Clinical Utility of Liver Frailty Index for Predicting Muscle Atrophy in Chronic Liver Disease Patients with Hepatocellular Carcinoma

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Short title: Frailty and muscle atrophy in hepatoma patients

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Abbreviations

CLD, chronic liver disease; HCC, hepatocellular carcinoma; JSH, Japan Society of Hepatology; LFI, Liver Frailty Index; CT, computed tomography; L3, the third lumbar vertebra level; BMI, body mass index; PS, performance status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALBI, albumin-bilirubin; SMI, skeletal muscle index; VFA, visceral fat area; ROC, receiver operating characteristic; IQR, interquartile range; AUC, area under the curve; SPPB, short physical performance battery; EWGSOP, European Working Group on Sarcopenia in Older People.

Abstract

Introduction: Muscle atrophy is a prognostic factor for patients with chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Liver Frailty Index (LFI) is a simple physical function test; however, an association between LFI and muscle mass remains unclear. We aimed to investigate utility of LFI for predicting muscle atrophy in CLD patients with HCC.

Subjects and Methods: We enrolled 138 CLD patients with HCC (77 years, female/male 34.8%/65.2%). Muscle mass was assessed by skeletal muscle index and patients were classified in to Muscle atrophy group (n=109) or Non-muscle atrophy group (n=29). Physical frailty was assessed by LFI. The optimal cut-off value of LFI for predicting muscle atrophy was identified by receiver operating characteristic (ROC) analysis.

Results: In the Muscle atrophy group, the prevalence of pre-frail/frail was significantly higher than the Non-muscle atrophy group (87.2% vs. 58.6%, P=0.0005). In the logistic regression analysis, female and pre-frail/frail were identified as independent factors associated with muscle atrophy (pre-frail/frail; OR 3.601, 95%CI 1.381-9.400, P=0.0088). In patients with normal grip strength, 71.1% of patients were pre-frail/frail, in which 82.8% of patients showed muscle atrophy. ROC statistics provided an AUC of 0.74 and an LFI cut-off value of 2.94 for predicting muscle atrophy (sensitivity 88.06%, specificity 52.17%, accuracy 77.91%).

Conclusions: We demonstrated that pre-frail/frail was an independent factor for muscle atrophy in CLD patients with HCC. Furthermore, LFI predicted muscle atrophy with high sensitivity even in patients with normal grip strength.

Thus, LFI may be useful screening tool for muscle atrophy in CLD patients with HCC.

Introduction

Sarcopenia is characterized by progressive loss of skeletal muscle mass and strength, and is prevalent in chronic liver disease (CLD) patients with hepatocellular carcinoma (HCC) [1]. In addition, muscle atrophy itself is known to be a prognostic factor in patients with CLD and HCC [2-4]. Thus, muscle atrophy is an important factor for the management of CLD patients with HCC.

Recently, the Japan Society of Hepatology (JSH) proposed a diagnostic criteria of sarcopenia for patients with liver disease, which consists of measurements for grip strength and skeletal muscle mass [5]. This criteria is useful for clinical practice [6, 7]. In this criteria, the initial assessment is grip strength and patients with normal grip strength is classified as non-sarcopenia without assessment of skeletal muscle mass. However, an impairment of physical function of the lower limbs is reported to be associated with sarcopenia [8]. Thus, it seems to be important to evaluate muscle mass in CLD patients with impairment of lower limbs function even patients showed normal grip strength.

Walking speed is widely employed for physical function of the lower limbs in the various diagnostic criteria [9]. However, we have previously reported that walking speed was not associated with muscle mass and sarcopenia in CLD patients with HCC [10]. While, lower limb strength and static balance are reported to be more relevant measure than grip strength in the context of mobility outcomes [11]. Liver Frailty Index (LFI) is a simple and easily manageable vulnerability index which includes both lower limb strength and static balance. LFI consists of three performance-based tests such as grip strength, chair stand, and balance tests [12] and physical function is classified into robust, pre-

frail, or frail using LFI cut-off values [13]. LFI is useful for predicting mortality in patients with end-stage liver disease [14]. However, an association between LFI and muscle mass remains unclear in CLD patients with HCC. In addition, there is no study, which investigates usefulness of LFI as a screening tool for muscle atrophy in CLD patients with HCC.

The aim of this study is to investigate an association between LFI and muscle mass in CLD patients with HCC. In addition, we evaluate usefulness of LFI as a screening tool for muscle atrophy in CLD patients with HCC.

Patients and Methods

Study design

This study was an observational study aimed to investigate 1) an association between SMI and LFI in CLD patients with HCC and 2) usefulness of LFI as a screening tool for muscle atrophy in CLD patients with HCC.

Ethics

The study protocol conformed to the ethical guidelines of the declaration of Helsinki as reflected in the prior approval given by the institutional review board of Kurume University. An opt-out approach was used to obtain informed consent from the patients, and personal information was protected during data collection. None of the patients were institutionalized.

Patients

From December 2018 to May 2019, we enrolled 138 consecutive patients who met following inclusion and exclusion criteria. Inclusion criteria were patients with HCC who (1) were 20 years of age or more, (2) had undergone all of three performance tests (grip strength, chair stand, and balance tests), and (3) had undergone biochemical examination and abdominal computed tomography (CT) scans including the third lumbar vertebra level (L3) for evaluation of HCC. Exclusion criteria were patients with HCC who (1) had refractory ascites, (2) had hepatic encephalopathy of grade 2 or more, (3) had severe heart, pulmonary, renal, or brain failure.

