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Skeletal muscle volume loss among liver cirrhosis patients receiving levocarnitine predicts poor prognosis

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Abstract

Sarcopenia has a negative impact on the prognosis of patients with liver cirrhosis (LC). We investigated the significance of skeletal muscle volume and its changes in LC patients taking levocarnitine (L-carnitine).

We retrospectively analyzed 51 LC patients taking L-carnitine from December 2012 to March 2019. Skeletal mass index was calculated as the left-right sum of the major × minor axis of psoas muscle at the third lumbar vertebra, divided by height squared (psoas muscle index [PMI]). Patients were classified into 2 groups (low and normal PMI) depending on PMI < 6.0 and < 3.4 cm^2/m^2 for men and women, respectively. Changes in PMI per month during L-carnitine administration (ΔPMI/m) were calculated, and we classified the patients into 2 groups (severe and mild muscle atrophy) depending on ΔPMI/m below the lower quartile. We assessed overall survival (OS).

At the start of L-carnitine administration, there were no significant differences in OS between groups with low and normal PMI. Multivariate analysis showed that ΔPMI/m (hazard ratio [HR], 0.007; $P = .005$) and L-carnitine administration period (HR, 0.956; $P = .021$) were significantly associated with OS. Patients with severe muscle atrophy had a significantly lower OS than those with mild muscle atrophy. There was the positive correlation relationship between ΔPMI/m and L-carnitine administration period.

Among LC patients taking L-carnitine, progressive muscle volume loss was a predictor of poor prognosis. L-carnitine administration for longer may be able to prevent muscle volume loss and lead to a better prognosis in LC patients.

Abbreviations: LC = liver cirrhosis, L-carnitine = levocarnitine, PMI = psoas muscle index, OS = overall survival, HR = hazard ratio.

Keywords: levocarnitine, liver cirrhosis, sarcopenia, skeletal muscle volume

1. Introduction

Sarcopenia is defined as skeletal muscle volume loss and a decrease of muscle strength.[1] One report showed that skeletal muscle mass decreased by 2.2% per year in patients with liver cirrhosis (LC), and the rate of decrease increased in parallel with the severity of cirrhosis.[2] Sarcopenia has a negative impact on mortality in patients with LC or hepatocellular carcinoma (HCC).[3–6]

Levocarnitine (L-carnitine) transports long chain fatty acids from the cytosol into the mitochondorial matrix for subsequent β-oxidation. About 75% of L-carnitine is absorbed from food such as beef, lamb, fish and milk, and 25% is synthesized in the kidney and liver.[7–10] Most L-carnitine in the body is maintained in the skeletal muscle.[7–10] Deficiency of L-carnitine is classified as primary, due to organic cation transporter 2 deficiency, and secondary, due to LC, Fanconi syndrome, dialysis, or other factors.[11] L-carnitine deficiency leads to metabolic disorders that impact fatty acids and carbohydrates.[12] L-carnitine administration is effective not only for these symptoms but also for sarcopenia in elderly persons.[13] Previous studies reported that L-carnitine administration prevented skeletal muscle volume loss in patients with LC.[14,15] However, these studies did not show an association between L-carnitine administration and prognosis. The present study aimed to investigate whether L-carnitine administration improved muscle volume loss or prognosis in patients with LC.

2. Methods

2.1. Patients

We retrospectively analyzed 70 patients with LC who took L-carnitine between December 2012 and March 2019 at Fukushima Medical University Hospital. The patients took L-carnitine because of hepatic encephalopathy (HE), hyperammonemia, muscle cramps, fatigue, or a combination of these conditions. When there was no effect, when the symptoms improved and the

Editor: YX Sun.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Fujita M, Abe K, Hayashi M, Takahashi A, Ohira H. Skeletal muscle volume loss among liver cirrhosis patients receiving levocarnitine predicts poor prognosis. Medicine 2020;99:28(e21061).

Received: 4 April 2020 / Accepted: 29 May 2020

http://dx.doi.org/10.1097/MD.0000000000021061

patients wanted to stop taking L-carnitine, or when administration of L-carnitine became difficult due to deterioration of the condition, administration of L-carnitine was discontinued. The dose of L-carnitine was determined at the discretion of the attending physician. All patients had undergone computed tomography (CT) within 3 months before or after the start of L-carnitine administration. Furthermore, they had undergone CT again within 3 months before or after the end of L-carnitine administration. We excluded 19 patients who had not undergone 2 CTs.

