ORIGINAL ARTICLE

Profiles Associated with Sarcopenia in Hepatoma Patients Underwent Transcatheter Arterial Chemoembolization: A Data-Mining Analysis

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Abstract

Aims Sarcopenia is a prognostic factor in patients with hepatocellular carcinoma (HCC). Transcatheter arterial chemoembolization (TACE) may aggravate sarcopenia because of post-embolization syndrome. The aims of this study are to investigate changes in skeletal muscle mass after TACE and its risk profiles in patients with HCC.

Methods and results We enrolled 104 HCC patients (age 73.5 [41.0-88.0] years, female/male 35/69, body mass index 22.4 [16.0-32.7]). Changes in skeletal muscle mass were evaluated by Δskeletal muscle index (SMI) using computed tomography before and after TACE. Factors correlated with ΔSMI were evaluated. Independent factors and profiles associated with a decrease in SMI were evaluated by multivariate analysis and decision-tree analysis, respectively. SMI was significantly decreased after TACE in patients with HCC (32.8 vs. 30.6 cm^2/m^2; P=0.0001). However, there was no significant correlation between the ΔSMI and other variables including Δalbumin. In the logistic regression analysis, no factor was significantly associated with a decrease in SMI. In the decision-tree analysis, sex was selected as the initial split and, in female, 74% of subjects showed a decrease in SMI. While, in male, an estimated glomerular filtration rate (eGFR) ≤81.7 ml/min/1.73 m^2 was the second split; of these patients, 74% of subjects had a decreased SMI.

Conclusions We demonstrated that skeletal muscle mass was decreased after TACE in patients with HCC. “female” and “male who had a lower eGFR” were profile for a decrease in skeletal muscle mass. Thus, such patients who have HCC treated with TACE may benefit from preventive treatment for sarcopenia.

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Keywords: Muscle mass, Hepatocellular carcinoma, Transcatheter arterial chemoembolization, Data-mining analysis

Received 03 May 2018 **Accepted** 04 July 2018

Introduction

Sarcopenia is the decline of skeletal muscle mass, muscle strength, and physical performance [1]. The prevalence of sarcopenia has regional and age-related variations and has been reported to be 1-29% in community-dwelling populations, 14-33% in long-term care populations, and 10% in acute care hospital populations [2]. Sarcopenia can lead to loss of independence, poor quality of life, and high mortality in elderly populations [3]. In addition, sarcopenia is associated with the pathogenesis of various diseases as well as prognosis and quality of life.

Sarcopenia is classified by its etiology into primary or secondary sarcopenia. Primary sarcopenia is a phenomenon of age-related loss of muscle mass and function, affecting up to 30% of older adults [4]. Secondary sarcopenia is the reduced muscle mass and strength that accompanies an underlying disease. The inflammatory muscle wasting of cancer, cardiac, and rheumatoid cachexia is secondary sarcopenia, which is driven by catabolic processes [4]. In patients with chronic liver disease (CLD), sarcopenia frequently occurs and is seen in 33.2%, 42.7%, and 57.8% of patients with chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC), respectively [5, 6]. Sarcopenia affects not only the activities of daily living but also the prognosis of patients with cirrhosis or HCC [7-9].

Transcatheter arterial chemoembolization (TACE) is a therapeutic strategy for HCC. The most frequent adverse events of TACE are the typical features of post-embolization syndrome, such as pain, fever, nausea, and vomiting [10]. These adverse events may cause reduced energy intake and physical activity, resulting in loss of skeletal muscle mass. Thus, patients with HCC who are treated with TACE are thought to be at

high risk for loss of skeletal muscle mass; however, the impact of TACE on skeletal muscle mass remains unclear in patients with HCC.

The aim of this study is to investigate changes in skeletal muscle mass in patients with HCC treated with TACE. In addition, we investigated the profiles associated with the depletion of skeletal muscle mass.

Patients and Methods

Study design

This study was a retrospective observational study that aimed to investigate changes in skeletal muscle mass and its risk factors in patients with HCC who underwent TACE.

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 March 2013 to June 2015, we enrolled 104 consecutive patients who met our inclusion and exclusion criteria. Inclusion criteria were patients with CLD and HCC who (1) were 20 years of age or more, (2) had a performance status of grade 0 to 2 as defined by the Eastern Cooperative Oncology Group [11], (3) had been treated with TACE, and (4) had undergone biochemical examination and abdominal computed tomography (CT) scans including the third lumbar vertebra level (L3) before and after TACE. Exclusion criteria were patients with HCC who (1) were undergoing a rehabilitation or exercise program, (2) had a performance status of grade 3 or more, (3) had refractory ascites, (4) had severe heart, pulmonary, renal, or brain failure, (5) had inflammatory diseases, (6) had other malignancy, (7) had endocrine diseases, (8) had malabsorption, or (9) had gastrointestinal disease.

