseases such as DM and hypertension. Smoking status was determined based on whether the participant had smoked at least 100 cigarettes in their lifetime and whether they were currently engaged in smoking. Alcohol consumption was assessed by asking the participant whether they had consumed at least 12 alcoholic beverages of any type in the past year. Physical activity was classified into three categories: vigorous, moderate, and inactive. A history of diabetes was established based on

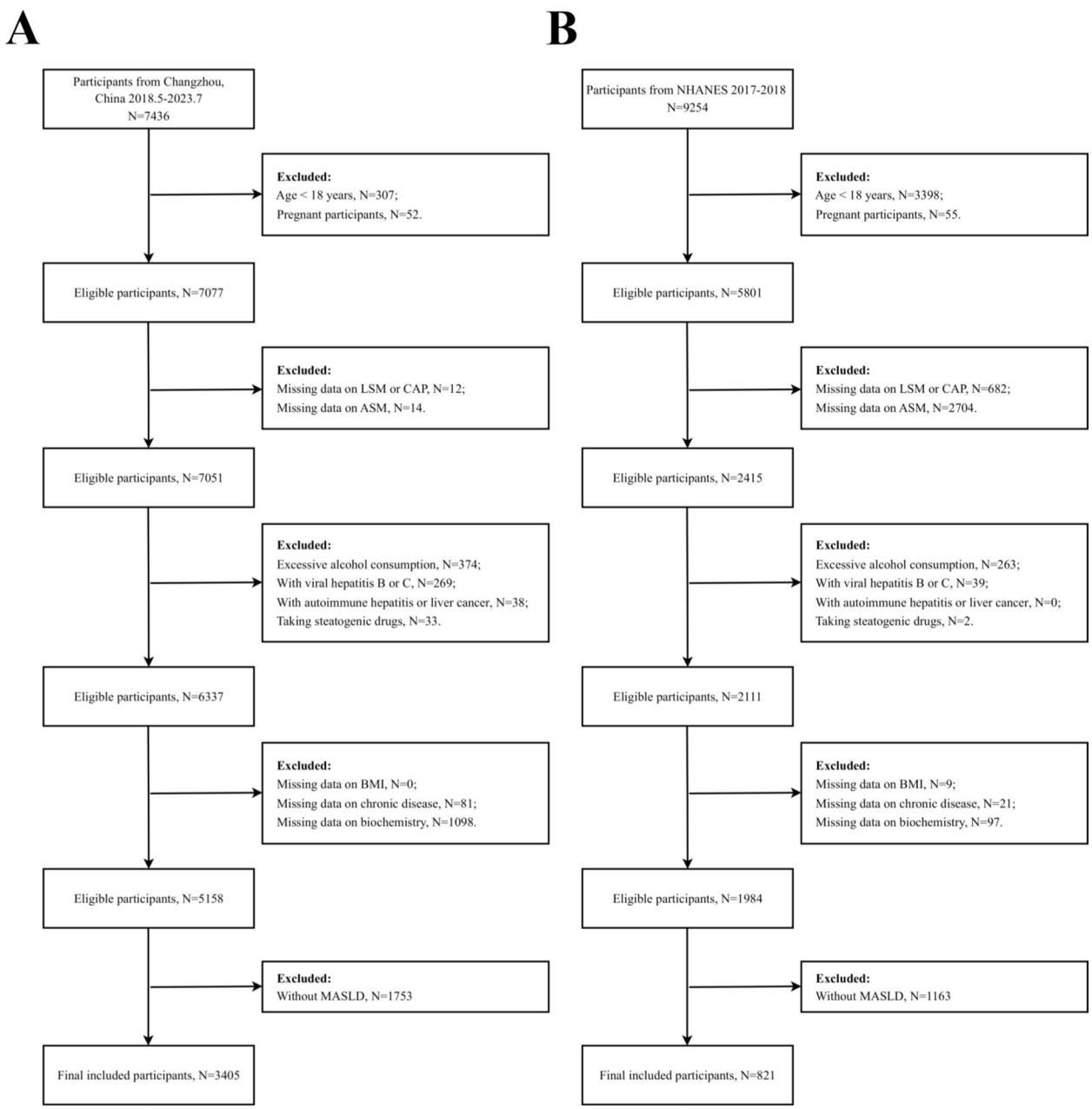


**Fig. 1** Participant screening flowchart. **A** the Chinese cohort; **B** the US cohort. Abbreviations: LSM, Liver stiffness measurement; CAP, Controlled attenuation parameter; ASM, Appendicular skeletal muscle mass; BMI, Body mass index; MASLD, Metabolic dysfunction-associated steatotic liver disease

whether the participant had been diagnosed with diabetes by a physician, exhibited an FPG level of 126 mg/dL or higher, demonstrated an HbA1C level of 6.5% or above, and was currently utilizing diabetes medication or insulin. A history of hypertension was established based on whether the participant had been diagnosed with hypertension by a physician or was currently undergoing treatment for hypertension.

### Statistical analysis

The Kolmogorov-Smirnov test was utilized to determine whether the continuous variables demonstrated a normal distribution. The data were expressed as mean ± standard deviation for variables that exhibited a normal distribution. In contrast, variables that did not conform to a normal distribution were expressed using the median (along with the 25th and 75th percentiles). To facilitate

the comparison of the variables above, we elected to utilize either the Student's t-test or the Mann-Whitney test for statistical analysis, contingent upon the distributional characteristics of the data. Frequencies and percentages were calculated for categorical variables, and the chi-square test was employed to assess differences between groups.

The objective of this study was to investigate the correlation between ASMI, ASMI quartiles, sarcopenia, and liver fibrosis in patients with MASLD. Logistic regression models were constructed to achieve this, and the odds ratio (OR) and its 95% confidence interval (CI) were calculated. Three multivariate-adjusted models were built to assess these relationships and address potential confounding variables more accurately. Model 1 was unadjusted; Model 2 was constructed based on Model 1 by incorporating gender and age as adjusting factors; and Model 3 was further constructed based on Model 2 by extending the adjustment for variables such as smoking, alcohol, physical activity, DM, and hypertension. Moreover, we utilized a restricted cubic spline (RCS) model to determine the potential dose-response relationship between ASMI and liver fibrosis in patients with MASLD. To gain further insight into the relationship between ASMI and the risk of liver fibrosis in different subgroups of patients with MASLD, a series of stratified analyses were conducted, dividing the variables into groups based on gender (male or female), age (18-39 or 40-59), smoking status (yes or no), alcohol (yes or no), physical activity (inactive, moderate, or vigorous), BMI (<28 or ≥28), DM (yes or no), and hypertension (yes or no). These analyses permitted the assessment of the potential interaction between these variables and their influence on the observed relationships.

All statistical analyses were conducted using a two-sided test, and a *P*-value of less than 0.05 was used to determine statistical significance. All statistical analyses were conducted using R 4.4.0 (provided by the R Foundation at http://www.R-project.org) and SPSS version 23.0 (provided by IBM, Armonk, NY, USA). The graphs were generated using GraphPad Prism version 9.0 (provided by GraphPad Software, Inc., USA).

