ISSN 2150-5330 (online)

World Journal of *Gastrointestinal Pathophysiology*

Bimonthly Volume 15 Number 1 April 22, 2024

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Pathophysiology

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AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pathophysiology* (*WJGP*, *World J Gastrointest Pathophysiol*) is to provide scholars and readers from various fields of gastrointestinal pathophysiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGP mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal pathophysiology and covering a wide range of topics including disorders of the esophagus, stomach and duodenum, small intestines, pancreas, biliary system, and liver.

INDEXING/ABSTRACTING

The *WJGP* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Gastrointestinal Pathophysiology

ISSN

ISSN 2150-5330 (online)

LAUNCH DATE

April 15, 2010

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

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PUBLICATION DATE

April 22, 2024

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https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT

https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION

https://www.f6publishing.com

World Journal of Gastrointestinal Pathophysiology

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Pathophysiol 2024 April 22; 15(1): 91100

DOI: 10.4291/wjgp.v15.i1.91100

ISSN 2150-5330 (online)

SYSTEMATIC REVIEWS

Prevalence and outcome of sarcopenia in non-alcoholic fatty liver disease

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Moriyama K, Japan

Received: December 21, 2023
Revised: February 9, 2024
Accepted: April 1, 2024
Published online: April 22, 2024

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Abstract

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of conditions, progressing from mild steatosis to advanced fibrosis. Sarcopenia, characterized by decreased muscle strength and mass, shares common pathophysiological traits with NAFLD. An association exists between sarcopenia and increased NAFLD prevalence. However, data on the prevalence of sarcopenia in NAFLD and its impact on the outcomes of NAFLD remain inconsistent.

AIM

To analyze the prevalence and outcomes of sarcopenia in patients with NAFLD.

METHODS

We conducted a comprehensive search for relevant studies in MEDLINE, Embase, and Scopus from their inception to June 2023. We included studies that focused on patients with NAFLD, reported the prevalence of sarcopenia as the primary outcome, and examined secondary outcomes, such as liver fibrosis and other adverse events. We also used the Newcastle-Ottawa scale for quality assessment.

RESULTS

Of the 29 studies included, the prevalence of sarcopenia in NAFLD varied widely

(1.6% to 63.0%), with 20 studies reporting a prevalence of more than 10.0%. Substantial heterogeneity was noted in the measurement modalities for sarcopenia. Sarcopenia was associated with a higher risk of advanced fibrosis (odd ratio: 1.97, 95% confidence interval: 1.44-2.70). Increased odds were consistently observed in fibrosis assessment through biopsy, NAFLD fibrosis score/body mass index, aspartate aminotransferase to alanine aminotransferase ratio, diabetes (BARD) score, and transient elastography, whereas the fibrosis-4 score showed no such association. Sarcopenia in NAFLD was associated with a higher risk of steatohepatitis, insulin resistance, cardiovascular risks, and mortality.

CONCLUSION

This systematic review highlights the critical need for standardized diagnostic criteria and measurement methods for sarcopenia in NAFLD patients. The variability in study designs and assessment methods for sarcopenia and liver fibrosis may account for the inconsistent findings. This review demonstrates the multidimensional impact of sarcopenia on NAFLD, indicating its importance beyond liver-related events to include cardiovascular risks, mortality, and metabolic complications.

Key Words: Non-alcoholic fatty liver disease; Sarcopenia; Hepatic fibrosis; Low muscle mass; Hand grip strength; Bioelectric impedance analysis; Dual X-ray absorptiometry

Core Tip: The prevalence of sarcopenia in nonalcoholic fatty liver disease (NAFLD) varies widely. Sarcopenia in NAFLD is consistently associated with a higher risk of advanced fibrosis. In addition to liver-related events, sarcopenia in NAFLD is associated with adverse outcomes, including an increased risk of nonalcoholic steatohepatitis, mortality, cardiovascular risks, and metabolic complications. The heterogeneity in prevalence and associations highlights the importance of accurately defining measurement modalities and cutoff criteria. Establishing consensus guidelines is crucial for advancing research and enhancing clinical management in the complex relationship between sarcopenia and NAFLD.

Citation: Giri S, Anirvan P, Angadi S, Singh A, Lavekar A. Prevalence and outcome of sarcopenia in non-alcoholic fatty liver disease. *World J Gastrointest Pathophysiol* 2024; 15(1): 91100
URL: https://www.wjgnet.com/2150-5330/full/v15/i1/91100.htm
DOI: https://dx.doi.org/10.4291/wjgp.v15.i1.91100

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of liver conditions, beginning with mild steatosis and potentially advancing through steatohepatitis, fibrosis, and cirrhosis[1]. Sarcopenia, prevalent in aging populations, is defined by a reduction in muscle strength and/or function, often evidenced by a decrease in muscle mass observed in cross-sectional imaging[2]. Sarcopenic obesity is characterized by the concurrent presence of sarcopenia and increased fat mass, typically measured by body mass index (BMI) or waist circumference[3]. Factors such as hyperammonemia, endotoxemia, and endocrine disturbances, including insulin resistance and decreased testosterone levels, contribute to the increased prevalence of sarcopenia in individuals with liver cirrhosis[4]. Several pathophysiological similarities exist between NAFLD and sarcopenia, including insulin resistance, myostatin and adiponectin dysregulation, hormonal imbalances, chronic inflammation, impaired glucose uptake, and myosteatosis[5,6].

