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Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry

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Background **Sarcopenia evaluated by computed tomography (CT) scan at the lumbar site has been identified as a risk factor for morbidity and mortality in cirrhosis.**

Aim **The aim of this study was to compare the measurement of muscle mass through CT scan, considered the gold standard, with other reliable techniques to evaluate the rate of agreement between different available methods for the assessment of muscle mass in cirrhosis. The correlation between measurements of muscle mass and of muscle strength was also investigated.**

Patients and methods **Adult patients eligible for liver transplantation were studied. Lumbar skeletal muscle cross-sectional area was measured by CT and muscle depletion was defined using previously published cut-offs. Mid-arm muscle circumference was calculated following anthropometric measures. The Fat-Free Mass Index and the Appendicular Skeletal Muscle Index were calculated using dual-energy X-ray absorptiometry. Muscle strength was evaluated using the Hand Grip test.**

Results **Fifty-nine patients with cirrhosis were included. Sarcopenia was diagnosed in 76% of the patients according to CT evaluation. A significant reduction in Fat-Free Mass Index and Appendicular Skeletal Muscle Index was observed in 42–52% of the patients, whereas 52% showed a mid-arm muscle circumference less than 10th percentile. Skeletal muscle mass evaluation through CT was only weakly correlated with dual-energy X-ray absorptiometry and anthropometry evaluation. No correlation was observed between CT measurement of muscle mass and Hand Grip test.**

Conclusion **CT scan can identify the highest percentage of sarcopenia in cirrhosis and no other techniques are actually available as a replacement. Future efforts should focus on approaches for assessing both skeletal muscle mass and function to provide a better evaluation of sarcopenia in cirrhotic patients.** ***Eur J Gastroenterol Hepatol*** **00:000–000**

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Keywords: cirrhosis, computed tomography scan, sarcopenia, skeletal muscle

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Introduction

Skeletal muscle wasting is a common feature of malnutrition in patients with liver cirrhosis [1] and is widely recognized as an independent predictor of poor outcome and mortality in this setting [2–5]. In the last few years, the term 'sarcopenia' has been introduced to describe a condition of progressive and generalized loss of muscle mass and strength [6] and a recent European Consensus Statement has identified computed tomography (CT) as the gold standard for the detection of muscle wasting in clinical trials [7]. Dual-energy X-ray absorptiometry (DEXA) and anthropometry, despite some limitations, have been utilized frequently to evaluate muscle mass in cirrhotic patients [8–10].

The definition of sarcopenia should also include an assessment of muscle function. There are few well-validated techniques to measure muscle strength; among these, the Hand Grip (HG) test has been shown to be frequently compromised in cirrhotic patients even at early stages [11–13]. Recent reports have investigated the presence of sarcopenia in patients with end-stage liver disease [14–23]. In these studies, the prevalence of muscle wasting, determined using CT, and its accuracy as a prognostic factor were investigated [14–18,21–23], although an assessment of muscle function, through HG or physical performance tests, was lacking. Muscle depletion was found to be associated with higher mortality in patients awaiting liver transplantation (LT) [15–17], whereas controversial results were obtained for mortality after LT [8,18,22,23]. Nevertheless, caution has been suggested in the use of CT for the detection of sarcopenia in cirrhosis [24,25]. Indeed, methods and threshold values for the diagnosis of muscle wasting in patients with cirrhosis have not been examined extensively. Furthermore, the possible correlation with other

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methods to evaluate muscle mass, such as DEXA and anthropometry, or muscle function has not been explored.

In the present study, we primarily aimed to verify the concordance between muscle wasting, determined by CT scan with other techniques providing muscle mass measurements, such as DEXA and anthropometry, or functions such as the HG test. As a secondary aim, we evaluated the correlation between muscle wasting, liver impairment, and survival.

