Validation of cutoffs for skeletal muscle mass index based on computed tomography analysis against dual energy X-ray absorptiometry in patients with cirrhosis: the KIRRHOS study

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Abstract

Background Accurate assessments of muscle mass in patients with cirrhosis are necessary in clinical practice. Computed tomography (CT) of the upper abdomen has been proposed as a useful method for quantifying muscle mass. Recently, Carey *et al* developed specific cutoffs for muscle wasting based on the skeletal muscle index at the L3 vertebra (L3-SMI) for cirrhotic patients. The aim of the present study was to assess the concurrent validity of the newly proposed cutoffs of Carey *et al*, along with others widely used in several clinical contexts, using dual energy X-ray absorptiometry (DXA) as the reference method.

Methods Data were evaluated from 97 Caucasian patients (59.8% male, 59.1±11.6 years old, 45.4% decompensated) with cirrhosis of various etiologies. Muscle mass was assessed using the appendicular lean mass index (ALMI) by DXA and the L3-SMI by CT. Low L3-SMI was defined in relation to 5 different cutoffs.

Results Low muscle mass prevalence was 13.4% according to ALMI and 26.8-45.4% according to the different cutoffs applied for L3-SMI. The Carey *et al*, Prado *et al* and Montano-Loza *et al* cutoffs showed similar sensitivity (all 69.2%) and specificity (79.8%, 76.2% and 75.0%, respectively) and high accuracy (78.4%, 75.3% and 74.2%). The Carey *et al* cutoffs showed the highest diagnostic validity against DXA: the multivariate odds ratio adjusted for age, sex, body mass index category, disease etiology and model for end-stage liver disease score (95% confidence interval) was 5.88 (1.36-25.4), P=0.018.

Conclusion Compared to DXA, the cutoffs for identifying muscle wasting proposed by Carey *et al* were proven to be the most accurate.

Keywords Cirrhosis, muscle mass, muscle wasting, DXA, computed tomography

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Introduction

Muscle wasting is quite prevalent in cirrhosis, because of the metabolic changes that occur because of liver malfunction [1]. Lately, muscle mass quantification methods have attracted a lot of attention among the scientific community, mainly because of the significant negative impact of muscle wasting on the manifestation of disease complications and survival in patients with advanced liver disease [2]. Therefore, it has been suggested that muscle mass assessment should be performed routinely in this group of patients, using validated but also widely available techniques.

Radiological methods, i.e., dual energy X-ray absorptiometry (DXA) and computed tomography (CT) image analysis, have been proposed for muscle mass quantification in liver disease patients [3]. DXA, although costly and not widely available in clinical practice, is considered a highly accurate method, since it overcomes the possible accuracy

burden in cases of overhydration by estimating limb muscle mass [4,5]. Thus, it has been used as the reference method for the validation of other muscle mass quantification techniques, such as CT [6,7].

Muscle mass area by CT image analysis in the L3 vertebra has been positively correlated with whole body muscle mass in oncology patients [8] and negatively with survival specifically in patients with advanced liver disease [9]. Since this method was originally developed for muscle mass quantification in oncology patients, its application in cirrhotic patients has until recently been performed arbitrarily, using cutoffs developed for the oncological population [10,11]. During the past few years, specific cutoff points have been developed for liver disease patients [12,13]. The most recent ones, proposed by Carey *et al* [13], have been supported by the European Association for the Study of the Liver (EASL) for muscle mass assessment of cirrhotic patients, though with a note that additional validation studies are needed [5]. Similarly, Carey *et al* [13] urged for validation of their proposed cutoff values in other groups of patients. Therefore, the aim of the present study was to assess the concurrent validity of the newly proposed cutoffs of Carey *et al*, as well as other cutoff points widely used in several clinical conditions, against DXA as the reference method.