Studies have reported an association of sarcopenia with a higher prevalence of NAFLD and more severe liver damage in individuals with NAFLD. An increased fat mass in patients with NAFLD is associated with a higher incidence of sarcopenic obesity. A meta-analysis of five cross-sectional studies involving 27804 patients identified an increased risk of NAFLD in individuals with sarcopenia[7]. However, data regarding the prevalence of sarcopenia among patients with NAFLD are inconsistent. Moreover, the effects of sarcopenia on the outcomes of patients with NAFLD remain unclear. Thus, this systematic review aimed to analyze the prevalence and impact of sarcopenia in individuals with NAFLD.

MATERIALS AND METHODS

The current systematic review was conducted in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[8].

Database search

We searched for relevant studies in MEDLINE, Embase, and Scopus from the inception of these databases until June 31, 2023, by using the following keywords: (NAFLD OR Fatty liver OR Steatotic liver disease OR MAFLD OR NASH) AND

(Sarcopenia OR sarcopenic OR Muscle wasting). The titles and abstracts of the retrieved studies were screened by two independent reviewers, who then assessed the full texts for eligibility before inclusion. Furthermore, the bibliographies of the included studies were reviewed to identify additional relevant studies. Any disagreements between the two independent reviewers were resolved by a third reviewer.

Study inclusion

Both prospective and retrospective studies that met the following criteria were included in this systematic review: (1) Studies including patients with NAFLD as determined by serology, ultrasonography (USG), transient elastography (TE), or magnetic resonance imaging (MRI); (2) Studies examining the prevalence of sarcopenia as the primary outcome; and (3) Studies evaluating the effect of sarcopenia on the risk of liver fibrosis or other adverse outcomes as secondary outcomes. Editorials, correspondences, case reports, case series, and review articles were excluded. Moreover, studies with insufficient or irrelevant clinical data were excluded.

Data extraction and quality assessment

Two reviewers independently extracted the data, and a third reviewer resolved any disagreements. The extracted information for each study included the title, first author, year of publication, country, number of patients, age and sex distribution, BMI, prevalence of metabolic syndrome parameters, diagnostic method used for fatty liver diagnosis, assessment method for sarcopenia, prevalence of sarcopenia, and the effect of sarcopenia on the outcomes of patients with NAFLD. The quality of the included studies was assessed by two independent reviewers by using the Newcastle-Ottawa Scale for cohort studies[9,10]. In case of a disagreement, a third reviewer was consulted.

RESULTS

Study characteristics and quality assessment

A total of 2134 records were identified using the predefined search strategy, with 29 studies ultimately included in the systematic review. Figure 1 illustrates the PRISMA flowchart detailing the study selection and inclusion process. Table 1 presents the baseline characteristics and outcomes of the included studies. The majority of the studies were from Asia, followed by North America. The mean age of participants in the included studies ranged from 41.9 to 67.8 years, and the proportion of male participants varied from 19.5% to 89.8%. Only three studies included biopsy-proven NAFLD cases[11-13], whereas the remaining studies used noninvasive methods for NAFLD diagnosis. Among the studies using noninvasive modalities, four used serological tests[10,14-16], 16 used USG[17-32], two used MRI[33,34], and four used TE with controlled attenuation parameters[35-38]. Bioimpedance analysis was the most common modality used for the assessment of sarcopenia (16 studies)[11,12,17,18,20-23,28,30-37], followed by dual X-ray absorptiometry (DEXA; 7 studies)[10,19,14,25,26,28,29], computed tomography (1 study)[13], hand-grip strength (1 study)[15], and MRI (1 study)[33]. Both the studies by Wijarnpreecha *et al*[18] and Kim *et al*[23] analyzed the data from the third National Health and Nutrition Examination Survey conducted from 1988 to 1994 but analyzed different outcomes. Six studies were of good quality[1-13,30,35,37], 20 were of fair quality[10,14,15,17-23,24-29,31-34,38], and three were of poor quality[16,24,35].

Prevalence of sarcopenia in NAFLD

A total of 24 studies reported the prevalence of sarcopenia in NAFLD. The overall prevalence varied significantly, from 1.6% when determined using MRI[33] to 63.0% when assessed using DEXA[24]. Four studies reported a prevalence of less than 10.0%[17,20,33,34], 14 reported a prevalence of 10.0%-30.0%[10,11,13,14,19,22,26-31,35,38], four reported a prevalence of 30.0%-50.0%[12,14,33,38], and two reported a prevalence of more than 50.0%[24,36]. In studies using DEXA, the prevalence of sarcopenia ranged from 12.2% when using an appendicular skeletal muscle mass (ASM)/BMI (cutoff of 0.789 in men and 0.521 in women)[10] to 63.0% when using ASM/weight (cutoff of 29.0 in men and 22.9 in women[25]). In studies using BIA, the prevalence of sarcopenia ranged from 4.4% by using a combination of ASM/weight, ASM/height^2, and ASM/BMI[34] to 54.8% using ASM/height^2 (cutoff of 7.0 in men and 5.7 in women)[32].

Risk of advanced fibrosis in NAFLD with sarcopenia

Ten studies examined the correlation between advanced fibrosis and sarcopenia in NAFLD[11-13,18,22,29,35,37]. The combined analysis of these studies revealed that sarcopenia was associated with a higher risk of advanced fibrosis, with an odds ratio (OR) of 1.97 [95% confidence interval (95%CI): 1.44-2.70; I^2 = 79.8%]. When considering individual modalities for the assessment of fibrosis, including biopsy, NAFLD fibrosis scores/BMI, the ratio of aspartate aminotransferase to alanine aminotransferase, diabetes (NFS/BARD) scores, and TE, sarcopenia was consistently associated with an increased risk of advanced fibrosis with ORs of 1.98 (95%CI: 1.39-2.82; I^2 = 0.0%), 2.09 (95%CI: 1.55-2.81; I^2 = 0.0%), and 3.71 (95%CI: 2.62-5.24; I^2 = 0.0%), respectively, indicating no heterogeneity (Figure 2). However, when using the fibrosis-4 (FIB-4) score, no association was observed between sarcopenia and advanced fibrosis with an OR of 1.38 (95%CI: 0.96-1.99; I^2 = 63.3%), indicating moderate heterogeneity.

