ORIGINAL ARTICLE

*Journal of Cachexia, Sarcopenia and Muscle* 2018; **9**: 860–870
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12333

# Impact of sarcopenia on prognostic value of cirrhosis: going beyond the hepatic venous pressure gradient and MELD score

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## Abstract

**Background** Sarcopenia has been reported as a prognostic factor. We evaluated the impact of sarcopenia to the conventional prognostic factors [Model for End-Stage Liver Disease (MELD) score, Child–Turcotte–Pugh (CTP) score, hepatic venous pressure gradient (HVPG)] in cirrhosis.

**Methods** Overall, 452 patients with cirrhosis were stratified by MELD score (low $< 15$, high $\geq 15$), CTP class, and HVPG [non-clinically significant portal hypertension (CSPH), 6–9 mmHg; CSPH, 10–19 mmHg; extremely severe PH, ≥20 mmHg]. L3 skeletal muscle index as marker of sarcopenia was subdivided into quartiles (47.01–52.25–58.22 $cm^2/m^2$).

**Results** Among the patients, 42% (190/452) presented with sarcopenia. During a median follow-up period of 21.2 months, sarcopenia was associated with mortality (adjusted hazard ratio = 2.253, $P < 0.001$) and specifically with compensated and early decompensated stages of cirrhosis, but not with advanced decompensated stages; low ($P < 0.001$) and high ($P = 0.095$) MELD scores; CTP classes A ($P = 0.034$), B ($P < 0.001$), and C ($P = 0.205$); and non-CSPH ($P = 0.018$), CSPH ($P < 0.001$), and extremely severe PH ($P = 0.846$). In quartiles of sarcopenia, MELD score, CTP class, and HVPG were independent predictors of mortality in non-sarcopenia, but not in severe sarcopenia (MELD, $P = 0.182$; CTP, $P = 0.187$; HVPG, $P = 0.077$).

**Conclusions** Sarcopenia is associated with mortality in compensated and early decompensated cirrhosis, and existing conventional prognostic factors had limited value in severe sarcopenia. Therefore, incorporating sarcopenia in the conventional prognostic factors had added value, particularly in compensated and early decompensated cirrhosis. Subclassification of prognostic factors according to sarcopenia may help to better assess the prognosis of cirrhosis.

**Keywords** Sarcopenia; Prognosis; Portal hypertension; HVPG; MELD

*Received: 7 March 2018; Revised: 3 June 2018; Accepted: 21 June 2018*
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## Introduction

The Model for End-Stage Liver Disease (MELD) and Child–Turcotte–Pugh (CTP) scores are known as the best tools for predicting mortality and can be easily derived from laboratory data of patients with cirrhosis.[1] In addition, the hepatic venous pressure gradient (HVPG) is a well-known predictor for the risk of developing complications related to portal hypertension (PH), as well as mortality.[2] Despite certain advantages, the major limitation of these scores is the lack of nutritional evaluation and functional status of patients.

Sarcopenia is a syndrome characterized by skeletal muscle loss with ageing, which is prevalent in adults with cancer and those with chronic comorbidities such as liver cirrhosis.[3] The

prevalence of concomitant sarcopenia in patients with cirrhosis is reported to be >40%.[4] Sarcopenia, estimated by measuring the cross-sectional area of several muscles on computed tomography (CT) imaging at the L3 vertebral level, reflects protein malnutrition, making the evaluation of nutritional status appealing because it is a quantitative, objective, noninvasive, and simple method.[5] Sarcopenia has emerged as an important and novel prognostic predictor in a variety of clinical conditions. Several studies have reported that sarcopenia is associated with a poor prognosis, as well as reduced survival, before and after liver transplantation.[6,7] Moreover, the MELD–sarcopenia score, which combines MELD score and the psoas muscle area score, was found to be better than the MELD and MELD-Na scores in predicting waiting-list mortality, and its predictive value was found to be superior to that of the MELD score in a recent study.[8] However, there is no consensus on the relationship between sarcopenia and existing prognostic factors (i.e., MELD score, CTP class, and HVPG) in patients with cirrhosis. Moreover, inter-individual differences, such as severity of cirrhosis, may have an impact on sarcopenia.

We evaluated the impact of sarcopenia on survival of categorized individuals based on the MELD score, CTP class, and HVPG. In addition, we compared the discriminative ability of the MELD score, CTP class, and HVPG to assess prognosis in patients with cirrhosis according to the severity of sarcopenia.

