An improved method to assess skeletal muscle mass in patients with liver cirrhosis based on computed tomography images

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Abstract

Aim: Conventionally, the skeletal muscle area with computed tomography (CT) attenuation ranging from -29 to +150 Hounsfield unit (HU) divided by height squared (the conventional skeletal muscle index [SMI]) was used as an index of skeletal muscle mass. However, it includes fat-infiltrated skeletal muscle, which is known to have poor function. This study aims to determine whether the low-fat SMI, which uses skeletal muscle mass with CT attenuation ranging from +30 to +150 HU, or conventional SMI appropriately reflects the function of skeletal muscle.

Methods: We retrospectively analyzed 120 patients with cirrhosis whose handgrip strength was measured. Among them, 48 patients underwent a physical performance assessment such as liver frailty index (LFI) and short physical performance battery (SPPB), and 80 underwent quality of life (QOL) assessment. The relationships between each SMI and handgrip strength, LFI, SPPB, and QOL were evaluated.

Results: Low-fat SMI was significantly correlated with handgrip strength (males, R = 0.393, $P = 0.002$; females, R = 0.423, $P < 0.001$) and LFI (males, R = -0.535, $P = 0.035$; females, R = -0.368, $P = 0.039$), whereas conventional SMI was not. When using low-fat SMI, patients with low skeletal muscle mass had significantly low handgrip strength, LFI, SPPB, and physical and social-related QOL score than those without. By contrast, no significant differences were found for any items when using conventional SMI.

Conclusions: Low-fat SMI is a good index of skeletal muscle mass that appropriately reflects skeletal muscle function.

Keywords: body fat distribution, liver cirrhosis, muscle strength, quality of life, sarcopenia, skeletal muscle

Introduction

Sarcopenia is characterized by low skeletal muscle mass and strength and impaired physical performance.[1] In patients with liver cirrhosis, the presence of sarcopenia worsens prognosis and reduces health-related quality of life (HRQOL),[2,3,4] therefore, making accurate diagnosis essential. Sarcopenia is diagnosed if both muscle strength and skeletal muscle mass are decreased. Grip strength is generally used to assess muscle strength, whereas several methods have been proposed to evaluate skeletal muscle mass.[1,5] In primary care settings, bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry are used to assess skeletal muscle mass due to their versatility and relatively low cost. However, these methods have the disadvantage of being affected by fluid retention.[5,6] On the other hand, skeletal muscle mass assessment using computed tomography (CT) is considered the gold standard because it is less susceptible to fluid retention in addition to its accuracy and high reproducibility.[5,6] Although skeletal muscle mass assessment using CT has a high cost and radiation exposure, patients with liver cirrhosis often have fluid retention, i.e., edema and ascites, and frequently undergo abdominal CT scans to evaluate the presence of hepatocellular carcinoma (HCC). Therefore, CT imaging analysis is recommended to assess skeletal muscle mass in cirrhosis patients.[6] When assessing skeletal muscle mass using CT images, the range of CT attenuation for delimitation of the skeletal muscle need to be determined. The CT attenuation of skeletal muscle has a range of -190 to +150 Hounsfield unit (HU) with a peak of approximately +50 HU. However, there is adipose

tissue between skeletal muscles, called inter-muscular adipose tissue, whose CT attenuation is -190 to -30 HU.[7] Therefore, the skeletal muscle area in the range of -29 to +150 HU, which excludes the intermuscular adipose tissue, is commonly used,[8] and it has been shown to be in strong agreement with the skeletal muscle area of the cadaver in the same cross section.[9] However, fat deposition occurs not only around the skeletal muscle but also in the skeletal muscle. Fat deposition in skeletal muscle is also represented as decreased CT attenuation of skeletal muscle,[10] and reduces muscle contractility.[11] Therefore, some studies defined skeletal muscles in the range of -29 to +29 HU as "poor-quality skeletal muscles" due to high fat infiltration, and those in the range of +30 to +150 HU as "good-quality skeletal muscles" with less fat infiltration.[7,12] Based on the above facts, we hypothesize that skeletal muscle mass with CT attenuation of +30 to +150 HU, representing skeletal muscle with less fat infiltration, would be an appropriate skeletal muscle mass index that correlates well with skeletal muscle function, rather than the conventionally used skeletal muscle mass with CT attenuation of -29 to +150 HU.

This study aims to determine whether the conventionally used skeletal muscle mass with CT attenuation ranging from -29 to +150 HU and the low-fat skeletal muscle mass with CT attenuation ranging from +30 to +150 HU reflects the function of skeletal muscle in patients with liver cirrhosis.

