World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i25.7637

World J Gastroenterol 2015 July 7; 21(25): 7637-7647
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Sarcopenia in the prognosis of cirrhosis: Going beyond the MELD score

Hee Yeon Kim, Jeong Won Jang

Hee Yeon Kim, Jeong Won Jang, Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, Seoul 137-701, South Korea

Author contributions: Kim HY and Jang JW contributed to this paper equally.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Correspondence to: Jeong Won Jang, MD, PhD, Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, the Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 137-701, South Korea. garden@catholic.ac.kr
Telephone: +82-2-22586015
Fax: +82-2-34814028

Received: January 26, 2015
Peer-review started: January 27, 2015
First decision: March 10, 2015
Revised: March 20, 2015
Accepted: May 7, 2015
Article in press: May 7, 2015
Published online: July 7, 2015

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 score or 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 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

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.

Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: Going beyond the MELD score. *World J Gastroenterol* 2015; 21(25): 7637-7647 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i25/7637.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i25.7637

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) 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 have 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 optimize prognostic scoring systems further. 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, for example, 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 work 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 about 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 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 *vs* 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

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 SMI (cm^2/m^2)	Men: ⩽ 52.4 cm^2/m^2 Women: ⩽ 38.5 cm^2/m^2	70% (men 76%)	
DiMartini *et al*[40]	338	223 (66)	L3-4 SMI (cm^2/m^2)	Men: ⩽ 52.4 cm^2/m^2 Women: ⩽ 38.5 cm^2/m^2	68% (men 76%, women 51%)	80% prevalence in alcoholic liver disease *vs* 31%-71% in other diseases 80% prevalence in normal-weight *vs* 62% in obese
Hanai *et al*[8]	130	76 (58)	L3 SMI (cm^2/m^2)	Men: ⩽ 52.4 cm^2/m^2 Women: ⩽ 38.5 cm^2/m^2	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 SMI (cm^2/m^2)	Men BMI ⩾ 25 kg/m^2: ⩽ 53 cm^2/m^2 BMI < 25 kg/m^2: ⩽ 43 cm^2/m^2 Women: ⩽ 41 cm^2/m^2	30% (men 31%, women 28%)	Age was older (61 ± 1 yr *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 SMI (cm^2/m^2)	Men: ⩽ 52.4 cm^2/m^2 Women: ⩽ 38.5 cm^2/m^2	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 kg/m^2 *vs* 29 ± 0.8 kg/m^2, P = 0.003)
Montano-loza *et al*[45]	248	169 (68)	L3 SMI (cm^2/m^2)	Men BMI ⩾ 25 kg/m^2: ⩽ 53 cm^2/m^2 BMI < 25 kg/m^2: ⩽ 43 cm^2/m^2 Women: ⩽ 41 cm^2/m^2	45% (men 52%, women 30%)	Sarcopenia was more common in men (P = 0.002), patients with ascites (P = 0.02), patients with 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 SMI (cm^2/m^2)	Men: ⩽ 52.4 cm^2/m^2 Women: ⩽ 38.5 cm^2/m^2	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

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 (cm^2/m^2), called the L3 skeletal muscle index (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 cm^2/m^2 for women and ⩽ 52.4 cm^2/m^2 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 cm^2/m^2 for women and ⩽ 53 cm^2/m^2 for men with a BMI ⩾ 25 kg/m^2 and ⩽ 43cm^2/m^2 for patients with BMI < 25 kg/m^2) (Table 1). In addition, new sarcopenia cutoff values for patients with cirrhosis have been reported (L3 SMI: ⩽ 42 cm^2/m^2 for women and ⩽ 50 cm^2/m^2 for men)[52] and are 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

