Original article

Obesity and myosteatosis: the two characteristics of dynapenia in patients with cirrhosis

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Objective In patients with liver cirrhosis, the clinical characteristics of dynapenia, a condition in which skeletal muscle mass is maintained but muscle strength is reduced, are not yet known. This study aimed to clarify the characteristics of dynapenia and its impact on quality of life (QOL) in patients with liver cirrhosis.

Methods We retrospectively analyzed 116 patients with cirrhosis. Based on grip strength and skeletal muscle mass measured by the bioelectrical impedance analysis method, patients were divided into four groups: normal muscle status, dynapenia, pre-sarcopenia (a condition involving only low muscle mass), and sarcopenia. The characteristics of dynapenia and its influence on QOL were examined.

Results Fourteen patients had dynapenia. Liver function did not differ among the four groups. In patients with dynapenia, BMI was highest and computed tomography attenuation of skeletal muscle at the third lumbar spine vertebra was lowest among the four groups. The percentage of patients with both BMI ≥25 kg/m^2 and myosteatosis was significantly higher in patients with dynapenia [9/14 (64.3%)] than in those with sarcopenia [2/23 (8.7%), $P = 0.004$] and pre-sarcopenia [0/18 (0%), $P < 0.001$] and tended to be higher than those with normal muscle status [16/61 (26.2%), $P = 0.065$]. The physical QOL in patients with dynapenia was as low as that in those with sarcopenia and significantly lower than that in those with normal muscle status.

Conclusion Cirrhotic patients with dynapenia had high BMI and myosteatosis, and impaired physical QOL. Eur J Gastroenterol Hepatol XXX: 00–00

Introduction

Sarcopenia is a condition characterized by low skeletal muscle mass and muscle strength [1,2] that is associated with adverse health outcomes such as impaired activities of daily living and death in the elderly [3]. Reductions in skeletal muscle strength are generally accompanied by a reduction in skeletal muscle mass [4]; however, some people lose only muscle strength, but not skeletal muscle mass [5,6]. This condition is called dynapenia, and it has been shown to be associated with mortality [7] and low quality of life (QOL) [8]. Therefore, in addition to sarcopenia, dynapenia has been identified as a clinically important muscle alteration in the field of nursing care prevention and rehabilitation [9]. In 2019, the Asia Working Group for Sarcopenia (AGWS) proposed that dynapenia is a precondition of sarcopenia, and early detection and intervention at the stage of dynapenia are necessary to improve prognosis and QOL [10].

Patients with liver cirrhosis have a high prevalence of sarcopenia because of several factors such as malnutrition, malabsorption, and increased protein catabolism (due to inflammatory cytokines) that are known to cause sarcopenia [11], and the presence of sarcopenia in patients with liver cirrhosis is associated with poor prognosis [12]. However, the clinical characteristics of dynapenia and its impact on QOL in patients with cirrhosis have not yet been fully elucidated.

This study aimed to clarify the clinical characteristics and QOL in cirrhotic patients with dynapenia.

Materials and methods

Patients and study design

We retrospectively reviewed 230 adult patients who were admitted to our institution and underwent handgrip strength measurement, body composition measurement by bioelectrical impedance analysis (BIA) and computed tomography (CT) scans between May 2017 and October 2020. Based on the radiological and clinical examinations, 38 patients were excluded because they were not diagnosed with liver cirrhosis. Patients with malignancies other than hepatocellular carcinoma (HCC; $n = 15$), uncontrolled HCC ($n = 23$), poorly controlled cardiac, respiratory, and renal diseases ($n = 7$), neurological and muscular diseases ($n = 1$), and severe encephalopathy ($n = 1$) were excluded.