Methods

Patients and study design

We retrospectively reviewed 183 adult patients with radiologically diagnosed liver cirrhosis who were admitted to our institution and underwent handgrip strength measurement, as well as body composition measurement by BIA method and CT scans, between May 2017 and October 2020. A radiologist diagnosed cirrhosis based on the following findings: irregularity of the liver surface, atrophy of the right lobe of the liver, enlargement of the left lobe of the liver, splenomegaly, and development of collateral vessels of the portal vein. Patients with malignancies other than HCC (n = 11) and those with uncontrolled HCC (n = 23), poorly controlled cardiac, respiratory, and renal diseases (n = 7), neurological and muscular diseases (n = 1), and severe encephalopathy (n = 1) were excluded. We also excluded patients with more than a 1-year gap between the date of CT and the date of handgrip strength measurement (n = 6). Patients with massive ascites (grade 3 as defined on the consensus conference of the International Ascites Club)[13] diagnosed on CT scan (n = 12) and patients whose abdomen was not included in the CT scan (n = 2) were also excluded. Finally, 120 patients were enrolled in the study. Among the 120 enrolled study participants, 48 patients underwent physical performance assessment, and 80 patients underwent an HRQOL assessment. The characteristics of patients who underwent the physical performance or HRQOL assessment are shown in the Supplement data (Table S1, S2).

Data collection

Data on blood biochemical tests, image findings, skeletal muscle mass, muscle strength, physical performance, and HRQOL were collected retrospectively. The fibrosis-4 (FIB-4) index was used as an indicator of liver fibrosis and was calculated using the following formula: age ([years] × aspartate aminotransferase [U/L]) / ((platelet count [10^9/L]) × (alanine aminotransferase [U/L])$^{1/2}$). [14] Skeletal muscle mass was assessed using two different parameters: the skeletal muscle area at the middle of the third lumber spine vertebra (L3) level on CT images and skeletal muscle mass measured using the BIA method. The visceral fat area at the umbilical levels was also assessed on CT images. CT images were taken when clinically necessary. For the diagnosis of HCC, nodules with hyperattenuation in the arterial phase followed by washout in the portal or equilibrium phase on contrast-enhanced CT or contrast-enhanced magnetic resonance imaging were defined as HCC. The HCC stage was determined according to the Barcelona Clinic Liver Cancer classification.[15]

Assessment of skeletal muscle mass

Skeletal muscle area was calculated using the SYNAPSE VINCENT software (version 4.3, Fujifilm Co., Tokyo, Japan), which enables specific tissue demarcation using HU thresholds. Skeletal muscle was quantified in two different settings of CT attenuation: an HU range of -29 to +150 HU, which has been conventionally used, and an HU range of +30 to +150 HU, which displays skeletal muscle with less fat infiltration.[7,12] Tissue boundaries were manually corrected as needed. Since CT images taken

for the evaluation of HCC and/or ascites were used for skeletal muscle mass measurements, the date of CT scan and the date of grip strength measurement differed with a median of 24 days (interquartile range [IQR]: 1–77 days). Visceral fat are (an HU range of -150 to -50 HU) was also calculated by using the SYNAPSE VINCENT software. BIA for skeletal muscle mass assessment was performed using the InBody S10 (InBody Co., Ltd., Seoul, Korea) on the same day as the grip strength measurement. The InBody S10 uses a multi-frequency segmental measurement method with an 8-point tactile electrode. The multi-frequency measurement is conducted by using multiple frequencies at 1, 5, 50, 250, 500, and 1,000 kHz for each body segment (arms, trunk, and legs). The analyzer automatically displays measurements of body composition. The CT-based skeletal muscle index (SMI) was calculated as the total skeletal muscle area (cm^2) divided by the square of the height (m^2). The SMI based on BIA assessment (BIA-SMI) was calculated as the amount of appendicular skeletal muscle mass (kg) divided by the square of the height (m^2).

Assessment of handgrip strength and physical performance

Handgrip strength was measured twice in the participant's dominant hand using a Smedley-type digital grip strength dynamometer (B07CXL4K8W N-FORCE; CORVETTE Inc., Wakayama, Japan) in a standardized procedure.[1]

The skeletal muscle function of the lower extremities was assessed according to the proposal by the

Asia Working Group for Sarcopenia (AWGS), using the following three methods.[1]

1. The 6-m walk test: measured the time required to walk 6 meters at a normal walking speed. The test is performed twice and the average value is used. We used the same method to measure the 6-meter walking speed at maximum speed.

2. The standing balance test: measured as the number of seconds the participant can balance for a maximum of 10 seconds in each of the three postures: feet on the side, semi-tandem, and tandem.

3. The 5-time chair stand test: measured as the number of seconds it takes to stand up from a chair five times with arms folded across the chest.

Using handgrip strength and the results of these tests, physical function was scored using the liver frailty index (LFI), a physical function assessment tool developed for patients with cirrhosis,[16] and the short physical performance battery (SPPB), an objective assessment tool for lower limb function developed for community-dwelling adults.[17] The LFI was calculated using the following equation (calculator available http://liverfrailtyindex.ucsf.edu): (-0.330 × gender-adjusted grip strength) + (-2.529 × number of chair stands per seconds) + (-0.040 × seconds holding 3 position balance) + 6. The higher the physical ability, the lower the score. Regarding grip strength, the original study used the average value of grip strength measured three times. [16] However, in the present study, since grip strength was measured only twice, the average value of the grip strength measured twice was used. The SPPB was based on the results of the walking test at normal walking speed, the standing balance

test, and the 5-time chair stand test; each of which was scored on a scale of 0 to 4 and expressed as a total score (ranging from 0 [worst performance] to 12 [best performance]). The walking speed test of the SPPB was divided into four categories using the time at 2.4 m (Category 1: ≥5.7 s, Category 2: 4.1–5.6 s, Category 3: 3.2–4.0 s, Category 4: ≤3.1 s) in the original study.[17] However, we performed the 6-m walk test, so we converted the results into four categories using the time at 6.0 m (Category 1: ≥14.2 s, Category 2: 10.2–14.1 s, Category 3: 7.9–10.1 s, Category 4: ≤7.8 s).