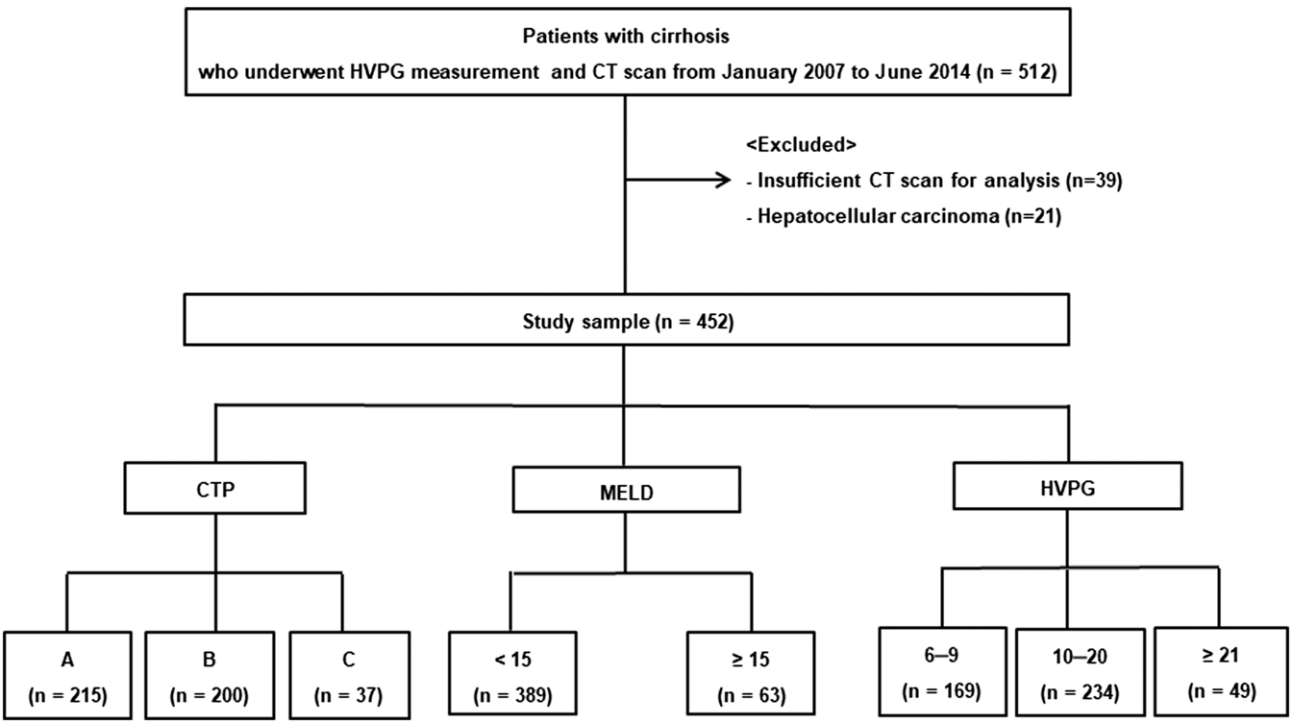
## Materials and methods

### *Study cohort*

We enrolled 512 consecutive patients who were diagnosed with cirrhosis at a single tertiary hospital between January 2007 and June 2014, retrospectively. These patients had been evaluated for their eligibility for receiving liver transplant, but not yet listed; moreover, these patients had also undergone HVPG measurements to assess the severity of portal hypertension and enable decision making when several complications are encountered. We excluded 60 patients who did not have CT scan data available for analysis within 3 months before or after HVPG measurement and patients diagnosed with hepatocellular carcinoma (Figure 1). The remaining 452 patients constituted our study population. Data recovered from medical charts included sex, age, weight, height, cirrhosis aetiology, presence of ascites or hepatic encephalopathy, liver biochemistry, serum creatinine, and prothrombin time (PT).

Cirrhosis was diagnosed based on clinical findings: (i) platelet count of <100 000/μL and ultrasonography findings suggestive of cirrhosis, including a blunted, nodular liver edge accompanied by splenomegaly (bipolar diameter > 12cm) or (ii) clinical signs of portal hypertension, such as ascites, esophageal or gastric varices, and hepatic encephalopathy.[9] The patients underwent HVPG measurement to estimate

**Figure 1** Patient flow diagram.





DOI: 10.1002/jcsm.12333

portal pressure. HVPG was defined as the difference between wedged hepatic venous pressure and free hepatic venous pressure.[10] Clinical and laboratory data used for analysis and the MELD score and CTP class were calculated on the same day as the HVPG measurement.

Two cohorts were established according to the presence of sarcopenia: sarcopenia and non-sarcopenia cohorts. Patients were also divided into four groups according to the MELD score and CTP class as well as HVPG: low MELD ($<15$) and high MELD ($\geq 15$); CTP classes A, B, and C; and non-clinically significant PH (CSPH; HVPG, 6–9 mmHg), CSPH (HVPG, 10–19 mmHg), and extremely severe PH (HVPG, $\geq 20$ mmHg). The primary endpoint of our study was overall survival. Overall survival was evaluated at the maximum duration of follow-up. The date of overall survival was obtained from the patients' medical records and from the Korean Ministry of Government Administration and Home Affairs. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR316048), and the requirement for informed consent was waived. This study was performed in accordance with the Declaration of Helsinki.

### *Assessment of the skeletal muscle mass*

The cross-sectional area of the skeletal muscles ($cm^2$) was measured on CT imaging at the caudal end at the level of the third lumbar (L3) vertebra.[5] In this study, an in-house software was used to identify subcutaneous fat, visceral fat, and muscle (i.e., the psoas, paraspinal muscles, transversus abdominis, rectus abdominis, and internal and external obliques) in CT images for body composition analysis based on Matlab version R2010a (Mathworks Inc., Natick, MA, USA). This open-source software (BMI_CT) is available on following URL (https://sourceforge.net/projects/muscle-fat-area-measurement/).[11] The L3 skeletal muscle index (SMI) was normalized for stature by dividing the muscle area by height squared.[12] Sarcopenia cut-offs for the lumbar SMI were based on a CT-based sarcopenia study of patients with cancer; the L3 muscle area was $\leq 52.4$ $cm^2/m^2$ in men and $\leq 38.5$ $cm^2/m^2$ in women.[13] We performed the validation using the criteria for the SMI by Carey *et al*. (i.e. $<50$ $cm^2/m^2$ for men and $<39$ $cm^2/m^2$ for women)[14] and Martin *et al*. (i.e. men with BMI $<25$: $<43$ $cm^2/m^2$, men with BMI $\geq 25$: $<53$ $cm^2/m^2$, women: $<41$ $cm^2/m^2$).[15] We plotted the cumulative survival with and without sarcopenia according to the criteria of Prado *et al*. (Sarcopenia), Carey *et al*. (SarcopeniaC), and Martin *et al*. (SarcopeniaM). The muscle cross-sectional area at this level was used because it best corresponds to the whole-body muscle mass in patients with and without cancer.[13,16] Muscle areas were analysed by a radiologist who was trained in musculoskeletal anatomy using tissue-specific Hounsfield unit thresholds and was blinded to clinical data. We categorized individuals by L3 SMI quartiles.

