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...
the Model of End-Stage Liver disease (MELD) Scores.[11] The main limitation of both tools is the lack of nutritional assessment.[12] Malnutrition is prevalent in the cirrhotic population and results from an altered metabolism and decreased protein intake.[13] 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.[13] (Table 1).

Loss of skeletal muscle mass may be accompanied by decreased muscle strength and impaired physical performance,[14] and is linked to several adverse health outcomes, including cognitive impairment,[15] depression,[16] 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 I² statistics and was considered significant with I² > 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.[15] 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,[25,29,32,35,36–40] 5 that enrolled patients with...
| Author, year | Patients' characteristic | Muscle mass measurement | Cut-off value for low muscle mass | Definition of sarcopenia | Derived 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 | ≤25.4 cm²/m² for men and ≤19.5 cm²/m² for women | Not mentioned | 142 (60/82) | Median: 53 (total); Interquartile range: 47–67 | All-cause mortality (crude and adjusted HRs); 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 major muscle thickness measured at the L3 or L4 level or at the level of umbilicus | ≤14 mm | Histological confirmation of sarcopenia or based on clinical, biochemical parameters and imaging examinations | 65 (34/31) | Mean: 55±9.2 (total) | All-cause (crude HRs) and infection-related mortality | Age, sex, weight, BMI, etiology of cirrhosis, creatinine, albumin, prothrombin time, MELD score |
| Hein et al 2015 | Patients with any degree of cirrhosis who were evaluated for liver transplantation candidates | Total psoas area measured at the L3 level with the CV density set between -29 and 150 HU | ≤25.4 cm²/m² for men and ≤19.5 cm²/m² 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, creatinine, albumin, prothrombin time, MELD score |
| Hira et al 2016 | Patients with any degree of liver cirrhosis | Biomechanical impedance analysis | 1.7 kg/m² for men and 1.2 kg/m² 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±10 (normal); 74±4 (sarcopenic obesity); 67±10 (sarcopenia); 66±7 (obesity) | All-cause(adjusted HRs) and 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 | ≤52.4 cm²/m² 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 |
| Ibiha et al 2017 | Patients with cirrhosis and acute gastrointestinal (without bleeding) | The total cross-sectional area of bilateral psoas muscles at the L3 level | ≤45.2 cm²/m² for men and ≤32.6 cm²/m² for women | Based on clinical, laboratory, radiological, and histological data | 122 (30/92) | Mean±SD: 51.8±12.3 (total) | All-cause mortality (crude and adjusted HRs) | Age, sex, alcohol use, serum bilirubin, creatinine, albumin, total bilirubin, prothrombin time, MELD score |
| Nishikawa et al 2017 | Patients with liver cirrhosis | Psoas muscle index estimated on CT images | ≤6.36 cm²/m² for men and ≤3.38 cm²/m² for women | Not mentioned | 198 (90/108) | Mean±SD: 61.6±12.9 (total) | All-cause mortality (crude and adjusted HRs) | In-hospital and infection-related mortality |
| Abay et al 2018 | Nonalcoholic steatohepatitis cirrhotic patients evaluated for liver transplantation | Cross-sectional areas of the left and right psoas muscles at L3 | ≤1565 mm² in men and ≤1404 mm² in women | Based on abdominal CT scan or MRI | 146 (94/52) | Median: 59 (total) | Overall mortality | Age, sex, serum albumin, prothrombin time, MELD score, liver stiffness, CT-Pugh score |
| Bhani et al 2018 | Patients with cirrhosis who were evaluated for liver transplantation | Cross-sectional areas of the muscles and adipose tissue at L3 | ≤39 cm²/m² for females and ≤50 cm²/m² 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, cirrhosis, creatinine, serum albumin, prothrombin time, MELD score, sodium, ammonium, Chl-Pugh score, ascites |
| Badi et al 2018 | Patients with cirrhosis listed for liver transplantation | Total skeletal muscle cross-sectional area, and psoas muscle area at L3 | ≤39 cm²/m² in men and ≤50 cm²/m² in women | Based on abdominal CT scan | 353 (107/246) | Mean±SD: 56±9 (total) | All-cause mortality (crude and adjusted HRs) | Age, sex, BMI, MELD score, age, MELD, ascites, creatinine, serum albumin, total bilirubin, sodium, prothrombin time, MELD score, sodium, ammonium, MELD score, Chl-Pugh score, ascites |
