Annals of Hepatology 29 (2024) 101544

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Original article

Relationship between sarcopenia and metabolic dysfunction-associated steatotic liver disease (MASLD): A systematic review and meta-analysis

Adnan Malik[a,*], Sadia Javaid[b], Muhammad Imran Malik[c], Shahbaz Qureshi[a]

[a] Mountain Vista Medical Center, Mesa Arizona, USA
[b] Medigan Army Medical Center WA, USA
[c] Airedale general hospital, West Yorkshire, England

ARTICLE INFO

Article History:
Received 25 October 2023
Accepted 17 June 2024
Available online 29 August 2024

Keywords:
NAFLD
Fatty liver
Sarcopenia
SMI
Fibrosis

ABSTRACT

Introduction and Objectives: Metabolic dysfunction-associated steatotic liver disease (MASLD) formerly known as Nonalcoholic fatty liver disease (NAFLD) is a common chronic disease. Identifying MASLD risk factors could help early intervention and reduce the burden of the disease. Previous studies investigated the association between sarcopenia and NAFLD. Several trials were published after the last meta-analysis with indecisive results. This is an updated meta-analysis which aims to assess the association between sarcopenia, MASLD, and MASLD-related fibrosis.

Materials and Methods: Relevant trials published on PubMed, Web of Science, Scopus, and Cochrane Library databases until October 2022 were included. We included studies in which skeletal mass index (SMI) or sarcopenia was compared between patients with and without NAFLD now MASLD. Also, studies comparing fibrosis between MASLD patients with and without sarcopenia were included. Data were pooled as odds ratios (ORs) and 95 % confidence intervals (CIs) using Review Manager Software.

Results: A total of 25 studies were included. The incidence of sarcopenia was significantly higher in MASLD than controls (OR, 1.25; 95 % CI, 1.08-1.44; P = 0.003). SMI odds showed no significant difference between MASLD patients and controls (OR, 1.02; 95 % CI, 0.91-1.15; P = 0.7). MASLD patients with sarcopenia had higher odds of fibrosis than MASLD patients without sarcopenia (OR, 1.49; 95 % CI, 1.03-2.14; P = 0.03).

Conclusions: Sarcopenia increased MASLD's probability and was associated with a higher probability of liver fibrosis in MASLD patients. However, SMI had no predictive value of MASLD occurrence.

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) formerly known as non alcoholic fatty liver disease (NAFLD) occurs due to excessive hepatic fat accumulation in obese patients in the absence of alcohol use [1–4]. It is associated with insulin resistance and other metabolic disorders including diabetes, dyslipidemia and hypertension [1]. NAFLD is diagnosed when fatty changes in the liver occur in the absence of heavy alcohol consumption. In the United States, it is observed in 31 % of adults as well as in 33 % of potential live liver donors noted on liver biopsy [4].

MASLD's pathophysiology is influenced by diet, lifestyle, and inflammation, which directly affects the severity of MASLD's clinicopathologic outcome [5]. The precise pathophysiology and factors causing progressive hepatocellular damage after triglyceride accumulation are unknown; however, it appears that changes in local and systemic factors (particularly insulin resistance) regulate the balance between hepatic lipid influx or synthesis and their export or oxidation, leading to hepatic triglyceride accumulation [1,6]. The pathophysiology of MASLD is influenced by circulating lipids and the various compounds released from adipose, muscle, and liver tissues, as well as pancreatic and gut hormones [5].

MASLD therapy's main aim is to slow the disease's development and prevent liver-related illness and death [7]. There is currently no cure for MASLD, but a variety of medications—including the treatment of high blood pressure, high cholesterol, type 2 diabetes, and obesity—can help slow down the disease progression [8]. Some measures for lowering MASLD risk include losing weight, maintaining a healthy diet, exercising regularly, and quitting smoking [8].

Abbreviations: Metabolic Dysfunction Associated Steatotic Liver Disease, (MASLD); Nonalcoholic fatty liver disease, (NAFLD); Nonalcoholic Steatohepatitis, (NASH); Odds Ratio, (OR); body mass index, (BMI); skeletal muscle index, (SMI); Aspartate aminotransferase, (AST); Alanine aminotransferase, (ALT); and gamma-glutamyl transferase, (GGT),preferred reporting items for systematic reviews and meta-analyses, (PRISMA); and confidence interval, (CI); are all, used in this study

* Corresponding author.
E-mail addresses: adnanmalik892@hotmail.com, adnan.malik@steward.org (A. Malik).

https://doi.org/10.1016/j.aohep.2024.101544
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Sarcopenia is a disorder characterized by a widespread progressive loss of skeletal muscle mass and strength, leading to physical and psychological deterioration and, eventually death. Although sarcopenia is more likely to affect the elderly, its onset can occur early in association with other disorders affecting younger patients [9].

Multiple combined factors, including age, gender, and level of physical activity, predispose to sarcopenia development [9]. Its prevalence ranges from 5−13 percent in people 60−70 years old, while the prevalence ranges from 11 to 50 percent in people >80 years old [9].

Sarcopenia's etiopathogenesis is not well understood. Resistance exercise is particularly effective at slowing the age-related loss of skeletal muscle, and age, gender, and level of physical activity are all well-known risk factors for sarcopenia. Obesity, osteoporosis, type 2 diabetes, and insulin resistance are all serious sarcopenia co-morbidities [9].

MASLD and sarcopenia have several risk factors in common [10], of which suggest a possible association between the two conditions. By revising the current literature, we noticed some conflict between the different studies' results regarding the relationship between sarcopenia and MASLD and the impact of MASLD on the skeletal mass of patients with sarcopenia [11−34]. The exact relation between MASLD and sarcopenia is not fully established yet. Hence we aimed to assess the association between sarcopenia, MASLD, and MASLD-related fibrosis by summarizing the data of 25 studies.

2. Materials and methods

This study was conducted in strict accordance with the "Preferred items for systematic reviews and meta-analyses" (PRISMA) guidelines [35].