## Results

### Baseline characteristics of MASLD patients with and without sarcopenia in the Chinese cohort

In the cohort of Chinese patients with MASLD, the prevalence of sarcopenia was found to be 18.4%. Significant differences were observed between the non-sarcopenia and sarcopenia patient groups about several baseline characteristics. The prevalence of sarcopenia was higher in males (87.04%). Although there was no significant difference in age between the two groups ($P = 0.090$), patients with sarcopenia exhibited significantly higher BMI and WC than non-sarcopenia patients (BMI: 30.10 kg/m$^2$ vs. 27.50 kg/m$^2$, $P < 0.001$; WC: 101.20 cm vs. 96.10 cm, $P < 0.001$). Moreover, the levels of aspartate transferase (AST), alanine transferase (ALT), gamma-glutamyl transpeptidase (GGT), creatinine, uric acid, LSM, and CAP were markedly elevated in patients with sarcopenia in comparison to those without sarcopenia. In contrast, HDL-c levels were significantly decreased in the former group. These findings suggest that sarcopenia may be a clinically significant factor in patients with MASLD, associated with more severe metabolic and hepatic pathological changes. It is noteworthy that the presence of sarcopenia was significantly associated with significant liver fibrosis, advanced liver fibrosis, and cirrhosis (all $P < 0.001$) (Table 1).

### Baseline characteristics of MASLD patients with and without sarcopenia in the US Cohort

In the United States cohort of patients with MASLD, the prevalence of sarcopenia was 16.2%. Patients with sarcopenia ($n$=133) exhibited notable differences in baseline characteristics compared to non-sarcopenia patients ($n$=688). No significant difference was observed in gender distribution ($P = 0.200$). However, age (48.00 vs. 42.00 years, $P = 0.002$), BMI (36.00 kg/m$^2$ vs. 31.20 kg/m$^2$, $P$ <0.001), or WC (113.30 cm vs. 103.00 cm, $P$ <0.001) between patients with sarcopenia and non-sarcopenia patients were significantly higher in the former group. Moreover, FPG, HbA1c, TG, GGT, and LSM were also markedly elevated in patients with sarcopenia compared to those without sarcopenia, whereas HDL-c and creatinine were significantly decreased in the former group. As observed in the Chinese cohort, the presence of sarcopenia was significantly associated with significant liver fibrosis, advanced liver fibrosis, and cirrhosis (all $P$ <0.05) (Table 2).

### Relationship between ASMI, sarcopenia, and liver fibrosis in Chinese patients with MASLD

In patients with MASLD in China, a significant correlation was observed between the presence of sarcopenia and ASMI and the degree of liver fibrosis. After adjusting for gender, age, smoking, Alcohol, physical activity, DM, and hypertension, patients with sarcopenia exhibited a significantly elevated risk of developing significant liver fibrosis (OR=1.27, 95% CI: 1.04-1.54, $P$=0.018), advanced liver fibrosis (OR=1.27, 95% CI: 1.01-1.60, $P$=0.047), and cirrhosis (OR=1.65, 95% CI: 1.19-2.28, $P$=0.002) compared to non-sarcopenia patients. Conversely, the risk of significant liver fibrosis, advanced liver fibrosis, and cirrhosis was found to decrease significantly with increasing quartiles of ASMI. These findings suggest that sarcopenia

**Table 1** Baseline characteristics of MASLD patients with and without sarcopenia in the Chinese cohort

| Variables | Total (*n* = 3405) | Non-Sarcopenia (*n* = 2780) | Sarcopenia (*n* = 625) | *P* |
|---|---|---|---|---|
| Gender, n (%) | | | | < 0.001 |
| Male | 2287 (67.17) | 1743 (62.70) | 544 (87.04) | |
| Female | 1118 (32.83) | 1037 (37.30) | 81 (12.96) | |
| Age (years) | 39.00 (31.00, 48.00) | 39.00 (31.00, 49.00) | 39.00 (31.00, 48.00) | 0.090 |
| BMI (kg/m$^2$) | 27.90 (25.50, 30.60) | 27.50 (25.30, 30.00) | 30.10 (27.60, 33.30) | < 0.001 |
| WC (cm) | 97.00 (90.90, 104.60) | 96.10 (90.20, 103.40) | 101.20 (94.00, 110.50) | < 0.001 |
| FPG (mg/dL) | 97.20 (91.80, 110.52) | 97.20 (91.80, 109.80) | 99.00 (90.36, 111.60) | 0.610 |
| HbA1c (%) | 5.50 (5.10, 6.10) | 5.50 (5.10, 6.10) | 5.50 (5.10, 6.20) | 0.129 |
| TC (mg/dL) | 183.73 (160.91, 209.65) | 183.34 (160.14, 209.26) | 186.44 (164.78, 211.19) | 0.109 |
| TG (mg/dL) | 152.39 (105.43, 225.93) | 152.39 (103.66, 225.93) | 155.05 (111.64, 222.39) | 0.263 |
| HDL-c (mg/dL) | 42.13 (36.33, 48.31) | 42.13 (36.33, 48.41) | 40.97 (35.94, 47.54) | 0.033 |
| AST (U/L) | 28.00 (20.00, 46.00) | 28.00 (20.00, 45.00) | 29.00 (21.00, 48.00) | 0.046 |
| ALT (U/L) | 45.70 (26.70, 87.00) | 44.35 (26.00, 86.28) | 49.80 (29.00, 92.40) | 0.022 |
| GGT (IU/L) | 44.00 (26.40, 77.00) | 43.05 (25.20, 76.93) | 48.00 (31.00, 78.00) | 0.002 |
| Total Bilirubin (mg/dL) | 0.76 (0.60, 1.01) | 0.76 (0.59, 1.00) | 0.78 (0.61, 1.01) | 0.248 |
| Creatinine (mg/dL) | 0.83 (0.71, 0.97) | 0.83 (0.70, 0.97) | 0.85 (0.75, 0.97) | 0.015 |
| Uric acid (mg/dL) | 6.26 (5.25, 7.39) | 6.21 (5.22, 7.35) | 6.52 (5.56, 7.64) | < 0.001 |
| BUN (mg/dL) | 13.72 (11.76, 16.24) | 13.72 (11.73, 16.24) | 14.00 (11.87, 16.18) | 0.177 |
| C-Reactive Protein (mg/L) | 2.64 (1.35, 3.85) | 2.56 (1.29, 3.73) | 3.13 (1.63, 4.59) | < 0.001 |
| Smoke, n (%) | | | | 0.028 |
| Yes | 1355 (39.79) | 1082 (38.92) | 273 (43.68) | |
| No | 2050 (60.21) | 1698 (61.08) | 352 (56.32) | |
| Alcohol, n (%) | | | | < 0.001 |
| Yes | 940 (27.61) | 816 (29.35) | 124 (19.84) | |
| No | 2465 (72.39) | 1964 (70.65) | 501 (80.16) | |
| Physical Activity, n (%) | | | | < 0.001 |
| Inactive | 1518 (44.58) | 1168 (42.01) | 350 (56.00) | |
| Moderate | 945 (27.75) | 798 (28.71) | 147 (23.52) | |
| Vigorous | 942 (27.67) | 814 (29.28) | 128 (20.48) | |
| Diabetes mellitus, n (%) | | | | 0.144 |
| Yes | 680 (19.97) | 542 (19.50) | 138 (22.08) | |
| No | 2725 (80.03) | 2238 (80.50) | 487 (77.92) | |
| Hypertension, n (%) | | | | 0.670 |
| Yes | 1021 (29.99) | 838 (30.14) | 183 (29.28) | |
| No | 2384 (70.01) | 1942 (69.86) | 442 (70.72) | |
| LSM (kpa) | 6.40 (5.10, 8.50) | 6.30 (5.00, 8.20) | 6.90 (5.50, 9.30) | < 0.001 |
| CAP (dB/m) | 329.00 (301.00, 356.00) | 328.00 (300.00, 354.00) | 335.00 (305.00, 362.00) | < 0.001 |
| ASMI | 0.80 (0.67, 0.90) | 0.84 (0.66, 0.92) | 0.74 (0.68, 0.77) | < 0.001 |
| Significant fibrosis, n (%) | | | | < 0.001 |
| Yes | 1121 (32.92) | 861 (30.97) | 260 (41.60) | |
| No | 2284 (67.08) | 1919 (69.03) | 365 (58.40) | |
| Advanced fibrosis, n (%) | | | | < 0.001 |
| Yes | 571 (16.77) | 432 (15.54) | 139 (22.24) | |
| No | 2834 (83.23) | 2348 (84.46) | 486 (77.76) | |
| Cirrhosis, n (%) | | | | < 0.001 |
| Yes | 230 (6.75) | 167 (6.01) | 63 (10.08) | |
| No | 3175 (93.25) | 2613 (93.99) | 562 (89.92) | |