HCC diagnosis and staging

HCC was diagnosed by a tumor biopsy or a combination of tests for serum tumor makers, such as alpha-fetoprotein and des-γ-carboxy prothrombin, and imaging procedures, such as ultrasonography, CT, magnetic resonance imaging, and or angiography. The clinical stage of HCC was evaluated by the Liver Cancer Study Group of Japan criteria [15].

Data collection

Data on the following parameters were collected at study entry; age, sex, body mass index (BMI), and performance status (PS) which is defined by the Eastern Cooperative Oncology Group [16].

We evaluated liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as previously described [17]. Albumin-bilirubin (ALBI) score was calculated as previously described [18, 19]. Cut points for ALBI grade were as follows: ≤ −2.60 (ALBI grade 1), more than −2.60 to ≤ −1.39 (ALBI grade 2), and more than −1.39 (ALBI grade 3) [18, 19].

Evaluation of skeletal muscle mass and definition of muscle atrophy

Skeletal muscle mass was evaluated according to skeletal muscle index (SMI) using CT scans at the L3 [20, 21]. The CT scan used for this study was performed as part of HCC assessment. SMI were calculated by normalizing the L3 skeletal muscle areas by the square of the height (m^2) [22], respectively. The muscle mass evaluated in the L3 region were the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques,

and rectus abdominis. This analysis was performed using diagnostic software ImageJ [23].

Muscle atrophy was defined as SMI < 42 cm^2/m^2 for male or < 38 cm^2/m^2 for female according to previous reports [5, 24]. Sarcopenia was defined as grip strength < 26 kg for male or < 18 kg for female, and muscle atrophy according to the JSH diagnostic criteria for sarcopenia in patients with liver disease [5].

Evaluation of visceral fat area (VFA)

We measured VFA using diagnostic CT scans at umbilical level as previously described [20, 21]. The CT scan images have already been performed for the assessment of HCC. The VFA was measured by the diagnostic software ImageJ [23].

Diagnosis of Sarcopenia (JSH)

The diagnosis of sarcopenia was assessed by the JSH diagnostic criteria for sarcopenia in patients with liver disease [5]. According to the JSH criteria, patients with decreased grip strength were defined as those with grip strength < 26 kg for male or < 18 kg for female. Patients with decreased skeletal muscle mass were defined as those with SMI < 42 cm^2/m^2 for male or < 38 cm^2/m^2 for female. Patients with decreased grip strength and decreased skeletal muscle mass were diagnosed as sarcopenia. The other patients were classified as non-sarcopenia.

Liver Frailty Index

All patients underwent objective measurement of frailty using grip strength, timed chair stands and balance testing [12]. These three tests methods are followings: (1) Grip strength: the average of three trials, measured in the subject's dominant hand using a hand dynamometer (Digital Grip Dynamometer®, Takei Scientific Instruments Co., Ltd, Niigata, Japan). (2) Timed chair stands: measured as the number of seconds it takes to do five chair stands with the subject's arms folded across the chest. (3) Balance testing: measured as the number of seconds that the subject can balance in three positions (feet placed side-to-side, semi-tandem, and tandem) for a maximum of 10 sec each. These three tests were evaluated by government certified physical therapists with more than 7 years-experience. With these three individual tests of frailty, the LFI was calculated using the following equation as previously described [12]. Based on the results of the test, patients were classified into three groups: robust (score;<3.2), pre-frail (score;3.2-4.5), and frail (score;>4.5) as previously described [14].

Diagnostic accuracy of LFI for muscle atrophy in patients with normal grip strength

The optimal cut-off value of LFI for predicting muscle atrophy was identified by receiver operating characteristic (ROC) analysis. The significance for the cut-off value of LFI was evaluated by sensitivity, specificity, accuracy, positive likelihood ratio and negative likelihood ratio [25].

Statistics

Data are expressed as the median (interquartile range [IQR]), range, or number. Differences between the two groups were analyzed using the Wilcoxon rank-sum test. Factors correlated with SMI were evaluated by pairwise correlations [26]. In addition, independent factors associated with muscle atrophy were analyzed using a logistic regression analysis, as previously described [21]. Briefly, in this study, we didn't conduct the univariate analysis for selection of candidates for logistic regression analysis. By the stepwise manner minimizing the Bayesian information criterion as previously described [27], explanatory variables were selected from following variables: age, sex, HCC stage, visceral fat area, performance status, severity of liver disease (chronic hepatitis/Child-Pugh class A/B/C), LFI (frail or pre-frail/robust), and use of BCAA-related agent, levels of hemoglobin, AST, ALT, albumin, total bilirubin BUN, HbA1c. All analyses were performed using JMP Pro® 13 (SAS Institute Inc., Cary, NC). The level of statistical significance was set at $P < 0.05$.

Results

Patients' characteristics

The patients' characteristics are summarized in Table 1. The median age of patients was 77 years, of whom 34.8% were female (48/138). The median BMI was 23.1 kg/m^2 and 93.5% of patients were PS of grade 0 or 1. Patients with ALBI grade 1, 2, and 3 were 57.3%, 40.6%, and 2.8%, respectively. HCC stage I, II, III, and IV were 22.4%,28.3%,28.3%, and 21.0%, respectively (Table 1).

