Prevalence and clinical impact of sarcopenia in liver transplant recipients: A meta-analysis

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Abstract

BACKGROUND

The prevalence of sarcopenia in patients undergoing liver transplantation (LT) remains to be determined partly because of different diagnostic criteria. Sarcopenia has recently been recognized as a new prognostic factor for predicting outcomes in LT candidates.

AIM

To estimate the prevalence of sarcopenia and evaluate its clinical effect on LT candidates.

METHODS

This systematic search was conducted in PubMed, Web of Science, Embase, and Cochrane Library for original English-language articles that investigated the prevalence and influence of sarcopenia in patients undergoing LT from database inception to November 30, 2022. Cohort studies of the definition of sarcopenia that estimate sarcopenia prevalence and evaluate its effect on clinical outcomes and the risk of mortality were included.

RESULTS

Twenty-five studies involving 7760 patients undergoing LT were included. The pooled prevalence of sarcopenia in patients undergoing LT was 40.7% [95% confidence intervals (95%CI): 32.1–49.6]. The 1-, 3-, and 5-year cumulative probabilities of post-LT survival in patients with preoperative sarcopenia were all lower than those without sarcopenia ($P < 0.05$). Sarcopenia was associated with an increased risk of post-LT mortality in patients undergoing LT (adjusted hazard ratio: 1.58; 95%CI: 1.21–2.07). Patients with preoperative sarcopenia had a longer intensive care unit stay, a high risk ratio of sepsis, and serious post-LT complications than those without sarcopenia.

CONCLUSION
Sarcopenia is prevalent in a substantial proportion of patients undergoing LT and is strongly and independently associated with higher a risk of mortality risk.

Key Words: Sarcopenia; Liver transplantation; Mortality; Clinical outcomes

Core Tip: The prevalence and effect of sarcopenia on patients undergoing liver transplantation (LT) remains to be determined partly because of different diagnostic criteria. Twenty-five studies involving 7760 patients undergoing LT were included in this meta-analysis. The pooled prevalence of sarcopenia in patients undergoing LT was 40.7%. Sarcopenia was associated with an increased risk of post-LT mortality in patients undergoing LT.

INTRODUCTION

According to the Global Burden of Disease project, liver disease accounts for approximately 2 million deaths annually worldwide, including one million patients who died from complications of cirrhosis and one million patients who died from liver cancer and viral hepatitis[1]. Liver transplantation (LT) has become the standard treatment for patients with decompensated end-stage liver disease (ESLD)[2]. However, less than 10% of global organ transplantation needs are met at current rates of transplantation[1]. With the widespread shortage of human organs, rigorous selection of LT candidates is essential[3]. Therefore, choosing which patients are clinically suitable for LT is one of the hardest challenges for clinicians. Waiting-list mortality and post-LT survival are key determinant factors in waiting-list placement[3]. The model for ESLD (MELD) score is the most common tool used to predict outcomes in patients for LT[4]. Although the MELD score has a strong predictive value for pre-LT outcomes, it underestimates disease severity in approximately 15%–20% of patients with cirrhosis, leading to an inaccurate prediction of post-LT outcomes[4]. A common but often overlooked complication in patients with ESLD is malnutrition[5]. Undeniably, patients who are malnourished are more likely to suffer from adverse outcomes and have a high mortality risk[6,7]. Given the importance of nutritional status, an appropriate nutritional assessment must be established to determine the effect of nutritional status on patients undergoing LT.

Sarcopenia is a progressive and generalized loss of skeletal muscle mass, strength, and function and is a major component of malnutrition[8]. A previous study discovered that patients with cirrhosis have a high protein oxidation rate and a low carbohydrate oxidation rate, leading to an imbalance in skeletal muscle protein synthesis and breakdown[9]. Hepatocellular dysfunction and portosystemic shunting also result in biochemical and hormonal perturbations in patients with ESLD that contribute to sarcopenia[7]. The prevalence of sarcopenia in patients with ESLD ranges from 30% to 70%, depending on the liver disease etiology, disease stage, and diagnostic criteria[10]. Regardless of how sarcopenia is defined, it is a robust predictor of clinically relevant adverse outcomes, including poor quality of life, mortality in patients on the LT waitlist, longer stays in the hospital or intensive care unit, high incidence of infection following LT, and higher overall healthcare costs[11].

Over the past few years, sarcopenia has become a topic of prolific exploration in patients with ESLD[11]. A meta-analysis published in 2016 indicated that sarcopenia was associated with post-LT mortality; however, overlapping patients were included in this article[3]. Since then, several large and rigorously designed studies with long-term follow-up have been published. Considering the large variability in the prevalence of sarcopenia, the effect of sarcopenia on a broader range of clinically important LT-related outcomes remains unclear. Thus, this meta-analysis aimed to systematically evaluate the literature about patients who underwent LT to summarize the diagnostic criteria for sarcopenia, estimate its prevalence, and assess its effect on clinical outcomes.

MATERIALS AND METHODS

This meta-analysis was conducted based on the PRISMA checklist and was registered in PROSPERO (CRD42022379765).

Search strategy and Selection criteria

A systematic search was conducted in PubMed, Web of Science, Embase, and Cochrane Library for original English-language articles that investigated the prevalence and effect of sarcopenia on patients undergoing LT from database

inception to November 30, 2022. The search keywords and search strategies for all the included databases are shown in Supplementary Table 1. To find additional potential studies, the reference lists of the included articles were also manually searched. In addition, the study only included human studies.