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant.

*Abbreviations*: *MASLD* Metabolic dysfunction-associated steatotic liver disease, *BMI* Body mass index, *WC* Waist circumference, *FPG* Fasting plasma-glucose, *HbA1c* Hemoglobin A1c, *TC* Total cholesterol, *TG* Triglyceride, *HDL-c* High-density lipoprotein cholesterol, *AST* Aspartate aminotransferase, *ALT* Alanine transaminase, *GGT* Gamma-glutamyl transferase, *BUN* Blood urea nitrogen, *LSM* Liver stiffness measurement, *CAP* Controlled attenuation parameter, *ASMI* Appendicular skeletal muscle mass index

and lower ASMI are independent risk factors for liver fibrosis progression in Chinese patients with MASLD (Table 3).

### Relationship between ASMI, sarcopenia, and liver fibrosis in US patients with MASLD

In patients with MASLD in the United States, sarcopenia and ASMI were similarly strongly correlated with the severity of liver fibrosis. After adjusting for relevant covariates, patients with sarcopenia exhibited a significantly elevated risk of significant liver fibrosis (OR=1.79, 95% CI: 1.12-2.86, *P*=0.014), advanced liver fibrosis (OR=2.83, 95% CI: 1.55-5.16, *P*<0.001), and cirrhosis (OR=2.45, 95% CI: 1.08-5.58, *P*=0.032) compared to the risk observed in patients with non-sarcopenia. Moreover, the risk of significant liver fibrosis, advanced liver fibrosis, and cirrhosis was observed to decline markedly with increasing quartiles of ASMI. These findings provide support for the hypothesis that sarcopenia and ASMI may serve as valuable biomarkers for predicting the progression of liver fibrosis in US patients with MASLD (Table 4).

### RCS analysis

Figure 2 depicts the relationship between the RCS fitting and the severity of liver fibrosis in patients with MASLD in two cohorts from China and the United States. All analyses were adjusted for potential confounding variables, including gender, age, smoking status, alcohol, physical activity, DM, and hypertension. In the Chinese cohort, the proportion of odds of developing significant liver fibrosis (Fig. 2A), advanced liver fibrosis (Fig. 2B), and cirrhosis (Fig. 2C) exhibited a gradual decline with increasing ASMI, and the association was statistically significant (all $P$ <0.05). The nonlinearity test indicated the presence of a nonlinear association between ASMI and cirrhosis (P-nonlinear = 0.034). In contrast, the association with significant liver fibrosis and advanced liver fibrosis exhibited a linear trend (P-nonlinear = 0.179 and P-nonlinear = 0.289). A comparable trend was observed in the US cohort, whereby the risk of significant liver fibrosis (Fig. 2D), advanced liver fibrosis (Fig. 2E), and cirrhosis (Fig. 2F) were all significantly reduced with increasing ASMI (all $P$ <0.05). Nevertheless, the nonlinear tests did not indicate a statistically significant nonlinear relationship between ASMI and the three liver fibrosis indicators for the U.S. cohort (all P-nonlinear > 0.05). These findings reinforce the potential of ASMI as a biomarker for predicting the progression of liver fibrosis in patients with MASLD and demonstrate consistency across ethnically diverse cohorts.

### Subgroup analysis

We performed a subgroup analysis of patients with MASLD in order to investigate the relationship between sarcopenia and the severity of liver fibrosis. The analysis considered a number of variables, including gender, age, smoking status, alcohol, physical activity, BMI, diabetes mellitus, and hypertension. However, these stratification variables were not taken into account in the analysis itself. As illustrated in Fig. 3, the findings from the Chinese cohort indicated that sarcopenia was a significant risk factor for significant liver fibrosis, advanced liver fibrosis, and cirrhosis in patients with MASLD. Moreover, additional stratified analyses revealed that although the impact of sarcopenia on liver fibrosis differed across various subgroups, no significant interaction was observed in any of the subgroups. This indicates that the deleterious impact of sarcopenia on liver fibrosis was consistent across all identified subgroups. As illustrated in Fig. 4, the U.S. cohort exhibited a similar pattern, with sarcopenia significantly increasing the risk of significant liver fibrosis, advanced liver fibrosis, and cirrhosis in patients with MASLD. A further stratified analysis revealed that in the age subgroup, the risk of sarcopenia with advanced liver fibrosis was more significant in the subgroup of individuals aged 18-39 years old compared to those aged 40-59 years old (P for interaction = 0.025). No significant interactions were identified in any subgroups, with the exception of the age subgroup. This indicates that the detrimental effect of sarcopenia on liver fibrosis is similarly pervasive in the US cohort. The results of the subgroup analyses provided further support for the hypothesis that sarcopenia represents a significant risk factor for the progression of liver fibrosis in patients with MASLD.

