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Changes in skeletal muscle mass after endoscopic treatment in patients with esophageal varices

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Abstract

To the best of our knowledge, no available data with regard to changes in skeletal muscle mass for liver cirrhosis (LC) patients with esophageal varices (EVs) undergoing endoscopic therapy as a primary prophylaxis could exist. As endoscopic therapies, such as endoscopic injection sclerotherapy or endoscopic band ligation for EVs, accompany invasive procedure and patients with EVs receiving endoscopic therapies mostly rest in bed during hospitalization, clarifying these issues are clinically of importance. The purposes of this study were therefore to examine changes in skeletal muscle mass for LC patients with EVs undergoing endoscopic therapy as a primary prophylaxis and to identify pretreatment predictors which are associated with the amelioration in skeletal muscle mass. This is a subgroup analysis in our previous randomized controlled trial. A total of 51 LC patients with EVs were analyzed. Skeletal muscle mass was assessed using bioimpedance analysis (BIA). Skeletal muscle index (SMI) was defined as sum of skeletal muscle mass in body trunk and upper and lower extremities divided by height squared (cm^2/m^2) using data for BIA. We compared the changes in SMI at baseline and SMI at Day 50 after endoscopic treatment for EVs. Our study cohort included 33 males and 18 females with median (range) age of 62 (29–81) years. There were 31 patients with Child–Pugh A and 20 with Child–Pugh B. The median SMI for the entire cohort at baseline was 8.96 cm^2/m^2 (range, 5.87–13.11 cm^2/m^2), while the median SMI for the entire cohort at Day 50 was 8.83 cm^2/m^2 (range, 5.59–12.29 cm^2/m^2) ($P = .9995$). In baseline characteristics, prealbumin ($P = .0477$), branched-chain amino acid to tyrosine ratio (BTR) ($P = .0056$), and retinol-binding protein ($P = .0296$) in the increased SMI group (n = 15) were significantly higher than those in the nonincreased SMI group (n = 36). Multivariate analysis for the above 3 significant factors showed that only BTR was a significant prognostic pretreatment factor linked to the presence of increased SMI ($P = .0235$). In conclusion, pretreatment BTR level can be helpful for predicting increased SMI after endoscopic therapy as a primary prophylaxis for LC patients with EVs.

Abbreviations: BCAA = branched-chain amino acid, BIA = bioimpedance analysis, BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, EBL = endoscopic band ligation, EIS = endoscopic injection sclerotherapy, EV = esophageal varix, F = form, LC = liver cirrhosis, RBP = retinol-binding protein, RC signs = red color signs, RCT = randomized controlled trial, SMI = skeletal muscle index.

Keywords: endoscopic treatment, esophageal varices, predictor, skeletal muscle mass

1. Introduction

Liver cirrhosis (LC) is one of major causes for death in industrialized countries.[1] In LC patients with ascites, the 5-year mortality rate is estimated to be 40% to 50%.[1–5] In Japan, endoscopic therapies are central for the management of esophageal varices (EVs), which is recognized as a major complication of LC.[2–4] EVs are found in 30% to 40% of compensated LC patients and in about 60% of decompensated LC patients.[2–4] The 2 major endoscopic procedures for EVs are: endoscopic injection sclerotherapy (EIS) and endoscopic band ligation (EBL).[2–4]

Skeletal mass can exert essential roles for protein, glucose, and ammonia metabolism.[6–11] Skeletal muscle mass depletion has been shown to be an adverse predictor in LC patients, and it has attracted much caution among clinicians due to its linkage to dismal outcomes.[6–13] Compelling evidences have demonstrated that skeletal muscle mass depletion is one of major complications in LC patients due to the LC-associated protein metabolic disorder and energy metabolic disorder.[8,9,12–24] In addition, skeletal

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muscle mass depletion can be characterized by both muscle mass reduction and muscular fat increment (myosteatosis).[25] Currently, reversing muscle mass loss has been a point of focus for LC patients with skeletal muscle loss.[6,9,26] Sinclair et al[27] demonstrated in their double-blinded randomized controlled trial (RCT) that testosterone therapy for male LC patients with low serum testosterone safely increased muscle mass and reduced fat mass. Koya et al[28] reported that therapeutic exercise ameliorated physical ability without deteriorating liver function during hospitalization for the treatment of hepatocellular carcinoma (n=54) and that branched-chain amino acid (BCAA) therapy minimized the skeletal muscle atrophy.