Patients and methods

Adult patients with liver cirrhosis who were under evaluation for elective LT at our University Hospital between 2011 and 2013 were considered. Exclusion criteria were acute liver failure, hepatocellular carcinoma (HCC) beyond the Milan criteria [26], previous LT, or listing for multivisceral or living-related LT.

In our center, CT scan is performed routinely in patients considered for LT to evaluate vascularization to exclude HCC or biliary disease. Moreover, in the last few years, a complete nutritional assessment on the basis of anthropometry and HG test together with an evaluation of osteoporosis and body composition using DEXA has been proposed to all patients in our center.

Fifty-nine patients, out of 77 patients listed for LT in our center, in whom CT, DEXA, nutritional, and clinical assessments were available and in whom these exams were performed within a 30-day period were included in the present investigation. The study was approved by the Ethical Committee of our University Hospital and a written informed consent was signed by all the participants before the enrollment to authorize the use of their personal data.

Clinical and biochemical assessment

All the patients were evaluated according to the standard protocol of our Transplant Centre. Demographic data, origin of liver disease, clinical examination, and parameters of liver function were recorded. The severity of cirrhosis was classified according to the Child–Pugh [27] and Model for End-Stage Liver Disease (MELD) score [28].

Assessment of muscle mass by computed tomography scan

CT scans used for analysis were carried out as part of the preoperative evaluation for LT. For the quantitative analysis, the axial plane passing through the intersomatic disk between L3 and L4 was chosen. Images were analyzed using a dedicated workstation (Leonardo Syngo; Siemens Medical System, Erlangen, Germany) that enables specific tissue demarcation using previously reported Hounsfield unit (HU) thresholds. Skeletal muscle tissue was separated according to different density thresholds: a density value of +35 HU was used to separate fat from muscle tissue and +150 HU to separate muscle from bone tissue [29]. Muscles in the L3 region encompass psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. Cross-sectional areas (cm^2) were computed automatically by summing tissue pixels and multiplying by the pixel surface area. All CT images were analyzed by two trained observers (B.L., M.D.M.). The cross-sectional area of muscle and intramuscular adipose tissue was always normalized for stature (cm^2/m^2). The L3 Skeletal Muscle Index (SMI) was expressed as cross-sectional muscle area/$height^2$. The cut-off for muscle depletion was based on the study of Prado *et al.* [30], which has been utilized previously in cirrhotic patients [18].

Assessment of muscle mass by dual-energy X-ray absorptiometry

All patients were subjected a whole-body scan using a dual-energy X-ray fan beam densitometer (Lunar Prodigy Advance; GE Healthcare, Madison, Wisconsin, USA) and dedicated software. The principles behind body composition analysis with fan beam DEXA have been explained elsewhere [31]. Fat-Free Mass Index (FFMI) was calculated on the basis of the following equation: FFMI (kg/m^2) = total body weight (kg)–fat mass (kg)/height (m^2). For the definition of sarcopenia, FFMI less than 10th percentile of an age-matched and sex-matched Italian population was considered for the diagnosis of sarcopenia [32]. To possibly exclude the interference of ascites, the composition of upper and lower limbs, given by the machine's software, was also calculated; the Appendicular Skeletal Muscle Index (ASMI) was expressed as the summing of the muscle mass of the upper and lower limbs (kg)/height (m^2). On the basis of Baumgartner *et al.* [33], the cut-off for ASMI was adopted for the diagnosis of sarcopenia.

Assessment of muscle mass by anthropometry

Anthropometric measurements were always performed by the same investigator (M.G.). BMI was computed as body weight (kg)/height (m^2). Body weight was measured after treatment of ascites and/or water retention, if present. Mid-arm circumference was measured at the midpoint between the tip of the acromion and the olecranon process on the nondominant side of the body using a flexible tape measure. Triceps skin fold thickness was also taken on the nondominant side of the body, with the patients standing in a relaxed position, using a Harpenden Skinfold Caliper (John Bull British Indicators Ltd, St. Albans, UK). Mid-arm muscle circumference (MAMC) was calculated using the mid-arm circumference and triceps skin fold thickness according to a standard equation. MAMC below the 10th percentile was identified by comparison with an age-matched and sex-matched population [34].

