Computed tomography, not bioelectrical impedance analysis, is the proper method for evaluating changes in skeletal muscle mass in liver disease

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Abstract

Background  Sarcopenia is associated with poor prognosis in patients with chronic liver disease (CLD). As rapid skeletal muscle wasting predicts worse prognosis and a novel therapy for sarcopenia needs to be evaluated for validation, accurate evaluation methods for relative changes in muscle mass are crucial.

Methods  We screened CLD patients who had skeletal muscle mass evaluation between June 2015 and December 2017. Patients were included if they had adequate information, were followed for >6 months, and had skeletal muscle mass evaluation by both bioelectrical impedance analysis (BIA) and computed tomography (CT) imaging at baseline and the second evaluation point. We compared BIA and CT imaging in terms of their ability to quantify skeletal muscle mass and identify relative changes in muscle mass in CLD patients.

Results  Of the screened 447 CLD patients, 110 were included in this study, and 71 (64.5%) were men. The median age was 68 (range 21 to 90) years. In total, 83 (75.5%) and 32 (29.1%) patients had liver cirrhosis and hepatocellular carcinoma, respectively. Of them, 50 (45.5%) patients were liver cirrhosis patients without hepatocellular carcinoma through the observation period. Skeletal muscle mass index (SMI) by BIA, psoas muscle mass index (PMI), and SMI based on CT imaging were significantly correlated at baseline [SMI by simple CT method and SMI by BIA (r = 0.61, P < 0.01), SMI by BIA and PMI (r = 0.65, P < 0.01), and SMI by simple CT method and PMI (r = 0.82, P < 0.01), respectively] and second evaluation point [SMI by simple CT method and SMI by BIA (r = 0.51, P < 0.01), SMI by BIA and PMI (r = 0.58, P < 0.01), and SMI by simple CT method and PMI (r = 0.92, P < 0.01), respectively]. Similar to previous reports, based on the PMI and SMI by simple CT method, patients with more severe liver dysfunction experienced more rapid skeletal muscle mass loss (ΔSimple method/years and ΔPMI/years in patients with Child Pugh Classes A, B, and C: Child Pugh A, −3.34%; B, −11.77%; C, −18.78%; and Child Pugh A, −0.78%; B, −6.33%; C, −7.71%, respectively). Completely opposite results were obtained based on SMI by BIA (Child Pugh A, −0.70%; B, 1.42%; C, 12.48%). A subgroup analysis revealed that in patients with fluid retention and diuretic administration, SMI by BIA increased with time (P < 0.01).

Conclusions  For accurate evaluation of the relative changes in skeletal muscle mass in patients with CLD, CT imaging method, and not BIA, is one of the proper methods.

Keywords  Secondary sarcopenia; Psoas muscle mass index; BIA; Computed tomography
Introduction

Sarcopenia is defined as the loss of skeletal muscle mass and strength.\textsuperscript{1,2} It is associated with poor quality of life and prognosis,\textsuperscript{3} making it a clinically relevant pathological condition. In the elderly, skeletal muscle mass decreases progressively every year because aging negatively affects protein synthesis. This is referred to as primary sarcopenia, an age-related condition. Secondary sarcopenia is defined as the loss of skeletal muscle mass and strength due to causes other than aging, including inflammatory disease, malignancy, chronic kidney disease (CKD), and chronic liver disease (CLD).\textsuperscript{3} Thus, patients with secondary sarcopenia have various clinical conditions, including diseases that cause progressive fluid retention such as liver cirrhosis (LC), malignancy, and CKD.

In patients with LC, the prevalence of sarcopenia is high,\textsuperscript{4} and the progressive loss of skeletal muscle mass is rapid,\textsuperscript{5} which in turn results in poor prognosis.\textsuperscript{6,7} Consequently, an accurate and concise method for the evaluation of changes in skeletal muscle mass is crucial. Recently, the Japan Society of Hepatology (JSH) defined the criteria for sarcopenia assessment in patients with CLD.\textsuperscript{8} According to the criteria, sarcopenia in liver disease is diagnosed by the measurement of muscle strength and mass. The recommendation provided two methods for skeletal muscle mass measurement: one by calculating the sum of the L3 level cross-sectional area of skeletal muscle mass in CT imaging using a special software\textsuperscript{9} and the other by bioelectrical impedance analysis (BIA).\textsuperscript{8} Additionally, for concise measurement of skeletal muscle mass in CT imaging without the use of a special software, a simple CT method is also mentioned in the recommendation.\textsuperscript{8} This method involves the multiplication of the left–right sum of the transversal and axial psoas muscle thickness at the level of L3,\textsuperscript{10} and the measurement of psoas muscle mass index (PMI) by manual tracing.\textsuperscript{11}