2.1. Search strategy and data collection

We conducted our search on four electronic databases: PubMed, Cochrane CENTRAL, Web of Science (WOS), and Scopus, for all published clinical trials till October 2022. The search was conducted using the following keywords: "Non-alcoholic Fatty Liver," "NAFLD," "Nonalcoholic Fatty Liver," "Nonalcoholic Fatty Liver," "Nonalcoholic Fatty Livers," "Nonalcoholic Steatohepatitis," "Nonalcoholic Steatohepatitides," "Non-alcoholic steatohepatitis," "non-alcoholic steatohepatitis," "NASH," "Non-alcoholic Fatty Liver," "Skeletal Muscle," "Skeletal Muscles," "Sarcopenia." We removed the duplicates using Endnote software, and then we screened all retrieved citations for eligibility in two steps; titles and abstracts screening and full texts screening, and studies that matched our criteria were included in our study. We manually screened the references of the included studies for any missed relevant papers.

2.2. Selection criteria

We included prospective and retrospective studies and cross-sectional that assessed the association between sarcopenia and NAFLD or NAFLD-related fibrosis (now MASLD). No restrictions for age, sex, site, or publication date were applied. We excluded animal studies, non-English studies, non-available studies, thesis, reviews, and if the abstract only is available.

2.3. Data extraction

At least two independent reviewers did the data extraction and any discrepancies were solved by discussion. The extracted data were related to the following [1]: Summary of the included trials, including study arms, patients' number, total sample, method of MASLD diagnosis, and the study conclusion [2]; baseline characteristics of the enrolled population, including the number of patients in each group, age, body mass index (BMI), percentage of sarcopenic patients, skeletal muscle index (SMI), smoking percentage in the study population, total cholesterol level, triglyceride level, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) levels [3]; outcomes [4]; quality assessment domains.

2.4. Study outcomes

We compared the odds of both sarcopenia and low SMI in MASLD patients with non-MASLD controls. In addition, we compared the odds of MASLD-related fibrosis in MASLD patients with and without sarcopenia. While extracting data, crude analysis results were extracted when available. Otherwise, model-one-adjusted results were extracted.

2.5. Quality assessment

We used the NIH tool for observational and cross-sectional studies to assess the quality of included studies [36]. The tool includes 14 questions for the judgment of each study. These questions comprise judgment of the research question clarity, study population specification, participation rate, pre-specification and application of the study inclusion and exclusion criteria, sample size justification and power, measurement of the exposures prior to the outcomes, sufficient timeframe, examination of different levels of exposures, reliability, and consistency of exposure measurements, multiple exposure assessments overtime, reliability, and consistency of outcome measurements, blinding of the outcome assessor, loss of follow-up percentage, and statistical adjustment of the critical potential confounding variables between exposures and outcomes.

2.6. Statistical analysis

Analyses were conducted using the Review Manager Software (version 5.4). Outcomes were pooled as odds ratios (ORs) and 95 % confidence intervals (CIs) using the generic inverse-variance method under the random-effects model. Heterogeneity was assessed by chi-square and I-Square tests. If I-Square: 0 % to 40 %, it may not be important, 30 % to 60 % show moderate heterogeneity, 50 % to 90 % show substantial heterogeneity, and 75 % to 100 % show a considerable level of heterogeneity. Also, we considered heterogeneity to be significant if at chi-square P-value <0.1 and I^2 >50 % [37]. Heterogeneity was solved, when possible, by performing a sensitivity analysis. We also used Review Manager Software (version 5.4) to do the sensitivity analysis according to the definition of sarcopenia in each study. According to Egger's funnel-plot-based methods, publication bias was assessed for outcomes reported by more than ten studies [38]. Publication bias was assessed by visual inspection of the funnel plot.

3. Results

3.1. Literature search results

Our search results retrieved 1941 records from all searched databases. After removing duplications, 1756 records were identified. By title and abstract screening, we excluded 1673 records, and the remaining 83 were eligible for full-text screening. We finally included 25 prospective, retrospective, and cross-sectional studies in the