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We also excluded patients with more than a one-year gap between the date of the CT scan and the date of handgrip strength measurement (n = 6), because patients with cirrhosis show skeletal muscle loss at an annual rate of 2.2% [13]. Patients with ascites (grade 2 to refractory ascites) [14,15] diagnosed on CT scan (n = 21) and patients whose abdomen was not included in the CT scan (n = 2) were also excluded. After excluding 114 patients, 116 patients were enrolled in this study. The median patient age was 71 years [interquartile range (IQR): 67–78 years], and 52 patients (44.8%) were men. Hepatitis C virus infection was the most common etiology (48 patients, 41.4%), followed by miscellaneous liver diseases, including autoimmune hepatitis, primary biliary cholangitis, and nonalcoholic steatohepatitis (40 patients, 34.5%), alcoholic liver disease (16 patients, 13.8%), and hepatitis B virus infection (12 patients, 10.3%). More than half of the patients (83 patients, 71.6%) were diagnosed with Child–Pugh classification A. Thirty-five patients had mild ascites, 11 had a history of hepatic encephalopathy, and 65 had esophagogastric varices. HCC was present in almost one-third of the patients (36 patients, 31.0%; Table 1).

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

Table 1. Patient characteristics

Variables	Overall cohort (n = 116)
Age (years)	71 (67–78)
Sex (male/female)	52/64
Etiology (HCV/HBV/alcohol/ miscellaneous)	48/12/16/40
Total bilirubin (mg/dl)	1.0 (0.7–1.4)
Albumin (g/dl)	3.6 (3.2–3.9)
Prothrombin time (INR)	1.08 (1.03–1.21)
Ascites (none/present)	81/35
History of hepatic encephalopathy (present/absent)	*11/105*
Child–Pugh class (A/B/C)	83/29/4
Esophagogastric varices (present/absent)	*73/43*
Type 2 diabetes (present/absent)	*43/73*
Dyslipidemia (present/absent)	*25/91*
Cardiovascular disease (present/absent)	*14/102*
Hepatocellular carcinoma (present/absent)	36/80
BCLC stage (A/B/C)	16/16/4
BMI (kg/m^2)	23.7 (21.1–26.8)
Skeletal muscle index (kg/m^2)	
Male	7.37 (6.93–8.03)
Female	6.10 (5.54–6.62)
Handgrip strength (kg)	
Male	32.0 (26.9–36.3)
Female	19.2 (16.4–21.8)
Low skeletal muscle (present/absent)	41/75
Low muscle strength (present/absent)	37/79
Visceral fat area (cm^2)	79.4 (59.8–107.1)
Health-related quality of life	
Physical component summary	42.8 (34.0–48.9)
Mental component summary	50.9 (43.7–55.4)
Role-social component summary	49.9 (39.6–57.5)

Skeletal muscle index and BMI were calculated as skeletal muscle (kg) and body weight (kg) divided by the square of the height (m^2).
Low skeletal muscle was defined as a skeletal muscle index <7.0 kg/m^2 in males and <5.7 kg/m^2 in females. Low muscle strength was defined as handgrip strength of <28 kg in males and <18 kg in females. Data are presented as median (interquartile range).
BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio.

Data collection

Data on blood biochemical tests, image findings, muscle strength, skeletal muscle mass, and QOL were collected retrospectively. Handgrip strength was measured twice on each side using a Smedley-type digital grip strength dynamometer (B07CXL4K8W N-FORCE; CORVETTE Inc., Wakayama, Japan) in a standardized procedure, and the maximal value was used for analysis [16]. The BIA method (In Body S10; In Body Japan Inc., Nagoya, Japan) was used to measure skeletal muscle mass and BMI. The InBody S10 uses a direct segmental multi-frequency BIA (DSM-BIA) system with an 8-point tactile electrode. The multi-frequency measurement is conducted by using multiple frequencies at 1, 5, 50, 250, 500, and 1000 kHz for each body segment (arms, trunk, and legs). The analyzer automatically displays measurements of body composition. This tool does not depend on statistical data of any specific population; therefore, it is capable of accurately assessing people of very different physical types including obese, elderly, or athletic [17,18]. Furthermore, the amount of skeletal muscle, calculated using the DSM-BIA system, has been shown to be less affected by ascites [19]. Skeletal muscle index (SMI) was calculated as the amount of limb skeletal muscle mass (kg) divided by the square of the height (m). CT imaging performed at the level of the umbilicus was used for the evaluation of the visceral fat area. CT attenuation of skeletal muscle was calculated using the following method. First, skeletal muscle area at the third lumbar spine vertebra (L3) ranging from −29 to +150 Hounsfield units (HU) was calculated using the SYNAPSE VINCENT software (Fujifilm Co. Tokyo, Japan). Second, the mean HU measurement in the skeletal muscle area was recorded. Individuals performing these analyses were blinded to outcome variables.

