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**Role of sarcopenia in the prognosis of cirrhosis: Going beyond the model for end-stage liver diseases score**

Kim HY *et al.* Sarcopenia in liver cirrhosis

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**Abstract**

Estimating the prognosis of patients with cirrhosis remains challenging, because the natural history of cirrhosis varies according to the cause, presence of portal hypertension, liver synthetic function, and the reversibility of underlying disease. Conventional prognostic scoring systems, including the Child–Turcotte–Pugh scoreor Model for End-Stage Liver Diseases are widely used; however, revised models have been introduced to improve prognostic performance. Although sarcopenia is one of the most common complications related to survival of patients with cirrhosis, the newly proposed prognostic models lack a nutritional status evaluation of patients. This is reflected by the lack of an optimal index for sarcopenia in terms of objectivity, reproducibility, practicality, and prognostic performance and of a consensus definition for sarcopenia in patients with cirrhosis in whom ascites and edema may interfere with a body composition analysis. Quantifying skeletal muscle mass using cross-sectional abdominal imaging is a promising tool for assessing sarcopenia. As radiological imaging provides direct visualization of body composition, it is useful to evaluate sarcopenia in patients with cirrhosis whose body mass index, anthropometric measurements, or biochemical markers are inaccurate on a nutritional assessment. Sarcopenia defined by cross-sectional imaging-based muscular assessment is prevalent and predicts mortality in patients with cirrhosis. Sarcopenia alone or in combination with conventional prognostic systems shows promise for a cirrhosis prognosis. Including an objective assessment of sarcopenia with conventional scores to optimize the outcome prediction for patients with cirrhosis needs further research.

**Key words:** Liver Cirrhosis; Model for end-stage liver diseases score; Mortality; Prognosis; Sarcopenia

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**Core tip:** Sarcopenia is one of the most common complications associated with survival in cirrhotic patients. However, the lack of an objective and reliable method to quantify muscle mass has limited the general incorporation of sarcopenia into cirrhosis prognostic scores. In this article, we highlight cross-sectional imaging-based estimation of skeletal muscle mass for diagnosing sarcopenia and assessing the prognosis of cirrhosis patients. In addition, we explore the possibility of incorporating sarcopenia into conventional prognostic scoring systems for better prognostication in cirrhosis patients.

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**INTRODUCTION**

Cirrhosis is a consequence of chronic liver injury that leads to necroinflammation, fibrosis, hepatocellular dysfunction, and vascular remodeling. Although liver transplantation is the only curative treatment for cirrhosis, this option is not available for most patients. Therefore, management is generally focused on preventing and controlling complications. Complications including ascites, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, or hepatocellular carcinoma (HCC) are the most widely recognized[1]. Malnutrition is one of the most frequent complications in patients with cirrhosis, and it adversely affects other complications, quality of life, survival, and outcome after liver transplantation[2]. Despite its high prevalence and important prognostic role, muscle wasting or sarcopenia, which is a major feature of malnutrition, has not been highlighted until recently.

Conventional prognostic scores for patients with cirrhosis, such as the Child–Turcotte–Pugh (CTP) score or the model for end-stage liver diseases (MELD) score, have limitations, including the lack of a nutritional status evaluation. This may be caused by the lack of a clear definition and the complexity of a nutritional assessment in patients with cirrhosis and fluid overload[3-5]. Several tools have been introduced to measure the nutritional status of patients with cirrhosis; however, a lack of objectivity, reproducibility, and prognostic performance limits their wide application[3]. Currently, muscular assessments using cross-sectional imaging obtained by computed tomography (CT) scans or magnetic resonance imaging (MRI) constitute objective and reproducible methods for nutritional assessment and detection of sarcopenia. Quantifying skeletal muscle mass is not biased by edema or ascites, which frequently presents in decompensated patients with cirrhosis, and reflects a chronic decrease in overall health rather than the acute severity of liver disease[6].

Several investigators reported that sarcopenia is highly prevalent and an independent prognostic factor for mortality in patients with cirrhosis[7-11]. Adding muscle wasting to the currently accepted prognostic scores has shown promising results[12]. Therefore, sarcopenia quantified by an objective method combined with commonly used prognostic systems has the potential to improve prognostication of patients with cirrhosis; however, prospective validation in large cohorts remains elusive. We discuss the current prognostic models and investigate the prevalence and prognostic value of sarcopenia in patients with cirrhosis.

