Research article
Cirrhosis and Liver Failure

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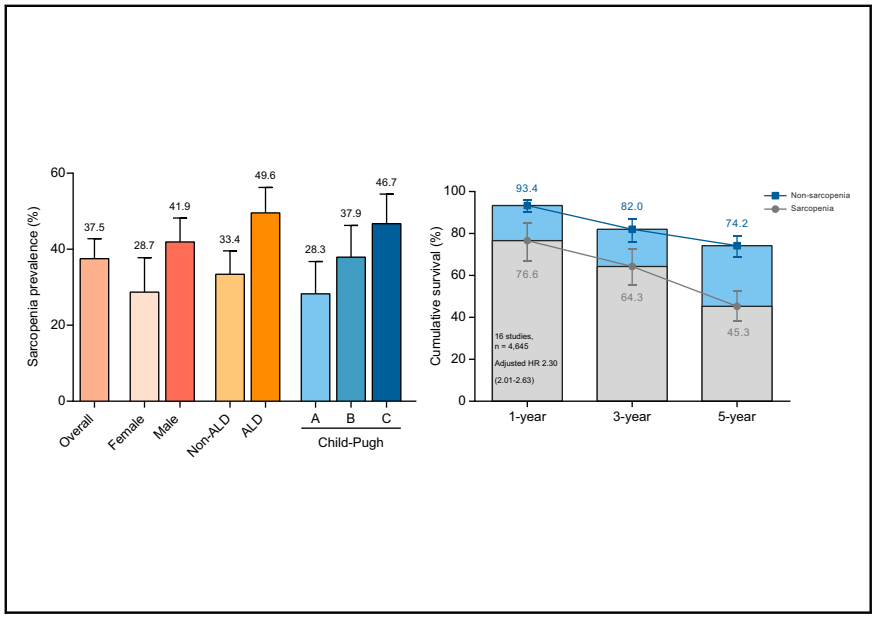
Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis

Graphical abstract



Highlights

- The overall prevalence of sarcopenia among patients with cirrhosis is 37.5%, with higher prevalence in males, patients with alcohol-related liver disease, and greater severity of cirrhosis.
- The 1-, 3-, and 5-year cumulative probabilities of survival in patients with sarcopenia were 76.6%, 64.3%, and 45.3%, respectively. By comparison, they were 93.4%, 82.0%, and 74.2%, respectively in patients without sarcopenia
- Sarcopenia is associated with an approximately 2-fold higher risk of death in patients with cirrhosis
- Every 1 cm^2/m^2 increase in L3-SMI and 1 mm/m increase in umbilicus-TPMT were associated with a 3% and 12% decrease in mortality risk, respectively.

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Lay summary

The prevalence of sarcopenia and its association with death in patients with cirrhosis remain unclear. This meta-analysis indicated that sarcopenia affected about one-third of patients with cirrhosis and up to 50% of patients with alcohol-related liver disease or Child-Pugh class C cirrhosis. Sarcopenia was independently associated with an ~2-fold higher risk of mortality in patients with cirrhosis. The mortality rate increased with greater severity or longer durations of sarcopenia. Increasing awareness about the importance of sarcopenia in patients with cirrhosis among stakeholders must be prioritized.

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Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis

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Background & Aims: The association between sarcopenia and prognosis in patients with cirrhosis remains to be determined. In this study, we aimed to quantify the association between sarcopenia and the risk of mortality in patients with cirrhosis, stratified by sex, underlying liver disease etiology, and severity of hepatic dysfunction.

Methods: PubMed, Web of Science, EMBASE, and major scientific conference sessions were searched without language restriction through 13 January 2021 with an additional manual search of bibliographies of relevant articles. Cohort studies of ≥100 patients with cirrhosis and ≥12 months of follow-up that evaluated the association between sarcopenia, muscle mass and the risk of mortality were included.

Results: Twenty-two studies involving 6,965 patients with cirrhosis were included. The pooled prevalence of sarcopenia in patients with cirrhosis was 37.5% overall (95% CI 32.4%-42.8%), and was higher in male patients, those with alcohol-associated liver disease, those with Child-Pugh grade C cirrhosis, and when sarcopenia was defined by L3-SMI (third lumbar-skeletal muscle index). Sarcopenia was associated with an increased risk of mortality in patients with cirrhosis (adjusted hazard ratio [aHR] 2.30, 95% CI 2.01-2.63), with similar findings in a sensitivity analysis of patients with cirrhosis without hepatocellular carcinoma (aHR 2.35, 95% CI 1.95-2.83) and in subgroups stratified by sex, liver disease etiology, and severity of hepatic dysfunction. The association between quantitative muscle mass

Keywords: sarcopenia; skeletal muscle index; alcohol-associated liver disease; cirrhosis; prognosis.
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index and mortality further supports the association between sarcopenia and poor prognosis (aHR 0.95, 95% CI 0.93-0.98). There was no significant heterogeneity in any of our analyses.
Conclusions: Sarcopenia was highly and independently associated with higher risk of mortality in patients with cirrhosis.
Lay summary: The prevalence of sarcopenia and its association with death in patients with cirrhosis remain unclear. This meta-analysis indicated that sarcopenia affected about one-third of patients with cirrhosis and up to 50% of patients with alcohol-related liver disease or Child-Pugh class C cirrhosis. Sarcopenia was independently associated with an ~2-fold higher risk of mortality in patients with cirrhosis. The mortality rate increased with greater severity or longer durations of sarcopenia. Increasing awareness about the importance of sarcopenia in patients with cirrhosis among stakeholders must be prioritized.

Introduction

Cirrhosis is the end stage of various chronic liver diseases. The prognosis of cirrhosis varies according to the severity of hepatic dysfunction, with a median survival time of about 12 years in patients with compensated cirrhosis and about 1.8 years in those with hepatic decompensation.[1] Prognostic assessment of patients with cirrhosis is critical but remains challenging and is generally performed in routine practice using the Child-Pugh and the model for end-stage liver disease (MELD) scores.[2] However, the Child-Pugh grading system includes subjective variables, such as encephalopathy and ascites, limiting its reproducibility and reliability.[3] Meanwhile, initially designed for assessing survival after a transjugular intrahepatic portosystemic shunt (TIPS) procedure, the MELD score includes only objective laboratory parameters, but its performance may also be inaccurate in about 15% to 20% of patients with cirrhosis.[4] In addition, both scoring systems lack important parameters that reflect the nutritional and functional status of patients with cirrhosis.