Patients and methods

Study sample

Ninety-seven Caucasian adult (>18 years old) cirrhotic patients (58 male; mean age 59.1±11.6 years) from the KIRRHOS study (study for the evaluation of dietary intake, body composition and performance status in cirrhotic patients) for whom CT scans were available participated in this analysis. Patients' enrollment was performed in 2 outpatient liver clinics (Academic Department of Gastroenterology, Laiko General Hospital of Athens, and 2nd Academic Department of Internal Medicine, Hippokratio General Hospital of Athens) from June 2015 to July 2018. The diagnosis of cirrhosis was based on liver biopsy or a combination of clinical, laboratory and imaging data (Fibroscan values >14 kPa or clinical picture of decompensated cirrhosis, i.e., manifestation of ascites, edema, esophageal or gastric varices and/or encephalopathy). Exclusion criteria included pregnancy or lactation, presence of hepatocellular or other forms of cancer, hepatic coma, diagnosed acquired immunodeficiency syndrome, renal or pancreatic insufficiency and active enteral feeding. Patients with alcoholic cirrhosis were included in the study only if alcohol intake had already ceased for at least one month before enrollment in the study. A consent form was signed by all participants, after they had been fully informed about the aims of the study. The protocol was approved by the Bioethics Committee of Harokopio University and the Scientific Committees of all participating Hospitals and it has been registered in the ClinicalTrials.gov system (ID NCT03242798).

Medical assessment

Medical assessment was implemented by the study physician. Disease etiology and any clinical manifestations related to cirrhosis, such as ascites, edema, esophageal or gastric varices and encephalopathy, as well as their severity, were recorded. Patients were classified as compensated or decompensated, based on the absence or presence of the abovementioned clinical complications, respectively. Recent measurements (within a month prior to baseline evaluation) of total bilirubin, serum creatinine and prothrombin time were also collected from the medical records. Based on the biochemical data collected, the model for end-stage liver disease (MELD) score [14] was calculated for the estimation of disease severity.

Anthropometry and body composition

Body weight (BW) was measured using an analog scale and height using a stadiometer (Seca 711). Dry weight was calculated by subtracting 5% of the measured BW for mild ascites, 10% for moderate ascites and 15% for tense ascites, with an additional 5% subtracted if bilateral pedal edema was present, as suggested by EASL [5]. Dry body mass index (BMI) was also calculated [15].

Body composition analysis was performed using the DXA method and the appendicular lean mass index (ALMI, kg/m^2) was calculated. Low ALMI was defined using the cutoffs of <7.59 kg/m^2 for men ≤65 years old and <7.64 for men >65 years old, and <5.47 kg/m^2 for women ≤65 years old and <5.78 for women >65 years old, derived from a Mediterranean population [16]. Muscle mass estimation was also performed by computing the muscle mass area at the level of the L3 vertebra (L3-SM), using appropriate software (SliceOmatic V4.3 software, Tomovision, Montreal, PQ). More specifically, an individual section of the CT scan at the L3 vertebra level was isolated and the areas of the psoas, paraspinal and abdominal wall (including rectus abdominis, transversus abdominis, and internal and external oblique) muscles were outlined. Using the Hounsfield unit (HU) range for which muscle mass absorbs X-rays (-29, +150), the cross-sectional area of the above mentioned muscles was semi-automatically quantified, leading to an estimation of the total cross-sectional area of the abdominal skeletal muscles at the L3 level (L3-SM in cm^2). The estimated muscle mass area was then normalized to height to calculate skeletal muscle index: L3-SMI (cm^2/m^2) = L3-SM in cm^2/height^2 in m^2. Five different cutoff values were applied in the present study, most of which had been previously applied in cirrhotic patients:

- <39 cm^2/m^2 for women and <50 cm^2/m^2 for men, developed for cirrhotic patients by Carey *et al* [13]
- <42 cm^2/m^2 for women and <50 cm^2/m^2 for men, developed for cirrhotic patients by Montano-Loza *et al* [12]
- <39 cm^2/m^2 for women and <55 cm^2/m^2 for men, also developed for the oncological population by Mourtzakis *et al* [17] and endorsed by the European Society of Clinical Nutrition and Metabolism (ESPEN) [18]

- <41 cm²/m² for women, irrespective of dry BMI, and <43 cm²/m² for men with dry BMI <25kg/m² and <53 cm²/m² for men with dry BMI ≥25kg/m², also developed for oncological patients by Martin *et al* [19]
- <38.5 cm²/m² for women and <52.4 cm²/m² for men, developed for the oncological population by Prado *et al* [20].

Statistical analysis

We calculated that a total of 94 patients would be required to evaluate 2-sided differences at a 5% significance level (i.e., 95% confidence interval [95%CI]), based on the following assumptions: i) the prevalence of low muscle mass in a sample of chronic liver disease patients of various disease stages and etiologies is around 13% [21]; and ii) the annual population size of cirrhotic patients who visit the outpatient clinics participating in the study and are eligible for recruitment is 200. The achieved statistical power (i.e., 1 minus Type-II error) was 95%.