**CONVENTIONAL PROGNOSTIC SYSTEMS FOR LIVER CIRRHOSIS**

Predicting prognosis is crucial in the management of patients with cirrhosis. A number of prognostic models have been derived and validated. The CTP and MELD scores are the most widely used systems to predict mortality in patients with cirrhosis. The CTP score was originally designed to predict the outcome of patients with cirrhosis during surgery[13] and was extended for determining prognosis, treatment response, and prioritizing patients for liver transplantation (LT) who were on the waiting list[14]. The MELD scoring system was initially developed to predict early mortality in patients with cirrhosis undergoing a transjugular intrahepatic portosystemic shunt[15] and is composed of three objective parameters, including serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine. Subsequently, the MELD score has been shown to be useful for predicting short-term mortality in various patients with cirrhosis[16,17]. Since 2002, the MELD score has replaced the CTP score for organ allocation in patients waiting for LT in the United States, due to the advantage of including only objective laboratory variables and its superior ability to predict short-term outcomes compared to the CTP score[18].

 However, the MELD score also has some drawbacks, including variability in laboratory parameters, misclassification of some patients with a low MELD score, and the lack of a nutritional status assessment[19]. Many researchers have tried to improve the prognostic performance of the MELD score. Hyponatremia accurately predicts short-term mortality independently of the MELD score and is often associated with ascites, hepatorenal syndrome, and liver-related mortality[20-22]. Incorporating serum sodium into the MELD score, known as MELD-Na, improves its predictive ability, particularly for patients with a low MELD score[22]. The MELD-to-sodium ratio (MESO) index and the ReFit MELD-Na have been proposed to further optimize prognostic scoring systems. The MESO index provides better predictive ability compared to the original MELD score[23], and the ReFit MELD-Na shows better performance for predicting short-term mortality in patients waiting for LT compared to the original MELD score and MELD-Na[24]. In addition, hypoalbuminemia negatively impacts waiting-list mortality after adjusting for the MELD score, serum sodium, and other covariates. A novel model including the MELD score and serum sodium and albumin, called the five-variable MELD, improves the predictive performance of short-term mortality among patients on the LT waiting list[25].

Despite these efforts to modify the original MELD scoring systems, little has been done to incorporate nutritional status into conventional prognostic models. This may be caused by the heterogeneity in the definition of malnutrition and the complexity of a nutritional assessment in patients with cirrhosis and water retention or ascites[3-5]. Adding an objective and readily available marker of nutritional status to the conventional prognostic scoring systems is a promising target to further improve prognostication in patients with cirrhosis.

**NUTRITIONAL ASSESSMENT IN PATIENTS WITH CIRRHOSIS**

Numerous tools for nutritional assessment, *e.g.,* body mass index (BMI), anthropometric measures, and subjective global assessment (SGA), have been introduced[26,27]. However, the usefulness of these methods is limited due to their subjectiveness and the impact of body composition changes in patients with cirrhosis and edema or ascites[28].
 Standard laboratory tests have been used to estimate nutritional status, including prothrombin time, albumin, prealbumin, the creatinine height index, and transferrin. Because these common nutritional status parameters are confounded by cirrhosis, their utility in patients with cirrhosis is limited. Serum albumin, prealbumin, and transferrin levels decrease, and prothrombin time is prolonged due to impaired hepatic synthetic function, which results in an underestimation of nutritional status in patients with cirrhosis[29]. In addition, the creatinine height index is not an accurate marker of malnutrition due to frequently impaired kidney function in patients with cirrhosis[30].

The interpretation of anthropometric measures is also confusing, because they are influenced by ascites, edema, and salt or diuretic intake in patients with cirrhosis[31]. The SGA scale assesses weight changes, dietary intake, gastrointestinal symptoms, medical diagnoses, and a physical examination. However, the SGA underestimates nutritional status in patients with cirrhosis[26].

Body composition (*i.e.,* body fat mass and lean mass) is essential to estimate nutritional status. Several indirect methods have been used to measure body composition in patients with cirrhosis, including total-body electrical conductivity, bioelectrical impedance, dual energy X-ray absorptiometry, air displacement plethysmography, and magnetic resonance spectroscopy[32-34]. These tools are on the basis of the two-compartment model composed of body fat mass and fat-free mass. Nonfat or lean mass is estimated from the weight remaining after determining whole body weight and fat mass. Because skeletal muscle mass accounts for approximately 50% of lean body mass, measures of lean body or fat-free mass indirectly estimate whole body skeletal muscle mass[35]. A bioelectrical impedance analysis measures the body’s resistance to the flow of alternating current, and dual energy X-ray absorptiometry estimates body composition using low-dose X-rays. Yet, there is a lack of accuracy in these methods in the presence of fluid retention, which is frequently encountered in patients with cirrhosis[34,36].

 CT scans or MRI is the gold standard method to quantify skeletal muscle mass. Muscle area determined from a single-slice abdominal scan obtained by CT or MRI is highly correlated with total body skeletal muscle quantified by whole body multislice analysis[37]. Single abdominal CT or MRI cross-sectional images have emerged as a novel way to objectively and reproducibly assess nutritional status and detect muscle wasting in patients with cirrhosis. Skeletal muscle area is quantified using tissue-specific Hounsfield unit thresholds of −29 to +150[38]. Quantifying psoas muscle or total abdominal muscle areas on a single abdominal CT section at the L3 or L4 level is linearly associated with whole body muscle mass[39] and is a reliable, noninvasive marker of muscle wasting in patients with cirrhosis[8,11,40-45]. Psoas muscle thickness rather than cross-sectional area has also been investigated to improve simplicity and applicability in daily practice[7,9].