Assessment of muscle strength

HG strength was measured in the nondominant hand using a hydraulic dynamometer Jamar (Sammons Preston Rolyan Inc., Chicago, Illinois, USA). The best of three

consistent readings, allowing ~1 min of recovery between each attempt, was recorded as the maximum grip strength. Data were compared with that obtained from an age-matched and sex-matched population [35], and HG below the 10th percentile was considered to identify reduction in muscle strength. The HG test was always performed in the absence of clinically evident encephalopathy to exclude possible confounding factors.

Statistical analysis

All data resulting from the continuous variables are presented as mean ± SD and/or median, range; the data resulting from categorical variables are expressed in percentages or counts. Agreements between the central muscle area on CT, DEXA, and anthropometric measurements were investigated using Kendall's τ statistic. The correlation of central muscle depletion evaluated by CT scan and hepatic function evaluated through MELD and Child–Pugh scores were also analyzed using linear regression models. Patients were followed from the date of the index CT (time 0), performed as part of the LT assessment and used to determine the SMI, until the date of death or the last visit.

Two separate time to event outcomes were analyzed: one before LT, with patients transplanted censored as alive until the date of transplantation, and one restricted to patients who had undergone LT, with time between LT and death (or censoring) being the outcome. Time to event outcomes were evaluated using the Cox regression model after confirming the hypothesis of proportionality of hazards. The software used for the analysis was R (version 2.15; Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and prevalence of muscle wasting

Patients were mainly men (78%), with a median age of 59 years (range 26–68 years). The origin of liver disease was post-viral (hepatitis C and B) in 56% of our population and postalcoholic in 22%. All patients had stopped alcohol consumption for at least 6 months at the time of enrollment. A concomitant HCC within the Milan criteria was diagnosed in 32% of the patients ($T \geq 2$ in 22%). The median biological MELD score was 16 in patients without HCC and 11 in patients with HCC. Two-thirds of the patients were Child–Pugh B–C. During a median follow-up of 28 months (range 4–42 months), 37 (63%) patients underwent LT.

According to the threshold values available, muscle wasting was present in 76% of the patients according to CT scan evaluation (SMI). A lower prevalence of muscle depletion was evidenced by DEXA (42 and 52% whether ASMI or FFMI was considered, respectively) and by anthropometry (52%) (Table 1). Muscle depletion was largely different for sex, being higher in male patients with respect to female patients, when limb measurements were considered (MAMC and ASMI). Evaluation of central muscles (FFMI and SMI) led to increased diagnosis of muscle depletion in women (from three of 12 patients, 25%, to six of 12 patients, 50%) (Table 1).

The origin of liver cirrhosis and the presence of HCC failed to affect the prevalence of muscle wasting. Muscle function could be evaluated by HG in 50 patients (41 men, nine women) (85%). In nine patients, HG test could not be performed because of hepatic encephalopathy and/or patients' low compliance to the test. Twenty-three patients showed a significant reduction in muscle strength (HG ≤ 10th percentile). Among the 50 patients in whom both CT and HG test were available, a significant muscle depletion associated with impaired HG was present in 19 (38%), no muscle depletion and no HG reduction was

Table 1 Anthropometric and skeletal muscle mass characteristics of the population studied