Risk of other events in NAFLD with sarcopenia

Eight studies explored the outcome of NAFLD with sarcopenia in addition to the increased risk of advanced hepatic fibrosis. Koo *et al*[11] reported a higher risk of nonalcoholic steatohepatitis (NASH) in NAFLD with sarcopenia (aOR: 2.59; 95%CI: 1.22-5.48). Petta *et al*[12] reported that the prevalence of NASH was higher in the presence of sarcopenia (88.7% *vs*.

Table 1 Baseline characteristics of the included studies showing the prevalence and outcome of sarcopenia in patients with non-alcoholic fatty liver disease

Ref.	Country, study design	Population and size	Age, in years, male sex, in %	Comorbidities	Definition of NAFLD	Definition and prevalence of sarcopenia	Outcome	Study quality
Lee *et al*[10], 2016	South Korea, retrospective	Korean National Health and Nutrition Examination Surveys 2008-2011, *n* = 2761	55.8 ± 14.3, 45%	BMI: 25.8 ± 3.1; MS: 81%; DM: 30%	NAFLD liver fat score	DEXA was used for the calculation of SI = ASM/BMI. Sarcopenia was defined using a cut-off point of SI < 0.789 in men and < 0.521 in women; *n* = 337 (12.2%)	Significant fibrosis was defined as FIB-4 ≥ 2.67. After adjusting for all covariates, a higher value of SI was associated with a lower risk of significant fibrosis with aOR: 0.67 (95%CI: 0.49-0.91)	Fair
Koo *et al*[11], 2017	South Korea, prospective	Boramae NAFLD registry, *n* = 240	53.3 ± 14.3, 48.7%	BMI: 27.4 ± 3.5; DM: 39.6%; HTN: 40.4%; smoking: 22.5%	≥ 5% macrovesicular steatosis on liver biopsy	BIA was used to calculate ASM, which was divided by weight = ASM%. ASM% < 29.0 in men or < 22.9 in women was considered as sarcopenia. *n* = 64 (26.7%) (21/117 in NAFLD and 43/123 in NASH)	Among patients with NAFLD, sarcopenia was associated with a higher risk of NASH (aOR: 2.59; 95%CI: 1.22-5.48). Sarcopenia was also associated with the presence of significant fibrosis (F2-F4) on liver biopsy (aOR: 2.21; 95%CI: 1.10-4.44)	Good
Petta *et al*[12], 2017	Italy, prospective	Consecutive patients with NAFLD at a single center, *n* = 225	48.3 ± 13.4, 62.7%	BMI: 30.3 ± 5.2; DM: 45.3%; HTN: 32.9%; obesity: 71.1%	≥ 5% macrovesicular steatosis on liver biopsy	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. Sarcopenia was defined as an SMI ≤ 37 in males and ≤ 28 in females. *n* = 98 (43.6%)	Sarcopenia was also associated with the presence of advanced fibrosis (F3-F4) on liver biopsy (aOR: 2.36; 95%CI: 1.16-4.77). The prevalence of NASH was higher in the presence of sarcopenia (88.7% *vs* 76.3% in nonsarcopenic cases, *P* = 0.01)	Good
Kang *et al*[17], 2019	South Korea, retrospective	Adults undergoing comprehensive health screening at a single center from 2010-2017, *n* = 10711	47.9 ± 11.6, 52.8%	BMI: 23.9 ± 2.9; MS: 12.5%; DM: 5.9%; HTN: 11.6%; obesity: 34.1%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight = ASM/BW%; ASM/BW% < 29.0 in men or < 22.9 in women was considered as sarcopenia; *n* = 615 (5.7%)	Advanced fibrosis was defined as NFS ≥ 0.676 and FIB-4 ≥ 2.670. Sarcopenia was also associated with the presence of advanced fibrosis (F3-F4) as defined by NFS with aOR: 2.68 (95%CI: 1.28-5.59), but not using FIB-4 (aOR: 1.58, 95%CI: 0.87-2.85)	Fair
Wijarnpreecha *et al*[18], 2019	United States, retrospective	Analysis of the third National Health and Nutrition Examination Survey (NHANES), conducted from 1988 to 1994, *n* = 4188	45.4 ± 0.4[2], 50.4%	BMI: 28.9 ± 0.2[2]; HTN: 31.6%; DM: 7.5%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. Sarcopenia was defined as an SMI ≤ 37 in males and ≤ 28 in females; *n* = 2023 (48.3%)	Advanced fibrosis was defined as NFS ≥ 0.676; sarcopenia was significantly associated with advanced fibrosis (aOR: 2.39, 95%CI: 1.50-3.84)	Fair
Gan *et al*[19], 2020	China, prospective	Lanxi cohort, a community-based prospective cohort with a focus on obesity-related diseases, *n* = 1088	55.2 ± 11.5, 32.9%	BMI: 25.9 ± 2.9; MS: 59.5%; DM: 12.9%; HTN: 48.1%	Abdominal ultrasound[1]	DEXA was used for the calculation of SMI = total appendicular lean mass (ALM)/weight. The cut-off points for sarcopenia were 28.64% for men and 24.12% for women; *n* = 246 (22.6%)	-	Fair
Golabi *et al*[14], 2020	United State, retrospective	Analysis of the National Health and Nutrition Examination	50.7 ± 0.7[2],	BMI: 32.5 ± 0.3[2]; obesity: 60.6%; HTN:	Fatty liver index (FLI) ≥ 30 based on age,	DEXA was used to calculate SI = ASM/BMI. Sarcopenia was defined using a cut-off point of	Sarcopenia was an independent predictor of mortality in NAFLD with	Fair