Indeed, a common but often overlooked complication in patients with cirrhosis is malnutrition and associated sarcopenia, defined as the generalized loss of muscle mass and muscle function.[5] Due to poor protein intake, malabsorption, reduced muscle formation, and increased muscle breakdown, up to 30-70% of patients with end-stage liver disease suffer from sarcopenia, with a higher prevalence among males.[6–11] The presence of sarcopenia has been shown to be associated with increased risk of falls, fractures, reduced quality of life, development of acute decompensation or acute-on-chronic liver failure, and death in patients with cirrhosis.[6–9,12–14] The impact of sarcopenia in patients with cirrhosis may also be influenced by sex, severity of hepatic dysfunction, and etiology of cirrhosis.[10–13,15,16]

Between 2016 and 2019, 3 meta-analyses evaluating the effect of muscle mass or sarcopenia on the survival of patients with cirrhosis and those on the liver transplant (LT) waiting list were published.[17–19] However, since then, newer data from several large and rigorously designed studies with long-term follow-up became available. Prior meta-analyses on this topic were also limited by inclusion of articles with overlapping populations, analyses with severe heterogeneity, limited subgroup analyses and/or lack of meta-regression analyses to explore the source of heterogeneity, limiting their study interpretation and conclusions.[17–19]

Therefore, we performed an updated and more comprehensive systematic review and meta-analysis to assess the impact of sarcopenia on survival of patients with cirrhosis, with a larger sample size and without overlapping cohorts. Our primary goal was to estimate the risk of mortality in patients with cirrhosis who were affected by sarcopenia. Our secondary aims were to estimate the pooled prevalence of sarcopenia in patients with cirrhosis. We also conducted detailed subgroup analyses to determine the distribution of sarcopenia and risk of mortality with sarcopenia stratified by sex, severity of hepatic dysfunction, and etiology of cirrhosis.

Materials and methods

Search strategy and selection criteria

This meta-analysis was performed in accordance with the updated PRISMA (2020) and MOOSE guidelines,[20–22] and its protocol was registered on PROSPERO (CRD42021229225). We searched PubMed, Embase, and Web of Science from inception to Jan 13, 2021 and without language restriction to identify relevant full-text studies which examined the association between sarcopenia or muscle mass and mortality (or waitlist mortality) in patients with cirrhosis.

The search keywords included cirrhosis, sarcopenia, muscle mass, muscle function, prognosis, study type, and the search strategy were developed by consultation with a medical librarian (JZ). Table S1 exhibits the search strategies for all included databases. We restricted the search to human studies. We also reviewed conference abstracts of the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asian-Pacific Association for the Study of Liver Diseases (APASL), Digestive Disease Week (DDW), and Asia Pacific Digestive Week (APDW) in 2019-2020 to look for additional potential studies. Lastly, we searched for potential studies by manually going through the reference lists of included studies and relevant reviews. XT and YL independently completed the title/abstract screening for eligibility using a pre-planned list of inclusion/exclusion criteria (Appendix 2), with discrepancies resolved by consensus or discussion with either JW or FJ. For studies with overlapping cohorts, we included the one with more recent data, larger sample size, and/or more data available for subgroup analysis.

Data extraction and quality assessment

We used a standardized extraction form to abstract data from each included study. The following information was extracted independently by 2 reviewers (XT and YL): the first author's name, year of publication, study design, study location, inclusion and exclusion criteria, source of cirrhosis cohort (transplant wait listed or general), definition of sarcopenia, methods of measuring muscle mass or muscle function, number of participants, and patient demographics and clinical characteristics including age, sex, etiology of cirrhosis, liver function, presence of hepatocellular carcinoma (HCC), duration of follow-up, adjusted variables, and relevant outcomes. If relevant data were not readily accessible, authors were contacted to obtain additional data and/or clarification.

The quality of included studies was also scored by at least 2 authors (XT, YL, NL and ZL) independently using a scale based on the Newcastle-Ottawa scale (NOS),[23] with disagreements

resolved by consensus or discussion with a third author (YHY, JW or FJ). The detail of assessment is described in Appendix 3. The GRADE approach was used to assess the evidence on prognosis.[24]

Statistical analysis

The prevalence of sarcopenia was pooled using a meta-analysis of single proportions. Subgroup data were provided according to method used to define sarcopenia, sex, severity of liver disease and etiology of cirrhosis. The differences between 2 groups were tested using the random-effects meta-regression method.

The primary outcome of this meta-analysis was mortality (or waitlist mortality) risk of sarcopenia in patients with cirrhosis. The impact of sarcopenia on the incidence of death was evaluated by the pooled unadjusted HR or adjusted HR and 95% CIs using random effects modelling (DerSimonian-Laird Method) with heterogeneity across studies assessed by the I^2 and the Cochran's Q statistic. P value of Q statistic ≤0.1 or I^2 ≥50% was defined as significant heterogeneity. Pre-planned subgroup analyses were carried out according to sex, severity of liver disease, etiology of cirrhosis, study location, study design, source of cirrhosis cohort, methods for measuring muscle mass, and risk of bias. We also pooled 1-year, 3-year, and 5-year cumulative mortality for patients with sarcopenia and patients without sarcopenia using the Freeman-Tukey double arcsine transformation method.[25] The association between quantitative muscle mass index and risk of death was also assessed.

Meta-regression was used to determine the effect of sample size, participants' average age, proportion of males, proportion of patients with alcohol-associated liver disease (ALD), average follow-up time, and number of confounding factors being adjusted on the pooled adjusted HR.