Assessment of HRQOL

HRQOL was assessed using the 36-item Short-Form Health Survey version 2 questionnaire. This tool consists of 36 questions and assesses eight health concepts: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Furthermore, three component scores—physical component summary, mental component summary, and role-social component summary—were calculated from these eight subscales. The scores of the three summary components were converted into norm-based scores to achieve the same mean values of 50 and a standard deviation of 10 in the general Japanese population, to allow for easier interpretation of the results. Higher scores indicate better HRQOL.[18,19]

Definitions

In accordance with the AWGS 2019 criteria, low muscle strength was defined as a handgrip strength <28 kg in males and <18 kg in females.[1] The skeletal muscle area determined with CT attenuation ranging from -29 to +150 HU divided by height squared was defined as "conventional SMI," whereas that assessed with values ranging from +30 to +150 HU (i.e., skeletal muscle with less fatty infiltration) was defined as "low-fat SMI." Following the Japan Society of Hepatology guidelines, low skeletal muscle mass was diagnosed by conventional SMI of < 42 cm^2/m^2 for males and < 38 cm^2/m^2 for females or by BIA-SMI of < 7.0 kg/m^2 for males and < 5.7 kg/m^2 for females.[20] Sarcopenia was defined as low skeletal muscle mass and strength, dynapenia as normal skeletal muscle mass and low muscle strength, pre-sarcopenia as low skeletal muscle mass and normal muscle strength, and normal muscle status as normal skeletal muscle mass and muscle strength.[1] Type 2 diabetes mellitus was defined as any of the following: fasting plasma glucose ≥126 mg/dL, hemoglobin A1c (National Glycohemoglobin Standardization Program value) ≥6.5%, or the use of antidiabetic medication based on the diagnostic guidelines of the Japan Diabetes Society.[21] Dyslipidemia was defined as low-density lipoprotein ≥140 mg/dL or the use of anti-lipidemia medicines based on the diagnostic guidelines of the Japan Atherosclerosis Society.[22]

Statistical analysis

Qualitative and quantitative variables were compared using the Mann-Whitney U test, the Kruskal-

Wallis test, and the Fisher's exact test. The Bonferroni post-hoc test was used for multiple comparisons. Correlation coefficients were tested using Spearman's rank correlation coefficient. All statistical analyses were performed using R (R Statistical Software; Foundation for Statistical Computing, Vienna, Austria) and EZR (version 1.40).[23] For all analyses, $P < 0.05$ was considered statistically significant.

Ethics

Informed consent was obtained from each patient. The Ethics Committee at the Nagoya University Hospital approved this study (no. 2018-0291-3), which proceeded according to the principles of the Declaration of Helsinki (1975).

Results

Patient characteristics

The median patient age was 71 years (IQR: 66–78 years), and 58 patients (48.3%) were males. Hepatitis C virus infection was the most common etiology (48 patients, 40.0%), followed by miscellaneous liver diseases (39 patients, 32.5%), alcoholic liver disease (20 patients, 16.7%), and hepatitis B virus infection (13 patients, 10.8%). More than half of the patients (80 patients, 66.7%) were diagnosed with Child-Pugh classification A. HCC was present in about a third of the patients (38

patients, 31.7%; Table 1).

Correlation of conventional SMI and low-fat SMI with BIA-SMI

There was a significant correlation between conventional SMI and BIA-SMI and low-fat SMI and BIA-SMI (R = 0.684 [$P < 0.001$] and R = 0.559 [$P < 0.001$], respectively).

Association of conventional SMI, low-fat SMI, and BIA-SMI with handgrip strength

The correlations between grip strength and SMIs were as follows. Conventional SMI and handgrip strength were not significantly correlated with either sex (males, R = 0.209, $P = 0.116$; females, R = 0.187, $P = 0.145$; Figures 1a, 1d). On the other hand, low-fat SMI and handgrip strength showed significant correlations in males and females (males, R = 0.393, $P = 0.002$; females, R = 0.423, $P < 0.001$; Figures 1b, 1e). Similarly, BIA-SMI showed significant correlations with handgrip strength in males and females (males, R = 0.561, $P < 0.001$; females, R = 0.351, $P = 0.005$; Figures 1c, 1f).