However, to the best of our knowledge, no available data with regard to changes in skeletal muscle mass for LC patients with EVs undergoing endoscopic therapy as a primary prophylaxis could exist. In addition, identifying pretreatment predictors associated with the amelioration in skeletal muscle mass may provide useful information for clinicians on nutritional plans for LC patients with EVs receiving endoscopic therapy. As endoscopic therapies for EVs accompany invasive procedure and patients with EVs receiving endoscopic therapy mostly rest in bed during hospitalization, clarifying these issues are clinically of importance. The purposes of this study were therefore to examine changes in skeletal muscle mass for LC patients with EVs undergoing endoscopic therapy as a primary prophylaxis and to identify pretreatment predictors which are associated with the amelioration in skeletal muscle mass.

2. Patients and methods

2.1. Protocol for our previous RCT

In our previous study, we performed prospective interventional study (RCT) to investigate the optimal nutritional support therapy for maintaining and improving the nutritional status of LC patients receiving prophylactic endoscopic therapy for EVs.[29] In brief, in our previous study, a total of 75 LC subjects with EVs were randomized and were analyzed.[29] Prophylactic endoscopic therapy for EVs were performed on an inpatient basis.

2.2. Patients in the present study and skeletal muscle mass measurement

In our previous RCT, skeletal muscle mass was assessed using bioimpedance analysis (BIA).[29] Of these patients (n=75), changes in skeletal muscle mass between pretreatment level (before endoscopic therapy, baseline) and posttreatment level (at Day 50) could be evaluated in 51 subjects, who were thus analyzed in this study. Day 50 was the day at first visit in an outpatient after discharge. Skeletal muscle index (SMI) was defined as sum of skeletal muscle mass in body trunk and upper and lower extremities divided by height squared (cm^2/m^2) using data for BIA. We compared the changes in SMI at baseline and SMI at Day 50. Patients with increased SMI were defined as those with SMI at Day 50 more than SMI at baseline. Nonprotein respiratory quotient, rest energy expenditure, and basal metabolic rate were measured using indirect calorimetry as reported previously.[30] We identified baseline parameters associated with the increased SMI using univariate and multivariate analyses. Further, changes in other variables than SMI were also examined. The ethical committee meeting in Hyogo College of Medicine acknowledged our present study protocol, and this study strictly followed all regulations of the Declaration of Helsinki.

2.3. Nutritional therapies after endoscopic treatments

As a post-EIS or EBL nutritional therapy, general liquid nutrient containing only calories (210 kcal of RACOL, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) was administered in 8 patients, BCAA-enriched nutrient mixture composed of both BCAA and calories (210 kcal of Aminoleban EN; BCAA: 6 g, Otsuka Pharmaceutical Co., Ltd.) in 24, BCAA-granules containing only BCAA orally (16 kcal of Livact; BCAA: 4 g, Ajinomoto Pharmaceutical Co., Ltd., Tokyo, Japan) in 15 and no specific nutritional therapy in 4. All these nutrients were randomly assigned based on our previous protocols.[29]

2.4. Endoscopic findings for EVs

EVs were graded as reported elsewhere and red color signs (RC signs) on esophageal were defined as reported elsewhere.[31]

2.5. Statistical analysis

Categorical parameters were compared by Fisher exact test. Continuous parameters were compared by unpaired *t* test, paired *t* test, Mann–Whitney *U* test, or Spearman rank correlation coefficient r_s as applicable. For predicting increased SMI, candidate parameters were chosen by the univariate analysis; statistically significant parameters ($P<.05$) were subjected into a multivariate logistic regression analysis. Clinical data were demonstrated as median value (range) unless otherwise mentioned. Statistical significance was set at $P<.05$. Statistical analysis was performed with the JMP 11 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

Baseline characteristics in this study are presented in Table 1. The current cohort (n=51) included 33 males and 18 females with median (range) age of 62 (29–81) years. There were 31 patients with Child–Pugh A and 20 with Child–Pugh B. There were 9 hepatocellular carcinoma cases. As for endoscopic findings, F (form) 1 EVs were observed in 13 patients, F2 in 25, and F3 in 13. RC signs were observed in 45 patients. SMI for male at baseline ranged from 5.87 to 13.11 cm^2/m^2 (median, 9.60 cm^2/m^2), while SMI for female at baseline ranged from 6.54 to 8.97 cm^2/m^2 (median, 8.32 cm^2/m^2). The median (range) sessions of EIS or EBL therapy were 2 (1–3). The median (range) hospitalization days were 21 (10–37) days. All study subjects had performance status 0.