Laboratory determinations

Venous blood samples were drawn in the morning after a 12-h overnight fast. Red blood cell count, hemoglobin, white blood cell count, lymphocytes, prothrombin activity, and serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total protein, albumin, total bilirubin, direct bilirubin, total cholesterol, triglycerides, alpha-fetoprotein (AFP), des-γ-carboxy prothrombin, blood urea nitrogen (BUN), creatinine, uric acid, sodium, potassium, chloride, cholinesterase, and creatine kinase were measured using standard clinical methods as previously described [12, 13]. The AST to platelet ratio index and Fib-4 index were calculated as previously described [14, 15]. The estimated glomerular filtration rate (eGFR) was also calculated as previously described [16].

Evaluation of skeletal muscle mass

Skeletal muscle mass was measured by diagnostic CT scans at L3 as previously described [5, 17, 18]. The CT scans used for analysis were carried out as part of the HCC assessment. Skeletal muscle mass was evaluated by the psoas muscle index (PMI) and the skeletal muscle index (SMI), which were calculated by normalizing the L3 psoas muscle area and L3 skeletal muscle areas by the square of the height (m^2) [9, 18], respectively. The muscles 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 [19]. Enrolled patients were classified into the muscle atrophy or non-muscle atrophy groups according to changes in SMI between before and after TACE.

Evaluation of visceral fat area (VFA)

VFA was measured as previously described [20]. Briefly, the VFA was measured by diagnostic CT scanning at the umbilical level [21]. CT scanning was performed for HCC evaluation. The VFA was measured by the diagnostic software ImageJ [19].

Changes in skeletal muscle mass, VFA, and biochemical examinations

Changes of skeletal muscle mass and VFA were evaluated by the differences in PMI, SMI, and VFA between before and after TACE (ΔPMI, ΔSMI, and ΔVFA, respectively). Similarly, changes in each biochemical examination were evaluated by the Δvariable.

Diagnosis, tumor node metastasis (TNM) staging, and treatment of HCC

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 TNM staging based on the Liver Cancer Study Group of Japan criteria [22]. The treatment for HCC was selected based on the evidence-based clinical practice guidelines for HCC of The Japan Society of Hepatology [23].

Statistical analysis

Data are expressed as the median (interquartile range [IQR]), range, or number. Changes in SMI between before and after TACE were evaluated by Wilcoxon signed rank tests. Differences between the two groups were analyzed by using Wilcoxon rank sum tests. Factors correlated with ΔSMI were evaluated by pairwise correlations [24]. Independent factors associated with a decrease in SMI were evaluated by multivariate stepwise analysis [25]. In addition, a decision-tree analysis was performed to identify the profiles associated with a decrease in SMI [26]. The level of statistical significance was set at $P<0.05$.

Results

Patient characteristics

The patient characteristics are summarized in Table 1. The median age was 73.5 years, and the ratio of female to male was 1:1.97 (35:69). The median body mass index (BMI) was 22.4 kg/m^2. TNM stage II and stage III were seen in 32.7% (34/104) and 28.8% (30/104) of patients, respectively. The median period of hospitalization was 14.5 days (range: 8-65 days).

The median level of SMI before TACE was 26.5 cm^2/m^2 in female patients and 36.6 cm^2/m^2 in male patients (Table 1). Branched-chain amino acid (BCAA) supplementation was administered to 57.7% (60/104) of enrolled patients. Patients diagnosed with muscle atrophy accounted for 81.7% (85/104) of enrolled patients according to the Japan Society of Hepatology guideline (Table 1).

The median level of ALT, albumin, prothrombin activity, total bilirubin, and eGFR was 34.0 IU/L, 3.4 g/dL, 78.0%, 0.9 mg/dL, and 74.5 mL/min/1.73 m^2, respectively. The median AST to platelet ratio index and Fib-4 index were 1.55 and 6.18, respectively (Table 1).

Table 1 Patient characteristics

	Reference Value	Median (IQR)	Range (min–max)
Number	N/A	104	N/A
Age (years)	N/A	73.5 (67.0–78.0)	41.0–88.0
Sex (female/male)	N/A	35/69	N/A
Body mass index (kg/m^2)	18.5–24.9	22.4 (20.7–24.7)	16.0–32.7
TNM stage (I/II/III/IVa)	N/A	6/34/30/10	N/A
Etiology of liver disease (HCV/HBV/Alcohol/NASH/AIH)		84/3/13/3/1	
Hospitalization (days)	N/A	14.5 (13.0–20.8)	8.0–65.0
PMI (cm^2/m^2)	N/A	5.0 (3.7–6.0)	1.9–10.7
SMI (cm^2/m^2)	N/A	32.8 (24.8–39.8)	13.8–60.7
SMI (female/male) (cm^2/m^2)	N/A	26.5 (22.9–30.8)/36.6 (27.7–42.1)	13.8–41.9 /17.9–60.7
VFA (cm^2)	N/A	45.5 (28.1–74.2)	5.0–193.1
BCAA supplementation (Yes/No)	N/A	60/44	N/A
Presence of muscle atrophy according to the Japan Society of Hepatology guideline	N/A	81.7% (85/104)	N/A
Biochemical examinations			
Red blood cell count (×10^4/μL)	435–555	385 (353–434)	207–515

