Title

Decreased appetite is associated with the presence of sarcopenia in patients with cirrhosis

Running head:

Appetite and sarcopenia in patients with cirrhosis

Yoji Ishizu [1], Masatoshi Ishigami [1], Takashi Honda [1], Norihiro Imai [1], Takanori Ito [1], Kenta Yamamoto [1], Shinya Yokoyama [1], Tetsuya Ishikawa [2], Hiroki Kawashima [1]

[1] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, 466-8550 Japan

[2] Department of Radiological and Medical Laboratory Science, Nagoya University Graduate School of Medicine, 1-1-20 Daiko-Minami, Higashi-ku, Nagoya, 461-8673 Japan

Authorship

YI and MI were involved in the conception and design of the study. YI, MI, TH, NI, TI, KY, SY, TI and HK were involved in generation, collection, assembly, analysis, and interpretation of data. YI and MI were involved in drafting or revision of the manuscript. All the authors read and approved the final version of the manuscript.

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Corresponding Author:

Yoji Ishizu, MD, PhD

Department of Gastroenterology and Hepatology,

Nagoya University Graduate School of Medicine

65 Tsuruma-cho, Showa-ku

Nagoya 466-8550

Japan

Tel: +81-52-744-2169

Fax: +81-52-744-2178

E-mail: y-ishizu@med.nagoya-u.ac.jp

ORCID: 0000-0002-1255-5201

Ethics

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There is no conflict of interest.

Decreased appetite is associated with the presence of sarcopenia in patients with cirrhosis[1]

Abstract

Objective: The relationship between appetite and sarcopenia in patients with cirrhosis is currently unknown. This study aimed to examine the factors associated with decreased appetite and clarify the relationship between appetite and sarcopenia.

Research Methods & Procedures: Sixty-one patients with cirrhosis were included in the study. The patients were asked to describe their appetite using a numerical rating scale (NRS) from 0 (none at all) to 10 (most), with ≤ 5 defined as decreased appetite. The clinical characteristics, gastrointestinal symptoms as assessed using the Gastrointestinal Symptom Rating Scale, handgrip strength, and

[1] Abbreviations:
BCLC: barcelona clinic liver cancer
BIA: bioelectrical impedance analysis
CRP: C-reactive protein
CT: computed tomography
GSRS: gastrointestinal symptom rating scale
HCC: hepatocellular carcinoma
IGF: insulin-like growth factor
MELD: model for end-stage liver disease
NLR: neutrophil-to-lymphocyte ratio
NRS: numerical rating scale
SMI: skeletal muscle index

skeletal muscle area at the third vertebra were collected retrospectively. Sarcopenia was diagnosed according to the criteria of the Japan Society of Hepatology. The differences in these factors between patients with and without decreased appetite, and the factors associated with the presence of sarcopenia were examined.

Results: Alcoholic liver disease was the most common etiology. The median Model for End-Stage Liver Disease score was 8 (interquartile range; 7–10) and hepatocellular carcinoma was present in 35 patients. Overall, 36.1 % of the patients with cirrhosis had decreased appetite. Patients with decreased appetite had a higher frequency of abdominal pain and acid reflux-related symptoms and significantly lower handgrip strength compared to patients without, among both men (P = 0.034) and women (P = 0.017). The multivariate analysis identified a decrease in appetite as a significant factor associated with the presence of sarcopenia (NRS one increase, odds ratio; 0.701, 95% confidence interval; 0.502–0.977, P = 0.036).

Conclusion: Decreased appetite was associated with the presence of sarcopenia.

Keywords: appetite, inflammatory cytokine, gastrointestinal symptoms, grip strength, sarcopenia, cirrhosis

Introduction

The prevalence of sarcopenia in patients with cirrhosis is approximately 40%–70%,[1] and the presence of sarcopenia worsens the prognosis and reduces the quality of life [1,2]. Therefore, it is important to prevent the development of sarcopenia. In addition to increased protein catabolism due to chronic inflammation and increased myostatin due to hyperammonemia, poor nutritional status due to decreased dietary intake is considered to be an important factor in the development of sarcopenia [1]. Therefore, an adequate energy and protein intake is recommended [3]. However, more than half of the patients with cirrhosis do not have sufficient energy intake [4], due partly to decreased appetite [5].