Next, the optimal cutoff value for defining low skeletal muscle mass in low-fat SMI (equivalent to BIA-SMI < 7.0 kg/m^2 in males and < 5.7 kg/m^2 in females) was calculated using the receiver operating characteristic (ROC) curve analysis. The cutoff value for low-fat SMI was determined as 25.2 cm^2/m^2 in males (area under the curve [AUC] in the ROC curve analysis, 0.79; sensitivity, 72%; specificity, 80%; Figure 2a) and 24.8 cm^2/m^2 in females (AUC, 0.73; sensitivity, 96%; specificity, 46%; Figure

2b). Then, differences in handgrip strength between patients with and without low skeletal muscle mass assessed using the three indices (conventional SMI, low-fat SMI, and BIA-SMI) were evaluated. Based on conventional SMI, there was no significant difference in handgrip strength between patients with and without low skeletal muscle mass. By contrast, patients with low skeletal muscle mass, as categorized by low-fat SMI or BIA-SMI, had significantly reduced handgrip strength compared to those without (Table 2).

Relationships of conventional SMI, low-fat SMI, and BIA-SMI with physical performance

The correlations between LFI and SMIs were as follows. Conventional SMI and LFI were not significantly correlated with either sex (males, R = -0.485, $P = 0.059$; females, R = -0.102, $P = 0.577$). On the other hand, low-fat SMI and LFI showed significant correlations in males and females (males, R = -0.535, $P = 0.035$; females, R = -0.368, $P = 0.039$). BIA-SMI showed significant correlations with LFI in males (R = -0.637, $P = 0.004$), but not in females (R = -0.057, $P = 0.758$).

When skeletal muscle mass was assessed using low-fat SMI, patients with low skeletal muscle mass had significantly poorer performances in LFI, SPPB, and the 5-time chair stand test, as well as marginally poorer performances in the 6-m walk test at maximal walking speed and the standing balance test, than those without. In contrast, when skeletal muscle mass was assessed with conventional SMI or BIA-SMI, no significant difference was found in any item between patients with

and without low skeletal muscle mass (Table 2).

Relationships of conventional SMI, low-fat SMI, and BIA-SMI with HRQOL

Patients with low skeletal muscle mass determined by low-fat SMI had significantly lower scores in physical component summary and role-social component summary than those without. When skeletal muscle mass was assessed by BIA-SMI, patients with low skeletal muscle mass had significantly lower scores only in physical component summary. By contrast, patients with low skeletal muscle mass according to conventional SMI had significantly lower scores than those without only in role-social component summary (Table 3).

Impact of differences in skeletal muscle mass assessment using low-fat and conventional SMI on the diagnosis of sarcopenia

The concordance rate of low skeletal muscle mass diagnosis assessed by low-fat SMI and conventional SMI was 73.3% (88/120), and 27 patients (22.5%) diagnosed with normal skeletal muscle mass by conventional SMI were diagnosed with low skeletal muscle mass by low-fat SMI. In contrast, only 5 patients (4.2%) diagnosed with low skeletal muscle mass by conventional SMI were diagnosed with normal skeletal muscle mass by low-fat SMI.

Next, we examined the impact of differences in skeletal muscle mass assessment by low-fat SMI and

conventional SMI on the diagnosis of sarcopenia. When skeletal muscle mass was assessed using conventional SMI, 20 patients were diagnosed with sarcopenia, and 19 of those patients were diagnosed with sarcopenia when low-fat SMI was used. However, among the 23 patients who were diagnosed with dynapenia (defined as low muscle strength but normal skeletal muscle mass) based on conventional SMI, 14 (60.9%) patients were classified as having low skeletal muscle mass and diagnosed with sarcopenia when skeletal muscle mass was assessed using low-fat SMI (Table 4). The discrepancies in the diagnosis of low skeletal muscle mass between assessment by using low-fat SMI and BIA-SMI were similar for Child Pugh class A and class B or C (Table S3) and for males and females (Table S4).

Clinical characteristics of patients who were diagnosed with normal skeletal muscle mass by conventional SMI and low skeletal muscle mass by low-fat SMI

Patients who were diagnosed as having normal skeletal muscle mass by conventional SMI but low skeletal muscle mass by low-fat SMI have more Grade 2 ascites and visceral fat area than patients in whom two SMIs were consistent in their assessment of skeletal muscle mass (Table 5).

Discussion

The current study revealed that skeletal muscle mass was significantly associated with muscle strength,

physical performance, and HRQOL when assessed using low-fat SMI.

Fatty infiltration of skeletal muscles impairs skeletal muscle strength and physical function.[11,24,25] Especially in patients with liver cirrhosis, more than half of the patients have fat deposits in skeletal muscles,[26] the correlation between skeletal muscle mass and muscle strength and physical function can be weak. In fact, with regard to the correlation between skeletal muscle mass and grip strength, it has been reported that the correlation is weak in males and no correlation or only a very weak correlation is observed in females.[27–29] Also, with regard to physical function, no correlation has been found between skeletal muscle mass and SPPB[27] or physical function-related QOL.[30] In addressing this issue, in addition to the quantity of skeletal muscle, the need to assess the quality of skeletal muscle with CT attenuation values has also been noted.[5,8] However, at this time, the guidelines for assessment of sarcopenia do not state the need to assess skeletal muscle quality when using CT to assess skeletal muscle mass.[20] The current study revealed that the skeletal muscle area in the range of +30 to +150 HU with less fat infiltration rather than the conventionally used skeletal muscle area in the range of -29 to +150 HU, is associated with grip strength, physical function, and HRQOL. In other words, skeletal muscle quality was taken into account by excluding skeletal muscles with high fat infiltration, resulting in a significant association between skeletal muscle mass and muscle strength and physical function.