Hemoglobin (g/dL)	13.7–16.8	12.1 (10.7–13.0)	7.1–16.4
White blood cell count (/μL)	3300–8600	3,650 (2725–4700)	1700–9100
Lymphocytes (%)	30.0–43.0	29.7 (21.0–35.2)	3.3–61.6
Platelet count (x 10^3/mm^3)	15.8–34.8	10.8 (6.9–15.2)	2.8–24.4
AST (IU/L)	13–30	47 (34.3–65.8)	14.0–177.0
ALT (IU/L)	10–30	34 (23.3–52.8)	7.0–101.0
Lactate dehydrogenase (IU/L)	119–229	231 (201.3-276.8)	118.0—498.0
ALP (IU/L)	115–359	373 (288.0–531.8)	52.0–1489.0
GGT (IU/L)	13–64	42 (27.0–86.0)	12.0–395.0
Total protein (g/dL)	6.6–8.1	7.2 (6.9–7.6)	5.7–9.4
Albumin (g/dL)	4.1–5.1	3.4 (3.1–3.7)	2.3–4.5
Cholinesterase (U/L)	201–421	150 (95–206)	36–418
Prothrombin activity (%)	80–120	78.0 (63.0–92.0)	14.6–126.0
Total bilirubin (mg/dL)	0.40–1.20	0.9 (0.7–1.3)	0.3–5.0
Total cholesterol (mg/dL)	142–219	147 (127–171)	80–254
Triglyceride (mg/dL)	40–149	87 (62–125)	32–271
Child-Pugh class (A/B/C)	N/A	66/39/4	N/A
AFP (ng/mL)	≤7.0	26.3 (8.1–120.5)	1.3–22385.0
Des-γ-carboxy prothrombin (mAU/mL)	<40	138 (29.3–2056.8)	9.0–745283.0
BUN (mg/dL)	8.0–20.0	16.1 (13.3–20.0)	9.0–31.2
Creatinine (mg/dL)	0.65–1.07	0.73 (0.6–.0.9)	0.3–8.5
eGFR (mL/min/1.73 m^2)	> 90.0	74.5 (58.4–93.9)	5.5–156.7
Uric acid (mg/dL)	2.30–7.00	5.1 (4.3–6.2)	2.5–19.1
Sodium (mmol/L)	138–145	140 (139–142)	121–146
Potassium (mmol/L)	3.6-4.8	3.9 (3.6–4.3)	2.9–6.5

Chloride (mmol/L)	101–108	106 (104–108)	82–112
Creatine kinase (U/L)	59–248	129 (78–170)	34－386
Blood glucose (mg/dL)	80–109	110 (95–135)	60–258
HbA1c (%)	4.3–5.8	5.6 (5.2–6.3)	4.4–8.0
Ammonia (μg/dl)	12–66	54 (42-78)	14–205
APRI		1.55 (0.90-2.79)	0.19－14.4
Fib-4 index		6.18 (3.53-9.79)	1.27－30.24

Note. Data are expressed as median (interquartile range [IQR]), range, or number. Abbreviations: N/A, not applicable; TNM, tumor node metastasis; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; AIH, autoimmune hepatitis; PMI, psoas muscle index; SMI, skeletal muscle index; VFA, visceral fat area; BCAA, branched-chain amino acids; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AFP, alpha-fetoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; APRI, AST to platelet ratio index

Differences in variables between before and after TACE

During the period of hospitalization, no patients underwent rehabilitation or exercise. Table 2 summarizes the differences in BMI and biochemical examinations between before and after TACE. BMI was significantly decreased after TACE compared to that before TACE (Table 2). There was no significant change in PMI or VFA between before and after TACE (Fig. 1A and C). However, a significant decrease was seen in SMI after TACE compared to that before TACE (Fig. 1B). Serum levels of albumin and cholinesterase and eGFR value were significantly decreased after TACE compared to those before TACE. No change was seen in prothrombin activity, serum total bilirubin level, or blood ammonia level between before and after TACE (Table 2).