		Survey (NHANES), from 1999 to 2004, *n* = 1351	60.0%	68.4%; MS: 63.9%; DM: 20.7%	race/ethnicity, waist circumference, GGT, activity, fasting insulin, and fasting glucose	SI < 0.789 in men and < 0.521 in women. *n* = 239 (17.7%)	aHR 1.78 (95%CI: 1.16-2.73)	
Hsieh *et al*[13], 2021	Taiwan, prospective	Boramae NAFLD cohort, *n* = 521	52.0 ± 15.0, 50.9%	BMI: 27.8 ± 3.8; DM: 39.3%; HTN: 42.4%	≥ 5% macrovesicular steatosis on liver biopsy	Cross-sectional CT images at L3 was used to calculate SMI; Sarcopenia defined by L3-SMI < 50 cm^2/m^2 for men and < 39 cm^2/m^2 for women. *n* = 122 (23.4%)	Sarcopenia was also associated with the presence of significant fibrosis (F2-F4) on liver biopsy (aOR: 1.72; 95%CI: 1.05-2.84)	Good
Kang *et al*[15], 2020	South Korea, retrospective	Korean National Health and Nutrition Examination Surveys 2014-2016 with age 35-65 yr, *n* = 2092	45.6 ± 0.2[2], 42.4%	BMI: 23.8 ± 0.0[2]; DM: 10.7%; HTN: 24.1%; obesity: 33.6%	HIS was calculated based on ALT, AST, BMI, DM, sex, NAFLD defined by HIS > 36	Hand grip strength was calculated using a dynamometer, and sarcopenia was defined for individuals in the 1st quartile (Q1) of muscle strength	Advanced fibrosis was defined as either a FIB-4 score ≥ 1.30 or a BARD score ≥ 2.00. Sarcopenia was also associated with the presence of advanced fibrosis as defined by BARD with aOR: 1.68 (95%CI: 1.07-2.62), but not using FIB-4 (aOR: 1.35, 95%CI: 0.75-2.45)	Fair
Park *et al*[20], 2020	South Korea, retrospective	Patients attending annual health examination at a single center, *n* = 747	48.9 ± 10.8, 68.1%	BMI: 24.9 ± 3.1	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. ASM/BW% < 29.1 in men or < 23.0 in women was considered as sarcopenia. *n* = 66 (8.8%)	-	Fair
Seo *et al*[21], 2020	South Korea, retrospective	Seoul Metabolic Syndrome Cohort, *n* = 1278	55.8 ± 10.8, 53.6%	BMI: 26.5 ± 3.3; DM: 100%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight = ASM/BW%. ASM/BW% < 29.0 in men or < 22.9 in women was considered as sarcopenia. *n* = 528 (41.3%)	-	Fair
Kang *et al*[22], 2021	South Korea, retrospective	Patients undergoing carotid ultrasound at a single center, *n* = 683	49.1 ± 10.0, 86.1%	BMI: 26.4 ± 2.6; DM: 15.2%; obesity: 67.0%; HTN: 29.1%; MS: 43.6%	Abdominal ultrasound[1]	BIA was used to calculate SI = ASM/BMI. Sarcopenia was defined using a cut-off point of SI < 0.789 in men and < 0.521 in women. *n* = 75 (11.0%)	Sarcopenia was an independent predictor of increased intima-media thickness (OR: 2.26, (95%CI: 1.26-4.04) and carotid plaque (OR: 2.74, 95%CI: 1.30-5.78)	Fair
Kim *et al*[23], 2021	United States, retrospective	Analysis of the third National Health and Nutrition Examination Survey (NHANES), conducted from 1988 to 1994, *n* = 3773	45.5 ± 0.45[2], 50.5%	BMI: 29.0 ± 0.23[2]; DM: 12.1%; HTN: 30.9%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. Sarcopenia was defined as an SMI ≤ 37 in males and ≤ 28 in females. *n* = 1822 (48.3%)	Sarcopenia was an independent predictor of mortality in NAFLD with aHR 1.44 (95%CI: 1.16-1.80)	Fair
Lee *et al*[24], 2021	South Korea, retrospective	Gangnam Severance Hospital Check-up (GSHC) dataset from 2016 to 2019, *n* = 4168	51.2 ± 11.5, 65.5%	BMI: 26.1 ± 3.5	Abdominal ultrasound[1]	*n* = 1288 (30.9%)	-	Poor
Lee *et al*[25], 2021	South Korea, retrospective	Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population data, *n* = 320	65.7 ± 7.6, 63.6%	BMI: 26.9 ± 2.9; DM: 67.9%; HTN: 60.5%	Abdominal ultrasound[1]	57 (39.6%), 107 (59.8%), and 148 (63.0%) participants had low muscle mass adjusted for height, BMI, and body weight in the NAFLD group, respectively	Appendicular muscle mass adjusted for body weight only was associated with hepatic fibrosis but not when adjusted for height and BMI	Fair
Linge *et al*[33], 2021	United Kingdom, retrospective	Participants of United Kingdom Biobank study, aged 40-69 yr at recruitment in 2006-2010, *n* = 1204	62.9 ± 7.4, 53.5%	BMI: 30.1 ± 4.8	MRI liver PDFF > 5%	Sarcopenia, defined as low hand grip strength [< 16/27 kg (females/males)] and low muscle quantity [MRI threshold of 3.0 and 3.6 L/m^2 for thigh FFMV/height^2 (females/males)]. *n* =	-	Fair