A previous study reported that approximately 20%–30% of the patients with cirrhosis have decreased appetite [6,7]. Several factors are involved in the regulation of appetite, among which inflammation is considered an important factor [8]. Basic research has shown that inflammatory cytokines decrease appetite, either directly in the central nervous system or via leptin, ghrelin, and the vagus nervous system [9]. In addition, gastrointestinal symptoms are more common in patients with cirrhosis than in healthy individuals [10] because of impared peristalsis in the gastrointestinal tract and impaired gastric expansion capacity of the stomach due to ascites [8]. These impairments in gastrointestinal motility lead to a decrease in appetite [8,11]. However, the factors that actually relate to appetite are not fully understood. Furthermore, the relationship between appetite and sarcopenia is

currently unknown. This study aimed to clarify the factors associated with decreased appetite and the relationship between decreased appetite and sarcopenia in patients with liver cirrhosis.

Material and methods

Patients

Among patients with radiologically diagnosed cirrhosis who were admitted to our hospital between May 2017 and March 2018, 61 agreed to participate and were therefore included in this study. Cirrhosis was diagnosed based on the following radiological findings on computed tomography (CT): irregularity of the liver surface, atrophy of the right lobe of the liver, enlargement of the left lobe of the liver, splenomegaly, and the development of collateral vessels of the portal vein. Patients with refractory ascites, uncontrolled hepatocellular carcinoma (HCC), and malignancies other than HCC were not included.

Data collection

Data on blood biochemical tests, image findings, muscle strength, and skeletal muscle mass were collected retrospectively.

The neutrophil-to-lymphocyte ratio (NLR) was used as an index of chronic inflammation [12]. In 41 patients, the TNF-α (R&D Systems Minneapolis, USA) and IL-6 (R&D Systems Minneapolis,

USA) levels were measured using enzyme-linked immune-sorbent assays with sera that were collected on admission and promptly stored at –4°C. Transthyretin and insulin-like growth factor (IGF)-1 levels were measured as indicators of nutrition.

Appetite was assessed subjectively using a numerical rating scale (NRS) [13]. This scale runs from 0 to 10 at equal intervals, with 0 being the case of no appetite and 10 being the case of the highest appetite so far. The patients themselves were asked to circle the points on the scale that corresponded to their appetite state. An NRS of ≤ 5 was defined as decreased appetite. Patients were also asked about whether they had experienced weight loss within 3 months and decreased food intake.

Gastrointestinal symptoms were assessed using the Gastrointestinal Symptom Rating Scale (GSRS). The GSRS was developed to assess gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease [14]. Although there is no established method of assessing gastrointestinal symptoms in patients with cirrhosis, the GSRS has been used to study these symptoms in patients with cirrhosis and has shown a correlation with health-related quality of life, making it a valid method for the assessment of gastrointestinal symptoms [7,10,15]. The GSRS consists of 15 questions designed to assess the impact of upper and lower gastrointestinal symptoms. For each question, a score of 0 is assigned if the patient has few symptoms, and a score of 3 is assigned if the patient has strong symptoms.

