Systematic Review and Meta-Analysis

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Association of loss of muscle mass with mortality in liver cirrhosis without or before liver transplantation

A systematic review and meta-analysis

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Abstract

Background: Liver cirrhosis is a risk factor for the loss of muscle mass, which is associated with numerous adverse health outcomes. This meta-analysis aimed to examine whether loss of muscle mass was a predictor of increased mortality in cirrhotic patients without or before liver transplantation.

Methods: Without language restriction, PubMed and Embase were searched for articles published from the earliest records to December 2018 investigating the influence of loss of muscle mass on survival of cirrhotic patients. Those who had undergone liver transplantation and had hepatocellular carcinoma were excluded. The main outcome was the hazard ratio (HR) for the association of mortality with loss of muscle mass, and the secondary outcome was the association of loss of muscle mass with Child-Pugh class and death caused by severe infection.

Results: The meta-analysis included 16 observational studies, comprising 4070 participants. The pooled crude and adjusted HRs for the association of mortality with loss of muscle mass were 2.05 (95% confidence interval [CI], 1.51–2.78) and 2.36 (95% CI, 1.61–3.46). Using Child-Pugh Class A as reference, the odds ratios (ORs) for the association of loss of muscle mass with Child-Pugh Class B and Class C were 1.68 (95% CI, 0.96–2.92) and 1.94 (95% CI, 0.66–5.65). Patients with loss of muscle mass were likely to have infection-related mortality (OR=3.38, 95% CI, 0.61–18.88) but the association did not reach statistical significance.

Conclusions: *Loss of muscle mass is associated with mortality in cirrhotic patients without or before liver transplantation.* Future studies should be conducted to explore whether exercise and nutritional supplementation can reverse muscle mass loss and improve long-term survival.

Abbreviations: CT = computed tomography, HR = hazard ratio, MELD = Model of End-Stage Liver disease, OR = odds ratio.

Keywords: liver cirrhosis, liver transplantation, mortality, muscle mass, sarcopenia

1. Introduction

Liver cirrhosis is a diffuse parenchymal hepatic disease characterized by extensive fibrosis and formation of irreversible nodules. Cirrhosis results in derangement of the hepatic vascular architecture and leads to life-threatening complications such as portal hypertension, gastroesophageal varices, and hepatic encephalopathy. Alcoholism and hepatitis B and C are common causes of liver cirrhosis and also exert a substantial influence on long-term outcomes. The conventional prognostic systems for predicting survival in cirrhotic patients are the Child-Pugh and

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the Model of End-Stage Liver disease (MELD) Scores.[1] The main limitation of both tools is the lack of nutritional assessment.[2] Malnutrition is prevalent in the cirrhotic population and results from an altered metabolism and decreased protein intake.[2] A compromised nutritional status is associated with a poor prognosis in patients with chronic liver disease and can be reflected in changes in body composition, such as loss of skeletal muscle mass[3] (Table 1).

Loss of skeletal muscle mass may be accompanied by decreased muscle strength and impaired physical performance,[4] and is linked to several adverse health outcomes, including cognitive impairment,[5] depression,[6] and mortality.[7] Cirrhotic patients are vulnerable to loss of muscle mass due to reduced nutritional intake required for muscle generation, increase in myostatin, which inhibits muscle growth, and abnormal consumption of protein for energy production.[2] Recently, a meta-analysis explored the relationship between sarcopenia and mortality in cirrhotic patients.[8] The study was composed of a variety of patient groups including those not eligible for liver transplantation, those on the transplantation waiting list, those who underwent liver transplantation, and with hepatocellular carcinoma. However, the heterogeneity in the severity of underlying disease and subsequent treatments might cloud the association between loss of muscle mass with long-term survival in cirrhotic patients. Therefore, this meta-analysis focused on cirrhotic patients without or before liver transplantation and examined whether loss of muscle mass was a predictor of increased mortality in the target population.

2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses and the Meta-analysis of Observational Studies in Epidemiology statements and was based on a predefined but unpublished protocol.[9] As the work is a review article, no ethics committee or institutional review board approval is needed.

2.1. Data sources and literature search strategy

Two investigators independently searched electronic databases (PubMed and Embase) without language restriction for articles published from the earliest records to December 2018. Clinical studies investigating the association between loss of muscle mass and survival of patients with liver cirrhosis were included. The following strategy was used for literature searches: (sarcopenia, OR frailty, OR skeletal muscle) AND (liver cirrhosis OR liver fibrosis) (Appendix 1, http://links.lww.com/MD/C798). Reference lists of the retrieved studies were also manually searched to identify relevant articles.

2.2. Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were use of a case-control or a cohort study design, recruitment of patients with liver cirrhosis, evaluation of skeletal muscle mass, with or without physical performance, and reporting of data on all-cause mortality. Studies were excluded if they were case series or case reports that included patients with hepatocellular carcinoma on the initial enrollment following liver transplantation, if they lacked a clear definition of loss of muscle mass based on the measurement of skeletal muscle mass and/or physical performance, or if a hazard ratio (HR) or an odds ratio (OR) analyzing the association between loss of muscle mass and mortality could not be computed from the available data.

2.3. Assessment of study quality

Two investigators independently investigated the quality of included studies using the Newcastle–Ottawa Scale.[10] The following aspects were evaluated: participant selection (representativeness of patients and controls, validated measurements of exposure, and assurance of outcome of interest not present at the start of the research), study comparability, and outcome assessment (appropriateness of outcome measurement, adequate follow-up period, and adequate number of participants being followed up). Discrepancy of opinion between reviewers was resolved through discussion or was settled by the corresponding author.

2.4. Data synthesis and statistical analysis

The following details were extracted from the included studies: author name, year of publication, patient characteristics, enrolled numbers, sex ratio, methods of muscle mass measurement, definition of loss of muscle mass, outcome variables, and adjusted confounders. The main outcomes were the crude and adjusted HRs investigating the association between loss of muscle mass and mortality. The summary adjusted HR was derived from pooling each adjusted HR reported in the included studies.