Some reports demonstrated that BIA is a tool for sarcopenia assessment.\textsuperscript{12,13} BIA is a noninvasive, portable, quick, and inexpensive method for measuring body composition based on the relationship between the volume of a conductor and its electrical resistance.\textsuperscript{14} However, in patients with ascites, the accuracy of skeletal muscle mass assessment by BIA is controversial.\textsuperscript{4,8,15} Actually, the introductory lines of the Japanese recommendations on the assessment criteria for sarcopenia in patients with liver disease state that results for BIA should be interpreted carefully in patients with severe ascites or oedema.\textsuperscript{8} Additionally, the evaluation potential of BIA for time-dependent changes in skeletal muscle mass has not been properly clarified. Specifically, direct comparison between BIA and CT methods for evaluation of time-dependent changes in skeletal muscle in the patients evaluated by two methods simultaneously is absent.

Recently, novel potent therapeutic options, such as branched-chain amino acids and L-carnitine, for sarcopenia in patients with liver disease, were reported.\textsuperscript{16,17} To properly evaluate their effects, an accurate and concise evaluation of time-dependent relative changes in skeletal muscle mass is extremely vital. Using a specialized software, Hanai et al. demonstrated that the relative time-dependent changes in skeletal muscle mass, observed on CT imaging, could predict the prognosis of patients with LC.\textsuperscript{5} Thus, evaluating relative time-dependent changes in skeletal muscle mass in patients with liver disease is clinically important. However, the most suitable method for such evaluation remains unclear.

In this retrospective study, we aimed to investigate time-dependent changes in skeletal muscle mass and determine the proper method for skeletal muscle mass evaluation in patients with liver disease. We evaluated the PMI and skeletal muscle mass index (SMI) based on CT imaging, and the SMI by BIA of the patients at baseline and a second evaluation point. The results of evaluations by both methods were then compared.

Patients and methods

In this retrospective study, we screened CLD patients who underwent skeletal muscle mass evaluation at Hokkaido University Hospital between June 2015 and December 2017. Patients were included if they had adequate clinical information and skeletal muscle mass evaluation by both BIA and CT imaging methods (simple CT method and PMI) at two points, that is, baseline and a second evaluation point (Figure 1). In patients who had several evaluations by both BIA and CT imaging methods, the latest evaluation results for both methods were used for the second evaluation point. Patients who did not have adequate clinical information, whose skeletal muscle mass was evaluated using either BIA or CT imaging methods alone (but not both), or who were observed for a period of <6 months, were excluded. In this study, LC was diagnosed based on liver biopsy, Fibroscan\textsuperscript{®} data, or radiologic findings, such as CT or magnetic resonance imaging, and laboratory data. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Hokkaido University Hospital. All patients provided written informed consent to participate. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN 000030755.

Skeletal muscle mass calculation by bioelectrical impedance analysis and computed tomography imaging methods

Skeletal muscle mass index (SMI) was calculated using BIA (InBody770; Inbody Japan Inc., Tokyo, Japan) as follows:
appendicular skeletal muscle mass/height squared (kg/m\(^2\)). PMI was calculated in CT imaging as follows: the sum of the L3 level cross-sectional area of the right and left psoas muscle mass was identified by manual tracing and divided by height squared (cm\(^2\)/m\(^2\)). For the SMI calculation in CT imaging, the following simple CT method was employed: the left–right sum of the long axis was multiplied by the short axis of the iliopsoas muscles at the level of L3, and the product was divided by the height squared. The yearly changes in PMI ($\Delta$PMI/year (%)) was calculated as follows: $\Delta$PMI/year (%) = [(psoas muscle area on the second CT scan − psoas muscle area on the initial CT scan)/psoas muscle area on the initial CT scan] × 100/interval between CT scans (years). $\Delta$SMI/year by BIA and $\Delta$SMI/year by the simple CT method were also measured in like manner.