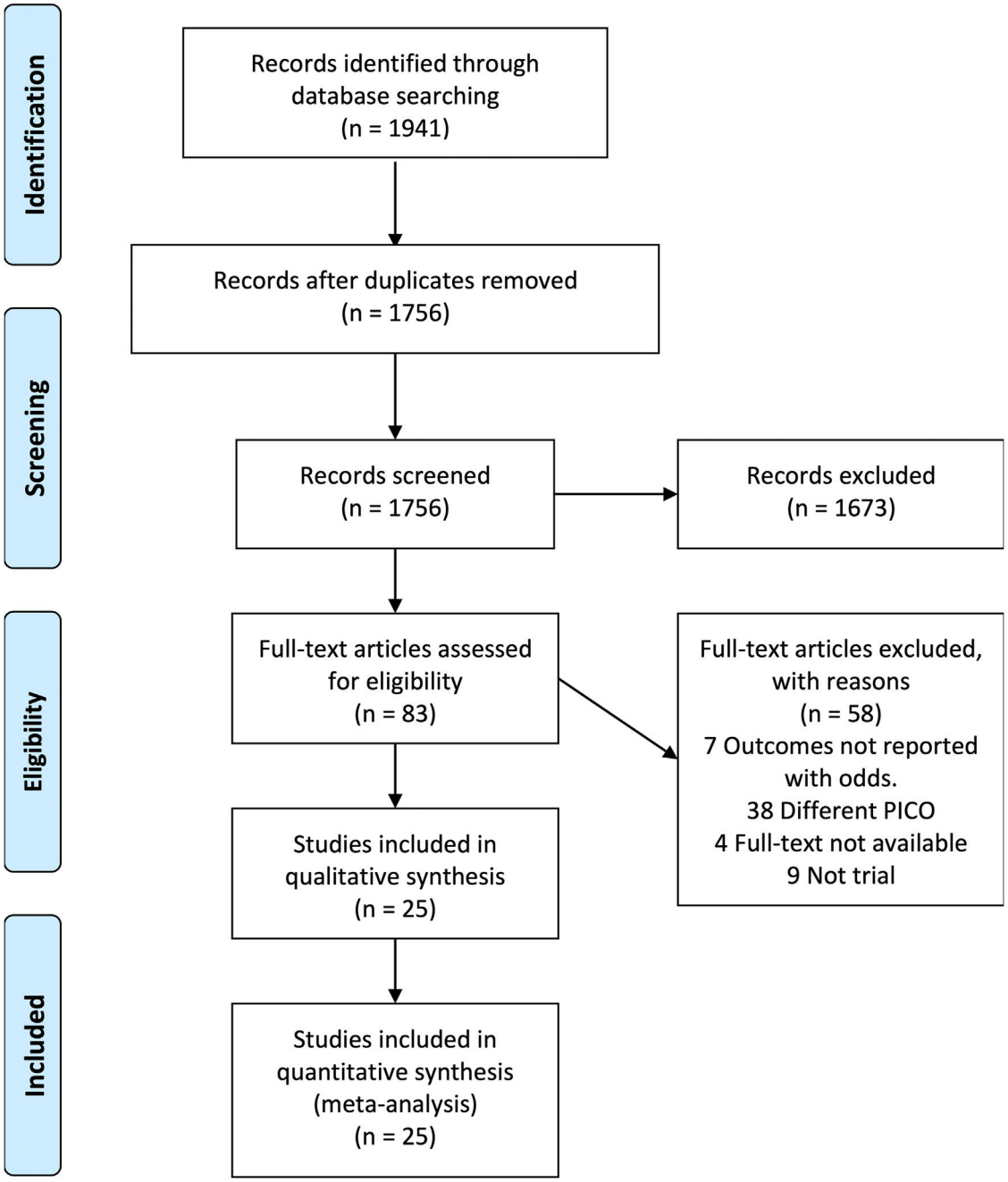

Fig. 1. The PRISMA flow chart summarizing the literature search, and study selection process.

analysis. Figure 1 shows the flow of data collection and screening process (PRISMA flow diagram).

3.2. Characteristics of the included studies

The included studies varied in their design and patients' age, gender distribution, BMI, lipid profile, and liver enzymes. Mean age ranged from 10 to 70 years, mean BMI ranged from 21 to 34 kg/m^2, and male percentage ranged from less than 1% to 94%. The mean total cholesterol level went from 175 to 225 mg/dl; the mean triglyceride level ranged from 95 to 224 mg/dl, the mean AST level ranged from 20 to 72 IU/L; the mean ALT level ranged from 13 to 63 IU/L, and mean GGT ranged from 21.2 to 98 IU/L. Ultrasonography was used for MASLD diagnosis in most studies. A summary of the included studies and baseline characteristics of enrolled subjects are shown in Tables 1 and 2, respectively.

3.3. Quality assessment results

According to the NIH tool for quality assessment, the overall risk of bias revealed a fair quality of most included studies and a good quality of four included studies. Details of each study domain judgment are shown in supplementary Table 1.

3.4. Outcomes

3.4.1. Sarcopenia (Fig. 2)

The total estimate showed that MASLD was significantly associated with sarcopenia (OR = 1.25; 95% CI [1.08, 1.44]; $P = 0.003$) [11–13,15,16,18,21,23,25–27,29,32,33]. The pooled studies were heterogenous ($P < 0.00001$, $I^2 = 63\%$). The heterogeneity was best resolved by conducting subgroup analysis according to the definition

Table 1
Summary of the included studies.

ID	Design	NAFLD diagnosis	Sample size	Conclusion
Alferink 2019	Cross sectional	-	499	SMI was associated with less NAFLD in normal weight women.
Bhanji 2019	Retrospective Cohort	Biopsy	265	Sarcopenia and frailty occur with differing prevalence, with variable impact on outcomes in waitlisted patients with NASH and ALD
Choe 2018	Cross sectional	US	487	Low skeletal muscle mass, which was precisely measured by CT, is independently associated with NAFLD, suggesting that sarcopenia is a risk factor for NAFLD.
Chung 2019	Retrospective cohort	US	5989	Sarcopenia was significantly associated with the presence and the severity of ultrasonography graded NAFLD in our study population independent of visceral fatness and another metabolic confounder.
Gan 2019	Prospective cohort	-	3536	Low muscle mass and low muscle strength were positively and independently associated with NAFLD.
Golabi 2020	Prospective cohort	FLI > 60	4611	Inactivity is associated with presence of sarcopenia, whilst sarcopenia is associated with increased mortality amongst NAFLD patients. Sarcopenia should be a part of clinical assessment of patients with NAFLD.
Hashimoto 2016	Cross sectional	Electrography	79	SMI was negatively associated with hepatic steatosis in men with type 2 diabetes.
Hong 2014	Prospective cohort	US	452	Individuals with lower muscle mass exhibited increased risk of NAFLD. This result may provide a novel insight into the mechanism linking between sarcopenia and NAFLD
Hong 2020	Cross sectional	US	850	Sarcopenia was associated with an increased risk for NAFLD in patients with COPD, independent of age, sex, lung function, and metabolic factors.
Hsieh 2020	Prospective cohort	US	521	Muscle alterations and visceral adiposity assessed by CT are associated with significant fibrosis in NAFLD
Kang 2019	Cross sectional	CT	10711	Low skeletal muscle mass is associated with advanced fibrosis in NAFLD patients independent of metabolic risk factors.
Kang 2020	Cross sectional	US	443	The prevalence of non-alcoholic fatty liver in inflammatory bowel disease patients was 11.1 % and sarcopenia was an independent risk factor.
Kim 2016	Cross sectional	CT	1184	Low SMI is associated with the risk of fatty liver index (FLI) defined NAFLD independent of other well-known metabolic risk factors in both genders.
Koo 2017	Prospective cohort	Biopsy	309	Sarcopenia was significantly associated with NASH and significant fibrosis.
Kwon 2020	Cross sectional	US	126	NAFLD is significantly associated with relatively low SMM in non-obese children and adolescents. Increasing SMM, such as weight training, can be suggested as one of the treatment strategies in pediatric NAFLD without obesity.
Lee 2015	Cross sectional	NFS	10479	Sarcopenia is associated with increased risks of NAFLD and advanced fibrosis, independent of obesity or metabolic control.
Lee 2016	Retrospective cohort	NFS	2761	Sarcopenia is associated with significant liver fibrosis in subjects with NAFLD, and the association is independent of obesity and insulin resistance.
Lee 2021	Longitudinal cohort	NFS	9691	LSMI and NAFLD showed a relationship. Maintaining muscle mass should be emphasized in the management of NAFLD.
Pacifico 2020	Longitudinal cohort	US	159	There was an association between low muscle mass and NAFLD/NASH in overweight/obese youths.
Peng 2019	Cross sectional	US	1949	NAFLD is associated with a lower risk of sarcopenia when using the height adjusted SMI. In contrast, it showed the opposite result when using the weight adjusted SMI.
Petta 2017	Prospective cohort	US	225	In Western patients with NAFLD, with high prevalence of metabolic disorders and advanced liver disease, sarcopenia was associated with the severity of fibrosis and steatosis, independently of hepatic and metabolic risk factors.
Seo 2019	Cross sectional	US	2160	Sarcopenia is independently associated with NAFLD in men with T2DM, which suggests that sarcopenia may be a risk factor for NAFLD in men with T2DM
Su 2019	Cross sectional	US	236	T2DM patients who have lower SVR levels are associated with higher risks of developing the NAFLD-related complications. Besides, SVR shows independent correlation with NAFLD in female T2DM patients, suggesting that SVR may be a useful index to predict the high risk of hepatic steatosis in T2DM.
Wang 2021	Cross sectional	US	486	The occurrence of sarcopenia was associated with a higher risk of NAFLD, especially in men, as demonstrated by lower muscle mass and lower muscle strength.
Wijarnpreecha 2019	Cross sectional	Biopsy	11325	Sarcopenia was independently associated with increased odds of NAFLD and NAFLD-associated advanced fibrosis independent of well-defined risk factors.