## Discussion

The results of this study demonstrate a notable correlation between sarcopenia and the severity of liver fibrosis in patients with MASLD aged 18-59 years. Patients with sarcopenia exhibited a markedly elevated risk of significant liver fibrosis, advanced liver fibrosis, and cirrhosis in comparison to non-sarcopenia patients across both the Chinese and US cohorts. Moreover, the study demonstrated a significant inverse correlation between ASMI and the severity of liver fibrosis in patients with MASLD. In the Chinese cohort, the risk of liver fibrosis exhibited a gradual decline with increasing ASMI, and this relationship demonstrated a nonlinear feature in specific liver fibrosis indicators. In contrast, the potential of ASMI as an essential biomarker for predicting the progression of liver fibrosis in patients with MASLD was similarly

**Table 2** Baseline characteristics of MASLD patients with and without sarcopenia in the US cohort

| Variables | Total (*n* = 821) | Non-Sarcopenia (*n* = 688) | Sarcopenia (*n* = 133) | *P* |
|---|---|---|---|---|
| Gender, n (%) | | | | 0.200 |
| Male | 415 (50.55) | 341 (49.56) | 74 (55.64) | |
| Female | 406 (49.45) | 347 (50.44) | 59 (44.36) | |
| Age (years) | 43.00 (32.00, 52.00) | 42.00 (31.00, 51.00) | 48.00 (32.00, 54.00) | 0.002 |
| BMI (kg/m$^2$) | 31.70 (27.80, 36.50) | 31.20 (27.70, 35.50) | 36.00 (29.80, 41.20) | < 0.001 |
| WC (cm) | 104.20 (95.40, 116.10) | 103.00 (94.60, 113.73) | 113.30 (100.60, 123.50) | < 0.001 |
| FPG (mg/dL) | 95.00 (88.00, 106.00) | 94.00 (88.00, 104.00) | 97.00 (91.00, 115.00) | < 0.001 |
| HbA1c (%) | 5.60 (5.30, 6.10) | 5.60 (5.30, 6.00) | 5.80 (5.40, 6.20) | 0.006 |
| TC (mg/dL) | 193.00 (168.00, 217.00) | 194.00 (167.75, 217.25) | 190.00 (176.00, 215.00) | 0.752 |
| TG (mg/dL) | 145.00 (100.00, 215.00) | 144.00 (97.00, 214.00) | 152.00 (121.00, 223.00) | 0.039 |
| HDL-c (mg/dL) | 45.00 (39.00, 53.00) | 45.00 (39.00, 54.00) | 42.00 (38.00, 50.00) | 0.015 |
| AST (U/L) | 20.00 (16.00, 25.00) | 20.00 (16.00, 25.00) | 20.00 (16.00, 24.00) | 0.723 |
| ALT (U/L) | 23.00 (16.00, 33.00) | 23.00 (16.00, 33.00) | 24.00 (16.00, 34.00) | 0.319 |
| GGT (IU/L) | 26.00 (18.00, 41.00) | 25.00 (17.00, 39.00) | 29.00 (20.00, 50.00) | 0.005 |
| Total Bilirubin (mg/dL) | 0.40 (0.30, 0.50) | 0.40 (0.30, 0.50) | 0.40 (0.30, 0.50) | 0.433 |
| Creatinine (mg/dL) | 0.80 (0.67, 0.95) | 0.82 (0.68, 0.96) | 0.73 (0.62, 0.88) | < 0.001 |
| Uric acid (mg/dL) | 5.60 (4.60, 6.50) | 5.60 (4.60, 6.50) | 5.50 (4.70, 6.80) | 0.533 |
| BUN (mg/dL) | 13.00 (11.00, 16.00) | 13.00 (11.00, 16.00) | 13.00 (11.00, 15.00) | 0.297 |
| C-Reactive Protein (mg/L) | 2.72 (1.24, 5.51) | 2.57 (1.21, 5.31) | 3.28 (1.48, 6.66) | 0.015 |
| Smoke, n (%) | | | | 0.777 |
| Yes | 263 (32.03) | 219 (31.83) | 44 (33.08) | |
| No | 558 (67.97) | 469 (68.17) | 89 (66.92) | |
| Alcohol, n (%) | | | | 0.013 |
| Yes | 345 (42.02) | 302 (43.90) | 43 (32.33) | |
| No | 476 (57.98) | 386 (56.10) | 90 (67.67) | |
| Physical Activity, n (%) | | | | 0.054 |
| Inactive | 169 (20.58) | 135 (19.62) | 34 (25.56) | |
| Moderate | 260 (31.67) | 212 (30.81) | 48 (36.09) | |
| Vigorous | 392 (47.75) | 341 (49.56) | 51 (38.35) | |
| Diabetes mellitus, n (%) | | | | 0.009 |
| Yes | 166 (20.22) | 128 (18.60) | 38 (28.57) | |
| No | 655 (79.78) | 560 (81.40) | 95 (71.43) | |
| Hypertension, n (%) | | | | 0.998 |
| Yes | 253 (30.82) | 212 (30.81) | 41 (30.83) | |
| No | 568 (69.18) | 476 (69.19) | 92 (69.17) | |
| LSM (kpa) | 5.40 (4.40, 6.60) | 5.30 (4.30, 6.50) | 6.00 (4.80, 7.80) | < 0.001 |
| CAP (dB/m) | 309.00 (288.00, 341.00) | 308.00 (287.00, 339.00) | 316.00 (293.00, 349.00) | 0.005 |
| ASMI | 0.73 (0.60, 0.90) | 0.79 (0.61, 0.92) | 0.68 (0.49, 0.75) | < 0.001 |
| Significant fibrosis, n (%) | | | | < 0.001 |
| Yes | 131 (15.96) | 96 (13.95) | 35 (26.32) | |
| No | 690 (84.04) | 592 (86.05) | 98 (73.68) | |
| Advanced fibrosis, n (%) | | | | < 0.001 |
| Yes | 59 (7.19) | 38 (5.52) | 21 (15.79) | |
| No | 762 (92.81) | 650 (94.48) | 112 (84.21) | |
| Cirrhosis, n (%) | | | | 0.013 |
| Yes | 31 (3.78) | 21 (3.05) | 10 (7.52) | |
| No | 790 (96.22) | 667 (96.95) | 123 (92.48) | |

Data are shown as median (25th, 75th percentiles) or percentages, $p < 0.05$ considered statistically significant

*Abbreviations*: *MASLD* Metabolic dysfunction-associated steatotic liver disease, *BMI* Body mass index, *WC* Waist circumference, *FPG* Fasting plasma-glucose, *HbA1c* Hemoglobin A1c, *TC* Total cholesterol, *TG* Triglyceride, *HDL-c* High-density lipoprotein cholesterol, *AST* Aspartate aminotransferase, *ALT* Alanine transaminase, *GGT* Gamma-glutamyl transferase, *BUN* Blood urea nitrogen, *LSM* Liver stiffness measurement, *CAP* Controlled attenuation parameter, *ASMI* Appendicular skeletal muscle mass index