Variables	Median (range) or *N* (%)
Body weight (kg)	
Males	72 (54–106)
Females	67 (52–76)
Height (cm)	
Males	172 (155–187)
Females	162 (149–172)
BMI (kg/m^2)	
Males	25.1 (17.2–35)
Females	24.7 (21–29)
CT evaluation	
Skeletal Muscle Mass Index (cm^2/m^2)	
Males	46.9 (26.9–69.3)
Females	36 (23–45)
Below cut-off	
Males	36 (78)
Females	9 (69)
All patients	45 (76)
DEXA evaluation	
Appendicular Skeletal Muscle Mass Index (kg/m^2)	
Males	7.3 (5.4–10.1)
Females	6.2 (5.3–21.9)
Below cut-off	
Males	22 (48)
Females	3 (23)
All patients	25 (42)
DEXA evaluation	
Fat-Free Mass Index (kg/m^2)	
Males	17.7 (14.5–23.1)
Females	14.7 (13.2–18.1)
Below cut-off	
Males	25 (54)
Females	6 (46)
All patients	31 (52.5)
Anthropometric evaluation	
Mid-arm muscle circumference (cm)	
Males	24.6 (16.7–33)
Females	22.5 (20.4–29.4)
Below cut-off	
Males	28 (90)
Females	3 (10)
All patients	31 (52.5)
Hand Grip test	
Hand grip (kg)	
Males	28.4 (11–45.6)
Females	19 (7–30)
Below cut-off	
Males	14 (30)
Females	2 (15)
All patients	16 (39)

CT, computed tomography; DEXA, dual-energy X-ray absorptiometry.

observed in nine patients, but discordant results were obtained in the others (20 patients presented low SMI, but normal HG and two patients presented the opposite result).

Features associated with muscle wasting at computed tomography scan and concordance of parameters of muscle wasting and function

The demographic and clinical characteristic were similar among patients with and without sarcopenia according to CT scan (Table 2). Male patients with sarcopenia were more likely to show a significant reduction in BMI and muscle mass evaluated through both DEXA and anthropometry, whereas female patients with sarcopenia at CT scan showed only a significant reduction in parameters of muscle mass evaluated through DEXA. The HG test was found to be similar among patients with and without sarcopenia at CT scan in both men and women. A significant correlation was observed between CT (SMI) and DEXA (FFMI, ASMI) or anthropometry (MAMC) measurements of muscle mass both in men and in women (Table 3 and Fig. 1).

Functional measurements of muscle strength by an HG dynamometer failed to correlate with CT (SMI) muscle evaluation in men and women. HG was found to correlate with anthropometry (MAMC), but only in men (Kendall's $\tau = 0.274$; $P = 0.012$).

Correlation between muscle wasting, severity of liver disease, and survival

The decrease in SMI was not significantly associated with a worse liver function (MELD vs. SMI, $P = 0.33$; Child–Pugh vs. SMI, $P = 0.76$). Even after stratification for sex, there was no significant effect of MELD or of Child–Pugh on the degree of muscle depletion (MELD vs. SMI, $P = 0.35$ for men and $P = 0.27$ for women; Child–Pugh vs. SMI, $P = 0.29$ for men and $P = 0.81$ for women).

Six patients died because of complications of liver cirrhosis before LT. Thirty-seven patients underwent transplantation: among these, six died during the first 6 months after LT (two of multiorgan failure, one of cardiac complication, one of primary nonfunction, and two of sepsis).

When muscle depletion, evaluated either with CT, DEXA, or anthropometry, was analyzed as a possible predictive factor for mortality both in the waiting list and after LT, MAMC and FFMI were found to be independent predictors of mortality after LT. In particular, a significant inverse interaction for each unit increase of MAMC and mortality [hazard ratio (HR) = 1.05; $P < 0.001$] was found after adjusting for sex, MELD, age, and interaction between sex and MAMC. Similarly, a significant inverse interaction for each unit increase of FFMI and mortality (HR = 1.12; $P < 0.001$) was found after adjusting for the same variables. At variance, SMI did not show any association with mortality either before or after LT.