Categorical variables were represented as absolute numbers and relative frequencies. The normality of the continuous variables was examined using the Shapiro-Wilk test and graphically through Q-Q plots. Normally distributed continuous variables were expressed as mean values ± standard deviation (SD) and non-normally distributed as median and 1st-3rd quartiles. The χ^2 test was used for comparisons between categorical variables and the agreement between them was examined using Cohen's kappa coefficient (kappa). The independent samples *t*-test was used for comparison of normally distributed continuous variables between patients with low and adequate muscle mass according to DXA, while the Mann-Whitney test was used for non-normally distributed variables.

The correlation between the quantification of muscle mass as estimated by ALMI, by DXA and L3-SMI by CT analysis was assessed using Pearson's correlation coefficient (r). Study participants' z-scores for muscle mass estimated by ALMI and L3-SMI were calculated according to sex, based on the mean of the ALMI and L3-SMI and the corresponding standard deviations from the study sample. Bland-Altman plots [22] were used to evaluate the relative validity of L3-SMI against ALMI, according to sex. The plots showed the difference between each individual's z-scores derived from ALMI and L3-SMI against their means [22]. The bias (mean difference between ALMI z-scores and L3-SMI z-scores in our study sample) and the corresponding limits of agreement (±2 SD) of the mean difference were calculated.

Sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (PLR and NLR) and accuracy were calculated for the various cutoffs against the reference DXA method. Logistic regression analysis was applied to assess the relationship between muscle wasting identification based on DXA and muscle wasting as identified using 5 different cutoffs based on CT analysis, after adjusting for the following confounders: age (years), sex (male/female), disease etiology (viral/alcoholic/non-alcoholic steatohepatitis/primary biliary cholangitis [PBC]-autoimmune/unknown), BMI category (underweight/normal weight/overweight/obese), MELD score, and presence of ascites (yes/no).

Results

Participants' descriptive characteristics in relation to muscle mass category according to ALMI are presented in Table 1. Among the study participants, 74.3% had high BW. Chronic viral infection (by hepatitis B or C virus) was the leading cause of cirrhosis among study participants, accounting for the 53.6% of disease etiology. Almost half of the study participants had decompensated cirrhosis (45.4%). Low muscle mass prevalence according to ALMI was estimated at 13.4% in the total study sample. Moreover, patients with high BW (overweight and obese altogether) were more likely to have adequate muscle mass compared with normal and underweight patients (P=0.041). It should also be noted that a higher percentage of patients with alcoholic etiology was found in the low muscle mass subgroup compared with the normal muscle mass group (46.2% vs. 20.2%, P=0.041), while the relevant difference observed for patients with PBC/autoimmune etiology did not appear to be statistically significant (0.0% vs. 16.7%, P=0.112). Overall, there were 5 patients with PBC etiology among the study participants, most of them with compensated cirrhosis (80%) and with increased BW (80%), but none with low ALMI (0%).

Correlation of muscle mass estimation between ALMI and L3-SMI by CT

Quantification of muscle mass by estimation of ALMI by DXA and L3-SMI by CT were highly correlated in the total sample (r=0.613, P<0.001) and in both sexes (r=0.392, P=0.002 for men and r=0.641, P<0.001 in women). When the z-scores for each patient were calculated based on the mean of the ALMI and the L3-SMI according to sex (ALMI mean ± SD for men: 8.17±1.0 and for women: 6.99±0.92, and L3-SMI mean ± SD for men: 53.1±6.6 and for women: 45.2±9.1), 2 Bland-Altman plots were constructed to compare the 2 methods of muscle mass quantification based on the relative z-scores according to sex (Fig. 1). The bias and the corresponding limits of agreement (±SD) of the mean difference were 0.00 (±1.10) for men (Fig. 1A) and 0.07 (±0.73) for women (Fig. 1B). Based on the plots depicted in Fig. 1 A,B, no statistically significant correlations between average and difference were detected in either sex (P=0.996 for men and P=0.269 in women in the regression analyses between the average and the difference of the z-scores between methods in each sex). Consequently, L3-SMI showed acceptable agreement with the reference method of ALMI in both sexes.

Concurrent validity of 5 cutoffs for muscle mass assessment based on CT analysis against ALMI by DXA

Compared to ALMI categorization (low vs. adequate) of muscle mass, considered the reference for muscle wasting diagnosis, the Carey *et al* cutoffs, followed by the Prado *et al* and the Montano-Loza *et al* cutoffs, were the most accurate

(accuracy: 78.4%, 75.3% and 74.2%, respectively) (Table 2), estimating muscle wasting prevalence at 26.8%, 29.9% and 30.9%, accordingly. The cutoffs by Mourtzakis *et al* showed the highest sensitivity (84.6%), but low specificity (60.7%), leading to less accurate results.