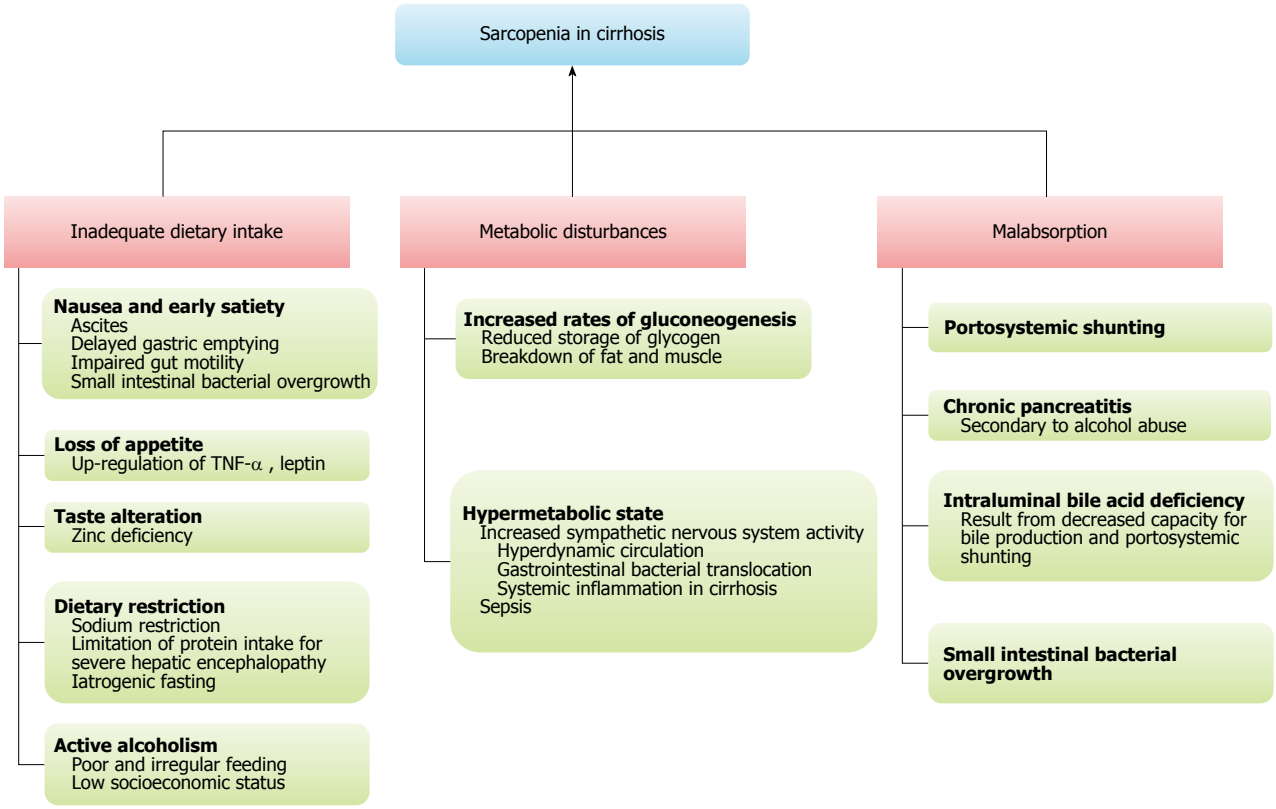

Figure 1 Pathogenesis of sarcopenia in cirrhosis.

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,

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	TPMT/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	SMI, cm^2/m^2	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-yr 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	PMTH, 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	SMI, cm^2/m^2	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-mo, and 1-yr 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	SMI, cm^2/m^2	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-mo and 1-yr 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	SMI, cm^2/m^2	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-yr 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 patients *vs* 31% in nonsarcopenic patients (P = 0.48)

BCAA: Branched chain amino acid; PMTH: Psoas muscle thickness by height.

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 pathophysiological 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 mm^2 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.

Table 3 Impact of pretransplant sarcopenia on outcomes after liver transplantation

Ref.	*n*	Unit of measure	Level of measure	Impact on the post-transplant survival	Impact on the post-transplant infection	Impact on the length of post-transplant hospitalization
Cruz *et al*[60]	234	SMI, cm^2/m^2	L3-4	SMI was significantly associated with survival post-transplantation (HR, 95%CI: 0.97, 0.94-0.99); $P = 0.014$)		
DiMartini *et al*[40]	338	SMI, cm^2/m^2	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	TPMT/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	TPA, mm^2	L4	The risk of post-transplantation mortality increased as psoas area decreased (HR = 3.7/1000 mm^2 decrease in psoas area; $P < 0.0001$)		
Krell *et al*[42]	207	TPA, mm^2	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 muscle, cm^2	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	SMI, cm^2/m^2	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 d *vs* 25 ± 3 d, $P = 0.005$) and longer ICU stays (12 ± 2 d *vs* 6 ± 1 d, $P = 0.001$) after liver transplantation than nonsarcopenic patients

ICU: Intensive care unit.