Table 2 Clinical and biochemical characteristics of patients according to the presence or absence of sarcopenia with computed tomography scan

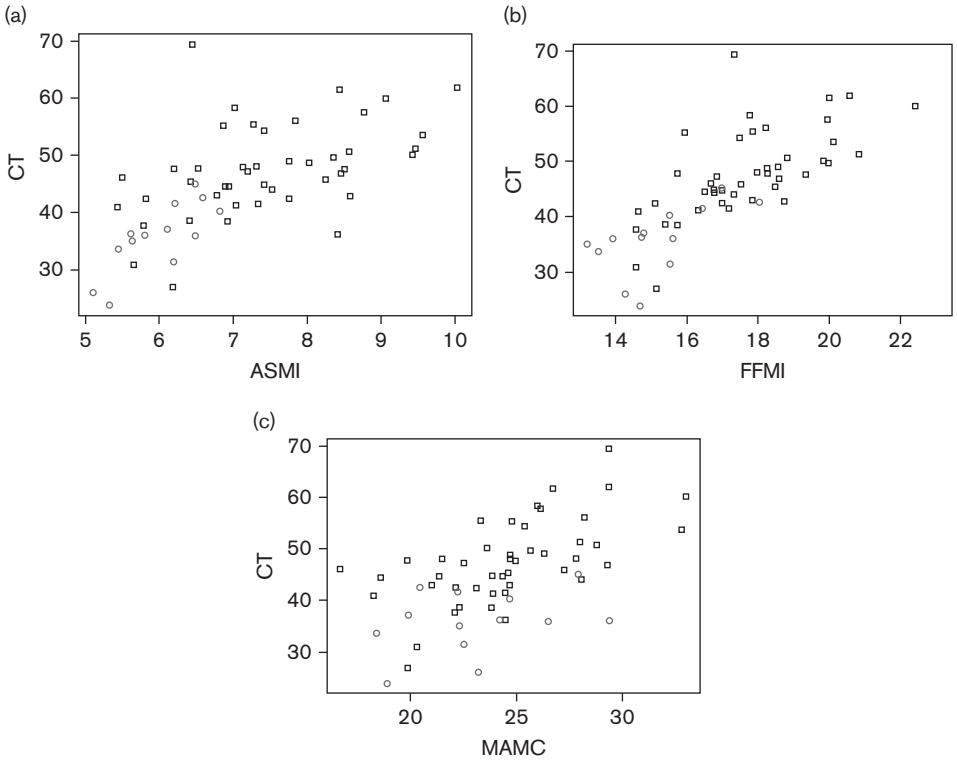
Variables	Patients with sarcopenia ($n = 45$)	Patients without sarcopenia ($n = 14$)	P
Age [median (range)] (years)	59 (37–68)	59 (28–66)	0.68
Sex (male/female) (n)	36/9	10/4	0.49
Child–Pugh A/B/C (n)	16/12/17	4/7/3	0.24
MELD [median (range)]	13.5 (7–25)	13.1 (7–23)	0.68
Hepatocellular carcinoma (n)	20	4	0.29
Cirrhosis etiology (n)			
Viral	26	7	0.4
Alcohol	7	6	
Others	12	1	
Ascites (none/mild/severe) (n)	21/18/6	9/4/1	0.71
BMI [median (range)] (kg/m^2)			
Males	24.4 (17.2–32.3)	28.3 (23.6–35.2)	0.005
Females	24.9 (23.4–28.9)	26.1 (21.3–29.3)	0.56
DEXA evaluation			
Appendicular Skeletal Muscle Mass Index [median (range)] (kg/m^2)			
Males	7.1 (5.4–9–5)	8.2 (6.4–10.1)	0.02
Females	5.8 (5.3–6.5)	6.5 (6.2–6.8)	0.01
Below cut-off [n (%)]			
Males	20 (55.5)	2 (20)	0.04
Females	1 (11.1)	2 (50)	0.1
All patients	21 (46.7)	4 (28.6)	0.2
DEXA evaluation			
Fat-Free Mass Index [median (range)] (kg/m^2)			
Males	17.1 (14.5–23.1)	19.1 (17.3–22.4)	0.01
Females	14.6 (13.2–15.6)	16.7 (15.5–18.1)	0.008
Below cut-off [n (%)]			
Males	21 (58.3)	4 (40)	0.3
Females	6 (66.7)	0 (0)	0.02
All patients	27 (60)	4 (28.6)	0.03
Hand Grip test			
Hand grip (kg) [median (range)]			
Males	28.3 (11–45.6)	28.6 (23.3–37)	0.73
Females	19 (7–30)	22 (16–28)	0.69
Below cut-off [n (%)]			
Males	12 (33.3)	2 (20)	0.1
Females	2 (22.2)	0 (0)	0.2
All patients	14 (31.1)	2 (14.3)	0.09
Anthropometric evaluation			
MAMC [median (range)] (cm)			
Males	24.3 (16.7–29.3)	27.4 (23.3–33)	0.0007
Females	22.4 (18.4–29.4)	23.4 (20.4–27.9)	0.6
Below cut-off [n (%)]			
Males	27 (75)	1 (10)	0.0001
Females	3 (33.3)	0 (0)	0.2
All patients	30 (66.6)	1 (7)	0.00009