Since the mortality rate differs in patients according to the severity of liver cirrhosis and is unlikely to be a fixed number, a random-effects model was applied to pool the effect sizes.[11] A stratified analysis was conducted based on patient characteristics. Heterogeneity across studies was assessed using Cochran's Q test and I^2 statistics and was considered significant with $I^2 > 50\%$.[12] Publication bias was determined by visually inspecting the symmetry of the effect size distribution on funnel plots and using Egger's test.[13] We also employed the Duval and Tweedie trim and fill procedure to observe the change in summary effects following imputation of potential unpublished literature.[5] All calculations were performed using Comprehensive Meta-analysis Software version 3 (Biostat, Englewood, NJ), with a $P < .05$ considered statistically significant.

3. Results

3.1. Search results

The literature search initially yielded 989 non-duplicated articles. After the titles and abstracts were reviewed, 27 articles were retrieved for full text review. Among these, 11 were excluded: 5 used the same patient group as the included trials,[14–18] 2 evaluated skeletal muscle mass loss in cirrhotic patients but lacked survival analysis,[19,20] only 1 included cirrhotic patients with different rates of muscle mass loss,[21] and 3 explored the association between loss of muscle mass and hepatic encephalopathy but not all-cause mortality.[22–24] The final meta-analysis included 16 studies (Fig. 1).[25–40]

3.2. Study and participant characteristics

The meta-analysis consisted of 4070 participants, 29.8% (n = 1215) of whom were females. The age range in the selected citations was between 49.7 and 74 years. The 16 retrieved studies included 7 that enrolled patients on the waiting list for liver transplantation,[25,29,32,35,38–40] 5 that enrolled patients with

Table 1

Summary of the included studies.

Author, year	Patients' characteristic	Muscle mass measurement	Cut-off value for low muscle mass	Definition of cirrhosis	Enrolled number, (female/male)	Age in years	Outcome variables	Confounders adjusted for the association between loss of muscle mass and mortality
Tandon et al 2012	Patients with cirrhosis who were evaluated for liver transplantation	The muscle cross-sectional area measured at the L3 level	$\leq$52.4 cm^2/m^2 for men and $\leq$38.5 cm^2/m^2 for women	Not mentioned	142 (56/86)	Median: 53 (total); *Interquartile range*: 47–57	All-cause mortality (crude and adjusted HR); predictors of sarcopenia	Age, sex, BMI, cirrhosis etiology, creatinine, bilirubin, sodium, albumin, prothrombin time, MELD score
Kim et al 2014	Cirrhotic patients with ascites	The psoas muscle thickness measured at the L3 or L4 level or at the level of umbilicus	Psoas major muscle thickness $\leq$ 14 mm/m	Histological confirmation of cirrhosis or based on clinical, biochemical parameters and imaging examinations	65 (24/41)	Mean: 55$\pm$9.2 (total)	All-cause (crude HR)and infection- related mortality	Not applicable
Hanai et al 2015	Patients with any degree of cirrhosis but not transplantation candidates	Total psoas area measured at the L3 level with the CT density set between -29 and 150 HU	$\leq$52.4 cm^2/m^2 for men and $\leq$38.5 cm^2/m^2 for women	Liver biopsy specimens and/or clinical and laboratory data	130 (54/76)	Median: 64 (sarcopenia); 65 (non-sarcopenia)	All-cause (crude and adjusted HRs) and infection-related mortality; predictors of sarcopenia	Age, sex, height, weight, BMI, etiology of cirrhosis, Child-Pugh class, branched chain amino acid, ALT, albumin, total bilirubin, ammonia, prothrombin time
Hara et al ,2016	Patients with any degree of liver cirrhosis	Bioelectrical impedance analysis	1.7 kg/m^2 for men and 1.2 kg/m^2 for women of the lean body mass	Based on abdominal ultrasound, CT and MRI, blood test findings, and portal hypertension (or liver biopsy in difficult cases)	161 (67/94)	Mean: 66$\pm$10 (normal) 74$\pm$4 (sarcopenic obesity) 67$\pm$10 (sarcopenia) 66$\pm$7 (obesity)	All-cause of mortality (crude HR); predictors of sarcopenia	Not applicable
Sinclair et al 2016	Men with liver cirrhosis referred for liver transplantation evaluation	Total psoas area measured at the L4 level with the density set between 0 and 100 HU	52.4cm^2/m^2 for men	Not mentioned	145 (all men)	Median:54 (total); Interquartile range: 47-59	All-cause mortality (crude and adjusted HRs)	Age, testosterone, MELD score
Ishizu et al 2017	Patients with cirrhosis and acute gastroesophageal variceal bleeding	The total cross-sectional area of bilateral psoas muscles at the L3 level	4.24 cm^2/m^2 for men and 2.50 cm^2/m^2 for women	Based on clinical, laboratory, radiological, and histological data.	122 (30/92)	Mean$\pm$SD: 61.6$\pm$12.8 (total)	In-hospital and infection-related mortality	Age, sex, etiology of alcohol, serum bilirubin, serum albumin, prothrombin time, serum creatinine, serum sodium, HCC, re-bleeding within 6 weeks
Nishikawa et al 2017	Patients with liver cirrhosis	Psoas muscle index estimated on CT images	Psoas muscle index: $<$6.36 cm^2/m^2 for men and $<$3.92 cm^2/m^2 for women	Not mentioned	198 (90/108)	Median: 67.5 (total)	All-cause mortality (crude and adjusted HRs)	Age, sex, serum myostatin, serum ammonia, serum albumin, total bilirubin, prothrombin time, Child-Pugh score
Aby et al 2018	Nonalcoholic steatohepatitis cirrhosis patients evaluated for liver transplantation	Cross-sectional areas of the left and right psoas muscles at L3	Psoas muscle area of $<$ 1561mm^2 in men and, 1464 mm^2 in women	Based on abdominal CT scan or MRI	146 (84/62)	Median: 62 (sarcopenia); 59 (non-sarcopenia)	Overall mortality	Not applicable
Bhanji et al 2018	Patients with cirrhosis who were evaluated for liver transplantation	Cross-sectional areas of the muscles and adipose tissue at L3	L3 skeletal muscle index: $<$39 cm^2/m^2 for females and $<$50 cm^2/m^2 for males	Based on abdominal CT scan	675 (221/454)	Median:57 (total); Interquartile range: 21-76	All-cause mortality (crude and adjusted HRs)	Age, sex, race, BMI, of cirrhosis, creatinine, serum bilirubin, prothrombin time, albumin, sodium, ammonia, Child-Pugh score, ascites
Ebadi et al 2018	Patients with cirrhosis listed for liver transplantation	Total skeletal muscle cross-sectional area, and psoas muscle area at L3	SMI $<$39 cm^2/m^2 in women and $<$50 cm^2/m^2 in men.	Based on abdominal CT scan	353 (107/246)	Mean$\pm$SD: 56$\pm$9 (total)	All-cause mortality (crude and adjusted HRs)	Age, sex, albumin, MELD score, ascites, sodium, HCC, hepatic encephalopathy, SMI, PMI
Gu et al 2018	Patients with liver cirrhosis	Psoas muscle cross-sectional area and thickness at L3	SMI $\leq$52.4 cm^2/m^2 in men and $\leq$38.5 cm^2/m^2 in women; PMTH $<$ 16.8mm/m	Based on abdominal CT scan	653 (154/499)	Mean$\pm$SD: 53.6$\pm$10.2 (total)	All-cause mortality (crude and adjusted HRs)	Age, sex, BMI, underlying liver disease, diabetes, prothrombin time, platelet count, AST, ALT, bilirubin, albumin, creatinine, sodium
Kalafateli et al 2018	Patients with liver cirrhosis	Psoas muscle cross-sectional area at L4/L5	ATPD $<$ 34.48 HU	Based on abdominal CT scan	98 (27/71)	Median:63 (total); Interquartile range: 27-93	All-cause mortality (crude and adjusted HRs)	Not applicable
Kang. et al 2018	Patients with liver cirrhosis who were evaluated for liver transplantation	Cross-sectional areas of the muscles and adipose tissue at L3	SMI $\leq$50 cm^2/m^2 in men and $\leq$39 cm^2/m^2 in women; men with BMI $<$ 25: $<$ 43 cm^2/m^2, men with BMI $\geq$ 25: $<$53 cm^2/m^2, women: $<$41 cm^2/m^2	Based on abdominal CT scan	452 (73/379)	Mean$\pm$SD: 51.8$\pm$8.8 (total)	All-cause mortality (crude and adjusted HRs)	Age, sex, Child-Pugh stage, height,, BMI, albumin, total bilirubin, prothrombin time, creatinine, MELD score, sarcopenia
Lucidi et al 2018	Cirrhotic patients hospitalised for sepsis	Mid-arm muscle circumference of the non-dominant arm	MAMC $<$ 5th percentile and hand grip strength	Not mentioned	74 (18/56)	Mean$\pm$SD: 49.7$\pm$16 years (total)	In-hospital mortality	Not applicable
Praktiknjo et al 2018	Cirrhotic patients with transjugular intrahepatic portosystemic shunt	Total erector spinae muscle area and the intramuscular fat tissue area using MRI	Men: MA $<$ 3523 mm^2 and FFMA $<$ 3197 mm^2; women: MA $<$ 3153 mm^2 and FFMA $<$ 2895 mm^2	Not mentioned	71 (29/42)	Median:58 (total); Interquartile range: 18–78	All-cause mortality (crude and adjusted HRs)	Age, sex, total MA, FFMA, fat area, sarcopenia, number connection test, HE, hepatorenal syndrome, ascites, MELD, bilirubin, prothrombin time