**Table 3** Relationship between ASMI, sarcopenia and hepatic fibrosis in patients with MASLD in the Chinese cohort

| Variables | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* | OR (95%CI) | *P* |
| **Significant fibrosis** | | | | | | |
| ASMI | 0.40 (0.25 ~ 0.64) | < 0.001 | 0.07 (0.03 ~ 0.15) | < 0.001 | 0.26 (0.12 ~ 0.59) | 0.001 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 0.94 (0.77 ~ 1.15) | 0.577 | 0.61 (0.47 ~ 0.79) | < 0.001 | 0.75 (0.57 ~ 0.99) | 0.040 |
| Quartile 3 | 0.95 (0.78 ~ 1.16) | 0.648 | 0.50 (0.37 ~ 0.68) | < 0.001 | 0.68 (0.49 ~ 0.94) | 0.019 |
| Quartile 4 | 0.65 (0.53 ~ 0.79) | < 0.001 | 0.33 (0.24 ~ 0.46) | < 0.001 | 0.54 (0.38 ~ 0.76) | < 0.001 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 1.59 (1.33 ~ 1.90) | < 0.001 | 1.59 (1.33 ~ 1.91) | < 0.001 | 1.27 (1.04 ~ 1.54) | 0.018 |
| **Advanced fibrosis** | | | | | | |
| ASMI | 0.34 (0.19 ~ 0.62) | < 0.001 | 0.07 (0.03 ~ 0.19) | < 0.001 | 0.25 (0.09 ~ 0.69) | 0.007 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 0.88 (0.69 ~ 1.12) | 0.289 | 0.58 (0.42 ~ 0.80) | 0.001 | 0.69 (0.49 ~ 0.97) | 0.032 |
| Quartile 3 | 0.88 (0.69 ~ 1.12) | 0.289 | 0.48 (0.33 ~ 0.71) | < 0.001 | 0.63 (0.42 ~ 0.94) | 0.023 |
| Quartile 4 | 0.59 (0.46 ~ 0.77) | < 0.001 | 0.32 (0.22 ~ 0.48) | < 0.001 | 0.51 (0.33 ~ 0.77) | 0.002 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 1.55 (1.25 ~ 1.93) | < 0.001 | 1.58 (1.27 ~ 1.97) | < 0.001 | 1.27 (1.01 ~ 1.60) | 0.047 |
| **Cirrhosis** | | | | | | |
| ASMI | 0.31 (0.13 ~ 0.75) | 0.009 | 0.03 (0.01 ~ 0.12) | < 0.001 | 0.13 (0.03 ~ 0.57) | 0.007 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 1.02 (0.71 ~ 1.45) | 0.928 | 0.57 (0.35 ~ 0.92) | 0.022 | 0.69 (0.42 ~ 1.14) | 0.152 |
| Quartile 3 | 0.92 (0.64 ~ 1.32) | 0.642 | 0.41 (0.24 ~ 0.71) | 0.002 | 0.56 (0.31 ~ 0.99) | 0.048 |
| Quartile 4 | 0.58 (0.39 ~ 0.87) | 0.009 | 0.26 (0.14 ~ 0.47) | < 0.001 | 0.44 (0.24 ~ 0.83) | 0.010 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 1.75 (1.29 ~ 2.38) | < 0.001 | 1.73 (1.26 ~ 2.36) | < 0.001 | 1.65 (1.19 ~ 2.28) | 0.002 |

Model 1: crude

Model 2: adjusted for Gender, Age

Model 3: adjusted for Gender, Age, Smoke, Alcohol, Physical Activity, Diabetes mellitus, Hypertension

*Abbreviations*: *ASMI* Appendicular skeletal muscle mass index, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *OR* Odds ratio, *CI* Confidence interval

supported in the US cohort. However, the relationship between ASMI and liver fibrosis was found to be closer to linear. These findings provide support for the hypothesis that sarcopenia represents an independent risk factor for the progression of liver fibrosis in patients with MASLD.

The findings of this study align with those of previous investigations into the relationship between sarcopenia and liver fibrosis, furthering our comprehension of this association. Prior research has demonstrated that sarcopenia is linked to the advancement of liver fibrosis in a multitude of chronic liver disorders [12, 14]. Some studies in patients with NAFLD have confirmed that sarcopenia is associated with the severity of liver fibrosis [15, 16, 23, 24]. Furthermore, several other studies have demonstrated that reduced ASMI is an independent risk factor for liver fibrosis [25, 26]. A recent meta-analysis that included 25 relevant studies also showed that sarcopenia is associated with an increased chance of liver fibrosis in patients with NAFLD [12]. These studies highlight sarcopenia's crucial role in hepatic fibrosis in fatty liver disease.

This study represents the first investigation into the relationship between sarcopenia and hepatic fibrosis in patients with MASLD. Utilizing a cross-national cohort

**Table 4** Relationship between ASMI, sarcopenia and hepatic fibrosis in patients with MASLD in the US cohort

| Variables | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* | OR (95%CI) | *P* |
| **Significant fibrosis** | | | | | | |
| ASMI | 0.14 (0.05 ~ 0.42) | < 0.001 | 0.01 (0.00 ~ 0.06) | < 0.001 | 0.02 (0.00 ~ 0.17) | < 0.001 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 0.68 (0.41 ~ 1.12) | 0.132 | 0.59 (0.34 ~ 1.01) | 0.054 | 0.65 (0.37 ~ 1.13) | 0.128 |
| Quartile 3 | 0.78 (0.48 ~ 1.27) | 0.324 | 0.29 (0.12 ~ 0.70) | 0.007 | 0.38 (0.15 ~ 0.96) | 0.041 |
| Quartile 4 | 0.30 (0.16 ~ 0.55) | < 0.001 | 0.10 (0.04 ~ 0.27) | < 0.001 | 0.15 (0.05 ~ 0.42) | < 0.001 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 2.20 (1.42 ~ 3.43) | < 0.001 | 2.07 (1.32 ~ 3.24) | 0.002 | 1.79 (1.12 ~ 2.86) | 0.014 |
| **Advanced fibrosis** | | | | | | |
| ASMI | 0.06 (0.01 ~ 0.32) | < 0.001 | 0.00 (0.00 ~ 0.02) | < 0.001 | 0.00 (0.00 ~ 0.04) | < 0.001 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 0.47 (0.23 ~ 0.97) | 0.040 | 0.39 (0.17 ~ 0.86) | 0.020 | 0.42 (0.18 ~ 0.95) | 0.038 |
| Quartile 3 | 0.73 (0.38 ~ 1.38) | 0.330 | 0.27 (0.08 ~ 0.95) | 0.042 | 0.35 (0.09 ~ 1.28) | 0.113 |
| Quartile 4 | 0.19 (0.07 ~ 0.50) | < 0.001 | 0.06 (0.01 ~ 0.29) | < 0.001 | 0.10 (0.02 ~ 0.46) | 0.003 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 3.21 (1.81 ~ 5.67) | < 0.001 | 3.15 (1.77 ~ 5.61) | < 0.001 | 2.83 (1.55 ~ 5.16) | < 0.001 |
| **Cirrhosis** | | | | | | |
| ASMI | 0.03 (0.00 ~ 0.27) | 0.002 | 0.00 (0.00 ~ 0.09) | 0.002 | 0.00 (0.00 ~ 0.40) | 0.019 |
| Categories | | | | | | |
| Quartile 1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Quartile 2 | 0.68 (0.28 ~ 1.62) | 0.383 | 0.60 (0.23 ~ 1.56) | 0.296 | 0.77 (0.28 ~ 2.11) | 0.617 |
| Quartile 3 | 0.60 (0.24 ~ 1.48) | 0.267 | 0.29 (0.06 ~ 1.43) | 0.128 | 0.46 (0.09 ~ 2.43) | 0.361 |
| Quartile 4 | 0.07 (0.01 ~ 0.56) | 0.012 | 0.03 (0.00 ~ 0.38) | 0.006 | 0.07 (0.01 ~ 0.83) | 0.036 |
| **S**arcopenia | | | | | | |
| No | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 2.58 (1.19 ~ 5.62) | 0.017 | 2.56 (1.16 ~ 5.64) | 0.020 | 2.45 (1.08 ~ 5.58) | 0.032 |

