Observational Study

Medicine®

OPEN

Effect of psoas muscle mass after endoscopic therapy for patients with esophageal varices

Hiroki Nishikawa, MD, PhD, Yukihisa Yuri, MD, Hirayuki Enomoto, MD, PhD*, Akio Ishii, MD, PhD, Yoshinori Iwata, MD, PhD, Yuho Miyamoto, MD, Noriko Ishii, MD, Kunihiro Hasegawa, MD, Chikage Nakano, MD, Takashi Nishimura, MD, PhD, Kazunori Yoh, MD, PhD, Nobuhiro Aizawa, MD, PhD, Yoshiyuki Sakai, MD, PhD, Naoto Ikeda, MD, PhD, Tomoyuki Takashima, MD, PhD, Ryo Takata, MD, Hiroko Iijima, MD, PhD, Shuhei Nishiguchi, MD, PhD

Abstract

We aimed to investigate the impact of decrease of muscle mass on survival after eradication of esophageal varices (EVs) treated by endoscopic therapies as a primary prophylaxis in patients with liver cirrhosis (LC). In all, 177 LC individuals with EVs undergoing endoscopic therapies were analyzed. We retrospectively examined the impact of muscle mass decrease as determined by psoas muscle mass (PMM) at the third lumber on computed tomography (depletion of PMM [DPMM]) on survival as compared with serum sodium combined Model for End-stage Liver Disease (MELD-Na). In comparison of the effects of these parameters, we used time-dependent receiver-operating characteristics (ROC) analysis. We also investigated parameters related to overall survival in the univariate and multivariate analyses. This study included 116 males and 61 females with a median age of 66 years. The median follow-up periods were 2.7 years (range 0.1–9.6 years). In all, 110 patients (62.1%) had DPMM. The median MELD-Na score was 7.200 (range −3.451 to 30.558). The MELD-Na score in patients with DPMM (median 7.685) was significantly higher than that in patients without DPMM (median 6.235) ($P = .0212$). In the multivariate analysis, presence of hepatocellular carcinoma ($P < .0001$), presence of DPMM ($P < .0001$), and MELD-Na ≥7.2 ($P = .0438$) were revealed to be significant predictors related to overall survival. In time-dependent ROC analyses, all area under the ROCs for DPMM in each time point were higher than those for MELD-Na in the entire cohort and in patients without hepatocellular carcinoma at baseline (n = 133). In conclusion, for LC patients treated by endoscopic therapies for EVs, DPMM had stronger prognostic impact than MELD-Na.

Abbreviations: AUROC = area under the receiver-operating characteristic curve, BCAA = branched-chain amino acid, CT = computed tomography, DPMM = decrease of psoas muscle mass, EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, EVs = esophageal varices, HCC = hepatocellular carcinoma, L3 = third lumbar vertebra, LC = liver cirrhosis, MELD = Model for End-stage Liver Disease, OS = overall survival, PMI = psoas muscle index, PMM = psoas muscle mass, RC signs = red color signs, RCT = randomized controlled trial, ROC = receiver-operating characteristic curve.

Keywords: comparison, esophageal varices, Model for End-stage Liver Disease, muscle mass depletion, serum sodium

1. Introduction

The liver is the essential organ for the metabolism and creates an interorgan network that metabolizes the 3 major nutrients (ie, carbohydrates, lipids, and proteins) in response to dynamic changes in the human body.[1–7] Liver cirrhosis (LC) is a terminal form in liver diseases, and it is characterized by several metabolic disorders, nutritional disorders, and clinical complications, which denotes that LC is not a single disease entity.[1–8]

In Japan, endoscopic therapies are central to the management of esophageal varices (EVs), which is well-known to be a major complication of LC.[8–10] The frequency of EVs in LC subjects is reported to be 30% to 40% in compensated LC subjects and to be around 60% in decompensated LC subjects.[11,12] The 2 principal treatment methods for EVs are: endoscopic injection sclerotherapy (EIS) and endoscopic variceal ligation (EVL).[8–10] A previous prospective randomized controlled trial (RCT) of comparison of prophylactic EIS and EVL for EVs reported that the recurrence of EVs was higher in the EVL group than in the EIS group (31% vs 11%; $P = .01$).[13] Another prospective RCT demonstrated that the incidence of bleeding after prophylactic EVL for EVs was significantly higher than that after prophylactic EIS.[14] In our country, EIS is currently the first prophylactic endoscopic treatment method for EVs.[8]

The Model for End-stage Liver Disease (MELD) score is calculated by 3 easily available and reproducible laboratory tests.[15] While, MELD-Na score consisted of the MELD score and the serum sodium concentration and using the MELD-Na score is highly predictable for candidates of liver transplantation than the MELD score alone.[16] On the contrary, sarcopenia is a

Editor: Rui Marinho.