Ultrasonography (US), Fatty liver index (FLI), Computerized tomography (CT), NAFLD fibrosis score (NFS), systemic vascular resistance (SVR)
Non-Alcoholic Fatty Liver Disease (NAFLD), Non-Alcoholic Steatohepatitis (NASH), Alcoholic Liver diseases (ALD)
Type 2 Diabetes Mellitus (T2D), Skeletal Muscle Mass Index (SMI), Chronic Obstructive Pulmonary Diseases (COPD)

of sarcopenia in each study, whether depending on body weight, height, body mass index (BMI), or other variables.

In the subgroup defining sarcopenia depending on body weight, MASLD was significantly associated with sarcopenia (OR = 1.29; 95 % CI [1.07, 1.56]; P = 0.007 [11,13,15,21],) and the pooled studies were homogenous (P = 0.99, I^2 = 0 %). While MASLD was not associated with sarcopenia in the subgroup defining sarcopenia depending on height (OR = 0.92; 95 % CI: [0.81, 1.03], P = 0.15) [13,21], The pooled studies were homogenous (P = 0.66, I^2 = 0 %). Also, MASLD was not associated with sarcopenia in the subgroup defining sarcopenia depending on BMI (OR = 1.31; 95 %CI: [0.99, 1.73], P = 0.06). The pooled studies were homogenous (P = 0.99, I^2 = 0 %) [11,15,21]. For publication bias assessment, visual inspection of the funnel plot showed an asymmetrical distribution of the included studies around the effect estimate in the direction of large SE, suggesting the presence of publication bias (Fig. 3).

3.4.2. Skeletal mass index (SMI) (Fig. 4)

The pooled estimate from nine studies [13,15,17,19,20,24,26,30,31] showed no significant relationship between low SMI and MASLD (OR = 1.02; 95 % CI [0.91, 1.15]; P =0.7). The pooled studies

Table 2
Baseline characteristics of the included studies.