The median grip strength was 16.7 kg and 30.4 kg in female and male, respectively and 34.8% of patients (48/138) showed low grip strength according to the JSH criteria. The median SMI was 29.1, and 37.7 cm^2/m^2 in female and male patients, respectively and 79.0% of patients (109/138) showed muscle atrophy according to the JSH criteria. Patients diagnosed with sarcopenia were accounted for 30.4% (42/138) of enrolled patients according to the JSH criteria for sarcopenia. On the other hand, 69.6% (96/138) of patients were diagnosed as non-sarcopenia. Physical function was assessed by FLI and patients with frail or pre-frail were 81.2% of enrolled patients, respectively (Table 1).

Comparison of body composition, muscle mass, and biochemical tests between patients with muscle atrophy and non-muscle atrophy

In the Muscle atrophy group, BMI and VFA were significantly lower than the Non-muscle atrophy group (Table 2). However, there was no significant difference in PS, the prevalence of low grip strength, ALBI score and HCC stage between the two groups. In the Muscle atrophy group, the prevalence of pre-

frail/frail was significantly higher than the Non-muscle atrophy group. Serum levels of creatinine and creatine kinase were significantly lower in the Muscle atrophy group than the Non-muscle atrophy group.

Pairwise correlations between SMI and each variable

Pairwise correlation analysis was performed between SMI and each variable. SMI was positively correlated with BMI, VFA, creatine kinase, and hemoglobin; while, SMI was negatively correlated with age and LFI (Table 3). There was a significant positive correlation between SMI and grip strength in male, but not in female. SMI was not significantly correlated with ALBI score (Table 3).

Independent factors associated with muscle atrophy

Independent factors related to muscle atrophy was examined by multivariate stepwise analysis. Female and pre-frail/frail were selected in the extraction multivariate stepwise procedure. In the logistic regression analysis, both female and frail/pre-frail were identified as independent factors associated with muscle atrophy (Table 4).

Comparison of SMI between patients with frail/pre-frail and robust.

SMI was significantly lower in patients with frail/pre-frail than patients with robust (Figure 1).

The diagnostic accuracy of LFI and grip strength alone in CLD patients with

HCC

The diagnostic accuracy of LFI and grip strength alone for predicting muscle atrophy was examined. LFI predicted muscle atrophy with sensitivity of 87.16%, specificity of 48.28%, AUC of 0.72 (P=0.0007). While, there is a sexual difference in the reference value of grip strength and the diagnostic accuracy of grip strength was examined according to sex. Grip strength alone predicted muscle atrophy with sensitivity of 55.55% and 26.56%, specificity of 33.33% and 84.62%, AUC of 0.50 (P=0.9279) and 0.68 (P=0.0021) in female and male (Table 5).

An impact of screening of LFI on diagnosis of sarcopenia in patients with normal grip strength

According to the JSH criteria, 34.8% of patients (48/138) had low grip strength in this study. Of these, 87.5% (42/48) had muscle atrophy. Thus, 30.4% (42/138) of all patients were diagnosed with sarcopenia (Group 6 in Figure 2). On the other hand, in patients with normal grip strength, 71.1% (64/90) of patients were classified as pre-frail/frail based on LFI. Of these, 82.8% (53/64) showed muscle atrophy (Group 4 in Figure 2). Thus, muscle atrophy was seen in 58.9% (53/90) of patients with normal grip strength. In patients with robust, 53.8% (14/26) of patients showed muscle atrophy (Group 2 in Figure 2). Although patients with robust was 12.8% of all of patients with muscle atrophy (14/109).

Diagnostic accuracy of LFI for muscle atrophy in patients with normal grip

strength

ROC statistics provided an area under the curve (AUC) of 0.74 (P=0.0009) and an LFI cut-off value of 2.94 for predicting muscle atrophy (Figure 3). Respective diagnostic performances for distinguishing muscle atrophy from non-muscle atrophy were shown in Table 5. The sensitivity, specificity, accuracy, positive-likelihood ratio, and negative-likelihood ratio were 88.06%, 52.17%, 77.91%, 1.52, and 0.28 (Table 6).

Discussion

In this study, we demonstrated that LFI was negatively correlated with SMI. Frail/pre-frail based on LFI was an independent factor for muscle atrophy in CLD patients with HCC. We also demonstrated that, muscle atrophy was seen in 82.8% of patients with frail/pre-frail, although the patients showed normal grip strength. Thus, LFI may be useful screening tool for muscle atrophy in CLD patients with HCC who showed normal grip strength.

Based on the sarcopenia assessment criteria proposed by JSH, the prevalence of sarcopenia was 30.4% of enrolled patients in this study. The prevalence of sarcopenia is also reported to be 27.0% to 29.9% in patients with HCC in Japan [7, 17]. Thus, our data were in good agreement with previous results, suggesting that enrolled patients in our study were representative of CLD patients with HCC in Japan.

In our study, female was identified as an independent factor of muscle atrophy. Yang et al. reported that female was a risk factor for sarcopenia in a large population-based cohort study [28]. Ohashi K et al. also reported that an independent predictive factor for pre-sarcopenia was female in patients with CLD [29]. A possible reason why female is more likely to have muscle atrophy than male is physical activity of female, since female is known to have lower physical activities than male [30]. In addition, testosterone is a powerful anabolic agent that promotes muscle protein synthesis and subsequently increase muscle mass [31]. Female has low plasma testosterone levels, which cause muscle atrophy [32]. Thus, physical activity and sex hormonal could be possible reasons for the sexual difference of muscle mass in this study.