To support the findings mentioned above, logistic regressions were performed to examine the probability of a patient having low muscle mass according to the reference method of ALMI when categorized as having low muscle mass based on CT analysis using the 5 different cutoffs.

After adjustment for age, sex, BMI category, disease etiology, presence of ascites and MELD score, patients found to have low muscle mass according to Carey *et al* cutoffs, had a 5.88 times higher probability of having low muscle mass according to ALMI (95%CI 1.36-25.4, P=0.018). Assessment of low muscle mass with either the Prado *et al* or the Montano-Loza *et al* cutoffs was also correlated with low muscle mass according to ALMI (odds ratio [OR] 4.24, 95%CI 1.01-17.8, P=0.049; and OR 5.27, 95%CI 1.22-22.8, P=0.026, respectively).

Table 1 Descriptive characteristics of the total study sample in relation to muscle mass adequacy, as identified by ALMI derived from DXA

Characteristics*	Total sample (n=97)	Low muscle mass (according to ALMI, n=13)	Adequate muscle mass (according to ALMI, n=84)	P-value†
Age (years)	59.1±11.6	61.2±9.72	58.8±11.8	0.441
Sex, n (%)				0.050
Male	58 (59.8%)	11 (84.6%)	47 (56.0%)	
Dry BMI (kg/m²)	28.1±4.73	24.6±4.04	28.6±4.61	0.004
BMI categories, n (%)				0.012
Underweight	1 (1%)	1 (7.7%)	0 (0.0%)	
Normal weight	24 (24.7%)	5 (38.5%)	19 (22.6%)	
Overweight	38 (39.2%)	6 (46.1%)	32 (38.1%)	
Obese	34 (35.1%)	1 (7.7%)	33 (39.3%)	
Cause of cirrhosis, n (%)				0.225
Viral (HBV/HCV)	52 (53.6%)	6 (46.2%)	46 (54.8%)	
Alcohol	23 (23.7%)	6 (46.2%)	17 (20.2%)	
NASH	7 (7.2%)	1 (7.7%)	6 (7.1%)	
PBC-autoimmune	14 (14.4%)	0 (0.0%)	14 (16.7%)	
Unknown etiology	1 (1.0%)	0 (0.0%)	1 (1.2%)	
Disease stage, n (%)				0.208
Decompensated	44 (45.4%)	8 (61.5%)	36 (42.9%)	
MELD score	9.4 (7.5-12.6)	10.5 (7.7-12.7)	9.2 (7.5-12.6)	0.582

*Data are presented as means ± SD or frequencies
†Probability values as derived by chi-square test or 2-samples t-test for comparisons between patients with low or adequate muscle mass
ALMI, appendicular lean mass index; DXA, dual energy X-ray absorptiometry; BMI, body mass index; CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis
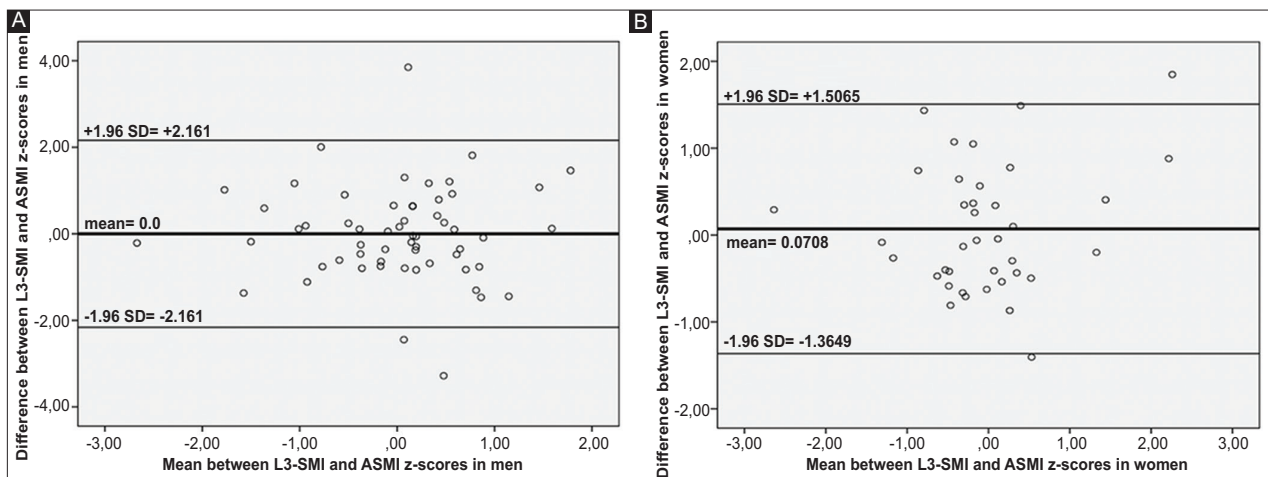