We performed sensitivity analysis by excluding studies that included patients with HCC. Since the HRs from Cox-proportional hazard regression, as opposed to competing risk analysis, may overestimate the risk of death, especially in patients being waitlisted for LT,[26] we conducted a sensitivity

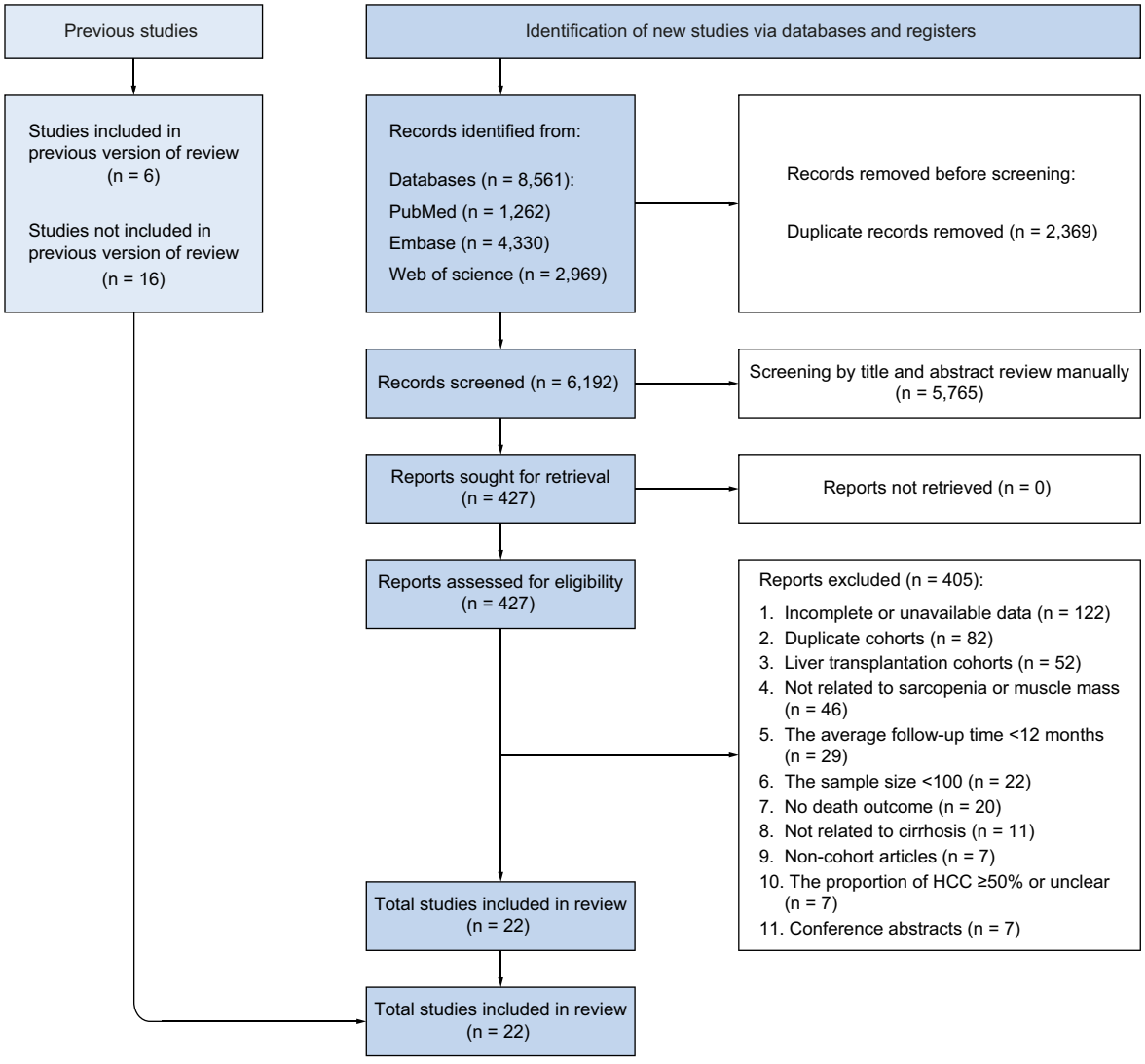

Fig. 1. PRISMA flow diagram of search strategy.

Table 1. Summary characteristics of included studies.

Author (year)	Study design	Source of cirrhosis cohort	Methods for measuring muscle mass	Definition of sarcopenia	Country	Sample size	Mean age, years	Male%	ALD%	HCC, %	Follow-up, months
Praktiknjo *et al.* 2019[13]	Prospective	General patients	CT: umbilicus-TPMT	umbilicus-TPMT <17.8 mm/m in men <14.0 mm/m in women	Germany	186	56.0	58.6	69.4	NO	25.0
Kang *et al.* 2018[15]	Retrospective	Patients evaluated for LT	CT: L3-SMI	L3-SMI ≤52.4 cm^2/m^2 in men, ≤38.5 cm^2/m^2 in women	Korea	452	51.9	83.8	69.2	NO	21.2
van Vugt *et al.* 2018[26]	Prospective	Patients listed for LT	CT: L3-SMI	L3-SMI <43 cm^2/m^2 in men with BMI <25 or <53 cm^2/m^2 in men with BMI ≥25, and <41 cm^2/m^2 in women	Netherlands	585	56.0	69.1	15.6	33.0	54.0
Beer *et al.* 2020[28]	Retrospective	General patients	MRI: L3-TPMT	L3-TPMT <12 mm/m in men, <8 mm/m in women	Austria	209	58.0 *vs.* 59.0	65.6	23.0	NO	30.2
Belarmino *et al.* 2021[29]	Retrospective	General patients	DXA: ASMI	DXA-ASMI ≤7 kg/m^2 and ND-HGS ≤25 kg	Brazil	124	n.a.	100.0	n.a.	NO	≥12
Hamaguchi *et al.* 2020[30]	Retrospective	Patients listed for LT	CT: L3-SMI	L3-SMI <40.31 cm^2/m^2 in men, <30.88 cm^2/m^2 in women	Japan	173	50.0	56.1	n.a.	8.0	24.3
Hanai *et al.* 2015[31]	Retrospective	General patients	CT: L3-SMI	L3-SMI ≤52.4 cm^2/m^2 in men, ≤38.5 cm^2/m^2 in women	Japan	130	66.0	58.5	22.3	NO	33.0
Hiraoka *et al.* 2018[32]	Retrospective	General patients	CT: L3-PMI	L3-PMI <4.24 cm^2/m^2 in men, <2.50 cm^2/m^2 in women	Japan	346	68.3	59.0	13.3	34.0	35.7
Hou *et al.* 2020[33]	Retrospective	General patients	CT: L3-SMI	L3-SMI ≤46.96 cm^2/m^2 in men, ≤32.46 cm^2/m^2 in women	China	274	62.2	52.6	21.1	NO	36.0
Jeong *et al.* 2018[34]	Retrospective	General patients	CT: L3-SMI	L3-SMI ≤52.4 cm^2/m^2 in men, ≤38.5 cm^2/m^2 in women	Korea	131	53.7	71.8	69.5	NO	46.2
Lattanzi *et al.* 2019[35]	Retrospective	General patients	CT: L3-SMI	L3-SMI <50 cm^2/m^2 in men, <39 cm^2/m^2 in women	Italy	249	60.0	76.3	32.0	45.0	15.1
Mauro *et al.* 2020[36]	Retrospective	Patients listed for LT	CT or MRI: L3-SMI	L3-SMI <50 cm^2/m^2 in men, <39 cm^2/m^2 in women	Argentina	144	59.0	60.0	27.8	11.7	13.0
Sinclair *et al.* 2019[37]	Retrospective	Patients evaluated for LT	DXA: APLM	APLM <7.26 kg/m^2 in men	Australia	420	55.4	100.0	12.6	28.3	58.5
Wang CW *et al.* 2016[38]	Prospective	Patients listed for LT	CT: L3-SMI	L3-SMI <43 cm^2/m^2 in men with BMI <25 or <53 cm^2/m^2 in men with BMI ≥25, and <41 cm^2/m^2 in women	USA	292	61.0	66.1	11.0	46.0	15.0
Wang NC *et al.* 2020[39]	Prospective	General patients	CT: L4-PMI	L4-PMI <7.8 cm^2/m^2 in men, <6.4 cm^2/m^2 in women	USA	254	57.3	56.3	20.5	NO	62.4
Engelmann *et al.* 2018[40]	Retrospective	Patients listed for LT	CT: L3/L4-SMI	L3/L4-SMI <41.90 cm^2/m^2 in men, <35.30 cm^2/m^2 in women	Germany	711	53.7	70.6	62.0	21.8	12.0

