

## Cutoff Values for the Diagnosis of Sarcopenia in Pre-Liver Transplant Patients

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**Conflict-of-interest statement:** The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: March 8, 2020

Revised: March 20, 2020

Accepted: March 26, 2020

Published online: August 21, 2020

### ABSTRACT

**RATIONALE AND OBJECTIVE:** Sarcopenia, a syndrome characterized by progressive and generalized loss of skeletal muscle mass, strength, and function, is commonly associated with several chronic diseases including liver diseases. In this study, we diagnosed sarcopenia in pre-liver transplant patients according to European Working Group on Sarcopenia in Older People criteria.

**METHODS:** This cross-sectional study evaluated pre-liver transplant patients with sarcopenia of different etiologies who underwent outpatient follow-up between January 2016 and December 2017. Clinicopathological characteristics were identified, and sarcopenia was assessed using European Working Group criteria, including the 6-minute walk test (6MWT), mid-arm muscle circumference (MAMC), and peak torque (PT).

**RESULTS:** The study included 106 patients (mean age, 58 years) and model for end-stage liver disease score of 12 points; there was a predominance of men. The most common etiology (60.4%) was

hepatitis C virus. The cutoff values were MAMC  $\leq$  25.09 cm for muscle mass, PT  $\leq$  93.4 Nm for muscle strength, and 6MWT  $\leq$  459 m for muscle function.

**CONCLUSION:** After extrapolating European Working Group on Sarcopenia in Older People criteria to classify sarcopenia in pre-liver transplant patients, test cutoffs and accuracies used to determine muscle mass, strength, and function by the MAMC, PT, and 6MWT were  $\leq$  25.09 cm and 77.9%,  $\leq$  93.4 Nm and 72.72%, and  $\leq$  459 m and 75%, respectively.

**Key words:** Diagnosis. Sarcopenia. Body composition. Liver transplant

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Cabral T, da Rosa LHT, Marroni CA, Galant LH, D'Avila AF, Berleze KJ, Pereira JLF, Rossi D. Cutoff Values for the Diagnosis of Sarcopenia in Pre-Liver Transplant Patients. *Journal of Gastroenterology and Hepatology Research* 2020; 9(4): 3270-3274 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2823>

### INTRODUCTION

Liver cirrhosis is the final stage of the chronic and progressive development of several liver dysfunctions, leading to hepatocellular damage and portal hypertension due to a decreased hepatocyte production capacity and hemodynamic disorders including hyperdynamic circulation secondary to portal hypertension<sup>[1]</sup>. Liver cirrhosis is histologically characterized by diffuse nodular regenerative hyperplasia surrounded by fibrous septa with the subsequent collapse of liver structures, leading to significant impairment of the vascular architecture of the liver<sup>[2]</sup>.

Liver transplantation (LT) is the only treatment currently available for cirrhosis; however, it is not available to most waiting list patients, most of whom wait more than 1 year<sup>[3]</sup>. During the waiting period, these patients are vulnerable to easily diagnosed complications of cirrhosis, including spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome, progression to hepatocellular carcinoma<sup>[2]</sup>, and other subtle but lethal complications such as muscle loss (sarcopenia), malnutrition, and

functional decline<sup>[4]</sup>.

In cirrhosis, sarcopenia depends on etiology, age, comorbidities, and disease duration and severity<sup>[5]</sup>. Sarcopenia is among the most prevalent complications of cirrhosis, with a prevalence similar to that of portal-systemic encephalopathy (40-70%)<sup>[6-9]</sup>. This disease affects more men than women<sup>[7]</sup>.

Sarcopenia is associated with worse outcomes of LT, including reduced survival<sup>[8,10,11]</sup>, increased health-related costs for waiting list patients<sup>[12]</sup>, and higher infection rates. Moreover, the long-term consequences of this disease are not well known. The sarcopenia-related mortality rate is higher in Asian populations than in Western populations<sup>[13]</sup>.

Sarcopenia was defined in 1989 as the loss of skeletal muscle mass<sup>[14]</sup>. Over time, this quantitative definition has evolved into a quantitative and qualitative definition that correlates the decrease in muscle mass with a reduction in muscle strength and function. The diagnosis is usually made by quantifying skeletal muscle mass, strength, and function<sup>[15]</sup>.

These measurements are complementary but have limitations. Patients with cirrhosis present changes in body composition due to ascites and edema, which overestimate lean body mass assessed by dual-energy X-ray absorptiometry<sup>[13]</sup> and bioimpedance analysis<sup>[16]</sup>. Cutoff values for sarcopenia have been determined by computed tomography (CT) and magnetic resonance imaging. However, these diagnostic methods are expensive, involve significant radiation exposure<sup>[16,17]</sup>, and require special software for calculating muscle surface area<sup>[17]</sup>. The anthropometric analysis of mid-arm muscle circumference (MAMC) is an accurate and predictive measure of clinical outcomes, although edema may overestimate muscle mass. Functional assessments with exercises can help diagnose cardiovascular, pulmonary, neurological, hematological, and musculoskeletal conditions<sup>[7]</sup>. This study aimed to determine cutoff values and assess the performance of tests used to diagnose sarcopenia in pre-liver transplant patients.