The inclusion criteria were as follows: (1) Patients who underwent LT; (2) a definite diagnosis of sarcopenia based on either muscle mass or muscle function parameters; (3) studies that included the prevalence of sarcopenia in patients who underwent LT and clinical outcomes for post-LT patients; and (4) prospective or retrospective cohort studies. The exclusion criteria were as follows: (1) Case reports or review articles; (2) unclear definition of sarcopenia; (3) studies that only examined the effect of sarcopenia on pre-LT patients or patients awaiting LT; (4) duplicate studies; and (5) studies with insufficient data or unclear study information. Two reviewers independently read the full text and screened the articles that met the inclusion and exclusion criteria. The discrepancies between reviewers regarding inclusion were settled through consensus or by consulting with third-party experts.

Data extraction and quality assessment

Data were independently extracted and coded from each included study by two researchers (Jiang MJ and Wu MC) using an Excel spreadsheet. The basic information gathered from the studies included in this analysis encompasses the first author, year of publication, study design, study location, age or sex distribution, total number of participants, definition of sarcopenia, crude prevalence of sarcopenia, clinical characteristics, including the etiology of liver disease, liver function, presence of hepatocellular carcinoma, follow-up duration, and relevant outcomes. The quality of the included studies was also scored by at least two authors (Jiang MJ, Wu MC, Duan ZH, and Xiao TX) independently using the Newcastle–Ottawa Scale (NOS; 9 items in total, out of 9 points)[12]. Disagreements were resolved by consensus or discussion with a third author (Wu J, Li J, and Meng QH).

Statistical analysis

The prevalence of sarcopenia was determined through a meta-analysis. Subgroup data were collected according to the method used to define sarcopenia, sex, region, etiology of liver disease, and severity of liver disease. The primary outcome of this meta-analysis was mortality risk in patients undergoing LT with sarcopenia. The effect of sarcopenia on the incidence of post-LT survival was evaluated using the pooled unadjusted hazard ratio (HR) or adjusted HR and 95% confidence intervals (95%CI). The 90-day, 1-year, 3-year, and 5-year cumulative mortality were also pooled for patients with and without sarcopenia using the Freeman–Tukey double arcsine transformation method[13]. Continuous outcome data evaluated using homogenous metrics (*e.g.*, same test instrument) were summarized as weighted mean difference (WMD) and 95%CI. Dichotomous variables were tested using both risk ratios (RR) and 95%CI. Random-effects meta-regression was used to test the difference between two groups. Sensitivity analysis was used to evaluate the stability of the model. Egger's and Begg's tests combined with the observation funnel plot were used to evaluate publication bias. Heterogeneity was statistically assessed using the I^2 measurement and Cochran's Q statistic. A random effects model was used if heterogeneity was high (P value of Q statistic ≤ 0.1 or I^2 ≥ 50%). Stata 16 software was used for the meta-analysis. Two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the included studies

A detailed flowchart of the literature search is shown in Figure 1. Of the 7573 records identified from four databases (PubMed, n = 1,042; EMBASE, n = 4312; Cochrane Library, n = 289; Web of Science, n = 1930), 1863 duplicates and 5408 ineligible titles/abstracts were excluded. Of the other 302 articles that underwent full-text review, 25 retrospective cohort studies with data on 7760 patients were included. The detailed characteristics of all the studies in this meta-analysis are summarized in Table 1. Overall, 10 of the 25 studies were from Asia, 6 from Europe, 5 from North America, and 2 from Africa. Only one study was from Australia, and one was a multicenter international study. The number of patients of the included studies ranged from 47 to 2816. The mean age of the patients ranged from 41.6 to 57.0 years among the included researches. All studies were rated high quality with an NOS score of ≥ 7 (Supplementary Table 2).

Diagnosis of sarcopenia

All the studies included in this meta-analysis used a low muscle mass as the basis of diagnosis. No studies have used low muscle strength or low physical performance as diagnostic criteria. Twenty-four studies used skeletal muscle area-based CT to diagnose sarcopenia, and only one study used dual-energy X-ray absorptiometry (DEXA) to assess sarcopenia. Fifteen studies reported the cross-sectional muscle area with the third lumbar-skeletal muscle index (L3-SMI), whereas the psoas muscle area or psoas muscle index (PMI) was reported in nine studies. Twenty-three studies used different diagnostic criteria based on sex. As the most used diagnostic method for sarcopenia, the cutoff values of L3-SMI ranged from 39.0-52.4 cm²/m² in men and from 28.9-42 cm²/m² in women. A summary of the diagnostic criteria used to assess sarcopenia in the included studies is presented in Table 1.

