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Sarcopenia and Frailty in Chronic Liver Damage: Common and Different Points

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Abstract. *Aim: To elucidate the common and different points between sarcopenia and frailty in chronic liver damage (CLD). Patients and Methods: Patients with both grip strength decline and skeletal muscle index decline were regarded as sarcopenia. Frailty was defined as a syndrome in which 3 or more of the following criteria were met: i) exhaustion, ii) body weight loss, iii) slow walking speed, iv) muscle weakness, and v) low physical activity. Results: Sarcopenia and frailty were identified in 52 patients (15.2%) and 46 (13.5%), respectively. The prevalence of sarcopenia and frailty was well stratified according to age and the liver cirrhosis (LC) status. In the multivariate analysis, we identified significant factors for sarcopenia: i) age, ii) LC, iii) body mass index and iv) extracellular water (ECW) to total body water (TBW) ratio, while only the ECW to TBW ratio was significant for frailty. Conclusion: Sarcopenia and frailty in CLD should be separately evaluated.*

In individuals with chronic liver damage (CLD), metabolic functions are frequently damaged leading to several nutritional disorders, including protein-energy-malnutrition, or muscle abnormalities (1). Since sarcopenia, as assessed by muscle mass decrease and muscle strength impairment in patients with CLD, can be related to falls, poor quality of life or poor prognosis, it has become a very interesting topic to examine for physicians (2-8). Sarcopenia is one of the most common consequences found in patients with liver cirrhosis (LC), affecting 30% to 70% of LC patients, and it can be a main determinant for the incidence of hepatic encephalopathy in LC patients (1, 9, 10-13). Japanese CLD patients can now be found in aging populations, and this fact is also a crucial public health issue since aging itself can cause sarcopenia (14-16). To avoid unfavorable consequences related to sarcopenia one needs to assess this disease as a condition with a systemic involvement (17-19). Improving physical activity or nutrition and adequately managing any underlying diseases are essential steps for avoiding sarcopenia (6).

Frailty is a concept globally used in geriatrics that precedes disability, and is defined as a condition of increased vulnerability associated with physiological decline (20-22). Originally, it was proposed to identify elderly people at an elevated risk of adverse health outcomes, dependencies, falls, disabilities, and mortality (20-22). Frailty is determined based on the evaluation of physical, functional and cognitive abilities. The frailty phenotype is defined as the presence of 3 or more of the following criteria: i) body weight (BW) loss, ii) self-reported exhaustion, iii) skeletal muscle function decline, iv) slow walking speed (WS) and v) low physical activity (23, 24). Sarcopenia is an important component of frailty (22). Aging is indeed closely linked to changes in body composition, especially skeletal muscle mass decline, resulting in disability and mortality (14, 16, 24). While any chronic organ dysfunction can also lead to physiological vulnerability (25-27). CLDs are not the exception. Carey, *et al*. have reported that a six-minute walk reflecting physical function shows a good prediction of mortality for liver

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transplant candidates (25). It was this study that raised an awareness for frailty in patients with CLDs.

The strong overlap between sarcopenia and frailty that can be seen in CLD leads to a condition termed physical frailty (19, 25). To translate the clinical relevance of sarcopenia and frailty into practice, borders and bridges between the two should be clearly defined. The aims of the study were to identify the common and different points between sarcopenia and frailty in patients with CLD.

Patients and Methods

Patients. Three hundred and forty-one CLD patients subjected to evaluation for both sarcopenia and frailty consulted our hospital between July 2015 and October 2019. LC was determined by: i) liver biopsy analysis, ii) radiological findings (deformation of the liver surface, varices or splenomegaly, *etc*.), iii) liver fibrosis markers, and iv) laboratory data (lower platelet count or prolonged prothrombin time, *etc*.) (28-31).

Grip strength (GS) was measured according to the current guidelines, and decreased GS was defined as <26 kg for men and <18 kg for women (14). The skeletal muscle index (SMI) was tested using bioimpedance analysis (BIA) as described previously (32). SMI decline was defined as <7.0 kg/m^2 in men and <5.7 kg/m^2 in women referring to the guidelines (14). Patients with both GS decline and SMI decline were regarded as having sarcopenia (14). In all analyzed subjects, the six-meter walking test was done. The test was performed twice in each subject and the walking speed (WS; m/s) was defined as the mean value of the two measured speeds.

Frailty was defined as a clinical syndrome in which 3 or more of the following criteria were met: i) unintentional BW loss (2 or 3 kg or more within the past 6 months), ii) self-reported exhaustion, iii) muscle weakness (GS<26 kg in men and <18 kg in women), iv) slow WS (<1.0 m/s), and v) low physical activity (doing light exercise or not), while pre-frailty was defined as patients with one or two of the aforementioned phenotypes. Patients with none of the 5 phenotypes were regarded as having a robust status (23, 24).

Due to the intrinsic limitations of BIA, such as the presence of ascites (14), patients with severe ascites were not included in this study. We compared the impact of sarcopenia and frailty in CLD patients in a retrospective manner. Factors associated with sarcopenia or frailty were identified in both univariate and multivariate analysis. In addition, we classified the study cohort into four groups: i) patients with sarcopenia alone (type A), ii) patients with frailty alone (type B), iii) patients with both sarcopenia and frailty (type C) and iv) patients with neither sarcopenia or frailty (type D). Baseline characteristics were compared among the four types.

The institutional review board in our hospital acknowledged this research protocol, and the 1975 Declaration of Helsinki was strictly adhered to ensure the rights of the patients. Due to the retrospective nature of this study, an opt out approach was employed in order to obtain informed consent from the subjects.