3.2. Changes in SMI for the entire cohort (n=51)

The median SMI for the entire cohort at baseline was 8.96 cm^2/m^2 (range, 5.87–13.11 cm^2/m^2), while the median SMI for the entire cohort at Day 50 was 8.83 cm^2/m^2 (range, 5.59–12.29 cm^2/m^2) ($P=.9995$, Fig. 1). The proportion of increased SMI at Day 50 compared with SMI at baseline was 29.4% (15/51, 9 males and 6 females).

3.3. Changes in SMI according to nutritional therapy after endoscopic treatment

For patients receiving RACOL after endoscopic treatment (n=8), SMI at Day 50 did not significantly increase as compared with baseline levels ($P=.1896$, Fig. 2A). Similarly, for patients receiving Aminoleban EN (n=24) and Livact (n=15) after endoscopic

Table 1

Baseline data (n = 51).

Variables	Number or median, range
Age, y	62 (29–81)
Gender, male/female	33/18
Body mass index, kg/m^2	22.8 (13.1–34.4)
Skeletal muscle index, cm^2/m^2, male	9.60 (5.87–13.11)
Skeletal muscle index, cm^2/m^2, female	8.32 (6.54–8.97)
Endoscopic findings at initial therapy	
Esophageal varices (F1/F2/F3)	13/25/13
Red color signs on esophageal, yes/no	45/6
Presence of HCC, yes/no	9/42
Child–Pugh classification, A/B	31/20
Serum albumin, g/dL	3.4 (2.5–4.4)
Prealbumin, mg/dL	10.3 (2.9–25.8)
Glycoalbumin, %	17.8 (12.4–41.4)
HOMA-IR	2.42 (0.83–12.00)
Serum creatinine, mg/dL	0.66 (0.36–1.23)
Serum ammonia, μg/dL	44 (17–103)
BTR	3.66 (1.61–7.58)
npRQ	0.824 (0.718–1.107)
REE/BMR	1.017 (0.517–1.290)
Retinol-binding protein, mg/dL	1.2 (0.4–4.4)
BCAA therapy post-EIS or EVL, yes/no	39/12
Ascites, yes/no	13/38

Data are expressed as number or median (range). BCAA = branched-chain amino acid, BMR = basal metabolic rate, BTR = branched-chain amino acid to tyrosine ratio, EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, F = form, HCC = hepatocellular carcinoma, HOMA-IR = homeostasis model assessment of insulin resistance, npRQ = nonprotein respiratory quotient, REE = resting energy expenditure.

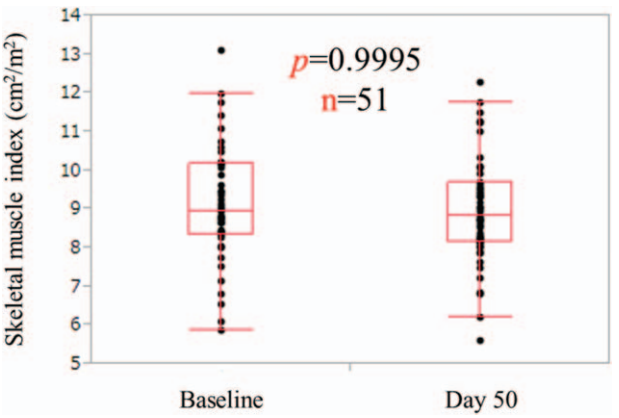

Figure 1. Changes in skeletal muscle index (SMI) for the entire cohort (n = 51). The median SMI for the entire cohort at baseline was 8.96 cm^2/m^2 (range, 5.87–13.11 cm^2/m^2), while the median SMI for the entire cohort at Day 50 was 8.83 cm^2/m^2 (range, 5.59–12.29 cm^2/m^2) ($P = .9995$).

treatment, no significant differences were found in SMI between at baseline and at Day 50 ($P = .9930$ and .9811, Fig. 2B and C).