Model 1: crude

Model 2: adjusted for Gender, Age

Model 3: adjusted for Gender, Age, Smoke, Alcohol, Physical Activity, Diabetes mellitus, Hypertension

*Abbreviations*: *ASMI* Appendicular skeletal muscle mass index, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *OR* Odds ratiom, *CI* Confidence interval

study design, the prevalence of sarcopenia was identified as an independent risk factor for the progression of hepatic fibrosis. Compared to previous studies, the present study not only included two large cohorts from disparate cultural backgrounds but also effectively controlled for potential confounding variables through meticulous data screening and multivariate adjustment modeling, thus enhancing the reliability and generalisability of the findings. Furthermore, the present study employed the RCS model to elucidate the potential non-linear relationship between ASMI and liver fibrosis severity, thereby offering a novel perspective on the role of sarcopenia in the pathogenesis of liver fibrosis. In conclusion, this study underscores the utility of ASMI as a valuable tool for evaluating the risk of hepatic fibrosis in patients with MASLD, offering a novel approach for the early identification of high-risk patients in clinical settings. These insights enhance our comprehension of the association between sarcopenia and hepatic fibrosis and illuminate promising avenues for future research.

The precise mechanisms through which sarcopenia is associated with liver fibrosis in patients with MASLD

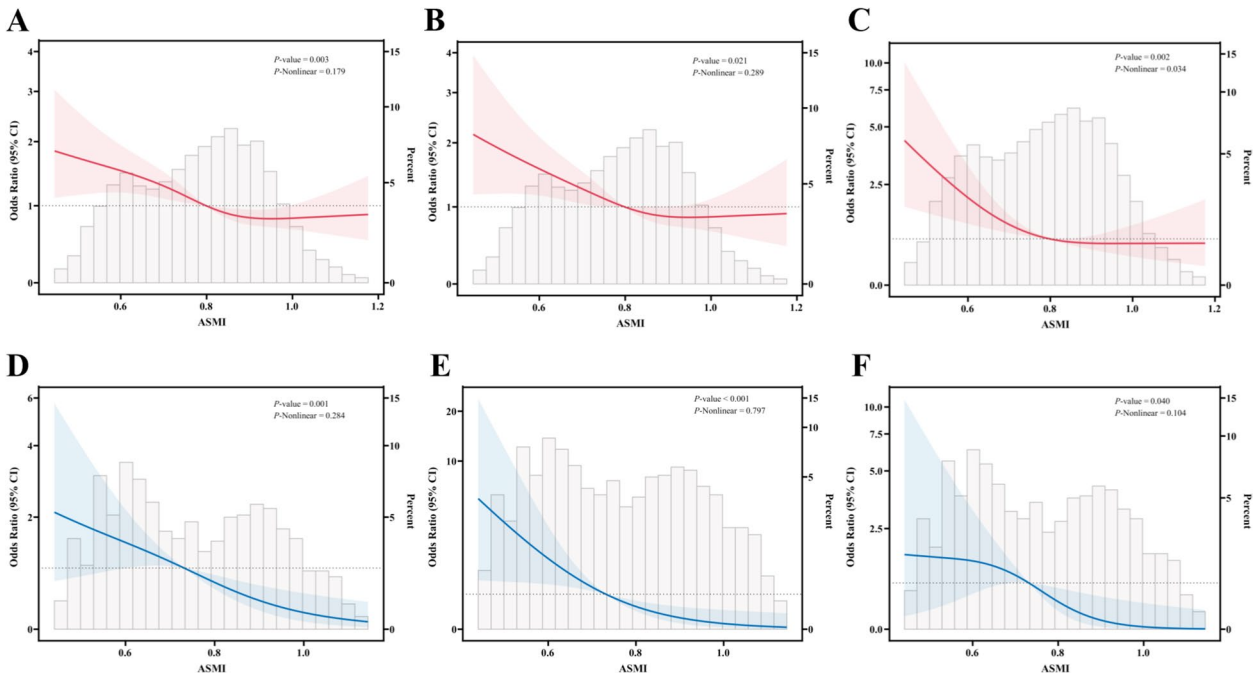


**Fig. 2** Restricted cubic spline fitting for the association between ASMI and hepatic fibrosis in patients with MASLD. **A** association between ASMI and significant fibrosis in the Chinese cohort; **B** association between ASMI and advanced fibrosis in the Chinese cohort; **C** association between ASMI and cirrhosis in the Chinese cohort; **D** association between ASMI and significant fibrosis in the US cohort; **E** association between ASMI and advanced fibrosis in the US cohort; **F** association between ASMI and cirrhosis in the US cohort. The solid line displays the odds ratio, with the 95% CI represented by shading. They were adjusted for gender, age, smoke, alcohol, physical activity, diabetes mellitus, hypertension. Abbreviations: ASMI, Appendicular skeletal muscle mass index; MASLD, Metabolic dysfunction-associated steatotic liver disease; CI, Confidence interval

encompass a range of interrelated factors that collectively contribute to the advancement of liver fibrosis. Patients with sarcopenia frequently exhibit insulin resistance, which represents a crucial pathophysiological basis of MASLD [27, 28]. Insulin resistance results in hyperglycemia, hyperinsulinemia, and dyslipidemia, which can directly damage hepatocytes and promote hepatic fat deposition and oxidative stress. This, in turn, gives rise to an inflammatory response and fibrosis [29–32]. Furthermore, a reduction in muscle mass results in a decline in glucose uptake and utilization, thereby exacerbating systemic metabolic abnormalities and accelerating the onset and progression of liver fibrosis [33]. In this study, patients with sarcopenia exhibited higher levels of metabolic abnormalities, including BMI, waist circumference, blood glucose, and lipid levels, compared to patients without sarcopenia. These findings also demonstrate a robust correlation between sarcopenia and metabolic abnormalities. The elevated glucose and lipid levels observed in sarcopenia patients may serve to further exacerbate the metabolic burden on the liver, thereby promoting the occurrence and development of liver fibrosis.

Patients with sarcopenia frequently present with a chronic, low-grade inflammatory state within their bodies. This may be associated with releasing inflammatory factors and cellular debris during muscle tissue degeneration [34]. The levels of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP), are typically elevated in patients with sarcopenia [34, 35]. These inflammatory factors enter the liver via the circulatory system, thereby activating inflammatory pathways within the liver. This

(See figure on next page.)