Statistics. The JMP 14 software (SAS Institute Inc., Cary, NC) was used for our statistical analyses. For the numerical variables, Mann-Whitney *U*-test, Student's *t*-test, analysis of variance or Kruskal-Wallis tests were used to adequately assess group characteristics. For the categorical variables, Fisher's exact *test or* Pearson χ^2 test was used to assess *group* characteristics. Baseline significant items in our univariate analysis were subjected to the multivariate logistic regression analysis to select candidate parameters. Data were demonstrated as median values [interquartile range (IQR)]. The statistically significant level was set at $p<0.05$.

Table I. *Baseline characteristics (n=341).*

Variables	All cases (n=341)
Age (years)	66 (55, 72)
Gender, male/female	164/177
Liver disease etiology	
HCV/HBV/HBV and HCV/NBNC	174/61/7/99
Presence of sarcopenia, yes/no	52/289
Presence of frailty, yes/no	46/295
Presence of LC, yes/no	122/219
Body mass index (kg/m^2)	22.7 (20.5, 25.65)
SMI (kg/m^2), male	7.42 (6.83, 7.93)
SMI (kg/m^2), female	5.91 (5.42, 6.45)
Walking speed (m/s)	1.303 (1.1005, 1.4445)
Grip strength (kg), male	33.3 (27.925, 38.925)
Grip strength (kg), female	20.8 (17.6, 24.45)
ECW to TBW ratio	0.390 (0.384, 0.396)
Total bilirubin (mg/dl)	0.8 (0.6, 1.1)
Serum albumin (g/dl)	4.3 (4.0, 4.5)
ALBI score	–2.9 (–3.12, –2.6)
ALBI grade, 1/2/3	256/78/7
Prothrombin time (%)	91.2 (80.55, 99.05)
Platelet count (×10^4/mm^3)	17.5 (12.6, 22.0)
AST (IU/l)	25 (19, 34)
ALT (IU/l)	19 (14, 33)
ALP (IU/l)	243 (194, 308.5)
GGT (IU/l)	26 (17, 46)
Total cholesterol (mg/dl)	181 (151.25, 213)
Triglyceride (mg/dl)	88 (67, 124)
HbA1c (NGSP)	5.7 (5.4, 6.1)
eGFR (ml/min/1.73m^2)	81 (68, 93)
Serum sodium (mmol/l)	140 (139, 141)
Branched-chain amino acid to tyrosine ratio	5.645 (4.2125, 6.795)

Data are expressed as number or median value (interquartile range). HbA1c: Glycated haemoglobin; HCV: hepatitis C virus; HBV: hepatitis B virus; NBNC: non-B and non-C; LC: liver cirrhosis; SMI: skeletal muscle index; ECW: extracellular water; TBW: total body water; ALBI: albumin-bilirubin; AST: aspartate aminotransferase: ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltranspeptidase; NGSP: National Glycohemoglobin Standardization Program; eGFR: estimated glomerular filtration rate.

Results

Baseline features. Baseline features of the study cohort (n=341) are presented in Table I. The study cohort included 164 males and 177 females with the median age (IQR) of 66 (55, 72) years. LC was identified at baseline in 122 cases (35.8%). There were 256 patients (75.1%) with albumin-

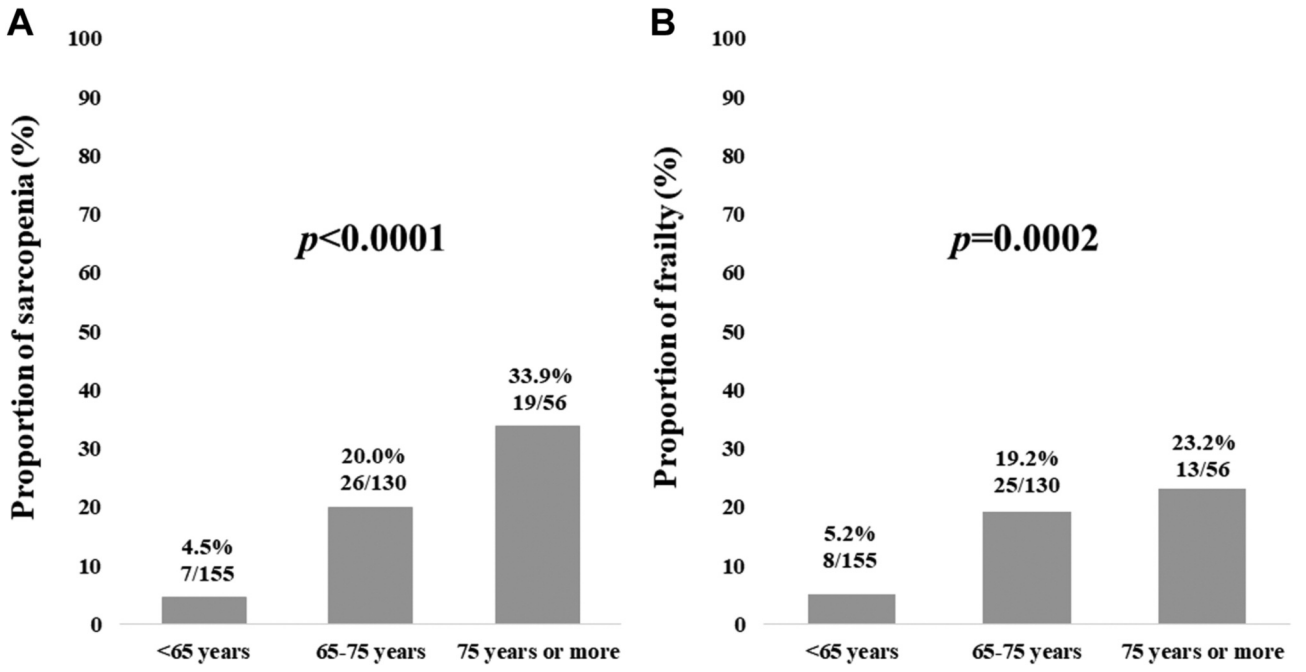

Figure 1. *Prevalence of sarcopenia and frailty according to age. (A) Shows prevalence of sarcopenia in patients <65 years, 65-75 years and ≥75 years. (B) Prevalence of frailty in patients <65 years, 65-75 years and ≥75 years.*

bilirubin (ALBI) grade 1, 78 (22.9%) with ALBI grade 2 and 7 (2.1%) with ALBI grade 3 (33).