DEXA, dual-energy X-ray absorptiometry; MAMC, mid-arm muscle circumference; MELD, Model for End-Stage Liver Disease.

Table 3 Correlation between dual-energy X-ray absorptiometry/anthropometry measurements and computed tomography scan according to sex

	Kendall's τ/P	
	Males	Females
Fat-Free Mass Index (kg/m^2)	0.44/ < 0.0001	0.54/0.010
Appendicular Skeletal Muscle Index (kg/m^2)	0.37/0.0002	0.56/0.006
Mid-arm muscle circumference (cm)	0.48/ < 0.0001	0.18/0.435

Fig. 1



Scatterplot of the Appendicular Skeletal Muscle Index (ASMI) evaluated by dual-energy X-ray absorptiometry (DEXA) (kg/m^2) (a), Fat-Free Mass Index (FFMI) evaluated by DEXA (kg/m^2) (b), and mid-arm muscle circumference (MAMC) evaluated by anthropometry (cm^2) (c) versus computed tomography (CT) measurement of Skeletal Muscle Index [muscle area (cm^2)/height (m^2)]. Women are represented as circles, whereas men are represented as squares.

Discussion

Sarcopenia has been defined in a recent consensus as muscle depletion and decreased muscle function [6,7]. Central muscle depletion evaluated by CT scan has recently been proposed as a possible objective and reproducible measure that can also be applied in cirrhotic patients [2]. It is important to recognize that the high cost, the possible limited access to the equipment, and the concern in terms of radiation exposure may limit the use of this technique for routine clinical practice unless the patient needs to perform a CT scan for other purposes. This was the case in our series of cirrhotic patients being investigated for LT. Our study found a high prevalence (76%) of muscle depletion in cirrhotic patients evaluated for LT. The prevalence of CT muscle wasting that we observed was even higher than reported previously with the same techniques [16,17,23]. The lower median BMI of our population with respect to the population included in other studies may provide a possible explanation for these discrepancies.

We also found that muscle mass area measured through CT analysis correlated with the MAMC at anthropometry and FFMI evaluation through DEXA; however, this correlation was rather weak. At the same time, the prevalence of a diagnosis of muscle depletion was lower using these methods (Table 2). Some observations need to be taken into account. All these techniques are centered on selected group of muscles, which are not the same for CT scan, anthropometry, or DEXA. Muscle groups at different sites may be affected nonhomogeneously during the progression of liver disease and secondary/malnutrition [36,37]. Indeed, sarcopenia is not a uniform condition as it may affect postural muscles more than nonpostural ones and the lower limbs more than the upper limbs also depending on race, age, sex, muscle use, and physical activity [38–41]. Janssen *et al.* [38] used a whole-body MRI to examine skeletal muscle mass in 468 healthy individuals and observed that, as expected, men had significantly ($P = 0.001$) more skeletal mass and that the sex differences were greater in the upper (40%) than in the lower (33%) body ($P = 0.01$). A noticeable decrease in absolute skeletal mass was observed starting from the end of the fifth decade, which was primarily attributed to a decrease in lower body skeletal mass [38]. These data confirmed similar observations by Gallagher *et al.* [41]. Physical activity may also influence and counterbalance the effect of sarcopenia in a