We diagnosed patients as having LC based on laboratory data, imaging such as CT or magnetic resonance imaging (MRI), elastography such as MRI or share wave imaging in ultrasonography, and liver biopsy. The ethics committee of Fukushima Medical University School of Medicine approved the study protocol (No. 2019–203), which complied with the Helsinki Declaration.

2.2. Evaluation of HCC, skeletal muscle volume loss, and other variables

The Japan Society of Hepatology (JSH) guidelines for sarcopenia in liver disease recommend using grip strength and skeletal mass index (SMI, muscle mass of all 4 limbs determined using bioelectrical impedance analysis [BIA] divided by height squared) for a diagnosis of sarcopenia.[16] Because this study was a retrospective study, and grip strength was not measured in all patients, we identified skeletal muscle volume loss by SMI alone. SMI calculated as the left-right sum of the major × minor axis of the psoas muscle at the third lumber vertebra (L3) on CT, divided by height squared (psoas muscle index [PMI]) is regarded as simple method to assess SMI (Fig. 1A) .[16] This measuring method is indirectly correlated with SMI using BIA.[16] Thus, we used PMI in the present study. Patients were classified into a low PMI group (PMI $< 6.0\,cm^2/m^2$ for men and $< 3.4\,cm^2/m^2$ for women), and a normal PMI group (PMI $\geq 6.0\,cm^2/m^2$ for men and $\geq 3.4\,cm^2/m^2$ for women), based on the Japanese guidelines for sarcopenia in liver disease.[16] We defined the administration period (months) as the period from the time of start of L-carnitine administration (Pre) to the time of end of L-carnitine administration or observation (Post) (Fig. 1B). The monthly change in PMI during the administration period (ΔPMI/month [ΔPMI/m]) was calculated using the following formula: (L3 PMI [Post CT] - L3 PMI [Pre CT])/administration period as an index of progressive muscle atrophy. Patients were classified into 2 groups (severe and mild muscle atrophy) depending on ΔPMI/m below or above the lower quartile. We evaluated overall survival (OS, months), characteristics including age, liver function reserves, presence of HCC, stage of HCC, and laboratory findings. HCC was diagnosed and evaluated by CT or MRI. Tumor node metastasis stage was determined based on the Japanese criteria.[17]

2.3. Statistical analysis

Continuous variables were expressed as medians and ranges. The 2 PMI groups were compared using the χ^2 test and Fisher exact test for categorical variables and the Mann-Whitney *U*-test for continuous variables. OS was evaluated by the Kaplan-Meier analysis (using the log-rank test). We determined risk factors for OS using Cox hazard analysis. If there were missing values, statistical analysis was performed with available data. All *P*-values were 2-tailed, and *P*-values $< .05$ were considered statistically significant. Statistical analyses were performed using Easy R (Available at: http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[18]

3. Results

3.1. Baseline characteristics

Table 1 shows baseline characteristics of all patients at the start of L-carnitine administration. The median age was 64 years (range, 37–83 years), and 26 patients (50.9%) were men. The median observation period was 23.5 months (range, 1.0–85.6 months). There were only 2 patients with good liver function reserves of