Other post-transplantation outcomes

The frequency of post-transplantation 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-mo 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-mo mortality (0.67, 0.55-0.79; $P = 0.02$) but not 3-mo 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-mo mortality was 0.68 (0.60-0.76) for MELD and 0.72 (0.65-0.79) for MELD-sarcopenia][65].

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 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 cm^2/m^2 for women and ≤ 52.4 cm^2/m^2 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 cm^2/m^2 for women and ≤ 53 cm^2/m^2 for men with a BMI ≥ 25 kg/m^2 and ≤ 43 cm^2/m^2 for patients with a BMI < 25 kg/m^2)[51]. A preliminary report that included 350 patients with cirrhosis established new sarcopenia cutoff values for patients with cirrhosis (L3 SMI: ≤ 42 cm^2/m^2 for women and ≤ 50 cm^2/m^2 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

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-mo 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 gender–specific 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 prospective studies are required to validate the prognostic implication of sarcopenia in addition to conventional prognostic systems.

REFERENCES

1 **Tsochatzis EA**, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014; **383**: 1749-1761 [PMID: 24480518 DOI: 10.1016/s0140-6736(14)60121-5]

2 **Periyalwar P**, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. *Clin Liver Dis* 2012; **16**: 95-131 [PMID: 22321468 DOI: 10.1016/j.cld.2011.12.009]

3 **Johnson TM**, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. *Nutr Clin Pract* 2013; **28**: 15-29 [PMID: 23319353 DOI: 10.1177/0884533612469027]

4 **Juakiem W**, Torres DM, Harrison SA. Nutrition in cirrhosis and chronic liver disease. *Clin Liver Dis* 2014; **18**: 179-190 [PMID: 24274873 DOI: 10.1016/j.cld.2013.09.004]

5 **O'Brien A**, Williams R. Nutrition in end-stage liver disease: principles and practice. *Gastroenterology* 2008; **134**: 1729-1740 [PMID: 18471550 DOI: 10.1053/j.gastro.2008.02.001]

6 **Montano-Loza AJ**. Clinical relevance of sarcopenia in patients with cirrhosis. *World J Gastroenterol* 2014; **20**: 8061-8071 [PMID: 25009378 DOI: 10.3748/wjg.v20.i25.8061]

7 **Durand F**, Buyse S, Francoz C, Laouénan C, Bruno O, Belghiti J, Moreau R, Vilgrain V, Valla D. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *J Hepatol* 2014; **60**: 1151-1157 [PMID: 24607622 DOI: 10.1016/j.jhep.2014.02.026]

8 **Hanai T**, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, Takai K, Shimizu M, Moriwaki H. Sarcopenia impairs prognosis of patients with liver cirrhosis. *Nutrition* 2015; **31**: 193-199 [PMID: 25441595 DOI: 10.1016/j.nut.2014.07.005]

9 **Kim TY**, Kim MY, Sohn JH, Kim SM, Ryu JA, Lim S, Kim Y. Sarcopenia as a useful predictor for long-term mortality in cirrhotic patients with ascites. *J Korean Med Sci* 2014; **29**: 1253-1259 [PMID: 25246744 DOI: 10.3346/jkms.2014.29.9.1253]

10 **Montano-Loza AJ**, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, Sawyer MB. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012; **10**: 166-173, 173.e1 [PMID: 21893129 DOI: 10.1016/j.cgh.2011.08.028]

11 **Tandon P**, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl* 2012; **18**: 1209-1216 [PMID: 22740290 DOI: 10.1002/lt.23495]

12 **Montano-Loza AJ**, Meza-Junco J, Prado CMM, Baracos VE, Sawyer MB, Beaumont C, Ma M, Kneteman N, Myers RP. Inclusion of sarcopenia within MELD (MELD-Sarcopenia) and the prediction of mortality in patients with cirrhoiss. *Hepatology* 2013; **58** Suppl: 1041A