A radiological assessment of skeletal muscle mass has several advantages over traditional methods for patients with cirrhosis. First, it provides direct visualization and measurements of tissue compartments and is not biased by fluid retention that commonly presents in patients with cirrhosis. Second, additional scanning is not required to quantify body tissues, because abdominal CT scans are routinely performed to screen for HCC in patients with cirrhosis. Third, it provides an accurate, objective, and reproducible measure of skeletal muscle mass.

**DEFINITION OF SARCOPENIA**

Sarcopenia is generally defined as a reduction in muscle mass two standard deviations below the healthy young adult mean[46]. Sarcopenia is traditionally associated with aging; however, it can occur earlier in patients with malignancy and chronic disease[47]. Despite the recent consensus statement of the European Working Group on Sarcopenia in Older People that recommends taking into account both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia[48], the use of muscle mass versus function to define sarcopenia remains controversial. Moreover, muscle mass alone has been widely used to define sarcopenia and is associated with prognosis in patients with various conditions[49]. As CT or MRI imaging is the gold standard tool to quantify skeletal muscle mass, skeletal muscle mass calculated from abdominal cross-sectional images is a great resource to define sarcopenia.

 Recent studies investigating sarcopenia in patients with cirrhosis utilized cross-sectional muscle area normalized for stature (cm2/m2), called the L3 skeletal muscle index (L3 SMI). In most studies[8,10,11,40], the L3 SMI cutoffs for defining sarcopenia were chosen based on a sarcopenia study of patients with cancer[50] (L3 SMI: ≤ 38.5 cm2/m2 for women and ≤ 52.4 cm2/m2 for men). More recent studies[43,45] have adopted sarcopenia cutoffs based on a study that optimally stratified patients with solid tumors[51] (L3 SMI: ≤ 41 cm2/m2 for women and ≤ 53 cm2/m2 for men with a BMI ≥ 25 kg/m2 and ≤ 43 cm2/m2 for patients with BMI < 25 kg/m2) (Table 1). In addition, new sarcopenia cutoff values for patients with cirrhosis have been reported (L3 SMI: ≤ 42 cm2/m2 for women and ≤ 50 cm2/m2 for men)[52] and were similar to those of cancer patients.

**PATHOGENESIS OF SARCOPENIA IN CIRRHOSIS**

The pathogenesis of sarcopenia in cirrhosis is multifactorial and not fully understood. The mechanisms that contribute to sarcopenia include inadequate dietary intake, metabolic disturbances, and malabsorption (Figure 1).

Inadequate dietary intake is common in patients with cirrhosis. Nausea and early satiety secondary to ascites, delayed gastric emptying, impaired gut motility, and small intestinal bacterial overgrowth contribute to poor intake[53]. Loss of appetite related to upregulation of tumor necrosis factor-α and leptin[54,55] and altered taste sensation associated with zinc deficiency[56] also contribute to decreased dietary intake. Dietary restriction, such as sodium restriction, decreased protein intake, and iatrogenic fasting during hospitalization can aggravate poor oral intake. Additionally, poor and irregular feeding is common in cirrhotic patients with active alcoholism, and might be aggravated by low socioeconomic status[57].

Because cirrhotic liver tissue exhibits impaired synthesis and storage of glycogen, relatively short periods of fasting in patients with cirrhosis result in the breakdown of fat and muscle and promote gluconeogenesis from non-carbohydrate sources[58]. Unless dietary protein intake is sufficient, this can lead to muscle wasting. About 15%–30% of cirrhotic patients are hypermetabolic. The cause of hypermetabolism is unclear; activation of the sympathetic nervous system through hyperdynamic circulation, intestinal bacterial translocation, or systemic inflammation may partially explain the underlying mechanism of hypermetabolism in cirrhosis. Increased energy expenditure in cirrhotic patients accelerates the degradation of protein, which may be aggravated by sepsis[5].

Malabsorption of nutrients in cirrhotic patients is caused by portosystemic shunting, chronic pancreatitis secondary to alcohol abuse, intraluminal bile salt deficiency in cholestasis, and overgrowth of bacteria in the small intestine[59].

**PREVALENCE AND PREDICTORS OF SARCOPENIA IN CIRRHOSIS**

Cross-sectional imaging studies have reported that the prevalence of sarcopenia is 30%–70% among patients with cirrhosis (Table 1). This wide range is partly explained by the lack of an operational definition for sarcopenia in patients with cirrhosis, patient baseline characteristics, and diversity in the cause and severity of liver disease among studies[8,10,11,40,43,45,60].