Prevalence of sarcopenia

The prevalence of sarcopenia was reported in 25 studies (n = 7760) and ranged from 11.0% to 78.3%, yielding a pooled prevalence of 40.7% (95%CI: 32.1-49.6; Figure 2A). Given the significant heterogeneity, subgroup analyses of sarcopenia rates were conducted for different definitions, sexes, regions, basic diseases, and Child–Pugh class (Table 2). The

Table 1 Characteristics of the included studies

Ref.	Country	Methods for measuring muscle mass	Definition of sarcopenia	Sample size (*n*)	Mean age (yr)	Male (%)	HCC (%)	BMI (Kg/m²)	Follow-up time	NOS
Kumar *et al*[2], 2020	India	CT: L3-SMI	L3-SMI < 52.4 cm²/m² for male and < 38.5 cm²/m² for female	115	46.30 ± 10.20	90.4	-	24.5 ± 4.3	90 d	7
Bhanji *et al*[8], 2019	United States	CT: L3-SMI	L3-SMI < 50 cm²/m² in men and < 39 cm²/m² in women	293	51.95 ± 11.00	70.3	30.4	27.51 ± 5.73	13	8
Shafaat *et al*[26], 2023	United States	CT: L3-SMI	L3-SMI < 50 cm²/m² in men, < 39 cm²/m² in women	454	57.00 ± 8.89	65.0	-	29.0 ± 5.7	11yr	9
Sim *et al*[27], 2022	Korea	CT: L3-SMI	L3-SMI < 39.9cm²/m² in men, < 28.9 cm²/m² in women	2816	53.00 ± 7.41	75.0	52.8	24.2 ± 3.1	7.8 yr	8
Prakash *et al*[28], 2022	India	CT: L4-PMTH	L4-PMTH < 1 mm/m for men and < 10.4 mm/m for women	51	46.40 ± 9.10	96.1	37.3	23.34 ± 5.1	-	7
Wu *et al*[29], 2021	Taiwan China	CT: L3-PMI	L3-PMI < 2.63 cm²/m² for female	122	52.32 ± 7.98	55.0	24.6	24.83 ± 4.45	10 yr	8
Kuo *et al*[30], 2019	United States	CT: L3-SMI	L3-SMI < 48 cm²/m² for men	126	53.00 ± 8.89	63.0	14.0	28 ± 6.67	10.6 yr	8
Golse *et al*[31] 2017	France	CT: L3-4 PMA	L3-4 PMA < 1464 mm² in women and < 1561 mm² in men	256	5.003 ± 10.50	76.6	40.0	25.3 ± 10.5	8 yr	8
Beumer *et al*[32], 2022	Multicenter international study	CT: L3-SMI	L3-SMI < 37 cm²/m² for women with a BMI < 25 kg/m² or 42 cm²/m² for women with a BMI ≥ 25 kg/m², and < 45 cm²/m² for men with a BMI < 25 kg/ m², or < 51 cm²/m² for men with a BMI ≥ 25 kg/m²	528	57.00 ± 9.00	86.0	100.0	26.67 ± 5.02	5 yr	8
Pinto Dos Santos *et al*[33], 2020	Germany	CT: L3-PSMI	L3-PSMI < 18.6 cm²/m²	368	56.80 ± 9.70	69.3	44.6	25.2 ± 4.37	10 yr	7
Izumi *et al*[34], 2017	Japan	CT: L3-PMI	L3-PMI < 612.5 mm²/m² in men and < 442.9 mm²/m² in women	47	54.00 ± 10.00	51.1	23.4	-	120 d	7
Hamaguchi *et al* [35], 2017	Japan	CT: L3-SMI	L3-SMI < 40.31 cm²/m² in men and < 30.88 cm²/m² in women	250	54.00 ± 14.07	44.8	33.0	22.7 ± 3.63	5 yr	8
Irwin *et al*[36], 2021	South Africa	CT: L3-SMI	L3-SMI < 39 cm²/m² for women and < 50 cm²/m² for men	106	-	60.4	-	-	1 yr	9
Tan *et al*[14], 2022	China	CT: L3-PMI	L3-PMI < 6.25 cm²/m² for man	70	41.60 ± 9.70	100.0	-	22.9 ± 2.9	10 yr	8
Masuda *et al*[37], 2014	Japan	CT: L3-PMA	< 800 cm² for men and < 380 cm² for women	204	54.32 ± 9.60	50.49	-	23.6 ± 3.4	8 yr	7
Miarka *et al*[38], 2021	Poland	CT: L3-SMI	L3-SMI < 50 cm²/m² for men and 39 cm²/m² for women	98	55.00 ± 8.00	76.5	26.5	27 ± 4	1224 d	7

Montano-Loza et al [39], 2014	Canada	CT: L3-SMI	L3-SMI ≤ 41 cm²/m² for women and ≤ 53 cm²/m² for men with a BMI ≥25 kg/m² and L3 SMI ≤ 43 cm²/m² for patients with a BMI < 25 kg/m²	248	55.00 ± 1.00	68.0	39.0	27.19 ± 2.23	5 yr	9
Kalafateli et al[23], 2017	United Kingdom	CT: L3-PMI	L3-PMI < 340 mm²/m² for men and < 264 mm²/m² for women	232	54.00 ± 12.00	69.8	25.0	25 ± 6.43	1 yr	8
Czigany et al[40], 2020	Germany	CT: L3-SMI	L3-SMI < 50 cm²/m² in men and < 39 cm²/m² in women	225	54.00 ± 12.00	66.7	28.0	27 ± 5	90 d	8
Hey et al[41], 2022	Australia	DEXA: APLM	APLM < 7.26 kg/m² for male and < 5.5 kg/m² for female	469	55.00 ± 10.59	72.1	26.0	-	1 yr	8
Lindqvist et al[42], 2019	Sweden	CT: L3-SMI	L3-SMI < 43 cm²/m² for men with BMI < 25 kg/m² and < 53 cm²/m² for BMI > 25 kg/m² and < 41 cm²/m² for women in all BMI ranges	53	57.00 ± 11.11	69.8	52.8	25.1 ± 5.3	1 yr	8
Riccardo et al[43], 2019	Japan	CT: L3-SMI	L3-SMI < 42 cm²/m² for men and L3-SMI < 38 cm²/m² for women	138	57.00 ± 13	56.5	-	24.8 ± 5	10 yr	8
Andrea et al[21], 2013	United States	CT: L3-4 SMI	L3-4 SMI ≤ 38.5 cm²/m² for women and ≤ 52.4 cm²/m² for men	338	55.00 ± 10.00	65.9	-	28 ± 6	1021.2 d	9
Young et al[44], 2018	Korea	CT: L3-PMTH	L3-PMTH < 15.5 mm/m	92	53.33 ± 5.75	67.4	100.0	24.17 ± 2.81	36 months	8
Hassan et al[45], 2022	Egypt	CT: L3-SMI	L3-SMI < 52.4 cm²/m² for male and < 38.5 cm²/m² for female	61	48.70 ± 12.50	75,4	-	23.9 ± 3.9	6 months	7