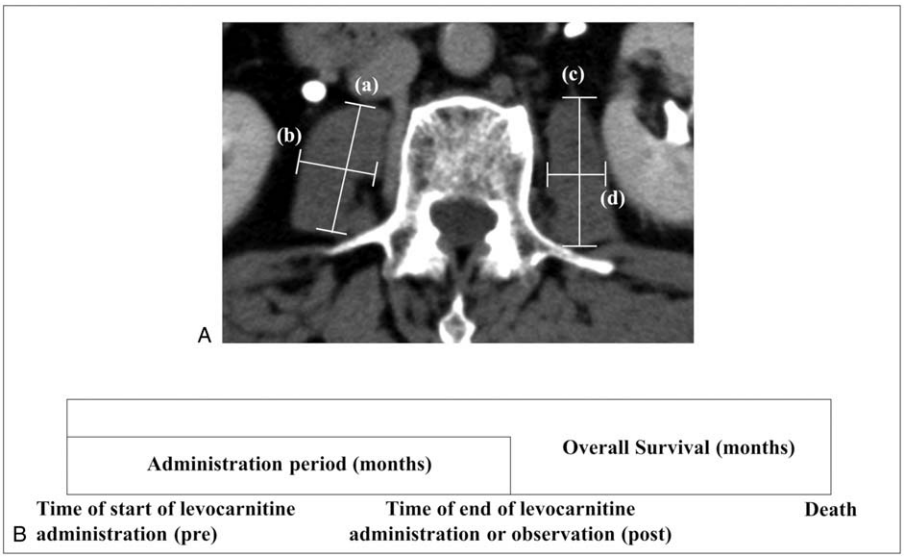

Figure 1. A. Computed tomography showing the psoas muscle at the third lumber vertebra. The length of the major or minor axis was indicated as (A)-(D). B. Overall survival was defined as the period from the time of start of levocarnitine (L-carnitine) administration to death. Administration period was defined as the period from the time of start of L-carnitine administration (Pre) to the end of L-carnitine administration (Post).

Table 1

Baseline characteristics of participants.

Variables	Total (N = 51)
Observation period (mo)	23.5 (1.0–85.6)
Sex (male/female)	26/25
Age (years)	64 (37–83)
BMI (kg/m^2)	24.2 (17.2–35.6)
PMI (cm^2/m^2)	4.38 (2.32–8.63)
Etiology (HBV/HCV/AL/NASH/Other)	4/21/13/6/7
Child-Pugh score	8 (5–14)
Child-Pugh class (A/B/C)	9/21/21
ALBI score	-1.55 (-2.99 - -0.25)
ALBI grade (1/2/3)	2/29/20
HCC (yes/no)	20/31
TNM stage (I/II/III/IVA/IVB)	1/5/9/3/2
Maximum tumor diameter (cm)	3 (0.5–9)
Number of tumors	3 (1–10)
Treatment of HCC (surgery/transplantation/local treatment/TACE/HAIC/radiation therapy)	1/3/1/13/3/2
Total bilirubin (mg/dL)	1.7 (0.4–16.9)
Albumin (g/dL)	2.8 (1.9–4.4)
Prothrombin time (%)	62.1 (6.3–98.2)
Creatinine (mg/dL)	0.75 (0.45–8.37)
Sodium (mmol/L)	138 (128–145)
Fasting blood glucose (mg/dL) *	117 (62–364)
Hemoglobin A1c (%) *	5.6 (3.0–10.3)
Total cholesterol (mg/dL) *	128 (47–274)
Triglyceride (mg/dL) *	69 (27–206)
LDL-cholesterol (mg/dL) *	65 (20–150)
Choline-esterase (U/L) *	116 (41–274)
Ammonia (μg/dL)	87 (13–287)
Change of ammonia (μg/dL)	-16 (-166–81)
AFP (ng/dL) *	14.6 (2–6900)
PIVKA-II (mAU/mL) *	69 (9–11712)
Hepatic encephalopathy (yes/no)	14/37
Other treatment (lactulose/rifaximin or kanamycin/BCAA/LES/nothing)	31/14/35/16/4
L-carnitine dose (mg)	1500 (600–2250)
L-carnitine administration period (mo)	12.4 (0.5–85.6)
L-carnitine discontinued (yes/no)	11/40
Cause of L-carnitine discontinuation (no effect/symptom improvement/edema/other)	1/7/1/2
Death (yes/no)	19/32
Cause of death (liver-related/infection/bleeding/others)	10/4/2/3

Values are presented as median (range). AFP = alpha fetoprotein, AL = alcohol, ALBI = albumin-bilirubin, BCAA = branched-chain amino acid, BMI = body mass index, HAIC = hepatic arterial infusion chemotherapy, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, L-carnitine = levocarnitine, LDL = low density lipoprotein, LES = late evening snack, NASH = non-alcoholic steatohepatitis, PIVKA-II = protein induced by Vitamin K absence or antagonists-II, PMI = psoas muscle index, TACE = transarterial chemoembolization, TNM = tumor node metastasis.
* There were only available data.