H.N. and Y.Y. equally contributed to this work.

The authors have no conflicts of interest to disclose.

Division of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan.

* Correspondence: Hirayuki Enomoto, Department of Hepatobiliary and Pancreatic Disease, Department of Internal Medicine, Hyogo College of Medicine, 1–1, Mukogawacho, Nishinomiyashi, Hyogo 663-8501, Japan (e-mail: enomoto@hyo-med.ac.jp).

Medicine (2017) 96:19(e6868)

Received: 12 November 2016 / Received in final form: 11 April 2017 / Accepted: 16 April 2017

http://dx.doi.org/10.1097/MD.0000000000006868

disease entity as determined by skeletal muscle mass depletion and poor muscle function, and it has attracted attention among clinicians because of the prognostic significance.[17–22] LC can cause secondary sarcopenia due to protein malnutrition and/or energy malnutrition.[18,21,22] Muscle mass depletion can be associated with poor clinical outcomes in patients with LC or hepatocellular carcinoma (HCC).[23–32]

In view of those backgrounds, both MELD-Na and muscle mass depletion may have strong effects on outcomes in patients with LC. However, which clinical entity has stronger impact on clinical outcomes in patients with LC treated by endoscopic therapies for EVs remains unknown. There seems to be urgent need for addressing these clinical questions. The aims of this study were to investigate the impact of decrease of muscle mass on survival after eradication of EVs by endoscopic therapies such as EIS or EVL as a primary prophylaxis in patients with LC.

2. Patients and methods

2.1. Patients

Between January 2007 and August 2015, a total of 212 endoscopic therapy-naive LC individuals with EVs (they had no apparent past history of acute variceal bleeding) were admitted at the Division of Hepatobiliary and Pancreatic disease, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan. All of them received endoscopic therapies for EVs. Of these patients, 10 had been lost to follow-up within 1 year after initial endoscopic treatment, and they were excluded from the current analysis. In the remaining 202 subjects, 177 had available data for psoas muscle mass (PMM) at the third lumbar vertebra (L3) level on computed tomography (CT) scan at baseline, and they were analyzed in this analysis. Follow-up observation after initial endoscopic therapy included periodical blood examinations, radiological evaluation by ultrasonography, CT or magnetic resonance imaging to detect initial HCC incidence, or HCC recurrence every 3 to 6 months. LC was diagnosed radiologically and/or pathologically. In patients who had lower serum albumin level (<3.5 g/dL), branched-chain amino acid (BCAA) therapy or late evening snack with BCAA-enriched snacks were in consideration.[8,33] In patients with LC caused by hepatitis virus, antiviral treatments such as direct-acting antivirals, interferon-based regimens, or nucleoside analogs were in consideration.[8,33] We evaluated muscle mass using CT scans obtained at baseline. We selected L3 level as a reference standard, and identified left and right psoas muscles at the L3 level on the CT images. We carefully measured cross-sectional areas (cm^2) of these muscles by manual tracing on the CT images and their sum was calculated. These sums were normalized for patient height (psoas muscle index [PMI], cm^2/m^2) and we defined male patients with PMI $\leq 6.36\,cm^2/m^2$ and female patients with PMI $\leq 3.92\,cm^2/m^2$ as having decrease of PMM (DPMM) based on the recommendations in Japanese guidelines.[22,34] MELD-Na score was calculated as reported previously.[16] We retrospectively examined the impact of DPMM on survival. In terms of comparison of the effects of DPMM and MELD-Na on survival, we used time-dependent receiver-operating characteristics (ROC) analysis.[35] We also investigated parameters related to overall survival (OS) in the univariate and multivariate analyses. HCC diagnosis and treatment strategies for HCC were as reported elsewhere.[36,37]

The ethical committee in Hyogo College of Medicine approved this study protocol and it strictly adhered to all provisions of the Declaration of Helsinki.

2.2. Endoscopic findings, endoscopic therapy, and follow-up

The EVs were graded according to the previous report: F1 (small), F2 (medium), and F3 (large).[38] Red color signs (RC signs) on esophageal were evaluated by the presence of cherry red spots, hematocystic spots, or red whale markings as reported previously.[38] In our department, for patients with EVs positive for RC signs or F2 or more EVs, prophylactic endoscopic therapies were in principle considered. In cases with well-preserved liver function, EIS monotherapy or EIS and EVL combination therapy was selected, whereas in cases with poor liver function such as cases with ascites or hyperbilirubinemia, EVL monotherapy was selected. Follow-up endoscopic examinations after initial endoscopic therapy were performed 1 to 3 months, and when eradication of EVs was incomplete, additional endoscopic therapies were carried out. Thereafter, endoscopic examinations were performed for the detection of recurrence every 6 to 12 months.