| Gu et al 2018 | Patients with liver cirrhosis | Psoas muscle cross-sectional area and thickness at L3 | ≤52.4 cm²/m² in men and ≤35.8 cm²/m² in women; 35th percentile and hand grip strength | Based on abdominal CT scan | 653 (154/499) | Mean±SD: 53.6±10.2 (total) | All-cause mortality (crude and adjusted HRs) | Age, sex, BMI, history of diabetes, diabetes, prothrombin time, platelet count, AST, ALB, bilirubin, albumin, creatinine, sodium |
| Kalafateli et al 2018 | Patients with liver cirrhosis | Psoas muscle cross-sectional area of L4/L5 | ≤3.48 HU | Based on abdominal CT scan | 98 (27/71) | Mean±SD: 51.8±9.8 (total) | All-cause mortality (crude and adjusted HRs) | Age, sex, Child-Pugh stage, height, BMI, total bilirubin, prothrombin time, creatinine, MELD score, sarcopenia |
| Wang et al 2018 | Patients with liver cirrhosis who were evaluated for liver transplantation | Cross-sectional areas of the muscles and adipose tissue at L3 | ≤30 cm²/m² in men and ≤39 cm²/m² in women; men with BMI ≥25: ≤43 cm²/m², men with BMI ≥25: ≤53 cm²/m², women ≤41 cm²/m² | Based on abdominal CT scan | 452 (123/329) | Mean±SD: 51.8±9.8 (total) | All-cause mortality (crude and adjusted HRs) | Not applicable |
| Lucid et al 2018 | Cirrhotic patients hospitalised for sepsis | Mid-arm muscle circumference of the non-dominant arm | ≤10% percentile | Not mentioned | 74 (18/56) | Mean±SD: 49.7±16 years (total) | In-hospital mortality | Not applicable |
| Praktiknjo et al 2018 | Cirrhotic patients with transjugular intrahepatic portosystemic shunt | Total vector spine muscle area and the intramuscular fat tissue area using MRI | Not mentioned | Not mentioned | 71 (20/42) | Median±SD: 58 (total); Interquartile range: 18–78 | All-cause mortality (crude and adjusted HRs) | Age, sex, total MA, FRA, fat area, sarcopenia, number connection test, HE, hepatorenal syndrome, AspCT, MELD, bilirubin, prothrombin time |
different severities of liver cirrhosis,\(^{1,27,28,31,36,37}\) 1 that enrolled patients with concomitant ascites,\(^{1,26}\) 1 that enrolled patients with cirrhotic admitted for treatment of sepsis,\(^{1,34}\) 1 that enrolled patients with cirrhotic receiving transjugular intrahepatic portosystemic shunts,\(^{25}\) and 1 that enrolled patients with acute variceal bleeding.\(^{1,30}\) 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,\(^{1,34}\) 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,\(^ {1,18,25–30}\) while the adjusted HRs were available in 11.\(^ {1,18,25,27,29–31}\) 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).
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 |
| Ishizu 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 |
| Prakrbojo et al 2018 | ★ ★ ★ ★ ★ ★ ★ ★ | 9 |
| van Vuigt et al 2018 | ★ ★ ★ ★ ★ ★ ★ ★ | 8 |
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. 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. 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.

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. Yu et al found that sarcopenia was associated with steatohepatitis or advanced liver fibrosis in patients with nonalcoholic fatty liver disease. Chang et al demonstrated that sarcopenia increased the mortality rate in
hepatocellular carcinoma, as well as the incidence of hepatic encephalopathy in cirrhotic patients. 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. 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. 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. 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 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.
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. 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. 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. Another possible mechanism is that muscle mass loss reflects the status of malnutrition, a well-known factor in immunodeficiency. 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. In contrast, the use
| 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 1.43–3.81) and between sarcopenia and advanced liver fibrosis (OR = 2.41, 95% CI 1.34–2.98) were found. |
| Chang et al, 2018| Patients with hepatocellular carcinoma                 | 2013 to 2017                   | 3111                             | Association 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 2.06 (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. 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 compared to those on the transplantation waiting list. 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.

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

Conceptualization: Ke-Vin Chang.
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