HCC: Hepatocellular carcinoma; NOS: Newcastle–Ottawa Scale; L3: The caudal end of the third lumbar vertebra; L3-SMI: Third lumbar-skeletal muscle index; PMA: The Area of the Psoas Muscle; PMTH: The psoas muscle thickness to height ratio; PSMI: Paraspinal muscle index; APLM: Appendicular lean mass; PMI: Psoas muscle index.

subgroup analysis based on the definition of sarcopenia showed that the prevalence of sarcopenia was 41.5% (95%CI: 29.6–53.9) when defined by L3-SMI, 36.4% (95%CI: 16.2–59.5) by L3-PMI, and 41.5% (95%CI: 26.7–57.1) by other definitions. A subgroup analysis by sex was also performed, which revealed that male patients had a higher pooled prevalence of sarcopenia (43.3%, 95%CI: 31.1–55.9) than female patients (33.1%, 95%CI: 21.6–45.6). Moreover, 23 studies were analyzed by regional subgroup, and Africa had the highest pooled prevalence of sarcopenia among patients undergoing LT (57.6%, 95%CI: 50.0–65.1). Among the different primary liver diseases, patients with alcoholic liver disease had the highest prevalence of sarcopenia (52.2%, 95%CI: 36.2–68.2). Finally, the prevalence for patients with Child–Pugh class C (54.3%, 95%CI: 43.9–64.8) was higher than those with Child–Pugh class B (38.9%, 95%CI: 30.8–47.0) or A (30.4%, 95%CI: 26.0–35.0).

Cumulative post-LT survival in patients with and without sarcopenia

The 90-day, 1-year, 3-year, and 5-year cumulative probabilities of post-LT survival in patients with sarcopenia were 92.9% (95%CI: 88.9–96.9), 79.8% (95%CI: 72.8–86.8), 74.3% (95%CI: 68.0–80.5), and 63.6% (95%CI: 56.5–70.6), respectively (Supplementary Figures 1-4). By comparison, they were 96.5% (95%CI: 94.7–98.3), 92.7% (95%CI: 90.2–96.2), 93.4% (95%CI: 90.6–96.2), and 79.5% (95%CI: 73.2–85.8), respectively, in patients without sarcopenia (Supplemen-tary Figures 1-4). The 1-, 3-, and 5-year cumulative probabilities of post-LT survival in patients with preoperative sarcopenia were all lower than those without preoperative sarcopenia ($P < 0.05$). However, regardless of whether patients had sarcopenia, no difference was found in the 90-day cumulative probabilities of survival post-LT ($P = 0.289$; Table 3).

Table 2 The pooled overall prevalence of sarcopenia in study subgroups

Subgroup	Studies (*n*)	Sarcopenia (*n*)	Prevalence [% (95%CI)]	I^2 (%)	*P* value
Definition of sarcopenia					
L3-SMI	15	1562	41.5 (29.6-53.9)	98.6	< 0.001[a]
L3-PMI	4	139	36.4 (16.2-59.5)	95.6	< 0.001[a]
Others	6	538	41.5 (26.7-57.1)	97.0	< 0.001[a]
Sex					
Male	17	1280	43.3 (31.1-55.9)	98.9	< 0.001[a]
Female	15	366	33.1 (21.6-45.6)	95.7	< 0.001[a]
World region					
Europe	6	458	37.7 (26.6-49.5)	94.0	< 0.001[a]
Asia	10	734	38.8 (23.3-55.5)	98.3	< 0.001[a]
North America	5	661	47.8 (33.4-62.4)	96.7	< 0.001[a]
Africa	2	96	57.6 (50.0-65.1)	0.0	< 0.001[a]
Disease types					
Viral	8	407	32.3 (18.9-47.2)	97.0	< 0.001[a]
ALD	11	477	52.2 (36.2-68.2)	96.8	< 0.001[a]
NAFLD	5	54	47.2 (25.7-68.6)	85.6	< 0.001[a]
AIH/PSC/PBC	4	141	33.6 (19.0-48.2)	63.5	0.042[a]
HCC	10	399	35.9 (18.6-53.2)	98.4	< 0.001[a]
Other	7	123	41.2 (22.6-59.8)	92.2	< 0.001[a]
Child-Pugh class					
A	4	121	30.4 (26.0-35.0)	44.6	0.144
B	5	157	38.9 (30.8-47.0)	56.8	0.055
C	7	446	54.3 (43.9-64.8)	88.2	< 0.001[a]

[a]*P* value < 0.05.