(*continued*)

Table 1
(continued).

Author, year	Patients' characteristic	Muscle mass measurement	Cut-off value for low muscle mass	Definition of cirrhosis	Enrolled number, (female/male)	Age in years	Outcome variables	Confounders adjusted for the association between loss of muscle mass and mortality
van Vugt et al 2018	Patients with cirrhosis listed for liver transplantation	The muscle cross-sectional area measured at the L3 level	SMI: men with BMI < 25: <43 cm^2/m^2, men with BMI ≥ 25: <53 cm^2/m^2, women: <41 cm^2/m^2	Based on abdominal CT scan	585 (181/404)	Median:56 (total); Interquartile range: 48–62	All-cause mortality (crude and adjusted HRs)	Age, sex, BMI, MELD score, bilirubin, creatinine, prothrombin time, albumin, HCC, sodium, complications

ALT = alanine *transaminase*, ATPD = assessment of total psoas muscle area density, AST = aspartate transaminase, BMI = body mass index, CT = computed tomography, FFMA = fat free mass area, HCC = hepatocellular carcinoma, *HR= hazard ratio*, HU = Hounsfield *unit*, MAMC = mid-arm muscle circumference of the non-dominant arm, MELD = Model for End-Stage Liver Disease, MRI = magnetic resonance imaging, NASH = nonalcoholic steatohepatitis, PMTH = *psoas* muscle thickness per height, SD = standard deviation, SMI = skeletal muscle mass index.

different severities of liver cirrhosis,[27,28,31,36,37] 1 that enrolled patients with concomitant ascites,[26] 1 that enrolled patients with cirrhotic admitted for treatment of sepsis,[34] 1 that enrolled patients with cirrhotic receiving transjugular intrahepatic portosystemic shunts,[33] and 1 that enrolled patients with acute variceal bleeding. [30] Based on the definition of loss of muscle mass, 13 retrieved studies used the cross-sectional area of the psoas muscle on computed tomography (CT), with or without adjacent paraspinal and abdominal muscle imaging,[25,27,29–33,35–40] 1 used psoas muscle thickness assessed with CT,[26] 1 used mid-arm muscle circumference and handgrip strength,[34] and 1 used skeletal muscle mass estimated using bioelectrical impedance analysis (BIA).[28] Most of the selected studies retrospectively analyzed the medical records from cohorts of liver cirrhotic patients to define loss of muscle mass. The result of quality assessment of the selected studies is shown in Table 2. The included studies fulfilled most of the items evaluated except for comparability of cohorts and adequate follow-up period.