albumin-bilirubin (ALBI) grade 1. Twenty patients (39.2%) had HCC, and 14 patients (27.5%) had hepatic encephalopathy. The median dose of L-carnitine was 1500 mg (600–2250 mg). The median administration period of L-carnitine was 12.4 months (0.5–85.6 months). Eleven patients (21.6%) discontinued L-carnitine due to lack of effect in 1 patient (9.1%), symptom improvement in 7 patients (63.6%), edema in 1 patient (9.1%), and other causes in 2 patients (18.2%). Nineteen patients (37.3%) died during the follow-up period. Causes of death were liver-related in 10 patients (52.6%), infection in 4 patients (21.1%), gastrointestinal bleeding in 2 patients (10.5%), and other causes in 3 patients (15.8%). Sixteen patients (31.4%) were treated with late evening snack administration with branched chain amino acids.

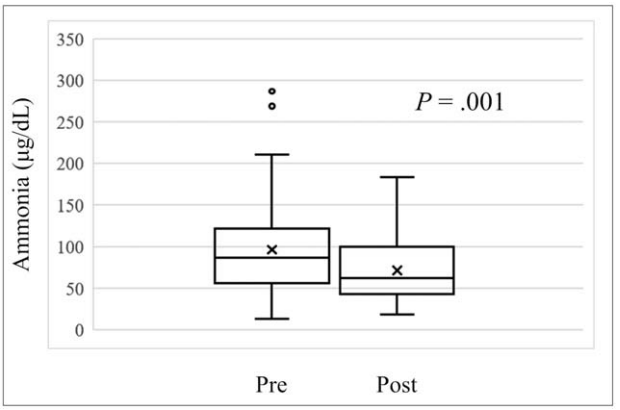

Figure 2. Serum ammonia levels at the end of levocarnitine (L-carnitine) administration (post) was significantly reduced compared to the start of L-carnitine (Pre) ($P = .001$).

Supplemental digital content (Table S1, Available at: http://links.lww.com/MD/E505) shows baseline characteristics of patients who have never had HCC during observation period at the start of L-carnitine administration. Although observation period was longer than 1 of all patients, other characteristics were similar to those of all patients.

3.2. Changes in ammonia levels

In all patients, the median serum ammonia levels at Pre were 87 μg/dL (13–287 μg/dL) and those at Post were 62 μg/dL (-166–81 μg/dL). There was a significant difference in serum ammonia between Pre and Post ($P = .001$) (Fig. 2). In logistic regression analysis, there were no significant factors including age, sex, liver function reserves, dose and administration period of L-carnitine, or muscle volume loss in changes of ammonia between Pre and Post.

There was also a significant difference in serum ammonia between Pre (median; 95 μg/dL, range; 13–189 μg/dL) and Post (median; 57 μg/dL, range; 20–136 μg/dL) in the patients who have never had HCC during observation period ($P = .004$) (Supplemental digital content [Figure S1, Available at: http://links.lww.com/MD/E502]).

3.3. Comparison between groups with low and normal baseline PMI

Among all 51 patients, 33 (64.7%) were classified as having low PMI. There were no significant differences in age, liver function reserves such as Child-Pugh classification and ALBI grade, morbidity of HCC, stage of HCC (including number and size), laboratory findings including ammonia and its changes, or dose and administration period of L-carnitine between patients with low and normal PMI. Significantly more men had low PMI than normal PMI ($P = .016$) (Table 2). Moreover, BMI was significantly lower in those with low PMI than in those with normal PMI (median, 23.1 vs. 26.1 kg/m^2; $P = .043$). There was no significant difference in OS between the low PMI group and the normal PMI group ($P = .56$) (Fig. 3A). In the subgroup analysis, there were no significant differences in OS between PMI groups in men ($P = .83$) or women ($P = .727$).

In the patients who have never had HCC during observation period, 23 (74.2%) were classified as having low PMI.

Table 2

Comparisons between groups with low (< 6.0 and < 3.4 cm^2/m^2 for men and women, respectively) and normal (≥ 6.0 and ≥ 3.4 cm^2/m^2 for men and women, respectively) baseline psoas muscle index (PMI).