(*continued on next page*)

Table 1. (*continued*)

Author (year)	Study design	Source of cirrhosis cohort	Methods for measuring muscle mass	Definition of sarcopenia	Country	Sample size	Mean age, years	Male%	ALD%	HCC, %	Follow-up, months
Nishikawa *et al.* 2017[41]	Retrospective	General patients	BIA: SMI	SMI <7.0 cm^2/m^2 in men, <5.7 cm^2/m^2 in women	Japan	382	66.0	53.4	n.a.	NO	38.4
Ruiz-Margáin *et al.* 2021[42]	Ambispective	General patients	CT: L3-SMI or BIA	L3-SMI ≤50 cm^2/m^2 in men, ≤39 cm^2/m^2 in women; PhA ≤5.6°in men, ≤5.4°in women	Mexico and USA	136	54.5	39.7	8.8	11.1	27.0
Gu *et al.* 2018[43]	Retrospective	General patients	CT: L3-SMI or umbilicus-TPMT	L3-SMI ≤52.4 cm^2/m^2 in men ≤38.5 cm^2/m^2 in women; umbilicus-TPMT ≤17.3 mm/m in men ≤10.4 mm/m in women	Korea	653	53.6	76.4	49.9	NO	≥12
Ebadi *et al.* 2018[44]	Retrospective	Patients listed for LT	CT: L3-SMI or PMI	L3-SMI <50 cm^2/m^2 in men <39 cm^2/m^2 in women; L3-PMI <5.1 cm^2/m^2 in men,<4.3 cm^2/m^2 in women	Canada	353	56.0	69.7	n.a.	41.0	≥12
Durand *et al.* 2014[45]	Retrospective	Patients listed for LT	CT: umbilicus-TPMT	umbilicus-TPMT ≤16.8 mm/m	France	562	53.0	81.0	42.0	46.0	≥12
Xiao *et al.* 2020[46]	Retrospective	General patients	BIA: ASMI	ASMI: <7.0 kg/m^2 in men, <5.7 kg/m^2 in women	China	199	55.8	74.8	29.1	NO	36.0

ALD, alcohol-associated liver disease; APLM, appendicular lean mass; ASMI, appendicular skeletal muscle mass(kg)/height (m^2); BIA, bioimpedance analysis; DXA, dual-energy x-ray absorptiometry; HCC, hepatocellular carcinoma; L3, 3rd lumbar vertebra; L4, 4th lumbar vertebra; LT, liver transplantation; n.a., not available; ND-HGS, nondominant handgrip strength; PhA, phase angle; PMI, psoas muscle index; SMI, skeletal muscle index; TPMT, transverse psoas muscle thickness.