### *Statistical analyses*

We analysed the sarcopenia and non-sarcopenia cohorts separately and used chi-square test or Fisher's exact probability test for categorical values and with Mann–Whitney *U* test for continuous variables. We used Cox proportional hazards model to assess the influence of the clinical variables on endpoints. Prognostic factors for survival were analysed by Cox regression univariate and multivariate analyses. For the multivariate analysis, we included covariates with *P* values $< 0.05$ in the univariate analysis. Initial models were adjusted for gender, aetiology of cirrhosis, CTP score, MELD score, and HVPG. In a second model, we adjusted additionally for sarcopenia.

We calculated the cumulative rates of overall survival using the Kaplan–Meier method and censored patients who were lost to follow-up. Patients who had a CT scan were followed from the date of the HVPG measurement until the date of death, liver transplantation, or the last visit. Patients undergoing liver transplantation were censored in survival analysis. We performed the log-rank test to compare the differences between the groups. A *P* value $< 0.05$ was considered significant. The statistical analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA).

## Results

### *Baseline characteristics*

The baseline characteristics of the 452 patients are summarized in Table 1. A total of 379 patients were men (83.8%), with mean age of 51.8 ± 8.8 years. Aetiology of liver cirrhosis was alcohol consumption (69.2%), viral hepatitis (26.5%), and other causes (4.2%). The mean MELD score and HVPG were 10.4 ± 3.6 and 14.3 ± 5.0. Median L3 SMI was 52.2 $cm^2/m^2$ [interquartile range (IQR), 46.9–58.2], and the median L3 SMI was higher in men [53.0 $cm^2/m^2$ (IQR, 47.9–58.8)] than in women [46.6 $cm^2/m^2$ (IQR, 40.9–54.0), $P < 0.001$].

Sarcopenia was present in 190 patients (42.0%). The proportion of men (93.7% vs. 76.7%) and alcoholic cirrhosis (80.0% vs. 61.5%) was higher in the sarcopenia than in the non-sarcopenia. Patients with sarcopenia had a lower body mass index, PT international normalized ratio, and MELD score than patients without sarcopenia. The proportions of the CTP class and mean HVPG were not different between groups.

### *Overall survival*

For 21.2 months (IQR, 8.0–38.2 months) follow-up period, 88 patients (19.5%) died. A univariate analysis showed that male sex [hazard ratio (HR) = 2.260, 95% confidence interval (CI)

**Table 1** Baseline characteristics of patients according to the presence of sarcopenia

| | All ($n$ = 452) | Sarcopenia ($n$ = 190) | No sarcopenia ($n$ = 262) | $P$ value |
|---|---|---|---|---|
| Age (years)[a] | 51.87 ± 8.83 | 51.54 ± 9.58 | 52.10 ± 8.27 | 0.506 |
| Sex | | | | |
| Male, $n$ (%) | 379 (83.8) | 178 (93.7) | 201 (76.7) | <0.001 |
| Aetiology, $n$ (%) | | | | <0.001 |
| Viral | 120 (26.5) | 36 (18.9) | 84 (32.1) | |
| Alcohol | 313 (69.2) | 152 (80.0) | 161 (61.5) | |
| Others | 19 (4.2) | 2 (1.0) | 17 (6.4) | |
| Child–Pugh stage, $n$ (%) | | | | 0.250 |
| A | 215 (47.6) | 93 (48.9) | 122 (46.6) | |
| B | 200 (44.2) | 87 (45.8) | 113 (43.1) | |
| C | 37 (8.2) | 10 (5.3) | 27 (10.3) | |
| Height ($m^2$) | 2.72 (2.56, 2.89) | 2.78 (2.65, 2.92) | 2.68 (2.49, 2.83) | <0.001 |
| BMI ($kg/m^2$) | 23.05 (20.71, 24.77) | 20.86 (19.25, 22.87) | 24.15 (22.54, 26.29) | <0.001 |
| Albumin (g/dL) | 3.3 (3.0, 3.7) | 3.3 (3.0, 3.6) | 3.3 (2.9, 3.7) | 0.853 |
| Total bilirubin (mg/dL) | 1.2 (0.7, 2.1) | 1.1 (0.7, 1.9) | 1.2 (1.09, 1.35) | 0.477 |
| PT (INR) | 1.18 (1.08, 1.33) | 1.15 (1.04, 1.29) | 1.2 (1.09, 1.35) | 0.001 |
| Creatinine (mg/dL) | 0.7 (0.6, 0.88) | 0.7 (0.6, 0.8) | 0.74 (0.6, 0.9) | 0.263 |
| MELD score | 9.0 (8.0, 12.75) | 9.0 (7.0, 12.0) | 10.0 (8.0, 13.0) | 0.034 |
| HVPG, mmHg | 14.0 (11.0, 17.0) | 14.0 (10.0, 17.0) | 14.0 (11.0, 17.25) | 0.313 |

BMI, body mass index; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PT, prothrombin time.
[a]Data are reported as mean (±standard deviation).