L3-SMI: Third lumbar-skeletal muscle index; L3-PMI: Third lumbar- psoas muscle index; ALD: Alcoholic liver disease; NAFLD: Nonalcoholic fatty liver disease; AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cholangitis; HCC: Hepatocellular carcinoma.

Table 3 Pooled 90 d and 1, 3, and 5-year cumulative survival probabilities in patients with and without sarcopenia

Survival [% (95%CI)]	With sarcopenia	Without sarcopenia	*P* value
90-day	92.9 (88.9-96.9), 5 studies 422 patients	96.5 (94.7-98.3), 5 studies 891 patients	0.289
1-year	79.8 (72.8-86.8), 10 studies 894 patients	92.7 (90.2-95.2), 10 studies 3475 patients	0.015[a]
3-year	74.3 (68.0-80.5) 4 studies 185 patients	93.4 (90.6-96.2) 4 studies 291 patients	0.003[a]
5-year	63.6 (56.5-70.6) 8 studies 730 patients	79.5 (73.2-85.8) 8 studies 1316 patients	0.006[a]

[a]*P* value < 0.05.

The *P* value was produced using the random-effects meta-regression method.

Association between sarcopenia and post-LT mortality

Based on univariate analysis of data from 9 studies (*n* = 4845), sarcopenia was associated with an increased risk of post-LT mortality, with a pooled unadjusted HR of 1.72 (95%CI: 1.33–2.24, I^2 = 60.7%, *P* = 0.009; Supplementary Figure 5). In data from multivariate analysis (nine studies, *n* = 4430), sarcopenia was still significantly associated with increased post-LT mortality with a pooled adjusted HR of 1.58 (95%CI: 1.21–2.07, I^2 = 54.4%, *P* = 0.025; Figure 2B).
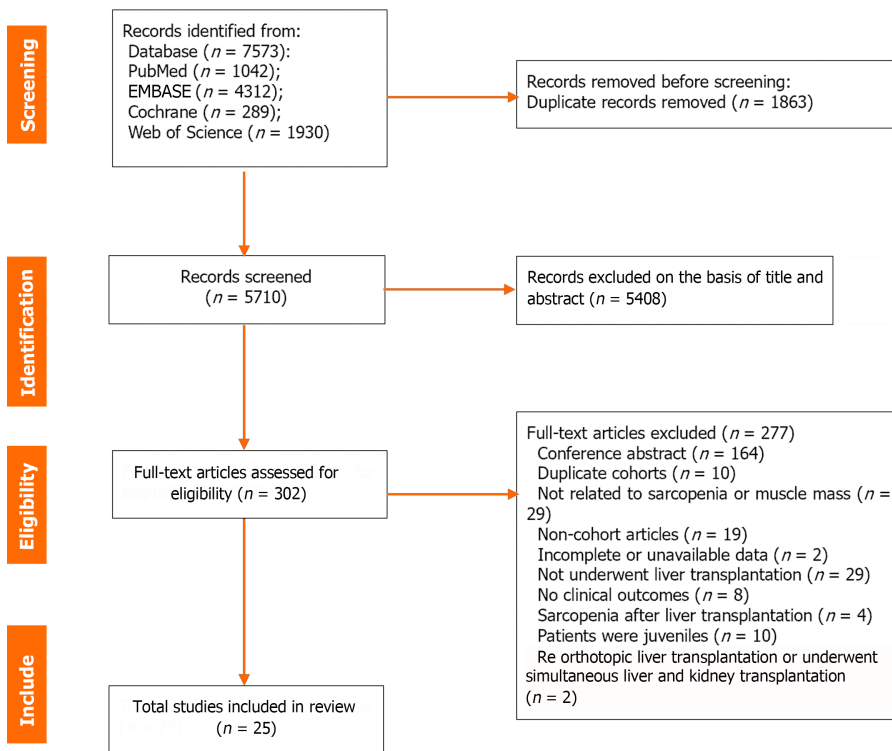
Figure 1 Literature identification process.

Impact of sarcopenia on clinical outcomes

Seven studies involving 1,369 patients reported data on the length of ICU stay that were available for meta-analysis. Patients with preoperative sarcopenia had longer ICU stays than those without sarcopenia post-LT (WMD: 4.503, 95%CI: 2.218–6.788, $P < 0.001$) (Supplementary Figure 6). Six studies involving 1001 patients reported data on the length of stay (LOS) and were included in the meta-analysis. LOS was not different in patients with or without preoperative sarcopenia (WMD: 9.352, 95%CI: 2.557–15.261, $P = 0.162$; Supplementary Figure 7). Data from four studies involving 606 patients were available for meta-analysis of developing sepsis post-LT, showing that patients with preoperative sarcopenia had a higher risk of sepsis post-LT than those without sarcopenia (RR: 2.00, 95%CI: 1.143–3.503, $P = 0.015$; Supple-mentary Figure 8). Four studies involving 643 patients reported data of the Clavien–Dindo classification and were included in the meta-analysis. Patients with preoperative sarcopenia had a higher RR of serious postoperative complications (Clavien–Dindo classification ≥ 3) than those without preoperative sarcopenia (RR: 1.287, 95%CI: 1.05–1.583, $P = 0.017$; Supplementary Figure 9).