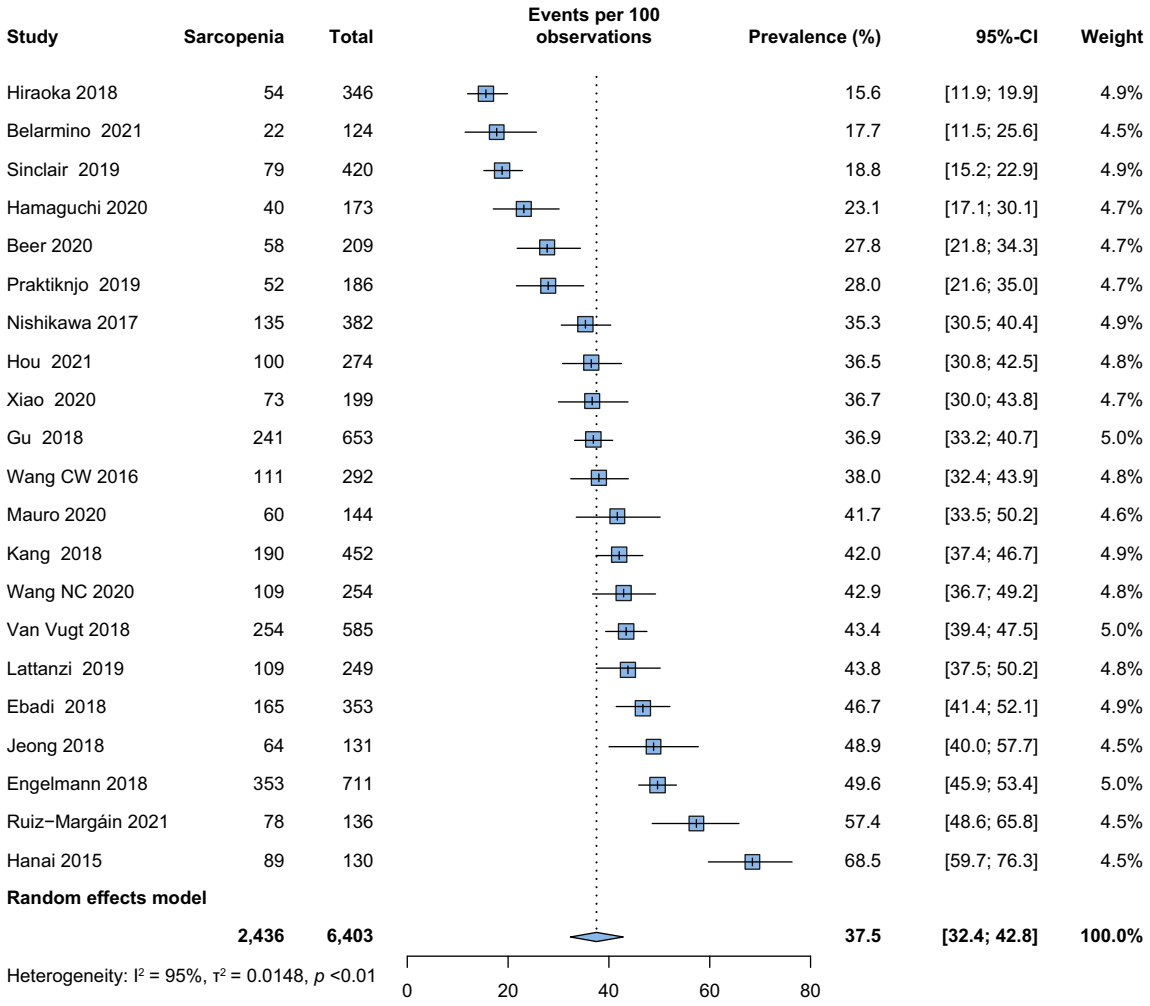

Fig. 2. The pooled overall prevalence of sarcopenia in patients with cirrhosis in the included studies.

analysis on studies which used the competing risk model and pooled the subdistribution hazard ratio.

Publication bias was evaluated using the funnel plot and Egger's and Begg's test. Given that potential publication bias was indicated, the trim-and-fill method was used to observe the change in pooled estimates following imputation of data from potentially unpublished articles.[27] Two-sided p <0.05 were considered statistically significant, and *meta* package in R software (version 4.0.2) was used for all statistical analyses.

Results

Study retrieval, characteristics of included studies, and prevalence of sarcopenia

Of the 8,561 records identified from the initial search, 2,369 duplicates and 5,765 ineligible titles/abstracts were excluded. Of the remaining 427 articles that underwent full-text review, we included 22 cohort studies with data on 6,965 patients (Fig. 1).[13,15,26,28–46] We also contacted authors of 26 studies and obtained detailed data from 7 of these studies for subgroup analyses.[13,26,30,34,36,39,40]

Table 2. Pooled 1, 3, 5-year cumulative probabilities of survival in patients with cirrhosis with and without sarcopenia, overall and in subgroup without hepatocellular carcinoma.

Survival (% and 95% CI)	With sarcopenia	Without sarcopenia	*p* value
All patients			
1-year survival	76.6 (66.4-85.5); 14 studies, 1,432 patients	93.4 (90.1-96.2); 14 studies, 2,483 patients	<0.001
3-year survival	64.3 (55.0-73.0); 11 studies, 1,131 patients	82.0 (75.9-87.4); 11 studies, 1,934 patients	<0.001
5-year survival	45.3 (37.9-52.7); 7 studies, 699 patients	74.2 (68.7-79.3); 7 studies, 1,205 patients	<0.001
Subgroup of patients without hepatocellular carcinoma			
1-year survival	79.5 (66.4-90.1); 9 studies, 1,121 patients	94.7 (91.6-97.2); 9 studies, 1,575 patients	0.002
3-year survival	68.1 (59.0-76.5); 8 studies, 959 patients	84.4 (79.1-89.1);8 studies, 1,451 patients	<0.001
5-year survival	46.6 (38.7-54.6); 6 studies, 645 patients	74.2 (67.2-80.6);6 studies, 913 patients	<0.001

The *p* value were produced using the random-effects meta-regression method.

Table 1 summarizes the characteristics of all studies included in this meta-analysis. Overall, 9 of the 22 included studies were from Asia,[15,30–34,41,43,46] and 13 studies were from non-Asian regions.[13,26,28,29,35–40,42,44,45] Seventeen of the 22 studies were retrospective cohort studies,[15,28–37,40,41,43–46] 4 studies were prospective cohort studies,[13,26,38,39] and one cohort study included both retrospective and prospective components.[42] The sample size of the included studies ranged from 124 to 711. The mean age of patients ranged from 50.0 to 68.3 years among the included studies. Ten studies excluded all patients with HCC,