Clinical and laboratory assessment

The patients included in this study underwent physical examinations and blood tests every 3 months. Clinical data collected included body mass index (kg/m\(^2\)), aetiology of CLD, Child Pugh grade, presence of hepatocellular carcinoma (HCC), stage of HCC, and blood test results (platelet count, prothrombin time, serum albumin, total bilirubin, aspartate transaminase, alanineaminotransferase, ammonia, creatinine, and C-reactive protein). The severity of liver disease was evaluated using the Child Pugh score and grade. We monitored the change in concomitant drugs during the observation period, including diuretics (e.g. furosemide, spironolactone, and tolvaptan) and branched-chain amino acids.

Statistical analysis

Continuous variables were analysed using the Mann–Whitney U test or Spearman’s rank correlation coefficient while categorical variables were analysed using the Fisher’s exact test. All P-values were two tailed, and the level of significance was set at $P < 0.05$. All statistical data were generated using Prism 7.03 (GraphPad Software, Inc., La Jolla, CA).

Results

Patient characteristics and clinical data at baseline and the second evaluation point

Of the 447 patients with CLD who underwent skeletal muscle mass evaluation at Hokkaido University Hospital between June 2015 and December 2018, 337 who did not meet the inclusion criteria were excluded. In total, 110 patients were included in the final analysis (Figure 1). Additionally, to make the patients’ background uniform, we conducted subgroup analysis in LC patients without HCC throughout the observation period.

Baseline patient characteristics and the clinical data at baseline and the second evaluation point are shown in Table 1. The median age of the patients was 68 years (range: 21 to 90), and 71 patients (64.5%) were men. A total of 83 (75.5%) and 32 (29.1%) patients had LC and HCC, respectively. Of them, 50 were LC patients without HCC throughout the observation period. The median observation period was 1 year (range: 0.5 to 3.4 years). As shown in Table 1, body weight and administration rate of diuretics at baseline and the second evaluation point were similar. Baseline SMI by
Table 1: Comparison of clinical and biochemical characteristics between baseline and the second evaluation point (2nd-P)

| Variables                                      | Initial point (n = 110) | Second point (n = 110) | P value |
|------------------------------------------------|-------------------------|------------------------|---------|
| Age (years)                                    | 68 (21–90)              | 67 (21–90)             | 0.88    |
| Gender (male/female)                           | 71/39                   | 73/37                  | 0.10    |
| Aetiology (HBV/HCV/NBNC)                      | 33/25/52                | 34/24/51               | 0.75    |
| CH/LC                                         | 27/83                   | 26/82                  | 0.96    |
| Hepatocellular carcinoma (+/-)                 | 32/78                   | 34/76                  | 0.80    |
| Stage (I/II/III/IV)                            | 12/10/7/3               | 14/7/9/4               | 0.75    |
| Child Pugh grade (A/B/C)                       | 79/24/7                 | 77/23/10               | 0.59    |
| Child Pugh score                              | 5 (5–11)                | 5 (5–12)               |         |
| Follow-up period (year)                        | 1.0 (0.5–3.4)           | 1.0 (0.5–3.4)          |         |
| BIA (kg/m²)                                    | M: 7.53 (5.70–10.19)    | M: 7.53 (5.49–11.06)   | 0.96    |
| Simple CT method (cm²/m²)                      | F: 5.87 (3.84–7.78)     | F: 5.82 (3.54–8.28)    | 0.84    |
| Psoas muscle mass index (cm²/m²)               | M: 4.16 (1.50–7.37)     | M: 3.95 (1.20–7.13)    | 0.32    |
| Ascites or pleural effusion (+/-)              | 9/101                   | 9/101                  | 0.20    |
| Diuretics (+/-)                                | 22/88                   | 25/85                  | 0.74    |
| Furosemide (+/-)                               | 13/97                   | 15/95                  | 0.84    |
| Spironolactone (+/-)                           | 18/92                   | 24/86                  | 0.39    |
| Tolvaptan (+/-)                                | 4/106                   | 9/101                  | 0.25    |
| BCAA (+/-)                                     | 36/74                   | 43/67                  | 0.40    |
| Height (cm)                                    | 163.0 (142.1–188.7)     | 163.0 (142.1–188.7)    | 0.84    |
| Body weight (kg)                               | 63.5 (32.5–102.9)       | 63.2 (30.7–105.7)      | 0.93    |
| Body mass index (kg/m²)                        | 23.9 (14.9–35.6)        | 23.8 (14.0–35.1)       | 0.95    |
| Body fat rate (%)                              | 28.1 (5.4–44.5)         | 28.8 (9.4–44.7)        |         |
| Platelet count (×10⁹/mm³)                      | 11.1 (1.6–37.6)         | 11.1 (2.0–33.1)        | 0.84    |
| Prothrombin time (%)                           | 79.3 (19.5–148.9)       | 85.1 (17.3–113.4)      | 0.14    |
| Serum albumin (g/dL)                           | 4.0 (1.8–5.0)           | 4.0 (1.9–4.9)          | 0.55    |
| Total bilirubin (mg/dL)                        | 0.9 (0.4–3.9)           | 0.9 (0.3–6.7)          | 0.08    |
| Aspartate transaminase (IU/L)                  | 31 (15–127)             | 30 (14–179)            | 0.67    |
| Alanine aminotransferase (IU/L)                | 25 (8–145)              | 21 (5–302)             | 0.52    |
| Ammonia (mg/dL)                                | 53 (12–334)             | 48 (9–262)             | 0.08    |
| Creatinine (mg/dL)                             | 0.75 (0.40–2.11)        | 0.78 (0.41–2.56)       | 0.17    |
| C-reactive protein (mg/dL)                     | 0.07 (0.02–1.74)        | 0.08 (0.02–3.16)       | 0.31    |