Figure 1 Sex-specific Bland-Altman plots of muscle mass z-scores derived from the ALMI by DXA and the L3-SMI by CT; (A) for men and (B) for women. Represents 95% limits of agreement between muscle mass z-scores derived from ALMI and L3-SMI
ALMI, appendicular lean mass index; CT, computed tomography; DXA, dual energy X-ray absorptiometry; L3-SMI, skeletal muscle mass index at the L3 vertebra

Table 2 Validation of 5 different cutoffs for muscle mass assessment based on CT analysis using ALMI by DXA as the reference method in the total sample (n=97)

Cutoffs	Prevalence	Se	Spe	PPV	NPV	PLR	NLR	Accuracy	P-value*	kappa
Carey *et al* [13]	26.8%	69.2%	79.8%	34.6%	94.4%	3.42	0.39	78.4%	<0.001	0.344
Montano-Loza *et al* [12]	30.9%	69.2%	75.0%	30.0%	94.0%	2.77	0.41	74.2%	0.001	0.285
Mourtzakis *et al* [18]	45.4%	84.6%	60.7%	25.0%	96.2%	2.15	0.25	63.9%	0.002	0.226
Martin *et al* [19]	30.9%	53.8%	72.6%	23.3%	91.0%	1.97	0.64	70.1%	0.055	0.170
Prado *et al* [20]	29.9%	69.2%	76.2%	31.0%	94.1%	2.91	0.40	75.3%	0.001	0.299

Low muscle mass prevalence as assessed by the reference method (ALMI by DXA) was 13.4%
*Probability values as derived by Chi-square test for the relation between muscle mass assessment according to the gold standard method DXA and the CT analysis based on 5 different cutoff points
ALMI, appendicular lean mass index; CT, computed tomography; DXA, dual energy X-ray absorptiometry; NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value; Se, sensitivity; Spe, specificity

Discussion

The present study aimed to estimate the validity of the cutoffs newly proposed by Carey *et al* for L3-SMI assessment by CT in cirrhotic patients, as well as other prominent cutoffs, against the reference method of ALMI. According to our results, the prevalence of low muscle mass in our population sample was estimated to be 11.3% according to ALMI. When assessed against ALMI, the Carey *et al* cutoffs showed the best accuracy and agreement compared to the other cutoffs examined, followed by the cutoffs proposed by Prado *et al* and Montano-Loza *et al*.

Low muscle mass has a significant prognostic value in liver disease [23]; thus, quantification and assessment of muscle mass in cirrhotic patients can be considered a crucial step in the nutritional assessment and management of these patients, especially in the light of emerging data suggesting possible therapeutic approaches [24]. There are many available methods for the assessment of muscle mass, all showing both strengths and limitations. Anthropometry, such as skinfold thickness measurement, is an easily applicable, rapid and low-cost method; however, it seems to lack accuracy in cirrhotic patients [25]. Bioelectrical impedance has also been applied in patients with advanced liver disease, offering the advantages of a low cost and portable equipment. However, the accuracy of this method is highly affected by the hydration status, unstable in cirrhotic patients [26]. The application of DXA in cirrhotic patients is highly supported [3,5], since the estimation of ALMI, by excluding the muscle mass assessed in the trunk area, overcomes the possible error due to ascites. However, the equipment is quite costly, thus limiting its application to the research area rather than clinical practice [5]. Cross-sectional imaging at the L3 vertebra by CT is widely accepted as a reliable method for direct muscle mass quantification [24], and low muscle mass estimation according to this method has been associated with an increased risk for mortality in cirrhotic patients [23]. The application of CT analysis in cirrhotic patients could be widely supported, as cirrhotic patients frequently undergo CT scanning as part of their medical follow up [5]. The only drawback so far has been the lack of widely accepted and validated cutoffs for this method in patients with advanced

liver disease [27]. Thus, muscle mass quantification through CT cross-sectional imaging analysis is emerging as a useful tool in the nutritional assessment of cirrhotic patients, but will find wide acceptance only if specific cutoffs can be established.