1.043–4.893, $P$ = 0.039], viral aetiology of cirrhosis (HR = 0.406, 95% CI 0.032–1.638, $P$ = 0.004), albumin level (HR = 0.322, 95% CI 0.208–0.498, $P < 0.001$), PT international normalized ratio (HR = 5.848, 95% CI 2.617–13.067, $P < 0.001$), total bilirubin level (HR = 1.083, 95% CI 1.035–1.134, $P < 0.001$), MELD score (HR = 1.140, 95% CI 1.083–1.199; $P < 0.001$), CTP class (HR 1.269; 95% CI 1.153–1.397, $P < 0.001$), HVPG (HR = 1.098, 95% CI 1.057–1.141, $P < 0.001$), and sarcopenia (HR = 2.316, 95% CI 1.518–3.534, $P < 0.001$) were significantly associated with overall survival. A multivariate analysis showed that sarcopenia was associated with higher mortality (adjusted HR = 2.253, 95% CI 1.442–3.519, $P < 0.001$) after adjusting for MELD score, CTP class, and HVPG (Table 2).

The Kaplan–Meier curve analysis also demonstrated an association between sarcopenia and overall survival (Figure 2). In the sarcopenia cohort, 49 (25.8%) patients died during the follow-up period. The cumulative probabilities of survival at 12, 24, 36, 60, and 72 months were 85.7, 75.7, 62.9, 42.4, and 42.4%, respectively. Thirty-nine (14.9%) patients died in the non-sarcopenia cohort. The cumulative probabilities of survival at 12, 24, 36, 60, and 72 months were 95.5, 86.8, 80.8, 72.8, and 72.8%, respectively. Causes of death are listed in Supporting Information, Table S1.

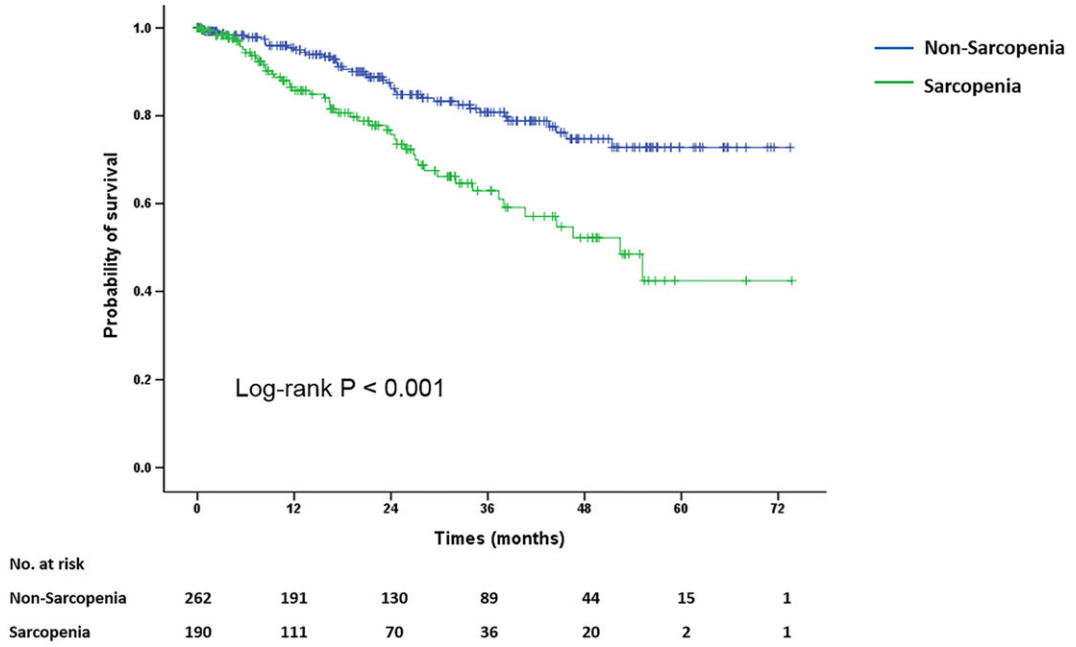
**Table 2** Variables independently associated with overall survival

| Variables | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | $P$ value | HR | 95% CI | $P$ value |
| Sex (male) | 2.260 | 1.043–4.893 | 0.039 | 1.226 | 0.522–2.880 | 0.640 |
| Age (year) | 0.981 | 0.958–1.005 | 0.123 | | | |
| Aetiology of cirrhosis | | | | | | |
| Alcohol | Reference | | | Reference | | |
| Viral | 0.406 | 0.221–0.748 | 0.004 | 0.469 | 0.249–0.885 | 0.020 |
| Others | 0.228 | 0.032–1.638 | 0.142 | 0.549 | 0.068–4.449 | 0.575 |
| Albumin (g/dL) | 0.322 | 0.208–0.498 | <0.001 | | | |
| Platelet | 1.000 | 1.000–1.000 | 0.121 | | | |
| Creatinine (mg/dL) | 1.347 | 0.863–2.101 | 0.190 | | | |
| PT (INR) | 5.848 | 2.617–13.067 | <0.001 | | | |
| Total bilirubin (mg/dL) | 1.083 | 1.035–1.134 | <0.001 | | | |
| CTP class | | | | | | |
| A | Reference | | | Reference | | |
| B | 1.949 | 1.213–3.132 | 0.006 | 1.197 | 0.690–2.077 | 0.523 |
| C | 3.856 | 2.019–7.365 | <0.001 | 1.831 | 0.812–4.129 | 0.145 |
| MELD score | 1.140 | 1.083–1.199 | <0.001 | 1.088 | 1.015–1.166 | 0.017 |
| HVPG (mmHg) | 1.098 | 1.057–1.141 | <0.001 | 1.066 | 1.024–1.111 | 0.002 |
| Sarcopenia | 2.316 | 1.518–3.534 | <0.001 | 2.170 | 1.398–3.369 | 0.001 |

CI, confidence interval; CTP, Child–Turcotte–Pugh; HR, hazard ratio; HVPG, hepatic venous pressure gradient; INR, international normalized ratio; MELD; Model for End-Stage Liver Disease; PT, prothrombin time.