Sensitivity analysis, meta-regression, and publication bias

Sensitivity analyses that excluded one study at a time and then pooled the remaining studies showed adjusted HRs ranging from 1.49 to 1.70, suggesting that our results were robust (Supplementary Figure 10). Meta-regression analyses showed no association of pooled adjusted HR with sample size ($P = 0.819$), percentage of male patients ($P = 0.660$), average follow-up time ($P = 0.746$), different regions ($P = 0.786$), diagnostic method ($P = 0.553$), and NOS ($P = 0.865$; Supplementary Table 3). The funnel plot was symmetrical (Figure 3). Egger's ($P = 0.526$) and Begg's ($P = 0.348$) tests suggested no significant statistical evidence of publication bias.

DISCUSSION

LT is the only potential treatment for ESLD[14]. To increase the survival rates of LT candidates, preoperative risk assessment for risk is essential. Most patients with ESLD who undergo LT are physically deconditioned, with low functional capacity, malnutrition, sarcopenia, and frailty[10,15]. Sarcopenia is a common symptom of ESLD that strongly affects adverse outcomes and mortality in this population[11]. Although a meta-analysis also evaluated the association between skeletal muscle mass and mortality in patients with cirrhosis, studies of post-LT patients were excluded[5]. Another systematic review reported sarcopenia-impaired outcomes in patients awaiting or undergoing LT; many patients evaluated for LT but did not undergo LT were also included in this meta-analysis[3]. However, since then, a number of large, rigorously designed, and long-term follow-up studies have provided updated data. Therefore, in this study, a more comprehensive search was performed, a much larger pool of potential studies was screened, studies with overlapping cohorts and only waiting-LT patients were excluded, and a comprehensive range of subgroup and sensitivity analyses was performed to summarize the prevalence, post-LT survival, and outcomes of sarcopenia in patients who underwent
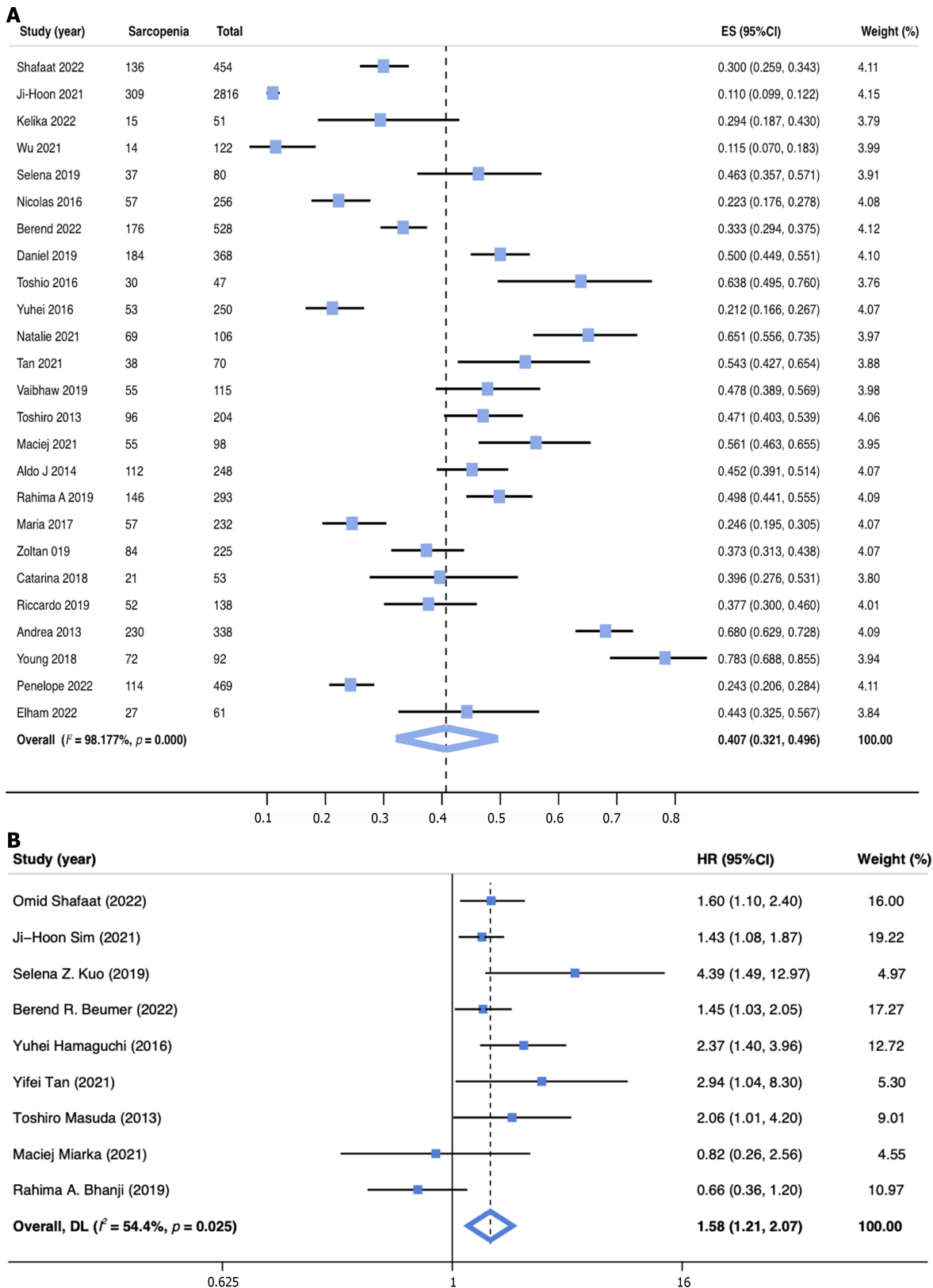
Figure 2 The prevalence and clinical impact of sarcopenia in patients underwent liver transplantation. A: The pooled overall prevalence of sarcopenia in patients underwent liver transplantation in the included studies; B: Forest plot for multivariate analysis assessing the association between sarcopenia and mortality risk.