2.3. Statistical analyses

Categorical parameters (sex, presence of HCC, and cause of liver disease) were compared by Fisher exact test. Continuous parameters (age, serum albumin, total bilirubin, prothrombin time, platelet count, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglyceride, fasting blood glucose, serum creatinine, and MELD-Na) were compared by unpaired *t* test or Mann–Whitney *U* test as applicable. In continuous variables, the median value in each variable was selected and was used to divide the study population into 2 groups, which was then regarded as dichotomous covariates. Survival curves were created using the Kaplan–Meier method and compared in the log-rank test. Parameters with a *P* value less than 0.05 in the univariate analysis were finally entered into the multivariate analysis in the Cox proportional-hazards model. OS was defined as the duration from the date of performing initial endoscopic treatment for EVs until death from any cause or the last follow-up visit. In addition, we analyzed time-dependent ROC curves of DPMM and MELD-Na for survival and compared between area under the ROCs (AUROCs) for DPMM and MELD-Na in each time point (1, 2, 3, 4, and 5 years).[35]

Data are shown as the median value (range) unless otherwise stated. Values with $P < .05$ were regarded as statistical significant values. Statistical analysis was performed with the JMP 11 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

The baseline characteristics of the analyzed patients (n = 177) are presented in Table 1. They included 116 males and 61 females with a median (range) age of 66 (22–86) years. In terms of endoscopic findings at initial therapy, F1 EVs were found in 18 patients, F2 in 148, and F3 in 11. RC signs on esophageal were identified in 130 patients (73.4%). At initial therapy, EIS monotherapy was performed in 134 patients, EVL monotherapy in 28, and EIS and EVL combination therapy in 15. The median follow-up periods were 2.7 years (range 0.1–9.6 years). As for causes for LC, hepatitis B virus-related LC was found in 20 patients, hepatitis C virus-related LC in 88 patients, and other causes in 69 patients. Forty-four patients (24.9%) had HCC on radiologic findings at baseline (stage I HCC in 9 patients, stage II

Table 1

Baseline characteristics (n = 177).

Variables	Number or median value (range)
Age, y	66 (22–86)
Sex, male / female	116/61
Cause of liver diseases	
HBV/HCV/others	20/88/69
Endoscopic findings at initial therapy	
Esophageal varices (F1/F2/F3)	18/148/11
Red color signs on esophageal, yes/no	130/47
Treatment, EIS/EVL/EIS and EVL	134/28/15
Presence of HCC, yes/no	44/133
Presence of ascites, yes/no	60/117
Total bilirubin, mg/dL	1.2 (0.3 to 5.6)
Serum albumin, g/dL	3.4 (1.9 to 4.9)
Prothrombin time, %	71.0 (39.6 to 109.2)
Platelet count, $\times 10^4/mm^3$	7.3 (2.4 to 31.2)
AST, IU/L	43 (15 to 371)
ALT, IU/L	32 (8 to 209)
Total cholesterol, mg/dL	146 (68 to 287)
Triglyceride, mg/dL	71 (23 to 341)
Fasting blood glucose, mg/dL	103 (76 to 340)
Serum sodium, mmol/L	140 (117 to 145)
Serum creatinine, mg/dL	0.71 (0.36 to 6.39)
MELD-Na score	7.200 (−3.451 to 30.558)
Decrease of psoas muscle mass, yes/no	110/67

Data are expressed as number or median (range).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, EIS = endoscopic injection sclerotherapy, EVL = endoscopic variceal ligation, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = Model for End-stage Liver Disease.

in 16, stage III in 14, and stage IV in 5). The median PMI for male was 5.41 cm^2/m^2 (range 1.69–9.25 cm^2/m^2), whereas the median PMI for female was 3.97 cm^2/m^2 (range 1.17–8.08 cm^2/m^2). The proportion of DPMM as defined by Japanese Society of Hepatology criteria in male was 70.7% (82/116) and that in female was 45.9% (28/61).[22] Thus, in all, 110 patients (62.1%) had DPMM. In this study, the median MELD-Na score was 7.200 (range −3.451 to 30.558). The MELD-Na score in patients with DPMM (median 7.685, range −2.508 to 22.590) was significantly higher than that in patients without DPMM (median 6.235, range −3.451 to 30.558) ($P = .0212$) (Fig. 1).

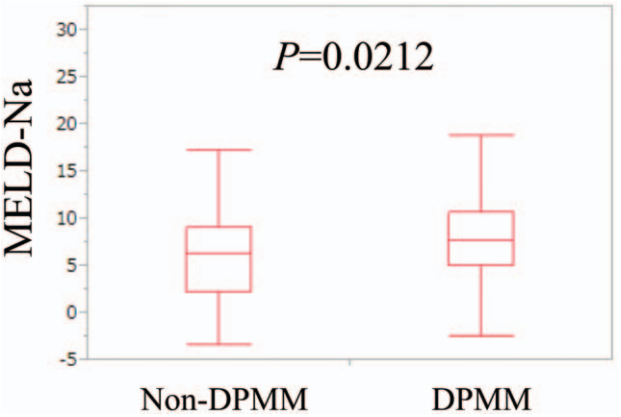

Figure 1. Comparison of MELD-Na score in patients with DPMM and without DPMM. The MELD-Na score in patients with DPMM (median 7.685; range −2.508 to 22.590) was significantly higher than that in patients without DPMM (median 6.235; range −3.451 to 30.558) ($P = .0212$). DPMM = decrease of psoas muscle mass, MELD = Model for End-stage Liver Disease.