Variables	Normal PMI (N = 18)	Low PMI (N = 33)	*P* value
Observation period (mo)	29.3 (1.0–85.6)	19.1 (1.8–70.8)	.452
Sex (male/female)	**5/13**	**21/12**	**.016**
Age (years)	65 (37–82)	64 (43–83)	.574
BMI (kg/m^2)	**26.1 (20.1–35.6)**	**23.1 (17.2–33.9)**	**.043**
PMI (cm^2/m^2)	**5.12 (3.63–8.63)**	**3.8 (2.32–5.64)**	**.002**
ΔPMI/mo (cm^2/m^2)	-0.016 (-0.571–0.13)	-0.007 (-0.464–0.09)	.66
Etiology (HBV/HCV/AL/NASH/Other)	0/11/2/2/3	4/10/11/4/4	
Child-Pugh score	8 (5–12)	9 (5–14)	.765
Child-Pugh class (A/B/C)	3/9/6	6/12/15	.572
ALBI score	-1.44 (-2.96 - -0.25)	-1.62 (-2.99 - -0.47)	.187
ALBI grade (1/2/3)	1/9/8	1/20/12	.683
HCC (yes/no)	10/8	10/23	.083
TNM stage (I/II/III/IVA/IVB) *	1/3/4/1/1	0/2/5/2/1	.378
Maximum tumor diameter (cm) *	2 (1–4)	2.3 (0.5–9)	.71
Number of tumors *	2 (1–10)	3 (1–10)	.424
Treatment of HCC *			
Surgery	1	0	.368
Transplantation	2	1	.583
Local treatment	1	0	.368
TACE	5	8	.185
HAIC	2	1	.583
Radiation therapy	1	1	1
Total bilirubin (mg/dL)	1.8 (0.5–16.9)	1.5 (0.4–10.4)	.225
Albumin (g/dL)	2.8 (1.9–4.4)	2.8 (2.0–4.4)	.547
Prothrombin time (%)	58.8 (6.3–98.2)	62.4 (18.2–95.7)	.539
Creatinine (mg/dL)	0.70 (0.47–1.76)	0.77 (0.45–8.37)	.945
Sodium (mmol/L)	140 (133–143)	138 (128–145)	.258
Fasting blood glucose (mg/dL) *	118 (62–208)	116 (71–364)	.63
Hemoglobin A1c (%) *	5.5 (3.0–7.7)	5.6 (3.8–10.3)	.774
Total cholesterol (mg/dL) *	107 (73–173)	141 (47–274)	.14
Triglyceride (mg/dL) *	79 (34–206)	65 (27–198)	.485
LDL-cholesterol (mg/dL) *	57 (27–100)	68 (20–150)	.068
Choline-esterase (U/L) *	101 (48–274)	122 (41–208)	1
Ammonia (μg/dL)	84 (33–189)	87 (13–287)	.935
Change of ammonia (μg/dL)	-33 (-93–31)	-13 (-166–81)	.112
AFP (ng/dL) *	20.9 (4.4–752)	7.3 (2.0–6900)	.133
PIVKA-II (mAU/mL) *	92 (14–5601)	67 (9–11712)	.691
Hepatic encephalopathy (yes/no)	4/14	10/23	.549
Other treatment (yes/no)	15/3	32/1	.091
Lactulose	11	20	.699
Rifaximin or kanamycin	7	7	.23
BCAA	12	23	.481
LES	5	11	.533
L-carnitine dose (mg)	1650 (900–1800)	1500 (600–2250)	.267
L-carnitine administration period (month)	11.6 (1.0–85.6)	14.5 (0.5–70.8)	.76
L-carnitine discontinued (yes/no)	6/12	5/28	.139
Cause of L-carnitine discontinuation (no effect/symptom improvement/edema/other)	0/4/1/1	1/3/0/1	.525
Death (yes/no)	6/12	13/20	.68
Cause of death (liver-related/infection/bleeding/other)	2/3/1/0	8/1/1/3	

Values are presented as median (range). AFP = alpha fetoprotein, AL = alcohol, ALBI = albumin-bilirubin, BCAA = branched-chain amino acid, BMI = body mass index, HAIC = hepatic arterial infusion chemotherapy, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, L-carnitine = levocarnitine, LDL = low density lipoprotein, LES = late evening snack, NASH = non-alcoholic steatohepatitis, PIVKA-II = protein induced by Vitamin K absence or antagonists-II, PMI = psoas muscle index, TACE = transarterial chemoembolization, TNM = tumor node metastasis.

* There were only available data.