Sarcopenia is more frequent in men than in women[8,10,11,45] and in patients with a low BMI[8,10,11,40,45]. The proportion of patients with sarcopenia is higher in those with alcoholic liver disease (80%) compared to other diseases (31%–71%)[40]. In some reports, CTP or MELD scores were predictors of sarcopenia[11,45], whereas others found that sarcopenia was not correlated with the degree of liver dysfunction assessed by conventional scoring systems (CTP or MELD score)[8,10,43].

**CLINICAL IMPACT OF SARCOPENIA**

***Effect of sarcopenia on survival in patients with cirrhosis***

The survival rates of patients with cirrhosis are significantly lower in those with sarcopenia than in those without (Table 2). The median survival is 19 ± 6 mo in patients with sarcopenia, compared to 34 ± 11 mo in patients without sarcopenia (log-rank, *P* = 0.005)[10]. Another study evaluating patients with concurrent cirrhosis and HCC reported a median survival of 16 ± 6 mo for patients with sarcopenia compared to 28 ± 3 mo for those without sarcopenia (log-rank, *P* = 0.003)[43]. The 1-year probability of survival in patients with sarcopenia is significantly lower than that in patients without sarcopenia (85% *vs* 97%, *P* = 0.01[8]; 52% *vs* 82%, *P* = 0.003[43]; 53% *vs* 83%, *P* = 0.005[10]; 63% *vs* 79%, *P* = 0.04[11]).

***Causes of mortality in patients with sarcopenia and cirrhosis***

The lower survival rate in cirrhotic patients with sarcopenia is thought to be related to a higher proportion of sepsis-related deaths. The sepsis-related mortality rates in patients with and without sarcopenia patients are 22% and 8%, respectively (*P* = 0.02)[10]. As previously reported, the risk of infection is higher in elderly patients with sarcopenia than in those without[61]; therefore, sarcopenia, which reflects impaired immunity, may increase the risk for severe infections in patients with cirrhosis[62]. However, other studies have reported no difference in the frequency of sepsis-related death between patients with and without sarcopenia[8,11,43] (Table 2). Because sarcopenia affects immunity and physiological function[63], sepsis is considered one of the leading causes of death in sarcopenic cirrhosis patients. However, the pathophysiologic mechanism linking sarcopenia and mortality in cirrhosis is unproven. Conflicting results on causes of death call for further research regarding the pathogenic mechanism of sarcopenia in the prognosis of cirrhosis.

***Post-transplantation survival***

Several investigators have reported that muscle mass is significantly associated with post-transplantation mortality (Table 3). In an exploratory analysis, the SMI was significantly associated with post-transplantation survival (HR = 0.97, *P* = 0.014)[60]. DiMartini *et al*[40] demonstrated that muscle mass is a significant predictor of survival in men (HR = 0.95, *P* = 0.01), but not in women (HR = 0.98, *P* = 0.55). Englesbe *et al*[41]showed that the risk of post-transplantation mortality increases as the psoas muscle cross-sectional area decreases (HR = 3.7/1000 mm2 decrease in psoas area; *P* < 0.0001). It has also been reported that sarcopenia is an independent prognostic factor for post-transplant mortality (HR = 2.06, *P* = 0.047)[64]. However, other studies have reported that sarcopenia is not associated with increased mortality after LT[7,45]. Some differences in the units of measure and definitions of sarcopenia used may partly explain dissimilarities between the results of these studies. Further prospective studies are needed to identify the association between sarcopenia and post-transplantation survival.

***Other post-transplantation outcomes***

The frequency of post-transplantion infection is higher in patients with sarcopenia than in those without (17.7% *vs* 7.4%, *P* = 0.03[64]; 26% *vs* 15%, *P* = 0.04[45]). Krell *et al*[42] also showed that as the total psoas area (TPA) decreases, the risk of developing infection increases (odds ratio for tertile 1 *vs* tertile 3, 4.6; 95%CI: 2.25–9.53). Moreover, patients with sarcopenia have longer hospital and intensive care unit stays after LT compared to those of patients without sarcopenia[40,45] (Table 3).

**PROGNOSTIC IMPLICATIONS FOR PATIENTS WITH SARCOPENIA AND CIRRHOSIS**

As described previously, a growing body of literature has emphasized the negative impact of sarcopenia assessed by imaging on the outcome of patients with cirrhosis. Sarcopenia or a measure of muscle mass is an independent predictor of survival for patients with cirrhosis[7-11,43].

The c-statistics for the L3 SMI for predicting 3- and 6-month mortality are 0.64 (0.46–0.83; *P* = 0.1) and 0.67 (0.54–0.81; *P* = 0.02), respectively[43]. The c-statistics for the L3 SMI was also significant for predicting 6-month mortality (0.67, 0.55–0.79; *P* = 0.02) but not 3-month mortality (0.61, 0.47–0.75; *P* = 0.2)[10]. The predictive ability of sarcopenia alone was inferior to that of the MELD or CTP score[10,43].