ID	Arms	Number of the patient	Sarcopenic patients (%)	Age in years Mean (SD)	Male (%)	BMI (Kg/m2) Mean (SD)	SMI (Kg/m2)	Smoking, n (%)	Total cholesterol, mg/dL	Triglycerides, mg/dL	Aspartate aminotransferase (IU/L) Mean (SD)	Alanine aminotransferase (IU/L) Mean (SD)	Gamma-glutamyl transferase (GGT) (IU/L) Mean (SD)
Alferink 2019	NAFLD (+)	67	16.70%	-	-	-	7.43 (0.74)	-	-	-	-	-	-
	NAFLD (-)	432	20.90%	-	-	-	7.41 (0.69)		-	-	-	-	-
Bhanji 2019	NAFLD (+)	136	22%	60.2 (7.8)	52%	34.9 (8.0)	-	-	-	-	-	-	-
	NAFLD (-)	129	47%	53.7 (10.1)	69%	27.6 (5.1)	-	-	-	-	-	-	-
Choe 2018	NAFLD (+)	184	-	58.1 (9.2)	73.40%	27.0 (1.8)	7.4 (0.7)	11%	191.3 (33.7)	95.7 (55.4)	25.4 (8.6)	30.7 (16.3)	42.5 (36.1)
	NAFLD (-)	303	-	53.5 (9.0)	94.10%	26.6 (1.5)	9.3 (0.8)	4.10%	200 (36.9)	109 (65.3)	25.4 (19.3)	29.8 (23.0)	43.4 (39.6)
Chung 2019	NAFLD (+)	315	69.50%	57.1 (11.4)	73.00%	27.8 (3.6)	-	-	-	-	28.8 (13.4)	35.9 (23.5)	48.1 (42.7)
	NAFLD (-)	5674	36.50%	53.0 (9.2)	56.40%	23.2 (2.8)	-	-	-	-	25.1 (30.3)	25.8 (35.3)	34.5 (38.7)
Gan 2019	NAFLD (+)	1088	22.61%	55.20 (11.48)	32.90%	25.91 (2.86)	26.44 (3.32)	-	-	-	3.12 (0.26)[a]	3.07 (0.44)[a]	3.12 (0.62)[a]
	NAFLD (-)	2448	4.86%	51.72 (13.66)	26.88%	22.05 (2.51)	28.47 (3.75)	-	-	-	3.03 (0.26)[a]	2.74 (0.44)[a]	2.68 (0.54)[a]
Golabi 2020	NAFLD (+)	1351	5.10%	49.04 (0.61)	1.97%	32.05 (0.22)	–	-	-	-	-	-	-
	NAFLD (-)	3260	3.90%	43.02 (0.50)	0.92%	25.63 (0.11)	-	-	-	-	-	-	-
Hashimoto 2016	NAFLD (+)	58	-	63.2 (11.7)	58%	25.7 (4.2)	-	-	-	-	29.7 (20.7)	36.2 (32.6)	53.1 (53.0)
	NAFLD (-)	21	-	70.0 (8.4)	21%	21.4 (2.4)	-	-	-	-	20.0 (4.3)	16.0 (5.3)	25.3 (16.0)
Hong 2014	NAFLD (+)	128	-	60 (52.7)	75%	25.9	33.2	-	-	-	20	18	-
	NAFLD (-)	324	-	51 (38, 61)	58.00%	23.5	40.3	-	-	-	20	17	-
Hong 2020	NAFLD (+)	124	34.70%	63.0 (10.2)	66.90%	27.0 (2.6)	19.6 (4.4)	-	-	-	25.0 (10.8)	33.1 (18.0)	-
	NAFLD (-)	726	18%	65.4 (9.5)	68.60%	22.9 (2.4)	17.8 (3.9)	-	-	-	22.8 (8.0)	19.0 (9.4)	-
Hsieh 2020	NAFLD (+)	178	-	58.7 (13.7)	36%	27.7 (3.9)	47.29 (9.56)	19%	174.9 (40.6)	149.5 (82.5)	71.6 (57.4)	63.8 (47.6)	98.2 (150.5)
	NAFLD (-)	343	-	49.3 (15.2)	59%	27.8 (3.8)	50.95 (9.11)	23%	187.6 (39.8)	162.5 (83.5)	41.7 (29.7)	59.9 (56.4)	54.1 (56.3)
Kang 2019	NAFLD (+)	615	-	52.5 (14.1)	69.90%	29.1 (3.6)	-	-	-	-	31.8 (14.4)	41.5 (29.6)	42.51 (40.98)
	NAFLD (-)	10096	-	47.6 (11.5)	51.80%	23.6 (2.9)	-	-	-	-	25.0 (12.8)	26.2 (20.7)	30.0 (33.8)
Kang 2020	NAFLD (+)	49	51.00%	45.1 (13.6)	63.30%	23.0 (2.7)	-	36.70%	-	-	-	-	-
	NAFLD (-)	394	33%	38.6 (15.7)	64.20%	20.8 (3.3)	-	7.40%	-	-	-	-	-
Kim 2016	NAFLD (+)	208	-	44.0 (1.1)	-	28.0 (0.3)	29.8 (0.2)	-	203.5 (3.1)	224.3	26.8	36.1	58.1
	NAFLD (-)	976	-	43.2 (0.8)	-	23.3 (0.1)	32.4 (0.1)	-	180.7 (1.4)	100.9	20.9	20.5	25.7
Koo 2017	NAFLD (+)	70	-	54.9 (17.0)	44.30%	30.2 (4.0)	-	21.40%	178.6 (35.3)	121	36	41	53
	NAFLD (-)	239	-	52.5 (13.2)	47.70%	26.0 (3.0)	-	23%	187.5 (40.7)	133	32	34	41
Kwon 2020	NAFLD (+)	53	-	10.8 (1.3)	62.30%	21.5 (1.3)	-	-	-	-	33.7 (19.2)	45.6 (42.9)	-
	NAFLD (-)	73	-	10.8 (1.4)	54.80%	21.0 (1.5)	-	-	-	-	19.5 (3.4)	13.3 (4.2)	-
Lee 2015	NAFLD (+)	2004	-	56.7 (16.3)	65%	22.8 (1.6)	26.5 (3.3)	-	193.3 (36.4)	134.3 (85.9)	21.5 (7.5)	19.9 (12.1)	-
	NAFLD (-)	8475	-	47.9 (16.8)	65%	21.6 (2.1)	31.1 (4.1)	-	182.8 (34.0)	-	20.7 (9.2)	17.9 ± 11.5	-
Lee 2016	NAFLD (+)	337	-	65.5 (11.8)	61%	27.1 (3.3)	-	-	-	-	25.7 (11.1)	27.8 (18.6)	46.8 (52.8)
	NAFLD (-)	2424	-	54.5 (14.1)	54%	25.7 (3.1)	-	-	-	-	-	-	-
Lee 2021	NAFLD (+)	4168	-	51.2 (11.5)	65.50%	26.1 (3.5)	-	22.70%	208.3 (41.2)	141	27	29 (20, 41)	-
	NAFLD (-)	5523	-	47.4 (13.1)	37.60%	22.5 (3.0)	-	13.30%	201.8 (36.3)	88	24	18 (13, 25)	-
Pacifico 2020	NAFLD (+)	78	55.20%	11.3 (2.3)	48.70%	28.3 (4.5)	-	-	-	-	25	25	-
	NAFLD (-)	81	33.30%	12.5 (3.0)	75.30%	24.6 (3.3)	-	-	-	-	23	20	-
Peng 2019	NAFLD (+)	480	-	66.63 (4.31)	49.80%	-	-	30.80%	225.20 (42.4)	-	-	-	-
	NAFLD (-)	1469	-	66.74 (4.34)	46.70%	-	-	43.30%	-	-	-	-	-
Petta 2017	NAFLD (+)	98	-	52.5 (12.4)	40.80%	33.4 (5.1)	-	-	196.3 (45.7)	146.0 (69.7)	-	-	-
	NAFLD (-)	127	-	45.0 (13.3)	34.60%	27.8 (3.8)	-	-	200.3 (44.4)	139.8 (75.3)	-	-	-
Seo 2019	NAFLD (+)	1475	-	56.6 (11.1)	68.30%	23.9 (2.7)	-	-	-	-	29.1 (20.6)	29.2 (22.6)	29.2 (22.1)
	NAFLD (-)	685	-	53.1 (11.7)	31.70%	26.6 (3.1)	-	-	148 (40)	204 (160)	29 (20)	29 (22)	29.2 (22.1)
Su 2019	NAFLD (+)	89	-	59.4 (9.8)	37.7%	26.2 (3.4)	-	43.80%	177.9 (54.1)	203.7 (194.9)	25.4 (11.5)	28.5 (18.2)	-
	NAFLD (-)	147	-	57.6 (9.4)	62.30%	23.0 (2.9)	-	44.20%	162.4 (42.5)	124 (79.7)	22.6 (10.5)	24.2 (14.5)	-
Wang 2021	NAFLD (+)	124	0.153%	67.5 (10.1)	-	24.7 (2.8)	-	-	-	-	26.1 (7.2)	24.5 (14.6)	28.4 ± 18.4
	NAFLD (-)	362	0.08 &	62.9 (12.1)	-	22.5 (2.6)	-	-	-	-	21.3 (6.0)	17.6 (10.2)	21.2 ± 16.8
Wijarnpreecha 2019	NAFLD (+)	4188	48.30%	45.4 (0.43)	50.40%	28.98 (0.22)	-	29.80%	208.7 (1.45)	179.5 (3.60)	23.0 (0.28)	21.6 (0.59)	-
	NAFLD (-)	7137	10.30%	41.3 (0.45)	45.40%	25.49 (0.11)	-	22.50%	201.5 (0.88)	118.1(2.13)	15.4 (0.29)	19.8 (0.17)	-