Health-related QOL (HRQOL) was assessed using the 36-item Short-Form Health Survey version 2 (SF-36 v2). This tool consists of 36 questions and assesses eight health concepts: physical function, role physical, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Furthermore, three-component scores – physical component summary (PCS), mental component summary (MCS), and role-social component summary (RCS)—were calculated from these eight subscales. The scores of the three summary components were converted into norm-based scores to achieve the same mean values of 50 and a SD of 10 in the general Japanese population, to allow for easier interpretation of the results. Higher scores indicate better HRQOL [20].

Hyper-attenuated nodules in the arterial phase followed by washout in the portal or equilibrium phase on contrast-enhanced CT or contrast-enhanced MRI were imaging features that defined HCC. The stage of HCC was determined according to the Barcelona Clinic Liver Cancer (BCLC) classification [21].

Definition

In accordance with the AWGS 2019 criteria, low muscle strength was defined as handgrip strength <28 kg for men and <18 kg for women, and low skeletal muscle mass was defined as SMI <7.0 kg/m^2 for men and <5.7 kg/m^2 for women [10]. Sarcopenia was defined as both low skeletal muscle mass and strength, dynapenia as low muscle strength but maintained skeletal muscle mass,

pre-sarcopenia as low skeletal muscle mass but maintained muscle strength, and the fourth group had normal muscle status. BMI ≥25 kg/m^2 was defined as obesity [22]. Myosteatosis was defined as follows: radiation attenuation of skeletal muscle at L3 of <41 HU for patients with a BMI up to 24.9 kg/m^2 and that of <33 HU for patients with a BMI ≥25 kg/m^2 [23]. Type 2 diabetes was defined as any of the following: fasting plasma glucose ≥126 mg/dl, hemoglobin A1c (NGSP) ≥6.5%, or use of anti-diabetic medication based on the diagnostic guidelines of the Japan Diabetes Society [24]. Dyslipidemia was defined as a low-density lipoprotein ≥140 mg/dl or use of lipid-lowering drugs based on the diagnostic guidelines of the Japan Atherosclerosis Society [25].

Statistical analysis

Quantitative and qualitative variables were compared using the Kruskal–Wallis test and Fisher's exact test. Each comparison between three or more groups was examined using the Bonferroni post-hoc test for multiple comparisons. Correlation coefficients were tested using Spearman's rank correlation coefficient. All statistical analyses were performed using R (R Statistical Software; Foundation for Statistical Computing, Vienna, Austria) and EZR (version 1.40) [26]. In all analyses, $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of patients with dynapenia

Of the 116 patients, 14 (12.1%) were diagnosed with dynapenia, 18 (15.5%) with pre-sarcopenia, 23 (19.8%) with sarcopenia, and the remaining 61 (52.6%) with normal muscle status. Clinical characteristics for each muscle status group are shown in Table 2. Patients with sarcopenia were significantly older (median: 78 years; IQR: 73–81 years) than those with normal muscle status (median: 69 years; IQR: 61–72 years; $P < 0.001$). The Child–Pugh score, frequency of HCC, and stage of BCLC were not significantly different among the four groups. BMI was significantly higher in patients with dynapenia (27.6 kg/m^2; IQR: 25.2–29.2) than that in patients with sarcopenia (21.4 kg/m^2; IQR: 19.7–23.7, $P < 0.001$) and that in patients with pre-sarcopenia (20.1 kg/m^2; IQR: 18.9–22.0; $P < 0.001$; Fig. 1a). The proportion of patients with obesity was highest in the group of patients with dynapenia (78.6%, 11/14), while most patients with pre-sarcopenia and sarcopenia did not have obesity (0%, 0/18, and 8.7%, 2/23, respectively; Table 3). In addition, visceral fat area was also significantly higher in patients with dynapenia (113.4 cm^2; IQR: 94.3–146.0) than that in patients with sarcopenia (78.0 cm^2; IQR: 19.7–23.7; $P = 0.002$) and that in patients with pre-sarcopenia (60.5 cm^2; IQR: 44.9–67.9; $P < 0.001$; Fig. 1b). The prevalence of type 2 diabetes and dyslipidemia were not significantly different among the four groups. Cardiovascular disease was more prevalent in patients with dynapenia (4/14, 28.6%) than in patients with normal muscle status (4/61, 6.6%), but this did not reach significance ($P = 0.21$).