## METHODS

### Patients and study design

This cross-sectional study evaluated patients with cirrhosis of different etiologies who were followed up at the Liver Transplant Outpatient Clinic of the Santa Casa Hospital of Porto Alegre, Brazil, from January 2016 to December 2017. The sample included cirrhotic patients older than 18 years of both sexes who were candidates for LT and agreed to participate in the study. The exclusion criteria were illiteracy, encephalopathies, cognitive or visual impairment, hepatopulmonary or portal-pulmonary syndrome. We also excluded candidates for double transplantation (liver + kidney) or re-transplantation, patients with orthopedic dysfunction and/or difficulty walking; and those hospitalized within the last 6 months. Data were collected after the study was approved by the Research Ethics Committee of the Santa Casa Hospital of Porto Alegre under protocol no. 1,171,170.

Patients were invited to participate in the study after consultation at the outpatient clinic. Clinical examination, 6-minute walk test, mid-arm muscle performance (MAMC) assessments, and muscle strength evaluations using peak torque (PT) were performed in patients who agreed to participate. All tests were conducted by trained professionals at a single time point.

### Clinical Evaluation

Anamnesis included identification data, age, date of birth, sex, current

weight, and smoking and drinking history. Data on disease etiology and staging were obtained from the patients' medical records.

Body mass index (BMI) was calculated according to the formula proposed by the World Health Organization [weight (kg) divided by height squared (m<sup>2</sup>)], and obesity was defined as a BMI >30 kg/m<sup>2</sup>.

Wiesner *et al.* (2001) reported that the model for end-stage liver disease (MELD) could be used to stratify the 3-month mortality rate based on the following scores: ≤ 9, 4%; 10-19, 27%; 20-29, 76%; 30-39, 83%; and ≥ 40, 100%<sup>[18]</sup>. MELD is also used for disease staging and prioritizing patients on waiting lists. In this respect, patients with a MELD > 15 points can improve sooner after LT, except in special situations<sup>[19]</sup>.

### Evaluation Of Sarcopenia

**Six-minute walk test:** The 6MWT was performed in a standardized manner to assess muscle function according to published guidelines<sup>[20]</sup>.

**Measurement of MAMC:** Skeletal muscle mass was estimated by MAMC using a standard formula that included arm circumference (AC) and triceps skinfold thickness (TSF). AC was measured with a non-extensible tape measure at the midpoint between the olecranon and the acromial process in the non-dominant arm in the hanging position. TSF was measured in the same region using a plicometer (Cescorf Equipamentos Esportivos, Brazil). Measurements were made in triplicate by a trained investigator, and median values were included in the analysis. The following equation was employed in the calculation:  $MAMC = AC - (0.314 \times TSF)$ <sup>[21]</sup>.

**Peak torque:** Muscle strength was measured by an isokinetic dynamometer during knee extension, and the maximum isokinetic muscle strength (PT, in Newtons [N]) was evaluated using a dynamometer (Biodex System 3 Pro; Biodex Medical Systems, USA). Only the concentric PT of the knee extensor was evaluated to prevent worsening of the portal hypertension<sup>[22]</sup>.

The patient remained seated with the hips at a 90° angle, and the shin pad was placed next to the malleolus. Stabilization strips were positioned around the patient's thorax, pelvis, and thigh of the evaluated limb. The lever arm axis was aligned with the knee joint axis.

The dominant limb was evaluated. After a warm-up, the patients were verbally instructed to push and pull with maximum force in the range of motion. One test was performed with three concentric repetitions at a controlled speed of 60° s<sup>-1</sup>. Data were included in the analysis if the coefficient of variation for PT was < 10% to exclude submaximal performance. The patient was retested after a 2-min rest period in cases in which the coefficient of variation was > 10%.

The diagnosis was made by quantifying skeletal muscle mass and assessing muscle strength and function according to the criteria of the European Working Group on Sarcopenia in Older People. Cutoff values were proposed based on dataset quantiles and the characteristics of the associated variables according to the statistical description.

### Statistical Analysis

Data were analyzed using Statistics Package for the Social Sciences software version 22. The normality of continuous data was verified using the Kolmogorov-Smirnov test with Lilliefors correction. Categorical data are described as absolute frequencies and percentages.