[a] These data are log transformed.

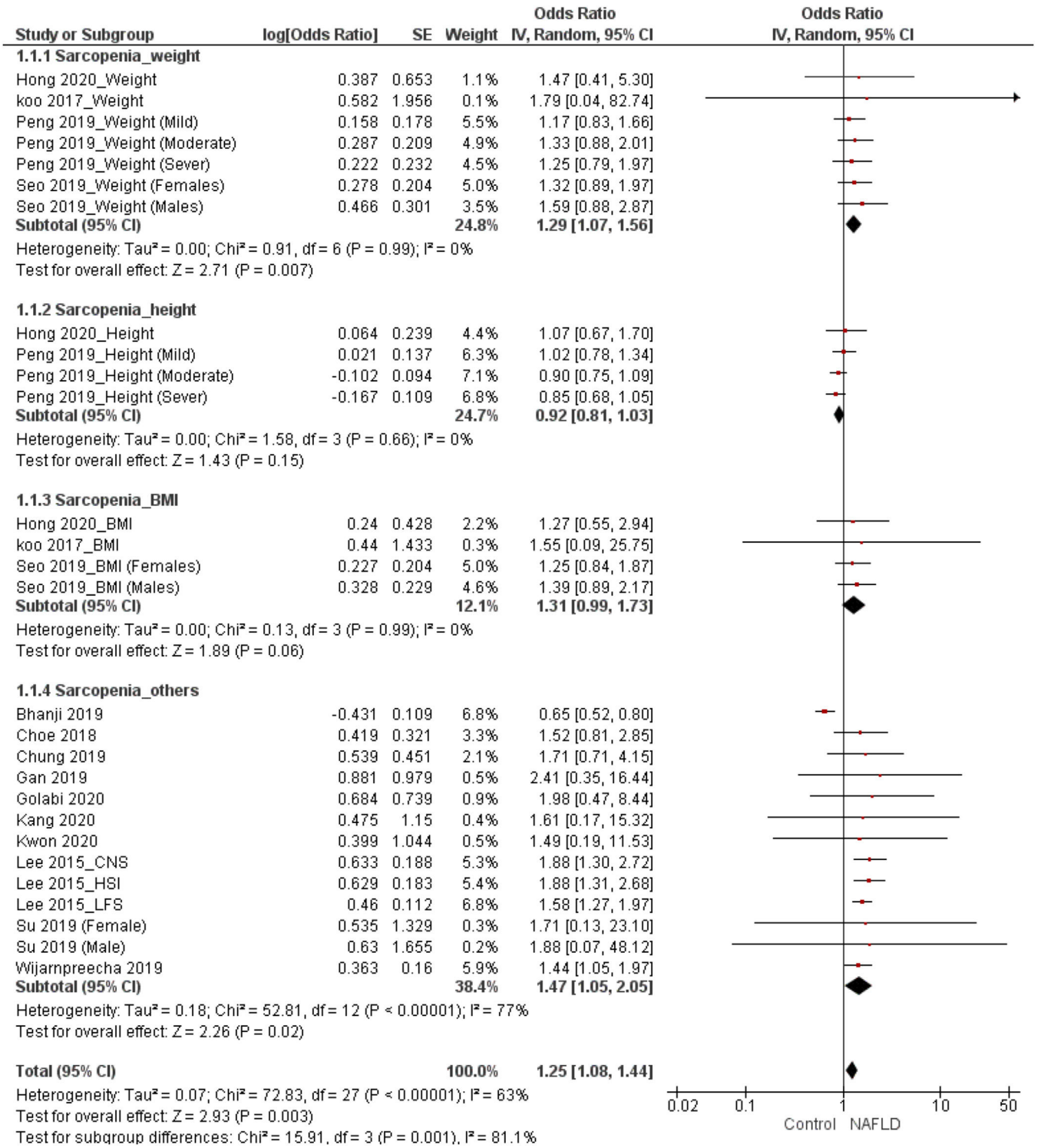

Fig. 2. A forest plot comparing the odds of sarcopenia in NAFLD patients with the controls.

were heterogenous ($P < 0.00001$; $I^2 = 70\%$). Heterogeneity cannot be solved. The asymmetrical distribution of the included studies around the effect estimate in the direction of large SE in the funnel plot suggests a significant publication bias (Fig. 5).

3.4.3. Fibrosis (Fig. 6)

The total estimate showed higher odds of liver fibrosis in MASLD patients who had sarcopenia than in NAFLD patients with no sarcopenia (OR = 1.49; 95 % CI [1.03, 2.14]; $P = 0.03$) [11,14,16,22,25,27,30]. The pooled studies were homogenous ($P = 1.00$; $I^2 = 0\%$).

