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Sarcopenia As a Predictor of Survival and Complications of Patients With Cirrhosis After Liver Transplantation: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: This systematic review/meta-analysis evaluated the impact of sarcopenia in patients with cirrhosis before liver transplantation (LT) on outcomes after LT.

Methods: A systematic search was conducted in six medical databases until February 2022. The primary outcome was overall mortality after LT, while several secondary outcomes including liver graft survival and rejection, the need for transfusions, the length of the intensive care unit (ICU) and hospital stay, and surgical complications were evaluated. Sub-group analyses and meta-regression analyses were also performed.

Results: Fifty-three studies were evaluated in the systematic review, of which 30, including 5875 patients, were included in the meta-analysis. All studies included were cohort studies of good/high quality on the Newcastle-Ottawa scale (NOS), while in our analysis no publication bias was found, although there was substantial heterogeneity between the studies. Muscle mass was assessed using skeletal muscle index (SMI) in 14 studies, psoas muscle area (PMA) in seven studies, and psoas muscle index (PMI) in four studies. The prevalence of pre-LT sarcopenia ranged from 14.7% to 88.3%. Pre-LT sarcopenia was significantly associated with post-LT mortality (Relative Risk [RR] = 1.84, 95% CI:1.41,2.39), as well as with a high risk of infections post-LT, surgical complications, fresh frozen plasma (FFP) transfusions, and ICU length of stay (LOS).

Conclusions: Pre-LT sarcopenia in patients with cirrhosis is a strong risk factor for clinically meaningful adverse outcomes after LT. Assessment may help identify patients at the highest risk for poor outcomes who may benefit from targeted interventions.

Abbreviations: ALMI, appendicular lean mass index; BMI, body mass index; CI, confidence interval; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; ICU, intensive care unit; LOS, length of stay; LT, liver transplantation; MELD, model for end-stage liver disease; NOS, Newcastle-Ottawa scale; PMA, psoas muscle area; PMI, psoas muscle index; RBC, red blood cells; RR, relative risk; SMD, standardized mean difference; SMI, skeletal muscle index.

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1 | Introduction

Sarcopenia is a progressive and generalized skeletal muscle disorder characterized by the accelerated loss of muscle mass and function, associated with increased adverse outcomes [1]. In patients with cirrhosis, sarcopenia is multifactorial, including malnutrition, malabsorption, altered metabolism, and physical inactivity [2]. Diagnosis is based on a combination of muscle mass imaging, muscle strength, and/or physical performance measurements [1, 3].

Liver transplantation (LT) is a life-saving procedure for patients with decompensated cirrhosis that has a significant impact on survival, quality of life, and healthcare systems [4]. Most LT centers, use Model for end-stage liver disease (MELD) score for evaluating the prognosis of patients with cirrhosis, and for prioritizing patients for LT.[5] However, these scores while efficient in predicting waitlist mortality, serve as poor predictors for post-LT outcomes [6, 7]. Several attempts have been made to create such predictive tools, and in this context, pre-LT sarcopenia has been suggested as an indicator of poor prognosis after LT [8–10]. One previous meta-analysis exists, which focused on the impact of sarcopenia assessed with computed tomography (CT) before LT, only on survival after LT [11]. Therefore, we aimed to perform a more comprehensive systematic review and meta-analysis to evaluate the effect of sarcopenia on mortality as well as on other LT outcomes, with a larger sample size and without limitations to the methods of assessment.

Summary

- Sarcopenia, a disorder that plays a significant role in the context of liver transplantation (LT), should be evaluated and included in the selection process of liver transplant candidates.
- The presence of sarcopenia in patients with cirrhosis before LT, is associated with worse outcomes after LT, including mortality, risk of infections, surgical complications, fresh frozen plasma (FFP) transfusions, and Intensive Care Unit (ICU) length of stay (LOS).
- Further research is needed in the field of sarcopenia in liver cirrhosis and transplantation as to the methods of evaluation and the prognostic role of each one in different outcomes.

2 | Materials and Methods

2.1 | Literature Search and Protocol Design

We performed an initial exploratory literature search, examining full-text reviews and abstracts of original publications that included the terms “sarcopenia” and “liver transplantation” in their title and/or abstract, through the PubMed database. Based on the literature we collected and under the supervision of our senior professors, we drafted the protocol of our systematic review and meta-analysis, which was registered on PROSPERO (ID: CRD42023339752).

2.2 | Data Sources and Searches

This systematic review and meta-analysis was performed in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines for a meta-analysis of observational studies and the Cochrane Handbook for Systematic Reviews [12, 13]. The Prisma checklist is presented in Table S1. We conducted a literature search via PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar databases, from inception to August 2020, and an additional search in PubMed to February 2022, to identify all relevant studies examining the impact of sarcopenia in patients with cirrhosis on post-LT outcomes. Additionally, we searched for potential studies manually by going through the reference lists of included studies and relevant reviews. The search keywords included sarcopenia, malnutrition, muscle mass or density, liver, hepatic, and transplantation. Table S2 exhibits the search strategies.

2.3 | Study Selection

Studies were included if they met all of the following criteria: (1) Participants: consecutive patients with cirrhosis who received LT for the first time; (2) Exposure: they provided data on sarcopenia before LT, or sarcopenia’s effect (odds ratio, relative risk [RR], or hazard ratio [HR]) on LT outcomes, using any chosen diagnostic method, including at least one radiological imaging method for muscle mass evaluation; (3) Comparison: sarcopenic patients were compared with non-sarcopenic patients; (4) Outcomes: they provided data on survival and/or other clinical outcomes after LT concerning pre-LT sarcopenia; (5) Study design: human observational studies (cohort or case-control). Studies were excluded for the following reasons: (1) all patients were children; (2) studies that included only urgent LT patients; (3) studies that included only re-transplanted patients; (4) studies that included only patients with hepatocellular carcinoma (HCC); (5) studies with insufficient data and no response from authors during our attempts to obtain additional relevant data and/or clarification of data. For studies with overlapping cohorts, we included only the one with the largest sample size and/or more data available per variable. Studies that did not present their results separately, for sarcopenic and non-sarcopenic patients or used the muscle mass measurement as a continuous variable but mentioned a conclusion on sarcopenia’s effect on LT outcomes, were excluded from the meta-analysis but were included in the systematic review.

2.4 | Data Extraction and Quality Assessment

The results from all databases were imported into EndNote (2013), Philadelphia, PA, Clarivate, v20.2. Deduplication was performed using a semi-automated finder tool. The literature search was conducted by two reviewers (G.E.M. and N.D.K.), who first screened titles and abstracts and then reviewed the full text of the selected articles. Discrepancies were resolved by consensus or discussion with a senior reviewer (E.C.).

Data extraction from the finally selected papers was carried out based on a predefined form, independently by two reviewers

(G.E.M. and N.D.K.). Queries were arbitrated by discussion with a senior author (E.C.). Microsoft Excel v.16.56 was used for data extraction. A table was created for selected studies, including all the characteristics predefined to be extracted, which consisted of the first author's name, country and center(s) of enrollment, year of publication, enrollment period, study design, primary study question, sample size, indication for LT, and underlying liver disease (viral hepatitis, alcoholic liver disease, non-viral non-alcohol liver disease, HCC), follow-up after LT, patients' demographics including age, sex, race, body mass index (BMI), MELD and Child-Turcotte-Pugh scores, method of sarcopenia evaluation, mean muscle mass measurement in the total population, and the number of patients with and without sarcopenia pre-LT. Based on our exploratory literature search, the most relevant outcomes of interest were chosen and extracted, including deaths in the total population, patient, and/or graft survival after LT, intensive care unit (ICU), and hospital length of stay (LOS), total infections, bacterial, viral or fungal infections, rejection episodes, perioperative transfusions (red blood cells [RBC], fresh frozen plasma [FFP], platelets) and patients' Clavien-Dindo classification score of surgery-related complications [14] after LT (as low or high, with a cut-off value of equal to or higher than 3 for high), for patients who were sarcopenic and non-sarcopenic before LT. Regarding effect estimates, the maximally adjusted RR for cohort studies was abstracted, together with their confidence interval (CI). When RRs were unavailable, 2×2 tables with data from the articles were used for calculating crude effect estimates and 95% CI. When necessary, mean and standard deviation were calculated using the transformations proposed by Hozo et al. [15]. Letters were sent to the authors of studies that did not report sufficient data. The corresponding authors were contacted twice (a reminder e-mail was sent 1 week after the first e-mail). We contacted the authors of 29 studies and received an answer with additional data for 4 of them [16–19]. From the table finally drafted, the authors (G.E.M. and T.S.) decided which studies were eligible for inclusion in each synthesis. When multiple methods of muscle measurement were reported, authors (G.E.M. and E.C.) decided which one to use in the analysis, based on clinical relevance and outcomes studied per method.

The quality of studies included in the meta-analysis was assessed independently by two reviewers (G.E.M., N.D.K.) using the Newcastle-Ottawa scale (NOS) [20]. Discrepancies were resolved by consensus or discussion with a senior reviewer (E.C.). The cut-off value for the desirable length of follow-up was set at 3 months, considering the time that post-LT complications related to pre-LT status occur [21]. The cut-off value for completeness of follow-up was set at 85%.