The cutoff values were proposed on the basis of the quantiles of the MAMC, PT, and 6-MWT data and the characteristics of the associated variables. A receiver operator characteristic (ROC) curve

was constructed to estimate the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the tests.

## RESULTS

A total of 153 LT patients were evaluated. Of them, 106 patients were included as the others were lost to follow-up (Figure 1).

The demographic characteristics of the study population are shown in Table 1. The age of the sample was 35 to 75 years, and MELD scores varied from 5 to 20 points. Most participants (67.9%) were men, and the most common (60.4%) etiology of liver disease was hepatitis C virus.

### Sarcopenia

The ROC curve analysis revealed 6MWT, PT, and MAMC cutoffs of  $\leq 459$  m,  $\leq 93.4$  N, and  $\leq 25.09$ , respectively (Tables 2 and 3; Figure 2).

## DISCUSSION

The analysis of the cutoff values of the ROC curve showed that the 6MWT was the best method to diagnose sarcopenia because of its good sensitivity and ability to evaluate all gait parameters<sup>[20]</sup>.

All tests had high specificity and a low negative predictive value, resulting in a lower false positive rate (a sarcopenic patient may be classified as non-sarcopenic, but a non-sarcopenic patient is not classified as sarcopenic).

MAMC had the best accuracy among the tests; therefore, it was the best for diagnosis. Nonetheless, it might be limited by the consensus of the decrease in muscle mass during the three stages of sarcopenia. For instance, if the diagnosis of sarcopenia by CT were adopted, an ROC curve could be adjusted to identify the MAMC, PT, and 6MWT cutoff values because CT can be adopted as the gold standard for quantifying muscle mass.

The cutoff for 6MWT was  $\leq 459$  m, which was significantly lower than the predicted value of  $526.90 \pm 60.30$  m for this sample<sup>[23]</sup> but similar to that reported by Santos *et al.* (2014) (464 m)<sup>[24]</sup>. Galant *et al.* (2012) compared the distances traveled by cirrhotic patients and found similar values among patients with hepatitis B or C virus and smaller among those with alcoholic cirrhosis ( $373.50 \pm 50.48$  m,  $464.16 \pm 32$  m, and  $475.94 \pm 27.8$  m, respectively)<sup>[25]</sup>.

The European Working Group on Sarcopenia in Older People considers 6MWT values  $<400$  m as indicative of sarcopenia<sup>[26]</sup>. The distances obtained in international studies were smaller than those observed in our study ( $306 \pm 111$  m<sup>[27]</sup>,  $309.4 \pm 134.6$  m<sup>[28]</sup>,  $341.1 \pm 139.7$  m<sup>[29]</sup>,  $369 \pm 122$  m<sup>[27]</sup>, and  $370.5 \pm 121.4$  m<sup>[30]</sup>) or higher than  $529.1 \pm 131.8$ <sup>[31]</sup>. These distances are reference values for specific populations and races<sup>[32]</sup> and are associated with muscle use and physical activity<sup>[33]</sup>. However, these results were not correlated with demographic or anthropometric data.

The 6MWT can be an independent predictor of survival<sup>[30]</sup> because it provides an unbiased measure of overall physical function. Cirrhotic patients who can walk less than 250 m have a higher risk of mortality after LT<sup>[27]</sup>. In patients with primary pulmonary hypertension, a 50-m increase in the performance of this test reduces mortality by 18%<sup>[34]</sup>.

The cutoff for MAMC was  $\leq 25.09$  cm, similar to that obtained by Bering *et al.* (2018) in compensated cirrhosis patients (26 cm) and positively correlated with the appendicular skeletal muscle mass index<sup>[35]</sup>. Giusto (2015) found that the MAMC in patients with cirrhosis was 24.6 ( $16.7 \pm 33$  cm) in men and 22.5 ( $20.4 \pm 29.4$  cm) in women<sup>[33]</sup>. These values are higher than those found by Román

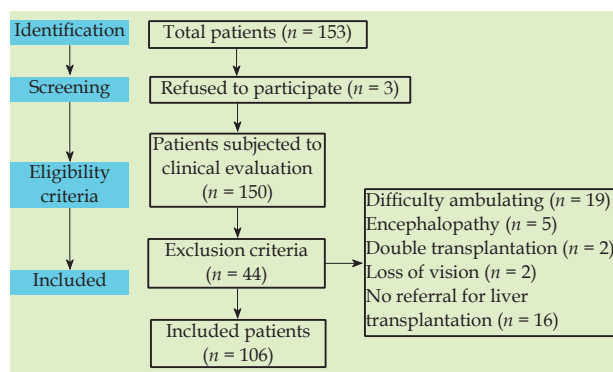


Figure 1 Flowchart of the patient selection process.