13 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

14 **Christensen E**. Prognostic models including the Child-Pugh, MELD and Mayo risk scores--where are we and where should we go? *J Hepatol* 2004; **41**: 344-350 [PMID: 15288486 DOI: 10.1016/j.jhep.2004.06.005]

15 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]

16 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

17 **Botta F**, Giannini E, Romagnoli P, Fasoli A, Malfatti F,

Chiarbonello B, Testa E, Risso D, Colla G, Testa R. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. *Gut* 2003; **52**: 134-139 [PMID: 12477775 DOI: 10.1136/gut.52.1.134]

18 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]

19 **Huo TI**, Lee SD, Lin HC. Selecting an optimal prognostic system for liver cirrhosis: the model for end-stage liver disease and beyond. *Liver Int* 2008; **28**: 606-613 [PMID: 18433390 DOI: 10.1111/j.1478-3231.2008.01727.x]

20 **Arroyo V**, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis: pathophysiological basis of therapy and current management. *J Hepatol* 2003; **38** Suppl 1: S69-S89 [PMID: 12591187]

21 **Heuman DM**, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology* 2004; **40**: 802-810 [PMID: 15382176 DOI: 10.1002/hep.20405]

22 **Kim WR**, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. *N Engl J Med* 2008; **359**: 1018-1026 [PMID: 18768945 DOI: 10.1056/NEJMoa0801209]

23 **Huo TI**, Wang YW, Yang YY, Lin HC, Lee PC, Hou MC, Lee FY, Lee SD. Model for end-stage liver disease score to serum sodium ratio index as a prognostic predictor and its correlation with portal pressure in patients with liver cirrhosis. *Liver Int* 2007; **27**: 498-506 [PMID: 17403190 DOI: 10.1111/j.1478-3231.2007.01445.x]

24 **Leise MD**, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. *Gastroenterology* 2011; **140**: 1952-1960 [PMID: 21334338 DOI: 10.1053/j.gastro.2011.02.017]

25 **Myers RP**, Shaheen AA, Faris P, Aspinall AI, Burak KW. Revision of MELD to include serum albumin improves prediction of mortality on the liver transplant waiting list. *PLoS One* 2013; **8**: e51926 [PMID: 23349678 DOI: 10.1371/journal.pone.0051926]

26 **Alvares-da-Silva MR**, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. *Nutrition* 2005; **21**: 113-117 [PMID: 15723736 DOI: 10.1016/j.nut.2004.02.002]

27 **Gunsar F**, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, Sabin C, Burroughs AK. Nutritional status and prognosis in cirrhotic patients. *Aliment Pharmacol Ther* 2006; **24**: 563-572 [PMID: 16827812 DOI: 10.1111/j.1365-2036.2006.03003.x]

28 **Peng S**, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. *Am J Clin Nutr* 2007; **85**: 1257-1266 [PMID: 17490961]

29 **Sobhonslidsuk A**, Roongpisuthipong C, Nantiruj K, Kulapongse S, Songchitsomboon S, Sumalnop K, Bussagorn N. Impact of liver cirrhosis on nutritional and immunological status. *J Med Assoc Thai* 2001; **84**: 982-988 [PMID: 11759979]

30 **Francoz C**, Prié D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, Valla D, Durand F. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. *Liver Transpl* 2010; **16**: 1169-1177 [PMID: 20879015 DOI: 10.1002/lt.22128]

31 **Thuluvath PJ**, Triger DR. Evaluation of nutritional status by using anthropometry in adults with alcoholic and nonalcoholic liver disease. *Am J Clin Nutr* 1994; **60**: 269-273 [PMID: 8030606]

32 **Horber FF**, Thomi F, Casez JP, Fonteille J, Jaeger P. Impact of hydration status on body composition as measured by dual energy X-ray absorptiometry in normal volunteers and patients on haemodialysis. *Br J Radiol* 1992; **65**: 895-900 [PMID: 1422663]

33 **Madden AM**, Morgan MY. The potential role of dual-energy X-ray absorptiometry in the assessment of body composition in cirrhotic patients. *Nutrition* 1997; **13**: 40-45 [PMID: 9058447]