Significantly more men had low PMI than normal PMI ($P = .022$) (Supplemental digital content [Table S2, Available at: http://links.lww.com/MD/E506]). Although serum ammonia level was higher in the normal PMI group (median; 106 μg/dL, range; 50–189 μg/dL) than in the low PMI group (median; 86 μg/dL, range; 13–153 μg/dL) ($P = .027$), it decreased more in normal PMI group (median; -53 μg/dL, range; -93–9 μg/dL) than in the low PMI group (median; -5 μg/dL, range; -130–81 μg/dL). There was no significant difference in OS between the low PMI group and the normal PMI group ($P = .531$) (Supplemental digital content [Figure S2A, Available at: http://links.lww.com/MD/E503]).

3.4. Predictive factors of OS

Univariate analysis revealed that ALBI grade, administration period of L-carnitine, and ΔPMI/m were significantly associated

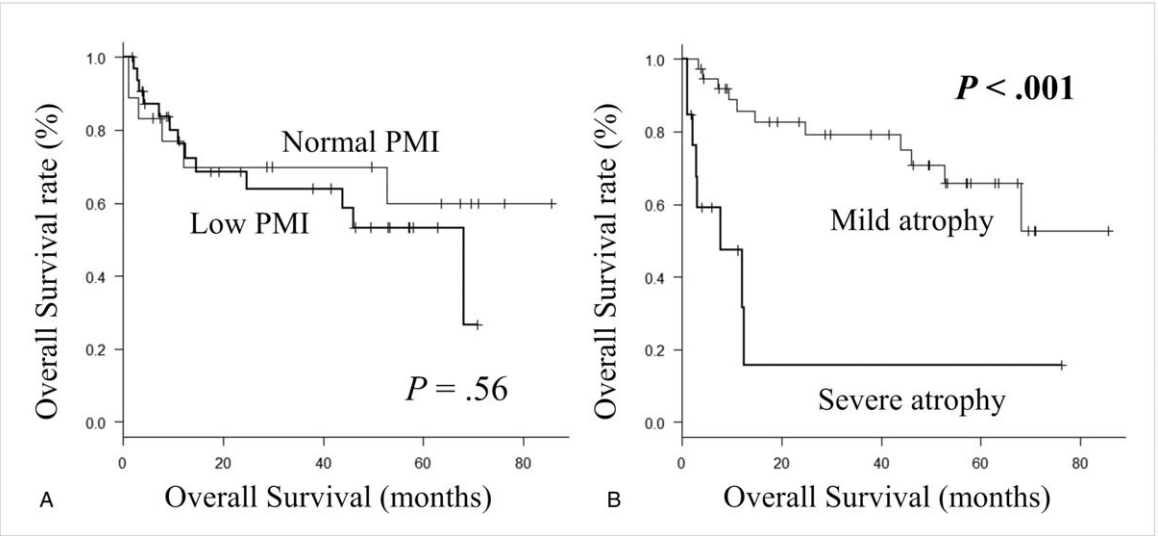

Figure 3. A. Kaplan-Meier curve for overall survival between the patients with normal psoas muscle index (PMI) (≥ 6.0 cm^2/m^2 for men and ≥ 3.4 cm^2/m^2 for women) and low PMI (< 6.0 cm^2/m^2 for men and < 3.4 cm^2/m^2 for women). B. Kaplan-Meier curve for overall survival between patients with mild (ΔPMI/month above the lower quartile) and severe atrophy (ΔPMI/month below the lower quartile) group.

with OS (Table 3). Multivariate analysis indicated that ΔPMI/m (hazard ratio [HR], 0.007; 95% confidence interval [CI], 0.0002–0.221; $P = .005$) and L-carnitine administration period (HR, 0.956; 95% CI, 0.921–0.993; $P = .021$) were significantly associated with OS. Thirteen patients (25.5%) with severe muscle atrophy had a significantly worse prognosis compared with patients with mild muscle atrophy ($P < .001$) (Fig. 3B). A positive correlation was observed between ΔPMI/m and L-carnitine administration period (R = .375; 95 CI, 0.111–0.59; $P = .001$) (Fig. 4). There was no significant association between ΔPMI/m and change in ammonia in logistic analysis.