Furthermore, the use of the skeletal muscle area with less fatty infiltration had an impact on the

diagnosis of sarcopenia. The current study showed that 22.5% of the total patients diagnosed with normal skeletal muscle mass by conventional SMI were diagnosed with low skeletal muscle mass by low-fat SMI. Thus, in approximately one-fifth of patients with cirrhosis, the apparent skeletal muscle mass was maintained, but the functional skeletal muscle was reduced. Clinical features of patients who were diagnosed with normal skeletal muscle mass by conventional SMI but low skeletal muscle mass by low-fat SMI were severe ascites and high visceral fat accumulation. CT attenuation of inter-muscular adipose tissue is in the range of -190 to -30 HU, while that of water is 0. The increased water content in the inter-muscular adipose tissue due to severe ascites and edema may increase the CT attenuation values of inter-muscular adipose tissue, which was included in the range of CT attenuation for skeletal muscle, from -29 to 150 HU, resulting in the overestimation of skeletal muscle mass. In addition, ectopic fat deposition is one of the causes of fatty infiltration into skeletal muscle,[31] and it has been shown that CT values of skeletal muscle are decreased in obese patients.[32] The results of the present study suggest that the amount of skeletal muscle mass may be overestimated in patients with severer ascites and visceral fat accumulation when skeletal muscle mass is assessed by conventional SMI. Therefore, the assessment of skeletal muscle mass using low-fat SMI is useful in such patients.

AWGS proposed that dynapenia is a preliminary stage of sarcopenia and needs to be properly diagnosed,[1] because patients with dynapenia have been shown to have a poor prognosis, similar to patients with sarcopenia.[33] However, the diagnostic algorithm for sarcopenia overlooks patients with

dynapenia.[1,5,20] The current study showed that, using low-fat SMI, 60.9% of patients who had been diagnosed with dynapenia assessed by conventional SMI were diagnosed with sarcopenia. Since sex and hepatic function are reported to be associated with the prevalence of sacropenia,[34,35] we examined whether the impact of differences in skeletal muscle mass assessment by low-fat SMI and conventional SMI on the diagnosis of sarcopenia differed by liver function and sex, but the discrepancies in diagnosis were similar for Child Pugh class A and class B or C and for males and females.

Because the BIA method is non-invasive and simple, it is the standard method of measuring skeletal muscle mass in the diagnosis of sarcopenia.[1,5] However, skeletal muscle mass assessed by the BIA method includes adipose tissue within the skeletal muscle.[36] In the current study, low-fat SMI had a stronger relationship with skeletal muscle function than BIA-SMI. Therefore, low-fat SMI should be used to assess skeletal muscle mass in patients undergoing abdominal CT in daily clinical practice.

This study has some limitations. First, the present study was a single-center, retrospective study with a relatively small number of patients. In addition, since no previous study has examined the relationship between skeletal muscle mass with CT attenuation ranging from +30 to +150 HU and skeletal muscle function, the current study was an exploratory study and hence it was not possible to set an appropriate sample size. Therefore, all patients with cirrhosis who were evaluated for skeletal muscle mass and function were included in the study. Second, there was a time difference between the

day the grip strength was measured and the day the CT was taken. However, since patients with cirrhosis exhibit skeletal muscle loss at an annual rate of only 2.2%,[37] we believe that this does not significantly affect the results.

In conclusion, low-fat SMI using skeletal muscle mass with CT attenuation ranging from +30 to +150 HU was found to be associated with muscle strength, physical function, and HRQOL, whereas conventional SMI using skeletal muscle mass with CT attenuation ranging from -29 to +150 HU was not. Low-fat SMI might be a more appropriate index for assessing skeletal muscle mass in patients with cirrhosis.

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None.

Conflicts of interest

There are no conflicts of interest to declare.

References

1 Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 2020;21:300–7.e2.

https://doi.org/10.1016/j.jamda.2019.12.012.

2 Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. *Nutrition* 2015;31:193–9. https://doi.org/10.1016/j.nut.2014.07.005.

3 Kikuchi N, Uojima H, Hidaka H, Iwasaki S, Wada N, Kubota K, et al. Prospective study for an independent predictor of prognosis in liver cirrhosis based on the new sarcopenia criteria produced by the Japan Society of Hepatology. *Hepatol Res* 2021;51:968–78. https://pubmed.ncbi.nlm.nih.gov/34269502/.

4 Ando Y, Ishigami M, Ito T, Ishizu Y, Kuzuya T, Honda T, et al. Sarcopenia impairs health-related quality of life in cirrhotic patients. *Eur J Gastroenterol Hepatol* 2019;31:1550–6. https://doi.org/10.1097/MEG.0000000000001472.

5 Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019;48:16–31. https://doi.org/10.1093/ageing/afy169.