3.2. Comparison of baseline characteristics between patients with DPMM (n = 110) and those without DPMM (n = 67)

In terms of comparison of baseline characteristics between patients with DPMM (n = 110) and those without DPMM (n = 67), age ($P = 0.0282$), serum creatinine level ($P = .0073$) and MELD-Na score ($P = .0212$) in the DPMM group were significantly higher than those in the non-DPMM group. The proportion of male ($P = .0018$) and HCC ($P = .0021$) in the DPMM group was significantly higher than that in the non-DPMM group (Table 2).

3.3. Comparison of OS in patients with DPMM and without DPMM

The median follow-up periods were 2.3 years (range 0.1–9.6 years) in patients with DPMM and 3.7 years (range 1.1–9.2 years) in patients without DPMM. The 1, 3, and 5-year cumulative OS rates in patients with DPMM (n = 110) were 83.6%, 53.4%, and 33.9%, respectively, whereas those in

Table 2

Comparison of baseline characteristics between patients with DPMM (n = 110) and those without DPMM (n = 67).

	DPMM (n = 110)	Non-DPMM (n = 67)	*P*
Age, y	67 (36 to 86)	63 (22 to 85)	.0282
Sex, male/female	82/28	34/33	.0018
Presence of HCC, yes/no	36/74	8/59	.0021
Cause of liver disease			
Hepatitis B/hepatitis C/others	11/58/41	9/30/28	.5538
Serum albumin, g/dL	3.4 (1.9 to 4.9)	3.5 (2.3 to 4.4)	.2635
Prothrombin time, %	71.1 (39.6 to 109.2)	70.8 (49.8 to 95.4)	.6835
Platelet count, $\times 10^4/mm^3$	8.2 (2.4 to 31.2)	6.7 (2.4 to 23.4)	.0572
Total bilirubin, mg/dL	1.2 (0.6 to 3.8)	1.2 (0.4 to 5.6)	.6180
AST, IU/L	45 (15 to 371)	39 (17 to 198)	.3315
ALT, IU/L	33.5 (8 to 209)	28 (10 to 145)	.5184
Total cholesterol, mg/dL	140.5 (68 to 287)	150 (87 to 222)	.7261
Triglyceride, mg/dL	72 (23 to 341)	67 (30 to 185)	.6457
Fasting blood glucose, mg/dL	103 (79 to 289)	102 (76 to 340)	.8160
Serum creatinine, mg/dL	0.73 (0.38 to 6.39)	0.65 (0.36 to 2.52)	.0073
MELD-Na	7.685 (−2.508 to 22.590)	6.235 (−3.451 to 30.558)	.0212

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DPMM = decrease of psoas muscle mass, HCC = hepatocellular carcinoma, MELD = Model for End-stage Liver Disease.

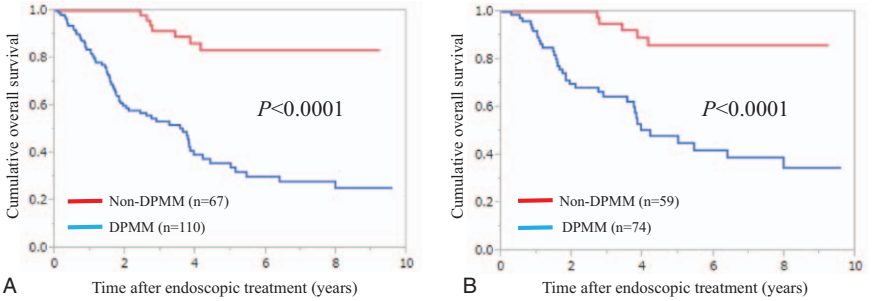

Figure 2. (A) Comparison of OS in patients with DPMM and without DPMM. The 1, 3, and 5-year cumulative OS rates in patients with DPMM were 83.6%, 53.4%, and 33.9%, respectively, whereas those in patients without DPMM were 100%, 91.4%, and 83.3%, respectively ($P < .0001$). (B) Comparison of OS in patients with DPMM and without DPMM (without HCC at baseline). The 1, 3, and 5-year cumulative OS rates in patients with DPMM (n = 74) were 91.9%, 64.5%, and 45.1%, respectively, whereas those in patients without DPMM (n = 59) were 100%, 94.9%, and 85.9%, respectively ($P < .0001$). DPMM = decrease of psoas muscle mass, HCC = hepatocellular carcinoma, OS = overall survival.

patients without DPMM (n = 67) were 100%, 91.4%, and 83.3%, respectively ($P < .0001$) (Fig. 2A). In patients without HCC at baseline (n = 133), the 1, 3, and 5-year cumulative OS rates in patients with DPMM (n = 74) were 91.9%, 64.5%, and 45.1%, respectively, whereas those in patients without DPMM (n = 59) were 100%, 94.9%, and 85.9%, respectively ($P < .0001$) (Fig. 2B).