3.3. Loss of muscle mass and all-cause mortality

The crude HRs for the association between loss of muscle mass and all-cause mortality were reported in 14 of the 16 retrieved studies,[18,25–30] while the adjusted HRs were available in 11.[18,25,27,29–31] The pooled crude and adjusted HRs were 2.05 (95% confidence interval [CI], 1.51–2.78; $I^2 = 87.5$, $P < .001$) and 2.36 (95% CI, 1.61–3.46; $I^2 = 89.4$, $P < .001$), respectively (Fig. 2). Sensitivity analysis was performed by eliminating studies not using CT to estimate skeletal muscle mass,[28,34] and the pooled crude HR changed to 2.11 (95% CI, 1.50–2.95; $I^2 = 89.0$, $P < .001$). Another sensitivity analysis was conducted by excluding the studies only reporting in-hospital mortality,[30,34] and the pooled crude HR and adjusted HR changed to 2.07 (95% CI, 1.48–2.90, $I^2 = 88.9$, $P < .001$) and 2.28 (95% CI, 1.54–3.35, $I^2 = 89.9$, $P < .001$).

We conducted a stratified analysis based on patient characteristics. In the group of cirrhotic patients on the waiting list for liver transplantation, the crude and adjusted HRs were 1.62 (95% CI, 1.09–2.39) and 1.86 (95% CI, 1.23–2.84), respectively. In the group not qualified or specified as candidates for liver transplantation, there was an insignificant increase in the crude and adjusted HRs (2.50, with 95% CI, 1.82–3.43 and 3.27, with 95% CI, 2.10–5.11, respectively). Significant publication biases were detected in the crude and adjusted HRs (both $P < .001$) with Egger's test (Fig. 3). Nevertheless, after imputation of potentially unpublished studies using the Duval and Tweedie trim and fill function, the level of statistical significance remained consistent with the pooled crude HR (1.68, 95% CI, 1.29–2.19) and adjusted HR (1.80, 95% CI, 1.33–2. 44) for the association between loss of muscle mass and all-cause mortality.

3.4. Loss of muscle mass and Child-Pugh class

Among the 16 included studies, 3 had available data that could be used to estimate the association between loss of muscle mass and Child-Pugh class in patients with liver cirrhosis.[25,27,28] Using Child-Pugh Class A as a reference, the ORs for the association of loss of muscle mass with Child-Pugh Class B and Class C were 1.68 (95% CI, 0.91–2.66; $I^2 = 0$, $P = .573$) and 1.94 (95% CI, 0.66–5.65; $I^2 = 45.1$, $P = .162$), respectively. Our analysis did not reveal significant associations between loss of muscle mass and Child-Pugh class (Fig. 4).

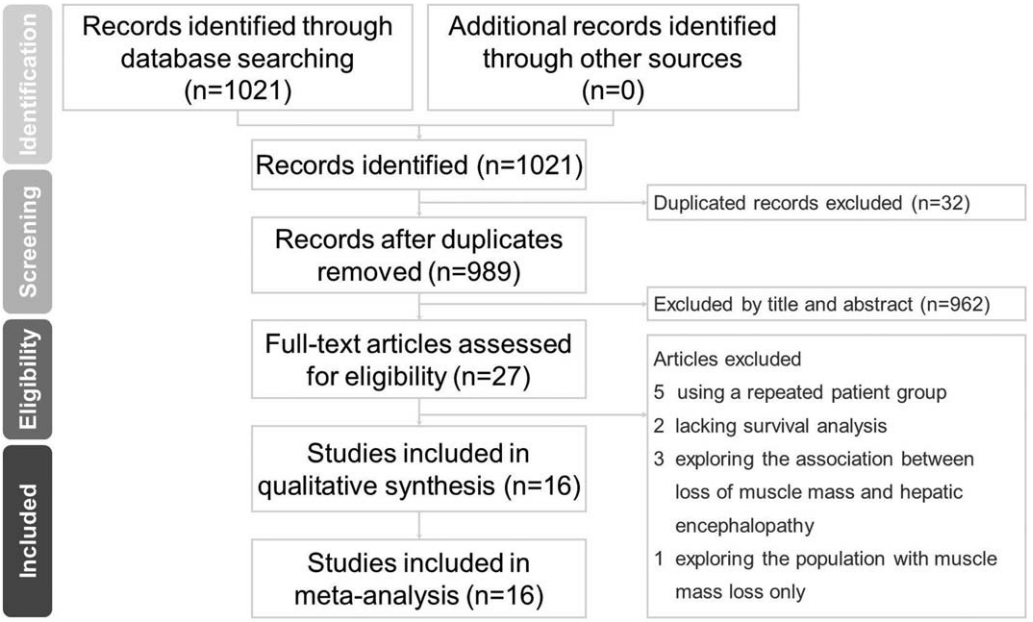

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection process.

3.5. Loss of muscle mass and infection

The number of deaths related to infection or sepsis was reported in 3 of the included studies.[26,27,30] Mortality in patients with loss of muscle mass was likely to be associated with infection (OR = 3.38, 95% CI, 0.61–18.88; $I^2 = 0$, $P = .542$) but the association did not reach statistical significance (Fig. 5).