Considering that the MELD lacks a nutritional assessment and the inferior predictive performance of sarcopenia alone, recent studies have investigated whether modifying the MELD score to include sarcopenia could improve mortality prediction in patients with cirrhosis. The discriminating ability of transverse psoas muscle thickness (TPMT)/height is inferior to that of the MELD score [overall C index (95%CI); 0.67 (0.47–0.82) for TPMT/height, 0.80 (0.60–0.91) for MELD score in a MELD-era cohort]. However, the overall C index (0.82; 95%CI: 0.64–0.93) of the MELD-psoas score, which combines MELD and TPMT/height, is superior to that of the MELD score (0.80; 95%CI: 0.60–0.91) and was similar to that of the MELD-Na score (0.82; 95%CI: 0.63–0.93) in the MELD-era cohort[7]. Another study showed that a novel MELD-sarcopenia score, derived from estimated values given by a Cox model including the MELD score and L3 SMI, is associated with a modest improvement for predicting mortality in patients with cirrhosis [c-statistic (95%CI) for 3-month mortality was 0.68 (0.60–0.76) for MELD and 0.72 (0.65–0.79) for MELD-sarcopenia][65].

Interestingly, the presence of sarcopenia was an independent predictor of mortality in patients with low MELD scores (< 15; log-rank, *P* = 0.02) but not in patients with higher MELD scores (≥ 15, *P* = 0.59)[11]. Another study also demonstrated that low TPMT/height is associated with increasing mortality among patients with refractory ascites and a MELD score ≤ 25, but not in patients without refractory ascites[7]. Therefore, sarcopenia may be useful for risk-stratifying in patients with low MELD scores.

Sarcopenia is an attractive prognostic factor to reduce waiting-list mortality and improve organ allocation in addition to conventional scores, because the CTP and MELD scores mainly reflect liver function but not nutritional status. However, prospective studies that include a large number of patients with cirrhosis are needed prior to the widespread use of sarcopenia alone or in combination with the MELD score as a prognostic factor.

**CHALLENGES IN CLINICAL APPLICATIONS**

***Standardizing the muscularity assessment***

Many studies that investigated the prevalence and impact of sarcopenia on waiting-list mortality or post-transplantation outcomes used muscle cross-sectional area on a single abdominal CT scan as the assessment of muscularity in patients with cirrhosis. Cross-sectional areas of surrounding muscles (*i.e.,* psoas, erector spinae, quadrates lumborum, transverses abdominis, external and internal obliques, and rectus abdominis) in the L3 or L3–4 regions have been quantified using specific computer software and tissue-specific Hounsfield unit thresholds[8,10,11,40,43,45,60]. Other investigators have used TPA measured by outlining the borders of both psoas muscles and computed the cross-sectional area of the psoas muscles[41,42,64]. Measuring psoas muscle mass on a CT scan is easy and accessible. However, total psoas muscle area is only part of the total skeletal muscle mass, and TPA has not been validated as a predictor of total body mass. In contrast, L3 SMI has been shown to be correlated with whole body muscle mass[37]. Because muscularity assessment based on the muscle cross-sectional area is complex and requires specific software, evaluations of the psoas muscle thickness were introduced and have been found to be associated with waiting-list and post-transplant mortality[7,9].

 The L3 vertebra level has been commonly used to calculate the cross-sectional area or psoas muscle thickness on CT scans[8,10,11,43,45,64] based on the finding that cross-sectional muscle area measured at the L3 level best correlates with whole body muscle mass in patients with or without malignancy[37]. However, others have measured cross-sectional muscle area or psoas muscle thickness at the level of L4[9,41,42], L3-4[40,60], or the umbilicus[7]. Although the umbilicus level is easily recognized on an abdominal CT scan, it may vary in patients with massive ascites. In contrast, the sacralization of the L4 vertebrae, lumbarization of the S1 vertebrae, and prominent lordosis in patients with refractory ascites may cause errors when identifying the vertebral level[7]. Thus, the best muscle measurement method that readily reflects whole body skeletal muscle needs to be determined.

***Cutoff values for sarcopenia measured by cross-sectional imaging***

As predefined sarcopenia cutoff values are lacking for patients with cirrhosis, most studies[8,10,11,40] defined sarcopenia using the L3 SMI sex-specific cutoff values from a previous study[50]. These values (L3 SMI: ≤ 38.5 cm2/m2 for women and ≤ 52.4 cm2/m2 for men) are derived from a sarcopenia study that stratified mortality in cancer patients; therefore, it may not be optimal for prognostication of patients with cirrhosis. More recent studies[43,45] adopted sex- and BMI-specific cutoff values for sarcopenia (L3 SMI: ≤ 41 cm2/m2 for women and ≤ 53 cm2/m2 for men with a BMI ≥ 25 kg/m2 and ≤ 43 cm2/m2 for patients with a BMI < 25 kg/m2)[51]. A preliminary report that included 350 patients with cirrhosis established new sarcopenia cutoff values for patients with cirrhosis (L3 SMI: ≤ 42 cm2/m2 for women and ≤ 50 cm2/m2 for men)[52].