Table 1 Distribution of sociodemographic and clinical data of pre-liver transplant patients.

	n (%)	Mean $\pm$ SD
Male	72 (67.9)	
Female	34 (32.1)	
Age (years)		58.8 $\pm$ 7.9
Height (cm)		166 $\pm$ 8.8
Weight (kg)		79.34 $\pm$ 16.6
BMI (kg/m <sup>2</sup> )		28.44 $\pm$ 5.1
MELD (points)		12.6 $\pm$ 3.1
HCV	64 (60.4)	
HCC	37 (34.9)	
Alcohol	27 (25.5)	
HBV	6 (5.7)	
NASH	5 (4.7)	
Autoimmune	2 (1.9)	
Others	11 (10.4)	

BMI: body mass index; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; NASH: nonalcoholic steatohepatitis; SD: standard deviation.

Table 2 Data distribution in quartiles to determine sarcopenia cutoff values for 106 pre-liver transplant patients.

	n	Minimum	Quartile	Median	Quartile	Maximum
MAMC (cm)	86	18.89	22.04	24.97	27.31	35.05
PT (Nm)	66	22.1	69.7	96.85	125.52	195
6MWT (m)	100	250	400	461	546	681

6MWT, 6-minute walk test; MAMC, mid-arm muscle circumference; PT, peak torque.

Table 3 Performance of cutoff values obtained by receiver operating characteristic curve analysis for the diagnosis of sarcopenia.

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
MAMC (cm)	$\leq 25.09$	67.16	100	100	46.34	77.9
PT (Nm)	$\leq 93.4$	66.66	100	100	52.94	72.72
6MWT (m)	$\leq 459$	68.42	95.83	98.11	48.93	75

6MWT, 6-minute walk test; MAMC, mid-arm muscle circumference; NPV, negative predictive value; PPV, positive predictive value; PT, peak torque.

*et al.* (2014) (22.2 cm) in cirrhotic patients<sup>[28]</sup> and by Oliveira *et al.* (2010) ( $22.86 \pm 3.52$  cm) in patients with chronic kidney disease associated with water retention who underwent dialysis<sup>[36]</sup>.

Similar to that reported by Andersen *et al.* (1998) in patients with alcoholic cirrhosis, the cutoff for PT was  $\leq 93.4$  N, approximately 80 N for knee extension, and was related to nutritional status and BMI<sup>[37]</sup>. Wiesinger (2001) observed that PT in patients on the waiting list for LT was  $\geq 101.96$  N and related to disease status by Child-

Pugh classification<sup>[22]</sup>. Gadelha et al. (2014) found that PT in older patients was  $\leq 83.59$  N<sup>[38]</sup>.

Muscle strength should be maintained at adequate levels in sarcopenic patients because it provides better functional capacity, promotes autonomy, and improves the performance of activities of daily living<sup>[38]</sup>.

Carias et al. (2016) showed that sarcopenia in cirrhotic patients was more prevalent in men (75%) than in women (24%)<sup>[19]</sup>. It is hypothesized that women are prone to lose more fat mass than muscle mass because of their higher baseline fat mass<sup>[39-41]</sup>.

Fat mass increases with age, peaking at 60-75 years, whereas muscle mass and strength begin to decrease progressively around the age of 30 years, with higher losses after the age of 60 years<sup>[39-41]</sup>.

In addition, hypotestosteronemia is implicated in sarcopenia in cirrhotic patients, in whom testosterone levels are significantly lower<sup>[43]</sup> as a result of a central hypothalamic-pituitary abnormality, increased peripheral androgen aromatization, and gonadal insufficiency<sup>[44]</sup>.

Skeletal muscle mass can also be affected by height; taller people tend to have higher mass than shorter people<sup>[45]</sup>.

Although the mechanisms of sarcopenia in cirrhotic patients are not well understood, a decreased protein intake and malnutrition may contribute to muscle wasting. Decreased muscle protein synthesis and increased myofibril degradation may contribute to sarcopenia and associated physical inactivity. In addition to muscle mass loss, motor dysfunction may result from biochemical and physiological abnormalities in the contractile properties and characteristics of the sarcolemma, leading to decreased concentrations of phosphorus and magnesium<sup>[37]</sup>. These factors aggravate sarcopenia in patients on the LT waiting list<sup>[46]</sup>.

The limitations of the present study are its selection of patients from an LT referral center, who may not represent the entire cirrhotic population. However, the study has internal validity because the presence of random errors undermines only the study's accuracy. Another limitation is the evaluation by isokinetic dynamometry without previous patient training.

In conclusion, the cutoff values and accuracies of the tests used to determine muscle mass, strength, and function by MAMC, PT, and 6MWT were  $\leq 25.09$  cm and 77.9%,  $\leq 93.4$  Nm and 72.72%, and  $\leq 459$  m and 75%, respectively.

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