4. Discussion

The present meta-analysis explored the association between loss of muscle mass and overall survival in liver cirrhotic patients. Loss of skeletal muscle mass was associated with an increase in all-cause mortality, and the association remained statistically significant after adjusting for common confounders. Loss of muscle mass could not be predicted by the severity of chronic liver disease, categorized by Child-Pugh class. Severe infection might play a role in the increased mortality in cirrhotic patients associated with loss of muscle mass.

Recently, loss of muscle mass has been recognized in several systematic reviews and meta-analyses to have a negative effect on health-related outcomes. Chang et al identified 10 studies that investigated the association of sarcopenia with mortality in a group mainly consisting of geriatric patients.[7] Beaudart et al included 17 studies that defined sarcopenia by using the protocol

Table 2

Quality assessment by using the Newcastle–Ottawa Scale for the included studies.

	Representative of sarcopenia patients	Selection of control	Ascertain of sarcopenia measurement	Outcome of interest not present at start	Comparability of cohorts	Assessment of outcome	Enough follow-up period	Adequacy of follow up	Total point
Tandon et al 2012	★	★	★	★	★★	★	★	★	9
Kim et al 2014	★	★	★	★	★★	★	★	★	9
Hanai et al 2015	★	★	★	★	★★	★	★	★	9
Hara et al 2016	★	★	★	★	★★	★	★	★	9
Sinclair et al 2016	★	–	★	★	★	★	★	★	7
Ischizu et al 2017	★	–	★	★	★	★	–	★	6
Nishikawa et al 2017	★	–	★	★	★	★	★	★	7
Aby et al 2018	★	★	★	★	★	★	★	★	8
Bhanji et al 2018	★	★	★	★	★★	★	★	★	9
Ebadi et al 2018	★	★	★	★	★★	★	★	★	9
Gu et al 2018	★	★	★	★	★★	★	★	★	9
Kalafateli et al 2018	★	★	★	★	★	★	★	★	8
Kang et al 2018	★	★	★	★	★	★	★	★	8
Lucidi et al 2018	★	★	★	★	★★	★	★	★	9
Praktiknjo et al 2018	★	★	★	★	★★	★	★	★	9
van Vugt et al 2018	★	★	★	★	★	★	★	★	8

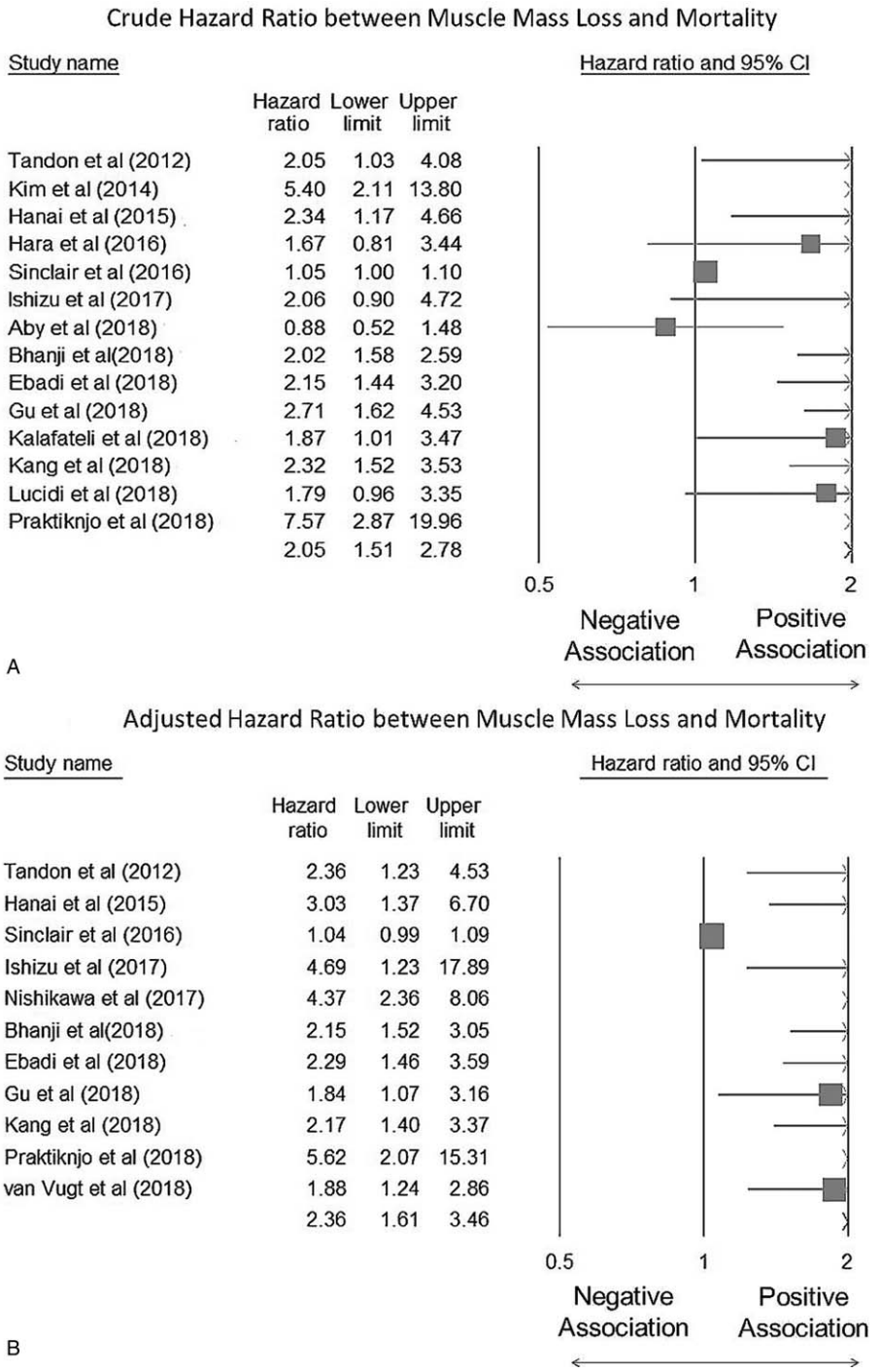

Figure 2. Forest plot of the crude (A) and adjusted (B) hazard ratios for the association between loss of muscle mass and all-cause mortality in patients with liver cirrhosis.