**Fig. 3** Subgroup analysis of the association between sarcopenia and hepatic fibrosis in patients with MASLD in the Chinese cohort. **A** association between sarcopenia and significant fibrosis; **B** association between sarcopenia and advanced fibrosis; **C** association between sarcopenia and cirrhosis. Adjusted variables: gender, age, smoking, alcohol, physical activity, diabetes mellitus, hypertension. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. Abbreviations: MASLD, Metabolic dysfunction-associated steatotic liver disease; OR: odds ratio; CI: confidence interval

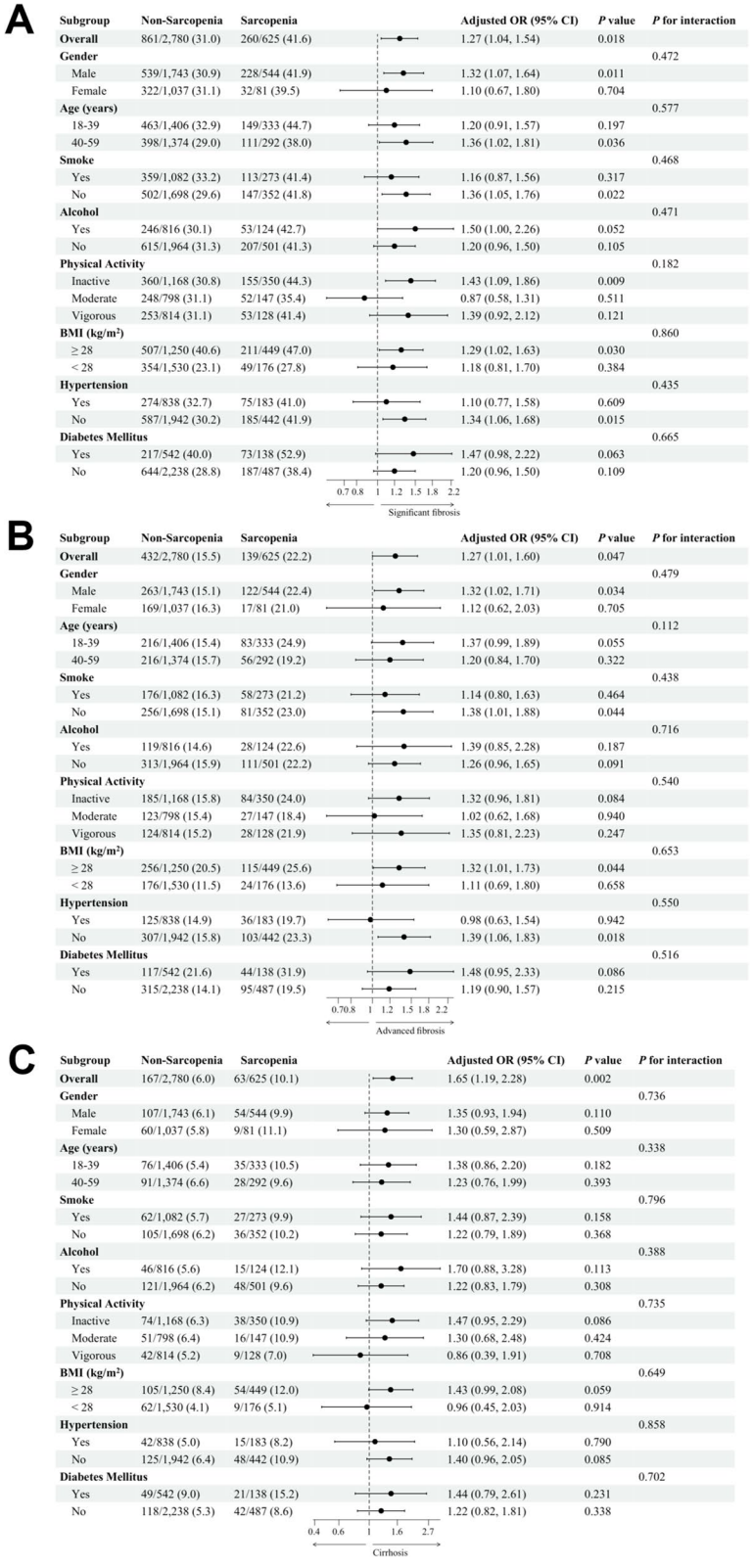


**Fig. 3** (See legend on previous page.)

results in hepatocyte damage and repair responses that ultimately lead to liver fibrosis [27, 35].

In patients with sarcopenia, there is a reduction in the body's antioxidant capacity and an increase in oxidative stress, elevating the level of lipid peroxidation products. These peroxidation products can directly damage hepatocyte membranes and organelles and activate hepatic stellate cells (HSC), prompting their transformation into myofibroblasts and secretion of large amounts of extracellular matrix (ECM). The latter process promotes the formation of liver fibrosis [36, 37]. Moreover, mitochondrial dysfunction in muscle and liver cells has been identified as a contributing factor in the development of sarcopenia and liver fibrosis [37]. Mitochondria play a crucial role in energy metabolism and cell death. Such dysfunction may result in cell injury and death, which in turn may contribute to developing liver fibrosis [38].

Muscle represents a significant source of several adipokines and cytokines, including leptin, lipocalin, and IL-6. The levels of these factors are frequently dysregulated in patients with sarcopenia [27]. Leptin resistance and diminished lipocalin levels are associated with insulin resistance and adipose accumulation in the liver [39–41]. Concurrently, elevated pro-inflammatory factors, such as IL-6, exacerbate the liver's inflammatory response and fibrotic process [42]. In conclusion, the relationship between sarcopenia and liver fibrosis in patients with MASLD can be attributed to a complex interplay of mechanisms, including insulin resistance and metabolic abnormalities, chronic low-grade inflammation, oxidative stress and lipid peroxidation, mitochondrial dysfunction, and dysregulation of adipokines and cytokines. These mechanisms interact with one another and collectively contribute to the onset and progression of liver fibrosis.

In subgroup analyses, we further investigated the influence of diverse demographic factors, including gender, age, smoking status, alcohol, physical activity, BMI, DM, and hypertension, on the relationship between sarcopenia and liver fibrosis. While the impact of sarcopenia on liver fibrosis was more pronounced in specific subgroups, the overall negative effect of sarcopenia on liver fibrosis remained consistent across all subgroups. This finding highlights the prevalence and stability of sarcopenia as a significant risk factor for liver fibrosis while also providing a scientific foundation for the development of tailored intervention strategies for diverse patient subgroups.

While the present study has yielded meaningful findings regarding the relationship between sarcopenia and hepatic fibrosis, it is essential to acknowledge its limitations. First, this study focused on the 18-59 age group, which may limit the generalizability of the findings to a broader age range, particularly the elderly population. The elderly population is at an elevated risk of both sarcopenia and hepatic fibrosis. Furthermore, the relationship between sarcopenia and hepatic fibrosis may vary by age. Consequently, future studies must include a more extensive age range to gain a deeper understanding of the influence of sarcopenia on liver fibrosis across different life stages. Secondly, although the present study controlled for some confounding factors, other factors that may influence liver fibrosis, such as genetic background and dietary habits, were not explored sufficiently. Genetic factors may play a significant role in the pathogenesis of sarcopenia and hepatic fibrosis, while dietary habits directly impact muscle mass and liver health. Failure to control for these factors may limit our ability to understand the relationship between sarcopenia and liver fibrosis fully. Future studies should consider these factors to more fully elucidate the complex mechanisms of hepatic fibrosis in patients with MASLD. Furthermore, this study employed the use of ASMI as a diagnostic tool for sarcopenia. While this is one of the standard diagnostic procedures, it may not fully account for the decline in muscle function, which is also a crucial aspect of the definition of sarcopenia. It would be beneficial for future studies to consider incorporating additional assessment methods, such as muscle strength testing and functional testing, to gain a more comprehensive understanding of sarcopenia. Finally, although the use of two cohorts from different geographic and ethnic backgrounds increased the generalizability and representativeness of the study, it is important to note that differences between the cohorts may affect the interpretation of the results. For example, the U.S. and Chinese cohorts exhibited notable differences in socioeconomic status, healthcare systems, and lifestyle factors. These discrepancies may indirectly influence the incidence and risk factors for sarcopenia and liver fibrosis. It would be beneficial for future studies to explore

(See figure on next page.)