2.5 | Data Synthesis and Analysis

Statistical analysis included pooling of studies, subgroup analyses, and meta-regression analyses. Statistical synthesis was performed for variables with two or more eligible studies, while meta-regression analysis was performed for variables of 10 or more pooled studies. Pooled effect estimates (RRs) for categorical outcomes and standardized mean differences (SMDs) for continuous outcomes, with 95% CI were estimated using random effect estimates (DerSimonian-Laird). Heterogeneity across studies was assessed by estimating Q-test and I^2 [22]. Preplanned subgroup analyses were carried out according to the definition method of sarcopenia, geographical region (continent), effect estimate calculation (univariate or multivariate), and type of publication (conference abstract/poster or full-text article). Meta-regression analysis aimed to assess whether sample size, (expressed as 100 subjects increase), gender (expressed as percentage of males in the individual studies), age (expressed as the mean age in the individual studies), publication year, HCC (expressed as percentage of patients with HCC in the individual studies), MELD (expressed as the mean MELD in the individual studies), BMI (expressed as the mean BMI in the individual studies), and liver disease (expressed as percentage of patients with viral, alcoholic or non-viral non-alcohol liver disease in the individual studies) modified the association between sarcopenia pre-LT with outcomes post-LT.

Statistical analysis, meta-regression analysis, and publication bias analysis were performed using STATA/SE version 13 (Stata Corp, College Station, TX, USA).

3 | Results

3.1 | Eligible Studies

A total of 5049 records were identified (PubMed:1264, EMBASE:1270, SCOPUS:1286, COCHRANE:72, WEB OF SCIENCE:957, Google Scholar:200), but 1943 duplicates and 2899 ineligible by title/abstract records were excluded. Finally, 207 records underwent full-text review, of which 53 [16-19, 21, 23-70] with a total of 9840 patients met the inclusion criteria for a systematic review, while 30 cohort studies [16-19, 21, 46-70] with a total of 5875 patients were included in the meta-analysis. All details about the successive steps for the selection of eligible studies and studies excluded with reason after full-text review are provided in Figures S1 and S2 and Tables S3 and S4. Tables 1 summarizes the characteristics of the studies included in the systematic review as well as those included only in the meta-analysis.

3.2 | Systematic Review

Overall, out of the 53 studies included in the systematic review, 19 studies originated from Europe [17, 18, 21, 23, 24, 27, 30s, 31, 35, 36, 39, 42, 49, 51, 53, 54, 63, 65, 66], 18 from Asia [16, 19, 34, 37, 38, 43, 45, 47, 52, 55, 59-62, 64, 69, 70], 14 from North America [25, 26, 28, 29, 32, 33, 40, 41, 46, 48, 58, 67, 68], 2 from Australia [44, 56], and 1 from Africa [57]. Thirty-four studies were published as full-text records [17, 21, 23, 25-28, 32-35, 38, 43, 45, 46, 48-55, 57-62, 64-67, 70], while 19 studies were retrieved as conference abstracts [16, 18, 19, 24, 29-31, 36, 37, 39-42, 44, 47, 56, 63, 68, 69]. The sample size of the included studies ranged from 10 to 596 patients, the percentage of males from 41.8% to 91.5%, the mean age from 46 to 60, the mean BMI from 20.9 to 30.1 kg/m^2, the percentage of patients with HCC from 0% to 58.5%, patients with viral hepatitis from 0% to 86.1% and patients with alcoholic liver disease from 0% to 53%. Methods used to evaluate muscle mass were appendicular lean mass by dual-energy x-ray absorptiometry (DXA) normalized for height (appendicular lean mass index [ALMI]) in one study [56], dorsal muscle group area in 1 study [33], fat free BMI in 1 study

TABLE 1 | Study characteristics.

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
A. Included only in the systematic review																
Alonchel F (2020)	2017	Europe	Spain	Full text	57	57	86.0%	28	NR	35.1%	29.8%	21.1%	PMI	Right psoas muscle area by CT or MRI at the level of L3 vertebrae, normalized for height	NR	NR
Bertuzzo VR (2019)	2008–2016	Europe	Italy	Abstract	287	NR	NR	NR	NR	NR	NR	NR	PMD	Psoas muscle density by CT	NR	NR
Dimartini A (2013)	2005–2008	North America	Pennsylvania, USA	Full Text	338	55	66.0%	28	20	NR	8.0%	6.8%	SMI	Cross sectional area of rectus abdominis, pyramidalis, transversus abdominis, internal and external obliques, latissimus dorsi, quadratus lumborum, psoas major and minor, and erector spinae by CT at the level of L3-L4 vertebrates normalized for height	Men SMI ≤ 52.4 cm^2/m^2 Women SMI ≤ 38.5 cm^2/m^2	68.0%
Englesbe MJ (2010)	2002–2008	North America	Michigan, USA	Full Text	163	53.2	63.2%	28.3	19.3	12.9%	35.0%	11.7%	PMA	Cross-sectional areas of the left and right psoas muscles by CT at the level of L4 vertebrae	NR	NR
Esser H (2019)	2011–2013	Europe	Austria	Full text	172	54.6	83.1%	25.8	15.7	NR	NR	NR	SMI	Skeletal mass area by CT at the level of L3 vertebrae normalized for height	Men SMI < 50 cm^2/m^2 Women SMI < 39 cm^2/m^2	41.3%
Figueiredo F (2000)	NR	North America	Minnesota, USA	Full text	53	50	58.5%	27.7	NR	NR	22.6%	15.1%	LBM-DXA	Lean Body Mass by DXA	NR	NR
Gupta T (2015)	2012–2013	North America	Louisiana, USA	Abstract	327	55	67.9%		23.5	NR	NR	NR	PMA	Psoas muscle cross-sectional area at L4 vertebrae level by CT	NR	19.6%
Herrera-Martinez AD (2016)	NR	Europe	Spain	Abstract	10	NR	NR	NR	NR	NR	NR	NR	PMA	Sum of psoas muscle areas by CT	NR	NR
Janout S (2019)	2008–2017	Europe	Austria	Abstract	132	NR	NR	NR	NR	NR	NR	NR	SMI	All areas of the skeletal muscles by CT at the level of L3 vertebrae, normalized for height	Men SMI ≤ 52.4 cm^2/m^2 Women SMI ≤ 38.5 cm^2/m^2	NR
Krell RW (2013)	2002–2008	North America	Michigan, USA	Full text	207	51.7	62.3%	27.77	19.8	25.1%	30.4%	14.5%	PMA	Cross-sectional areas of the psoas muscles by CT at the level of L4 vertebrae	Cohort's lower PMA tertile (vs. the highest tertile)	NR

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Lee CS (2014)	2000–2011	North America	Michigan, USA	Full Text	325	52	60.9%	28.09	18.3	39.1%	NR	NR	DMGA	Cross-sectional area of any muscle contained within the region posterior to the spine and ribs, and no more lateral than the lateral-most edges of the erector spinae muscles, by CT, at the T12 vertebral level	NR	NR
Lee J (2021)	1999–2013	Asia	Korea	Full text	72	53.01	72.2%	25.1	21.1	0.0%	86.1%	2.8%	SMI	Cross-sectional areas of the psoas, quadratus lumborum, erector spinae, external and internal obliques, transversus abdominis and rectus abdominis, by CT at the level of L3 vertebrae, normalized for height	NR	98.6%
Lindqvist C (2017)	2009–2012	Europe	Sweden	Full text	106	55.26	64.2%	NR	13.4	34.9%	34.9%	21.7%	FFMI	Sum of lean soft tissue and bone mineral content by DXA normalized for height	FFMI < cohort's 5th percentile by gender	15.1%
Mansour D (2017)	2014–2016	Europe	U.K.	Abstract	52	NR	NR	NR	NR	NR	NR	NR	PMA	NR	<5 cm^2/m^2	28.8%
Milgrom Y (2019)	2008–2011	Asia	Israel	Abstract	26	51	80.8%	NR	21.4	NR	76.9%	NR	WLMM	Whole-body Lean Muscle Mass by CT normalized for height	<650 (value not defined)	NR
Park J (2020)	2009–2018	Asia	Korea	Full Text	596	53	70.3%	24.2	15	43.5%	64.6%	23.0%	PMI	Average of the two psoas muscle area measurements by CT at the level of L3 vertebrae, normalized for height	NR	NR
Peteiro MC (2019)	2013–2018	Europe	Spain	Abstract	94	60.14	80.9%	NR	NR	NR	NR	NR	SMI	Skeletal mass area by CT at the level of L3 vertebrae normalized for height	Men SMI ≤ 52.4 cm^2/m^2 Women SMI ≤ 38.5 cm^2/m^2	76.6%
Sharma R (2019)	NR	North America	New York, USA	Abstract	65	NR	NR	NR	NR	NR	NR	NR	SMI	All areas of the skeletal muscles by CT or MRI at the level of L3 vertebrae, normalized by height	Men SMI ≤ 52.4 cm^2/m^2 Women SMI ≤ 38.5 cm^2/m^2	NR
Smith S (2019)	2015–2017	North America	Louisiana, USA	Abstract	257	58.1	NR	NR	19	NR	NR	NR	NR	NR	NR	23.7%