Differences in computed tomography attenuation of skeletal muscle according to body composition

The degree of fatty infiltration into skeletal muscle is related to muscle strength, and it can be assessed by measuring CT attenuation of skeletal muscle [27]. Thus, we compared the CT attenuation among the four skeletal muscle groups. The results showed that CT attenuation of skeletal muscle was lowest in patients with dynapenia (24.9 HU; IQR: 23.5–27.7), followed by sarcopenia (25.8 HU; IQR: 24.1–32.7) and pre-sarcopenia (27.3 HU; IQR: 25.1–33.1), and all values were significantly lower than in patients with normal muscle status (33.4 HU; IQR: 29.0–38.3; Fig. 1c). Myosteatosis was diagnosed in 83.6% of the patients overall. For each skeletal muscle condition, 79.2% of patients with normal muscle status, 87.5% of patients with dynapenia, 100% of patients with pre-sarcopenia, and 95.8% of patients with sarcopenia were diagnosed with myosteatosis (Table 3).

The proportion of patients with both obesity and myosteatosis was compared among each skeletal muscle

Table 2. Differences in patient characteristics according to muscle status

	Normal muscle status (n = 61)	Sarcopenia (n = 23)	Dynapenia (n = 14)	Pre-sarcopenia (n = 18)
Age (years)	69 (61–72)	78 (73–81)[a]	73 (69–78)	74 (69–77)
Sex (male/female)	32/29	11/12	4/10	5/13
Etiology (HCV/HBV/alcohol/miscellaneous)	30/4/10/17	7/2/4/10	4/3/0/7	7/3/2/6
Ascites (none/present)	43/18	14/9	9/5	15/3
History of hepatic encephalopathy (present/absent)	*8/53*	*1/22*	*2/12*	*0/18*
Child–Pugh class (A/B/C)	42/17/2	18/5/0	7/5/2	16/2/0
Esophagogastric varices (present/absent)	*43/18*	*13/10*	*10/4*	*7/11*
Type 2 diabetes (present/absent)	*19/42*	*10/13*	*7/7*	*7/11*
Dyslipidemia (present/absent)	*10/51*	*7/16*	*6/8*	*2/16*
Cardiovascular disease (present/absent)	*4/57*	*4/19*	*4/10*	*2/16*
HCC (present/absent)	18/43	10/13	4/10	4/14
BCLC stage (A/B/C)	9/6/3	3/7/0	2/1/1	2/2/0
Skeletal muscle index (kg/m^2)				
Male	7.74 (7.35–8.31)	6.60 (6.30–6.75)	7.80 (7.47–8.40)	6.80 (6.60–6.85)
Female	6.50 (6.20–6.90)	5.43 (5.19–5.70)	6.46 (6.00–6.68)	5.40 (5.10–5.54)
Handgrip strength (kg)				
Male	34.4 (32.2–38.1)	22.5 (21.6–24.6)	25.5 (23.7–26.6)	31.1 (30.0–37.0)
Female	21.7 (19.6–24.0)	15.2 (13.4–16.0)	15.4 (14.1–16.8)	19.8 (18.5–20.9)

Data are presented as median (interquartile range).
BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
[a]$P < 0.001$ (vs. normal muscle status).