from the European Working Group on Sarcopenia in Older People and found a higher rate of mortality, functional decline, falls, and hospitalization among sarcopenic adults.[41] Shachar et al summarized 38 studies enrolling patients with solid tumors and demonstrated that the loss of skeletal muscle mass determined by CT cross-sectional imaging was detrimental to overall survival.[42] In 2015 and 2016, Kim et al and Sinclair et al published 2 review articles, summarizing available evidence on the definition, etiology, prevalence, mechanism, and clinical impact of loss of muscle mass in patients with liver cirrhosis or following liver transplantation.[2,43]

Regarding the impact of sarcopenia in a population with chronic liver disease, Kim et al found that cirrhotic patients with sarcopenia tended to have higher mortality rates, regardless of the status of liver transplantation.[8] Yu et al found that sarcopenia was associated with steatohepatitis or advanced liver fibrosis in patients with nonalcoholic fatty liver disease.[44] Chang et al demonstrated that sarcopenia increased the mortality rate in

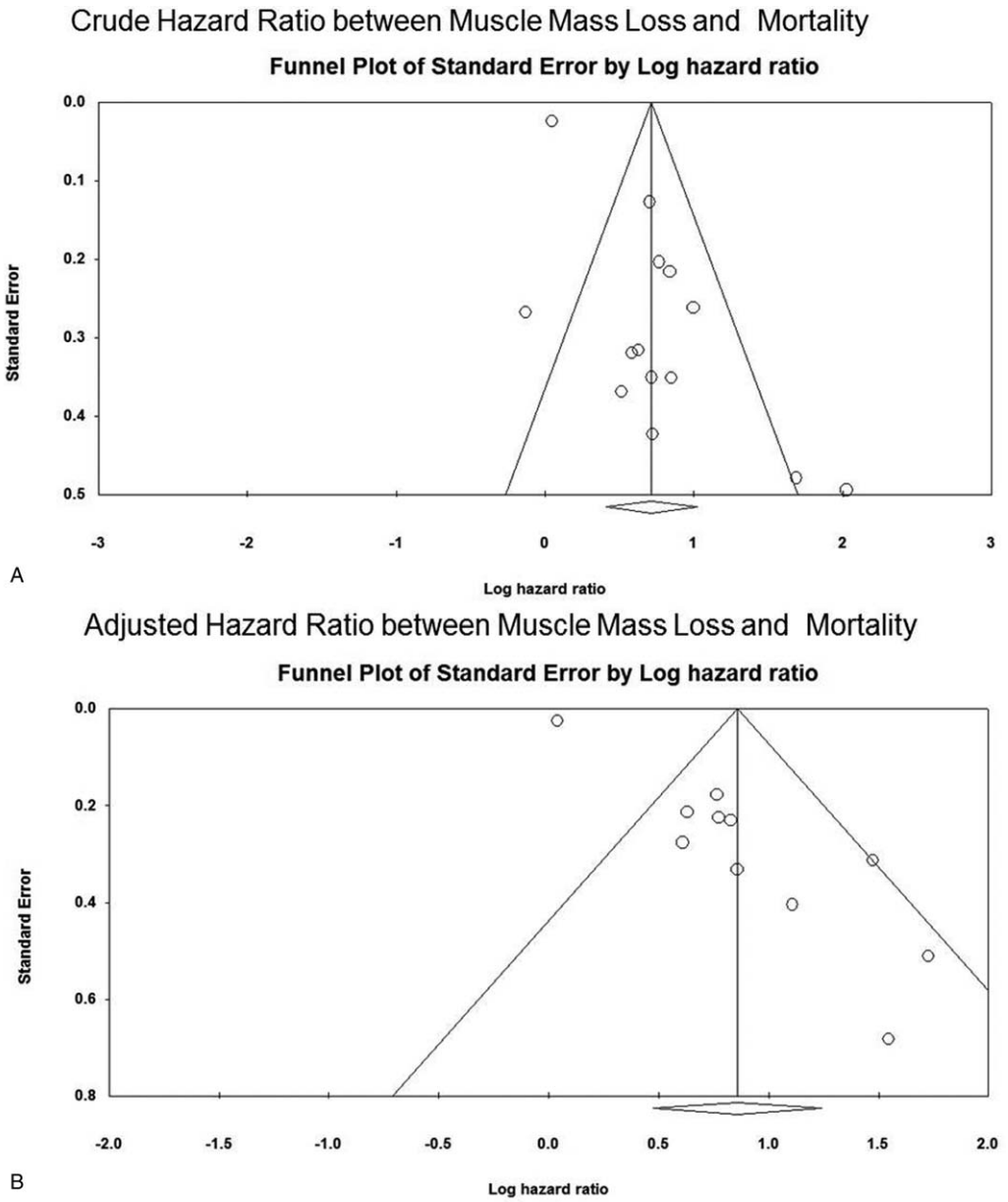

Figure 3. Funnel plot of the crude (A) and adjusted (B) hazard ratios for the association between loss of muscle mass and all-cause mortality in patients with liver cirrhosis.

hepatocellular carcinoma,[45] as well as the incidence of hepatic encephalopathy in cirrhotic patients.[46] However, a detailed pooled quantitative analysis exploring the association of loss of muscle mass with survival in patients with cirrhosis before or without liver transplantation has been lacking, increasing the importance of our meta-analysis. The comparison of the present and previous meta-analyses related to sarcopenia in patients with chronic liver disease is summarized in Table 3.