DOI: 10.1002/jcsm.12333

**Figure 2** Kaplan–Meier estimates of overall survival according to the presence of sarcopenia. Kaplan–Meier survival curves in patients with sarcopenia compared with those without sarcopenia. Log-rank test $P < 0.001$.




## *Prognostic value of sarcopenia according to the severity of Child–Turcotte–Pugh, Model for End-Stage Liver Disease, and hepatic venous pressure gradient*

We examined the impact of sarcopenia on mortality in categorized patients and determined the MELD score, CTP class, and HVPG to be independent predictive factors for survival in patients with cirrhosis.

In a subgroup analysis using the MELD score, the proportion with low MELD score (88.9% vs. 84.0%) and high MELD score (11.1% vs. 16.0%) was not significantly different between the sarcopenia and non-sarcopenia cohorts (Supporting Information, Table S2). The cumulative probability of survival was higher in patients without sarcopenia than in those with sarcopenia in the low-MELD-score group (<15, log-rank $P < 0.001$), whereas survival was not significantly different, regardless of the presence or absence of sarcopenia, in the high-MELD-score group (≥15, log-rank $P = 0.095$) (Figure 3A). In particular, the survival of the low-MELD-score group with sarcopenia was similar to that of the high-MELD-score group without sarcopenia (log-rank $P = 0.467$).

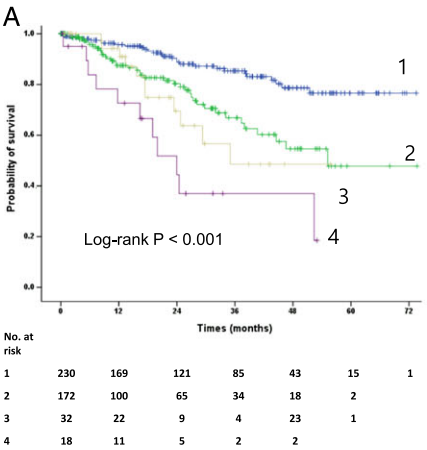
In a subgroup analysis using CTP class, the proportions of the CTP class (A, 48.9% vs. 46.6%; B, 45.8% vs. 43.1%; and C, 5.3% vs. 10.3%) were similar between the sarcopenia and non-sarcopenia cohorts (Supporting Information, Table S2). The cumulative probability of survival was higher among patients without sarcopenia than among those with sarcopenia in CTP classes A (log-rank $P = 0.034$) and B (log-rank $P < 0.001$), whereas survival was not significantly different between patients with or without sarcopenia in CTP class C (log-rank $P = 0.205$) (Figure 3B). Of note, patients with sarcopenia in CTP class A tended to have a higher mortality rate than those without sarcopenia in CTP class B, although the difference was not statistically significant.

In a subgroup analysis using HVPG, the proportion of non-CSPH (20.0% vs. 18.3%), CSPH (67.9% vs. 65.6%), and extremely severe PH (12.1% vs. 16.0%) was not significantly different between the sarcopenia and non-sarcopenia cohorts (Supporting Information, Table S2). The cumulative probability of survival was higher among patients without sarcopenia than among those with sarcopenia in the non-CSPH group (log-rank $P = 0.018$) and CSPH group (log-rank $P < 0.001$), but there was no difference in survival according to the presence of sarcopenia in the patient group with extremely severe PH (log-rank $P = 0.846$) (Figure 3C). Overall survival was similar for the sarcopenia cohort with non-CSPH and the non-sarcopenia cohort with CSPH. Specifically, the prognosis of the CSPH group with sarcopenia was like that of the patient group with extremely severe PH group (log-rank $P = 0.517$ and $P = 0.774$).

## *Prognostic value of L3 skeletal muscle index according to the severity of Child–Turcotte–Pugh, Model for End-Stage Liver Disease, and hepatic venous pressure gradient*

We also evaluated the L3 SMI as continuous values in patients classified by severity of liver function. As a result, L3 SMI was

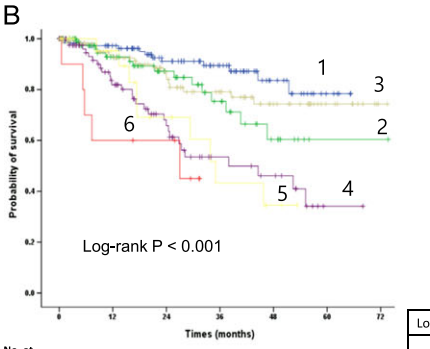
**Figure 3** Prognostic value of sarcopenia according to severity of liver cirrhosis. (A) Kaplan–Meier survival curves according to sarcopenia and the Model for End-Stage Liver Disease (MELD) score. The impact of sarcopenia was significant in patients with low MELD scores (<15) but not in patients with high MELD scores (≥15). (B) Kaplan–Meier survival curves according to sarcopenia and the Child–Turcotte–Pugh (CTP) class. The impact of sarcopenia was significant in patients with CTP A/B class but not in patients with a CTP C class. (C) Kaplan–Meier survival curves according to sarcopenia and the hepatic venous pressure gradient (HVPG). The impact of sarcopenia was significant in patients with low and moderate HVPG (<20 mmHg) but not in patients with high HVPG (≥20 mmHg). $^{*}P < 0.05$.