Data are presented as number of patients or median (range) values. BCAA, branched-chain amino acid; BIA, bioelectrical impedance analysis; CH, chronic hepatitis; CT, computed tomography; HBV, hepatitis B virus; HCV, hepatitis C virus; LC, liver cirrhosis; NBNC, non-HBV non-HCV.

BIA, SMI by the simple CT method, and PMI in males and females were 7.53 and 5.87 kg/m², 6.41 and 3.39 cm²/m², and 4.16 and 2.60 cm²/m², respectively.

**Correlation among baseline SMI by bioelectrical impedance analysis, PMI, and SMI by the simple computed tomography method**

We analysed the correlation among the baseline SMI by BIA, PMI, and SMI by the simple CT method. As shown in Figure 2A 2C, SMI by the simple CT method and SMI by BIA (Figure 2A, $r = 0.61, P < 0.01$), SMI by BIA and PMI (Figure 2B, $r = 0.65, P < 0.01$), and SMI by the simple CT method and PMI (Figure 2C, $r = 0.82, P < 0.01$) were significantly correlated. Similarly, significant correlations between these variables were observed in patients with Child Pugh Grade B or C (Figure 2G 2I), and patients with Child Pugh score > 8 (Supporting Information, Figure S1A S1C). Furthermore, we verified the correlation by including the SMI based on CT imaging that was analysed using the sliceOmatic® software, that is, the correlation among SMI by BIA, PMI, SMI by the simple CT method, and SMI by sliceOmatic® was evaluated (n = 92) (Figure S2A S2C).

**Correlation among SMI by bioelectrical impedance analysis, PMI, and SMI by the simple computed tomography method at the second evaluation point**

As shown in Figure 3A 3C, SMI by the simple CT method and SMI by BIA (Figure 3A, $r = 0.51, P < 0.01$), SMI by BIA and PMI (Figure 3E, $r = 0.63, P < 0.01$), and
(Figure 3B, $r = 0.58, P < 0.01$), and SMI by the simple CT method and PMI (Figure 3C, $r = 0.92, P < 0.01$) were also significantly correlated.

In the subgroup analysis (Figure 3D 3F), in LC patients without HCC, SMI by the simple CT method and SMI by BIA (Figure 3D, $r = 0.55, P < 0.01$), SMI by BIA and PMI (Figure 3E, $r = 0.59, P < 0.01$), and SMI by the simple CT method and PMI (Figure 3F, $r = 0.91, P < 0.01$) were significantly correlated at the second evaluation point. Similarly, significant correlations among these variables were observed.
in patients with Child Pugh Grade B or C (Figure 3G 3I), and in patients with Child Pugh score > 8 (Figure S3A S3C).