4. Discussion

Our analysis showed that sarcopenia is associated with a higher probability of developing MASLD. Also, MASLD patients with sarcopenia had a higher probability of liver fibrosis than MASLD patients with no sarcopenia. On the other hand, there was no significant relationship between low SMI values and MASLD.

Multiple cross-sectional observational studies have shown that sarcopenia is linked to an increased risk of MASLD and MASLD-related advanced fibrosis in MASLD patients and that this association

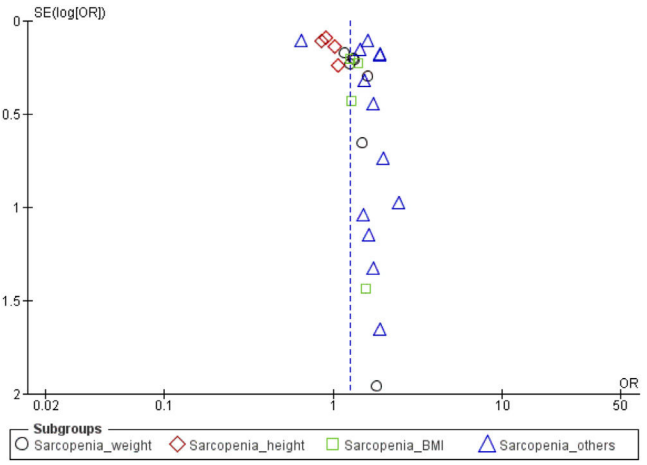

Fig. 3. A funnel plot for publication bias assessment in sarcopenia.

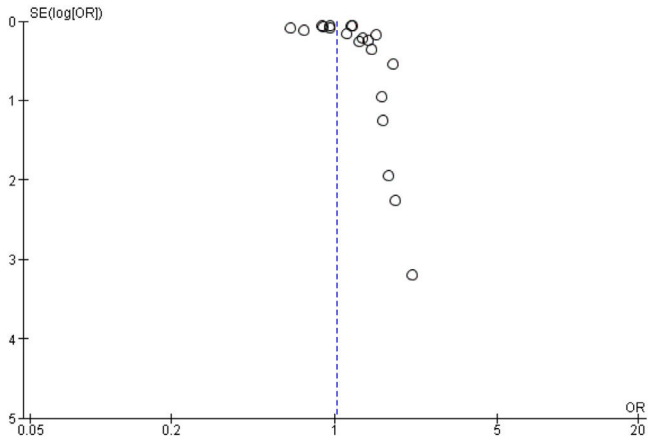

Fig. 5. A funnel plot of publication bias assessment in skeletal mass index.

is independent of obesity, metabolic syndrome, and insulin resistance [10].

MASLD patients' liver enzyme levels fluctuate, with typical values present in up to 78 percent of patients at any given time [39,40]. Although liver biopsy is the gold standard for diagnosing MASLD, ultrasonography, CT, and MRI scanning are valuable for detecting moderate to extreme fatty changes in the liver. The fatty liver appears darker and hypodense. The hepatic vessels appear lighter than the rest of the body, and this may be mistaken for contrast injection [41].

The discovery of a correlation between sarcopenia and MASLD could help prevent the disease from worsening. Sarcopenia and MASLD have been linked in several previous studies [42]. In Cruz et al.[43], an association was found between the sarcopenic index and non-alcoholic hepatic steatosis. Our results confirmed these findings after pooling different studies' results. On the other hand, Gan et al. [26], reported in their cross-sectional that low muscle mass and low muscle strength are independently associated with MASLD. Despite their large sample size, the range of age patients varied from 18 to 80 years, which may have affected the quality of evidence of their study [26]. Also, in the previous meta-analysis by Tovo et al.[44], Sarcopenia was independently associated with MASLD and possibly with advanced fibrosis.

Fibrogenesis in MASLD is a critical process that affects clinical management [45]. Non-alcoholic steatohepatitis clinical research network pathology committee developed a staging for MASLD [46]. Four out of 14 features in this staging system take a numerical score as follows: steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2), and fibrosis (0-4) [46]. Factors contributing to liver damage include direct cellular injury, cell degeneration and death through apoptosis and other forms of cell death, proinflammatory cytokine expression, hepatic stellate cell activation (HSCs), and irregular wound healing responses leading to fibrosis [47]. An imbalance between pro-oxidant species and antioxidant defense capacities causes oxidative stress. In the setting of hepatic steatosis, an overproduction of toxic lipid metabolites exacerbates oxidative damage to liver cells.

The role of sarcopenia in the development of MASLD may have significant therapeutic consequences in future research. Following our finding that sarcopenic MASLD patients have a higher risk for