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | 230 | 169 | 121 | 85 | 43 | 15 | 1 |
| 2 | 172 | 100 | 65 | 34 | 18 | 2 | |
| 3 | 32 | 22 | 9 | 4 | 23 | 1 | |
| 4 | 18 | 11 | 5 | 2 | 2 | | |

Log-rank test between each combined conditions

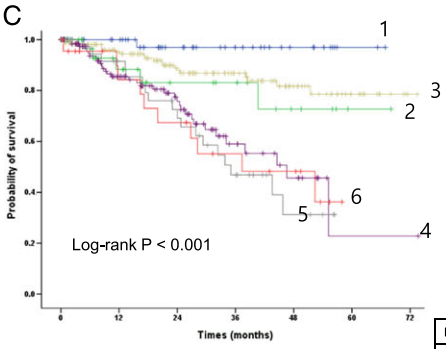
| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| 1 | - | < 0.001* | 0.001* | < 0.001* |
| 2 | | | 0.467 | 0.002* |
| 3 | | | | 0.095 |




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | 122 | 93 | 65 | 44 | 19 | 5 | |
| 2 | 93 | 56 | 36 | 21 | 9 | 1 | |
| 3 | 113 | 81 | 56 | 40 | 23 | 10 | 1 |
| 4 | 87 | 49 | 29 | 15 | 11 | 1 | |
| 5 | 27 | 17 | 9 | 5 | 2 | | |
| 6 | 10 | 6 | 5 | | | | |

Log-rank test between each combined conditions

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1 | - | 0.034* | 0.172 | < 0.001* | < 0.001* | < 0.001* |
| 2 | | | 0.471 | 0.011* | 0.058 | 0.002* |
| 3 | | | | < 0.001* | 0.010* | 0.004* |
| 4 | | | | | 0.966 | 0.384 |
| 5 | | | | | | 0.205 |




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1 | 97 | 72 | 48 | 36 | 21 | 7 | |
| 2 | 72 | 37 | 24 | 13 | 6 | 1 | |
| 3 | 131 | 94 | 65 | 43 | 21 | 8 | 1 |
| 4 | 103 | 65 | 40 | 17 | 10 | 1 | |
| 5 | 34 | 25 | 17 | 10 | 2 | | |
| 6 | 15 | 9 | 6 | 6 | 4 | | |

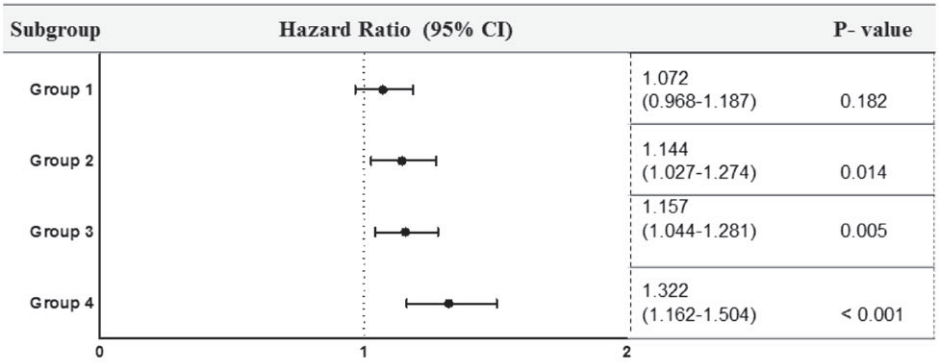
Log-rank test between each combined conditions

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1 | - | 0.018* | 0.056 | < 0.001* | < 0.001* | < 0.001* |
| 2 | | | 0.367 | 0.091 | 0.055 | 0.099 |
| 3 | | | | < 0.001* | < 0.001* | < 0.001* |
| 4 | | | | | 0.517 | 0.774 |
| 5 | | | | | | 0.846 |

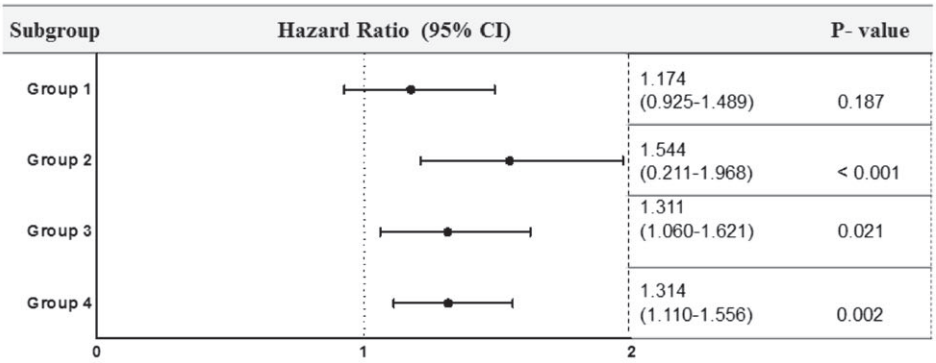
associated specifically with compensated and early decompensated stages of cirrhosis, but not with advanced decompensated stages; low (HR, 0.96; 95% CI, 0.94–0.99; *P* = 0.01) and high (HR, 1.02; 95% CI, 0.97–1.06; *P* = 0.35) MELD scores; CTP classes A, B (HR, 0.96; 95% CI, 0.94–0.99; *P* = 0.01), and C (HR, 1.03; 95% CI, 0.97–1.10; *P* = 0.21); and non-CSPH, CSPH (HR, 0.96; 95% CI, 0.94–0.99; *P* = 0.03), and extremely severe PH (HR, 1.01; 95% CI, 0.97–1.06; *P* = 0.47). These results with