Frail/pre-frail based on LFI was also identified as an independent factor of muscle atrophy in this study. LFI is a physical function test and is consist of grip strength, chair stand, and balance [14]. Wang CW et al. used another physical function test such as Short Physical Performance Battery (SPPB) and reported that SPPB is not associated with muscle mass of patients with CLD [33]. SPPB consists of walking speed, standing balance, and timed chair stands [34]. It remains unclear why no association was seen between SPPB and muscle mass, a possible reason is that walking speed, but not grip strength, is employed as an assessment item in SPPB. Auyeung et al. reported that the decline in grip strength is more evident than that of walking speed in general population [35]. We also previously demonstrated that walking speed is not associated with muscle mass in patients with CLD [10]. Thus, difference in assessment items between LFI and SPPB may be a possible reason for the discrepancy. LFI may be a suitable tool for predicting muscle atrophy in patients with CLD.

According to the sarcopenia assessment criteria proposed by JSH, muscle mass is not evaluated in patients with normal grip strength, because such patients are classified as non-sarcopenia. In this study, we demonstrated that muscle atrophy was seen in 82.8% of patients with normal grip strength and frail/pre-frail assessed by LFI. Chair stand and balance are assessment items in LFI. Lower limb strength and static balance are known to be more relevant measurement than grip strength for the mobility outcomes in general populations [11]. In our study, LFI showed higher diagnostic accuracy with higher sensitivity than grip strength alone. These previous results along with our

findings suggest that LFI may be useful for screening of muscle atrophy in CLD patients with normal grip strength. Muscle atrophy has been reported to be a prognostic factor in patients with CLD and HCC [2-4]; however, these studies did not evaluate grip strength. Thus, further study will be focused on the importance of muscle atrophy with normal grip strength and frail/pre-frail on prognosis of patients with CLD and HCC.

We investigated the diagnostic ability of frail/pre-frail assessed by LFI for muscle atrophy. The AUC for pre-frail/frail was 0.74. In general, an AUC between 0.5 and 1.0 is thus essential for clinical testing [36]. We also demonstrated that the sensitivity and specificity of frail/pre-frail/ were 88.06% and 52.17%, respectively. Locquet et al. reported that the sensitivity and specificity of European Working Group on Sarcopenia in Older People (EWGSOP) and SARC-F for diagnosis of sarcopenia are approximately 30% and 90%, respectively [37]. Regarding the clinical significance of predicting muscle atrophy, higher sensitivity is likely to be more practical and applicable than higher specificity. Although we did not compare the diagnostic ability of LFI with EWGSOP and SARC-F, LFI may be a good candidate of screening tool for muscle atrophy in patients with HCC.

There are several limitations in this study. This is an observational study conducted in a single center. In addition, we enrolled CLD patients admitted for HCC treatment and excluded patients who could not tolerate treatment for HCC, such as end-stage of liver cirrhosis, heart, pulmonary, or renal failure. Thus, there is a possibility of selection bias and further multi-center validation study is required with patients in various conditions. Furthermore, approximately 80% of

enrolled patients showed muscle atrophy and the sensitivity of muscle atrophy by LFI was still insufficient. Further study is required to improve the sensitivity of screening tool for muscle atrophy.

In conclusion, this study demonstrated that LFI was negatively correlated with SMI and Frail/pre-frail was an independent factor for muscle atrophy in CLD patients with HCC. Furthermore, muscle atrophy was seen in 82.8% of patients with frail/pre-frail assessed by LFI, although the patients showed normal grip strength. Thus, LFI may be useful screening tool for sarcopenia in CLD patients with HCC who showed normal grip strength.

Disclosure Statement

Takumi Kawaguchi received lecture fees from Mitsubishi Tanabe Pharma Corporation, MSD K.K., and Otsuka Pharmaceutical Co., Ltd. The other authors have no conflicts of interest.

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Table 1. Patient characteristics

	Reference Value	Median (IQR)	Range (min–max)
Number (n)	N/A	138	N/A
Age (years)	N/A	77 (70–81)	35–93
Sex (female/male)	N/A	34.8%/65.2% (48/90)	N/A
Body mass index (kg/m^2)		23.1 (20.8–25.6)	16.0–34.0
Performance status (0/1/2/3/4)	N/A	78.3%/15.2%/5.8%/0.7%/0% (108/21/8/1/0)	N/A
Severity of liver disease (chronic hepatitis/Child-Pugh class A/B/C)	N/A	80.4/%17.4%/2.2% (111/24/3)	N/A
ALBI score	N/A	-2.34 (-2.73–-2.02)	-3.20–-0.92
ALBI grade (1/2/3)	N/A	57.3%/40.6%/2.8% (79/56/3)	N/A
HCC stage (I/II/III/IV)	N/A	22.4%/28.3%/28.3%/21.0% (31/39/39/29)	N/A
BCAA supplementation (Yes/No)	N/A	42.0%/58.0% (58/80)	N/A
Grip strength (female/male) (kg)	N/A	16.7 (14.6–20.8) /30.4 (26.5–34.7)	6.7–31.4 /17.0–47.9
Grip strength (low/normal)	N/A	34.8%/65.2% (48/90)	N/A
SMI (female/male) (cm^2/m^2)	N/A	29.1 (24.6–31.4) /37.7 (32.2–42.2)	15.5–43.5 /13.7–53.6