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 obtained was used for the analysis [16]. Skeletal muscle mass was assessed using two different parameters: skeletal muscle mass measured using a bioelectrical impedance analysis (BIA) method and the skeletal muscle area at the middle of the third lumber spine vertebra (L3) level on CT images. The BIA for skeletal muscle mass assessment was performed using InBody S10 (InBody Co., Ltd., Seoul, Korea). InBody S10 uses a multi-frequency segmental measurement method with an 8-point tactile electrode. The multi-frequency measurement is conducted using multiple frequencies at 1, 5, 50, 250, 500, and 1,000 kHz for each body segment (the arms, trunk, and legs). The analyzer automatically displays the measurements of body composition. Skeletal muscle area was calculated using the SYNAPSE VINCENT software (version 4.3, Fujifilm Co., Tokyo, Japan), which enables a specific tissue demarcation using HU thresholds. Skeletal muscle was quantified within the HU ranges of –29 to +150 HU [17]. The tissue boundaries were manually corrected as needed. The CT images taken for the evaluation of HCC and/or ascites were also used for the skeletal muscle mass measurements. The SMI based on the BIA assessment was calculated as the amount of appendicular skeletal muscle mass (kg) divided by the square of the height (m^2). The CT-based skeletal muscle index (SMI) was calculated as the total skeletal muscle area (cm^2) divided by the square of the height (m^2).

In accordance with the Asian Working Group for Sarcopenia criteria [16] and the Japan Society of

Hepatology criteria [17], low muscle strength was defined as a handgrip strength < 28 kg for men and < 18 kg for women, BIA-based low skeletal muscle mass as SMI < 7.0 kg/m^2 for men and < 5.7 kg/m^2 for women, and CT-based low skeletal muscle mass as SMI < 42 cm^2/m^2 for men and < 38 cm^2/m^2 for women. Sarcopenia was defined as both low skeletal muscle mass based on CT assessment and low muscle strength.

The mid-arm circumference (cm) and triceps skinfold thickness (cm) of the non-dominant hand were measured, and the mid-arm muscle circumference was calculated using the following formula:

$$mid-arm\ \ circumference\ \ -\ \ (3.14\ \ \times\ \ triceps\ \ skinfold\ \ thickness)$$

Liver function was assessed using the Model for End-Stage Liver Disease (MELD) score [18].

Hyper-attenuated nodules in the arterial phase followed by a washout in the portal or equilibrium phase on contrast-enhanced CT were defined as HCC. The stage of HCC was determined according to the Barcelona Clinic Liver Cancer (BCLC) classification [19].

Statistical Analysis

Quantitative and qualitative variables were compared using the Mann–Whitney U test and Fischer's exact test. Correlations were determined using Spearman's rank correlation. A multiple logistic regression analysis was performed to determine the factors that contributed significantly to the presence of sarcopenia. *P* values of less than 0.05 were considered to indicate statistical significance.

The data were statistically analyzed using EZR on R commander (Version 1.38) [20] and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). The *post hoc* power of the proportion comparison test was estimated using G*Power software [21].

Ethics

Informed consent was obtained from each participant prior to enrollment. The study protocol was approved by the bioethics committee of our institution. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and its later amendments.

Results

Patients' characteristics

The median patient age was 70 years (interquartile range [IQR]; 64.0–75.0 years), and 29 of the patients were women. Alcoholic liver disease was the most common etiology (28 patients), followed by miscellaneous liver diseases, such as autoimmune hepatitis, primary biliary cholangitis, and nonalcoholic steatohepatitis (20 patients) and virus infections including hepatitis C and hepatitis B (13 patients). The median MELD score was 8 (IQR; 7–10), and HCC was present in about half of the patients (35 patients) (Table 1).

Clinical characteristics of patients with decreased appetite

The results of the NRS for appetite, indicating a bimodal pattern with a high frequency of NRS 5 and 8–10 are shown in Figure 1. Decreased appetite was observed in 22 patients (36.1 %). The proportion of females was significantly higher in patients with decreased appetite (68.2 %) than in patients without decreased appetite (35.9%, $P = 0.019$). With regard to the inflammatory markers, the NLR showed a tendency to be higher in patients with decreased appetite, while the TNF-α, IL-6, and C-reactive protein (CRP) levels showed no significant differences between the patients with and without decreased appetite. There were also no significant differences in the age, liver function, or status of HCC between the patients with and without decreased appetite. Patients with decreased appetite had decreased food intake, while there was no significant difference in the frequency of weight loss within 3 months between those with and without decreased appetite (Table 1).