In the patients who have never had HCC during observation period, sex, ALBI grade, administration period of L-carnitine, and ΔPMI/m were significantly associated with OS (Supplemental digital content [Table S3, Available at: http://links.lww.com/MD/E507]). Multivariate analysis indicated that ΔPMI/m (HR, 0.012; 95% CI, 0.0002–0.893; $P = .044$) and L-carnitine administration period (HR, 0.929; 95% CI, 0.858–0.986; $P = .016$) were significantly associated with OS. Eight patients (25.8%) with severe muscle atrophy had a significantly worse prognosis compared with patients with mild muscle atrophy ($P < .001$) (Supplemental digital content [Figure S2B, Available

Table 3

Predictive factors for overall survival.

	Univariate analysis		Multivariate analysis	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Sex (male vs female)	2.178 (0.851–5.571)	.104		
Age (yr)	0.979 (0.938–1.022)	.337		
BMI (kg/m^2)	1.067 (0.974–1.169)	.164		
ALBI grade (1/2/3)	**3.525 (1.432–8.676)**	**.006**	1.481 (0.536–4.092)	.449
HCC (yes/no)	0.716 (0.272–1.89)	.5		
TNM stage (I/II/III/IVA/IVB)	1.163 (0.508–2.661)	.721		
AFP (ng/dL, ≥14.6 vs < 14.6)	1.988 (0.62–6.378)	.248		
PIVKA-II (mAU/mL, ≥69 vs < 69)	0.881 (0.242–3.205)	.847		
Ammonia Pre (μg/dL)	0.997 (0.989–1.005)	.517		
Change of ammonia (μg/dL)	0.554 (0.22–1.394)	.21		
Hepatic encephalopathy (yes/no)	1.351 (0.508–3.597)	.547		
Other treatment (yes/no) *	2.115 (0.28–15.97)	.468		
L-carnitine dose (mg, ≥1500 vs < 1500)	2.138 (0.708–6.459)	.178		
L-carnitine administration period (month)	**0.939 (0.905–0.976)**	**.001**	**0.956 (0.921–0.993)**	**.021**
Low PMI Pre (yes vs no)	1.337 (0.502–3.562)	.561		
Low PMI Post (yes vs no)	1.709 (0.612–4.773)	.306		
PMI (cm^2/m^2)	1.325 (0.934–1.879)	.115		
ΔPMI/m (cm^2/m^2)	**0.001 (0.00003–0.026)**	**< .001**	**0.007 (0.0002–0.221)**	**.005**

AFP = alpha fetoprotein, ALBI = albumin-bilirubin, BMI = body mass index, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, L-carnitine = levocarnitine, PIVKA-II = protein induced by vitamin K absence or antagonists-II, PMI = psoas muscle index, TNM = tumor node metastasis.

* Other treatment included administration of lactulose, rifaximin, kanamycin, branched-chain amino acid, or late evening snack.

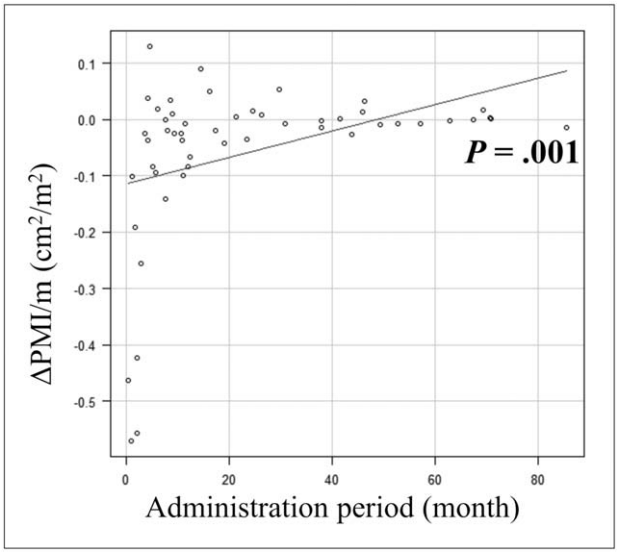

Figure 4. Positive correlation relationship between the monthly change in psoas muscle index (ΔPMI/m) and levocarnitine administration period.

at: http://links.lww.com/MD/E503]). A positive correlation was observed between ΔPMI/m and L-carnitine administration period (R = 0.466; 95 CI, 0.134–0.704; $P = .008$) (Supplemental digital content [Figure S3, Available at: http://links.lww.com/MD/E504]).