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Tavano D (2019)	2000–2015	Europe	Italy	Abstract	173	55.6	67.1%	NR	NR	NR	42.8%	16.2%	SMI	Skeletal mass area by CT at the level of L3 vertebrae normalized for height	NR	42.2%
Tsao (2021)	2011–2013	Asia	Taiwan	Full text	138	52.77	75.4%	NR	15.63	45.7%	34.8%	10.9%	PMI	The cross-sectional body areas of the left and right psoas muscles by CT at the level of L3 vertebrae, normalized for height	NR	NR
Woodward AJ (2018)	NR	Australia	Australia	Abstract	44	NR	NR	NR	NR	NR	NR	NR	DXA SMI	NR	EWGSOP sarcopenia classification system	NR
Wu MY (2021)	2005–2017	Asia	Taiwan	Full Text	271	51.93	55.0%	24.89	20.54	40.2%	40.2%	NR	PMI	The bilateral psoas muscle area by CT at the level of L3 vertebrae, normalized for height	NR	NR
B. Included in the systematic review and metanalysis																
Aby ES (2018)	2002–2015	North America	California, USA	Full text	146	58.3	41.8%	29.7	34.9	20.5%	0.0%	0.0%	PMA	Cross-sectional areas of the psoas muscles by CT or MRI at the level of L3 vertebrae	Men PMA < 1561 mm^2 Women PMA < 1464 mm^2	61.6%
Ascar S (2018)	2014–2017	Asia	Turkey	Abstract	109	51.04	68.8%	27.84	15.33	20.2%	NR	NR	PMA	Cross-sectional areas of the psoas muscles by CT at the level of L3-L4 vertebrates	Men PMA < 1561 mm^2 Women PMA < 1464 mm^2	14.7%
Atalan HK (2019)	2011-2014	Asia	Turkey	Abstract	261	53.13	51.7%	25.35	16	NR	NR	NR	PMI	Total psoas muscle area by CT normalized for height	Cohort's lower PMI quartile Men PMI ≤ 397 mm^2/m^2 Women PMI ≤ 298 mm^2/m^2	21.5%
Bhanji RA (2019)	2002–2006	North America	Minnesota USA	Full text	293	51.95	70.3%	27.5	17.95	47.1%	29.0%	25.3%	SMI	Skeletal muscle area of abdomen psoas. paraspinal and abdominal wall including rectus abdominis, transverse abdominis and internal and external oblique muscles by CT at the L3 vertebrae, normalized for height	Men SMI < 50 cm^2/m^2 Women SMI < 39 cm^2/m^2	49.8%

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Cabo SN (2020)	2013–2016	Europe	Spain	Full text	97	55.32	77.3%	NR	14.6	35.1%	20.6%	24.7%	PMI	Cross-sectional area of both psoas muscles by CT at the level of L4 vertebrae, normalized for height	Men PMI ≤ 784.0 mm^2/m^2 Women PMI ≤ 642.1 mm^2/m^2	44.3%
Carias S (2016)	2008–2013	North America	Kentucky, USA	Full text	207	54	68.6%	30.1	21	24.6%	38.2%	38.6%	SMI	Cross-sectional area of psoas, paraspinals, transversus abdominis, rectus abdominis, and internal and external obliques by CT at the level of L3 vertebrae normalized for stature	Men SMI ≤ 52.4 cm^2/m^2 Women SMI ≤ 38.5 cm^2/m^2	52.2%
Czigany Z (2019)	2010–2017	Europe	Germany	Full text	225	54	66.7%	27	20	28.0%	6.7%	20.0%	SMI	Cross-sectional area of psoas major, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis by CT at the level of L3 vertebrae, normalized for height	Men SMI ≤ 50 cm^2/m^2 Women SMI ≤ 39 cm^2/m^2	37.3%
Czigany Z (2021)	2010–2017	Europe	Germany	Full text	225	54	66.7%	27	20	28.0%	6.7%	20.0%	SMI	Psoas major, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis by CT at the level of L3 vertebrae, normalized for height	Men SMI ≤ 50 cm^2/m^2 Women SMI ≤ 39 cm^2/m^2	37.3%
Dai X (2021)	2016–2018	Asia	China	Full text	313	50.67	60.7%	23.75	14.64	NR	46.3%	8.0%	PMTH	The ratio of the transverse thickness of the right psoas muscle in the umbilical plane by CT, normalized for height	Men PMTH ≤ 17.9 cm/m^2 Women PMTH ≤ 14.1 cm/m^2	25.9%
Dos Santos DP (2020)	1998–2014	Europe	Germany	Full text	368	56.8	69.3%	25.2	16	44.6%	39.7%	39.9%	PSMI	Bilateral psoas muscle area (PMA) and bilateral erector spinae muscle area (ESA) combined, by CT at the level of L3 vertebrae, normalized for height	PSMI ≤ cohort's median PSMI	50.0%

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Golse N (2017)	2008–2011	Europe	France	Full text	256	53	76.6%	25.3	19.3	39.8%	42.2%	45.3%	PMA	Cross-sectional areas of the psoas muscles by CT at the level of L3-L4 vertebrates	Men PMA < 1561 mm^2 Women PMA < 1464 mm^2	22.3%
Harimoto N (2017)	2001–2016	Asia	Japan	Full text	366	55.8	48.4%	23.9	15.33	58.5%	NR	NR	SMA	Cross-sectional area of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis by CT at the level of L3 vertebrae	SMA: <75% of the calculated standard SMA (= 126.9 × body surface area −66.2 in men and 125.6 × body surface area −81.1 in women)	25.7%
Hey P (2019)	2002–2017	Australia	Australia	Abstract	428	54	72.7%	NR	15	NR	NR	NR	ALMI	Appendicular lean mass by DXA normalized for height	Previously reported cut-off values of appendicular lean mass/height^2	25.5%
Irwin NEA (2021)	2011–2019	Africa	South Africa	Full text	106		60.4%		17	9.4%	5.7%	NR	SMI	Total cross-sectional areas of the psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal oblique, and rectus abdominus muscles, by CT at the level of L3 vertebrae, normalized for height	Men SMI < 50 cm^2/m^2 Women SMI < 39 cm^2/m^2	65.1%
Ito T (2021)	2012–2018	North America	California, USA	Full text	217	56	59.0%	28.16	40.8	NR	30.0%	33.2%	SMI	Total cross-sectional area of the abdominal skeletal muscles (psoas, paraspinal, rectus abdominis, transverse abdominis, and internal and external oblique) by CT at the level of L3 vertebrae, normalized for height	Men SMI ≤ 30 cm^2/m^2 Women SMI ≤ 34 cm^2/m^2	44.2%
Izumi T (2016)	2001–2014	Asia	Japan	Full text	47	54	51.1%	NR	19	23.4%	48.9%	6.4%	PMI	The sum of the left and right outer margins of the cross-section of the major psoas muscle by CT at the level of L3 vertebrae normalized for stature	Men PMI < 612.5 mm^2/m^2 Women PMI < 442.9 mm^2/m^2	63.8%

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Kalafateli M (2017)	2008–2012	Europe	U.K.	Full text	232	53	69.8%	25	14	25.0%	34.9%	23.7%	PMI	Total psoas muscle area by CT at the level of L3 vertebrae, normalized for height	Men PMI < 340 mm^2/m^2 Women PMI < 264 mm^2/m^2	24.6%
Kamo N (2019)	2008–2016	Asia	Japan	Full text	203	54	66.0%	20.9	17	36.5%	29.6%	NR	SMI	All areas of the skeletal muscles by CT at the level of L3 vertebrae, normalized for height	Men SMI < 40.31 cm^2/m^2 Women SMI < 30.88 cm^2/m^2	27.1%
Kamo N (2020)	2008–2016	Asia	Japan	Full text	203	54	66.0%	20.9	17	36.5%	29.6%	NR	SMI	All areas of the skeletal muscles by CT at the level of L3 vertebrae, normalized for height	Men SMI < 40.31 cm^2/m^2 Women SMI < 30.88 cm^2/m^2	27.1%
Kumar V (2019)	2013–2015	Asia	India	Full text	115	45.75	90.4%	24.5	20.6	NR	10.4%	53.0%	SMI	The sum of the cross-sectional area of six abdominal muscles (erector spinae, quadrates lumborum, psoas, transversus abdominis, interior/exterior oblique, and rectus abdominis) at the level of L3, by CT, normalized for height	Men SMI < 52.4 cm^2/m^2 Women SMI < 38.5 cm^2/m^2	47.8%
Marrone G (2019)	2016–2018	Europe	Italy	Abstract	101	54.8	79.2%	NR	16.8	41.6%	32.7%	31.7%	muscle volume of the abdomen	3D muscle area, from the iliac crests to the base of the heart, excluding visceral content normalized for height	The lower quartile of indexed muscle volume in the analyzed population Men <629.9 cm^3/m^2 Women <583.7 cm^3/m^2	NR
Masuda T (2014)	2003–2011	Asia	Japan	Full text	204	54.4	50.5%	23.6	NR	NR	63.2%	4.9%	PMA	Cross-sectional areas of the psoas muscles by CT at the level of L3 vertebrae	Men PMA < 800 cm^2 Women PMA < 380 cm^2	47.1%

(Continues)

TABLE 1 | (Continued)