3.4. Relationship between SMI and baseline parameters for male and female

For male, age ($r_s = -0.5769$, $P = .0004$), body mass index (BMI) ($r_s = 0.8318$, $P < .0001$), serum creatinine ($r_s = -0.4674$, $P = .0061$), and retinol-binding protein (RBP) ($r_s = -0.3752$, $P = .0344$) significantly correlated with baseline SMI, while for female, no baseline parameters significantly correlated with SMI (Table 2).

3.5. Comparison of baseline parameters between subjects with and without increased SMI

Comparison of baseline characteristics between patients with increased SMI (n = 15) and without increased SMI (n = 36) was demonstrated in Table 3. Prealbumin ($P = .0477$), branched-chain amino acid to tyrosine ratio (BTR) ($P = .0056$), and RBP ($P = .0296$) in the increased SMI group were significantly higher than those in the nonincreased SMI group.

3.6. Multivariate analyses of factors associated with the presence of increased SMI

Multivariate analysis for the above 3 significant factors (i.e., prealbumin, BTR, and RBP) showed that only BTR was a

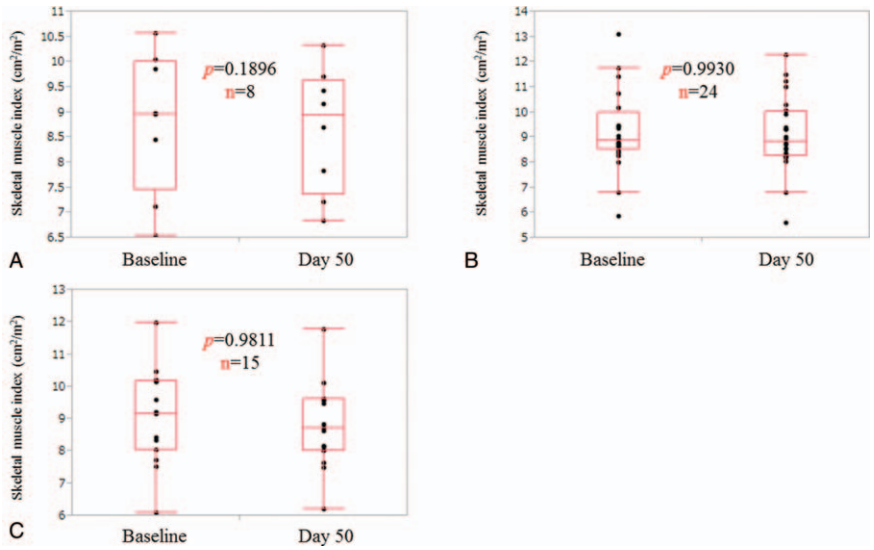

Figure 2. Changes in skeletal muscle index (SMI) according to nutritional therapy after endoscopic treatment. (A) For patients receiving RACOL after endoscopic treatment (n = 8), SMI at Day 50 did not significantly increase as compared with baseline levels ($P = 0.1896$). (B and C) For patients receiving Aminoleban EN (B, n = 24) and Livact (C, n = 15) after endoscopic treatment, there were no significant differences in SMI between at baseline and at Day 50 ($P = .9930$ and .9811).

Table 2

Relationship between SMI and baseline characteristics for male (n = 33) and female (n = 18).

	Male (n = 33)		Female (n = 18)	
	r_s	*P*	r_s	*P*
Age	−0.5769	.0004	0.0776	.7594
Body mass index	0.8318	<.0001	0.2623	.2931
Serum albumin	−0.0511	.7778	−0.1697	.5008
Prealbumin	−0.2576	.1546	−0.1662	.5110
Glycoalbumin	−0.3212	.0731	0.3849	.1147
HOMA-IR	−0.2196	.2272	−0.2054	.4136
Serum ammonia	0.0059	.9742	0.1538	.5422
Serum creatinine	−0.4674	.0061	−0.2143	.3932
BTR	−0.3328	.0585	−0.2003	.4184
npRQ	−0.0662	.7144	0.0526	.8357
REE/BMR	0.0976	.5890	−0.3127	.2065
RBP	−0.3752	.0344	−0.2853	.2512

BMR = basal metabolic rate, BTR = branched-chain amino acid to tyrosine ratio, HOMA-IR = homeostasis model assessment of insulin resistance, npRQ = nonprotein respiratory quotient, RBP = retinol-binding protein, REE = resting energy expenditure.

significant prognostic pretreatment factor linked to the presence of increased SMI ($P = .0235$) (Table 4). Hazard ratios and 95% confidence intervals were presented in Table 4.