Differences of gastrointestinal symptoms in patients with and without decreased appetite

Patients with decreased appetite scored significantly higher on symptoms such as abdominal pain and acid reflux-related items (heartburn, acid regurgitation, sucking sensations in the epigastrium, and nausea and vomiting), than those without decreased appetite. However, there was no significant difference in the scores for abdominal distension or symptoms related to abnormal bowel movements between patients with and without decreased appetite (Table 2).

Differences in the nutritional and skeletal muscle parameters in patients with and without decreased appetite

Grip strength was significantly lower in patients with decreased appetite than those without, among both men (30.0 kg [27.0–35.0] vs. 33.8 [29.5–36.3], $P = 0.034$) and women (15.5 kg [14.3–16.8] vs. 21.3 [17.3–22.5], $P = 0.017$). The percentage of patients with a low grip strength was significantly higher ($P < 0.001$) in patients with decreased appetite (72.7 %, 16/22) than in those without decreased appetite (25.6 %, 10/39). Regarding skeletal muscle mass, there were no differences in the SMIs between patients with and without decreased appetite, as assessed using both the BIA and CT methods. However, the percentage of decreased skeletal muscle assessed using the CT method mass was 45.5% (10/22) in the group of patients with decreased appetite, which was marginally higher (23.1%, 9/39) than that in those without decreased appetite ($P = 0.089$). Meanwhile, there were no significant differences in the BMI and mid-arm muscle circumferences between patients with and without decreased appetite. Similarly, there were no significant differences in the transthyretin, IGF-1, and albumin levels between the patients with and without decreased appetite (Table 3).

Factors associated with the presence of sarcopenia

Sarcopenia was found in 11 patients (15.9 %). By univariate analysis, increased age, presence of HCC,

and a low NRS for appetite were shown to be associated with the presence of sarcopenia. The multiple logistic regression analysis showed that appetite (NRS one increase, odds ratio [OR]; 0.701, 95% confidence interval [CI]; 0.502–0.977, $P = 0.036$) was significantly associated, while age (one year increase, OR; 1.13, 95% CI; 0.990–1.290, $P = 0.071$) and the presence of HCC in BCLC stage B or C (vs. absence of HCC, OR; 5.92, 95% CI; 0.817–42.9, $P = 0.078$) tended to be associated with the presence of sarcopenia.

Discussion

The present study showed that, in patients with cirrhosis, those with decreased appetite had more abdominal pain and acid reflux-related symptoms and lower grip strength than those without decreased appetite. Moreover, decreased appetite was a factor associated with the presence of sarcopenia.

In the present study, 36.1% of the patients with cirrhosis showed decreased appetite. This result was similar to those of previous reports [6, 7]. Patients with cirrhosis are in a chronic inflammatory state, and their levels of inflammatory cytokines, such as TNF-α and IL-6, are elevated [1]. These inflammatory cytokines are thought to decrease appetite; however, studies on humans have not reached any certain conclusions about the relationship between the inflammatory cytokines and appetite [22], and studies on patients with cancer have not shown an association between TNR-α or IL-6 and appetite [23]. In line with these previous study, the current study showed that no significant association between

inflammatory parameters and appetite was found in patients with cirrhosis.

Next, we examined the relationship between gastrointestinal symptoms and appetite. The results showed that the frequency and severity of abdominal pain and acid reflux-related symptoms, such as heartburn, acid regurgitation, sucking sensations in the epigastrium, nausea, and vomiting, were significantly higher in patients with decreased appetite than in those without decreased appetite. It has been reported that patients with cirrhosis are more prone to symptoms related to acid reflux due to the impaired contraction of gastrointestinal smooth muscles caused by nitric oxide [24], which may lead to greater decreases in appetite in patients with cirrhosis. In addition, while it has been reported that bloating due to ascites may cause decreased appetite [8], the present study did not show any relationship between abdominal bloating and appetite. The reason for this may be that patients with moderate to severe ascites were excluded, and the patients that were included in the study experienced only mild abdominal distention.