Author (year)	Study period	Continent	Region	Publi-cation type	Sample size	Mean age, years	Males	Mean BMI, kg/m^2	Mean MELD	HCC	Viral hepatitis	ALD	Method for muscle measurement	Definition of muscle measurement	Definition of sarcopenia	Prevalence of sarcopenia
Mazzarelli C (2019)	2012–2016	Europe	Italy	Abstract	399	54	91.5%	NR	17	51.9%	64.9%	16.8%	SMI	All areas of the skeletal muscles by CT at the level of L3 vertebrae, normalized for height	Previously published gender and BMI-specific cutoffs	17.3%
Mazzola A (2021)	2003–2018	Europe	France	Full text	43	58	55.8%	23.75	21	27.9%	27.9%	20.9%	PMA	Cross-sectional area of both psoas muscles by CT or MRI at the level of L3 vertebrae	Men PMA < 1561 mm^2 Women PMA < 1464 mm^2	72.1%
Melissa CSH (2020)	2010–2014	Asia	Singapore	Abstract	60	52.4	76.7%	NR	17.87	41.7%	75.0%	0.0%	SMI	All areas of the skeletal muscles by CT or MRI at the level of L3 vertebrae, normalized for height	Men SMI ≤ 50 cm/m^2 Women SMI ≤ 42 cm/m^2	88.3%
Miarka M (2021)	2015–2017	Europe	Polland	Full text	98	55	76.5%	27	18	26.5%	30.6%	42.9%	SMI	The cross-sectional area of the muscles at the superior aspect of L3 vertebrae by CT, normalized for height	Men SMI < 50 cm^2/m^2 Women SMI < 39 c^{m2}/m^2	56.1%
Montano-Loza AJ (2014)	2000–2012	North America	Canada	Full text	248	55	68.1%	27	18	39.1%	59.7%	18.5%	SMI	Cross-sectional area of psoas. erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis by CT at the level of L3 vertebrae normalized for stature	Men SMI < 53 cm2/m2 for BMI < 25 kg/m^2 and <43 cm^2/m^2 for BMI < 25 kg/m^2 Women SMI < 41 cm^2/m^2	45.2%
Nolte JV (2015)	2008–2014	North America	Texas, USA	Abstract	105	54.3	NR	NR	34.67	NR	NR	NR	PMA	Mean psoas area by CT at the level of L3 vertebrae	Cohort's lower PMA tertile	33.3%
Raut V (2016)	NR	Asia	India	Abstract	100	48.04	68.0%	NR	25.27	NR	NR	NR	PMA	Cross-sectional areas of the psoas muscles by CT at the level of L3 vertebrae	Men PMA < 800 mm^2 Women PMA < 380 mm^2	46.0%
Wakabayashi T (2018)	2005–2017	Asia	Japan	Full text	100	52.2	49.0%	22.8	18.8	28.0%	37.0%	14.0%	SMI	Cross-sectional skeletal mass area by CT at CT at the level of L3 vertebrae, normalized for height	Men SMI < 42 cm^2/m^2 Women SMI < 38 cm^2 /m^2	47.0%

Abbreviations: ALD, alcoholic liver disease; ALMI, appendicular lean mass index; BMI, body mass index; CT: computed tomography; DMGA, dorsal muscle group area; DXA, dual-energy x-ray absorptiometry; FFMI: fat-free body mass index; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease score; MRI, magnetic resonance imaging; NR, not reported; PMA, psoas muscle area; PMD, psoas muscle density; PMI, psoas muscle index; PMTH, psoas muscle thickness per height; PSMI, paraspinal muscle index; SMA, skeletal muscle area; SMI, skeletal muscle index; WLMM, whole-body Lean Muscle Mass.

[35], lean body mass by DXA in 1 study [28], muscle volume of the abdomen in 1 study [63], psoas muscle area (PMA) in 12 studies [26, 29, 30, 32, 36, 46, 47, 54, 64, 65, 68, 69], psoas muscle density in 1 study [24], psoas muscle index (PMI) in 8 studies [16, 17, 23, 38, 43, 45, 49, 59], psoas muscle thickness in 1 study [52], paraspinal muscle index in 1 study [53], skeletal muscle area in 1 study [55], skeletal muscle index (SMI) in 21 studies [18, 19, 21, 25, 27, 31, 34, 39, 40, 42, 48, 50, 51, 57, 58, 60-62, 66, 67, 70], DXA SMI in 1 study [44], and whole-body lean muscle mass in 1 study [37], while 1 study did not report the method utilized [41].

The prevalence of sarcopenia was available in 38 of the 53 studies and ranged from 14.8% to 98.6%. Forty-seven of the 53 studies reported on mortality of patients after LT in regard to their sarcopenic status before LT (45 unique–2 pairs of studies were overlapping [21, 51, 55, 64] and were included only for secondary outcomes). Twenty-one of the 45 studies [16-18, 24, 30-33, 39, 42, 48, 52-55, 59, 60, 63, 68, 69] including 4435 patients, reported an association between pre-LT sarcopenia and increased mortality post-LT, 23 studies [19, 23, 27-29, 34, 37, 40, 41, 43, 46, 47, 49-51, 56-58, 62, 65-67, 70] including 3366 patients, did not find an association, while one study [25] with 338 patients found an association between sarcopenia and increased mortality in male but not in female patients. Table 2 summarizes the outcomes after LT that each study evaluated, based on pre-LT sarcopenia.

The association of pre-LT sarcopenia and liver graft failure was evaluated in 18 of the 53 studies (17 unique as two studies [51, 71] overlapped): 16 studies [23, 27-29, 37, 42, 51-58, 62, 65] including 3245 patients did not find any association, while 1 study [70] with 100 patients found an association between sarcopenia and reduced incidence of graft rejection.

Whether sarcopenia was associated with ICU and LOS after LT, was evaluated by 23 and 27 studies, respectively. Eleven studies [18, 19, 25, 28, 31, 45, 53, 54, 62, 66, 69] including 2190 patients, and 9 studies [16-18, 25, 29, 48, 58, 67, 69] including 2415 patients found an association of pre-LT sarcopenia with increased ICU and hospital LOS after LT, respectively, while 11 studies [17, 29, 31, 35, 36, 42, 51, 52, 57, 65, 68] including 1782 patients and 16 studies [19, 27, 28, 31, 35, 36, 46, 51, 52, 54, 56, 57, 62, 65, 68, 70] including 2412 patients did not find any association with ICU and hospital LOS, respectively. One study [41] including 257 patients found an association between increased ICU and hospital LOS only for sarcopenic women, while one study [55] with 366 patients, concluded that hospital LOS was associated with pre-LT sarcopenia only when functional parameters were included in sarcopenia definition.

Twenty-four studies [17-19, 24, 28, 29, 32, 35, 37, 38, 44, 52, 54-56, 58, 61, 62, 64, 65, 67, 69, 70] (23 unique studies as 2 studies [55, 64] overlapped) evaluated infections after LT regarding pre-LT sarcopenia status. An increased incidence of post-LT infections in pre-LT sarcopenic patients was found in 14 studies including 3323 patients (with 4 studies examining overall infections [24, 29, 35, 54), 8 bacterial infections [38, 44, 55, 58, 61, 62, 69, 70], 1 study bacterial, viral and fungal [18], and 1 study all type of infections examining overall, bacterial, viral, and fungal [32]]. One study [67] including 248 patients found an increased incidence of bacterial infections after LT in pre-LT sarcopenic patients but no difference in overall, viral, or fungal infections. Seven studies including 1155 patients did not find any difference in sarcopenic patients concerning post-LT infections (6 studies examining overall [17, 19, 28, 37, 52, 65] and 1 study bacterial infections [56]).

Blood product transfusion perioperatively and/or during the first postoperative period was examined in five studies. Increased transfusions in sarcopenic patients were observed for RBC in 3 studies including 796 patients [52, 53, 62], and FFP in 2 studies including 681 patients [52, 53]. One study including 225 patients did not find any difference for either RBC or FFP transfusions [51], while another study with 257 LT recipients, found increased transfusions of blood products (in general) in sarcopenic men but not in women [41]. The only study examining platelet transfusions in 368 LT recipients did not find any difference between sarcopenic and non-sarcopenic patients [53].

Finally, 13 studies evaluated the difference in complication rates after LT according to the presence of pre-LT sarcopenia. The Clavien-Dindo classification score of surgery-related complications was used in all but two studies [33, 65] which did not use any scoring index. Five studies including 1030 patients [24, 33, 54, 59, 62] reported increased incidence of postoperative surgical complications in pre-LT sarcopenic patients, while one study [45] with 271 patients confirmed this finding only for pre-LT sarcopenic women. Finally, seven studies including 1282 patients [31, 49, 51, 52, 55, 57, 65] did not find any effect of pre-LT sarcopenia on postoperative surgical complications.

3.3 | Meta-Analysis

Thirty studies including 5875 patients were included in the meta-analysis (Table 1), Twenty-two were published as full-text [17, 21, 46, 48-55, 57-62, 64-67, 70] and eight as conference abstracts [16, 18, 19, 47, 56, 63, 68, 69]. Ten studies were conducted in Europe [17, 18, 21, 49, 51, 53, 54, 63, 65, 66], 6 in North America [46, 48, 50, 58, 67, 68], 12 in Asia [16, 19, 47, 52, 55, 59-62, 64, 69, 70], 1 in Africa [57], and 1 in Australia [56]. The sample size ranged from 43 to 428 and the mean age from 46 to 58 years. The methods used for sarcopenia evaluation were ALMI in 1 study [56], muscle volume of the abdomen in 1 study [63], PMA in 7 studies [46, 47, 54, 64, 65, 68, 69], PMI in 4 studies [16, 17, 49, 59], psoas muscle thickness in 1 study [52], paraspinal muscle index in 1 study [53], skeletal muscle area in 1 study [55], and SMI in 14 studies [18, 19, 21, 48, 50, 51, 57, 58, 60-62, 66, 67, 70] with sarcopenia prevalence ranging from 14.7% to 88.3%. All included cohorts were of good/high quality with an NOS rate ≥6 as illustrated in Table S5. Additionally, in the analysis of our primary endpoint, overall mortality, we did not detect a publication bias via Egger's test ($p = 0.224$), also reflected in the symmetric appearance of the Funnel Plot (Figure S3).

3.4 | Association Between Pre-LT Sarcopenia and Mortality After LT

Based on the available data from 25 studies [16-19, 21, 46-48, 50, 52-54, 56, 57, 59, 60, 62-70] including 4767 patients, pre-LT sarcopenia was associated with increased mortality post-LT by 1.84 times (RR = 1.84, 95% CI:1.41,2.39) irrespectively of publication type

TABLE 2 | Outcomes after LT for sarcopenic vs non sarcopenic patients.