6 Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021;74:1611–44. https://doi.org/10.1002/hep.32049.

7 Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, Mazurak VC.

Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta Physiol (Oxf)* 2014;210:489–97. https://doi.org/10.1111/apha.12224.

8 Poltronieri TS, de Paula NS, Chaves GV. Assessing skeletal muscle radiodensity by computed tomography: an integrative review of the applied methodologies. *Clin Physiol Funct Imaging* 2020;40:207–23. https://doi.org/10.1111/cpf.12629.

9 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;85:115–22. https://doi.org/10.1152/jappl.1998.85.1.115

10 Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol (1985)* 2000;89:104–10. https://doi.org/10.1152/jappl.2000.89.1.104.

11 Biltz NK, Collins KH, Shen KC, Schwartz K, Harris CA, Meyer GA. Infiltration of intramuscular adipose tissue impairs skeletal muscle contraction. *J Physiol* 2020;598:2669–83. https://doi.org/10.1113/JP279595.

12 Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: From pathogenesis to interventions. *J Gastroenterol* 2019;54:845–59. https://doi.org/10.1007/s00535-019-01605-6.

13 Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology* 2003;38:258–66. https://doi.org/10.1053/jhep.2003.50315.

14 Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. APRICOT Clinical Investigators. Development of a simple non- invasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006;43:1317–25. https://doi.org/10.1002/hep.21178.

15 European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;69:182–236. https://doi.org/10.1016/j.jhep.2018.03.019.

16 Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. *Hepatology* 2017;66:564–74. https://doi.org/10.1002/hep.29219.

17 Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85–94. https://doi.org/10.1093/geronj/49.2.M85.

18 Fukuhara S, Ware JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of

validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 1998;51:1045–53. https://doi.org/10.1016/S0895-4356(98)00096-1.

19 Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998;51:1037–44. https://doi.org/10.1016/S0895-4356(98)00095-X.

20 Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria. *Hepatol Res* 2016;46:951–63. https://doi.org/10.1111/hepr.12774.

21 Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, et al. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig* 2010;1:212–28. https://doi.org/10.1111/j.2040-1124.2010.00074.x.

22 Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, et al. Japan Atherosclerosis Society (JAS) Committee for Epidemiology and Clinical Management of Atherosclerosis. Diagnostic criteria for dyslipidemia. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb* 2007;14:155–8.

https://doi.org/10.5551/jat.E537.

23 Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244.

24 Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the context of skeletal muscle function deficit: An interdisciplinary workshop at the National Institute on Aging. *Front Physiol* 2020;11:963. https://doi.org/10.3389/fphys.2020.00963.

25 Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: the health ABC study. *J Appl Physiol (1985)* 2001;90:2157–65. https://doi.org/10.1152/jappl.2001.90.6.2157.

26 Ebadi M, Montano-Loza AJ. Clinical relevance of skeletal muscle abnormalities in patients with cirrhosis. *Dig Liver Dis* 2019;51:1493–9. https://doi.org/10.1016/j.dld.2019.05.034.

27 Wang CW, Feng S, Covinsky KE, Hayssen H, Zhou LQ, Yeh BM, et al. A comparison of muscle function, mass, and quality in liver transplant candidates: results from the functional assessment in liver transplantation study. *Transplantation* 2016;100:1692–8. http://doi.org/10.1097/TP.0000000000001232.

28 Sinclair M, Chapman B, Hoermann R, Angus PW, Testro A, Scodellaro T, et al. Handgrip strength adds more prognostic value to the model for end-stage liver disease score than

imaging-based measures of muscle mass in men with cirrhosis. *Liver Transpl* 2019;25:1480–7. http://doi.org/10.1002/lt.25598.

29 Hanai T, Shiraki M, Imai K, Suetsugu A, Takai K, Moriwaki H, et al. Reduced handgrip strength is predictive of poor survival among patients with liver cirrhosis: a sex-stratified analysis. *Hepatol Res* 2019;49:1414–26. http://doi.org/10.1111/hepr.13420.

30 Yadav A, Chang YH, Carpenter S, Silva AC, Rakela J, Aqel BA, et al. Relationship between sarcopenia, six-minute walk distance and health-related quality of life in liver transplant candidates. *Clin Transplant* 2015;29:134–41. http://doi.org/10.1111/ctr.12493.

31 Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med* 2014;371:1131–41. https://doi.org/10.1056/NEJMc1412427.

32 Sugiyama Y, Ishizu Y, Ando Y, Yokoyama S, Yamamoto K, Ito T, et al. Obesity and myosteatosis: the two characteristics of dynapenia in patients with cirrhosis. *Eur J Gastroenterol Hepatol* 2021;33:e916–21. https://doi.org/10.1097/MEG.0000000000002303.

33 Li R, Xia J, Zhang XI, Gathirua-Mwangi WG, Guo J, Li Y, et al. Associations of muscle mass and strength with all-cause mortality among US older adults. *Med Sci Sports Exerc* 2018;50:458–67. https://doi.org/10.1249/MSS.0000000000001448.