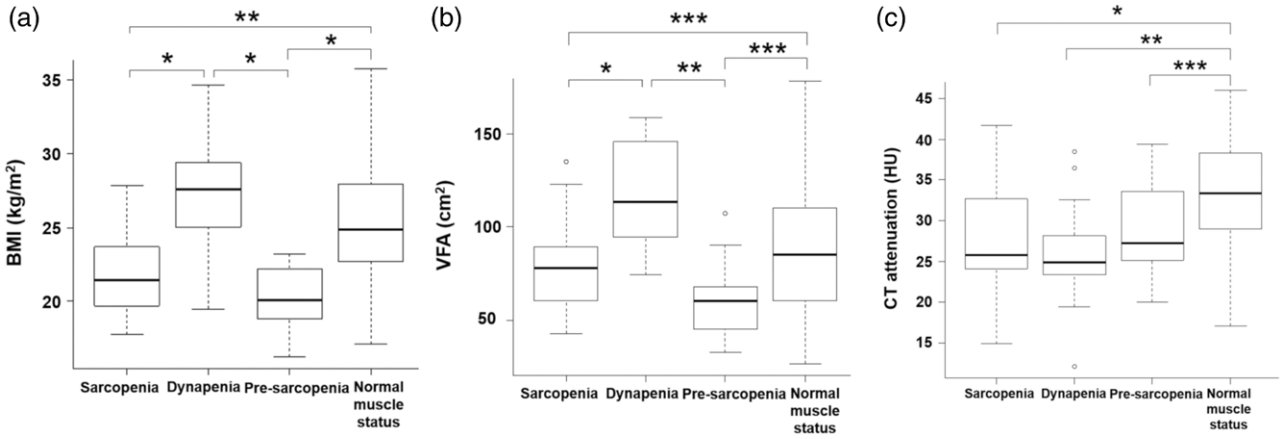

Fig. 1. Comparison of BMI, VFA, and CT attenuation among the four muscle status groups (a) BMI was significantly higher in patients with dynapenia than in patients with sarcopenia and patients with pre-sarcopenia. *P < 0.001, **P = 0.001. (b) VFA was significantly higher in patients with dynapenia than in patients with sarcopenia and patients with pre-sarcopenia. *P = 0.002, **P < 0.001, ***P < 0.05. (c) CT attenuation of skeletal muscle was lowest in patients with dynapenia, followed by sarcopenia and pre-sarcopenia, and all values were significantly lower than those in patients with normal muscle status. *P = 0.005, **P < 0.005, ***P < 0.05. Data were analyzed using the Kruskal–Wallis test, and comparisons between three or more groups were examined using the Bonferroni post-hoc test for multiple comparisons. CT, computed tomography; VFA, visceral fat area.

Table 3. The frequency of obesity and myosteatosis in patient characteristics according to muscle status

	Normal muscle status (n = 61)	Sarcopenia (n = 23)	Dynapenia (n = 14)	Pre-sarcopenia (n = 18)
BMI (≥25, <25) (kg/m^2)	28/33	2/21*,**	11/3	0/18*,***
Myosteatosis (present/absent)	45/16	22/1	12/2	18/0
BMI ≥ 25 and presence of myosteatosis (yes/no)	16/45****	2/21*	9/5	0/18*

*P < 0.01 (vs. dynapenia), **P < 0.05 (vs. normal muscle status), ***P < 0.01 (vs. normal muscle status), ****P = 0.065 (vs. dynapenia).

condition group. The percentage of patients with both obesity and myosteatosis was significantly higher in patients with dynapenia [9/14 (64.3%)] than in those with sarcopenia [2/23 (8.7%), P = 0.004] and pre-sarcopenia [0/18 (0%), P < 0.001], and tended to be higher than those with normal muscle status [16/61 (26.2%), P = 0.065; Table 3].

Influence of dynapenia on health-related quality of life

The PCS score in patients with dynapenia was 36.0 (IQR: 26.4–37.6), which was as low as that seen in those with sarcopenia (34.1; IQR: 22.6–44.6; P > 0.99), and significantly lower than that seen in patients with normal muscle status (47.0; IQR: 40.7–50.8; P = 0.002; Fig. 2a). There were no significant differences in MCS or RCS scores in relation to the muscle status (Fig. 2b and c).