SMI (muscle atrophy/non-muscle atrophy)	N/A	79.0%/21.0% (109/29)	N/A
VFA (cm^2)	N/A	62.4 (37.2–96.6)	2.2–244.1
Presence of sarcopenia according to the JSH criteria	N/A	30.4% (42/138)	N/A
LFI	N/A	3.66 (3.28–4.16)	1.95–6.03
Physical function assessed by LFI (Frail or Pre-frail/Robust)	N/A	81.2%/18.8% (112/26)	N/A
Red blood cell count ($\times 10^4/\mu L$)	435–555	398 (357–440)	247–530
Hemoglobin (g/dL)	13.7–16.8	12.4 (10.7–13.9)	6.9–16.4
White blood cell count (/μL)	3300–8600	4500 (3400–6100)	1500–10200
Lymphocytes (%)	30.0–43.0	25.3 (20.1–33.0)	6.6–58.2
Platelet count (x $10^3/mm^3$)	15.8–34.8	134.5 (84.0–176.3)	7.6–474.0
AST (IU/L)	13–30	37 (26–53)	12–150
ALT (IU/L)	10–30	26 (17–38)	8–146
Lactate dehydrogenase (IU/L)	119–229	213 (187–248)	143–624
ALP (IU/L)	115–359	363	148–984

		(252–496)	
GGT (IU/L)	13–64	54 (31–101)	8–830
Total protein (g/dL)	6.6–8.1	7.1 (6.8–7.5)	6.1–9.1
Albumin (g/dL)	4.1–5.1	3.6 (3.3–4.0)	2.3–4.6
Cholinesterase (U/L)	201–421	182 (124–225)	18–375
Prothrombin activity (%)	80–120	84 (72–97)	32–130
Total bilirubin (mg/dL)	0.40–1.20	0.8 (0.6–1.0)	0.3–3.0
Total cholesterol (mg/dL)	142–219	161 (144–187)	22–237
Triglyceride (mg/dL)	40–149	101 (71–139)	36–343
BUN (mg/dL)	8.0–20.0	17 (14–22)	10–31
Creatinine (mg/dL)	0.65–1.07	0.78 (0.67–0.92)	0.39–7.32
eGFR (mL/min/1.73 m^2)	> 90.0	64.7 (56.9–83.8)	4.7–153.1
Sodium (mmol/L)	138–145	141 (139–142)	133–147
Potassium (mmol/L)	3.6–4.8	4.1 (3.8–4.4)	3.0–9.7

Chloride (mmol/L)	101–108	104 (102–107)	94–114
Creatine kinase (U/L)	59–248	88 (57–141)	23–656
Blood glucose (mg/dL)	80–109	115 (98–152)	70–1389
HbA1c (%)	4.3–5.8	6.0 (5.6–6.8)	4.7–9.3
Ammonia (μg/dL)	12–66	44 (34–63)	13–176
FIB-4 index	<3.25	4.5 (3.1–7.1)	0.8–49.0
AFP (ng/mL)	<10	11.4 (4.4–292.0)	1.1–480874
des-γ-carboxy prothrombin (mAU/mL)		85 (24–1719)	10–143845

Note: data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: N/A, not applicable; ALBI; Albumin-bilirubin, HCC, hepatocellular carcinoma; BCAA, branched-chain amino acids; SMI, skeletal muscle index; VFA, visceral fat area; JSH, Japan Society of Hepatology; LFI, liver frailty index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate ; HbA1c, hemoglobin A1c; AFP, alpha-fetoprotein.

Table 2. Comparison of body composition, muscle mass, and biochemical tests between the muscle atrophy and muscle non-atrophy group

	Muscle atrophy		Non-muscle atrophy		
	Median (IQR)	Range (min–max)	Median (IQR)	Range (min–max)	P-value
Number (n)	109	N/A	29	N/A	N/A
Age (years)	77 (72–82)	35–90	76 (64–80)	49–93	0.1054
Sex (female/male)	45/64	N/A	3/26	N/A	0.0008
Body mass index (kg/m^2)	22.2 (19.9–24.4)	16.3–30.8	25.7 (24.5–27.8)	16.0–34.0	<.0001
Performance status (0/1/2/3/4)	77.1%/16.5%/5.5%/0.9%/0% (84/18/6/1/0)	N/A	82.8%/10.3%/6.9%/0%/0% (24/3/2/0/0)	N/A	0.7372
Severity of liver disease (chronic hepatitis/Child-Pugh class (A/B/C)	80.7%/17.4%/1.8% (88/19/2)	N/A	79.3%/17.2%/3.5% (23/5/1)	N/A	0.8822

ALBI score	-2.34 (-2.73– -2.00)	-3.20– -0.92	-2.36 (-2.71– -2.06)	-3.00– -0.92	0.9687
ALBI grade (1/2/3)	56.0%/43.1%/0.9% (61/47/1)	N/A	62.1%/31.0%/6.9% (18/9/2)	N/A	0.1410
HCC stage (I/II/III/IV)	21.1%/27.5%/29.4%/22.0% (23/30/32/24)	N/A	27.6%/31.0%/24.1%/17.2% (8/9/7/5)	N/A	0.5254
BCAA supplementation (Yes/No)	42.2%/57.8% (46/63)	N/A	41.4%/58.6% (12/17)	N/A	0.9364
Grip strength (low/normal)	38.5%/61.5% (42/67)	N/A	20.7%/79.3% (6/23)	N/A	0.0730
SMI (cm^2/m^2)	31.4 (26.7–36.9)	13.7–41.5	44.8 (42.3–48.6)	40.3–53.6	<.0001
VFA (cm^2)	74.1 (52.4–101.9)	5.3–1267.8	117.7 (86.0–147.9)	38.7–222.2	0.0177
LFI	3.84 (3.42–4.19)	2.14–6.03	3.22 (2.55–3.76)	2.14–6.03	0.0003
Physical function assessed by LFI (Frail or Pre-	87.2%/12.8% (95/14)	N/A	58.6%/41.4% (17/12)	N/A	0.0005