34 **Pirlich M**, Schütz T, Spachos T, Ertl S, Weiss ML, Lochs H, Plauth M. Bioelectrical impedance analysis is a useful bedside technique to assess malnutrition in cirrhotic patients with and without ascites. *Hepatology* 2000; **32**: 1208-1215 [PMID: 11093726 DOI: 10.1053/jhep.2000.20524]

35 **Chinn KS**, Hannon JP. Relationship of muscle protein to other components of the fat-free mass. *Am J Physiol* 1966; **211**: 993-997 [PMID: 5926591]

36 **Fiore P**, Merli M, Andreoli A, De Lorenzo A, Masini A, Ciuffa L, Valeriano V, Balotta MT, Riggio O. A comparison of skinfold anthropometry and dual-energy X-ray absorptiometry for the evaluation of body fat in cirrhotic patients. *Clin Nutr* 1999; **18**: 349-351 [PMID: 10634919 DOI: 10.1054/clnu.1999.0048]

37 **Shen W**, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, Heymsfield SB, Heshka S. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* (1985) 2004; **97**: 2333-2338 [PMID: 15310748 DOI: 10.1152/japplphysiol.00744.2004]

38 **Mitsiopoulos N**, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* (1985) 1998; **85**: 115-122 [PMID: 9655763]

39 **Mourtzakis M**, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* 2008; **33**: 997-1006 [PMID: 18923576 DOI: 10.1139/h08-075]

40 **DiMartini A**, Cruz RJ, Dew MA, Myaskovsky L, Goodpaster B, Fox K, Kim KH, Fontes P. Muscle mass predicts outcomes following liver transplantation. *Liver Transpl* 2013; **19**: 1172-1180 [PMID: 23960026 DOI: 10.1002/lt.23724]

41 **Englesbe MJ**, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, Holcombe SA, Wang SC, Segev DL, Sonnenday CJ. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg* 2010; **211**: 271-278 [PMID: 20670867 DOI: 10.1016/j.jamcollsurg.2010.03.039]

42 **Krell RW**, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, Malani PN. Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. *Liver Transpl* 2013; **19**: 1396-1402 [PMID: 24151041 DOI: 10.1002/lt.23752]

43 **Meza-Junco J**, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, Esfandiari N, Lieffers JR, Sawyer MB. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol* 2013; **47**: 861-870 [PMID: 23751844 DOI: 10.1097/MCG.0b013e318293a825]

44 **Montano-Loza AJ**. Muscle wasting: a nutritional criterion to prioritize patients for liver transplantation. *Curr Opin Clin Nutr Metab Care* 2014; **17**: 219-225 [PMID: 24613858 DOI: 10.1097/mco.0000000000000046]

45 **Montano-Loza AJ**, Meza-Junco J, Baracos VE, Prado CM, Ma M, Meeberg G, Beaumont C, Tandon P, Esfandiari N, Sawyer MB, Kneteman N. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. *Liver Transpl* 2014; **20**: 640-648 [PMID: 24678005 DOI: 10.1002/lt.23863]

46 **Baumgartner RN**, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755-763 [PMID: 9554417 DOI: 10.1093/oxfordjournals.aje.a009520]

47 **Marcell TJ**. Sarcopenia: causes, consequences, and preventions. *J Gerontol A Biol Sci Med Sci* 2003; **58**: M911-M916 [PMID: 14570858]

48 **Cruz-Jentoft AJ**, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412-423 [PMID: 20392703 DOI: 10.1093/ageing/afq034]

49 **Lang T**, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. *Osteoporos Int* 2010; **21**: 543-559 [PMID: 19779761 DOI: 10.1007/s00198-009-1059-y]

50 **Prado CM**, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* 2008; **9**: 629-635 [PMID: 18539529 DOI: 10.1016/S1470-2045(08)70153-0]

51 **Martin L**, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; **31**: 1539-1547 [PMID: 23530101 DOI: 10.1200/JCO.2012.45.2722]

52 **Montano-Loza AJ**, Meza-Junco J, Prado CMM, Tandon P, Bain VG, Ma M, Beaumont C, Estandiari N, Sawyer MB, Baracos VE. New cutoff values for sarcopenia for predicting 6-month mortality in cirrhotic patients. *J Hepatol* 2013; **58** Suppl: S95