**Table 3** The prognostic value of MELD score, Child-Turcotte-Pugh class, and HVPG according skeletal mass index

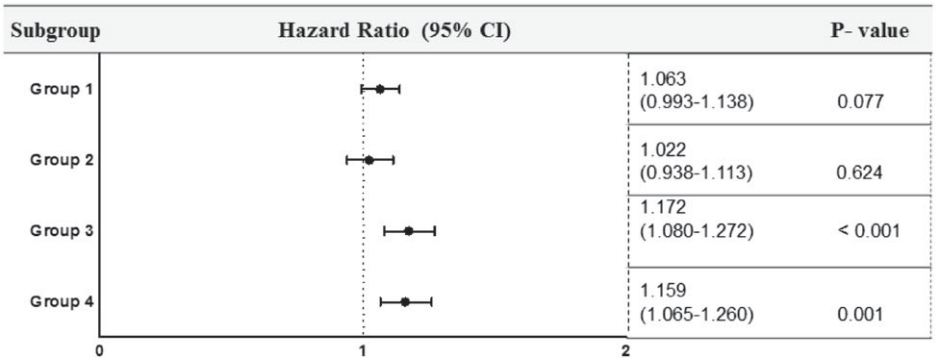
(A) Hazard ratio estimates for the effect of MELD score on mortality according skeletal mass index




(B) Hazard ratio estimates for the effect of Child-Turcotte-Pugh score on mortality according skeletal mass index




(C) Hazard ratio estimates for the effect of HVPG on mortality according skeletal mass index




Group 1: L3 skeletal muscle index (SMI) <47.01 ($cm^2/m^2$), Group 2: L3 SMI 47.01–52.25 ($cm^2/m^2$), Group 3: L3 SMI 47.01–52.25 ($cm^2/m^2$), Group 4: L3 SMI >58.22 ($cm^2/m^2$).
CI, confidence interval; HVPG, hepatic venous pressure gradient; MELD; Model for End-Stage Liver Disease.

L3 SMI as continuous variable are consistent original result in this study with sarcopenia as categorical variable.

### *Validation using the criteria for sarcopenia*

In validation results, sarcopeniaC was associated with mortality (HR = 1.570, $P$ = 0.037) (Supporting Information, Figure S1A). In a subgroup analysis using CTP class, the cumulative probability of survival was higher among patients without sarcopeniaC than among those with sarcopeniaC in CTP class B (log-rank $P$ = 0.037), whereas survival was not significantly different between patients with and without sarcopeniaC in CTP class A (log-rank $P$ = 0.110) and CTP class C (log-rank $P$ = 0.587) (Supporting Information, Figure S2A). However, in a subgroup analysis using MELD score and HVPG, sarcopeniaC was associated with mortality specifically with compensated and early decompensated stages of cirrhosis, but not with advanced decompensated stages; low (log-rank $P$ = 0.043) and high (log-rank $P$ = 0.545) MELD scores (Supporting Information, Figure S2B); and non-CSPH (log-rank $P$ = 0.003), CSPH (log-rank $P$ = 0.015), and extremely severe PH (log-rank $P$ = 0.130) (Supporting Information, Figure S2C). However, sarcopeniaM was not associated with mortality (HR = 1.225, $P$ = 0.474) (Supporting Information, Figure S1B).

### *The prognostic value of the Model for End-Stage Liver Disease, Child–Turcotte–Pugh, and hepatic venous pressure gradient according to the severity of sarcopenia*

To analyse the prognostic values of the MELD score, CTP class, and HVPG according to the degree of sarcopenia, we categorized individuals by L3 SMI quartiles ($<$46.9, 46.9–52.2, 52.2–58.2, and $>$58.2 $cm^2/m^2$) into Groups 1 to 4 (Table 3). Groups 1 and 2 were defined as the population with severe and moderate sarcopenia, respectively, and Groups 3 and 4 represented the population without sarcopenia.

In Group 1, the MELD score (HR = 1.072; $P$ = 0.182), CTP class (HR = 1.174; $P$ = 0.187), and HVPG (HR = 1.063; $P$ = 0.077) were not independent predictors of mortality. In Group 2, higher MELD score (HR = 1.144, 95% CI 1.027–1.274, $P$ = 0.014) and CTP class (HR = 1.544, 95% CI 1.211–1.968, $P < 0.001$) were associated with increased mortality. In Groups 3 and 4, the MELD score, CTP class, and HVPG were independent predictors of mortality. Overall, we found that MELD score, CTP class, and HVPG, which are the existing important prognostic factors in patients with cirrhosis, were good prognostic factors for survival in the non-sarcopenia group but not in the severe sarcopenia group across the L3 SMI categories.

Additionally, we classified all patients by L3 SMI with considering the gender. Male patients ($n$ = 379, 83.8%) were categorized individuals by L3 SMI quartiles ($<$47.0, 47.0–53.0, 53.0–58.8, and $>$58.8 $cm^2/m^2$) and into Groups 1 to 4 (Supporting Information, Table S3). In Group 1, the MELD score (HR = 1.094; $P$ = 0.078), CTP class (HR = 1.257; $P$ = 0.094), and HVPG (HR = 1.057; $P$ = 0.118) were not independent predictors of mortality. In Group 2, MELD score (HR = 1.142, $P$ = 0.057), CTP class (HR = 1.225, $P$ = 0.079), and HVPG (HR = 1.038, $P$ = 0.367) also were not associated with increased mortality. However, in Groups 3 and 4, the MELD score (Group 3; HR = 1.145, $P$ = 0.023, Group 4; HR = 1.320, $P < 0.001$) CTP class (Group 3; HR = 1.411, $P$ = 0.015, Group 4; HR = 1.296, $P$ = 0.003), and HVPG (Group 3; HR = 1.181, $P < 0.001$, Group 4; HR = 1.153, $P$ = 0.001) were independent predictors of mortality. Female patients ($n$ = 73, 16.2%) also were categorized individuals by L3 SMI quartiles ($<$40.0, 40.0–46.6, 46.6–54.0, and $>$54.0 $cm^2/m^2$) into Groups 1 to 4 (Supporting Information, Table S4). Unlike the results of men, the MELD score, CTP class, and HVPG were not independent predictors of mortality in all groups of female patients.