In men, the median (IQR) GS was 33.3 kg (27.925, 38.925 kg), while in women, the median (IQR) GS was 20.8 kg (17.6, 24.45 kg). Thirty-two men (19.5%) and 48 women (27.1%) had decreased GS. In men, the median (IQR) SMI was 7.42 kg/m^2 (6.83, 7.93 kg/m^2), while in female, the median (IQR) SMI was 5.91 kg/m^2 (5.42, 6.45 kg/m^2). Fifty-three men (32.3%) and 65 women (36.7%) had decreased SMI. Sarcopenia was identified in 52 patients (15.2%).

The median (IQR) WS was 1.30 m/s (1.10, 1.44 m/s). Fifty-one patients (15.0%) had decreased WS. One hundred and sixty-eight patients (49.3%) reported exhaustion. Fifteen patients (4.4%) reported BW loss. Ninety patients (26.4%) reported low physical activity. Frailty score ranged from 0 to 5 (median value=1). Robust (frailty score 0), pre-frail (score 1 or 2) and frail (frailty score 3 or more) were identified in 108 (31.7%), 187 (54.8%) and 46 (13.5%) CLD patients, respectively.

Prevalence of sarcopenia or frailty according to age. Prevalence of sarcopenia in patients <65 years, 65-75 years and ≥75 years were 4.5% (7/155), 20.0% (26/130) and 33.9% (19/56), respectively (p<0.0001) (Figure 1A). Prevalence of frailty in patients <65 years, 65-75 years and ≥75 years were 5.2% (8/155), 19.2% (25/130) and 23.2% (13/56), respectively (p=0.0002) (Figure 1B). Prevalence of pre-frailty or frailty in patients <65 years, 65-75 years and ≥75 years were 56.8% (88/155), 73.1% (95/130) and 89.3% (50/56), respectively (p<0.0001).

Prevalence of sarcopenia or frailty according to body mass index. Prevalence of sarcopenia in patients with body mass index (BMI) <20 kg/m^2, >20 kg/m^2, <25 kg/m^2 and ≥25 kg/m^2 were 25.8% (16/62), 20.0% (35/175), and 1.0% (1/104), respectively (p<0.0001) (Figure 2A). Prevalence of frailty in patients with BMI <20 kg/m^2, >20 kg/m^2, <25 kg/m^2 and ≥25 kg/m^2 were 17.7% (11/62), 12.0% (21/175), and 13.5% (14/104), respectively (p=0.5237) (Figure 2B).

Proportion of LC in patients with sarcopenia and non-sarcopenia, and in patients with frailty and non-frailty. The proportion of LC in sarcopenic patients was significantly higher compared to non-sarcopenic patients [55.8% (29/52) *vs*. 32.2% (93/289), p=0.0016] (Figure 3A). The proportion of LC in patients with frailty was significantly higher compared to patients with non-frailty [67.4% (31/46) *vs*. 30.9% (91/295), p<0.0001] (Figure 3B).

Proportion of WS decrease, fatigue, BW loss and low physical activity in patients with sarcopenia or non-sarcopenia. The proportion of WS decrease in patients with sarcopenia was significantly higher compared to patients with non-sarcopenia [36.5% (19/52) *vs*. 11.1% (32/289),

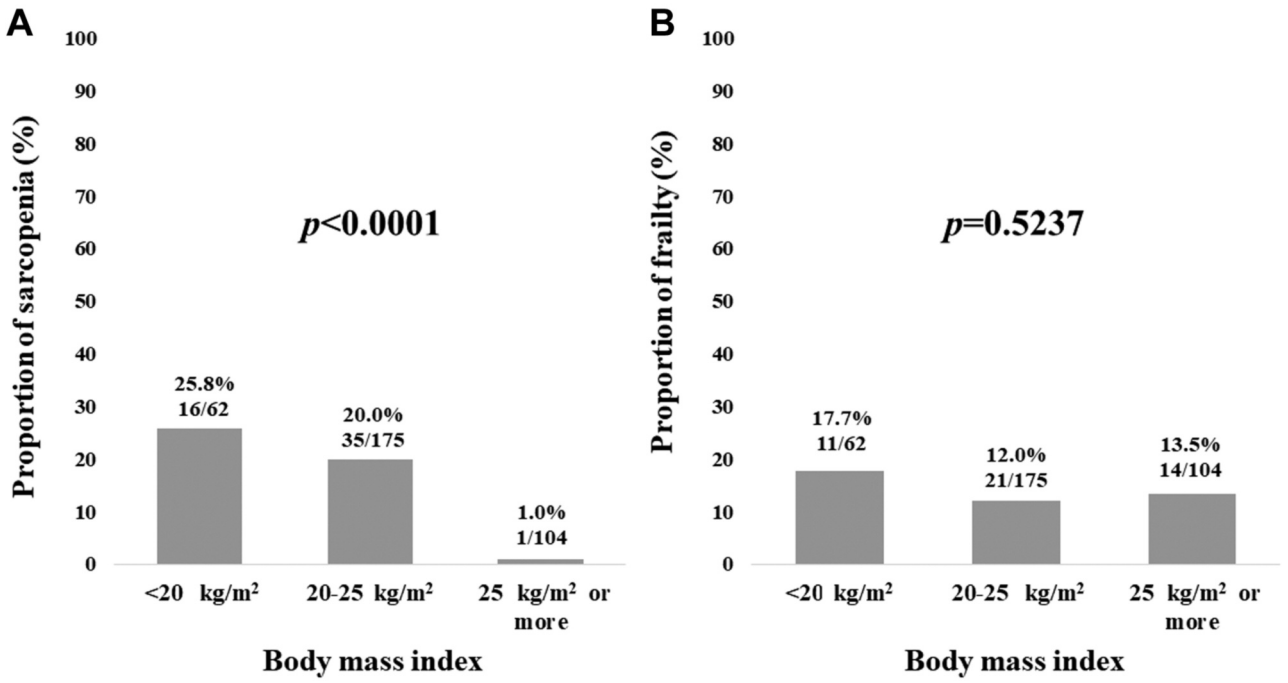

Figure 2. *Prevalence of sarcopenia and frailty according to body mass index. (A) Prevalence of sarcopenia in patients with body mass index (BMI)<20 kg/m², >20 kg/m², <25 kg/m² and ≥25 kg/m². (B) Prevalence of frailty in patients with BMI<20 kg/m², >20 kg/m², <25 kg/m² and ≥25 kg/m².*