Author (year)	Sample size	Mortality	Graft dysfunction	Hospital LOS	ICU LOS	Infections	Transfusions	Complications	Method for muscle measurement	Publication type	Comments
A. Included only in the systematic review											
Alonchel F (2020)	57	-	-						PMI	Full text	
Bertuzzo VR (2019)	287	↑				↑ overall		↑	PMD	Abstract	
Dimartini A (2013)	338	↑ -		↑ ↑	↑ ↑				SMI	Full text	Men women
Englesbe MJ (2010)	163	↑							PMA	Full text	
Esser H (2019)	172	-	-	-					SMI	Full text	
Figueiredo F (2000)	53	-	-	-	↑	- overall			LBM-DXA	Full text	
Gupta T (2015)	327	-	-	↑	-	↑ overall			PMA	Abstract	
Herrera-Martinez AD (2016)	10	↑							PMA	Abstract	
Janout S (2019)	132	↑		-	↑			-	SMI	Abstract	
Krell RW (2013)	207	↑				↑overall ↑ bacterial ↑ viral ↑ fungal			PMA	Full text	
Lee CS (2014)	325	↑						↑	DMGA	Full text	
Lee J (2021)	72	—							SMI	Full text	
Lindqvist C (2017)	106			-	-	↑ overall			FFMI	Full text	
Mansour D (2017)	52			-	-				PMA	Abstract	
Milgrom Y (2019)	26	-	-			- overall			WLMM	Abstract	
Park J (2020)	596					↑ bacterial			PMI	Full text	
Peteiro MC (2019)	94	↑							SMI	Abstract	
Sharma R (2019)	65	-							SMI	Abstract	

(Continues)

TABLE 2 | (Continued)

Author (year)	Sample size	Mortality	Graft dis-function	Hospital LOS	ICU LOS	Infections	Transfusions	Complications	Method for muscle measurement	Publication type	Comments
Smith S (2019)	257	- -		- ↑	- ↑		↑blood products - blood products		Not Reported	Abstract	Men women
Tavano D (2019)	173	↑	-		-				SMI	Abstract	
Tsao (2021)	138	-							PMI	Full text	
Woodward AJ (2018)	44					↑ bacterial			DXA SMI	Abstract	
Wu MY (2021)	271				↑ ↑			- ↑	PMI	Full text	Men women
B. Included in the systematic review and metanalysis											
Aby ES (2018)	146	-		-					PMA	Full text	Only NASH cirrhosis
Ascar S (2018)	109	-							PMA	Abstract	
Atalan HK (2019)	261	↑		↑					PMI	Abstract	
Bhanji RA (2019)	293	↑		↑					SMI	Full text	
Cabo SN (2020)	97	-						-	PMI	Full text	
Carias S (2016)	207	-							SMI	Full text	
Czigany Z (2019)	225	- †	- †	-	-		- RBCs - FFP	-	SMI	Full text	
Czigany Z (2021)	225	- †	- †						SMI	Full text	
Dai X (2021)	313	↑	-	-	-	- overall	↑ RBCs ↑ FFP	-	PMTH	Full text	
Dos Santos DP (2020)	368	↑	-		↑		↑ RBCs ↑ FFP - PLTs		PSMI	Full text	
Golse N (2017)	256	↑	-	-	↑	↑ overall		↑	PMA	Full text	
Harimoto N (2017)	366	↑ ‡ ↑ ‡	- ↑	- ↑		↑ bacterial‡ - bacterial‡		- ↑	SMA	Full text	Sarcopenia SMA sarcopenia: SMA + functional

(Continues)

TABLE 2 | (Continued)

Author (year)	Sample size	Mortality	Graft dysfunction	Hospital LOS	ICU LOS	Infections	Transfusions	Complications	Method for muscle measurement	Publication type	Comments
Hey P (2019)	428	-	-	-		- bacterial			ALMI	Abstract	
Irwin (2021)	106	-	-	-	-			-	SMI	Full text	
Ito T (2021)	217	-	-	↑		↑ bacterial			SMI	Full text	Meld ≥ 35
Izumi T (2016)	47	↑						↑	PMI	Full text	
Kalafateli M (2017)	232	↑		↑	-	- overall			PMI	Full text	
Kamo N (2019)	203	↑							SMI	Full text	
Kamo N (2020)	203					↑ bacterial			SMI	Full text	
Kumar V (2019)	115	-	-	-	↑	↑ bacterial	↑RBCs	↑	SMI	Full text	
Marrone G (2019)	101	↑							muscle volume of the abdomen	Abstract	
Masuda T (2014)	204	↑ ‡				↑ bacterial‡			PMA	Full text	
Mazzarelli C (2019)	399	↑		↑	↑	↑ bacterial ↑ viral ↑ fungal			SMI	Abstract	
Mazzola A (2021)	43	-	-	-	-	- overall		-	PMA	Full text	
Melissa CSH (2020)	60	-		-	↑	- overall			SMI	Abstract	
Miarka M (2021)	98	-			↑				SMI	Full text	
Montano-Loza AJ (2014)	248	-		↑	↑	- overall ↑ bacterial - viral - fungal			SMI	Full text	
Nolte JV (2015)	105	↑		-	-				PMA	Abstract	Meld ≥ 25
Raut V (2016)	100	↑		↑	↑	↑ bacterial			PMA	Abstract	Meld > 20
Wakabayashi T (2018)	100	-	↓	-	-	↑ bacterial			SMI	Full text	

Note: -: no effect, ↑: increase, ↓:decrease, ‡,†: effects from overlapping cohorts.

Abbreviations: DMGA, dorsal muscle group area; FFMI, fat-free body mass index; FFP, fresh frozen plasma; ICU, intensive care unit; LOS, length of stay; PLTs, platelets; PMA, psoas muscle area; PMI, psoas muscle index; PMTH, psoas muscle thickness per height; PSMI, paraspinal muscle index; RBC, red blood cells; SMI, skeletal muscle index; SMA, skeletal muscle area; SMI, skeletal muscle index; WLMM, whole-body lean muscle mass.

TABLE 3 | Results of the meta-analysis examining the association between sarcopenia and mortality after LT; subgroup analyses.

	n^a	RR (95% CI)	Heterogeneity (I^2, p)
Mortality	**25**	**1.84 (1.41–2.39)**	**67.3%, <0.001**
Subgroups by method of measurement			
ALMI	1	0.80 (0.23–2.81)	NC
Muscle volume of the abdomen	**1**	**7 (2.28–21.45)**	**NC**
PMA	**7**	**1.98 (1.31–3.00)**	**39.4%, 0.13**
PMI	3	5.27 (0.86–32.19)	85.8%, 0.001
PMTH	**1**	**5.98 (2.23–16.04)**	**NC**
PSMI	1	1.28 (0.96–1.73)	NC
SMI	**11**	**1.41 (1.02–1.95)**	**57.6%, <0.05**
Subgroups by geographical region			
Africa	1	2.64 (0.99–7.02)	NC
Asia	**8**	**2.04 (1.21–3.45)**	**54.5%, 0.03**
Australia	1	0.80 (0.23–2.81)	NC
Europe/North America	**10**	**1.80 (1.29–2.50)**	**74.2%, <0.001**
Subgroups by adjusted analysis			
Univariate	**22**	**1.88 (1.40–2.53)**	**69.4%, <0.001**
Multivariate	3	1.69 (0.96–.97)	55.7%, 0.11
Subgroups by type of publications			
Article	**17**	**1.49 (1.18–1.87)**	**51.8%, <0.05**
Abstract	**8**	**3.26 (1.68–6.34)**	**65%, <0.05**

Note: Bold cells denote statistically significant associations.

Abbreviations: ALMI, appendicular lean mass index; LT, liver transplantation; NC, noncalculable; PMA, psoas muscle area; PMI, psoas muscle index; PMTH, psoas muscle thickness per height; PSMI, paraspinal muscle index; RR, relative risk; SMI, skeletal muscle index.

[a]Number of studies.

(i.e. full-text articles [17 studies, RR = 1.49, 95% CI:1.18,1.87] or abstracts [8 studies, RR = 3.26, 95% CI:1.68,6.34]), although there was substantial heterogeneity between the studies (I^2:67.3%, $p < 0.001$). Results of the meta-analyses examining the association between pre-LT sarcopenia and mortality after LT as well as subgroup analyses can be found in Table 3 and the forest plots in Figures 1, 2, S4, and S5. Based on the available data, when subgroup analysis was performed per evaluation method, pre-LT sarcopenia remained a significant risk factor of mortality post-LT, in studies where the diagnosis of sarcopenia was based on PMA (7 studies, RR = 1.98, 95% CI:1.31,3.00) and SMI (11 studies, RR = 1.41, 95% CI:1.02,1.95), but not on PMI (3 studies, RR = 5.27, 95% CI:0.86,32.19) (Figure 1). Sarcopenia remained a predictor of post-LT mortality in studies from Asia (8 studies, RR = 2.04, 95% CI:1.21,3.45) and Europe/North America (15 studies, RR = 1.80, 95% CI: 1.29,2.50) (there was only one study from Africa and Australia) (Figure 2).

3.5 | Association Between Pre-LT Sarcopenia and Other Outcomes Post-LT

3.6 | Liver Graft Function

Four studies [21, 53, 55, 65] including 1002 patients, evaluated graft survival, and 8 studies [19, 51, 52, 54, 57, 58, 62, 70] with a total of 1392 patients, examined graft rejections. No association was found between pre-LT sarcopenia and graft survival (RR = 0.95, 95% CI:0.86,1.05) or rejection rates (RR = 0.83, 95% CI:0.55,1.26) (Table S6).