Table 2. Differences in body composition, muscle mass, and biochemical examinations between before and after TACE

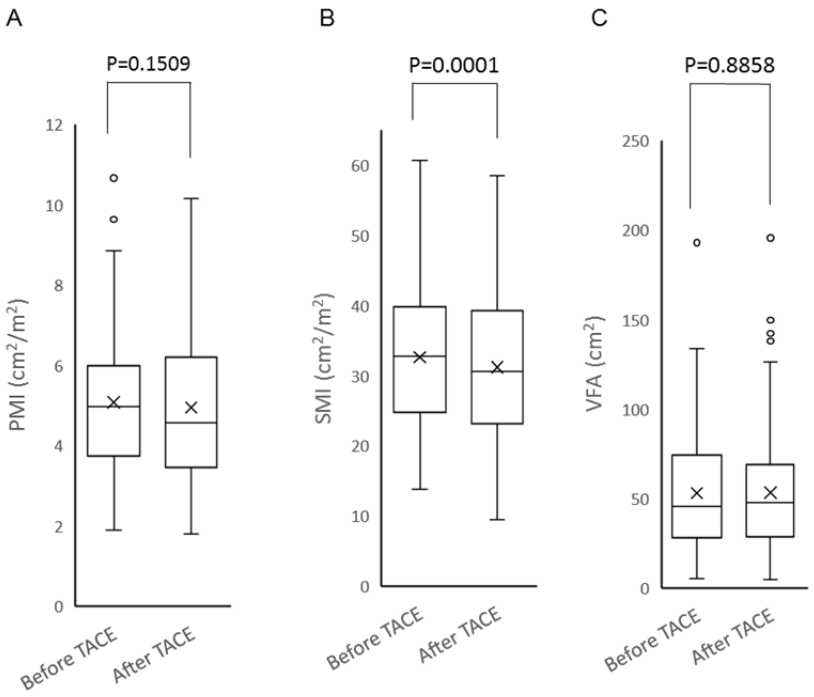
	Before TACE		After TACE		
	Median (IQR)	Range (min–max)	Median (IQR)	Range (min–max)	P
Body mass index (kg/m^2)	22.4 (20.7–24.7)	16.0–32.7	22.2 (20.0–24.5)	16.0–31.1	0.0002
Red blood cell count (×10^4/μL)	385.5 (353.3–423.8)	207.0–515.0	355 (320.3–395.8)	247.0–520.0	<0.001
Hemoglobin (g/dL)	12.1 (10.7–13.0)	7.1–16.4	11.2 (9.9–12.4)	6.6–16.3	<0.001
White blood cell count (/μL)	3650 (2725–4700)	1700–9100	4100 (3025–5400)	1400–15800	0.0034
Lymphocytes (%)	29.7 (21.0–35.2)	3.3–61.6	24.3 (19.7–31.4)	8.7–50.6	<0.001
Platelet count (x 10^3/mm^3)	10.8 (6.9–15.2)	2.8–24.4	10.6 (7.4–14.1)	0.3–37.7	0.0138
AST (IU/L)	47.0 (34.3–65.8)	14.0–177.0	46.0 (33.0–68.3)	15.0–206.0	0.7667
ALT (IU/L)	34.0 (23.3–52.8)	7.0–101.0	41.0 (26.0–61.0)	4.0–240.0	0.0591
Lactate dehydrogenase (IU/L)	231.0 (201.3–276.8)	118.0–498.0	205.0 (181.8–231.5)	91.0–427.0	<0.001
ALP (IU/L)	373.0 (288.0–531.8)	52.0–1489.0	344.5 (281.8–461.5)	64.0–1360.0	0.0312
GGT (IU/L)	42.0 (27.0–86.0)	12.0–395.0	42.0 (28.0–86.0)	13.0–346.0	0.9000
Total protein (g/dL)	7.2 (6.9–7.6)	5.7–9.4	6.6 (6.2–7.0)	5.2–8.2	<0.001
Albumin (g/dL)	3.4 (3.1–3.7)	2.3–4.5	3.0 (2.7–3.3)	2.2–4.0	<0.001
Cholinesterase (U/L)	150 (96–206)	36–418	103 (71–173)	1–356	<0.001
Prothrombin activity (%)	78.0 (63.0–92.0)	14.6–126.0	73.0 (63.0–85.0)	29.0–117.0	0.1232

Total bilirubin (mg/dL)	0.94 (0.70–1.30)	0.3–.5.0	0.90 (0.60–1.20)	0.3–4.4	0.0530
Total cholesterol (mg/dL)	147 (127–171)	32–271	118 (114–166)	93–188	0.1403
Triglyceride (mg/dL)	87 (62–125)	80–254	59 (50–83.5)	30–106	0.0873
BUN (mg/dL)	16.1 (13.3–20.1)	9.0–31.2	15.0 (11.6–18.6)	7.5–47.3	0.2224
Creatinine (mg/dL)	0.73 (0.60–0.91)	0.35–1.92	0.71 (0.58–0.85)	0.06–1.93	0.0414
eGFR (mL/min/1.73 m^2)	74.5 (58.4–93.9)	5.5–156.7	75.8 (59.9–93.2)	26.9–145.0	0.0192
Uric acid (mg/dL)	5.1 (4.3–6.2)	2.5–19.1	3.91 (3.3–5.5)	2.5–7.2	0.0528
Sodium (mmol/L)	140 (139–142)	121–146	139 (137–141)	130–146	0.7735
Potassium (mmol/L)	3.9 (3.6–4.3)	2.9–6.5	4.2 (4.0–4.5)	3.1–5.5	0.3767
Chloride (mmol/L)	106 (104–108)	82–112	104 (102–107)	88–112	0.6667
Direct bilirubin (mg/dL)	0.13 (0.09–0.25)	0.05–2.94	0.12 (0.07–0.23)	0.05–1.00	0.0645
Blood glucose (mg/dL)	110 (95–135)	60–258	96 (86.3–117)	64–192	0.0168
Creatine kinase (U/L)	129 (77.8–170.0)	34.0–386.0	43 (29–70)	18–312	0.0912
Ammonia (μg/dL)	54.0 (42.0–74.8)	14.0–205.0	50.5 (31.0–69.8)	10.0–146.0	0.0728