**Time-dependent relative changes in muscle mass**

We analysed and compared the relative time-dependent changes in skeletal muscle mass based on SMI by BIA, PMI, and SMI by the simple CT method. As shown in Figure 4A 4C, ΔPMI/year and ΔSMI/year by the simple CT method had a significant negative correlation with Child Pugh score (Figures 4C, \( r = -0.27, P < 0.01 \), and Figure 4B, \( r = -0.14, P = 0.15 \), respectively). In contrast, ΔBIA/year had a significant positive correlation with Child Pugh score (Figure 4A, \( r = 0.21, P = 0.03 \)). Furthermore, the average ΔBIA/year was significantly higher in patients with Child Pugh

**FIGURE 3** Correlation among SMI by BIA and SMI by the simple CT method, and PMI at the second evaluation point (2nd-P). (A) Correlation between SMI by BIA and PMI. (B) Correlation between SMI by BIA and PMI. (C) Correlation between SMI by the simple CT method and PMI. (D) Correlation between SMI by BIA and PMI. (E) Correlation between SMI by BIA and PMI. (F) Correlation between SMI by BIA and PMI. (G) Correlation between SMI by BIA and PMI. (H) Correlation between SMI by BIA and PMI. (I) Correlation between SMI by BIA and PMI. Data were analysed by Spearman’s rank correlation coefficient. SMI by BIA and SMI by the simple CT method are presented as BIA and simple method, respectively. BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index.
FIGURE 4 Comparison of changes in muscle mass according to Child Pugh score and grade. (A) Correlation between ΔSMI/year by BIA and Child Pugh score. (B) Correlation between ΔSMI/year by the simple CT method and Child Pugh score. (C) Correlation between ΔPMI/year and Child Pugh score. (D) Comparison of ΔSMI/year by BIA by Child Pugh grade. (E) Comparison of ΔSMI/year by the simple CT method by Child Pugh grade. (F) Comparison of ΔPMI/year by Child Pugh grade. (G) Correlation between ΔSMI/year by BIA and Child Pugh score in the LC patients without HCC. (H) Correlation between ΔSMI/year by the simple CT method and Child Pugh score in the LC patients without HCC. (I) Correlation between ΔPMI/year and Child Pugh score in the LC patients without HCC. (J) Comparison of ΔSMI/year by BIA by Child Pugh grade in the LC patients without HCC. (K) Comparison of ΔSMI/year by the simple CT method by Child Pugh grade in the LC patients without HCC. (L) Comparison of ΔPMI/year by Child Pugh grade in the LC patients without HCC. Data were analysed by the Mann–Whitney U test or Spearman’s rank correlation coefficient. ΔSMI/year by BIA and ΔSMI/year by the simple CT method are presented as ΔBIA/year and ΔSimple/year, respectively. BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index.
Grade C than in those with Child Pugh Grades A and B (Child Pugh Grade A, −0.70%; B, 1.42%; C, 12.48%) (Figure 4D). On the contrary, ΔSMI/year by the simple CT method and ΔPMI/year were lower in patients with Child Pugh Grade C than in those with Child Pugh Grades A and B (ΔSMI/year by the simple CT method: Child Pugh grade A, −3.34%; B, −11.77%; C, −18.78% and ΔPMI/year: Child Pugh Grade A, −0.78%; B, −6.33%; C, −7.71%) (Figure 4E and 4F), which is consistent with the findings of a previous report.\(^5\) Similarly, in the subgroup analysis (Figure 4G 4L), ΔPMI/year and ΔSMI/year by the simple CT method had a significantly negative correlation with Child Pugh score (Figure 4I, \(r = −0.30, P = 0.03\), and Figure 4H, \(r = −0.32, P = 0.02\), respectively) in LC patients without HCC (\(n = 50\)). In contrast, ΔBIA/year had a significantly positive correlation with Child Pugh score (Figure 4G, \(r = 0.34, P = 0.02\). Similar to all cohort analysis, in LC patients without HCC, the average ΔBIA/year was significantly higher in patients with Child Pugh Grade C than in those with Child Pugh Grades A and B (Child Pugh Grades A, −0.01%; B, 1.25%; C, 14.30%) (Figure 4I). On the contrary, ΔSMI/year by the simple CT method and ΔPMI/year were lower in patients with Child Pugh Grade C than in those with Child Pugh Grades A and B (ΔSMI/year by the simple CT method: Child Pugh Grades A, 1.72%; B, −11.95%; C, −17.17% and ΔPMI/year: Child Pugh Grades A, 0.95%; B, −3.73%; C, −5.99%) (Figure 4K and 4L).