p<0.0001], while no significant link was observed in patients presenting with fatigue and BW loss [fatigue: 55.8% (29/52) *vs*. 48.1% (139/289), p=0.3665; and BW loss: 5.8% (3/52) *vs*. 4.2% (12/289), p=0.7104] (Figures 4A-C). The proportion of low physical activity in patients with sarcopenia was higher with a tendency for significance compared to patients with non-sarcopenia [36.5% (19/52) *vs*. 24.6% (71/289), p=0.0870] (Figure 4D).

Uni- and multivariate analyses of factors related to the presence of sarcopenia. In the univariate analysis, i) age (p=0.0458), ii) presence of LC (p=0.0016), iii) serum albumin level (p=0.0017), iv) BMI (p<0.0001), v) ALBI score (p=0.0357), and vi) extracellular water (ECW) to total body water (TBW) ratio (p<0.0001) were significant factors associated with the presence of sarcopenia (Table II). The ALBI score includes total bilirubin and serum albumin; thus, the serum albumin level was not included in the multivariate analysis. In the multivariate analysis for the remaining 5 factors, i) advanced age (p=0.0114), ii) presence of LC (p=0.0227), iii) lower BMI (p<0.0001) and iv) higher ECW to TBW ratio (p=0.0002) were identified as significant for the presence of sarcopenia (Table III).

Uni- and multivariate analyses of factors related to the presence of frailty. In the univariate analysis, i) age (p=0.0002), ii) presence of LC (<0.0001), iii) serum albumin level (p<0.0001), iv) ALBI score (p<0.0001), v) alkaline phosphatase (ALP) (p=0.0065), vi) branched-chain amino acid to tyrosine ratio (BTR) (p=0.0083) and vii) ECW to TBW ratio (p<0.0001) were significant factors associated with the presence of frailty (Table IV). Serum albumin level was not included in the multivariate analysis due to the same reason as mentioned above. In the multivariate analysis for the remaining 6 factors, only a higher ECW to TBW ratio (p<0.0001) was found to be significantly linked to the presence of frailty (Table V).

Comparison of baseline characteristics among the four groups (type A, B, C and D). There were 32 patients (9.4%) with type A, 26 (7.6%) with type B, 20 (5.9%) with type C and 263 (77.1%) with type D. Comparing baseline characteristics among the four groups, overall significance was noted in terms of: i) age (p<0.0001) (Figure 5A), ii) BMI (p<0.0001) (Figure 5B), iii) ECW to TBW ratio (p<0.0001) (Figure 5C), iv) serum albumin level (p<0.0001) (Figure 5D), v) ALBI score (p=0.0002) (Figure 5E), vi) ALP (p=0.0017) (Figure 5F), vii) BTR (p=0.0015, Figure 5G), and viii) proportion of LC (p<0.0001) (Figure 6). The prevalence of LC in each type was: i) 53.1% (17/32) in type A, ii) 73.1% (19/26) in type B, iii) 60.0% (12/20) in type C, and iv) 28.1% (74/263) in type D. The p-Values from the

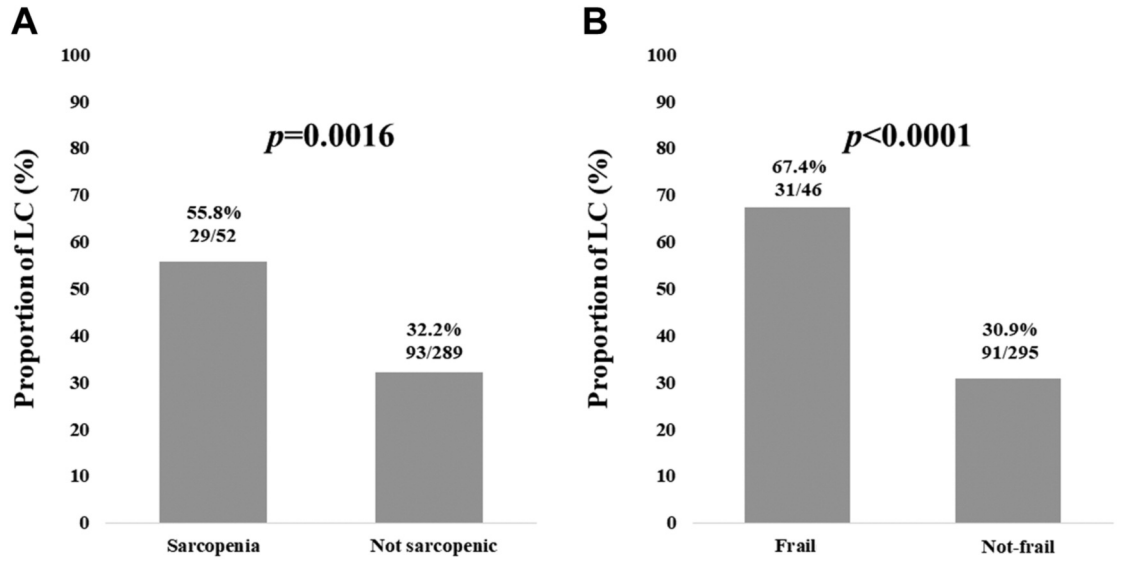

Figure 3. *Liver cirrhosis in sarcopenic and frail patients. (A) Proportion of liver cirrhosis (LC) in sarcopenic and non-sarcopenic patients. (B) Proportion of LC in patients with frailty and no frailty.*