3.4. Comparison of OS in patients with high MELD-Na score and low MELD-Na score

The median MELD-Na score in this analysis was 7.200. We thus defined patients with MELD-Na score ≥7.2 as high MELD-Na group (n = 89) and patients with MELD-Na score <7.2 as low MELD-Na group (n = 88). The 1, 3, and 5-year cumulative OS rates in the high MELD-Na group (n = 89) were 87.6%, 57.0%, and 38.4%, respectively, whereas those in the low MELD-Na group were 92.1%, 78.8%, and 66.7%, respectively ($P = .0004$) (Fig. 3).

3.5. Causes for death

During the follow-up period, 71 patients (40.1%) died. The causes for death were liver failure in 46 patients, HCC progression (advanced HCC-related death) in 16 patients, and miscellaneous causes in 9 patients.

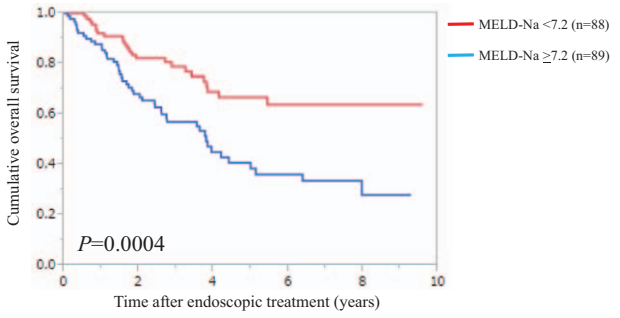

Figure 3. Comparison of OS in patients with high MELD-Na score (≥7.2) and low MELD-Na score (<7.2). The 1, 3, and 5-year cumulative OS rates in the high MELD-Na group (n = 89) were 87.6%, 57.0%, and 38.4%, respectively, whereas those in the low MELD-Na group were 92.1%, 78.8%, and 66.7%, respectively ($P = .0004$). DPMM = decrease of psoas muscle mass, MELD = Model for End-stage Liver Disease.

3.6. Univariate and multivariate analyses of parameters contributing to OS for the entire cohort

Univariate analysis identified the following parameters as significantly associated with OS for the entire cohort (n = 177): age ≥66 years ($P = .0465$); sex ($P = .0173$); presence of HCC ($P < .0001$); presence of ascites ($P = .0162$); serum creatinine ≥0.71 mg/dL ($P = .0327$); serum sodium ≥140 mmol/L ($P = .0140$); presence of DPMM ($P < .0001$); and MELD-Na ≥7.2 ($P = .0004$) (Table 3). Since MELD-Na included serum sodium concentration and serum creatinine level, these were not entered into the multivariate analysis. The hazard ratios and 95% confidence intervals calculated by using multivariate analysis for the 6 significant variables ($P < .05$) in the univariate analysis are presented in Table 2. Presence of HCC ($P < .0001$), presence of DPMM ($P < .0001$), and MELD-Na ≥7.2 ($P = .0438$) were revealed to be significant predictors related to OS in the multivariate analysis (Table 3).

3.7. Time-dependent ROC analyses for OS in all cases

Results for time-dependent ROC analyses at 1, 2, 3, 4, and 5-year of DPMM and MELD-Na in all cases are shown in Fig. 4A. All AUROCs for DPMM in each time point were higher than those for MELD-Na, denoting that DPMM had superior predictive ability for OS over MELD-Na.

3.8. Time-dependent ROC analyses for OS in patients without HCC at baseline

Results for time-dependent ROC analyses at 1, 2, 3, 4, and 5-year of DPMM and MELD-Na in patients without HCC at baseline are shown in Fig. 4B. Similarly, all AUROCs for DPMM in each time point were higher than those for MELD-Na, denoting that DPMM had superior predictive ability for OS over MELD-Na.

4. Discussion

In general, LC patients with EVs have poor prognosis.[11,12,39] To investigate the predictors for LC patients with EVs is clinically of importance. To our knowledge, this is the first comparative study between DPMM and MELD-Na on clinical outcomes in LC patients who underwent endoscopic therapy for EVs. As noted earlier, which of these clinical parameters has stronger prognostic impact in patients with LC treated by endoscopic therapies for

Table 3

Univariate and multivariate analyses of factors linked to overall survival for the entire cohort (n = 177).