3.7 | Infections

Studies were pooled for overall infections (6 studies [17-19, 52, 65, 67], 1295 patients), bacterial (9 studies [18, 56, 58, 61, 62, 64, 67, 69, 70], 1842 patients), and viral and fungal infections (2 studies [18, 67], 647 patients) (Table 4). Pre-LT sarcopenic patients had a significantly higher risk for overall infections (RR = 1.35, 95% CI:1.13,1.62), and bacterial infections (RR = 1.97, 95% CI:1.55,2.50) after LT. These findings were confirmed in all subanalyses except for overall infections in studies from Asia (2 studies, RR = 1.17, 95% CI:0.87,1.57). Finally, pre-LT sarcopenic patients had a significantly higher risk for fungal infections post-LT (RR = 4.99, 95% CI:1.60,15.5) and a tendency for increased risk for viral infections (RR = 1.91, 95% CI:0.41,8.91).

3.8 | Transfusions

Based on the available data, pre-LT sarcopenia was associated with a greater need for FFP transfusions (2 studies [51, 53], SMD

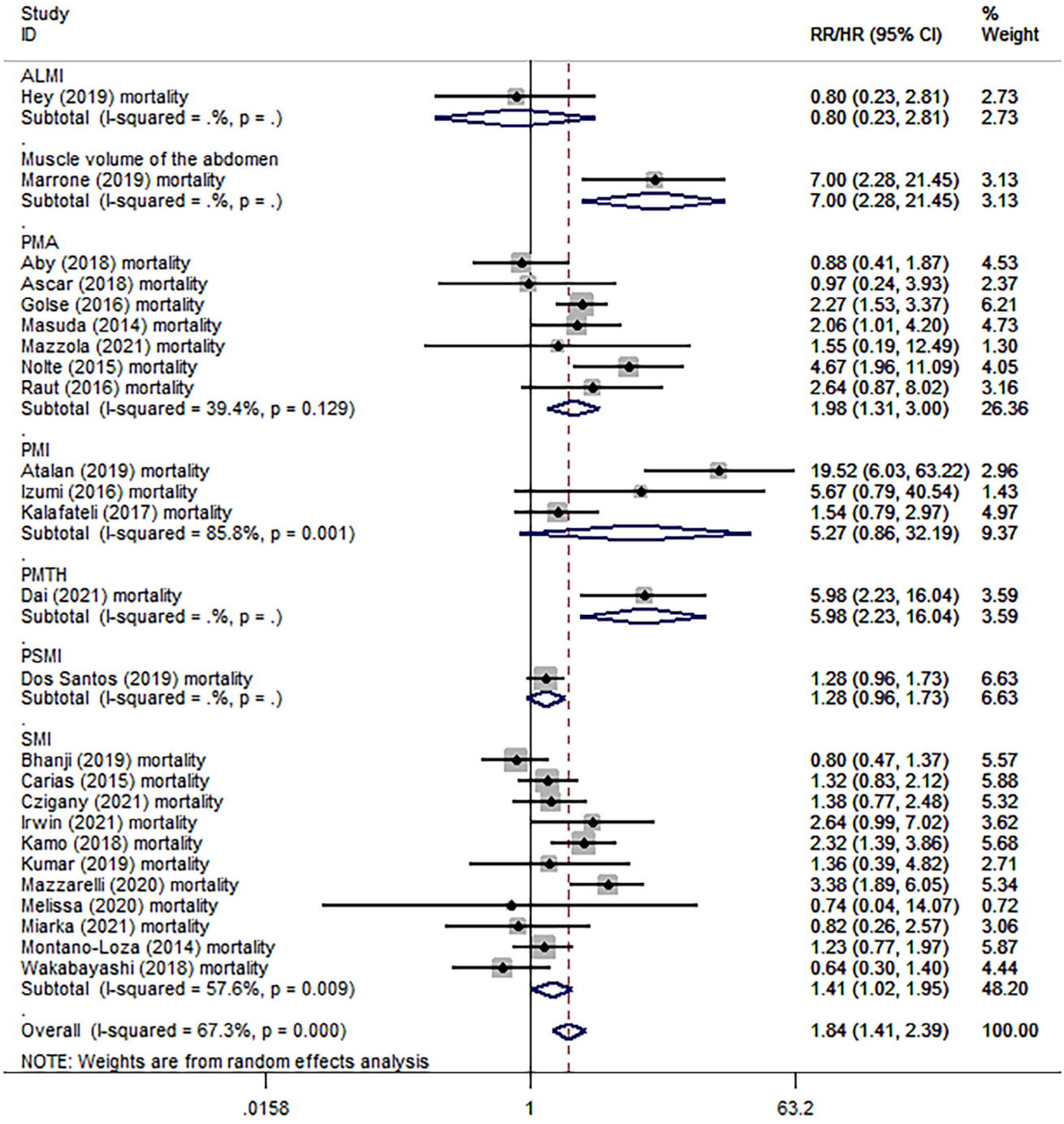

FIGURE 1 | Mortality, by method. Results of the meta-analyses examining the association between pre-LT sarcopenia and mortality after LT as well as subgroup analyses per evaluation method. ALMI indicates appendicular lean mass index; HR, hazard ratio; PMA, psoas muscle area; PMI, psoas muscle index; PMTH, psoas muscle thickness; PSMI, paraspinal muscle index; RR, relative risk; SMI, skeletal muscle index.

= 0.20, 95% CI:0.04,0.37). No difference was observed in the need for RBC transfusions (4 studies [51-53, 62], SMD = 0.26, 95% CI:-0.16,0.98), except in studies where SMI was used (3 studies, SMD = 0.31, 95% CI:0.10,0.53) (Table S7).

3.9 | LOS

Sarcopenic patients showed a significantly increased LOS in the ICU after LT (13 studies [17-19, 51-54, 57, 62, 65, 67, 68, 70], SMD = 0.41, 95% CI:0.17,0.66). These findings were confirmed in studies from European/North American countries (8 studies, SMD = 0.36, 95% CI:0.20,0.53) but not in those conducted in Asia (4 studies, SMD = 0.53, 95% CI: −0.29,1.36) (Table 5).

Finally, no significant impact of pre-LT sarcopenia on hospital LOS after LT was found overall (14 studies [16-19, 46, 51, 52, 54, 55, 57, 62, 65, 67, 68], SMD = 0.15, 95% CI:−0.04,0.33), as well as in sub-analyses.

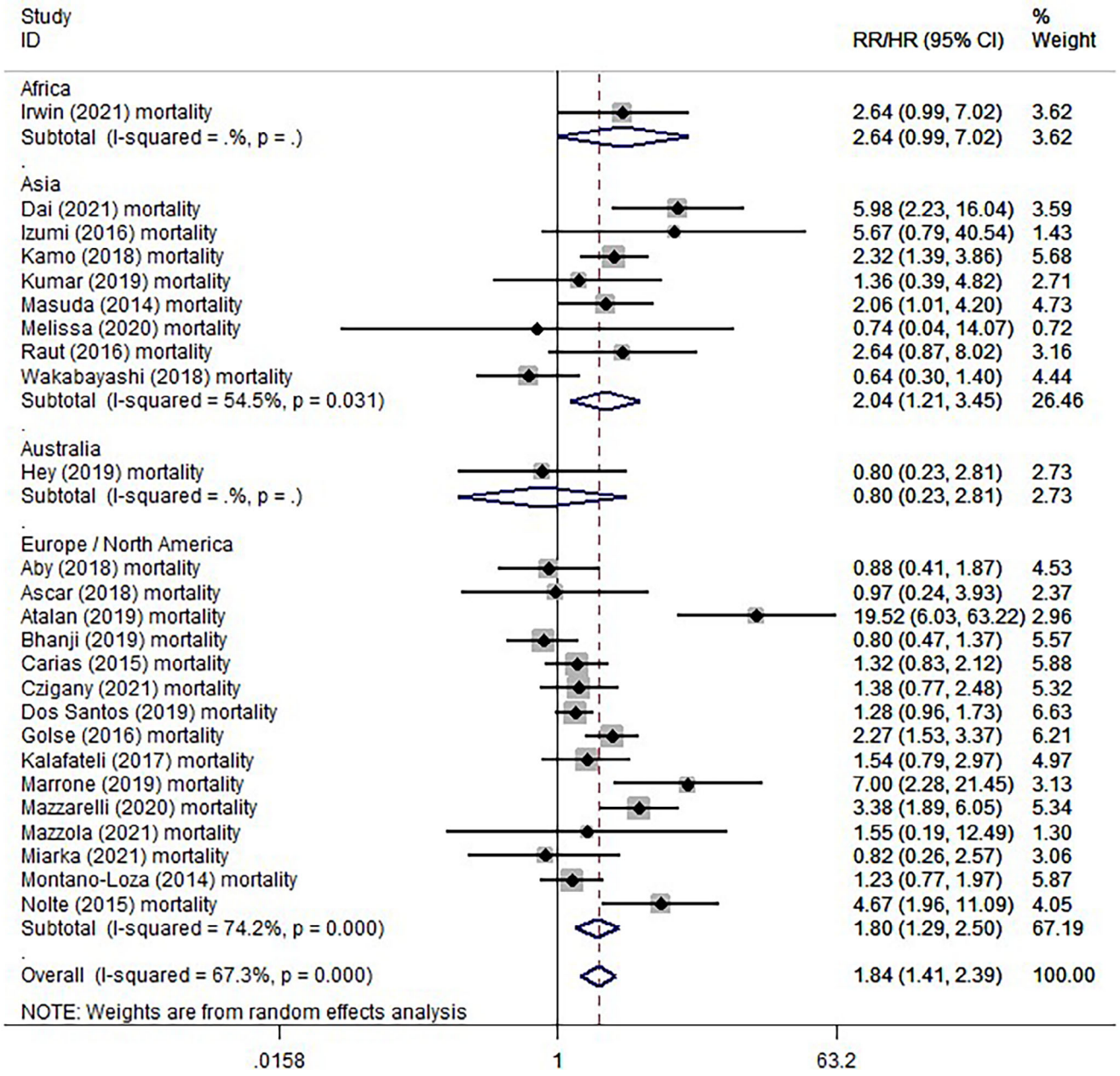

FIGURE 2 | Mortality, by continent. Results of the meta-analyses examining the association between pre-LT sarcopenia and mortality after LT as well as subgroup analyses per continent. HR indicates hazard ratio; RR, relative risk.