Regarding the relationship between nutritional and skeletal muscle parameters and appetite, we found that grip strength was significantly lower in patients with decreased appetite than in those without. Furthermore, decreased appetite was a significant factor that was associated with the presence of sarcopenia. Usually, a decrease in appetite leads to a deterioration in nutritional status, which in turn leads to a decrease in skeletal muscle function. However, there were no differences in serum nutritional and anthropometric parameters. Possible reasons for the lack of differences in these items

are discussed below. Transthyretin, IGF-1, and albumin are commonly used as indicators of nutritional status; however, all of them are synthesized in the liver and are strongly influenced by the liver function. Therefore, these factors are of little value as indicators of the nutritional status in patients with cirrhosis [25]. Anthropometric parameters such as body weight, BMI, and mid-arm muscle circumference are also affected by fluid retention, such as in cases of edema and ascites, which are frequently seen in patients with cirrhosis. Furthermore, skeletal muscle mass measured using the BIA can also be affected by fluid retention [25]. On the other hand, skeletal muscle mass assessment using CT is less susceptible to fluid retention in addition to its accuracy and high reproducibility [26], and skeletal muscle mass assessed using CT is more reliable than anthropometric parameters in the assessment of skeletal muscle mass [27]. Therefore, skeletal muscle mass assessment using CT is recommended in patients with cirrhosis [26]. In the current study, in assessing the skeletal muscle mass using CT, a higher percentage of patients with decreased appetite tended to have low skeletal muscle mass than those without; however, the difference was not significant. The lack of a significant difference in the skeletal muscle mass between the two groups, despite a significant difference in grip strength, may be because muscle strength decreases faster and to a greater extent than skeletal muscle mass during the development of sarcopenia [28]. More cases need to be investigated to clarify the relationship between decreased appetite and skeletal muscle mass loss.

In patients with cirrhosis, several factors are thought to cause sarcopenia, including protein

catabolism due to chronic inflammation; decreased IGF-1levels; increased levels of myostatin; and decreased appetite [1]. However, the association of these factors with sarcopenia has not yet been fully investigated. In the current study, chronic inflammatory markers, such as the NLR, C-reactive protein levels, and TNF-α levels, and IGF-1 levels showed no association with the presence of sarcopenia. Although myostatin levels were not measured in our study, ammonia is reported to increase in proportion with the expression of myostatin [1]. Therefore, we examined the difference in ammonia levels in patients with and without sarcopenia, but found no significant difference. Finally, only decreased appetite was shown to be significantly associated with the presence of sarcopenia.

At present, the only established treatments for sarcopenia are exercise and nutritional therapy, and drug treatment approaches have not yet reached clinical application. Therefore, new agents for sarcopenia are being actively developed, and ghrelin is one of the targets for therapeutic drug development [29]. Similar to patients with cirrhosis, decreased appetite is often observed in patients with cancer cachexia, and one of the factors common to both patient groups is decreased ghrelin levels [30,31]. Recently, in studies of patients with cancer cachexia, anamorelin, an agonist at the receptor for ghrelin, has been reported to improve appetite as well as increase lean body mass and BMI [32,33]. Since our study showed that decreased appetite is associated with the presence of sarcopenia, it is expected that in the future, the development of therapies targeting appetite will improve sarcopenia in patients with cirrhosis.

This study had some limitations. First, it was a single-center, retrospective study with a relatively small number of patients. Therefore, the generalizability of the results is limited. Second, as it was an exploratory study, it was not possible to set an appropriate sample size. Therefore, a *post-hoc* power analysis was performed, with the power being 71 % in males and 67.4 % in females. Based on these results, studies with larger patient populations need to be conducted to validate our findings.

Conclusions

Decreased appetite was observed in 36.1 % of the patients with cirrhosis and was a factor associated with the presence of sarcopenia.