***Muscle function***

It may be insufficient to define sarcopenia based only on skeletal muscle mass. Although using muscle function together with muscle mass is controversial [48], the nonlinear relationship between muscle strength and mass provides a basis for adopting both criteria to define sarcopenia[66].

***Sex-specific sarcopenia differences***

Interestingly, the prevalence of sarcopenia is higher in men than in women[8,10,11,40,45,60]. In addition, results regarding the impact of muscle mass on survival or other clinical outcomes differ between men and women[40]. Similarly, skeletal muscle mass predicts 3- and 6-month survival in men with cirrhosis waiting for LT but not in women[10].

Women have more abundant fat stores and more preferentially utilize fat stores compared to skeletal muscle stores[67]. Therefore, fat reserves are more depleted in women, whereas men have a more depleted skeletal muscle mass[68]. Moreover, sex hormone differences may play a role in the way skeletal muscle is turned over[69]. These factors may explain the sex-specific differences in the prevalence and pathophysiology of sarcopenia in patients with cirrhosis. These differences may influence the use of sarcopenia to assess nutritional status and on the utility of a sarcopenia-based prognostic score.

**CONCLUSION**

In view of emerging findings linking sarcopenia with a poor outcome in cirrhotic patients, adopting sarcopenia as a surrogate marker appears to be an appealing approach to prognostication in cirrhosis. Furthermore, sarcopenia determined by cross-sectional imaging-based muscular assessment is objective and reproducible and reflects nutritional and functional status, which is not included in current cirrhosis prognostic models. Accumulating evidence suggests a compelling rationale for the review of current prognostic scoring systems as well as the incorporation of sarcopenia into prognostic models for patients with cirrhosis. Although awareness of the effects of sarcopenia on the outcome of cirrhotic patients is increasing, there are many practical challenges to the application of these findings. Further studies are required to validate the methodology of quantifying muscle mass using cross-sectional imaging and to derive optimal genderspecific cutoffs of the muscle mass index as a determinant of mortality in cirrhotic patients.

In conclusion, optimizing a prognostic scoring system is a crucial topic when managing patients with cirrhosis. Despite the high prevalence of sarcopenia and its potential to influence morbidity and mortality in patients with cirrhosis, sarcopenia is not included in the conventional prognostic scores for cirrhosis, such as the MELD and CTP scores. The lack of an objective, available, and reproducible muscle wasting index has limited the inclusion of sarcopenia into prognostic scoring systems for cirrhosis. Quantifying skeletal muscle mass in patients with liver cirrhosis is challenging; however, a muscularity assessment using single-slice cross-sectional imaging provides a possible application for sarcopenia in the prognostication of patients with cirrhosis. Several novel attempts have been made to combine measurements of sarcopenia with current prognostic models to assess the severity of liver disease. To date, the proposed composite models have been associated with only modest improvement in the prognostication of cirrhosis. While there is still much to be defined, quantification of skeletal muscle mass sheds light on the prognostic role of sarcopenia and might hold promise for further development of prognostic models utilizing sarcopenia. Large-scale prospective studies are required to validate the prognostic implication of sarcopenia in addition to conventional prognostic systems.

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**Figure 1 Pathogenesis of sarcopenia in cirrhosis.**