In patients with ascites, the accuracy of skeletal muscle mass assessment by BIA is controversial.\(^4,8,14\) Thus, we conducted a stratified subgroup analysis, that is, with or without ascites and with or without diuretic administration, at baseline and/or at the second evaluation point. Based on the initial or secondary CT images, 19 patients had fluid retention, such as ascites or pleural effusion. As shown in Figure 5B, ΔSMI/year by BIA, ΔPMI/year, and ΔSMI/year by the simple CT method were similar in patients without ascites. In contrast, in patients with fluid retention at baseline and/or the second evaluation point, ΔSMI/year by BIA was significantly higher than ΔPMI/year and ΔSMI/year by the simple CT method (\(P < 0.01\) and \(P < 0.01\), respectively; Figure 5A). In addition, 28 patients (25.5%) received diuretics (furosemide, spironolactone, and tolvaptan) at baseline and/or the secondary evaluation point. As shown in Figure 5D, in patients without diuretic use, ΔSMI/year by BIA, ΔPMI/year, and ΔSMI/year by the simple CT method were similar, whereas in patients with diuretic administration at baseline and/or the second evaluation point, ΔSMI/year by BIA was significantly higher than ΔPMI/year and ΔSMI/year by the simple CT method (\(P < 0.01\) and \(P < 0.01\), respectively; Figure 5C). In the subgroup analysis in LC patients without HCC (Figure 5E 5H), similar correlation among ΔSMI/year by BIA, ΔPMI/year, and ΔSMI/year by the simple CT method was observed in patients with or without fluid retention at baseline and/or the second evaluation point (Figure 5E and 5F) and in those with or without diuretic administration (Figure 5G and 5H).

### Discussion

Previous studies demonstrated that prognosis is significantly poorer in CLD patients with sarcopenia than in those without it.\(^5,7,19,20\) Relative time-dependent changes in skeletal muscle mass strongly affect the prognosis of patients with LC\(^2\) and even that of patients with other diseases, such as metastatic renal cell carcinoma,\(^21\) metastatic colorectal cancer,\(^22\) and forget cancer.\(^23\) Therefore, the diagnosis of sarcopenia and assessment of skeletal muscle mass, including relative time-dependent changes, are crucial in patients with diseases that cause secondary sarcopenia, including liver diseases. The methods for quantifying muscle mass are diverse.\(^5,7,19,20,24\) The methods for skeletal muscle mass measurement include BIA, CT imaging using specialized software, CT imaging involving a simple CT method and PMI calculation, and dual-energy X-ray absorptiometry (DXA).

Bioelectrical impedance analysis (BIA) for skeletal muscle mass measurement has some advantages: it is quick, non-invasive, simple, reproducible, and low in cost. The European Working Group on Sarcopenia in Older People and Asian Working Group for Sarcopenia accept BIA methods for sarcopenia and muscle mass assessment.\(^25,26\) However, disadvantages also exist; the BIA method is affected by various patient factors, including adiposity degree, fluid and electrolyte status, and environmental factors, such as ambient temperature.\(^27\) BIA methods do not actually measure a skeletal muscle based on a calibration equation developed using a reference method such as DXA and CT.\(^28\) While CT imaging for skeletal muscle mass measurement also has disadvantages, including radiation exposure and high cost, it has high quantitative accuracy and high precision and is thus considered the gold standard for non-invasive muscle mass assessment.\(^27,29\)