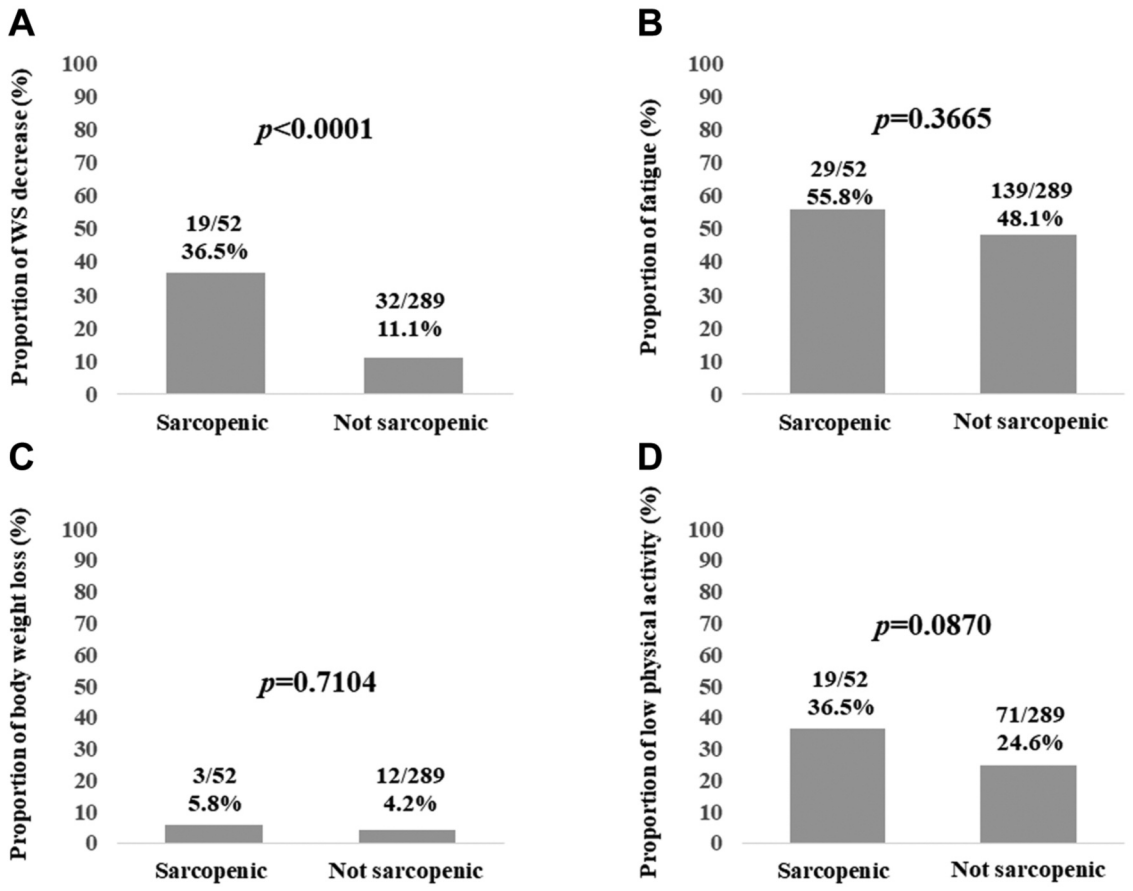

Figure 4. *Characteristics of patients with sarcopenia. (A) Proportion of walking speed decrease (<1.0 m/s), (B) fatigue, (C) body weight loss, and (D) low physical activity.*

Table II. *Univariate analyses of factors linked to the presence of sarcopenia.*

Variables	Sarcopenia (n=52)	Non-sarcopenia (n=289)	*p*-Value
Age (years)	73 (67,77)	64 (53, 71)	0.0458
Gender, male/female	21/31	143/146	0.4540
HCV/HBV/HBV and HCV/NBNC	28/5/1/18	146/56/6/81	0.3754
Body mass index (kg/m^2)	20.7 (19.8, 21.9)	23.5 (21, 26)	<0.0001
Presence of LC, yes/no	29/23	93/196	0.0016
Total bilirubin (mg/dl)	0.7 (0.525, 1.0)	0.9 (0.7, 1.1)	0.0511
Serum albumin (g/dl)	4.1 (3.725, 4.4)	4.3 (4.0, 4.6)	0.0017
ALBI score	–2.76 (–2.99, –2.48)	–2.91 (–3.14, –2.62)	0.0357
Prothrombin time (%)	90.25 (78.65, 99.8)	91.4 (81.0, 98.7)	0.9335
Platelet count (×10^4/mm^3)	16.15 (12.125, 18.85)	17.6 (12.9, 22.5)	0.4341
AST (IU/l)	25 (20.25, 40.75)	25 (19, 33)	0.8094
ALT (IU/l)	17 (13, 32)	20 (14, 33)	0.2578
ALP (IU/l)	275 (213.5, 368.5)	236 (193, 302)	0.4741
GGT (IU/l)	24 (16, 41.75)	26 (17, 47)	0.6026
Total cholesterol (mg/dl)	180.5 (140.5, 217.75)	181 (155.25, 213)	0.1867
Triglyceride (mg/dl)	92.5 (68.25, 116.5)	88 (67, 125.75)	0.9087
eGFR (ml/min/1.73m^2)	77.5 (62.75, 95.75)	81 (68.5, 92.5)	0.1721
HbA1c (NGSP)	5.7 (5.4, 6.075)	5.7 (5.4, 6.1)	0.2908
Serum sodium (mmol/l)	140 (138.25, 142)	140 (139, 141)	0.5353
BTR	5.23 (3.9275, 6.905)	5.72 (4.36,6.765)	0.5011
ECW to TBW ratio	0.3975 (0.392, 0.403)	0.388 (0.383, 0.394)	<0.0001

Data are expressed as number or median value (interquartile range). HbA1c: Glycated haemoglobin; HCV: hepatitis C virus; HBV: hepatitis B virus; NBNC: non-B and non-C; LC: liver cirrhosis; ALBI: albumin-bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltranspeptidase; eGFR: estimated glomerular filtration rate; NGSP: National Glycohemoglobin Standardization Program; BTR: branched-chain amino acid to tyrosine ratio; ECW: extracellular water; TBW: total body water.

comparisons (numerical parameters) between each two types are listed in Table VI.