4. Discussion

Sarcopenia is associated with unfavorable mortality in patients with LC or HCC, independent of liver function reserves.[2–6] In terms of HCC treatment, a previous report showed the negative impact of sarcopenia at the time treatment began in patients undergoing curative treatments such as hepatectomy and radiofrequency ablation.[3] On the other hand, the impact of skeletal muscle mass at the start of non-curative treatment such as transarterial chemoembolization (TACE) and sorafenib may be less compared with its impact during curative treatment. In fact, a few reports regarding sorafenib treatment showed no significant association between muscle volume mass at the time sorafenib treatment began and OS, although they showed progressive muscle volume loss as a significant prognostic factor for OS.[4,5] In terms of TACE, we previously reported no significant association between muscle volume loss at baseline and OS and a significant association between psoas muscle volume loss by month during the TACE treatment period and OS.[19] These reports imply that changes in muscle volume mass during non-curative treatment such as sorafenib and TACE may be a useful predictor of prognosis in patients with HCC receiving non-curative treatment. In the present study, there was no association between muscle volume loss at the start of L-carnitine administration and OS but there was an association between progressive muscle volume loss during the L-carnitine administration period and OS. Thus, in patients with LC, with or without HCC, there may be association between muscle volume loss not only at diagnosis of LC but also during the follow-up period and in terms of prognosis.

L-carnitine is indicated for various symptoms caused by LC such as muscle cramps, anorexia, fatigue, and HE due to hyperammonemia. A previous study reported that in LC patients with muscle cramps, L-carnitine was taken for 8 weeks and symptoms improved.[20] Another study reported that L-carnitine administration (1800 mg/d, 3 months) significantly reduced serum ammonia in LC patients with hyperammonemia (serum ammonia > 80 μg/dL).[21] Similarly, in our study, hyperammonemia improved with L-carnitine administration. Hyperammonemia causes elevation of myostatin, which suppresses muscle synthesis.[22] Thus, a reduction of ammonia with administration of L-carnitine might be 1 way to prevent muscle volume loss in patients with LC. However, in the present study, changes in ammonia were not associated with ΔPMI/m in the logistic analysis. Furthermore, another study reported that L-carnitine administration prevented monthly skeletal muscle volume loss, regardless of whether L-carnitine administration reduced serum ammonia.[14] In patients with LC, inflammation due to radical oxygen species causes skeletal muscle volume loss.[23] A previous study reported that L-carnitine administration had a positive impact on oxidative stress.[13,24] Thus, L-carnitine may prevent muscle volume loss via multiple effects including a reduction in serum ammonia and hepatic oxidative stress.

Two previous studies showed an association between L-carnitine administration and skeletal muscle volume loss in patients with LC.[14,15] In the present study, we retrospectively investigated these associations only in LC patients originally receiving L-carnitine. However, in the present study, ΔPMI/m and L-carnitine administration period had a significant association with OS in LC patients with or without HCC in Cox-Hazard analysis. Furthermore, there was a positive correlation between ΔPMI/m and L-carnitine administration period. These results imply that L-carnitine administration for longer might prevent skeletal muscle volume loss and lead to longer OS.

There were several limitations in the present study. First, this study was a retrospective single-center study, and the number of patients was small. Second, we did not measure muscular strength in patients; thus, a diagnosis of sarcopenia according to JSH guidelines for sarcopenia in liver disease was impossible. Third, because we measured the long or short axis of the psoas muscle at the L3 vertebra using manual tracing, there were likely some errors in PMI values. Prospective, large-scale studies to overcome the above-mentioned limitations, along with interventional studies to prevent sarcopenia, are needed to improve prognosis in patients with LC taking L-carnitine.

In conclusion, progressive loss of skeletal muscle volume was an important predictor of poor prognosis in LC patients treated with L-carnitine. L-carnitine administration for longer may be able to prevent skeletal muscle volume loss and lead to a better prognosis in patients with LC.

Acknowledgments

We gratefully acknowledge the work of past and present members of our department.

Author contributions

All authors participated in study conception and design. M. Fujita performed statistical analysis of the data. H. Ohira and K. Abe supervised the project. All authors participated in interpretation of the results and drafting of the manuscript, and approved the final version.

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