Variables	Number of each category	Univariate	Multivariate analysis		
		P	Odds ratio	95% CI	*P*
Age, y ≥66, yes/no	89/88	.0465	1.131	0.690–1.865	.6250
Sex, male/female	116/61	.0173	1.321	0.742–2.443	.3509
Cause of liver disease, HBV/HCV/others	20/88/69	.1870			
Presence of HCC, yes/no	44/133	<.0001	2.828	1.701–4.680	<.0001
Presence of ascites, yes/no	60/117	.0162	1.412	0.861–2.287	.1691
AST ≥43 IU/L, yes/no	92/85	.2167			
ALT ≥32 IU/L, yes/no	90/87	.4162			
Serum albumin ≥3.4 g/dL, yes/no	94/83	.0686			
Total bilirubin ≥1.2 mg/dL, yes/no	94/83	.6592			
Prothrombin time ≥71.0%, yes/no	90/87	.4002			
Platelet count $\geq 7.3 \times 10^4/mm^3$, yes/no	91/86	.5141			
Total cholesterol ≥146 mg/dL, yes/no	89/88	.2803			
Triglyceride ≥71 mg/dL, yes/no	89/88	.1822			
Serum creatinine ≥0.71 mg/dl, yes/no	89/88	.0327			
Serum sodium ≥140 mmol/L	97/80	.0140			
Fasting blood glucose ≥103 mg/dL, yes/no	89/88	.4798			
Decrease of psoas muscle mass, yes/no	110/67	<.0001	5.633	2.690–13.766	<.0001
Treatment, EIS or EIS and EVL/EVL	149/28	.2893			
MELD-Na ≥7.2, yes/no	89/88	.0004	1.553	1.083–2.709	.0438

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = Model for End-stage Liver Disease.

EVs remains an unresolved issue. We therefore performed this comparative analysis to answer this clinical question.

In our current results, although both DPMM and MELD-Na were revealed to be significant prognostic factors in the multivariate analysis, in time-dependent ROC analyses, all AUROCs for DPMM in each time point were higher than those for MELD-Na in the entire cohort and in patients without HCC at baseline. These results denote that DPMM had stronger influence on outcomes than MELD-Na. Our current findings can shed lights in terms of superiority of DPMM over MELD-Na on outcomes. Muscularity assessment as determined by PMI at the L3 level on CT is objective and reproducible, and is not biased by obesity or edematous state that is often seen in patients with decompensated LC. PMI at the L3 level using CT scan is a useful marker and the proposal by Hamaguchi et al[34] of DPMM was well verified in our analysis.

In this study, 110 (62.1%) out of 177 subjects had DPMM. As mentioned in the introduction section, the frequency of EVs in LC is reported to be 30% to 40% in compensated LC subjects and to be around 60% in decompensated LC.[11,12] In addition, the frequency of muscle mass depletion in LC or HCC patients was reported to be 10% to 70% in our country.[23–32] In view of this, LC patients with EVs can be expected to be complicated with muscle mass depletion with high probability, and in such patients, the presence of muscle mass depletion should be always taken into account.

Dietary restriction is essential for endoscopic therapies in patients with EVs, and thus endoscopic therapies can deteriorate protein-energy malnutrition (PEM), which is often seen in LC patients.[40] PEM is linked to decrease of muscle mass.[40] In that sense, some nutritional interventions before and after endoscopic therapies will be needed for ameliorating outcomes.[41] In our previous RCTs, we demonstrated that supplements including both BCAA and a nutritional energy supplement would be beneficial for LC subjects undergoing endoscopic therapies for EVs.[41]

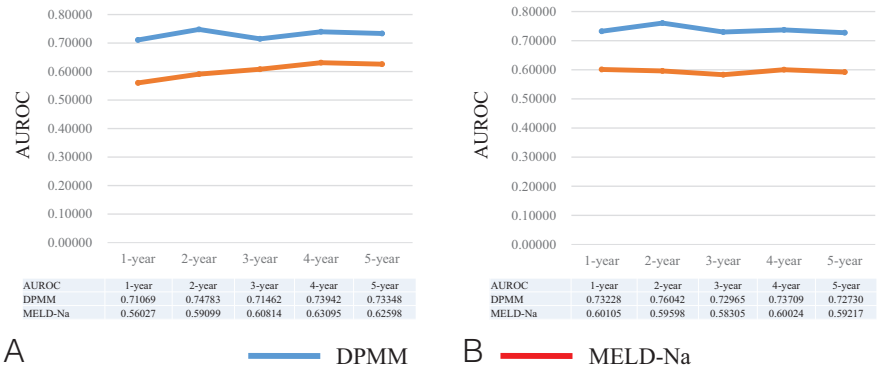

Figure 4. (A) Time-dependent ROC analyses for OS in all cases. All AUROCs for DPMM in each time point were higher than those for MELD-Na. (B) Time-dependent ROC analyses for OS in patients without HCC at baseline. All AUROCs for DPMM in each time point were higher than those for MELD-Na. AUROC = area under the receiver-operating characteristic curve, DPMM = decrease of psoas muscle mass, MELD = Model for End-stage Liver Disease, OS = overall survival, ROC = receiver-operating characteristic curve.