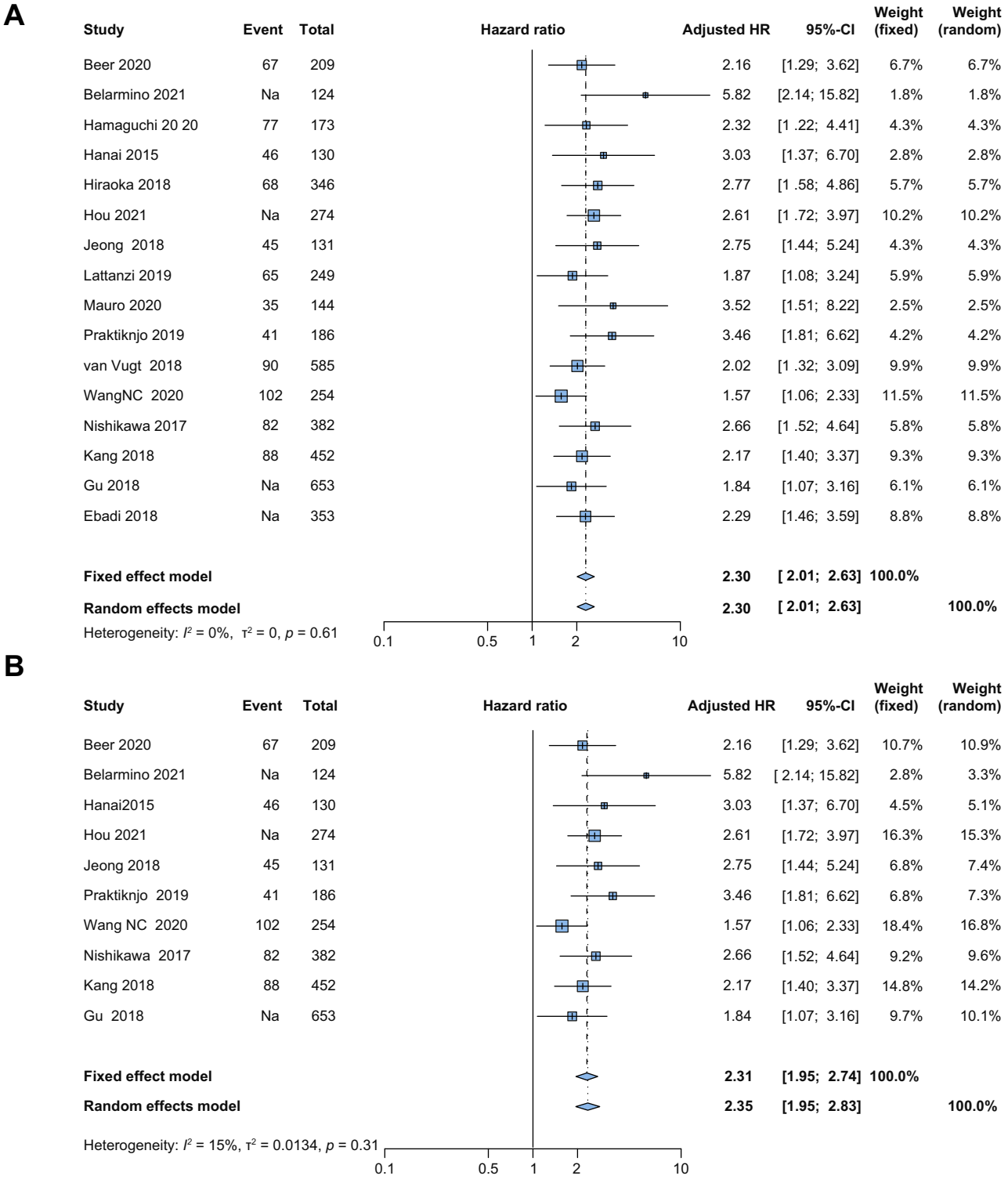

Fig. 3. Forest plot for multivariate analysis assessing association between sarcopenia and the risk of mortality. (A) The association was assessed in all included studies; (B) The association was assessed in studies without HCC. HCC, hepatocellular carcinoma; HR, hazard ratio.

while 8%-46% of patients had HCC in 12 studies. All studies were rated as high quality with NOS score ≥7 (Table S2).

Prevalence data for sarcopenia were available in 21 of the 22 included studies (n = 6,403), yielding a pooled prevalence of 37.5% (95% CI 32.4%-42.8%) (Fig. 2). Subgroup analysis by definitions of sarcopenia showed significant variation among the subgroups. The prevalence of sarcopenia was 44.4% (95% CI 39.0%-50.0%) when defined by third lumbar-skeletal muscle index (L3-SMI), 30.8% (95% CI 25.5%-36.4%) by L3/umbilicus-transverse psoas muscle thickness (TPMT), 26.4% (95% CI 13.0%-42.4%) by L3/L4-psoas muscle index, and 26.8% (95% CI 17.3%-37.5%) by other definitions (Fig. S1). There was a higher pooled prevalence of sarcopenia in male patients (41.9%, 95% CI 35.8%-48.2%, n = 3,141) compared to female patients (28.7%, 95% CI 20.5%-37.8%, n = 1,590, p = 0.012) (Fig. S2). The prevalence was also significantly higher in patients with ALD compared to those with other liver disease etiologies (49.6%, 95% CI 42.9%-56.3%, n = 1,219 *vs.* 33.4%, 95% CI 27.4%-39.6%, n = 2,166, p <0.001) (Fig. S3). Finally, patients with Child-Pugh class C cirrhosis also had a higher prevalence (46.7%, 95% CI 39.0%-54.5%, n = 585) than those with Child-Pugh class B (37.9%, 95% CI 29.9%- 46.3%, n = 1,320) or A (28.3%, 95% CI 20.5%-36.8%, n = 1,143) (p = 0.007) cirrhosis (Fig. S4).

Cumulative survival in patients with and without sarcopenia

The 1-, 3-, and 5-year cumulative probabilities of survival in patients with sarcopenia were 76.6% (95% CI 66.4%-85.5%), 64.3% (95% CI 55.0%-73.0%), and 45.3% (95% CI 37.9%-52.7%), respectively (Table 2). By comparison, they were 93.4% (95% CI 90.1%-96.2%), 82.0% (95% CI 75.9%-87.4%), and 74.2% (95% CI 68.7%-79.3%), respectively in patients without sarcopenia (all p <0.001). We also performed sensitivity analysis by excluding patients with HCC and found similar results (Table 2).

Association between sarcopenia and mortality

Analysis of the overall cohort

From 13 studies (n = 3,995) that provided data on univariate analysis, sarcopenia was associated with an increased risk of mortality, with a pooled unadjusted HR of 2.61 (95% CI 2.28-2.98). The heterogeneity between studies was very low (I^2=0%, p = 0.75) (Fig. S5). In data from multivariate analysis, sarcopenia remained significantly associated with increased mortality with a pooled adjusted HR of 2.30 (95% CI 2.01-2.63) (16 studies, n = 4,645) and also with very low likelihood of heterogeneity between studies (I^2=0%, p = 0.61) (Fig. 3A). The level evidence was low according to GRADE (Table S3).