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Discussion

The current study showed that, in patients with liver cirrhosis, the prevalence of dynapenia was 12.1%, similar to the 12.5% previously reported [28]. And, the patients with dynapenia were more likely to have obesity and myosteatosis, and their physical QOL was as poor as that of patients with sarcopenia.

Muscle strength and skeletal muscle mass are closely related to body weight. As body weight increases, the weight acts as a stimulus to the antigravity muscles, which increases muscle mass and strength. Therefore, obese patients generally have higher muscle mass and strength than non-obese patients [29]. However, in the present study, cirrhotic patients with dynapenia showed decreased muscle strength despite having the highest BMI and visceral fat area. Similar results have been reported in studies of the elderly [30].

The mechanisms of developing dynapenia are thought to be related to neurological and skeletal muscle abnormalities in the elderly [5]. Skeletal muscle abnormalities include changes in the function of force-generating proteins in skeletal muscle, impaired excitation-contraction coupling, and fatty infiltration of skeletal muscle [6]. Fatty infiltration of skeletal muscle decreases the contractility of skeletal muscle [31]. Since skeletal muscle and fat have different CT attenuation, measuring the CT attenuation of skeletal muscle can assess the degree of fat infiltration in skeletal muscle [32]. The condition of fat infiltration in skeletal muscle is called myosteatosis, and it has been shown that the presence of myosteatosis is associated with decreased physical performance in the elderly and patients with liver cirrhosis [27,33]. Therefore, we further investigated the difference of CT attenuation among the four groups. The CT values of skeletal muscle were significantly lower in the groups with skeletal muscle abnormalities: dynapenia, pre-sarcopenia, and sarcopenia, compared to the normal skeletal muscle group. Skeletal muscle cell progenitors degenerate into adipocytes [9]; therefore, as skeletal muscle mass decreases, fatty infiltration increases, resulting in a decrease in the CT attenuation of skeletal muscle. However, in addition to the sarcopenia and pre-sarcopenia groups, the dynapenia group also showed low skeletal muscle attenuation. Ectopic deposition of excess lipids in the skeletal muscle is thought to be another possible cause of progression of myosteatosis [34]. Since BMI and visceral fat area are high in patients with dynapenia, excessive lipids and not skeletal muscle mass loss may be a factor in the development of myosteatosis.

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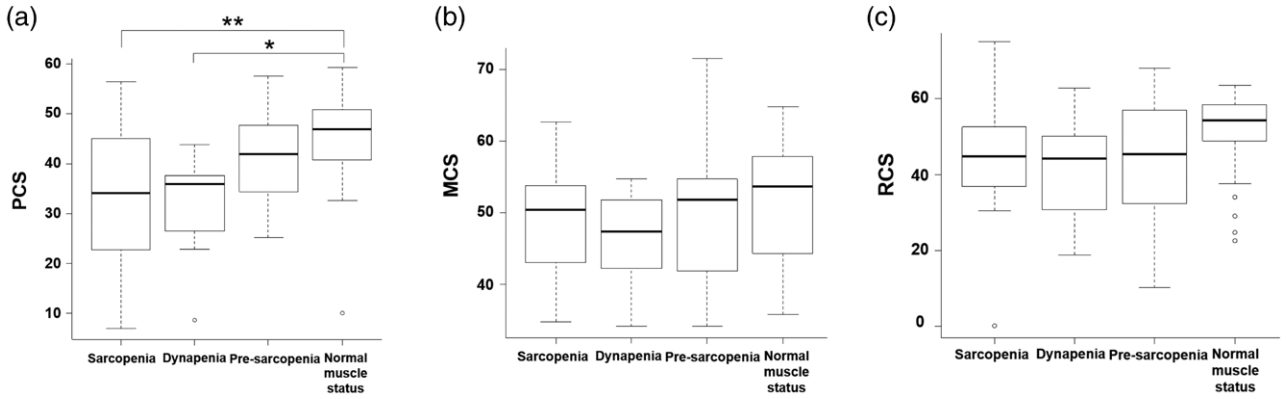