Serum sodium concentration is related to higher risk of mortality in compensated LC patients or in LC patients with EVs treated by EIS.[42,43] Owing to several drawbacks of MELD score, MELD-Na scoring system had been proposed and validated.[16,44] A limitation in MELD-Na scoring system is that during LC status, several factors including diuretics therapy and intravenous hypotonic fluids can cause marked changes in serum sodium concentration. Additionally, the contribution of hyponatremia to outcome prediction may be limited to a specific clinical setting (ie, a low MELD score).[45] Our current results that in time-dependent ROC analyses, all AUROCs for DPMM in each time point were higher than those for MELD-Na may be attributed to these limitations of MELD-Na scoring system.

As for comparison of baseline data in patients with and without DPMM, age and proportion of male and HCC, serum creatinine, and MELD-Na were significantly higher in patients with LSMM. Changes in fat mass and muscle mass are reported to occur with aging and renal function in LC may be associated with prognosis.[7,46–49] On the contrary, the reasons for higher proportion of male and HCC in patients with DPMM are unclear. Presence of HCC may cause cancer-induced cachexia, thus leading to muscle mass depletion.

We have to acknowledge several limitations in this analysis. Firstly, our study is a single-center retrospective observational study using data of PMM on CT imaging, and muscle function (ie, hang grip strength or walking speed) was not analyzed in this analysis. In future studies, not only muscle mass but muscle function should be included in outcome-based analyses. Secondly, the measurement of PMM in our analysis was performed by using manual tracing method, which may lead to under or overestimating the true PMM, potentially causing bias. Thirdly, the median follow-up periods in our study were short for survival analysis. However, our study results denoted that DPMM rather than MELD-Na had higher predictive ability in LC patients undergoing endoscopic therapies for EVs. Results in time-dependent ROC analysis support our claim for the predictive superiority of DPMM over MELD-Na.

In conclusion, in comparison of DPMM and MELD-Na on outcomes in LC patients treated by endoscopic therapies for EVs, DPMM had stronger prognostic impact than MELD-Na.

Acknowledgment

The authors would like to thank all medical staff in our endoscopy room for data collection.

References

[1] Alberino F, Gatta A, Amodio P, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445–50.
[2] Charlton MR. Branched-chain amino acid enriched supplements as therapy for liver disease. J Nutr 2006;136(1 suppl):295S–8S.
[3] Moctezuma-Velázquez C, García-Juárez I, Soto-Solís R, et al. Nutritional assessment and treatment of patients with liver cirrhosis. Nutrition 2013;29:1279–85.
[4] Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. Liver Int 2009;29:1396–402.
[5] Beyoğlu D, Idle JR. The metabolomic window into hepatobiliary disease. J Hepatol 2013;59:842–58.
[6] Kawaguchi T, Izumi N, Charlton MR, et al. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. Hepatology 2011;54:1063–70.
[7] Nishikawa H, Osaki Y. Liver cirrhosis: evaluation, nutritional status, and prognosis. Mediators Inflamm 2015;2015:872152.
[8] Fukui H, Saito H, Ueno Y, et al. Evidence-based clinical practice guidelines for liver cirrhosis 2015. J Gastroenterol 2016;51:629–50.
[9] Miyaaki H, Ichikawa T, Taura N, et al. Endoscopic management of esophagogastric varices in Japan. Ann Transl Med 2014;2:42.
[10] Dai C, Liu WX, Jiang M, et al. Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: a meta-analysis. World J Gastroenterol 2015; 21:2534–41.
[11] Triantos C, Kalafateli M. Endoscopic treatment of esophageal varices in patients with liver cirrhosis. World J Gastroenterol 2014;20:13015–26.
[12] O'Brien J, Triantos C, Burroughs AK. Management of varices in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2013;10:402–12.
[13] Svoboda P, Kantorová I, Ochmann J, et al. A prospective randomized controlled trial of sclerotherapy vs ligation in the prophylactic treatment of high-risk esophageal varices. Surg Endosc 1999;13:580–4.
[14] Gotoh Y, Iwakiri R, Sakata Y, et al. Evaluation of endoscopic variceal ligation in prophylactic therapy for bleeding of oesophageal varices: a prospective, controlled trial compared with endoscopic injection sclerotherapy. J Gastroenterol Hepatol 1999;14:241–4.
[15] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
[16] Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018–26.
[17] Sinclair M, Gow PJ, Grossmann M, et al. Review article: sarcopenia in cirrhosis: aetiology, implications and potential therapeutic interventions. Aliment Pharmacol Ther 2016;43:765–77.
[18] Periyalwar P, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. Clin Liver Dis 2012;16:95–131.
[19] Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748–59.
[20] Santilli V, Bernetti A, Mangone M, et al. Clinical definition of sarcopenia. Clin Cases Miner Bone Metab 2014;11:177–80.
[21] Hanai T, Shiraki M, Nishimura K, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition 2015;31:193–9.
[22] Nishikawa H, Shiraki M, Hiramatsu A, et al. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. Hepatol Res 2016;46:951–63.
[23] Itoh S, Shirabe K, Matsumoto Y, et al. Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. Ann Surg Oncol 2014;21:3063–8.
[24] Hamaguchi Y, Kaido T, Okumura S, et al. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. Liver Transpl 2014;20:1413–9.
[25] Fujiwara N, Nakagawa H, Kudo Y, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol 2015;63:131–40.
[26] Kaido T, Ogawa K, Fujimoto Y, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant 2013;13:1549–56.
[27] Harimoto N, Shirabe K, Yamashita YI, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 2013;100:1523–30.
[28] Masuda T, Shirabe K, Ikegami T, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl 2014;20:401–7.
[29] Iritani S, Imai K, Takai K, et al. Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. J Gastroenterol 2015;50:323–32.
[30] Kamachi S, Mizuta T, Otsuka T, et al. Sarcopenia is a risk factor for the recurrence of hepatocellular carcinoma after curative treatment. Hepatol Res 2016;46:201–8.
[31] Higashi T, Hayashi H, Taki K, et al. Sarcopenia, but not visceral fat amount, is a risk factor of postoperative complications after major hepatectomy. Int J Clin Oncol 2016;21:310–9.
[32] Harimoto N, Yoshizumi T, Shimokawa M, et al. Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma. Hepatol Res 2016;46:1247–55.
[33] Kumada H, Okanoue T, Onji M, et al. Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, Ministry of Health, Labour and Welfare of Japan. Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. Hepatol Res 2010;40:8–13.