Note. Data are expressed as median (interquartile range [IQR]), range, or number.
Abbreviations: TACE, transcatheter arterial chemoembolization; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate

Figure 1 Changes in (A) PMI, (B) SMI, and (C) VFA before and after TACE.

Figure 1



Differences in baseline characteristics between the muscle atrophy and non-muscle atrophy groups

Enrolled patients were classified into the muscle atrophy or non-muscle atrophy groups according to changes in the SMI between before and after TACE. Table 3 summarizes the differences in baseline characteristics between the muscle atrophy and non-muscle atrophy groups. There was no significant difference in age between the 2 groups (Table 3). In addition, there was no significant difference between the 2 groups in BMI, VFA, PMI, or SMI. No significant differences were seen in TNM stage or hospitalization period (Table 3). Moreover, there was no significant difference in prothrombin activity, eGFR, or serum levels of ALT, albumin, or total bilirubin (Table 3)

Table 3 Differences in baseline characteristics between the muscle atrophy and muscle non-atrophy group

	Muscle atrophy		Muscle non-atrophy		
	Median (IQR)	Range (min–max)	Median (IQR)	Range (min–max)	P
Number	68	N/A	36	N/A	N/A
Age (years)	74 (66–78)	41–88	74 (69–77)	50–83	0.6813
Body mass index (kg/m^2)	22.0 (20.5–24.7)	17.2–32.7	22.5 (21.2–24.7)	16.0–27.2	0.9394
VFA (cm^2)	42.4 (28.1–83.1)	5.5–193.1	48.2 (27.9–65.3)	5.0–90.1	0.6447
PMI (cm^2/m^2)	4.9 (3.7–6.2)	1.9–10.7	5.1 (3.7–5.9)	2.2–8.3	0.8510
SMI (cm^2/m^2)	33.0 (26.3–40.1)	13.8–60.7	30.9 (22.6–39.2)	14.6–57.0	0.3302
TNM stage (I/II/III/IVa/IVb)	6/27/27/3/5	N/A	1/13/19/3/0	N/A	0.1479
Etiology of liver disease (HCV/HBV/Alcohol/NASH/AIH/Others)	57/2/5/3/1	N/A	84/3/13/3/1	N/A	0.1642
Hospitalization period (days)	15 (13–19)	8–38	14 (11–25)	9–65	0.8369
Evaluation period for CT imaging (days)	53 (34–84)	7–309	49 (32–82)	9–211	0.5893
BCAA-related agents (Yes/No)	41/27	N/A	19/17	N/A	0.4604
Child-Pugh class (A/B/C)	41/24/3	N/A	21/14/1	N/A	0.8355
Red blood cell count ($\times 10^4/\mu L$)	383 (349–424)	302–511	391 (364–437)	207–515	0.5799
Hemoglobin (g/dL)	12.2 (10.6–13.0)	7.3–15.8	12.0 (10.9–13.1)	7.1–16.4	0.9482

White blood cell count (/μL)	3550 (2700–4475)	1700–8300	3850 (3025–5375)	2100–9100	0.1360
Lymphocytes (%)	29.7 (21.1–35.0)	11.9–53.4	29.5 (21.0–36.9)	3.3–61.6	0.8670
Platelet count (x 10^3/mm^3)	9.45 (6.9–15.4)	2.8–24.4	11.6 (6.9–14.6)	4.3–21.4	0.6994
AST (IU/L)	46.5 (32.0–67.8)	14.0–177.0	47.5 (39.3–58.5)	23.0–124.0	0.5728
ALT (IU/L)	34.0 (21.3–58.5)	7.0–101.0	33.5 (25.3–49.8)	14.0–89.0	0.9021
Lactate dehydrogenase (IU/L)	231.0 (206.3–276.3)	118.0–498.0	239.5 (186.0–279.0)	145.0–389.0	0.8644
ALP (IU/L)	371.5 (294.5–520.8)	144.0–1489.0	377.0 (270.5–578.3)	52.0–1265.0	0.9184
GGT (IU/L)	44 (30–71)	12.0–395.0	35.0 (27.0–118.0)	14.0–320.0	0.8837
Total protein (g/dL)	7.25 (6.9–7.6)	6.2–9.4	7.1 (6.9–7.6)	5.65–8.59	0.5163
Albumin (g/dL)	3.4 (3.1–3.7)	2.4–4.5	3.4 (3.0–3.6)	2.3–4.1	0.6012
Cholinesterase (U/L)	158 (107–220)	36–418	137 (91–203)	47–367	0.4748
Prothrombin activity (%)	78.5 (65.5–94.8)	14.6–126.0	75.0 (60.0–86.0)	24.0–118.0	0.1187
Total bilirubin (mg/dL)	0.9 (0.6–1.3)	0.4–.5.0	1.0 (0.8–1.3)	0.3–2.31	0.2226
Total cholesterol (mg/dL)	147 (126–171)	80–277	148 (125–170)	95–254	0.8654
Triglyceride (mg/dL)	87 (62–132)	32–240	90 (64–105)	44–271	0.6492
AFP (ng/mL)	32.9 (8.6–129.6)	1.3–22385.0	16.4 (7.8–84.1)	1.3–20427.0	0.8243