						19 (1.6%)		
Wang *et al*[26], 2021	China, prospective	Patients attending annual health examination at a single center in 2019, *n* = 154	67.8 ± 9.3, 19.5%	BMI: 24.9 ± 2.9	Abdominal ultrasound[1]	Sarcopenia, defined as low hand grip strength (< 18 kg in women and < 26 kg in men), a gait speed < 0.8 m/s, and DEXA-based ASM/height^2 < 5.4 in women and < 7.0 kg/m^2 in men. *n* = 25 (16.2%)	-	Fair
Almeida *et al* [27], 2022	Brazil, prospective	Consecutive patients with NAFLD at a single center, *n* = 57	52.7 ± 11.3, 24.6%	-	Abdominal ultrasound[1]	Probable sarcopenia, defined as low hand grip strength [< 16/27 kg (females/males)]. *n* = 15 (26.3%)	-	Fair
Guo *et al*[35], 2022	China, prospective	Patients undergoing health checkup at a single center from 2020-2021, *n* = 1830	47.4 ± 10.5, 80.2%	BMI: 27.1 ± 3.0	Transient elastography with fat attenuation parameter > 240 dB/m	BIA was used to calculate ASM, which was divided by height × 100 = SMI. SMI gradually decreased in a stepwise manner as the severity of hepatic steatosis increased	LSM values > 7.3 kPa were classified as having liver fibrosis. Participants in the tertile 1 of SMI had significantly higher odds of liver fibrosis (aOR: 3.7, 95%CI: 2.6-5.3) compared to tertile 3	Good
Seo *et al*[36], 2022	South Korea, retrospective	Patients undergoing health checkup at a single center from 2017-2019, *n* = 3198	54.2 ± 9.6, 89.8%	BMI: 26.2 ± 2.9; HTN: 40.2%; DM: 20.1%	Transient elastography with controlled attenuation parameter > 248 dB/m	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. ASM/BW% < 29.1 in men or < 23.0 in women was considered as sarcopenia. *n* = 517 (16.2%)	-	Poor
Song *et al*[37], 2023	South Korea, retrospective	Patients undergoing health checkup at a single center from 2007-2018, *n* = 1180	53.3 ± 10.3, 71.5%	BMI: 26.7 ± 3.67; DM: 20.7%	Transient elastography with fat attenuation parameter > 260 dB/m	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. ASM/BW% < 30.0 in men or < 26.8 in women was considered as sarcopenia	LSM values ≥ 7.5 kPa (≥ F2) were classified as having liver fibrosis. Sarcopenia was not a predictor of fibrosis in NAFLD with aOR: 3.80 (95%CI: 0.86-16.75)	Good
Zhang *et al*[28], 2022	China, retrospective	T2DM patients with BMI < 25 kg/m^2 were enrolled from a single center from 2017 to 2021, *n* = 1112	53.4 ± 10.7, 57.6%	BMI: 22.6; DM: 100%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight × 100 = SMI. ASM/BW% < 32.2 in men or < 25.5 in women was considered as sarcopenia. *n* = 290 (26.1%)	-	Fair
Zhu *et al*[29], 2023	China, prospective	Participants of Shanghai Changfeng Study, a community-based prospective cohort study of multiple chronic diseases Jun 2009 to Dec 2012, with age > 45 yr, *n* = 1305	62.6 ± 8.9, 33.1%	BMI: 25.7 ± 3.2	Fatty liver was diagnosed when liver fat content by ultrasound exceeded the cut-off value of 9.15%	DEXA was used to calculate SI = ASM/height^2. The cut-off SI for sarcopenia were 6.88 kg/m^2 in male and 5.67 kg/m^2 in female. *n* = 260 (19.9%)	Significant fibrosis was defined as FIB-4 ≥ 2.67. The presence of sarcopenia was associated with increased risk of carotid plaque (aOR: 2.22; 95%CI: 1.23-4.02) and liver fibrosis (aOR: 2.07; 95%CI: 1.24-3.44)	Fair
Cho *et al*[30], 2023	South Korea, retrospective	Patients with T2DM from the Seoul Metabolic Syndrome Cohort, *n* = 456	55.0 ± 9.4, 46.3%	BMI: 25.7 ± 2.8; DM: 100%; HTN: 36.0%	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was divided by weight = ASM/BW%; ASM/BW% < 29.0 in men or < 22.9 in women was considered as sarcopenia. *n* = 123 (27.0%)	Sarcopenia was an independent predictor carotid plaque progression (OR: 2.02, 95%CI: 1.32-3.08)	Good
Choe *et al*[16], 2023	South Korea, retrospective	Korean Genome and Epidemiology Study (KoGES) Ansung-Ansan cohort, *n* = 1442	51.7 ± 8.5, 40.0%	BMI: 27.9 ± 2.5; DM: 28.4%; HTN: 34.7%; MS: 69.7%	Hepatic steatosis index (HSI) based on ALT, AST, BMI, DM, sex. NAFLD defined by HSI > 36	-	Fibrosis was defined as FIB-4 ≥ 1.3 and APRI ≥ 0.5. In the adjusted model, low muscle mass (lowest quartile) did not contribute to progression to hepatic fibrosis (HR: 1.02, 95%CI: 0.85-1.22)	Poor
Chun *et al*[31],	South Korea,	Patients undergoing health	50.0 ±	BMI: 25.9 ± 3.3; DM:	Abdominal ultrasound[1]	BIA was used to calculate ASM, which was	-	Fair