Our study showed that loss of muscle mass was associated with all-cause mortality in patients with cirrhosis. Previous studies revealed that loss of muscle mass is prevalent in the population with liver cirrhosis, and the mechanism is multidimensional, comprising malnutrition, abnormal use of protein as an energy resource, increased production of proinflammatory cytokines to accelerate muscle breakdown, and inhibition of muscle growth through elevated myostatin and decreased testosterone.[2] The literature has shown that loss of muscle mass was independently associated with severe hepatic fibrosis, a predictor of mortality in patients with non-alcoholic liver disease.[47] Therefore, with a growing amount of evidence referring to loss of muscle mass as a byproduct of liver cirrhosis, it is anticipated that the loss of muscle mass varies according to severity of cirrhosis and is subsequently related to mortality.

The Child-Pugh and MELD scores are commonly used for predicting prognosis in chronic liver disease.[1,43] The former assesses total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy while the latter evaluates serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time. However, neither measurement tool includes a detailed evaluation of physical performance, body

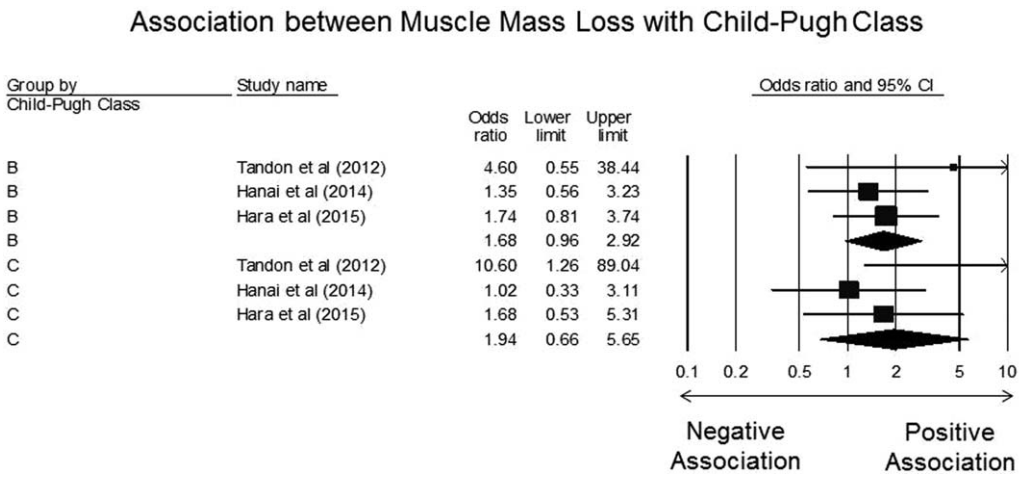

Figure 4. Forest plot of the association between loss of muscle mass and Child-Pugh Class in patients with liver cirrhosis.

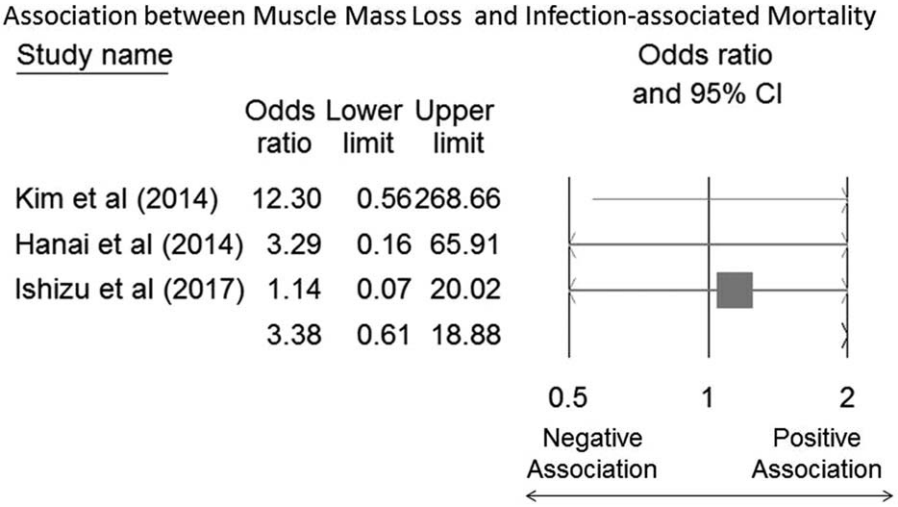

Figure 5. Forest plot of the association between loss of muscle mass and infection-associated mortality in patients with liver cirrhosis.

composition, and nutritional status. Thus, these prognostic tools present some limitations, with decreased predictive power in patients with lower MELD scores and inclusion of subjective assessment (hepatic encephalopathy and ascites) in the Child-Pugh score.[1,48] This meta-analysis explored the association between loss of muscle mass and the severity of disease as categorized by the Child-Pugh class (not the MELD score due to data availability). Our results revealed that loss of muscle mass was not associated with Child-Pugh class B and C. Therefore, loss of muscle mass should be treated as an adjuvant prognostic factor along with these commonly employed scores to predict the survival of patients with liver cirrhosis.

Our pooled analysis also revealed a likely higher rate of infection-related death in patients with loss of muscle mass. It is well-known that immune responses such as phagocytosis and migration of neutrophils, natural killer cell activity, and activation of the complement system are impaired in cirrhotic patients.[49] The skeletal muscles are considered to be an endocrine organ secreting and mediating various kinds of cytokines. Several studies reported that patients with sarcopenia had an increase in interleukin-6 and tumor necrosis factor-α and a decrease in interleukin 10, and were more vulnerable to significant systemic inflammatory reactions, which might be elicited by infection.[50,51] Another possible mechanism is that muscle mass loss reflects the status of malnutrition, a well-known factor in immunodeficiency.[52] Although the exact association between muscle volume loss and severe infection is still unknown, this connection might partially explain why patients with cirrhosis might have a shorter survival period in association with loss of muscle mass.