Discussion

Recently, the concept of frailty has been assigned to CLDs as part of clinical symptoms concerning impaired global physical function (25, 34-39). It has not yet been clearly delineated whether sarcopenia and frailty in CLDs are

Table III. *Multivariate analysis of factors associated with sarcopenia.*

Sarcopenia	HR	95%CI	*p*-Value
Age (per one year)	1.047	1.009-1.088	0.0114
ALBI score (per one)	2.205	0.959-5.072	0.0567
BMI (per one kg/m^2)	0.736	0.652-0.830	<0.0001
ECW to TBW ratio (per one)	2.55e+40	8.43e+18-7.71e+61	0.0002
Presence of LC	2.532	1.140-5.624	0.0225

HR: Hazard ratio; CI: confidence interval; ALBI: albumin-bilirubin; BMI: body mass index; ECW: extracellular water; TBW: total body water; LC: liver cirrhosis.

Table IV. *Univariate analyses of factors linked to the presence of frailty.*

Variables	Frailty (n=46)	Non-frailty (n=295)	*p*-Value
Age (years)	73 (68, 75.25)	65 (54, 71)	0.0002
Gender, male/female	20/26	144/151	0.7836
HCV/HBV/HBV and HCV/NBNC	20/5/1/20	154/56/6/79	0.1174
Body mass index (kg/m^2)	21.55 (19.975, 25.5)	22.8 (20.8, 25.7)	0.3701
Presence of LC, yes/no	31/15	91/204	<0.0001
Total bilirubin (mg/dl)	0.8 (0.6, 1.35)	0.8 (0.6, 1.1)	0.9042
Serum albumin (g/dl)	4.0 (3.075, 4.3)	4.3 (4.0, 4.6)	<0.0001
ALBI score	–2.65 (–2.9425, –1.715)	–2.93 (–3.15, –2.67)	<0.0001
Prothrombin time (%)	87.05 (71.175, 100.425)	91.4 (81.3, 98.7)	0.2037
Platelet count (×10^4/mm^3)	14.7 (9.35, 19.15)	17.9 (13.0, 22.2)	0.0543
AST (IU/)	28 (21, 43)	25 (19, 33)	0.0992
ALT (IU/l)	21 (13.75, 36.25)	19 (14, 32)	0.6717
ALP (IU/l)	276 (213.5, 414)	236 (193, 300)	0.0065
GGT (IU/l)	27 (15, 49.75)	26 (17, 46)	0.8044
Total cholesterol (mg/dl)	163 (141.5, 204.5)	183.5 (156.75, 215)	0.0815
Triglyceride (mg/dl)	83.5 (68.75, 106.25)	89.5 (67.0, 126.25)	0.2260
eGFR (ml/min/1.73m^2)	81 (64.5, 91.75)	81 (68, 93)	0.3615
HbA1c (NGSP)	5.85 (5.375, 6.525)	5.7 (5.4, 6.0)	0.1741
Serum sodium (mmol/l)	139.5 (138, 142)	140 (139, 141)	0.1778
BTR	4.22 (3.385, 6.3325)	5.815 (4.5175, 6.8475)	0.0083
ECW to TBW ratio	0.401 (0.397, 0.40625)	0.388 (0.383, 0.393)	<0.0001

Data are expressed as number or median value (interquartile range). HbA1c: Glycated haemoglobin; HCV: hepatitis C virus; HBV: hepatitis B virus; NBNC: non-B and non-C; LC: liver cirrhosis; ALBI: albumin-bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltranspeptidase; eGFR: estimated glomerular filtration rate; NGSP: National Glycohemoglobin Standardization Program; BTR: branched-chain amino acid to tyrosine ratio; ECW: extracellular water; TBW: total body water.