3.7. Comparison of parameters between at baseline and at Day 50 for subjects with and without increased SMI

For the increased SMI group, prealbumin ($P = .0087$), albumin ($P = .0002$), and RBP ($P = .0422$) at Day 50 significantly increased as compared with baseline levels while serum ammonia level at Day 50 significantly decreased ($P = .0130$) (Table 5). For the nonincreased SMI group, prealbumin ($P = .0396$), albumin ($P < .0001$), and RBP ($P = .0301$) at Day 50 significantly increased as compared with baseline levels while serum ammonia level ($P < .0001$) and BMI ($P < .0001$) at Day 50 significantly decreased as compared with baseline levels (Table 5).

Table 3

Comparison of baseline characteristics between patients with increased SMI (n = 15) and without increased SMI (n = 36).

	Increased SMI (n = 15)	Nonincreased SMI (n = 36)	*P*
Age, y	68 (49–78)	62 (29–81)	.1104
Gender, male/female	9/6	24/12	.7513
Body mass index, kg/m^2	21.8 (13.9–28.4)	23.15 (13.1–34.4)	.1164
Presence of HCC, yes/no	3/12	6/30	1.000
Child–Pugh classification, A/B	11/4	20/16	.3475
Serum albumin, g/dL	3.5 (2.9–3.9)	3.4 (2.5–4.4)	.4073
Prealbumin, mg/dL	11.9 (6.1–16.5)	8.6 (2.9–25.8)	.0477
Glycoalbumin, %	18.0 (14.6–41.4)	17.4 (12.4–25.9)	.2316
HOMA-IR	2.14 (1.11–8.03)	3.02 (0.83–12.00)	.4952
Serum creatinine, mg/dL	0.8 (0.5–1.01)	0.65 (0.36–1.23)	.2274
Serum ammonia, μg/dL	45 (21–103)	40.5 (17–96)	.8701
BTR	4.56 (2.70–7.58)	3.42 (1.61–6.38)	.0056
npRQ	0.827 (0.741–0.942)	0.819 (0.718–1.107)	.6117
REE/BMR	1.010 (0.756–1.177)	1.031 (0.517–1.290)	.9246
Retinol-binding protein, mg/dL	1.6 (0.9–2.5)	1.1 (0.4–4.4)	.0296
BCAA therapy post-EIS or EVL, yes/no	10/5	29/7	.3019
Ascites, yes/no	4/11	9/27	1.000

Data are expressed as number or median (range). BCAA = branched-chain amino acid, BMR = basal metabolic rate, BTR = branched-chain amino acid to tyrosine ratio, EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, HCC = hepatocellular carcinoma, HOMA-IR = homeostasis model assessment of insulin resistance, npRQ = nonprotein respiratory quotient, REE = resting energy expenditure.

4. Discussion

To the best of our knowledge, this is the first study of its kind for examining changes in skeletal muscle mass after endoscopic therapy as a primary prophylaxis for LC patients with EVs. This is also a subgroup analysis by utilizing data for our previous RCT for investigating the optimal nutritional support therapy for maintaining and improving the nutritional status of patients receiving prophylactic endoscopic therapy for EVs.[29] As described earlier, reversing skeletal muscle mass is a priority field for therapeutic strategies in LC patients.[5–10] The present study is not a confirmatory study but an exploratory study due to a nature of subgroup analysis. However, we believe that our current results are worthy of reporting in light of novel insights for this study.

In our multivariate analysis, only baseline BTR level was an independent predictor associated with increased SMI. BTR level has also been demonstrated to reduce in LC subjects, and BTR is extensively utilized in our country as an easily measurable laboratory parameter for amino acid asymmetry, and BTR is also closely associated with protein synthesis in the muscle.[6,32] In our preceding examination, we reported that lower BTR level was related to reduced skeletal muscle mass in chronic liver diseases, which are in line with our current results.[33] Further, according to nutritional therapies after endoscopic treatment, no significant

Table 4

Multivariate analysis of baseline variables contributing to the increased SMI.