In this study, the results of muscle mass quantification by BIA and CT imaging were significantly correlated, and this significant correlation was similarly observed at the second evaluation point. Thus, skeletal muscle mass evaluation by BIA seemed to be acceptable in patients with liver disease. These results were consistent with the results shown in the Japan Society of Hepatology recommendation.\(^8\) However, an important significant difference in the evaluation of relative time-dependent changes in muscle mass was observed between BIA and CT imaging methods (Figure 4). Hanai et al.\(^5\) reported that ΔPMI/year and ΔSMI/year by simple CT method (CT imaging methods) had a significant negative correlation with Child Pugh score (\(r = −0.27, P < 0.01\), and \(r = −0.14, P = 0.15\), respectively), whereas ΔBIA/year had a significant positive correlation with Child Pugh score (\(r = 0.21, P = 0.03\)) (Figure 4A 4C). The reason for such a discrepancy has not been fully clarified, but some hypotheses exist. As BIA devices measure body composition indirectly, skeletal muscle mass measurement by BIA in patients with fluid retention should be paid attention to.\(^4,8,15\) A recent report regarding haemodialysis patients revealed that in the
overhydrated status, which is before haemodialysis, the skeletal muscle mass of haemodialysis patients is overestimated by BIA, and after haemodialysis, the skeletal muscle mass by BIA decreases. Moreover, it is reported that an overhydrated status can easily occur even in non-LC patients with HCV infection and that severe liver dysfunction causes progressive fluid retention. Thus, in patients with a high Child Pugh score, BIA may overestimate the skeletal muscle mass with time as fluid retention worsens.

In our subgroup analysis, although SMI by the simple CT method, PMI, and SMI by BIA were significantly correlated in patients with fluid retention both at baseline and at the second evaluation point, the correlation became weak at the second evaluation point compared with that at baseline (Figures S4A, S4F, and S5A, S5F). Furthermore, in patients with fluid retention, ΔSMI/year by BIA was significantly higher than ΔPMI/year by BIA was significantly higher than ΔPMI/year by the simple CT method (P < 0.01 and P < 0.01, respectively; Figure 5A). Additionally, similar results were obtained in the subgroup analysis among patients with or without diuretic administration (Figures S6A, S6F, and S7A, S7F). Thus, in patients with a disease that causes sarcopenia and progressive fluid retention, including CLD, renal dysfunction, heart failure, and malignancy, evaluation of time-dependent changes in skeletal

**FIGURE 5** Comparison of changes in muscle mass in patients with fluid retention (with or without ascites, pleural effusion, and diuretics use) at baseline or the second evaluation point CT imaging. The following analyses (from A to D) were performed in all patients. Comparison of changes in muscle mass in patients (A) with ascites or pleural effusion, (B) without ascites or pleural effusion, (C) receiving diuretics, and (D) not receiving diuretics by muscle mass measurement (ΔSMI/year by BIA, ΔSMI/year by the simple CT method, and ΔPMI/year). The following analyses (from E to H) were performed in LC patients without HCC. Comparison of changes in muscle mass in patients (E) with ascites or pleural effusion, (F) without ascites or pleural effusion, (G) receiving diuretics, and (H) not receiving diuretics by muscle mass measurement. Data are analysed by the Mann–Whitney U test. ΔSMI/year by BIA and ΔSMI/year by the simple CT method are presented as ΔBIA/year and ΔSimple/year, respectively. BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index.
muscle mass by BIA should be performed with caution. These results were consistent with a previous report that the BIA method is affected by fluid retention. Moreover, the current guidelines on clinical nutrition in liver disease from the European Society for Clinical Nutrition and Metabolism (ESPEN) describe that DXA or CT/MRT should be used to diagnose sarcopenia. It was said of BIA that phase angle measured by BIA allows for the assessment of mortality risk. This study results indicated that in liver disease, BIA might not be suitable for the evaluation of skeletal muscle mass, and even time-dependent changes in muscle mass.

Recently, several causative mechanisms of sarcopenia in liver disease have been clarified. Following those novel findings, various therapeutic options for CLD patients with sarcopenia, including myostatin antagonists, testosterone therapy, insulin-like growth factor 1, and direct mTORC1 activators, are under investigation. Hence, an accurate and concise evaluation of time-dependent changes in skeletal muscle mass in patients with CLD is crucial, and this study’s results should be taken into consideration to choose the evaluation methods.