Sensitivity analysis

In our sensitivity analysis focusing only on studies that excluded patients with HCC (10 studies, n = 2,795), we found the pooled adjusted HR of mortality was similar to that of the main analysis at 2.35 (95% CI 1.95-2.83) and with very low heterogeneity (I^2 = 15%, p = 0.31) (Fig. 3B). In another sensitivity analysis of only studies that analyzed mortality risk using the competing risk

Subgroup	No. of studies	No. of patients	Adjusted HR (95% CI)	I^2(%)	$P_{heterogeneity}$
Sex					
Male	7	898	2.46 (1.86-3.25)	0	0.52
Female	6	467	2.16 (1.24-3.78)	49	0.08
Etiology of cirrhosis					
ALD	4	306	2.67 (1.60-4.47)	22	0.28
Non−ALD	5	577	2.09 (1.34-3.26)	32	0.21
Severity of liver dysfunction					
MELD <15	6	1,057	2.34 (1.78-3.09)	0	0.51
MELD ≥15	6	481	1.55 (1.15-2.09)	0	0.61
Study location					
Asia	8	2,541	2.44 (2.01-2.96)	0	0.95
Non−Asia	8	2,104	2.25 (1.79-2.84)	30	0.19
Study design					
Prospective	3	1,025	2.08 (1.40-3.09)	52	0.12
Retrospective	13	3,620	2.42 (2.08-2.83)	0	0.86
Methods for measuring muscle mass					
L3−SMI	10	3,144	2.28 (1.93-2.70)	0	0.93
Others	6	1501	2.81 (2.14-3.69)	0	0.48
Source of cirrhosis cohort					
General patients	11	2,938	2.35 (1.97-2.82)	13	0.32
Patients evaluated or listed for LT	5	1,707	2.25 (1.79-2.82)	0	0.85
Study quality score					
NOS score = 9	6	1,812	2.16 (1.74-2.68)	0	0.89
NOS score <9	10	2,833	2.43 (2.01-2.93)	16	0.30

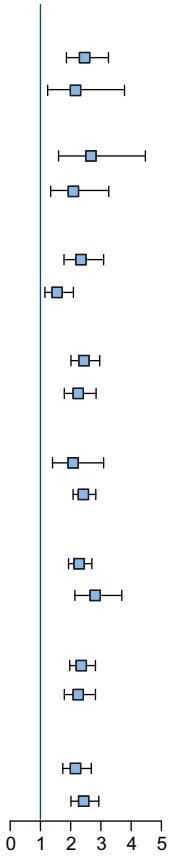

Fig. 4. Association of sarcopenia and risk of mortality in study subgroups. ALD, alcohol-associated liver disease; HR, hazard ratio; L3-SMI, third lumbar-skeletal muscle index; LT, liver transplantation; MELD, model for end-stage liver disease; NOS, Newcastle-Ottawa scale.

method, the pooled adjusted subdistribution HR from 4 studies (n = 1,331) was 1.99 (95% CI 1.49-2.67), also fairly similar to the adjusted HR observed in the main analysis. The heterogeneity between studies was low (I^2=18%, p = 0.30) (Fig. S6). Additional sensitivity analyses excluding one study at a time and then pooling the remaining studies showed adjusted HRs ranging from 2.26-2.42, further suggesting that our results were robust (Fig. S7).

Subgroup analysis

We found that sarcopenia was consistently associated with a higher risk of mortality across all subgroups analyzed (Fig. 4). Specifically, sarcopenia (*vs.* non-sarcopenia) was associated with a significantly increased risk of death in both males and females with pooled adjusted HR of 2.46 (95% CI 1.86-3.25) and 2.16 (95% CI 1.24-3.78) respectively, in those with ALD and in those without ALD (pooled adjusted HR 2.67, 95% CI 1.60-4.47 and 2.09, 95% CI 1.34-3.26, respectively), and in those with MELD <15 or ≥15 MELD (pooled adjusted HR 2.34, 95% CI 1.78-3.09 and 1.55, 95% CI 1.15-2.09, respectively). Patients with sarcopenia had a ≥2-fold risk of mortality from adjusted analyses regardless of study location (Asia *vs.* non-Asia), whether patients were listed for LT or not, whether study design was prospective or retrospective, whether sarcopenia was defined by L3-SMI or other methods, and whether the quality of studies were of very high or high quality (NOS score of 9 or <9).

Analysis of quantitative muscle mass index

We pooled unadjusted HRs (0.93, 95% CI 0.91-0.96) relating quantitative muscle mass index to mortality from univariable analyses and adjusted HRs (0.95, 95% CI 0.93-0.98) from multivariable analyses (Fig. S8), both of which suggested lower mortality with increased muscle mass index. Additionally, we found that every 1 cm^2/m^2 increase in muscle mass was associated with a 3% decrease in mortality risk (adjusted HR 0.97, 95% CI 0.95-0.98) in studies that use L3-SMI as a diagnostic method for sarcopenia, and every 1 mm/m increase in muscle mass by umbilicus-TPMT was associated with a 12% decrease in mortality risk (adjusted HR 0.88, 95% CI 0.81-0.96) (Fig. S9).

Meta-regression analyses

Meta-regression analyses showed no association of pooled adjusted HR with the sample size (p = 0.18), participants' average age (p = 0.33), percentage of males (p = 0.89), proportion of patients with ALD (p = 0.57), average follow-up time (p = 0.22), and the number of adjusted confounders (p = 0.70) (Table S4).

Publication bias

The funnel plot was asymmetric (Fig. S10A). Egger's (p = 0.001) and Begg's (p <0.001) test suggested that there was a potential publication bias. Therefore, the trim-and-fill method was performed by adding estimated HRs of 5 potential unpublished articles to reach symmetry in the funnel plot (Fig. S10B). The resulting pooled adjusted HR was 2.14 (95% CI 1.87-2.44) (I^2=13.4%, p = 0.28), similar to our main finding (2.30, 95% CI 2.01-2.63).

Discussion

In this systematic review and meta-analysis of 22 studies involving 6,965 patients with cirrhosis with very low heterogeneity across most analyses, sarcopenia was associated with significantly higher mortality risk – patients with sarcopenia had an ~2.6 times higher risk of death than those without sarcopenia. The association was further supported by the consistent significance across subgroups, a sensitivity analysis of studies without patients with HCC and studies with data from competing risk analysis, and by the robust dose-dependent association between quantified muscle mass index and mortality. We also reported an overall prevalence of sarcopenia of 37.5% in patients with cirrhosis, which was higher in males at 41.9%, higher when sarcopenia was defined by L3-SMI at 44.4% and as high as 50% in patients with ALD and in those with Child-Pugh class C cirrhosis.

While a prior systematic review and meta-analysis which included studies published before 2015 evaluated the association between skeletal muscle mass and waitlist mortality in 4 articles, 3 of the 4 studies were conducted in one center.[19] Another prior meta-analytic study included overlapping cohorts, a large number of post-LT patients, reported pooled HRs, and had a high level of heterogeneity.[18] A third meta-analysis included overlapping cohorts and did not provide comprehensive subgroup analyses.[17] In the current study, we performed a more comprehensive search, screened a much larger pool of potential studies, excluded overlapping cohorts and studies of post-LT patients, and performed a comprehensive range of subgroup and sensitivity analyses. As a result, our current meta-analysis included 16 new studies not previously included in prior meta-analyses, out of a total of 22 included studies. In addition, we excluded small studies (n <100) and were able to obtain additional data for 7 studies by direct contact with study authors, providing data for more robust subgroup and sensitivity analyses. Our strict inclusion and exclusion criteria also led to a high-quality score for all studies included in our meta-analysis and helped contribute to the low level of heterogeneity observed in our analyses.