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Tables

Table 1. Patients' characteristics

	Total patients (n = 61)	**Patients with decreased appetite (n = 22)**	**Patients without decreased appetite (n = 39)**	***P* value***
Age (years)	70.0 (64.0–75.0)	69.5 (65.3–75)	70.0 (63.0–75)	0.604
Sex (female/male)	29/32	15/7	14/25	0.019
Etiology (Alcohol/virus hepatitis/others)	28/13/20	9/3/10	19/10/10	0.275
MELD score	8 (7–10)	8 (7–11)	9 (7–11)	0.903
Ascites (none/mild/moderate)	37/14/10	12/6/4	25/8/6	0.750
Status of HCC (no/BCLC stage A/ BCLC stage B or C)	26/20/15	9/7/6	17/13/9	0.944
C-reactive protein levels (mg/dL)	0.14 (0.04–0.33)	0.17 (0.05–0.58)	0.14 (0.035–0.30)	0.411
Neutrophil-to-lymphocyte ratio	2.42	3.08	2.07	0.070

	(1.64–3.50)	(1.88–3.69)	(1.58–3.01)	
Tumor necrosis factor-α levels**	0.77	0.96	0.69	0.289
(pg/mL)	(0.50–1.15)	(0.58–1.27)	(0.49–1.10)	
Interleukin-6 levels (pg/mL)**	6.68	8.76	5.42	0.301
	(2.26–11.3)	(4.04–10.6)	(1.98–12.6)	
Body mass index (kg/m^2)	22.4	22.1	22.4	0.771
	(19.8–25.7)	(19.6–25.9)	(20.5–25.0)	
Decrease in food intake	16/41	12/10	4/31	< 0.001
(present/absent) ***				
Body weight loss within	8/49	5/17	3/32	0.239
3 months (present/absent) ***				

*P values for difference between patients with and without decreased appetite.

**Data were available for 41 patients.

*** Data were available for 57 patients.

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease

Data are expressed as medians (interquartile ranges).

Table 2. Differences in the gastrointestinal symptoms of patients with and without decreased appetite

Gastrointestinal symptoms	**Patients with decreased appetite (n = 22)**	**Patients without decreased appetite (n = 39)**	***P* value**
Abdominal pains (0/1/2/3)	15/4/3/0	35/3/1/0	0.034
Heartburn (0/1/2/3)	14/4/4/0	38/1/0/0	< 0.001
Acid regurgitation (0/1/2/3)	15/6/1/0	37/2/0/0	0.005
Sucking sensations in the epigastrium (0/1/2/3)*	14/5/2/0	35/4/0/0	0.024
Nausea and vomiting* (0/1/2/3)	15/4/2/0	37/2/0/0	0.010
Borborygmus (0/1/2/3)	13/8/1/0	31/5/3/0	0.138
Abdominal distension (0/1/2/3)	13/4/2/3	27/9/2/1	0.272
Eructation* (0/1/2/3)	14/6/1/0	33/6/0/0	0.100
Increased flatus (0/1/2/3)	9/10/2/1	22/14/2/1	0.229
Decreased passage of stools* (0/1/2/3)	16/2/0/0	28/3/1/0	0.872

Increased passage of stools* (0/1/2/3)	16/5/0/0	29/10/0/0	0.885
Loose stools* (0/1/2/3)	13/8/0/0	32/6/1/0	0.108
Hard Stools* (0/1/2/3)	18/2/0/0	25/4/1/1	0.352
Urgent need for defecation (0/1/2/3)	10/12/0/0	22/16/1/0	0.485
Feeling of incomplete evacuation* (0/1/2/3)	12/7/2/0	24/14/0/1	0.627

* Items for which some patients did not respond to the question.

Data were presented using a rating scale (0/1/2/3).