This study has several limitations. This is a retrospective single-centre study with a relatively small number of included patients. Several data were lacking, including the data of DXA, due to the retrospective nature of the study. Specifically, recent studies and the current guidelines on clinical nutrition in liver disease from ESPEN reveal that DXA is one of the radiologic methods that should be used to diagnose sarcopenia. Thus, further analyses including DXA should be conducted.

In addition, muscle mass evaluation by BIA includes the trunk and the four limbs, while CT measures are based on lean mass of axial muscles into the trunk. This difference is not captured in this study but ought to be taken into consideration when interpreting these results. Furthermore, the observation period was relatively short. Therefore, a larger prospective study is warranted to validate our results.

In conclusion, to accurately evaluate relative time-dependent changes in skeletal muscle mass in patients with a disease that causes sarcopenia and progressive fluid retention, the CT imaging method, which includes PMI calculation and the simple CT method, and not BIA, is one of the proper methods to use.

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The authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2017.

Conflict of interest

Professor Naoya Sakamoto received research grants from Gilead Sciences Inc. and AbbVie Inc. Dr Goki Suda received research grants from Bristol Myers Squibb, Jansen Pharmaceutical KK, and MSD K. K.

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Ethical statement

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Hokkaido University Hospital. All patients provided written informed consent to participate.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlation among skeletal muscle mass index (SMI) by BIA, SMI by the simple CT method, and PMI at baseline in patients with Child-Pugh score >8. (A) Correlation between SMI by BIA and SMI by the simple CT method. (B) Correlation between SMI by BIA and PMI. (C) Correlation between SMI by the simple CT method and PMI. Data were analyzed by Spearman’s rank correlation coefficient. SMI by BIA and SMI by the simple CT method are presented as BIA, simple method, and sliceOmatic, respectively. Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index.

Figure S2 Correlation between SMI by CT using special software (sliceOmatic™) and SMI by BIA, SMI by the simple CT method, or PMI at baseline. (A) Correlation between SMI by CT using sliceOmatic™ and SMI by BIA. (B) Correlation between SMI by CT using sliceOmatic™ and SMI by the simple CT method. (C) Correlation between SMI by CT using sliceOmatic™ and PMI. Data were analyzed by Spearman’s rank correlation coefficient. SMI by BIA, SMI by the simple CT method, and SMI by CT using sliceOmatic™ are presented as BIA, simple method, and sliceOmatic, respectively. Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index.

Figure S3. Correlation among SMI by BIA, SMI by the simple CT method, and PMI at the second evaluation point in...
patients with Child-Pugh score >8. (A) Correlation between SMI by BIA and SMI by the simple CT method. (B) Correlation between SMI by BIA and PMI. (C) Correlation between SMI by the simple CT method and PMI. Data were analyzed by Spearman’s rank correlation coefficient. SMI by BIA and SMI by the simple CT method are presented as BIA and simple method, respectively. Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index

Figure S4. Correlation among skeletal muscle mass index (SMI) by BIA, SMI by the simple CT method, and PMI at baseline in patients with or without fluid retention (ascites and/or pleural effusion). Correlations between (A) SMI by BIA and SMI by the simple CT method, (B) SMI by BIA and PMI, and (C) SMI by the simple CT method and PMI in patients without fluid retention and between (D) SMI by BIA and SMI by the simple CT method, (E) SMI by BIA and PMI, and (F) SMI by the simple CT method and PMI in patients without fluid retention are shown. Data were analyzed by Spearman’s rank correlation coefficient. SMI by BIA and SMI by the simple CT method are presented as BIA and simple method, respectively. Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index

Figure S5. Correlation among skeletal muscle mass index (SMI) by BIA, SMI by the simple CT method, and PMI at the second evaluation point in patients with or without fluid retention (ascites and/or pleural effusion). Correlations between (A) SMI by BIA and SMI by the simple CT method, (B) SMI by BIA and PMI, and (C) SMI by the simple CT method and PMI in patients without fluid retention and between (D) SMI by BIA and SMI by the simple CT method, (E) SMI by BIA and PMI, and (F) SMI by the simple CT method and PMI in patients with fluid retention are shown. Data were analyzed by Spearman’s rank correlation coefficient. SMI by BIA and SMI by the simple CT method are presented as BIA and simple method, respectively. Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; PMI, psoas muscle mass index; SMI, skeletal muscle mass index

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