2023	retrospective	checkup at a three center from 2014-2020, *n* = 23889	11.0, 69.5%	14.4%; HTN: 37%; obesity: 56.9%; MS: 47.1%		divided by weight = ASM/BW%; ASM/BW% < 29.0 in men or < 22.9 in women was considered as sarcopenia. *n* = 3092 (12.9%). Sarcopenia was defined using a cut-off point of ASM/BMI = SI < 0.789 in men and < 0.521 in women. *n* = 1577 (6.6%)		
Harring *et al* [38], 2023	United States, retrospective	Analysis of the third National Health and Nutrition Examination Survey (NHANES), from 2017 to 2018, *n* = 1056	41.9 ± 0.42[2], 54.8%	BMI: 33.5 ± 0.37[2]; obesity: 78.7%; DM: 18.1%; HTN: 53.9%; MS: 64.8%	Transient elastography with fat attenuation parameter > 263 dB/m	DEXA was used to calculate SI = ASM/BMI. Sarcopenia was defined using a cut-off point of SI < 0.789 in men and < 0.512 in women. *n* = 303 (28.7%)	-	Good
Lu *et al*[32], 2023	China, retrospective	Patients diagnosed with obesity during health checkup at a single center from 2020-2021, *n* = 476	51.0 ± 13.7, 52.7%	BMI: 27.9 ± 3.3; obesity: 100%	Abdominal ultrasound[1]	BIA was used to calculate SMI = appendicular skeletal mass/height^2. Sarcopenia defined as SMI ≤ 7.0 kg/m^2 for males and ≤ 5.7 kg/m^2 for females; *n* = 261 (54.8%)	-	Fair
Zhou *et al*[34], 2023	China, prospective	Consecutively enrolled subjects who underwent BIA at a single center, between May 2017 and July 2022, *n* = 1123	37.8 ± 10.6, 58.7%	BMI: 28.9 ± 5.1; DM: 17.6%	MRI liver PDFF > 5%	BIA was used to calculate the appendicular skeletal mass (ASM). Sarcopenia was defined as ASM/height^2 or ASM/weight or ASM/BMI less than 2 SD. *n* = 50 (4.4%)	The MAFLD patients with lower quartiles of ASM/W had a higher risk OR for insulin resistance, both in male and female (OR: 2.14, 95%CI: 1.16-3.97), and OR: 4.26, 95%CI: 1.29, 14.02) for Q4 *vs* Q1	Fair

[1]Abdominal ultrasound showing at least two of the following three abnormal findings: (1) Diffusely increased echogenicity in liver near field ('bright liver') with greater liver echogenicity than kidney or spleen; (2) vascular blurring; and (3) poor visualization of the posterior portion of the right lobe because of deep attenuation.

[2]Standard error.

ALT/AST/GGT: Alanine transaminase/aspartate transaminase/gamma-glutamyltransferase; aOR: Adjusted odds ratio; 95%CI: 95% confidence interval; ASM: Appendicular skeletal muscle mass; BIA: Bioelectrical impedance analysis; BMI: Body mass index; BW: Body weight; DM/HTN/MS: Diabetes mellitus/hypertension/metabolic syndrome; DEXA: Dual X-ray absorptiometry; LSM: Liver stiffness measurement; MRI-PDFF: Magnetic resonance imaging proton density fat fraction; SMI: Skeletal muscle mass index; HIS: Hepatic steatosis index; FIB-4: Fibrosis-4; NASH: Nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease.

76.3% in nonsarcopenic cases, *P* = 0.01). Two studies identified sarcopenia as a predictor of mortality in patients with NAFLD, with adjusted hazard ratios (aHRs) of 1.78 (95%CI: 1.16-2.73)[14] and 1.44 (95%CI: 1.16-1.80)[23]. Kang *et al*[22] reported sarcopenia as an independent predictor of increased intima-media thickness with an OR of 2.26 (95%CI: 1.26-4.04). Furthermore, Kang *et al*[22] and Zhu *et al*[29] reported that sarcopenia in NAFLD was associated with a higher risk of carotid plaque, with aORs of 2.74 (95%CI: 1.30-5.78) and 2.22 (95%CI: 1.23-4.02), respectively. However, Cho *et al*[30] reported higher odds of carotid plaque development with sarcopenia in those without carotid plaque at baseline (OR: 2.02, 95%CI: 1.32-3.08). Finally, Zhou *et al*[34] reported that NAFLD patients with sarcopenia had a higher risk of insulin resistance in both men and women (OR: 2.14, 95%CI: 1.16-3.97; OR: 4.26, 95%CI: 1.29-14.02).

DISCUSSION

An increasing number of studies have indicated the association between sarcopenia and NAFLD. However, the exact prevalence of sarcopenia in the NAFLD population remains unclear. This systematic review is the first to summarize the current evidence on the prevalence of sarcopenia in NAFLD patients. Of the 24 studies reporting the prevalence, fourteen,