34 Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with

cirrhosis. *J Cachexia Sarcopenia Muscle* 2016;7:126–35. https://doi.org/10.1002/jcsm.12039.

35 Hiraoka A, Michitaka K, Ueki H, Kaneto M, Aibiki T, Okudaira T, et al. Sarcopenia and two types of presarcopenia in Japanese patients with chronic liver disease. *Eur J Gastroenterol Hepatol* 2016;28:940–7. https://doi.org/10.1097/MEG.0000000000000661.

36 Zamboni M, Gattazzo S, Rossi AP. Myosteatosis: a relevant, yet poorly explored element of sarcopenia. *Eur Geriatr Med* 2019;10:5–6. https://doi.org/10.1007/s41999-018-0134-3.

37 Hanai T, Shiraki M, Ohnishi S, Miyazaki T, Ideta T, Kochi, T, et al. Rapid skeletal muscle wasting predicts worse survival in patients with liver cirrhosis. *Hepatol Res* 2016;46:743–51. https://doi: 10.1111/hepr.12616.

Figure legends

Figure 1. Spearman's rank correlation between handgrip strength and conventional SMI (a, d), low-fat SMI (b, e), and BIA-SMI (c, f) in males (a–c) and females (d–f)

BIA, bioelectrical impedance analysis, SMI, skeletal muscle index

Figure 2. ROC curves of low-fat SMI for low skeletal muscle mass assessed using BIA-SMI in male (a) and female (b) patients

BIA, bioelectrical impedance analysis; ROC, receiver operating characteristic; SMI, skeletal muscle index; skeletal muscle mass, skeletal muscle mass

Tables

Table 1. Patient characteristics

Variables	Overall cohort (n = 120)
Age (years)	71 (66–78)
Sex (male/female)	58/62
Etiology (HCV/HBV/alcohol/miscellaneous)	48/13/20/39
Platelet count (× 10^9/L)	104.0 (74.5–133.3)
Total bilirubin (mg/dL)	1.10 (0.70–1.50)
Albumin (g/dL)	3.50 (3.18–3.90)
Prothrombin time (INR)	1.08 (1.03–1.22)
FIB-4 index	5.16 (3.43–7.23)
Ascites (none/Grade 1/Grade 2)	77/35/8
Child–Pugh class (A/B/C)	80/33/7
Hepatocellular carcinoma (present/absent)	38/82
BCLC stage (A/B/C)	16/18/4
Body mass index (kg/m^2)	23.7 (21.1–26.2)
Visceral fat area (cm^2)	100.2 (63.5–140.6)

Handgrip strength (kg)	
Male	30.4 (25.5–35.7)
Female	18.8 (15.9–21.9)
Low muscle strength (present/absent)	43/77
Conventional SMI (cm^2/m^2)	
Male	45.5 (42.0–50.6)
Female	40.0 (35.0–43.3)
Low skeletal muscle mass (present/absent)	42/78
BIA-SMI (kg/m^2)	
Male	7.36 (6.87–7.97)
Female	6.10 (5.56–6.68)
Low skeletal muscle mass (present/absent)	42/78
Low-fat SMI (cm^2/m^2)	
Male	29.4 (23.6–34.2)
Female	20.1 (17.2–25.7)
Low skeletal muscle mass (present/absent)	63/57

BCLC, Barcelona Clinic Liver Cancer; BIA, bioelectrical impedance analysis; FIB-4, fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; SMI, skeletal muscle index

Low muscle strength was defined as a handgrip strength of <28 kg in males and <18 kg in females. Low skeletal muscle mass assessed using conventional SMI was defined as a conventional SMI <42 cm^2/m^2 in males and <38 cm^2/m^2 in females. Low skeletal muscle mass assessed by BIA-SMI was defined as a BIA-SMI <7.0 kg/m^2 in males and <5.7 kg/m^2 in females. Low skeletal muscle mass assessed using low-fat SMI was defined as a low-fat SMI <25.2 cm^2/m^2 in males and <24.8 cm^2/m^2 in females. Data are presented as median (interquartile range).

Table 2. Relationships of conventional SMI, low-fat SMI, and BIA-SMI with handgrip strength and physical performance

	Conventional SMI			Low-fat SMI			BIA-SMI		
Low skeletal muscle mass	Present	Absent	*P* value	Present	Absent	*P* value	Present	Absent	*P* value
Handgrip strength (kg)									
Male	28.8	32.0	0.35	23.9	33.3	< 0.001	23.7	33.3	< 0.001
	(25.1–32.5)	(26.9–35.8)		(21.7–30.3)	(29.1–36.9)		(21.8–28.6)	(29.3–36.6)	
Female	17.8	20.3	0.061	18.0	20.4	0.009	17.4	20.3	0.005
	(15.5–17.6)	(17.8–22.5)		(15.5–21.0)	(18.5–25.4)		(15.3–19.4)	(17.4–22.9)	
LFI	4.03	3.84	0.30	4.10	3.65	0.010	4.06	3.77	0.074
	(3.63–4.30)	(3.39–4.18)		(3.77–4.40)	(3.00–4.00)		(3.78–4.25)	(3.12–4.23)	