frail/Robust)					
Red blood cell count (×10^4/μL)	396 (350–437)	274–528	413 (371–457)	281–530	0.1792
Hemoglobin (g/dL)	11.8 (10.6–13.8)	6.9–16.1	13.2 (12.0–14.5)	7.9–16.4	0.0482
White blood cell count (/μL)	4400 (3400–6050)	1500–1010	4800 (3800–6100)	2900–1020	0.1439
Lymphocytes (%)	25.7 (19.8–33.6)	6.6–58.2	24.4 (20.4–31.1)	10.0–56.6	0.8248
Platelet count (x 10^3/mm^3)	133 (85–175)	26–474	136 (83–181)	8–181	0.9209
AST (IU/L)	33 (27.5–55.5)	15–150	33 (26–45)	12–150	0.2134
ALT (IU/L)	26 (17–38)	8–95	24 (17–38)	9–146	0.6212
Lactate dehydrogenase (IU/L)	213 (190–245)	152–630	212 (177–260)	143–309	0.8289
ALP (IU/L)	374 (255–501)	148–984	314 (225–455)	156–718	0.1232
GGT (IU/L)	54 (31–101)	8–830	53 (30–107)	16–258	0.9978

Total protein (g/dL)	7.1 (6.8–7.4)	6.2–8.2	7.2 (6.8–7.4)	6.2–8.2	0.8118
Albumin (g/dL)	3.6 (3.3–4.0)	2.3–4.6	3.7 (3.5–4.1)	2.3–4.5	0.8259
Cholinesterase (U/L)	181 (126–229)	75–369	226 (157–267)	54–399	0.0541
Prothrombin activity (%)	96 (85–110)	20–130	90 (74–107)	25–128	0.2194
Total bilirubin (mg/dL)	0.8 (0.6–1.0)	0.3–2.9	0.8 (0.7–1.2)	0.4–3.0	0.2629
Total cholesterol (mg/dL)	156 (142–180)	101–226	185 (149–199)	22–237	0.0568
Triglyceride (mg/dL)	96 (63–128)	36–343	123 (92–158)	63–301	0.0199
BUN (mg/dL)	17 (14–22)	10–31	17 (13–21)	10–30	0.2363
Creatinine (mg/dL)	0.73 (0.64–0.91)	0.39–7.32	0.88 (0.72–1.04)	0.47–6.91	0.0018
eGFR (mL/min/1.73 m^2)	67.7 (58.1–84.2)	4.7–153.1	63.4 (51.8–79.0)	7.1–94.7	0.1986

Sodium (mmol/L)	140 (139–142)	133–147	141 (141–142)	135–144	0.1247
Potassium (mmol/L)	4.2 (3.9–4.4)	3.0–5.7	4.0 (3.6–4.5)	3.3–9.7	0.0914
Chloride (mmol/L)	104 (102–107)	94–114	104 (103–107)	100–109	0.7211
Creatine kinase (U/L)	78 (55–132)	23–338	112 (78–175)	43–656	0.0129
Blood glucose (mg/dL)	113 (98–159)	70–1389	116 (103–147)	84–244	0.6792
Ammonia (μg/dL)	45 (35–62)	16–176	43 (33–70)	13–130	0.8747
HbA1c (%)	6.1 (5.6–6.9)	4.7–9.3	5.9 (5.5–6.7)	4.7–8.2	0.4196
FIB-4 index	4.5 (3.2–7.3)	0.8–49.0	3.9 (2.5–6.2)	1.4–13.1	0.2492
AFP (ng/mL)	13.0 (4.8–474.8)	1.1–480874.0	8.4 (3.7–37.5)	1.6–202783.0	0.1620
des-γ-carboxy prothrombin (mAU/mL)	85 (25–1462)	11–143845	103 (23–2732)	10–125059	0.8219

Note: data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: N/A, not applicable; ALBI;

Albumin-bilirubin, HCC, hepatocellular carcinoma; BCAA, branched-chain amino acids; SMI, skeletal muscle index; VFA, visceral fat area; LFI, liver frailty index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CRP, HbA1c, hemoglobin A1c; AFP, alpha-fetoprotein.

Table 3. Pairwise correlations between SMI and each variable

Variable	Correlation coefficient	P-value
Age	-0.3001	0.0003
Body mass index	0.4011	<.0001
ALBI score	-0.0948	0.2686
VFA	0.3606	<.0001
LFI	-0.3382	<.0001
Grip strength (Female)	0.1717	0.2434
Grip strength (Male)	0.3552	0.0006
Red blood cell count	0.2823	0.0008
Hemoglobin	0.3355	<.0001
White blood cell count	0.1654	0.0526
Lymphocytes	0.0317	0.7134
Platelet count	-0.0123	0.8862
AST	-0.0827	0.3351
ALT	0.0571	0.5063
Lactate dehydrogenase	-0.0836	0.3313
ALP	-0.1193	0.1651