Table 3. Differences in the nutritional and skeletal muscle parameters of patients with and without decreased appetite

	Patients with decreased appetite (n = 22)	Patients without decreased appetite (n = 39)	*P* value
Anthropometric parameters			
Body mass index (kg/m^2)			
Male	22.4 (21.7–23.4)	22.7 (21.1–24.3)	0.859
Female	21.1(19.4–26.0)	21.7 (19.3–25.5)	0.949
Mid-arm muscle circumference (cm)			
Male	28.0 (26.3–28.5)	26.4 (24.4–30.1)	0.523
Female	25.5 (23.4–30.0)	24.8 (23.3–28.4)	0.712
Skeletal muscle parameters			
Grip strength (kg)			
Male	30.0 (27.0–35.0)	33.8 (29.5–36.3)	0.034
Female	15.5 (14.3–16.8)	21.3 (17.3–22.5)	0.017
Low grip strength (present/absent)	16/6	10/29	< 0.001

Skeletal muscle index (kg/m^2) using BIA*			
Male	7.12 (6.35–7.70)	7.35 (7.03–8.16)	0.317
Female	5.72 (5.33–5.98)	6.25 (5.54–6.63)	0.243
Low skeletal muscle mass using the BIA (present/absent)	9/11	9/28	0.140
Skeletal muscle index (cm^2/m^2) using CT			
Male	45.2 (42.3–55.4)	45.1 (42.0–50.6)	0.755
Female	37.4 (33.9–41.7)	42.3 (35.8–44.5)	0.331
Low skeletal muscle mass using CT (present/absent)	10/12	9/30	0.089
Serum nutritional parameters			
Insulin-like growth factor-1 (ng/mL)	41.0 (31.5–51.5)	46.5(35.0–66.0)	0.361
Transthyretin (mg/dL)	10.5 (7.9–13.4)	21.1 (8.90–16.1)	0.279
Albumin (g/dL)	3.3 (2.9–3.6)	3.5 (3.0–3.9)	0.359

* Data were available for 57 patients.

BIA; bioimpedance analysis, CT; computed tomography

Data are expressed as medians (interquartile ranges).

Table 4. Factors associated with the presence of sarcopenia

Variables	Univariate analysis			Multivariate analysis		
	Patients with sarcopenia (n = 11)	**Patients without sarcopenia (n = 50)**	***P* value**	**OR**	**95% CI**	***P* value**
Age	74.0 (71.0–78.0)	69.0 (62.3–73.8)	0.021	1.13	0.990–1.290	0.071
Sex (female/male)	8/3	21/29	0.096			
MELD score	7.00 (6.50–9.00)	9.00 (7.00–10.8)	0.125			
IGF-1 levels (ng/mL)	48.5 (35.8–57.8)	43.0 (34.0–63.0)	0.977			
CRP levels (mg/dL)	0.055 (0.035–0.583)	0.160 (0.043–0.330)	0.551			
TNF-α levels (pg/mL)	0.866 (0.549–1.149)	0.754 (0.499–1.144)	0.745			
Ammonia levels	48.0	3.0	0.464			

(μg/dL)	(38.5–51.5)	(40.3–78.0)				
Ascites (absence)	6	31	0.516			
vs. mild	4	10				
vs, moderate	1	9				
Status of HCC	2	24	0.043	Reference		
(absence)						
vs. BCLC stage A	3	17		1.53	0.199–11.7	0.683
vs. BCLC stage B or C	6	9		5.92	0.817–42.9	0.078
Appetite (NRS)	5.00	8.00	0.016	0.701	0.502–0.977	0.036
	(4.00–6.00)	(5.00–9.00)				
Decrease in food intake						
(present/absent) *	5/6	11/35	0.260			
Body weight loss within 3 months						
(present/absent) *	2/9	6/40	0.644			

* Data were available for 57 patients.