While the pooled adjusted HR relating sarcopenia to mortality was consistently about 2.0 or higher across almost all included subgroups, the pooled adjusted HR was lower at 1.55 for the subgroup of patients with MELD ≥15 but higher at 2.34 for those with MELD <15, though the association was statistically significant for both MELD groups. Patients with higher MELD are prone to more infection, hepatic decompensation, acute-on-chronic liver failure, prolonged hospitalization, and other factors that increase mortality.[4,47,48] Therefore, it is possible that the relative contribution of sarcopenia may be lower after other factors associated with mortality have been adjusted for, resulting in a lower adjusted HR in patients with high MELD. However, the higher mortality with sarcopenia across the MELD spectrum stresses the need for the screening and treatment of sarcopenia in patients with all stages of cirrhosis, to curtail the 2.34-fold higher hazard of death for those with low MELD and to prevent excess death among higher risk patients with MELD of 15 or higher. This finding also highlights the need to include measurements of muscle mass index or sarcopenia in prognostic scores for cirrhosis and lends further support to the application of the model of MELD-Sarcopenia and MELD-psoas, particularly in patients with refractory ascites or lower MELD scores.[45,49]

It should also be noted that while the overall pooled prevalence of sarcopenia was 37.5% and sarcopenia was common across subgroups, several subgroups appeared to be more affected and should be more targeted for screening and intervention. The highest risk groups were those with ALD and Child-Pugh class C cirrhosis, who exhibited a prevalence of sarcopenia

of about 50%. Malnutrition and unstable living situations are more common among patients with ALD, especially those with active alcohol use, and our finding is in line with results from a recent study that showed a lower baseline muscle mass and faster loss of muscle area in patients with cirrhosis with ALD compared to those with other etiologies.[16] Among patients with Child-Pugh class C cirrhosis, poor hepatic synthetic function and frequent portal systemic complications often lead to poor oral intake, prolonged immobilization, and increased catabolic state, which together contribute to malnutrition and sarcopenia.[4,50,51] These findings expand our knowledge from prior studies that reported conflicting results regarding the prevalence of sarcopenia among patients with cirrhosis of different liver disease etiologies or severity.[15,41,52–54]

We acknowledge the following limitations. First, given that a majority of included studies were retrospective cohort studies, the findings were subject to selection bias as only patients with a CT scan or MRI were included. However, subgroup analysis showed a consistent adjusted HR between studies with retrospective and prospective design (HR 2.42 *vs.* 2.08). Second, inclusion of patients with HCC may cause bias as HCC is associated with a high prevalence of sarcopenia and mortality risk. Therefore, in *a priori* study selection criteria, we limited the proportion of HCC in included studies to be less than 50%. Additionally, the adjusted HR from a sensitivity analysis that excluded studies that included patients with HCC was similar to the overall estimate. Third, due to the nature of meta-analysis, our study was limited by inadequate data from each of the included studies. To overcome this limitation, we contacted authors of included articles and were able to obtain data from 7 articles which allowed additional and more robust subgroup analyses. Variables including refractory ascites and kidney dysfunction were not available and warrant further investigations. Fourth, the confounding factors used on multivariable Cox regression model varied across studies. However, pooled adjusted HR in overall patients with cirrhosis and the majority of subgroups had low heterogeneity. Meta-analysis with individual patient level data is needed to further assess the association between sarcopenia and survival with adjustment for key confounding factors. Fifth, our study may be limited by factors that could lead to potential bias. These included different statistical methods (Cox regression analysis *vs.* competing risk analysis), measuring methods and cut-offs to defined sarcopenia. We performed subgroup and sensitivity analyses to overcome these limitations. However, meta-analyses using individual data with unified definition and measurement of sarcopenia are needed to further clarify the prevalence of sarcopenia and to better characterize patients with cirrhosis and sarcopenia. Sixth, the significance in Begg's and Egger's test implied the presence of publication bias. However, the adjusted HR from trim-and-fill analysis did not change substantially (2.30 *vs.* 2.14). Finally, due to the inclusion of observational studies and the presence of publication bias, the level of evidence of this study from GRADE was rated as low. The relatively large magnitude of effect estimate increased the rate, but the overall rate remained as low. Despite the quality of included articles being high (all NOS ≥7), the results of this meta-analysis should be interpreted cautiously.

In conclusion, this systematic review and meta-analysis demonstrated that sarcopenia affects about one-third of patients with cirrhosis and up to one-half of patients with ALD or Child-Pugh class C cirrhosis. The current study also showed that sarcopenia was associated with an ~2-fold higher risk of death among affected patients and consistently so in almost all patient subgroups, including patients with low MELD. Together, our findings suggest that i) sarcopenia should be part of the initial evaluation of all patients with cirrhosis, ii) all patients with cirrhosis regardless of degree of hepatic dysfunction should be monitored for sarcopenia on a regular basis, and iii) additional studies are needed to incorporate sarcopenia or muscle mass index/function into a formal prognostic scale for patients with cirrhosis.

Abbreviations

ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; L3, third lumbar vertebra; L4, fourth lumbar vertebra; LT, liver transplant; MELD, model for end-stage liver disease; NOS, Newcastle-Ottawa scale; TIPS, transjugular intrahepatic portosystemic shunt; TPMT, transverse psoas muscle thickness.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors: Data contribution, data interpretation, and approve the manuscript. XT, YL, HD, XG, JZ, LY, YC, YL: Literature search

and data extraction. XT, YL, NL, ZL: Study quality assessment. XT, YHY, YCH, FJ, MHN: Study design and data analysis. XT, YL, YHY, FJ: Drafting of the manuscript. MP, CE,VJLA, GLS: Critical review of the manuscript. MHN: Critical revision of the manuscript. YHY, JW, FJ: Study conception and study supervision.

Data availability statement

Some or all data, models, or code that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.11.006.

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Author names in bold designate shared co-first authorship

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