	Multivariate analysis	
	HR (95% CI)	*P*
Prealbumin, per 1 mg/dL	1.028 (0.763–1.396)	.8536
RBP, per 1 mg/dL	1.112 (0.205–5.921)	.8979
BTR, per 1	2.082 (1.098–4.532)	.0235

BTR = branched-chain amino acid to tyrosine ratio, CI = confidence interval, HR = hazard ration, RBP = retinol-binding protein.

Table 5

Comparison of parameters between at baseline and at Day 50 for the increased SMI group (n = 15) and the nonincreased SMI group (n = 36).

	Increased SMI group (n = 15)			Nonincreased SMI group (n = 36)		
	Baseline	Day 50	*P*	Baseline	Day 50	*P*
BMI, kg/m^2	21.8 (13.9–28.4)	21.9 (13.6–27.8)	.2750	23.2 (13.1–34.4)	22.7 (12.4–32.2)	<.0001
Prealbumin, mg/dL	11.9 (6.1–16.5)	12.9 (5.9–19.2)	.0087	8.6 (2.9–25.8)	10.5 (4.3–26.0)	.0396
Albumin, g/dL	3.5 (2.9–3.9)	3.9 (3.0–4.4)	.0002	3.4 (2.5–4.4)	3.7 (3.1–4.9)	<.0001
RBP, mg/dL	1.6 (0.9–2.5)	1.8 (1–2.5)	.0422	1.1 (0.4–4.4)	1.2 (0.5–5.2)	.0301
npRQ	0.83 (0.74–0.94)	0.82 (0.75–0.89)	.0603	0.82 (0.72–1.11)	0.84 (0.73–1.11)	.6947
Glycoalbumin	18.0 (14.6–41.4)	18.4 (14.5–32.8)	.2812	17.4 (12.4–25.9)	16.7 (11.8–20.6)	.8545
Ammonia	45 (21–103)	27 (16–79)	.0130	40.5 (17–96)	28 (10–67)	<.0001
BTR	4.56 (2.70–7.58)	4.19 (2.62–8.19)	.5284	3.42 (1.61–6.38)	3.70 (1.81–6.33)	.5267
HOMA-IR	2.14 (1.11–8.03)	1.97 (0.87–7.93)	.5811	3.02 (0.83–12.0)	3.27 (0.88–9.46)	.4722

BMI = body mass index, BTR = branched-chain amino acid to tyrosine ratio, HOMA-IR = homeostasis model assessment of insulin resistance, npRQ = nonprotein respiratory quotient, RBP = retinol-binding protein, SMI = skeletal muscle index.

differences in SMI were found between levels at baseline and at Day 50 for each therapy (i.e., RACOL, Aminoleban EN, and Livact) in the present study. In patients with lower baseline BTR level undergoing endoscopic therapy for EVs, nutritional support alone cannot ameliorate skeletal muscle mass, although it can lead to improvement in protein synthesis ability as reflected by serum albumin, prealbumin, and RBP. Exercise can be recommended for such patients. For compensated LC subjects, walking 5000 or more steps per day is reported to be ideal.[34]

It is of note that there were significant correlations between SMI and age ($r_s = -0.5769$, $P = .0004$) and BMI ($r_s = 0.8318$, $P < .0001$) for male, while not for female. One potential reason for these is that differences for lifestyle between genders could underlie. Aging-related muscle mass loss can be pronounced in male patients rather than in female patients. Further, body weight loss can directly reflect skeletal muscle loss for male patients rather than for female patients. In the nonincreased SMI group, BMI at Day 50 significantly decreased as compared with baseline levels. The higher prevalence of male patients at baseline and the relationship between SMI and BMI for male may account for these results. However, due to the small number of cases analyzed, further investigations will be necessary to confirm these results.

This study had limitations of small sample size for analysis and how these short-term clinical outcomes translate into long-term clinical outcomes has yet to be elucidated. Thus, future studies with large cohort and longer observation period will be required. However, our results denote that endoscopic treatments themselves for EVs did not affect the skeletal muscle mass and pretreatment BTR level is a useful indicator for amelioration in skeletal muscle mass after endoscopic therapy for LC patients with EVs. For LC patients undergoing invasive therapies, short-term nutritional therapy alone may not lead to amelioration for the skeletal muscle mass.

In conclusion, pretreatment BTR level can be helpful for predicting increased SMI after endoscopic therapy as a primary prophylaxis for LC patients with EVs.

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