**Table 1 Definition and prevalence of sarcopenia in cirrhosis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | ***n*** | **Men, *n* (%)** | **Unit of measure** | **Cutoffs for sarcopenia** | **Prevalence**  | **Predictors of sarcopenia** |
| Cruz *et al*[60] | 234 | 157 (67) | L3-4 SMI1(cm2/m2) | Men: ≤ 52.4 cm2/m2Women: ≤ 38.5 cm2/m2 | 70% (men 76%) |  |
| DiMartini *et al*[40] | 338 | 223 (66) | L3-4 SMI1(cm2/m2) | Men: ≤ 52.4 cm2/m2Women: ≤ 38.5 cm2/m2 | 68% (men 76%, women 51%) | 80% prevalence in alcoholic liver disease *vs* 31%–71% in other diseases80% prevalence in normal-weight vs. 62% in obese |
| Hanai *et al*[8] | 130 | 76 (58) | L3 SMI1(cm2/m2) | Men: ≤ 52.4 cm2/m2Women: ≤ 38.5 cm2/m2 | 68% (men 82%, women 50%) | In the multivariate analysis, only the male gender [OR (95%CI) = 5.65 (1.43–24.23), *P* = 0.01] and BMI [0.77 (0.66–0.87), *P* < 0.0001] were independent predictors of sarcopenia. |
| Meza-Junco *et al*[43] | 116 | 98 (84) | L3 SMI1(cm2/m2) | MenBMI ≥ 25 kg/m2: ≤ 53 cm2/m2BMI < 25 kg/m2: ≤ 43 cm2/m2Women: ≤ 41 cm2/m2  | 30% (men 31%, women 28%) | Age was older (61 ± 1 *vs* 57 ± 1 yr, *P* = 0.001), and the INR was higher (1.4 ± 0.08 *vs* 1.2 ± 0.03, *P* = 0.01) in sarcopenic patients than nonsarcopenic patients. |
| Montano-loza *et al*[10] | 112 | 78 (70) | L3 SMI1(cm2/m2) | Men: ≤ 52.4 cm2/m2Women: ≤ 38.5 cm2/m2 | 40% (men 50%, women 18%) | Sarcopenia was more frequent in men (50% *vs* 18%, *P* < 0.001) and patients with a low BMI (26 ± 0.7 *vs* 29 ± 0.8 kg/m2, *P* = 0.003).  |
| Montano-loza *et al*[45] | 248 | 169 (68) | L3 SMI1(cm2/m2) | MenBMI ≥ 25 kg/m2: ≤ 53 cm2/m2BMI < 25 kg/m2: ≤ 43 cm2/m2Women: ≤ 41 cm2/m2 | 45% (men 52%, women 30%) | Sarcopenia was more common in males (*P* = 0.002), patients with ascites (*P* = 0.02), patients with a low BMI (*P* < 0.001), and patients with higher bilirubin levels (*P* = 0.05), creatinine levels (*P* = 0.02), INR (*P* = 0.04), CTP scores (*P* = 0.002), and MELD scores (*P* = 0.002). |
| Tandon *et al*[11] | 142 | 85 (60) | L3 SMI1(cm2/m2) | Men: ≤ 52.4 cm2/m2Women: ≤ 38.5 cm2/m2 | 41% (men 54%, women 21%) | In a multivariate logistic regression analysis, male sex [OR (95%CI) = 5.91 (2.38–14.6)], CTP class C [*vs* CTP class A: 15.4 (1.44–165.7)], and a BMI [0.82 (0.74–0.90)] were independent predictors of sarcopenia. |

1SMI: Skeletal muscle cross-sectional area/height squared. SMI: Skeletal muscle index; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; INR: International normalized ratio; CTP: Child–Turcotte–Pugh; MELD: Model for end-stage liver disease.

**Table 2 Clinical impact of sarcopenia on mortality in cirrhosis patients**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **n** | **Unit of measure** | **Level of****measure** | **Factors associated with survival (HR, 95% CI)** | **Survival among sarcopenic and nonsarcopenic patients** | **Cause of death** |
| Durand *et al*[7] | 562 | TPMT1/ height,mm/m | umbilicus | MELD score (1.2, 1.14–1.27)TPMT/height (0.86, 0.78–0.94) in MELD-era cohort |  |  |
| Hanai *et al*[8] | 130 | SMI2, cm2/m2 | L3 vertebrae | CTP class B (2.39, 1.07–5.95)CTP class C (5.49, 2.11–15.12)BCAA (0.38, 0.19–0.79)Sarcopenia (3.03, 1.42–6.94) | The 1-, 3-, and 5-year survival rates in patients with sarcopenia and nonsarcopenia were 85% and 97%, 63% and 79%, and 53% and 79%, respectively (*P* = 0.01). | No significant difference was seen in cause of death between patients with and without sarcopenia |
| Kim *et al*[9] | 65 | PMTH3, mm/m | L4 vertebrae | PMTH (0.81, 0.68–0.97)  | The median survival was 16 (95%CI: 7–26) mo in patients with PMTH ≤ 14 mm/m.The 1- and 2-yr mortality rates in patients with PMTH ≤ 14 mm/m and PMTH > 14 mm/m were 41.6% and 2.6%, and 66.8% and 15.2%, respectively (*P* < 0.001).  |  |
| Meza-Junco *et al*[43] | 116 | SMI2, cm2/m2 | L3 vertebrae | Serum Na (0.89, 0.81–0.98)MELD (1.06, 1.01–1.12)CTP (2.39, 1.43–4.01)TNM stage (2.03, 1.45–2.84)Sarcopenia (2.20, 1.21–4.02) | The median survival was 16 ± 6 mo *vs* 28 ± 3 mo in sarcopenic patients compared to nonsarcopenic (*P* = 0.003).The 6-month–, and 1-year survival rates in patients with sarcopenia and nonsarcopenia were 67% and 90%, and 52% and 82%, respectively. | No significant difference was seen in the frequency of sepsis-related death between patients with and without sarcopenia (12% *vs* 4%, *P* = 0.2) |
| Montano-loza *et al*[10] | 112 | SMI2, cm2/m2 | L3 vertebrae | CTP (1.85, 1.02–3.36)MELD (1.08, 1.03–1.14)Sarcopenia (2.21, 1.23–3.95) | Median survival was 19 ± 6 mo *vs* 34 ± 11 mo in sarcopenia patients compared to nonsarcopenic patients (*P* = 0.005). The 6-month– and 1-year survival rates in patients with sarcopenia and nonsarcopenia were 71% and 90%, and 53% and 83%, respectively. | The rate of sepsis-related death was significantly higher in sarcopenic patients than nonsarcopenic patients (22% *vs* 8%, *P* = 0.02).  |
| Tandon *et al*[11] | 142 | SMI2, cm2/m2 | L3 vertebrae | Age (1.06, 1.01–1.10)MELD (1.13, 1.09–1.19)Sarcopenia (2.36, 1.23–4.53) | The 1-, 2-, and 3-year survival rates in patients with sarcopenia and nonsarcopenia were 63% and 79%, 51% and 74%, and 51% and 70%, respectively. (*P* = 0.04) | Rates of sepsis-related death: 47% in sarcopenic pateints *vs* 31% in nonsarcopenic patients (*P* = 0.48) |