Most of the included studies used CT images obtained at the L3 or L4 vertebral level to define skeletal muscle mass loss, while 1 study employed BIA and 1 employed mid-arm muscle circumference and handgrip strength. The BIA evaluates body composition by applying a low amplitude electrical current on the skin to estimate intra- and intercellular fluid. This estimation may be biased in patients with local or generalized edema, which is a common finding in patients with cirrhosis.[53] In contrast, the use

Table 3

Comparisons of the previous and present meta-analyses related to sarcopenia in patients with chronic liver disease.

Author, year	Target population	Number of the included studies	Timespan of the included studies	Total number of the included participants	Outcome variables	Result
Kim et al, 2017	Patients with liver cirrhosis	20	2013 to 2016	4037	Impact of sarcopenia on mortality in patients with cirrhosis	The OR of mortality was 3.23 (95% CI, 2.08–5.01; $P < .001$) for the sarcopenia group. Asians had a HR 2.45 (95% CI: 1.44–4.16) of mortality whereas Westerners had a HR 1.45 (95% CI: 1.002–2.09).
Yu et al, 2018	Patients with nonalcoholic fatty liver disease	3	2016 to 2017	3226	Association of sarcopenia with steatohepatitis and advanced liver fibrosis in nonalcoholic fatty liver disease	Significant associations between sarcopenia and steatohepatitis (OR = 2.35, 95%CI 1.45–3.81) and between sarcopenia and advanced liver fibrosis (OR = 2.41, 95%CI 1.94–2.98) were found.
Chang et al, 2018	Patients with hepatocellular carcinoma		2013 to 2017	3111	Associations of loss of skeletal muscle mass with overall survival and tumor recurrence.	There was a significant association between sarcopenia and all-cause mortality (crude HR = 2.04, 95% CI: 1.74–2.38; adjusted HR = 1.95, 95% CI: 1.60–2.37). Loss of skeletal muscle mass was associated with tumor recurrence (crude HR = 1.85, 95% CI: 1.44–2.37; adjusted HR = 1.76, 95% CI: 1.27–2.45).
Chang et al, 2018	Patients with liver cirrhosis	6	2013 to 2018	1795	Association between sarcopenia and hepatic encephalopathy	Sarcopenia was positively associated with the presence of hepatic encephalopathy (OR 2.74 with a 95% CI, 1.87–4.01).
Our meta-analysis	Cirrhotic patients without or before liver transplantation	16	2012 to 2018	4070	Association of loss of muscle mass with increased mortality in cirrhotic patients without or before liver transplantation	The pooled crude and adjusted HRs of loss of muscle mass with mortality were 2.05 (95% CI, 1.51–2.78) and 2.36 (95% CI, 1.61–3.46).

CI = confidence interval, HR = hazard ratio, OR = odds ratio.

of CT imaging at a fixed vertebral level to compute the skeletal muscle area allows the measurements to be more comparable among studies and is also less influenced by edema and ascites. Nevertheless, sensitivity analysis performed by excluding studies not using CT yielded no significant change in the association between loss of muscle mass and mortality. In recent years, various imaging tools have been used in evaluation of sarcopenia in patients waiting for liver transplantation, including CT, magnetic resonance imaging, dual-energy X-ray absorptiometry and ultrasonography. Although different methods have been used across studies, sarcopenia remains an independent factor predicting the prognosis waiting for or receiving liver transplantation.[54] Until now, there is lack of studies comparing the prognostic accuracy among various imaging tools. Therefore, when interpreting sarcopenia in the population with liver cirrhosis, we need to be cautious that different methods for measuring muscle mass loss might lead to different conclusions.

Another point worth noting is that there was an insignificant higher association between loss of muscle mass and mortality in patients who were not specific or qualified candidates for liver transplantation compared to those on the transplantation waiting list. Since there are strict enrollment criteria for liver transplantation,[55] we speculated that a discrepancy existed between both groups in terms of cirrhotic severity, which leads to a difference in the magnitude of association. In addition, the association between liver transplant contraindications and malnutrition (i.e., active excessive alcohol intake and noncompliance with therapy) and more intensive management of malnutrition before liver transplantation are possible factors that may modify the relationship between sarcopenia and mortality in patients with liver cirrhosis.

The present study has several limitations. First, all the enrolled studies used retrospective analyses, which were more subject to selection bias. Second, not all the outcomes were reported in each retrieved article, which could lead to potential publication bias. Third, the causes of death were limited in the selected studies and infection was the only item universally recorded. Therefore, the mortality in patients with cirrhosis are associated with loss of muscle mass may be mediated by other pathologic processes, such as hepatic encephalopathy, but these could not be identified through this meta-analysis. Fourth, the cut-off values for lower muscle mass varied among the included articles and all diagnostic protocols lacked assessment of muscle strength and physical performance. Future prospective studies using the criteria proposed by the European Working Group on Sarcopenia in Older People[56] or the Asian Working Group for Sarcopenia[57] should be conducted to determine whether the predictive power is improved after employing a more comprehensive algorithm to diagnose loss of muscle mass. Fifth, our meta-analysis did not separately report mortality according to the duration of follow-up. As the majority of the included studies used retrospective analysis and lacked uniform follow-up periods, we were unable to specify whether the mortality data were based on short-term or long-term follow-up. Sixth, the etiology of liver cirrhosis is an important factor influencing mortality. However, we could not analyze the impact of etiology of liver cirrhosis on our results because the HR in each study was not reported separately according to etiology.

In conclusion, loss of muscle mass was associated with all-cause mortality in patients with liver cirrhosis without or before liver transplantation. Loss of muscle mass in this population could not be predicted by the severity of cirrhosis categorized by the Child-Pugh class. The increased mortality rate in patients with loss of muscle mass might be related to severe infection. Future prospective studies should be conducted to explore whether exercise and nutritional supplementation can reverse muscle mass loss and improve long-term survival in patients with liver cirrhosis.

Author contributions

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