GGT	0.0353	0.6852
Total protein	0.0208	0.8091
Albumin	0.1306	0.1267
Cholinesterase	0.3151	0.0002
Prothrombin activity (%)	-0.1134	0.1872
Total bilirubin	0.0864	0.3135
Direct bilirubin	0.0604	0.5486
Total cholesterol	0.2052	0.0565
Triglyceride	0.2689	0.0091
BUN	-0.1330	0.1199
Creatinine	0.1726	0.0430
eGFR	-0.0137	0.8736
Sodium	0.0435	0.6125
Potassium	-0.0210	0.8066
Chloride	-0.0306	0.7215
Creatine kinase	0.1661	0.0830
Blood glucose	-0.0183	0.8381
HbA1c	0.0215	0.8301
Ammonia	0.0516	0.6082

FIB-4 index	-0.1465	0.0864
AFP	0.0891	0.3334
des-γ-carboxy prothrombin	0.1475	0.1094

Abbreviations: SMI, skeletal muscle mass index; ALBI; Albumin-bilirubin, VFA, visceral fat area; LFI, liver frailty index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase aminotransferase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; AFP, alpha-fetoprotein.

Table 4. Logistic regression analysis for muscle atrophy based on muscle atrophy

Factors	Odds ratio	95% Confidence interval	P-value
Sex (Female)	4.745	1.319–17.075	0.0172
Physical function assessed by LFI (Frail/Pre-frail)	3.601	1.381–9.400	0.0088

Abbreviations: SMI, skeletal muscle mass index; LFI, liver frailty index.

Table 5. Diagnostic accuracy of LFI and grip strength alone for predicting muscle atrophy

Variable	LFI	Grip strength	
		Female	Male
Sensitivity proportion (%)	87.16	55.55	26.56
Specificity proportion (%)	48.28	33.33	84.62
Accuracy proportion (%)	78.99	54.17	43.33
False-positive rate (%)	51.72	66.66	15.38
False-negative rate (%)	12.84	44.44	73.44
Positive predictive value probability (%)	86.36	92.59	80.95
Negative predictive value probability (%)	50.00	4.76	31.88
Positive likelihood ratio	1.69	8.33	1.73
Negative likelihood ratio	0.27	1.33	0.87

Abbreviations: LFI, liver frailty index.

Table 6. Diagnostic ability of LFI for muscle atrophy

Variable	Cut-off value of LFI > 2.94
Sensitivity proportion (%)	88.06
Specificity proportion (%)	52.17
Accuracy proportion (%)	77.91
False-positive rate (%)	47.83
False-negative rate (%)	11.94
Positive predictive value probability (%)	84.29
Negative predictive value probability (%)	50.00
Positive likelihood ratio	1.52
Negative likelihood ratio	0.28

Abbreviations: LFI, liver frailty index.

Figure legends

Figure 1. Difference in SMI between patients with robust and frail/pre-frail. Abbreviation: SMI, skeletal muscle index.

Figure 2. An impact of screening of LFI on diagnosis of muscle atrophy in patients with normal grip strength. Abbreviation: LFI, liver frailty index; SMI, skeletal muscle index.

Figure 3. ROC analysis of LFI for muscle atrophy in CLD patients with HCC who showed normal grip strength. Abbreviation: ROC, receiver operating characteristic; LFI, liver frailty index; CLD, chronic liver disease; HCC, hepatocellular carcinoma.