SPPB	10.5	11.0	0.17	11.0	12.0	0.010	11.0	11.0	0.40
(points)	(9.0–11.8)	(10.3–12.0)		(9.0–11.0)	(11.0–12.0)		(9.0–12.0)	(9.5–12.0)	
5-time chair stand test	10.3	10.3	0.28	11.0	9.12	0.007	10.3	10.0	0.25
(seconds)	(9.02–14.7)	(7.95–11.2)		(9.27–14.7)	(7.57–10.6)		(9.06–13.7)	(7.91–12.3)	
6-m walk test (seconds)									
Normal	5.46	6.10	0.37	6.09	5.59	0.31	6.46	5.55	0.11
	(5.09–6.38)	(5.03–6.93)		(5.26–7.28)	(4.92–6.18)		(5.27–7.60)	(4.93–6.15)	
Maximum	4.39	4.33	0.90	4.58	4.08	0.075	4.65	4.22	0.11
	(3.87–4.70)	(3.78–5.55)		(4.05–5.53)	(3.53–4.70)		(4.09–5.68)	(3.69–4.78)	

Standing balance test (points)	3.0 (3.0–4.0)	3.0 (3.0–4.0)	0.53	3.0 (3.0–4.0)	4.0 (3.0–4.0)	0.088	3.0 (2.0–4.0)	3.0 (3.0–4.0)	0.25

BIA, bioelectrical impedance analysis; LFI, liver frailty index; SMI, skeletal muscle index; SPPB, short physical performance battery

Data are presented as median (interquartile range).

Table 3. Relationships of conventional SMI, low-fat SMI, and BIA-SMI with HRQOL

	Conventional SMI			Low-fat SMI			BIA-SMI		
Low skeletal muscle mass	Present	Absent	*P* value	Present	Absent	*P* value	Present	Absent	*P* value
PCS	40.4 (32.8–47.9)	42.7 (32.2–48.9)	0.94	36.4 (23.9–45.4)	44.6 (39.0–50.1)	0.005	37.8 (25.8–45.6)	44.1 (37.3–49.8)	0.034
MCS	48.3 (41.5–53.9)	52.1 (45.1–57.2)	0.056	50.0 (43.6–54.9)	51.5 (43.9–56.9)	0.76	51.0 (43.2–54.2)	50.9 (44.4–57.3)	0.35
RCS	44.2 (36.2–51.3)	52.1 (44.4–58.1)	0.019	45.4 (36.9–54.2)	52.5 (44.5–58.0)	0.042	45.3 (36.7–54.9)	52.1 (44.2–57.8)	0.10

BIA, bioelectrical impedance analysis; MCS, mental component summary; PCS, physical component summary; RCS, role-social component summary; SMI, skeletal muscle index

Data are presented as median (interquartile range).

Table 4. Differences between the diagnosis based on conventional SMI and the presence of low skeletal muscle mass assessed using low-fat SMI

		Diagnosis using conventional SMI			
		Sarcopenia (n = 20)	Dynapenia (n = 23)	Pre-sarcopenia (n = 22)	Normal muscle status (n = 55)
Low skeletal muscle mass assessed by low-fat SMI	Present	19	14	17	13
	Absent	1	9	5	42

SMI, skeletal muscle index

Low skeletal muscle mass was defined as low-fat SMI <25.2 cm^2/m^2 in males and <24.8 cm^2/m^2 in females.

Data are presented as median (interquartile range).

Table 5. Clinical characteristics of patients with discordant diagnoses of low skeletal muscle mass based on conventional SMI and low-fat SMI

	Status of skeletal muscle mass (Conventional SMI/Low-fat SMI)		
	(Normal/Normal) or (Low/Low) (n = 88)	(Normal/Low) (n = 27)	*P* value
Age (years)	71 (66–78)	72 (67.5–78.5)	0.42
Sex (male/female)	43/45	11/16	0.514
Platelet count (× 10^9/L)	9.95 (7.68–13.7)	11.1 (6.85–12.7)	0.761
FIB-4 index	5.19 (3.42–7.10)	4.63 (3.47–7.37)	0.749
Ascites (none/Grade 1/Grade 2)	59/27/2	16/6/5	0.017
Child–Pugh class (A/B/C)	62/23/3	17/7/3	0.290
Hepatocellular carcinoma (present/absent)	15/73	6/21	0.574

Type 2 diabetes mellitus (present/absent)	31/57	14/13	0.176
Dyslipidemia (present/absent)	15/73	4/23	1.00
Past history of cardiovascular disease	19/69	2/25	0.152
Body mass index (kg/m^2)	23.2 (21.1–25.3)	25.1 (22.6–28.1)	0.051
Visceral fat area (cm^2)	87.2 (60.5–137.9)	134.5 (74.9–149.3)	0.036
Skeletal muscle attenuation (HU)	32.6 (26.6–37.5)	24.8 (22.5–26.9)	< 0.001

BIA, bioelectrical impedance analysis; FIB-4, fibrosis-4; HU, Hounsfield unit; SMI, skeletal muscle index

Data are presented as median (interquartile range).