Des-γ-carboxy prothrombin (mAU/mL)	134.0 (27.3–887.8)	9.0–71031.0	384.5 (32.5–7695.8)	9.0–745283.0	0.2013
BUN (mg/dL)	16.6 (13.3–21.2)	9.3–31.0	15.6 (14.0–19.0)	9.0–31.2	0.2224
Creatinine (mg/dL)	0.77 (0.60–0.94)	0.35–1.23	0.69 (0.60–0.84)	0.42–1.92	0.2894
eGFR (mL/min/1.73 m^2)	72.3 (55.1–93.9)	5.5–156.7	82.9 (65.6–94.1)	27.4–127.3	0.1907
Uric acid (mg/dL)	5.2 (4.0–.6.7)	2.5–8.66	5.06 (4.3–6.1)	2.8–19.1	0.8865
Sodium (mmol/L)	140 (139–142)	133–146	140 (139–143)	121–144	0.8096
Potassium (mmol/L)	4.0 (3.7–4.4)	3.3–5.2	3.8 (3.5–4.1)	2.9–6.5	0.0198
Chloride (mmol/L)	106 (104–108)	98–111	105 (104–108)	82–112	0.4577
Direct bilirubin (mg/dL)	0.12 (0.08–0.25)	0.05–2.94	0.15 (0.11–0.265)	0.05–0.55	0.1812
Blood glucose (mg/dL)	109 (98–130)	60–258	112 (90–191)	68–204	0.9435
Creatine kinase (U/L)	131 (80–173)	34–358	111 (77–165)	45–386	0.5579
Ammonia (μg/dL)	53 (42–67)	14–192	62 (44–86)	24–205	0.2139

Note. Data are expressed as median (interquartile range [IQR]), range, or number.
Abbreviations: N/A, not applicable; VFA, visceral fat area; PMI, psoas muscle index; SMI, skeletal muscle index; TMN, tumor node metastasis; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; AIH, Autoimmune hepatitis; CT, computed tomography; BCAA, branched-chain amino acids; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AFP, alpha-fetoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate

Pairwise correlations between ΔSMI and Δeach variable

The differences in body composition and biochemical examinations between admission and discharge were calculated, and pairwise correlations between ΔSMI and Δeach variable was performed (Table 4). A correlation was found between ΔSMI and ΔPMI; however, no significant correlation was seen between ΔSMI and Δany variable. In biochemical examinations, no significant correlation was seen between ΔSMI and Δany variable including Δalbumin (Table 4).

Table 4 Pairwise correlations between ΔSMI and Δeach variable

Variable	Correlation coefficient	P
ΔBody mass index	0.0886	0.4144
ΔPMI	0.4100	<0.001
ΔVFA	0.0447	0.6553
ΔAST	0.1297	0.1894
ΔALT	0.0050	0.9597
ΔLactate dehydrogenase	0.0190	0.8488
ΔALP	0.0289	0.0771
ΔGGT	0.0017	0.9865
ΔCholinesterase	-0.0444	0.7193
ΔTotal protein	-0.0217	0.8438
ΔAlbumin	-0.0383	0.7008
ΔTotal bilirubin	-0.1204	0.2304
ΔDirect bilirubin	-0.0213	0.8388
ΔBUN	0.1003	0.3157
ΔCreatinine	0.0025	0.9798
ΔeGFR	0.0652	0.5129
ΔUric acid	-0.2358	0.3623

ΔSodium	-0.0753	0.4521
ΔPotassium	0.0826	0.4068
ΔChloride	-0.0020	0.9841
ΔTotal cholesterol	0.1115	0.7302
ΔTriglyceride	0.3494	0.3567
ΔCreatine kinase	0.1678	0.2121
ΔBlood glucose	0.1243	0.3613
ΔAmmonia	0.1830	0.1265
ΔProthrombin activity (%)	0.1782	0.0893
ΔRed blood cell count	-0.1558	0.1142
ΔHemoglobin	-0.1380	0.1624
ΔWhite blood cell count	-0.0562	0.5709
ΔLymphocytes	0.0667	0.5051
ΔPlatelet count	-0.1200	0.2251