Fig. 2. PCS, MCS, and RCS scores of SF-36 v2 among the four body composition groups (a) PCS scores in patients with dynapenia were as low as that in patient with sarcopenia, and significantly lower than in patients with normal muscle status. *P = 0.002, **P = 0.011. (b) MCS was not significantly different among the four body composition groups. (c) RCS was not significantly different among the four body composition groups. Data were analyzed using the Kruskal–Wallis test, and comparisons between three or more groups were examined using the Bonferroni post-hoc test for multiple comparisons. MCS, mental component summary; PCS, physical component summary; RCS, role-social component summary; SF-36 v2, 36-item Short-Form Health Survey version 2.

AGWS proposed that dynapenia is a preliminary stage of sarcopenia and needs to be properly diagnosed [10]. In assessing skeletal muscle condition, grip strength is the first item to be assessed because it is a simple and reliable method of assessing muscle strength. However, in clinical practice, grip strength measurement in patients with cirrhosis is not always performed. On the other hand, since abdominal CT scans are frequently performed in patients with cirrhosis, many clinical studies on the clinical impact of skeletal muscle status use only CT-derived skeletal muscle mass as an index of skeletal muscle [12]. In patients with dynapenia, although the skeletal muscle was poor quality due to fat infiltration, skeletal muscle mass appeared to be maintained. Therefore, when assessed by skeletal muscle mass alone, dynapenia is considered to represent a normal skeletal muscle status. Based on our results, 64% of the patients with dynapenia had a BMI >25 and myosteatosis. As the prevalence of obesity among patients with cirrhosis has been increasing in recent years [35], it is likely that the number of patients with dynapenia will also increase. Therefore, in the treatment of patients with cirrhosis, BMI and skeletal status should be evaluated, and if obesity and myosteatosis are present, there is a possibility of dynapenia. In such cases, muscle strength should be measured to diagnose the presence of dynapenia.

Once a patient has been diagnosed with dynapenia, appropriate treatment is needed. Treatment for dynapenia is the same as that for sarcopenia: lifestyle interventions with exercise and adequate nutrition are recommended [10,11]. However, based on the results of the current study, the prevalence of obesity is high in patients with dynapenia. Therefore, when providing nutritional therapy to patients with dynapenia, the degree of obesity must be assessed and careful attention must be paid to avoid overnutrition.

Regarding QOL in patients with cirrhosis, the presence of sarcopenia was shown to be associated with poor HRQOL [20]. However, the influence of dynapenia or pre-sarcopenia on QOL has not been reported. The current study showed that physical QOL was poor in patients with dynapenia, which was as high as that seen in patients with sarcopenia. On the other hand, patients with pre-sarcopenia maintained a physical QOL similar to that in individuals with normal muscle status. The recent advent of antiviral drugs against hepatitis C and hepatitis B viruses and anti-cancer treatment for HCC have improved the prognosis of patients with liver disease. Therefore, improvement in QOL has become a more important issue for these patients [36]. Considering our result that the presence of dynapenia was associated with poor QOL, early intervention against dynapenia may improve QOL in patients with cirrhosis.

There are two limitations in this study. First, this was a single-center, retrospective study with a relatively small number of patients. Although dynapenia has been shown to be a poor prognostic factor in the elderly [7], the current study did not examine the association between body composition and prognosis because the number of cases was too small to provide sufficient statistical power. A multicenter, prospective study with larger patient population needs to be conducted in the future to validate our results and clarify the relationship between body composition and prognosis in patients with cirrhosis. Second, a liver disease-specific questionnaire was not used for assessment of HRQOL [37,38]. However, the SF-36 v2 is widely used, reliable, and allows comparison of scores from patients with other diseases and with healthy populations [39]. Therefore, the SF-36 v2 was used to assess HRQOL in the current study.

Conclusion

Dynapenia is found in 12.1% of cirrhotic patients and is characterized by obesity and myosteatosis. Our results indicate that the physical QOL of patients with dynapenia is as low as that of patients with sarcopenia.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest. AQ2

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