3.10 | Surgical Complications

Sarcopenia before LT was associated with a higher risk for post-LT surgical complications, as defined by the Clavien-Dindo score (7 studies [49, 51, 52, 54, 55, 59, 62], RR = 1.54, 95% CI:1.26,1.90) irrespective of effect estimate calculation. This finding was confirmed in studies where the evaluation of sarcopenia was based on PMI (2 studies, RR = 1.91, 95% CI:1.43,2.55), as well as in Asian studies (4 studies, RR = 1.71, 95% CI:1.42,2.05) (Table S8).

3.11 | Meta-Regression Analysis

Meta-regression analysis was only possible for overall mortality, ICU, and hospital LOS due to the small number of pooled studies available for the rest of the variables. Ten studies represent a minimum requirement for satisfactory power according to the Cochrane Handbook 32. Table S9 presents the results of meta-regression analyses. None of the sets of meta-regression analyses yielded a significant association.

4 | Discussion

The present systematic review/meta-analysis is the first study addressing several methods of sarcopenia measurement and assessing their association with post-LT mortality and other clinical outcomes through a separate meta-analysis for each one.

More specifically, in our meta-analysis, we found that pre-LT sarcopenia is associated with a nearly 2-fold increased risk of

TABLE 4 | Results of the meta-analyses examining the association between sarcopenia and infections after LT; subgroup analyses.

	n[a]	RR (95% CI)	Heterogeneity (I^2, p)
Overall infections	**6**	**1.35 (1.13, 1.62)**	**0%, 0.53**
Subgroups by method of measurement			
PMI	1	1.17 (0.78, 1.76)	NC
PMTH	1	1.18 (0.87, 1.61)	NC
SMI	**3**	**1.58 (1.19, 2.12)**	**0%, 0.45**
PMA	1	1.63 (0.80, 3.31)	NC
Subgroups by geographical region			
Asia	2	1.17 (0.87, 1.57)	0%, 0.82
Europe/North America	**4**	**1.48 (1.17, 1.86)**	**0%, 0.46**
Subgroups by adjusted analysis			
Univariate	**6**	**1.35 (1.13, 1.62)**	**0%, 0.53**
Subgroups by type of publications			
Article	**2**	**1.63 (1.00, 2.65)**	**21.8%, 0.26**
Abstract	**4**	**1.26 (1.03, 1.62)**	**0%, 0.77**
Bacterial infections	**9**	**1.97 (1.55, 2.50)**	**47.5%, 0.06**
Subgroups by method of measurement			
PMA	**3**	**4.10 (2.57, 6.55)**	**0%, 0.82**
SMI	**6**	**1.63 (1.38, 1.91)**	**0%, 0.92**
Subgroups by geographical region			
Asia	**5**	**2.03 (1.44, 2.87)**	**52.5%, 0.08**
Europe/North America	**4**	**1.96 (1.30, 2.94)**	**55.2%, 0.08**
Subgroups by adjusted analysis			
Univariate	**6**	**1.98 (1.48, 2.66)**	**54.7%, 0.05**
Multivariate	**3**	**2.19 (1.15, 4.15)**	**52.2%, 0.12**
Subgroups by type of publications			
Article	**7**	**1.89 (1.44, 2.48)**	**47.7%, 0.08**
Abstract	**2**	**2.36 (1.22, 4.60)**	**62.4%, 0.10**
Viral infections	2	1.91 (0.41, 8.91)	65.3%, 0.09
Subgroups by method of measurement			
SMI	2	1.91 (0.41, 8.91)	65.3%, 0.09
Subgroups by geographical region			
Europe/North America	2	1.91 (0.41, 8.91)	65.3%, 0.09
Subgroups by adjusted analysis			
Univariate	2	1.91 (0.41, 8.91)	65.3%, 0.09
Subgroups by type of publications			
Article	1	0.82 (0.20, 3.35)	NC
Abstract	**1**	**3.99 (1.25, 12.69)**	**NC**
Fungal infections	**2**	**4.99 (1.60, 15.5)**	**0%, 0.56**
Subgroups by method of measurement			
SMI	**2**	**4.99 (1.60, 15.5)**	**0%, 0.56**
Subgroups by geographical region			
Europe/North America	**2**	**4.99 (1.60, 15.5)**	**0%, 0.56**

(Continues)

TABLE 4 | (Continued)

	n^a	RR (95% CI)	Heterogeneity (I^2, p)
Subgroups by adjusted analysis			
Univariate	**2**	**4.99 (1.60, 15.5)**	**0%, 0.56**
Subgroups by type of publications			
Article	1	2.68 (0.25, 29.09)	NC
Abstract	**1**	**5.98 (1.65, 21.69)**	**NC**

Note: Bold cells denote statistically significant associations.

Abbreviations: ALMI, appendicular lean mass index; LT, liver transplantation; NC, noncalculable; PMA, psoas muscle area; PMI, psoas muscle index; PMTH, psoas muscle thickness per height; PSMI, paraspinal muscle index; RR, relative risk; SMI, skeletal muscle index.

[a]Number of studies.

post-LT mortality and this was confirmed with the two most commonly used methods for sarcopenia evaluation, namely PMA and SMI. In addition, pooled studies utilizing PMI demonstrated a tendency toward increased post-LT mortality, which could be attributed to the small number of the included studies and the significant heterogeneity among them (I^2 = 85.8%). In addition, pre-LT sarcopenia was significantly associated with post-LT mortality, irrespective of the region, and increased 1.8 times in studies from Europe/North America and over two times in studies from Asia.

To date, there has been only one relevant systematic review/meta-analysis published in 2016 regarding the impact of pre-LT sarcopenia on LT outcomes [11]. This study, including 19 partly overlapping cohorts with 3803 patients, evaluated only studies with assessment of sarcopenia based on CT, meta-analysis was performed only on mortality, while other LT outcomes (such as infections, graft rejection, and overall complications) were discussed as part of a systematic review. Nevertheless, it was found [11] that pre-LT muscle mass was independently associated with post-LT mortality (HR = 1.84, 95% CI:1.11,3.05). In the literature, there are two additional relevant articles, both correlating pre-LT sarcopenia with worse LT outcomes [72, 73], but they evaluated either only the effect of sarcopenic obesity on post-LT mortality [72] or the impact of pre-LT sarcopenia on post-LT outcomes only as a systematic review without meta-analysis [73]

Considering the current allocation system in LT, our findings are of significant clinical importance, highlighting sarcopenia as an independent prognostic factor through a series of subgroup and meta-regression analyses. MELD, the urgency-based allocation system score used globally to triage patients based on waitlist mortality, has not been proven to be a robust predictor of post-LT survival [74]. However, variables with a clear correlation to post-LT outcomes may make the selection process more efficient and beneficial to patients and healthcare systems. Up until today, there were no predictors for outcomes after LT [75]. Our results are coming to fill this scientific and practical gap, highlighting sarcopenia as the first validated predictor of post-LT outcomes, possibly placing it at the center of future triaging processes. Sarcopenia has been thoroughly studied and validated as an independent predictor of increased mortality in patients with cirrhosis [76]. On that basis, sarcopenia indices have been combined with the MELD score to improve the prediction of mortality in LT candidates [77]. Since pre-LT sarcopenia, increases the risk of death and complications, both before and after LT, it raises a reasonable question: should it weight triaging toward prioritizing or excluding patients on the waitlist? Only future research can offer an answer by seeking the optimal cutoff value, where patients will have the greatest survival benefit and the least complications, both before and after LT. In this context sarcopenia could be proven to be the missing link in creating a universal score, weighting both waitlist and post-LT outcomes.

Moreover, our results highlight the significance of pre-LT sarcopenia on secondary clinical post-LT outcomes. Sarcopenic patients with cirrhosis demonstrated increased overall, bacterial, and fungal, as well as a tendency of increased viral infections after LT. Although the literature has not established causality between sarcopenia and infections, our results can be explained through the emerging role of skeletal muscle as a potent regulator of the immune system function [78]. Muscle immune signaling pathways function through soluble myokines with autocrine, paracrine, and endocrine activity on numerous tissues, expression of immune modulatory cell-surface molecules, and muscle-immune cell interactions, which regulate muscle regeneration through inflammatory processes [78]. Consequently, the reduction of muscle mass could lead to impaired immunological processes (NK cells and T-cells regulation, neutrophil migration and phagocytosis, T- and B- lymphocytes development), the establishment of a malfunctioning pro-inflammatory environment, and be the main driver of immune senescence in sarcopenic patients [78] leading to an impaired ability toward infections. Interestingly, previous studies have demonstrated a glutamine deficiency in sarcopenic patients and have proposed a concept of higher susceptibility to infections in sarcopenic recipients due to increased intestinal wall permeability [79].