Figure 1

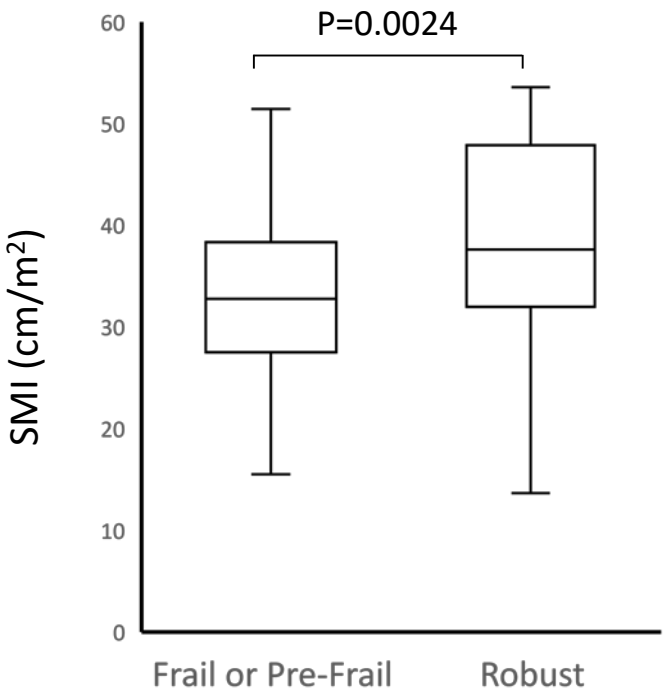


Figure 2

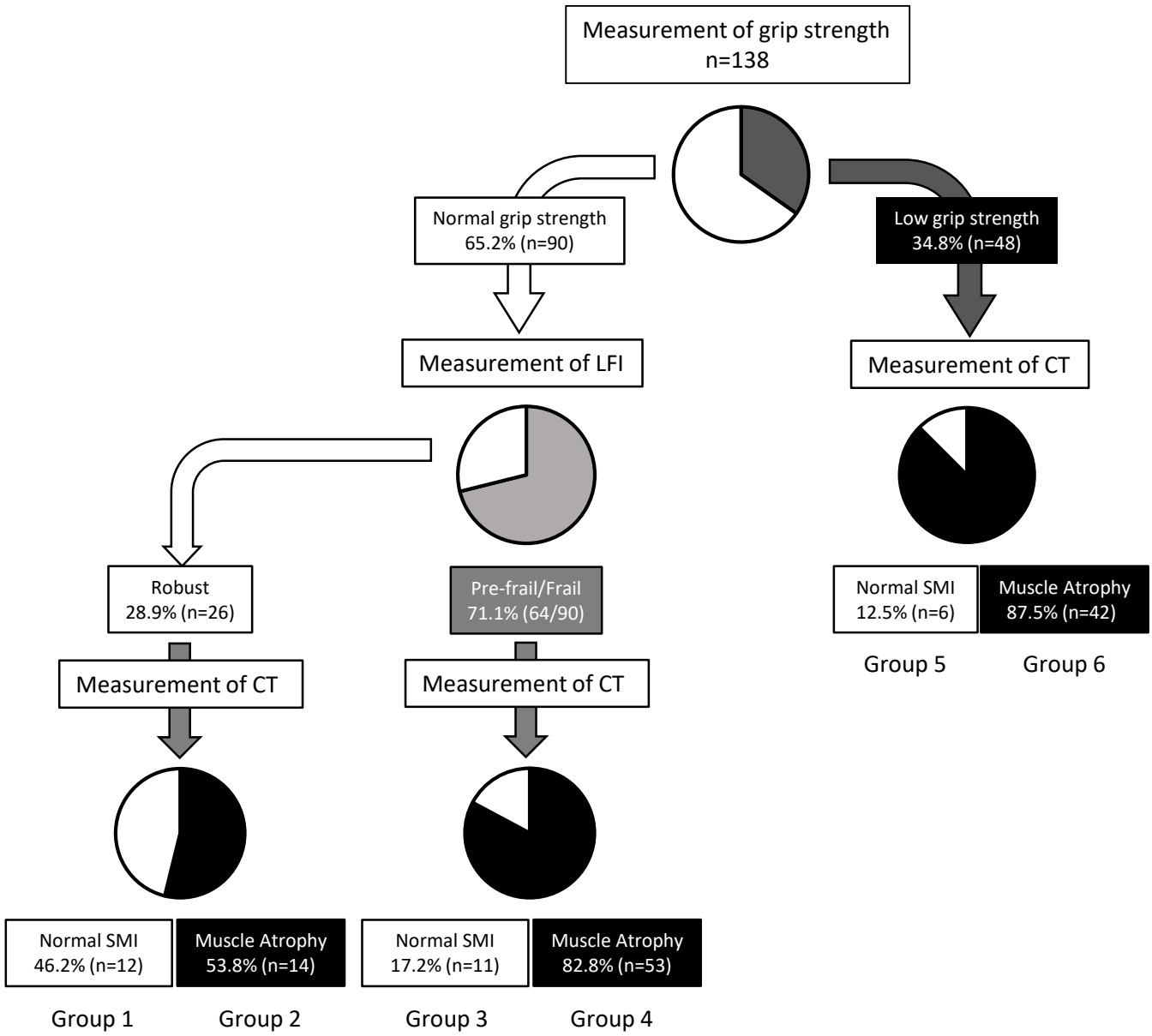
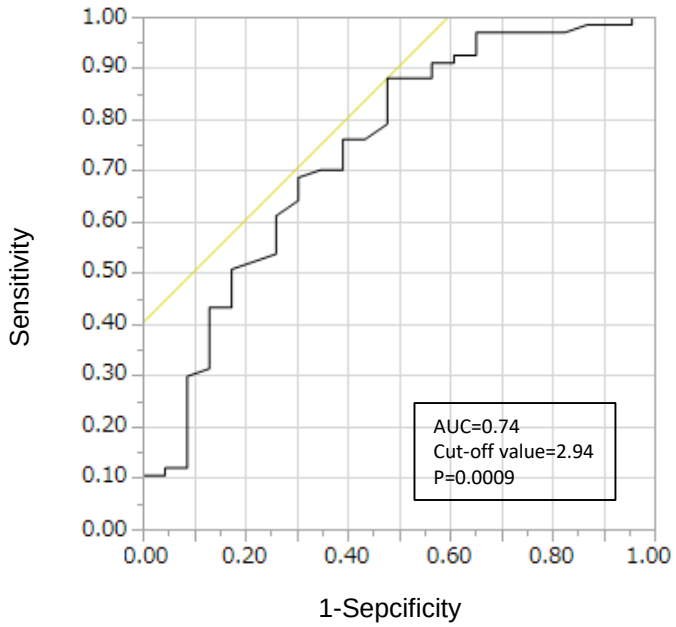

Measurement of grip strength
n=138
Normal grip strength
65.2% (n=90)
Low grip strength
34.8% (n=48)
Measurement of LFI
Measurement of CT
Robust
28.9% (n=26)
Pre-frail/Frail
71.1% (64/90)
Normal SMI
12.5% (n=6)
Muscle Atrophy
87.5% (n=42)
Group 5
Group 6
Measurement of CT
Measurement of CT
Normal SMI
46.2% (n=12)
Muscle Atrophy
53.8% (n=14)
Normal SMI
17.2% (n=11)
Muscle Atrophy
82.8% (n=53)
Group 1
Group 2
Group 3
Group 4

Figure 3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0.90
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Sensitivity
0.00
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0.40
0.60
0.80
1.00
1-Sepcificity
AUC=0.74
Cut-off value=2.94
P=0.0009