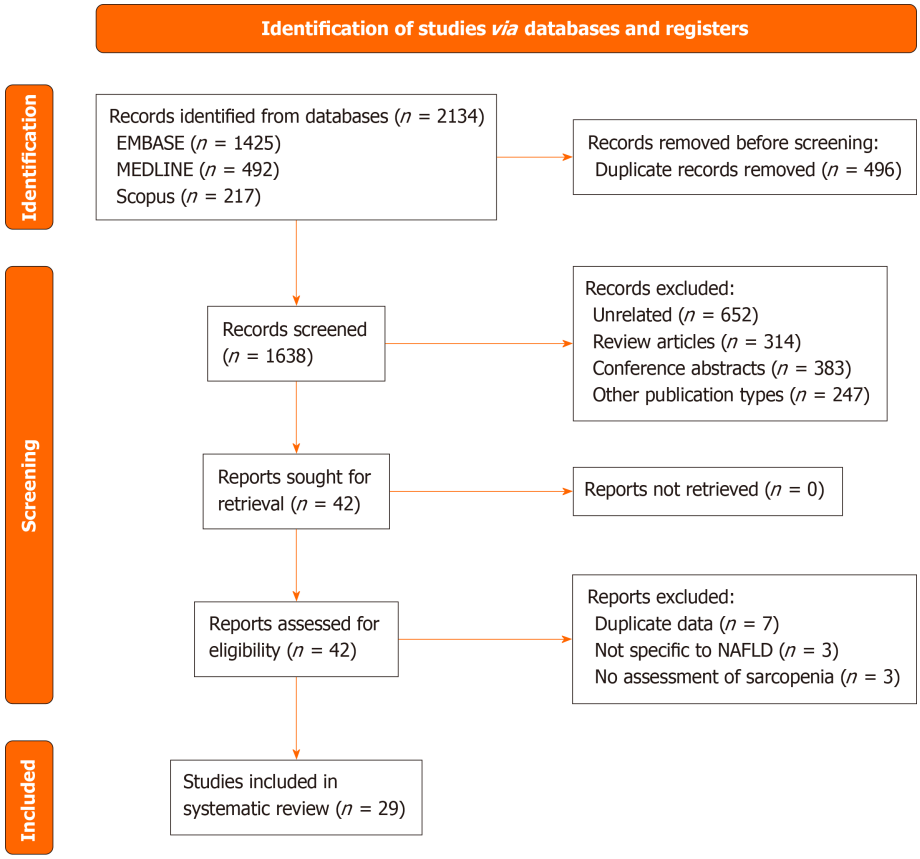

Figure 1 PRISMA flowchart for study identification, selection, and inclusion process. NAFLD: Nonalcoholic fatty liver disease.

four, and two studies reported prevalence rates of 10%-30%, 30%-50%, and more than 50%, respectively, whereas only four studies demonstrated a prevalence rate of less than 10%. This finding indicates that a considerable number of patients with NAFLD develop sarcopenia. In addition, sarcopenia was associated with an increased risk of advanced fibrosis in NAFLD, with an OR of 1.97 (95%CI: 1.44-2.70). Furthermore, sarcopenia in patients with NAFLD was associated with increased risks of NASH, insulin resistance, carotid plaque, and mortality.

Our systematic review highlighted a considerable variation in the reported prevalence of sarcopenia among patients with NAFLD. This variation is attributed to the diagnostic modality used, from 1.6% using MRI to 63.0% with DEXA. This discrepancy is amplified by using different cutoff values and indices within the same diagnostic modality, such as the normalization of ASM to BMI, weight, or height squared. This substantial variability in sarcopenia prevalence emphasizes the need for standardized diagnostic criteria and measurement techniques for sarcopenia in NAFLD patients. The European Working Group on Sarcopenia in Older People has proposed criteria and cutoffs for the three essential components of sarcopenia: muscle mass, muscle strength, and physical performance[2]. The choice of diagnostic modality and cutoff criteria markedly affects the reported prevalence rates, highlighting the necessity for consensus guidelines to ensure consistency across studies and populations. The variation in prevalence across different studies is primarily influenced by the distribution of muscle mass index in the population and the absolute values of the cutoff points. By contrast, variations in cutoff points for gait speed and grip strength appear to have a weak impact on the prevalence rates of sarcopenia[39].

The results of this systematic review revealed a significant relationship between sarcopenia and an increased risk of advanced fibrosis in NAFLD patients despite noticeable heterogeneity across the included studies. Upon examining the various modalities used for assessing fibrosis (such as biopsy, NFS/BARD scores, TE, and FIB-4 scores), a consistent association with sarcopenia was observed for all modalities except for the FIB-4 score. The absence of an association with the FIB-4 score indicates the necessity of selecting the appropriate fibrosis assessment method when exploring the relationship between sarcopenia and advanced fibrosis in NAFLD. Additionally, a recent study examined the effectiveness of noninvasive tests for estimating fibrosis, particularly in Asian populations. A recent multicentric study highlighted that only TE and TE-based combination tests accurately predicted liver fibrosis, whereas the internationally accepted thresholds for other NITs exhibited high false-negative rates[40].

Our systematic review sheds light on the extensive range of outcomes associated with sarcopenia in NAFLD patients. Key findings included an increased risk of NASH and a higher incidence of NASH in those with sarcopenia. Additionally, our meta-analysis revealed the predictive value of sarcopenia for mortality in NAFLD, as demonstrated by two studies with aHR of 1.78 (95%CI: 1.16-2.73) and 1.44 (95%CI: 1.16-1.80[14,23]). Sarcopenia in NAFLD was also associated with cardiovascular risk factors, such as increased intima-media thickness and a higher likelihood of carotid plaque formation. Moreover, sarcopenia was associated with a higher prevalence of insulin resistance, a key player in NAFLD pathogenesis. The relationship between sarcopenia and cardiovascular risks is particularly significant, con-