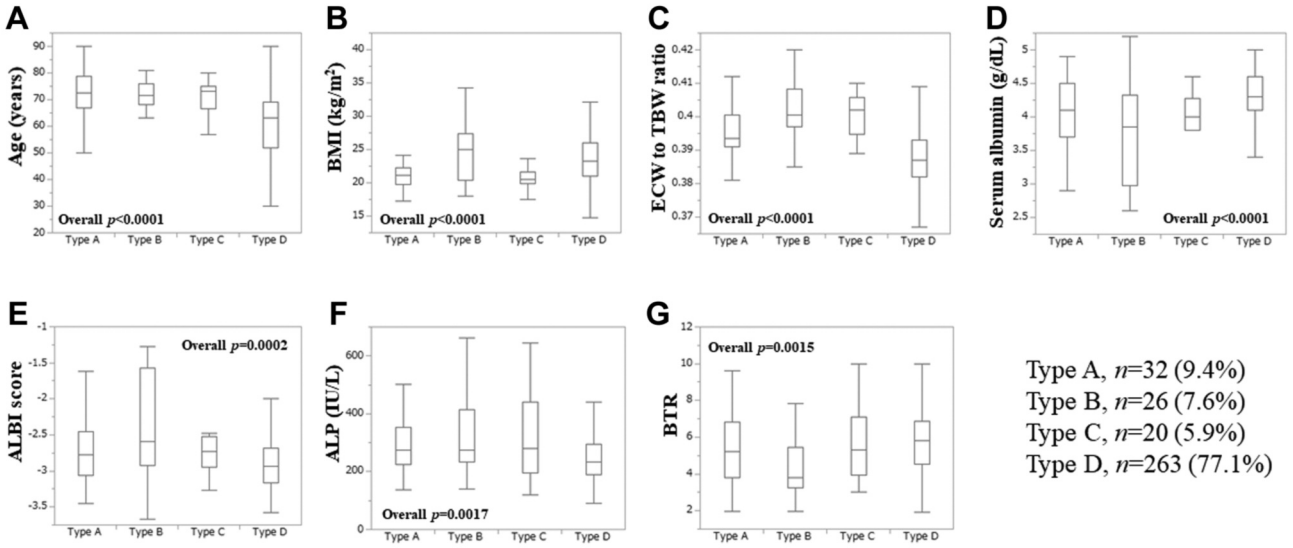

Figure 5. *Comparison of baseline characteristics (numerical parameters) among four types (type A, B, C and D). (A) age, (B) body mass index (BMI), (C) extracellular water (ECW) to total body water (TBW) ratio, (D) serum albumin level, (E) albumin-bilirubin (ALBI) score, (F) alkaline phosphatase (ALP), and (G) branched-chain amino acid to tyrosine ratio (BTR). Type A indicates patients with sarcopenia alone. Type B indicates patients with frailty alone. Type C indicates patients with both sarcopenia and frailty. Type D indicates patients with neither sarcopenia or frailty.*

Table V. *Multivariate analysis of factors associated with frailty.*

Frailty	HR	95%CI	*p*-Value
Age (per one year)	2.667	0.184-38.673	0.4710
ALBI score (per one)	1.003	0.355-2.838	0.9949
ECW to TBW ratio (per one)	8.69e+65	3.18e+40-2.37e+91	<0.0001
BTR (per one)	0.876	0.651-1.181	0.3862
ALP (per one IU/l)	1.001	0.999-1.004	0.1636
Presence of LC	2.395	0.806-7.117	0.1160

HR: Hazard ratio; CI: confidence interval; ALBI: albumin-bilirubin; ECW: extracellular water; TBW: total body water; BTR: branched-chain amino acid to tyrosine ratio; ALP: alkaline phosphatase; LC: liver cirrhosis.

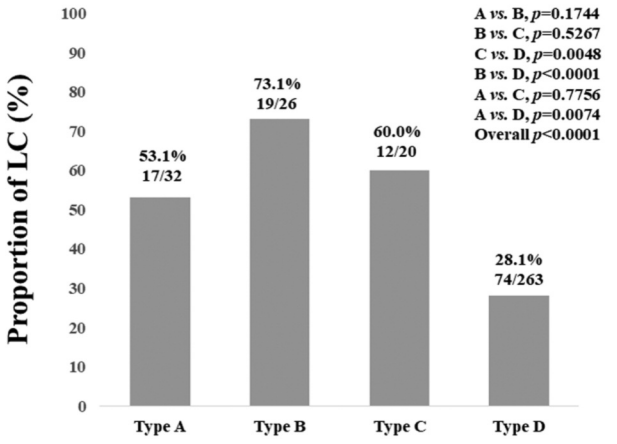

Figure 6. *The prevalence of liver cirrhosis among four types (type A, B, C and D). Type A indicates patients with sarcopenia alone. Type B indicates patients with frailty alone. Type C indicates patients with both sarcopenia and frailty. Type D indicates patients with neither sarcopenia or frailty. LC: Liver cirrhosis.*

synonyms. Few studies have assessed both sarcopenia and frailty as such in CLDs. Banjhi *et al*. have reported that in both alcoholic liver disease and non-alcoholic steatohepatitis, there was a large difference between the prevalence of sarcopenia on computed tomography scans and frailty (40). Despite the overlap between definitions and diagnostic criteria, sarcopenia is not identical to frailty. Frailty is a multidimensional clinical entity involving not only the muscle status but also the well-being, disabilities, exhaustion, dependencies and cognitive status. While skeletal muscle mass decline and functional decline can be a strong substratum of frailty (41), the opposite does not always stand true and the absence of sarcopenia certainly does not always deny the presence of frailty. Clues for frailty should lead to an assessment of body composition. Based on these facts regarding sarcopenia and frailty in CLDs, we believe that common and different points in sarcopenia and frailty for patients with CLDs should be clarified.

In our data, there were 32 patients (9.4%) with type A (sarcopenia alone), 26 (7.6%) with type B (frailty alone), and 20 (5.9%) with type C (both sarcopenia and frailty). In addition, i) advanced age, ii) presence of LC, iii) a lower BMI

Table VI. *Comparison of baseline characteristics in the four types (Type A, B, C and D).*