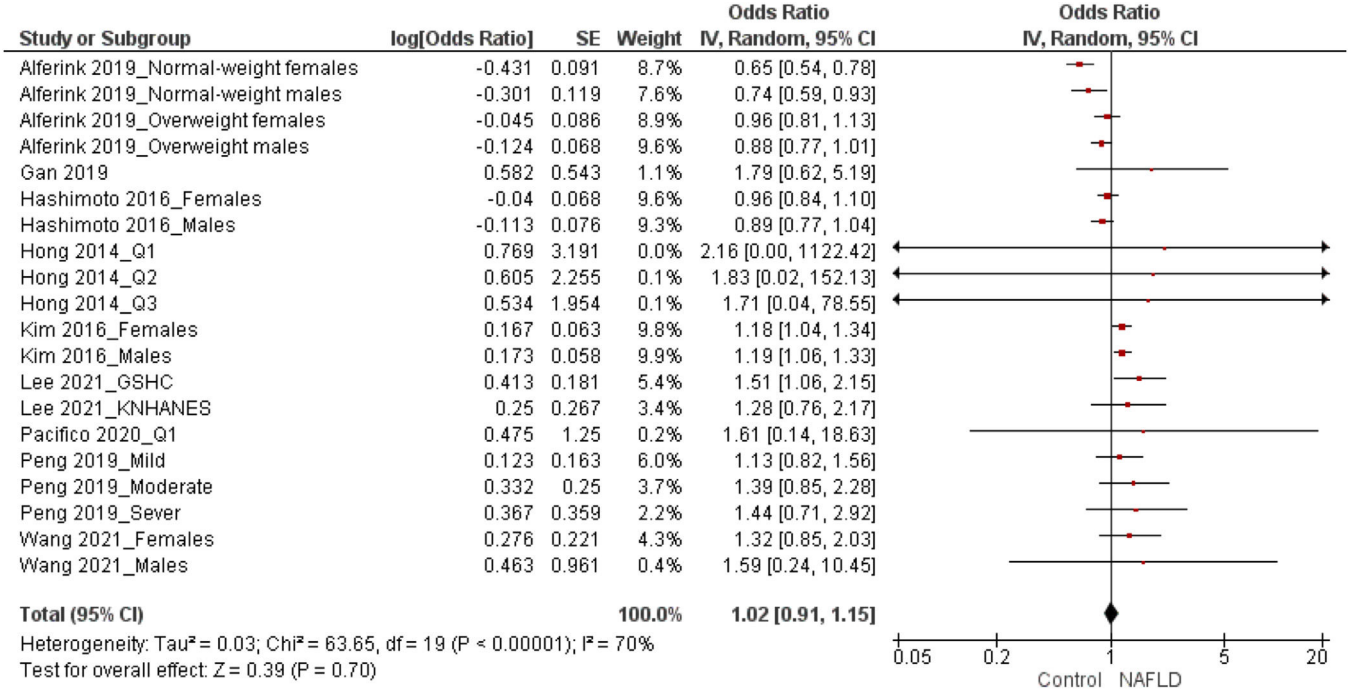

Fig. 4. A forest plot comparing the odds of low skeletal mass index in NAFLD patients with the controls.

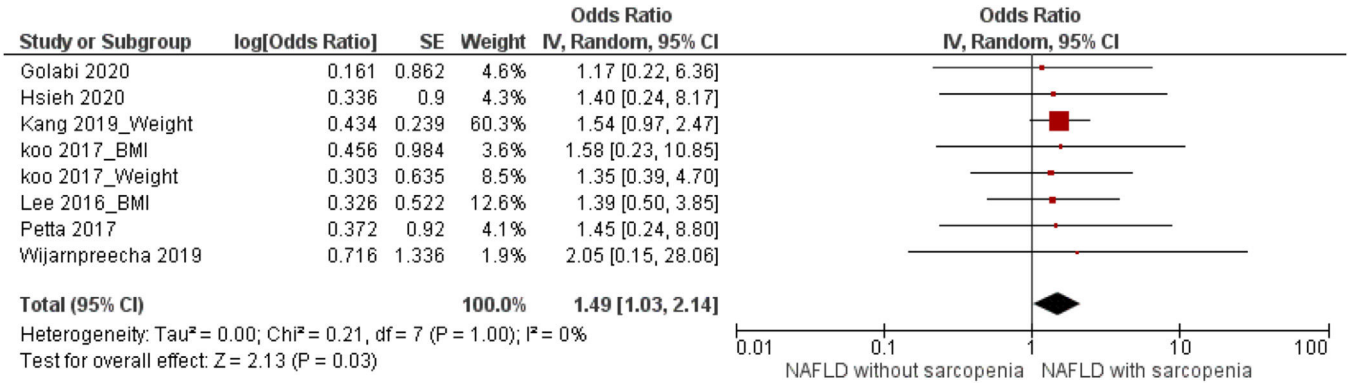

Fig. 6. A forest plot comparing the odds of liver fibrosis in sarcopenic NAFLD patients with the control NAFLD patients.

liver fibrosis, Yu et al.[48], linked sarcopenia to a higher risk of steatohepatitis or advanced liver fibrosis in patients with MASLD. In a biopsy-proven MASLD cohort studied by Koo et al.[11], sarcopenia was linked to metabolic dysfunction-associated steatohepatitis (MASH) and severe fibrosis. Besides, low muscle mass has been linked to the histological severity of MASLD [11]. Lee et al. [30] concluded that sarcopenia is associated with significant liver fibrosis.

Sarcopenic patients are evaluated using the skeletal muscle mass index (SMI), which is calculated by dividing the limb skeletal muscle mass (kg) by the square of the patient's height (m^2). Men with an SMI < 7.0 kg/m2 and women with an SMI < 5.7 kg/m2 were identified as having low muscle mass [49]. Our analysis showed no significant relationship between the odds of MASLD and SMI values. However, SMI should be considered in the diagnosis of MASLD [50]. In Kim et al. [28] a low SMI was associated with a high risk of MASLD, independent of other well-known metabolic risk factors; however, this link may vary depending on age group or menopausal status. Our results interfere with that of the previous meta-analysis by Cai et al. [51] stating that people with MASLD have a lower SMI than healthy people. More well-designed prospective studies are needed to reinforce the claims and confirm this relationship.

In this meta-analysis, we included many studies with large sample sizes. Included studies were of fair to good quality. At the same time, limitations include the different designs of included studies, the significant heterogeneity that could not be solved in some outcomes, and different definitions of sarcopenia across included studies. Also, our search strategy include studies until October 2022 and the results of crude analyses were not reported by some studies. Also, an age based subgroup analysis was not conducted due to non-uniform age related data reported in included studies.

5. Conclusions

In conclusion, sarcopenia raised the risk of MASLD and was linked to a higher risk of liver fibrosis in MASLD patients. However, SMI had no independent predictive value for developing NAFLD.

Authors contributions

Adnan Malik - Conceptualization, Methodology, Formal Analysis, Writing (Original Draft), and Review & Editing; Sadia Javaid - Conceptualization, Data Curation, Writing (Review and Editing); Muhammad Imran Malik - Methodology, Writing (Original Manuscript), and Review and Editing; Shahbaz Qureshi - Supervision, Writing, and Editing the manuscript.

Conflicts of interest

None.

Data availability statement

Data will be available to any researcher who contact the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.aohep.2024.101544.

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