Abbreviations: SMI, skeletal muscle mass index; PMI, psoas muscle index; VFA, visceral fat area; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase aminotransferase; GGT, gamma-glutamyl transpeptidase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate

Multivariate stepwise analysis for the factors associated with ΔSMI

Independent risk factors related to muscle atrophy were examined by multivariate analysis. Admission period, albumin level, and use of BCAA-related agents were selected in the extraction multivariate stepwise procedure. However, no significant association was seen between muscle atrophy and any variable by logistic regression analysis (Table 5).

Decision-tree analysis for muscle atrophy in patients with HCC who underwent TACE

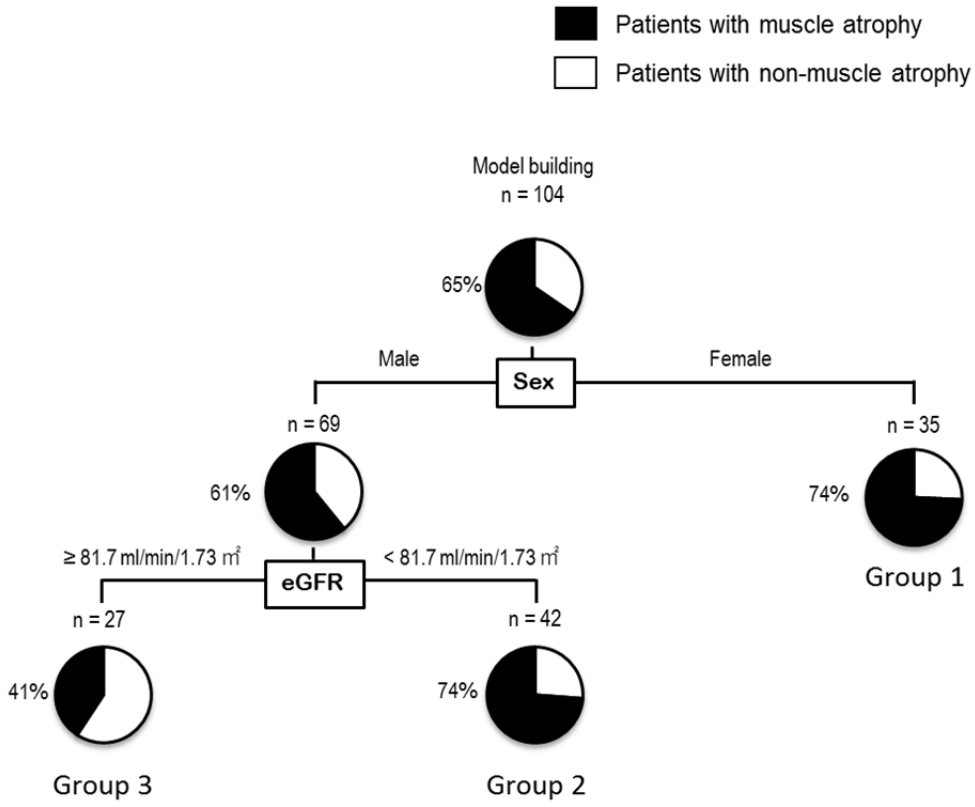
Muscle atrophy was seen in 65% (68/104) of enrolled subjects. Sex was selected as the variable for the initial split, and 74% of female patients had muscle atrophy (Group 1 in Fig. 2). While, 61% of male patients had muscle atrophy, and eGFR was selected as the second split. In the male patients with an eGFR ≤81.7 ml/min/1.73 m^2, 74% showed muscle atrophy (Group 2 in Fig. 2). On the other hand, 41% of male patients with an eGFR >81.7 ml/min/1.73 m^2 showed muscle atrophy (Group 3 in Fig. 2).

Table 5 Multivariate stepwise analysis for the factors associated with ΔSMI

Factors	Unit	Odds ratio	95% Confidence interval
Admission period	N/A	2.7	0.987156–1,987425
Albumin	1	0.47	0.162447–1.315912
BCAA-related agents	N/A	0.47	0.17225–1.261558

Abbreviations; SMI, skeletal muscle mass index; N/A, not applicable;
BCAA, branched-chain amino acids

Figure 2



Discussion

In this study, we demonstrated that skeletal muscle mass significantly decreased after TACE in patients with HCC. In addition, we revealed that sex and renal function, but not age and liver function, were factors associated with a decrease in SMI. Thus, among patients with HCC who underwent TACE, female patients were at a higher risk for depletion of skeletal muscle mass, as were male patients with impaired renal function.