	A *vs*. B *p*-Value	B *vs*. C *p*-Value	C *vs*. A *p*-Value	A *vs*. D *p*-Value	B *vs*. D *p*-Value	C *vs*. D *p*-Value	Overall *p*-Value
Age	0.3858	0.8853	0.3402	<0.0001	0.0004	0.0031	<0.0001
BMI	0.0008	0.0016	0.4814	<0.0001	0.2411	0.0001	<0.0001
ECW to TBW ratio	0.0134	0.7701	0.0467	<0.0001	<0.0001	<0.0001	<0.0001
Total bilirubin	0.0616	0.0583	0.7187	0.0751	0.2287	0.0593	0.0545
Serum albumin	0.1151	0.7223	0.3081	0.0161	0.0002	0.0011	<0.0001
ALBI score	0.0734	0.3292	0.5724	0.0650	0.0003	0.0193	0.0002
Prothrombin time	0.1648	0.1632	0.8661	0.7066	0.0338	0.9299	0.2077
Platelet count	0.2690	0.2976	0.9500	0.3740	0.0262	0.5218	0.1345
AST	0.1132	0.8166	0.0876	0.5055	0.1529	0.1180	0.1706
ALT	0.2123	0.9852	0.2558	0.1198	0.8534	0.8877	0.4564
ALP	0.5896	0.4714	0.7491	0.0081	0.0029	0.1875	0.0017
GGT	0.1569	0.5518	0.4891	0.4791	0.2401	0.7802	0.5454
Total cholesterol	0.7518	0.2060	0.1072	0.8598	0.5708	0.0341	0.1984
Triglyceride	0.2473	0.6034	0.5958	0.7788	0.2187	0.6077	0.6125
HbA1c	0.8411	0.2060	0.1325	0.9959	0.8005	0.0655	0.3278
eGFR	0.9377	0.5203	0.6515	0.6152	0.9764	0.3163	0.7674
Serum sodium	0.4120	0.8495	0.3181	0.7066	0.4037	0.2664	0.5685
BTR	0.0470	0.0101	0.4461	0.1745	0.0002	0.8232	0.0015

Type A: Patients with sarcopenia alone; Type B: patients with frailty alone; Type C: patients with both sarcopenia and frailty; Type D: patients without both sarcopenia and frailty; BMI: body mass index; ECW: extracellular water; HbA1c: glycated haemoglobin; TBW: total body water; ALBI: albumin-bilirubin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; GGT: γ-glutamyltranspeptidase; eGFR: estimated glomerular filtration rate; BTR: branched-chain amino acid to tyrosine ratio.

and iv) a higher ECW to TBW ratio were independent predictors for sarcopenia, while only a higher ECW to TBW ratio was an independent predictor for frailty. By comparing between type A and type B, significant differences were noted in terms of BMI, ECW to TBW ratio and BTR. These findings raised our awareness that sarcopenia and frailty in CLDs are not synonymous. On the other hand, a significantly high proportion of LC in sarcopenic and frailty patients compared with each counterpart (*i.e*., not sarcopenic and not frailty patients) implies that underlying liver diseases can be involved not only in sarcopenia but also in frailty, highlighting common points between the two conditions in CLDs. Stratification of the prevalence of sarcopenia or frailty according to age is another common points between the two conditions in CLDs. While sarcopenia was associated with a WS decline and a low physical activity, it was not associated with fatigue or BW loss. Sarcopenia in CLDs is indeed similar to physical frailty (41). Sarcopenia may be the dominant driver of the physical frailty phenotype, especially in LC patients where hepatic synthetic impairment may accelerate the skeletal muscle mass decrease (14, 42, 43).

In our data, 13.5% of our patients had frailty, while Fozouni *et al*. have reported that out of 291 LC patients, 54 LC patients (19%) had frailty (42). This is probably due to the difference of background patient population (prevalence of LC: 35.8% in our data *vs*. 100% in the study by Fozouni *et al*.) (42). Age-stratified meta-analyses reported by Kojima *et al*. have demonstrated that the pooled prevalence of frailty among elderly people living in Japan was 1.9% (65-69 years), 3.8% (70-74 years), 10.0% (75-79 years), 20.4% (80-84 years), and 35.1% (85 years or more) (44). In our data, the prevalence of frailty in patients <65 years, 65-69 years, 70-74 years, 75-79 years, 80-84 years and ≥85 years were 5.2% (8/155), 8.8% (6/68), 30.7% (19/62), 27.0% (10/37), 15.4% (2/13) and 16.7% (1/6), respectively. Especially in our CLD patients aged 70-74 years, the prevalence of frailty was prominently higher compared to similar age elderly people living in Japan, which may be linked to the influence of underlying CLDs on frailty. Notably, a pre-frailty status (frailty score 1 or 2) was identified in 54.8% of our patients. Clinicians should be aware of the high prevalence of the pre-frailty status in CLDs. Early identification of frailty in CLDs can lead to optimization of the CLD patients with the potential for avoiding poor outcomes (45).

Elevated ECW to TBW ratio was an independent factor associated with both the presence of sarcopenia and frailty. ECW to TBW ratio defines the extracellular fluid status (water homeostasis) in the whole body and the liver functional reserve (46, 47). Excessive extracellular fluid in CLDs may also lead to the physical functional decline as well as a cognitive decline, which can be linked to our current results (48-50). Excessive extracellular fluid in the brain can cause cognitive decline (49, 50). While, notably, the prevalence of sarcopenia was closely linked to BMI, however, frailty was

not in the multivariate analyses. These results suggest that lower BMI in CLDs involves a poorer muscle status, however, it does not involve phenotypes other than muscle status. Also, in CLDs, higher BMI itself cannot exclude the possibility of frailty although CLD patients with higher BMI have low possibility for sarcopenia. This can be a significant different point between sarcopenia and frailty in CLDs.

Several limitations associated with the study should be mentioned. Firstly, this was a retrospective cross-sectional observational study with patients from a single hospital. Secondly, our data included population data from CLDs patients in Japan, thus, additional studies on patients from other parts of the world are necessary to confirm and expand or adapt our results for each population. Thirdly, patients with large ascites who could suffer from a WS decline were excluded due to the limits of BIA, possibly making this a bias. Finally, due to the cross-sectional nature of our study, the causal relationship between sarcopenia and frailty is unclear. Interpretation with caution to our data is needed. Our study results nevertheless implied that sarcopenia and frailty in CLDs had several common and a few different points. In conclusion, sarcopenia and frailty in CLDs are not synonyms. These two important clinical entities should be separately evaluated.

Conflicts of Interest

The Authors have no conflicts to declare.

Authors' Contributions

Data curation: HN, KY, HE, YI, YS, KK, YS, NI, TT, NA, RT, KH, TK, YY, TN and SN. Formal analysis: HN, supervision: HE and HI. Writing of the original draft: HN and KY and manuscript review and editing: HI.

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