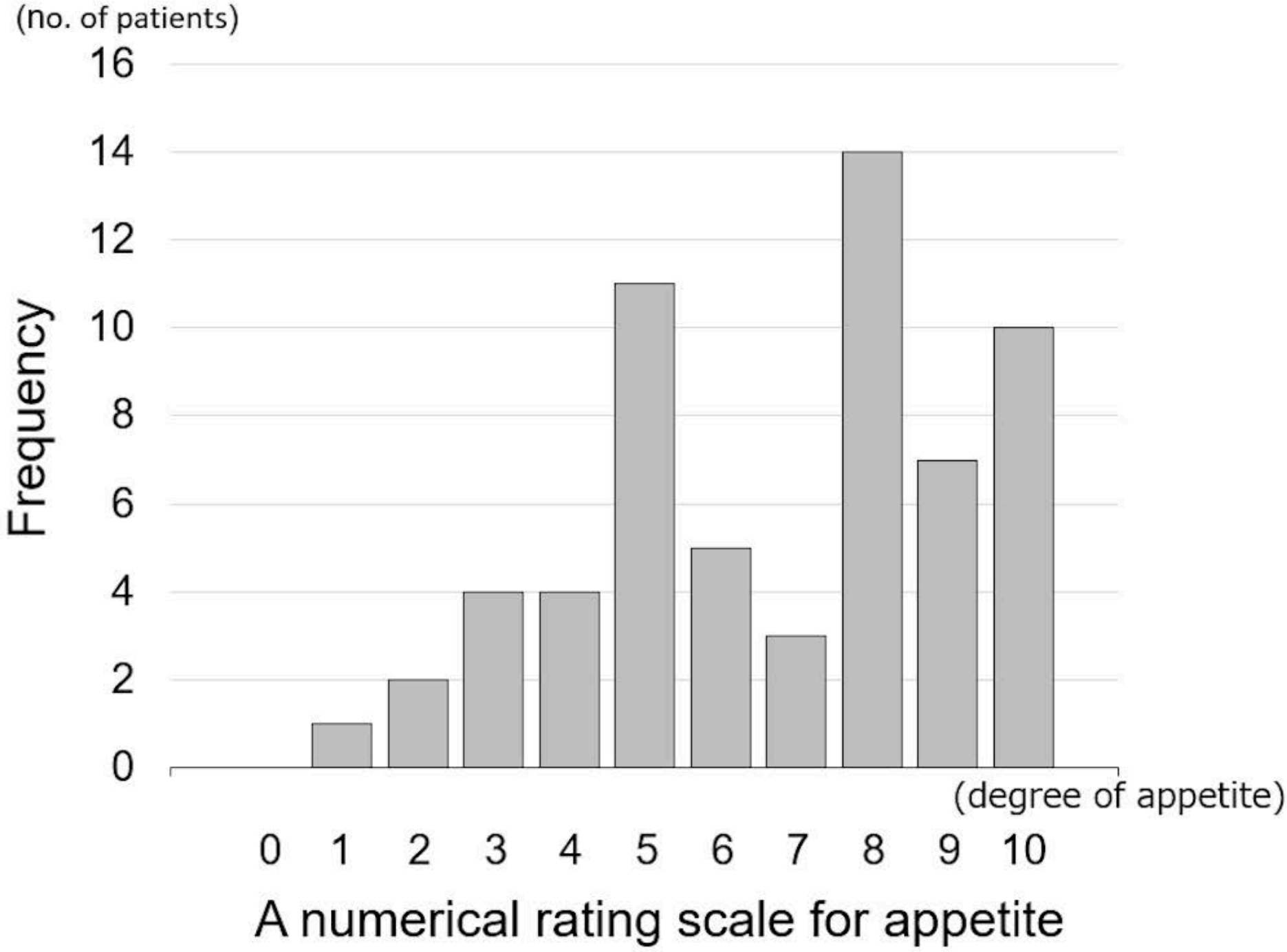
BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CRP, C-reactive protein; HCC, hepatocellular carcinoma; IGF-1, insulin-like growth factor-1; MELD, model for end-stage liver disease; NRS, numerical rating scale; OR, odds ratio; TNF, tumor necrosis factor

Data were expressed as median (interquartile range).

Figure legends

Figure 1. The results of a numerical rating scale for appetite

The numbers 0–10 on the horizontal axis represent the degree of appetite, with 0 representing no appetite and 10 representing the most appetite ever. The vertical axis represents the number of patients in each degree of appetite.


(no. of patients)
16
14
12
10
8
6
4
2
0
Frequency
(degree of appetite)
0 1 2 3 4 5 6 7 8 9 10
A numerical rating scale for appetite