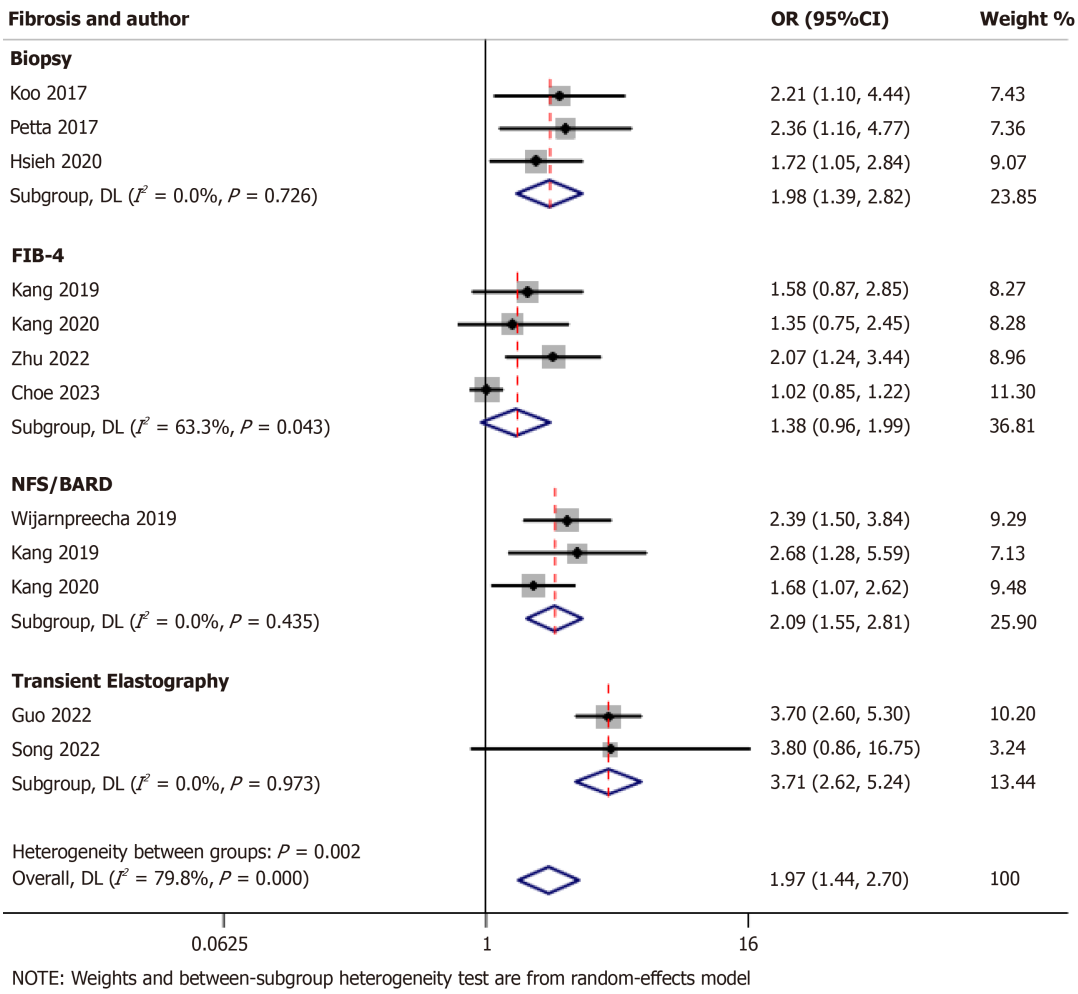

Figure 2 Forest plot showing the odds of advanced fibrosis with sarcopenia in patients with non-alcoholic fatty liver disease with subgroup analysis based on the method of fibrosis assessment. OR: Odds ratio; 95%CI: 95% confidence interval; FIB-4: Fibrosis-4; NFS/BARD: Non-alcoholic fatty liver disease fibrosis scores/body mass index, the ratio of aspartate aminotransferase to alanine aminotransferase, diabetes; DL: DerSimonian and Laird.

sidering the established relationship between NAFLD and adverse cardiovascular events[41]. This association not only highlights the multifaceted impact of sarcopenia in NAFLD but also opens avenues for future research aimed at reducing cardiovascular morbidity and mortality in this patient population.

The strengths of our systematic review include acknowledging the significant heterogeneity in sarcopenia prevalence reports among NAFLD patients and emphasizing the necessity for standardized guidelines in this area. In addition, we examined non-liver-related events in NAFLD patients and their correlation with sarcopenia. Variability in sarcopenia and liver fibrosis assessment methods contributes to the diverse results observed in our review. The inclusion of studies with varied designs and the demographic differences among patient populations could also affect the observed prevalence of sarcopenia and its association with NAFLD outcomes. Although our review explores the association of sarcopenia with mortality and cardiovascular risks, some specific outcomes, such as carotid plaque risk and progression, were only addressed in a limited number of studies, affecting the conclusiveness of these findings. For instance, Zhang *et al*[28] noted a higher sarcopenia prevalence in lean versus non-lean NAFLD patients, a detail we could not further analyze due to data limitations. Moreover, the review's focus on studies primarily from Asian populations, especially South Korea, may limit the generalizability of the findings to Western populations.

CONCLUSION

This systematic review highlights the multifaceted impact of sarcopenia on patients with NAFLD, extending beyond liver-related issues to include cardiovascular risks, mortality, and metabolic complications. The observed variations in prevalence and associations indicate the urgent need for standardized diagnostic criteria and measurement techniques. Our review offers crucial insights into the clinical implications of sarcopenia within the NAFLD context, potentially guiding future research and clinical practice.

FOOTNOTES

Author contributions: Giri S and Lavekar A contributed to the conception and design of the manuscript; Giri S, Angadi S, and Singh A contributed to the literature review, analysis, data collection, and interpretation; Giri S, Anirvan P, and Angadi S drafted the initial manuscript; Giri S and Lavekar A contributed to the critical revision of the initial manuscript; and all the authors approved the final version of the manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2021 Checklist, and the manuscript was prepared and revised according to the PRISMA 2021 Checklist.

Country/Territory of origin: India

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S-Editor: Chen YL
L-Editor: A
P-Editor: Zhao YQ

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