Our study showed that BMI and serum albumin level after TACE were significantly decreased compared to those before TACE in patients with HCC. A significant reduction in BMI is often seen in patients with HCC who have undergone TACE [27]. Decreased serum albumin levels also occur after TACE, and the underlying mechanism of this condition includes the extravasation of serum albumin into the embolized or ablated hepatic region and the involvement of inflammatory cytokine [28]. Thus, our data were good agreement with these previous reports and indicate that rapid wasting occurs in patients with HCC who have undergone TACE.

A high prevalence of sarcopenia is reported in patients with liver cirrhosis; however, decreased SMI was not associated with liver function in this study. Similarly, Montano-Loza et al. reported that sarcopenia does not correlate with the severity of liver disease [9]. Although the reason for this lack of association remains unclear, the development of sarcopenia has a complex pathogenesis in patients with CLD. In our study, all patients underwent TACE. Since TACE is an invasive treatment for HCC, TACE may be associated with the decrease in SMI found in this study. Lifestyle modifications such as physical activity are important for sarcopenia [29]. Recently, Hiraoka et al. demonstrated that nutritional supplementation and walking are effective for improving muscle volume and strength in patients with liver cirrhosis [30]. In our study, patients were instructed to rest, suggesting that physical activity is also important for maintaining muscle mass in patients with HCC who have undergone TACE.

In this study, sex was selected as the variable for the initial split for a decrease in SMI, and 74% of female patients showed a decrease in SMI. It remains unclear why the decrease in SMI was more significant in female patients than in male patients. Possibly, female patients engage in less physical activity than male patients [31]. In addition, a major cause of decreased muscle mass is an alteration in the hormonal networks involved in the inflammatory processes, muscle regeneration, and protein synthesis [32]. Estrogens help to maintain muscle mass [33], and in female patients, menopause leads to changes in the systemic steroid hormone profile from a regularly fluctuating estrogen cycle to very low estrogen levels [34]. The decreased estrogen concentrations are associated with an increase in pro-inflammatory cytokines, such as tumor necrosis factor alpha or interleukine-6, which might be implicated in the development of sarcopenia [34]. Furthermore, estrogen could have a direct effect on muscle mass, since skeletal muscle fibers have estrogen beta-receptors on the cell membranes, in the cytoplasm, and on the nuclear membrane [35]. Thus, physical activity and hormonal changes are possible reasons for the sex difference in the decrease of SMI.

In male patients, eGFR was the variable for the second split for a decrease in SMI in this study. Renal dysfunction often coexists with HCC and predicts a poor outcome in patients who have undergone TACE [36]. In addition, most patients with HCC and chronic kidney disease (CKD) were male (74.8%) [37]. Although it is unclear why renal function is associated with a decrease in skeletal muscle mass, we would assume the following: 1) Patients with CKD are often managed by a low protein diet. 2) Patients with advanced CKD may have metabolic acidosis due to the accumulation of uremic toxins. Metabolic acidosis promotes muscle protein wasting by increasing protein degradation and reducing protein synthesis [38]. 3) In patients with CKD, the enhancement of oxidative stress and inflammatory cytokines is closely related to muscle atrophy [39]. 4) Patients with CKD have hypogonadism such as testosterone deficiency [40], suggesting that low plasma testosterone levels can cause or accelerate sarcopenia [41]. Thus, various factors may be associated with a decrease in skeletal muscle mass in patients with renal dysfunction.

In conclusion, we demonstrated that SMI was significantly decreased after TACE compared to that before TACE in patients with HCC. Moreover, we found that sex and renal dysfunction were associated with muscle mass atrophy. Thus, in patients with HCC who have undergone TACE, “female” and “male with impaired renal function” are at risk of skeletal muscle mass depletion.

Acknowledgement

The authors certify that they comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports (von Haehling S, Ebner N, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle - Clinical Reports. J Cachexia Sarcopenia Muscle Clinical Reports 2016; 1;e28:1-2.)

Conflict of interest statement

Keisuke Hirota, Takumi Kawaguchi, Ryuki Hashida, Shunji Koya, Masafumi Bekki, Norihiro Goshima, Teruhito Yoshiyama, Takashi Otsuka, Ryousuke Nozoe, Dan Nakano, Tomotake Shirono, Shigeo Shimose, Hideki Iwamoto, Takashi Niizeki, Hiroo Matsuse, Hironori Koga, Naoto Shiba, and Takuji Torimura that they have no conflict of interest.

Abbreviations

CLD, chronic liver disease; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; CT, computed tomography; L3, the third lumbar spine vertebra level; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; AFP, alpha-fetoprotein; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; PMI, psoas muscle index; SMI, skeletal muscle index; VFA, visceral fat area; TNM, tumor node metastasis; IQR, interquartile range; BMI, body mass index; BCAA, branched-chain amino acid; CKD, chronic kidney disease.

Financial Support

This work was supported by JSPS Grant-in-Aid for Scientific Research (C) JP17K09444.

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