similar, nonhomogenous manner. In previous studies in healthy individuals undergoing physical training, the greatest absolute increases in muscle cross-sectional area were observed at the level of the shoulder, chest, upper thigh, and upper portion of the upper arm with respect to other regions of the body [40].

These observations explain why the use of techniques evaluating only one group of muscles may yield different results.

DEXA is an easy, reproducible, and accurate method to analyze body composition that enables not only a regional body composition but also a complete body scan to study changes in fat mass and fat-free mass. The main limitation of this technique is that its validity is dependent on the assumptions on the density and hydration fraction of the fat-free mass, which can be violated in patients with advanced liver disease because of water retention. In our series, 51% of the patients had no ascites, but 37% had mild ascites and 12% had moderate ascites at the time of the study. Water retention may have caused an overestimation of the FFMI because of an increase in the hydration factor in some of our patients.

Interestingly, CT scan is the first technique able to enable evaluation of the central muscle wasting, which might be less affected by sex, physical activity, and water retention. In our series, SMI was a sensitive parameter that could identify muscle depletion in female patients that was not diagnosed through FFMI, SMI, or MAMC (Table 2). This could be because of a low sensitivity of the upper limb modifications in women, whereas central muscles may be more appropriate for this evaluation.

With respect to muscle function in our study, we only examined HG strength. This parameter was correlated with MAMC in men, but not with SMI in the entire population and in men. This observation underlines the need to identify a global functional test not limited to the upper limb muscles to better assess sarcopenia.

From our results, CT evaluation (SMI) was not associated with liver function and failed to identify patients with lower survival in the waiting list. This finding is not in agreement with previously published data using our same cut-off [16]. The low rate of mortality in our population could explain this discrepancy. In agreement with the more recent studies analyzing the impact of sarcopenia on post-LT mortality, we did not observe a correlation between muscle wasting evaluated by CT scan and survival after LT [14,23].

This study is not without limitations. The cut-off we have utilized for the definition of muscle mass depletion by CT has been derived from a population of obese patients affected by neoplasia [30], which might not represent normal values. To date, validated reference values in healthy individuals on the basis of ethnicity, age, sex, and location, which will help us to specify more accurately the diagnosis of sarcopenia, are still lacking [25]. We have chosen the present cut-off values as they have been utilized previously in other already published studies carried out in cirrhotic patients [16,17,23]. The lack of measurement of muscle fat and connective tissue infiltration may have led to an underestimation of sarcopenia assessed by CT scan. In terms of the comparison between estimation of sarcopenia using different methods, a further limitation also derives from the need to include a heterogeneous population as control participants.

Another potential limitation is the relatively small cohort of patients from a single center, which could have affected the ability of our study to predict survival before and after LT. The reduced sample size also did not enable the identification of possible cut-offs of SMI values that could have been associated with mortality in our cohort.

In conclusion, CT scan can identify the highest percentage of sarcopenia in cirrhotic patients and no other techniques are actually available as a replacement. Clinicians should always be aware of the possible limitation of the use of CT scan in the evaluation of muscle mass because of the lack of normal values and uncertainty of cut-off for muscle depletion. Future efforts should focus on the identification of normal threshold values to provide a better evaluation of sarcopenia in cirrhotic patients.

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Manuela Merli and Michela Giusto contributed to study design, all authors participated in the study protocol. Manuela Merli, Michela Giusto, and Barbara Lattanzi contributed to the design and drafting the article, and all authors approved the final version.

Conflicts of interest

There are no conflicts of interest.

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