In our study, muscle mass quantification by DXA was largely correlated with that by CT analysis. Similar findings were reported by Lindqvist *et al* in patients with chronic liver disease during the pre-transplant period [28] and by Ishakawa *et al* in a sample of cirrhotic patients with and without hepatocellular carcinoma [29]. Notably, the prevalence of low muscle mass in our study did not reveal any statistically significant difference in relation to disease etiology in general; however, it should be noted that a significantly higher percentage of patients with an alcoholic etiology was found in the low muscle mass subgroup compared with the normal muscle mass group. This is finding is to be expected considering the detrimental effect of chronic alcohol abuse on muscle mass and protein balance in general [30].

Considering the strong association of the L3-SMI technique with the reference method of ALMI in our study, we sought to examine the validity of the newly proposed cutoffs by Carey *et al* [13] in comparison with another 4 widely applied cutoffs for L3-SMI assessment. According to our results, the cutoffs by Carey *et al*, specifically developed for cirrhotic patients, showed the best accuracy, agreement and correlation with the reference method, followed by the cutoffs proposed by Prado *et al* and Montano-Loza *et al*, which showed slightly inferior performance. The Carey *et al* cutoffs, derived from a large multicenter study and endorsed by EASL [5], as well as the Montano-Loza *et al* cutoffs, have been developed especially for cirrhotic patients; however, they have not yet been widely applied, and only the Carey *et al* cutoffs have been validated against survival in one study so far [31]. The cutoffs by Prado *et al*, although non-disease specific, have been previously applied in studies with cirrhotic patients [10,32], but their validity in this group of patients has never been examined before. In our study, the 3 abovementioned cutoffs showed similarly fair agreement, good accuracy and adequate sensitivity and specificity. The NPVs of the cutoffs were high, in contrast to the PPVs, which were quite low (all <35%), indicating that 2/3 of the patients categorized with low muscle mass according to the CT analysis would not be categorized as such by the reference method.

The present study has both strengths and limitations. To our knowledge, this is the first study ever to comparatively assess the concurrent validity of 5 different cutoffs for muscle mass assessment based on CT analysis in cirrhotic patients. Moreover, the study sample consisted of patients with cirrhosis from various causes, evenly distributed among sex and disease stage, allowing the results to be extrapolated to the whole range of the disease. Regarding limitations, the absence of a gold standard method for muscle mass assessment is a barrier in every study on this topic, creating a risk of bias. Although DXA, applied in the present study, exhibits some drawbacks, such as its high cost and the expertise needed by the operator, it has been suggested by both EASL and ESPEN as a method of muscle mass assessment in liver disease [3,5] and is generally considered a standardized, widely known and valid reference method, since the ALMI value does not appear to be affected by fluid accumulation in cirrhotic patients [4]. Thus, it was chosen in the present study as the reference method for muscle mass assessment.

In conclusion, muscle mass quantification by the reference method DXA showed a large correlation with CT cross-sectional imaging analysis. Regarding muscle mass assessment according to L3-SMI, of the 5 different cutoffs implemented in the present study, the Carey *et al* cutoffs [13] are confirmed to be the most accurate in detecting low muscle mass in cirrhotic patients, closely followed by the ones proposed by Prado *et al* and Montano-Loza *et al*. The present study is an additional validation of the diagnostic value of the Carey *et al* cutoffs and a step towards standardization of these cutoffs as the benchmark for muscle mass assessment in cirrhosis based on CT analysis.

Summary Box

What is already known:

- Muscle wasting has a significant negative impact on disease complications and survival in patients with advanced liver disease
- Radiological methods have been proposed for muscle mass quantification in liver disease patients
- Muscle mass area estimation by computed tomography (CT) image analysis has been recognized as a main method for muscle mass quantification globally, but no standard cutoffs have been established
- Recently, Carey *et al* proposed new cutoffs, which have been endorsed by the European Association for the Study of the Liver but have not yet been validated

What the new findings are:

- Muscle mass quantification by dual energy X-ray absorptiometry (DXA) is strongly correlated with the results from CT image analysis
- The cutoffs proposed by Carey *et al* proved to be the most accurate in identifying low muscle mass as assessed by the reference method (i.e., DXA)

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