[34] Hamaguchi Y, Kaido T, Okumura S, et al. Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. Nutrition 2016;32:1200–5.
[35] Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. Biometrics 2005;61:92–105.
[36] European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer: EASL-EORTC Clinical Practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908–43.
[37] Kudo M, Izumi N, Kokudo N, et al. HCC Expert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–64.
[38] Tajiri T, Yoshida H, Obara K, et al. General rules for recording endoscopic findings of esophagogastric varices (2nd edition). Dig Endosc 2010;22:1–9.
[39] Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). Hepatology 1996;23:1041–6.
[40] Furuichi Y, Imai Y, Miyata Y, et al. Branched-chain amino acid-enriched nutrient increases blood platelet count in patients after endoscopic injection sclerotherapy. Hepatol Res 2016;46:1129–36.
[41] Sakai Y, Iwata Y, Enomoto H, et al. Two randomized controlled studies comparing the nutritional benefits of branched-chain amino acid (BCAA) granules and a BCAA-enriched nutrient mixture for patients with esophageal varices after endoscopic treatment. J Gastroenterol 2015;50:109–18.
[42] Umemura T, Shibata S, Sekiguchi T, et al. Serum sodium concentration is associated with increased risk of mortality in patients with compensated liver cirrhosis. Hepatol Res 2015;45:739–44.
[43] Maruyama H, Kondo T, Sekimoto T, et al. Hyponatremia: a significant factor in a poor prognosis for cirrhosis with Child A/B after variceal eradication. J Hepatobiliary Pancreat Sci 2015;22:771–8.
[44] Kim HJ, Lee HW. Important predictor of mortality in patients with end-stage liver disease. Clin Mol Hepatol 2013;19:105–15.
[45] Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology 2004;40:802–10.
[46] St-Onge MP. Relationship between body composition changes and changes in physical function and metabolic risk factors in aging. Curr Opin Clin Nutr Metab Care 2005;8:523–8.
[47] Cholongitas E, Arsos G, Goulis J, et al. Glomerular filtration rate is an independent factor of mortality in patients with decompensated cirrhosis. Hepatol Res 2014;44:E145–55.
[48] Cholongitas E, Shusang V, Marelli L, et al. Review article: renal function assessment in cirrhosis: difficulties and alternative measurements. Aliment Pharmacol Ther 2007;26:969–78.
[49] Moon SJ, Kim TH, Yoon SY, et al. Relationship between stage of chronic kidney disease and sarcopenia in Korean aged 40 years and older using the Korea National Health and Nutrition Examination Surveys (KNHANES IV-2, 3, and V-1, 2), 2008-2011. PLoS One 2015;10:e0130740.