**Fig. 4** Subgroup analysis of the association between sarcopenia and hepatic fibrosis in patients with MASLD in the US cohort. **A** association between sarcopenia and significant fibrosis; **B** association between sarcopenia and advanced fibrosis; **C** association between sarcopenia and cirrhosis. Adjusted variables: gender, age, smoke, alcohol, physical activity, diabetes mellitus, hypertension. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. Abbreviations: MASLD, Metabolic dysfunction-associated steatotic liver disease; OR: odds ratio; CI: confidence interval

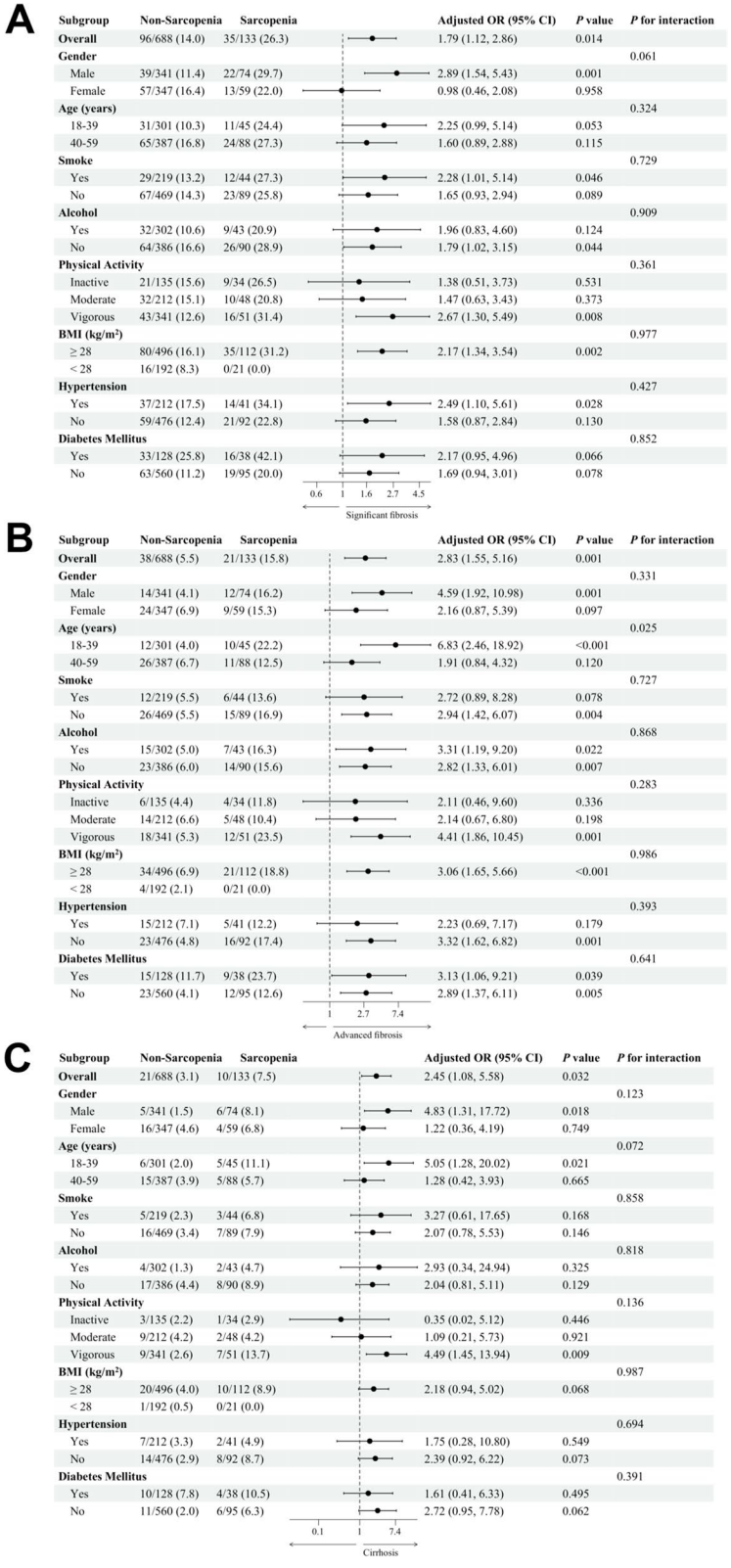


**Fig. 4** (See legend on previous page.)

these potential differences further and consider adjusting analytic methods to minimize their impact on the results.

## Conclusion

The present study observed an association between sarcopenia and the progression of liver fibrosis in patients with MASLD. Specifically, patients with sarcopenia exhibited a heightened risk of significant hepatic fibrosis, advanced hepatic fibrosis, and cirrhosis in two distinct national cohorts. Furthermore, a negative correlation was observed between ASMI and the severity of liver fibrosis, indicating that ASMI may serve as a valuable indicator for assessing the risk of liver fibrosis in patients with MASLD. To more effectively incorporate ASMI monitoring into the management of patients with MASLD, it is recommended that clinicians periodically assess ASMI in patients with MASLD to identify those at high risk for liver fibrosis. For patients with a low ASMI, a more detailed assessment of their sarcopenia status should be conducted, and targeted interventions should be considered. These may include nutritional support, resistance exercise training, and medications aimed at increasing muscle mass and improving muscle function, which may slow the progression of hepatic fibrosis. Further research is required to understand the specific mechanisms linking sarcopenia and hepatic fibrosis and assess the efficacy and safety of different intervention strategies. This will facilitate the development of more comprehensive and personalized treatment options for patients with MASLD.

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**Authors' contributions**
Conceptualization and methodology, project administration, data curation, and investigation, F.Z., L.L., and W.L.; formal analysis, visualization and supervision, W.L.; Writing - original draft, F.Z.; Writing - review and editing, W.L.; funding acquisition, F.Z.; All authors have read and agreed to the published version of the manuscript.

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**Data availability**
The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm). The Chinese cohort data utilized and analyzed in the present study are accessible from the corresponding author upon justified request.

## Declarations

**Ethics approval and consent to participate**
The studies involving humans in US cohort were approved by the National Center for Health Statistics Ethics Review Board. The participants provided their written informed consent to participate in this study. Accordingly, the Changzhou Third People's Hospital Ethics Committee has determined that no further ethical review approval is required to use NHANES data in this study. The Changzhou Third People's Hospital Ethics Committee approved the Chinese cohort study (No. 02A-A20230023).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]Department of Endocrinology, Changzhou Third People's Hospital, Changzhou 213001, China. [2]Department of Clinical Nutrition, Changzhou Third People's Hospital, Changzhou 213001, China. [3]Department of Liver Diseases, Changzhou Third People's Hospital, Changzhou 213001, China. [4]Department of Urology, Changzhou Third People's Hospital, Changzhou 213001, China. [5]Changzhou Clinical College, Xuzhou Medical University, Changzhou 213001, China.

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