LT.

As a major component of malnutrition, sarcopenia is a strong predictor of morbidity and mortality in patients with ESLD[16]. Despite the importance of sarcopenia, no consensus has been established regarding how to accurately measure and define sarcopenia in clinical settings[17]. The European Working Group on Sarcopenia defined sarcopenia as "a progressive and generalized skeletal muscle disorder associated with an increased likelihood of adverse outcomes
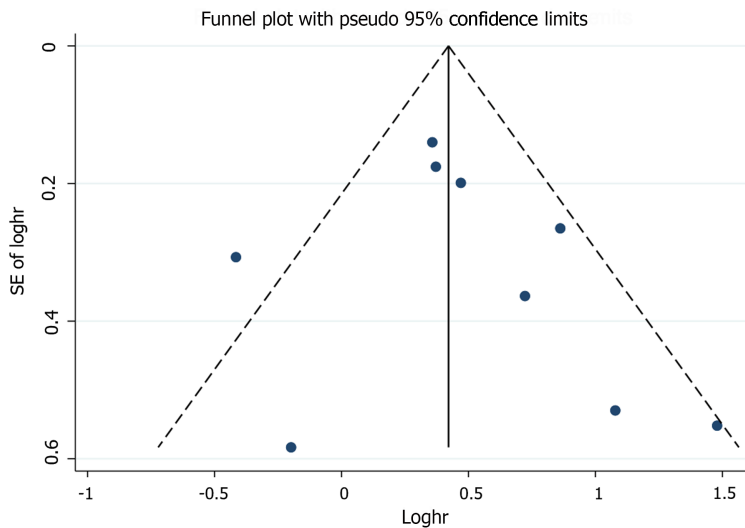
Figure 3 Funnel plot with 95% pseudo-confidence limits for all included studies.

including falls, fractures, disability, and mortality", combining both muscle mass and muscle strength or muscle performance[18]. In this study, 24 studies used skeletal muscle area measured by CT scans as the method to diagnose sarcopenia, and only one study used DEXA to assess sarcopenia. None of the included studies used low muscle strength or low physical performance as diagnostic criteria in this meta-analysis. While most working groups recommend considering both muscle mass and muscle function for the diagnosis of sarcopenia, most studies in patients with liver disease have investigated sarcopenia using measures of muscle mass alone[10,18,19]. Based on the available data on liver disease, some guidance developed a consensus definition for the operationalization of sarcopenia in liver disease as the phenotypic manifestation of loss of muscle mass alone[10,11]. In the future, muscle strength or physical performance should also be included in the diagnosis of sarcopenia, and consistent tests should be conducted to diagnose sarcopenia.

Owing to the varied definitions of sarcopenia, a wide range of the prevalence of sarcopenia in patients undergoing LT was reported[3]. In this meta-analysis, the overall pooled prevalence of sarcopenia for patients who underwent LT was 40.6%. In another meta-analysis, the prevalence of sarcopenia ranged from 22.2% to nearly 70% in patients undergoing LT or evaluated for LT[3]. A previous meta-analysis excluded post-LT patients, and sarcopenia affected 37.5% of patients with cirrhosis[5]. The etiology of liver disease has been associated with differences in the prevalence of sarcopenia[10,20]. Our finding is consistent with previous studies that have shown that patients with alcohol-associated liver disease (ALD) had a lower baseline muscle mass[20,21]. A previous study reported that sarcopenia is related to the severity of liver disease as estimated by the Child–Pugh class[22]. In another study, the muscle mass index was negatively correlated with the Child–Pugh score[16]. In this meta-analysis, patients with ALD and those in the Child–Pugh C class had the highest prevalence of sarcopenia of > 50%. Our study is in line with the results from a recent study that showed that sarcopenia is common in patients with ESLD and worsens with the progression of liver disease[16]. All studies that reported the prevalence of sarcopenia separately for different sexes included in this meta-analysis indicated a higher prevalence among men. Sex is believed as the most important factor influencing muscle mass in the general population[16]. Therefore, future studies to define sarcopenia are needed for clinical application with consideration of sex, age, ethnicity, and basic diseases.