1TPMT-the diameter of psoas muscle perpendicular to the largest axial psoas muscle diameter; 2SMI-skeletal muscle cross-sectional area/height squared; **3**PMTH- thickness of the right psoas muscle by height. MELD: Model for end-stage liver disease; CTP: Child–Turcotte–Pugh; BCAA: Branched chain amino acid; SMI: Skeletal muscle index; TPMT: Transverse psoas muscle thickness; PMTH: Psoas muscle thickness by height.

**Table 3 Impact of pretransplant sarcopenia on outcomes after liver transplantation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | ***n*** | **Unit of measure** | **Level of****measure** | **Impact on the posttransplant survival** | **Impact on the posttransplant infection** | **Impact on the length of posttransplant hospitalization** |
| Cruz *et al*[60] | 234 | SMI1, cm2/m2 | L3-4 | SMI was significantly associated with survival posttransplantation (HR, 95%CI: 0.97, 0.94–0.99); *P* = 0.014) |  |  |
| DiMartini *et al*[40] | 338 | SMI1, cm2/m2 | L3-4 | Muscle mass was a significant predictor of survival only in men (HR = 0.95, *P* = 0.01) |  | Muscle mass predicted ICU stay, total length of stay, and days of intubation |
| Durand *et al*[7] | 562 | TPMT2/height, mm/m | umbilicus | MELD-psoas score was not an independent prognostic factor for post-transplant mortality in pre-MELD and MELD-era cohorts. |  |  |
| Englesbe *et al*[41] | 163 | TPA3, mm2 | L4 | The risk of postransplantation mortality increased as psoas area decreased (HR = 3.7/1000 mm2 decrease in psoas area; *P* < 0.0001) |  |  |
| Krell *et al*[42] | 207 | TPA3, mm2 | L4 |  | Pretransplant TPA (HR = 0.38, *P* < 0.01) was an independent risk factor for developing a serious posttransplant infection |  |
| Masuda *et al*[64] | 204 | Area of the psoas muscle4, cm2 | L3 | Sarcopenia was an independent prognostic factor for posttransplant mortality (HR = 2.06, *P* = 0.047) | The rate of postoperative sepsis was higher in sarcopenic patients than in nonsarcopenic patients (17.7% *vs* 7.4%, *P* = 0.03). |  |
| Montano-loza *et al*[45] | 248 | SMI1, cm2/m2 | L3 | L3 SMI and the presence of sarcopenia were not associated with increased mortality after liver transplantation. | Bacterial infections within the first 90 d after liver transplantation were more common in sarcopenic patients than in nonsarcopenic patients (26% *vs* 15%, *P* = 0.04). | Sarcopenic patients had longer hospital stays (40 ± 4 *vs* 25 ± 3 d, *P* = 0.005) and longer ICU stays (12 ± 2 *vs* 6 ± 1 d, *P* = 0.001) after liver transplantation than nonsarcopenic patients. |

1SMI (skeletal muscle index): skeletal muscle cross-sectional area/height squared; 2TPMT (transverse psoas muscle thickness): the diameter of psoas muscle perpendicular to the largest axial psoas muscle diameter; 3TPA (transverse psoas area): cross-sectional areas of the left and right psoas muscles; 4Area of the psoas muscle: a × b × π (a and b are the lengths of the major and minor axes of the psoas muscle). HR: hazard ratio; ICU: intensive care unit; MELD: model for end-stage liver disease; OR: odds ratio; SMI: Skeletal muscle index; TPMT: Transverse psoas muscle thickness; TPA: Transverse psoas area.