53 **Quigley EM**. Gastrointestinal dysfunction in liver disease and portal hypertension. Gut-liver interactions revisited. *Dig Dis Sci* 1996; **41**: 557-561 [PMID: 8617136]

54 **Kalaitzakis E**, Bosaeus I, Ohman L, Björnsson E. Altered postprandial glucose, insulin, leptin, and ghrelin in liver cirrhosis: correlations with energy intake and resting energy expenditure. *Am J Clin Nutr* 2007; **85**: 808-815 [PMID: 17344504]

55 **Le Moine O**, Marchant A, De Groote D, Azar C, Goldman M, Devière J. Role of defective monocyte interleukin-10 release in tumor necrosis factor-alpha overproduction in alcoholics cirrhosis. *Hepatology* 1995; **22**: 1436-1439 [PMID: 7590660]

56 **Madden AM**, Bradbury W, Morgan MY. Taste perception in cirrhosis: its relationship to circulating micronutrients and food preferences. *Hepatology* 1997; **26**: 40-48 [PMID: 9214450 DOI: 10.1002/hep.510260106]

57 **Bergheim I**, Parlesak A, Dierks C, Bode JC, Bode C. Nutritional deficiencies in German middle-class male alcohol consumers: relation to dietary intake and severity of liver disease. *Eur J Clin Nutr* 2003; **57**: 431-438 [PMID: 12627180 DOI: 10.1038/sj.ejcn.1601557]

58 **Amodio P**, Caregaro L, Pattenò E, Marcon M, Del Piccolo F, Gatta A. Vegetarian diets in hepatic encephalopathy: facts or fantasies? *Dig Liver Dis* 2001; **33**: 492-500 [PMID: 11572577]

59 **Cheung K**, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. *Clin Gastroenterol Hepatol* 2012; **10**: 117-125 [PMID: 21893127 DOI: 10.1016/j.cgh.2011.08.016]

60 **Cruz RJ**, Dew MA, Myaskovsky L, Goodpaster B, Fox K, Fontes P, DiMartini A. Objective radiologic assessment of body composition in patients with end-stage liver disease: going beyond the BMI. *Transplantation* 2013; **95**: 617-622 [PMID: 23348896 DOI: 10.1097/TP.0b013e31827a0f27]

61 **Cosquéric G**, Sebag A, Ducolombier C, Thomas C, Piette F, Weill-Engerer S. Sarcopenia is predictive of nosocomial infection in care of the elderly. *Br J Nutr* 2006; **96**: 895-901 [PMID: 17092379]

62 **Merli M**, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, Ridola L, Attili AF, Venditti M. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol* 2010; **8**: 979-985 [PMID: 20621200 DOI: 10.1016/j.cgh.2010.06.024]

63 **Wong CH**, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, Bergman H. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. *Aging Clin Exp Res* 2010; **22**: 54-62 [PMID: 19940555 DOI: 10.3275/6675]

64 **Masuda T**, Shirabe K, Ikegami T, Harimoto N, Yoshizumi T, Soejima Y, Uchiyama H, Ikeda T, Baba H, Maehara Y. Sarcopenia is a prognostic factor in living donor liver transplantation. *Liver Transpl* 2014; **20**: 401-407 [PMID: 24357065 DOI: 10.1002/lt.23811]

65 **Montano-Loza AJ**, Meza-Junco J, Prado CM, Baracos V, Sawyer M, Beaumont C, Ma MM, Kneteman N, Myers RP. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. *Hepatology* 2013; **58**: 1041A

66 **Goodpaster BH**, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006; **61**: 1059-1064 [PMID: 17077199]

67 **Riggio O**, Angeloni S, Ciuffa L, Nicolini G, Attili AF, Albanese C, Merli M. Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. *Clin Nutr* 2003; **22**: 553-559 [PMID: 14613758]

68 **Carvalho L**, Parise ER. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. *Arq Gastroenterol* 2006; **43**: 269-274 [PMID: 17406753]

69 **Alberino F**, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. *Nutrition* 2001; **17**: 445-450 [PMID: 11399401]

P- Reviewer: Di Costanzo GG, Morales-Gonzalez JA, Ozenirler S, Pan WS
S- Editor: Qi Y **L- Editor**: Kerr C **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327
9 771007 932045 25>