The North American Expert Opinion Statement on Sarcopenia in LT recommends using sarcopenia to predict the prognosis of LT[11]. However, various clinical outcomes, such as overall mortality in evaluated patients, waitlist mortality in listed patients, post-LT mortality in patients undergoing LT, and short-term *vs* long-term outcomes, confound the comparison between published studies and the development of generalized definitions[11]. Our studies mainly focused on post-LT mortality and complications. From this meta-analysis, no difference in the 90-day cumulative probabilities of survival post-LT was found between patients with or without sarcopenia. However, the 1-, 3-, and 5-year cumulative probabilities of post-LT survival in patients with sarcopenia were all lower than those in patients without sarcopenia. In our meta-analysis, sarcopenia was associated with a pooled HR of 1.58 (95%CI: 1.21–2.07) for post-LT mortality similar to a prior meta-analysis with a pooled HR of 1.84 (95%CI: 1.11–3.05) for post-LT mortality[3]. Although multiple studies have shown sarcopenia to be associated with post-LT mortality[3,23,24], data reporting preoperative sarcopenia associated with adverse post-LT outcomes are limited. In this meta-analysis, patients with preoperative sarcopenia had longer ICU stays than those without sarcopenia post-LT. In addition, patients with preoperative sarcopenia had a higher RR of sepsis and serious post-LT complications than those without sarcopenia. This indicates that preoperative sarcopenia may play an important role in the clinical outcomes of patients undergoing LT. Given the lack of an objective metric of sarcopenia, some guidelines do not recommend using sarcopenia as a contraindication against LT [10,11]. However, sarcopenia may guide the decision about LT in an attempt to minimize liver-related complications and optimize overall patient recovery. Therefore, it is important to incorporate sarcopenia into the management and treatment of LT candidates to optimize nutrition and physical activity[25].

This study has several limitations. First, the wide inclusion criteria in this study generated significant heterogeneity that could not be explained. A random-effects model with subgroup analyses was used whenever possible to minimize the effect of heterogeneity. Subgroup analysis, meta-regression, and sensitivity analysis were used to identify the possible sources of heterogeneity. Second, significant heterogeneity in the means of defining sarcopenia and the diagnostic criteria employed was noted among the included studies. Thus, future studies should build uniform cutoff thresholds based on ethnicity to assess sarcopenia. Third, the included articles and all diagnostic protocols lacked an assessment of muscle strength and physical performance. Future prospective studies using the criteria including muscle mass and muscle strength/physical performance must determine whether the predictive power is improved after employing a more comprehensive algorithm to diagnose sarcopenia. Fourth, the number of studies on some variables for clinical outcomes was limited, so the application and promotion of the combined results were also restricted to a certain extent. Fifth, the etiology of liver diseases is an important factor associated with mortality. However, we could not analyze the effect of liver disease etiology on our results because the HR in each study was not reported separately according to etiology. Finally, although the quality of the included studies was evaluated using the NOS statement entries during the search and screening processes, some subjectivity remained in the evaluation of the literature because of the lack of accepted quality evaluation criteria, which may lead to some selection bias in the included studies.

CONCLUSION

This meta-analysis demonstrated that sarcopenia affects 40% of LT recipients. This study also showed that sarcopenia was associated with a 1.58-fold higher risk of post-LT mortality. Sarcopenia was also associated with long-term survival rates and adverse post-LT outcomes. Because of the high prevalence and adverse post-LT outcomes, sarcopenia should be considered a part of the initial evaluation of LT candidates. More future studies are needed are needed to incorporate sarcopenia or muscle mass index/function into a formal prognostic scale for LT patients.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation (LT) has become the standard treatment for patients with end-stage liver disease (ESLD). With the widespread shortage of human organs, rigorous selection of LT candidates is essential. Over the past few years, sarcopenia has become a topic of prolific exploration in patients with ESLD. Sarcopenia has recently been recognized as a new prognostic factor for predicting outcomes in LT candidates. Therefore, this study aimed to estimate the prevalence of sarcopenia and evaluate its clinical effect on LT candidates.

Research motivation

As a major component of malnutrition, sarcopenia is a strong predictor of morbidity and mortality in patients with ESLD. However, the link between sarcopenia and LT candidates is not well studied.

Research objectives

This meta-analysis aimed to systematically evaluate the literature about patients who underwent LT to summarize the diagnostic criteria for sarcopenia, estimate its prevalence, and assess its effect on clinical outcomes.

Research methods

This systematic search was conducted in PubMed, Web of Science, EMBASE, and Cochrane Library for original English-language articles that investigated the prevalence and influence of sarcopenia on patients undergoing LT from database inception to November 30, 2022. The prevalence of sarcopenia was determined through a meta-analysis. The effect of sarcopenia on the incidence of post-LT survival was evaluated using the pooled unadjusted hazard ratio (HR) or adjusted HR and 95% confidence intervals.

Research results

Twenty-five studies involving 7760 patients undergoing LT were included. The pooled prevalence of sarcopenia in patients undergoing LT was 40.7%. The 1-, 3-, and 5-year cumulative probabilities of post-LT survival in patients with preoperative sarcopenia were all lower than those without sarcopenia ($P < 0.05$). Sarcopenia was associated with an increased risk of post-LT mortality in patients undergoing LT. Patients with preoperative sarcopenia had a longer intensive care unit stay, a high risk ratio of sepsis, and serious post-LT complications than those without sarcopenia.

Research conclusions

Sarcopenia is prevalent in a substantial proportion of patients undergoing LT. This study also showed that sarcopenia was associated with a 1.58-fold higher risk of post-LT mortality. Sarcopenia was also associated with long-term survival rates and adverse post-LT outcomes.

Research perspectives

Because of the high prevalence and adverse post-LT outcomes, sarcopenia should be considered a part of the initial evaluation of LT candidates. More studies are needed to incorporate sarcopenia into a formal prognostic scale for LT recipients.

FOOTNOTES

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