Based on our findings, patients with cirrhosis and sarcopenia experienced a greater number of days in the ICU but no significant difference in the overall hospital LOS after the operation for LT. The need for prolonged mechanical ventilation post-LT in patients with pre-LT sarcopenia in previous studies [17] could explain our results. Additionally, we could not establish an effect of pre-LT sarcopenia on liver graft survival and rejection rates. Interestingly, although no difference was observed in the need for RBC transfusions, sarcopenic patients had a small but significantly increased need for FFP transfusions during operation for LT. In vitro studies have demonstrated the importance of myosin, a skeletal muscle protein, in hemostasis [80]. This could justify the increased need for pro-thrombotic factors during LT in

TABLE 5 | Results of the meta-analyses examining the association between sarcopenia and LOS in the ICU and the Hospital, after LT; subgroup analyses.

	n^a	SMD (95% CI)	Heterogeneity (I^2, p)
ICU stay	**13**	**0.41 (0.17, 0.66)**	**86.1%, <0.001**
Subgroups by method of measurement			
PMA	**3**	**0.56 (0.17, 0.95)**	**58.4%, 0.09**
PMI	**1**	**0.38 (0.07, 0.68)**	**NC**
PMTH	**1**	**1.27 (0.98, 1.56)**	**NC**
PSMI	**1**	**0.47 (0.26, 0.67)**	**NC**
SMI	7	0.22 (−0.11, 0.54)	83.6%, <0.001
Subgroups by geographical region			
Africa	1	0.00 (−0.40, 0.40)	NC
Asia	4	0.53 (−0.29, 1.36)	93.6%, <0.001
Europe/North America	**8**	**0.36 (0.20, 0.53)**	**58.6%, <0.05**
Subgroups by adjusted analysis			
Univariate	**13**	**0.41 (0.17, 0.66)**	**86.1%, <0.001**
Subgroups by type of publications			
Article	**10**	**0.52 (0.24, 0.80)**	**87.3%, <0.001**
Abstract	**3**	**0.07 (−0.15, 0.30)**	**6.2%, 0.35**
Hospital stay	14	0.15 (−0.04, 0.33)	77.1%, <0.001
Subgroups by method of measurement			
PMA	4	−0.05 (−0.24, 0.13)	0%, 0.64
PMI	2	0.56 (−0.03, 1.15)	86.4%, <0.05
PMTH	1	−0.18 (−0.44, 0.08)	NC
SMA	1	0.17 (−0.07, 0.40)	NC
SMI	6	0.17 (−0.13, 1.47)	78.2%, <0.001
Subgroups by geographical region			
Africa	**1**	**0.74 (0.33, 1.15)**	**NC**
Asia	4	−0.17 (−0.47, 0.14)	67.7%, 0.03
Europe/North America	**9**	**0.23 (0.03, 0.42)**	**71.2%, <0.05**
Subgroups by adjusted analysis			
Univariate	14	0.15 (−0.04, 0.33)	77.1%, 0.00
Subgroups by type of publications			
Article	10	0.11 (−0.08, 0.30)	72.7%, 0.00
Abstract	4	0.23 (−0.24, 0.70)	83.4%, 0.00

Note: Bold cells denote statistically significant associations.

Abbreviations: ALMI, appendicular lean mass index; LOS, length of stay; LT, liver transplantation; NC, noncalculable; PMA, psoas muscle area; PMI, psoas muscle index; PMTH, psoas muscle thickness per height; PSMI, paraspinal muscle index; RR, relative risk; SMD, standardized mean difference; SMI, skeletal muscle index.

[a]Number of studies

sarcopenic patients. Finally, Clavien-Dindo, a score developed to reflect short-term postoperative complications, was significantly increased in sarcopenic patients, reflecting the higher overall risk for complications perioperatively of sarcopenic patients.

Our analysis has some limitations. Increased heterogeneity between the studies could be attributed to differences such as geographical region, population size, definition, method, and cut-off used for sarcopenia. In an attempt to trace its origins, we conducted a series of subgroup and meta-regression analyses. Additionally, although modern sarcopenia definitions encompass functional factors, in hepatology, most studies have operationalized sarcopenia as a loss of muscle mass [81]. The main reason is that functional measurements remain widely undefined and thus difficult to group. Consequently, they were excluded from our analysis in an effort to perform a comprehensive systematic review and meta-analysis. Accordingly, myosteatosis, a promising index of muscle quality, correlated with clinically significant

events in cirrhosis [82], was not evaluated in our analysis regarding post-LT outcomes.

Sarcopenia, although an independent disorder, is also a component of the broader entity of patient fitness [83]. Physical fitness is a theoretical construct hard to evaluate but includes a set of attributes, either health-related (cardiorespiratory and muscular endurance, muscular strength, body composition, flexibility) or skill-related (agility, balance, coordination, speed, power, reaction time) that can be operationalized and measured [84]. The five health-related components are considered to play a significantly larger role in public health than the skill-related. Thus, clinical practice and research have focused on them. Nevertheless, in patients with cirrhosis, physical fitness has been addressed mainly through sarcopenia, frailty, and malnutrition [83, 84], which, although independent, are interconnected and often recognized simultaneously in clinical practice [85]. Malnutrition is the state that results from a pathological intake or uptake of nutrients followed by altered body composition, leading to diminished physical and mental function, and impaired clinical outcomes [86]. In the general population, easy-to-use food diaries and body composition assessments with anthropometric and laboratory indices are used to evaluate nutrition status, such as weight, BMI, body circumferences, skin folds, and serum albumin. However, in patients with cirrhosis, these measurements offer low accuracy and precision [87, 88]. Nevertheless, nutrition should be evaluated in all patients with cirrhosis [89] and two easy-to-use liver disease-specific tools for initial screening, are the Royal Free Hospital-nutritional prioritizing tool and the liver disease undernutrition screening tool [89]. In patients with cirrhosis at high risk for malnutrition, detailed nutritional assessment should be performed, as well as muscle mass and strength evaluation [89], while adverse physical effects of malnutrition are most commonly manifested phenotypically as frailty or sarcopenia [85].

Current liver research, to evaluate patient status and muscle health has indeed focused on sarcopenia, as well as on frailty [90], both powerful predictors of clinical outcomes [91]. Frailty, although not evaluated in our analysis, is contemporarily studied with sarcopenia in the literature since the question of whether one of the two or a combination of both offers a better predictive value in the LT setting. The European and the American associations of liver diseases have operationalized the definitions of frailty and sarcopenia in the context of hepatology [85, 86]. Frailty, as a global construct with its roots in geriatrics, was defined as the clinical state of decreased physiologic reserve and increased vulnerability to health stressors. In the context of cirrhosis, it has been replaced by "*physical* frailty," the clinical manifestations of impaired muscle contractile function [85]. Tools commonly used to asses frailty are the Fried Frailty Index and the Clinical Frail Scale which have been studied in cirrhotic patients, but the Liver Frailty Index is the only one developed specifically for patients with cirrhosis [92]. Other metrics used are the Karnofsky Performance Status scale, the Activities of Daily Living scale, the Short Physical Performance Battery test, the 6-minute walk test (6MWT), and short gait speed or grip strength [81]. Most of these tools are performance-based metrics. They necessitate active patient participation, limiting their use in severely ill LT candidates, or early after LT [81]. The loss of muscle mass is operationally represented in hepatology by sarcopenia. Primarily measured through cross-sectional imaging indexes (CT, MRI), it can serve as a more objective parameter [85]. Other metrics used for sarcopenia, have questionable reliability. DXA and bioelectrical impedance analysis are influenced by fluid retention, and anthropometrics lack precision and accuracy [85]. Thus, cross-sectional measures of sarcopenia, although costly and not readily available in everyday practice, are the most reliable and objective tools for muscle mass, while many frailty tools are quick, simple, and easily repeatable in the ambulatory setting. Therefore, the choice of measuring sarcopenia, frailty, or both should be individualized in each clinical scenario [85].

Despite the limitations, this meta-analysis has important strengths. Our updated search was performed in six online databases that cover almost entirely the biomedical literature, and it was not subject to any restriction. A broad search algorithm combined with a rigorous data collection process was implemented. The aforementioned was empowered by the inclusion of all eligible conference abstracts, eliminating significant publication bias, and at the same time maintaining data of high quality, with all studies included being of good/high quality. A satisfactory number of studies were included from Europe/North America, and Asia, providing our findings with external generalizability. Additionally, our meta-regression analysis demonstrated that confounding factors did not influence our results, while our sub analyses explored potential pathways of sarcopenia's effect on LT, which were lacking in previous relevant studies [11].

5 | Conclusion

In conclusion, our systematic review/meta-analysis including the largest number of patients and different methods for sarcopenia evaluation highlights the impact of pre-LT sarcopenia on peri- and post-LT outcomes. Sarcopenia should contribute to pre-LT risk assessment and gain a significant role as a unique modifiable factor in advanced liver diseases. Additional prospective studies are needed to clarify better the exact impact of sarcopenia and its changes in LT candidates on post-LT outcomes.

Author Contributions

George E. Markakis: concept/design, data analysis/interpretation, drafting article, and approval of article. Jennifer C. Lai: critical revision of article and approval of article. Nikolaos D. Karakousis: data collection and approval of article. George V. Papatheodoridis: critical revision of article and approval of article. Theodora Psaltopoulou: statistics, critical revision of article, and approval of article. Manuela Merli: critical revision of article and approval of article. Theodoros N. Sergentanis: statistics, critical revision of article, and approval of article. Evangelos Cholongitas: concept/design, critical revision of article, and approval of article.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article

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Supporting Information

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