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

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Abstract
We aimed to investigate the impact 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 lumbar 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. 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.

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.[13] 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
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.\cite{17,18,21,22} LC can cause secondary sarcopenia due to protein malnutrition and/or energy malnutrition.\cite{18,21,22} Muscle mass depletion can be associated with poor clinical outcomes in patients with LC or hepatocellular carcinoma (HCC).\cite{23,24,25,26}

In view of these 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.\cite{27,28} In patients with LC caused by hepatitis virus, antiviral treatments such as direct-acting antivirals, interferon-based regimens, or nucleoside analogs were in consideration.\cite{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 (cm²) 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], cm²/m²) and we defined male patients with PMI ≤6.36 cm²/m² and female patients with PMI ≤3.92 cm²/m² as having decrease of PMM (DPMM) based on the recommendations in Japanese guidelines.\cite{24,25} MELD-Na score was calculated as reported previously.\cite{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.\cite{35} We also investigated parameters related to overall survival (OS) in the univariate and multivariate analyses. HCC diagnosis and treatment strategies for HC were as reported elsewhere.\cite{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).\cite{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.\cite{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).\cite{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/Other                    | 20/88/69                       |
| Endoscopic findings at initial therapy |                     |
| Esophageal vearices (F1/F2/F3)   |                                |
| Red color signs on esophageal, yes/no | 130/47                       |
| Treatment, EIS/EVL/ES            | 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 4.3)               |
| Prothrombin time, %              | 71.0 (39.6 to 109.2)           |
| Platelet count, x10^9/mm³        | 7.3 (2.4 to 31.2)              |
| AST, IU/L                        | 45 (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.

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=0.0073) and MELD-Na score (P=0.0212) in the DPMM group were significantly higher than those in the non-DPMM group. The proportion of male (P=0.0018) and HCC (P=0.0021) in the DPMM group was significantly higher than that in the non-DPMM group (Table 2).

Table 2
Comparison of baseline characteristics between patients with DPMM (n=110) and those without DPMM (n=67).

| Variables                        | 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  |
| Cause of liver disease           |              |                 |        |
| Hepatitis B/hepatitis C/Others   | 11/58/41     | 9/50/28         | .5553  |
| Prothrombin time, %              | 3.4 (1.3 to 4.9) | 3.5 (2.3 to 4.4) | .2635  |
| Platelet count, x10^9/mm³        | 71.1 (39.6 to 109.2) | 70.8 (49.8 to 95.4) | .6835  |
| 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)  | .3915  |
| 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 (0.36 to 6.39) | 0.65 (0.36 to 2.52) | .0073  |
| MELD-Na score                    | 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.
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.

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
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]
Serum sodium concentration is related to higher risk of mortality in compensated LC patients or in LC patients with EVs treated by EIS.\cite{42,43} Owing to several drawbacks of MELD score, MELD-Na scoring system had been proposed and validated.\cite{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).\cite{143} 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.\cite{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.

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