## Discussion

We investigated the prognostic value of sarcopenia on mortality and its correlation with existing prognostic factors (i.e., MELD score, CTP class, and HVPG) in patients with cirrhosis. With the prognostic values of sarcopenia being based on liver function, sarcopenia was an independent predictor of survival in compensated and early decompensated cirrhosis (MELD $<$ 15; CTP classes A and B; non-CSPH and CSPH). However, sarcopenia was not a prognostic factor in advanced decompensated cirrhosis [MELD $\geq$ 15; CTP class C; extremely severe PH (HVPG $\geq$20 mmHg)]. Subsequently, when we analysed the existing conventional prognostic factors (MELD score, CTP class, and HVPG) in cirrhosis according to the degree of sarcopenia, interestingly, the survival predictabilities of MELD, CTP, and HVPG were maintained in the non-sarcopenia group. Conversely, the prognostic values of conventional prognostic indices were weaker or disappeared in those with moderate and severe sarcopenia. As a result, our study revealed the potential limitation of these conventional prognostic factors in patients with severe muscle depletion.

In our study, there was also a poor correlation between sarcopenia and Child–Pugh scores ($r$ = 0.04, $P$ = 0.398), MELD score ($r$ = 0.047, $P$ = 0.319), and HVPG ($r$ = 0.01, $P$ = 0.832). So we hypothesized that sarcopenia seems to reflect chronic deterioration in the general physical and nutritional condition rather than the severity of the liver disease. In other words, sarcopenia is crucial for assessment of nutritional and physical status of patients with cirrhosis and more accurate prognosis of outcomes and independent of liver function, which is emerging as a vital clinical assessment that relates to better treatment decisions and more accurate prognosis of outcomes.

Sarcopenia has been associated with poorer survival in patients with cirrhosis who are being evaluated for or are awaiting liver transplantation.[17,18] Our results confirm data from previous studies showing that sarcopenia may be considered a new prognostic factor. Up to date, patients with the highest MELD scores are prioritized during the allocation of donor livers. However, 71% of patients who died on the waiting list had a MELD score $\leq 25$ at registration.[19,20] As a result, the limitation of the MELD score is that it does not reflect the nutritional and functional status of patients. Durand *et al*. reported that the MELD–sarcopenia score, which combines MELD and psoas muscle area scores, is superior to the MELD score.[8,21] These findings are consistent with our results, suggesting that including a muscularity assessment could better assess patients, and a measure of sarcopenia represents an attractive prognostic factor to improve organ allocation in patients with cirrhosis, in addition to the MELD score.

Our study showed that the impact of sarcopenia was more pronounced in patients with MELD score $< 15$, CTP class A/B, and HVPG $<20$ mmHg. In contrast, there was no evidence that sarcopenia was significantly associated with mortality in patients with MELD score $\geq 15$, CTP class C, and HVPG $\geq 20$ mmHg. Tandon *et al*. also noted that the impact of sarcopenia was significant in patients with low MELD scores ($<15$), but not in patients with high MELD scores ($\geq 15$).[16] These results, together with our data, are consistent with those of the study by Merli *et al*., which demonstrated that muscle loss was predictive of mortality in CTP classes A and B patients, but not in class C patients.[22] Moreover, we also demonstrated a further validation with the HVPG. The HVPG is not only significantly correlated with the CTP and MELD scores, but also predicts haemodynamic and clinical features in patients with cirrhosis.[23–25] HVPG is a well-known, robust predictor of survival in cirrhosis and is associated with the severity of PH.[26] Although HVPG measurement has drawbacks of being invasive and not widely available, it is a reliable and accurate tools to estimate PH.[27] The HVPG data in our large population add valuable information on survival in compensated and decompensated cirrhosis. According to the literature, clinical decompensation is negligible in patients with an HVPG $\geq 10$ mmHg.[28] Therefore, HVPG $\geq 10$ mmHg has been denominated 'clinically significant PH'. Also, an HVPG $\geq 20$ mmHg identifies patients with greater probabilities of poorer evolution in decompensated cirrhosis.[29] Thus, an HVPG $\geq 20$ mmHg has been defined as extremely severe PH.[30,31] Therefore, we measured HVPG by stratifying severity of PH into three groups: 6–9, 10–19, and $\geq 20$ mmHg. Our results are meaningful in terms of the demonstration of the relevance between PH and sarcopenia. These HVPG results are in line with previous studies showing that sarcopenia appears to have a role as a predictor of mortality; however, its role differs according to the severity of cirrhosis. Therefore, sarcopenia may be useful as an objective and potentially modifiable prognostic factor for risk-stratifying patients with compensated and early decompensated cirrhosis. These results demonstrate the importance of immediate action in response to changes in the nutritional status of liver patients even in the early stages of the disease.

The strengths of the present study include the evaluation of the prognostic value of sarcopenia as a predictor of mortality in many patients. Our results revealed the limitations of conventional prognostic values in patients with cirrhosis by analysing the correlation between the conventional factors (i.e., MELD score, CTP class, and HVPG) and a new factor (i.e., sarcopenia). Moreover, we report herein the correlation between sarcopenia and HVPG as an independent prognostic factor for cirrhosis.

Nevertheless, a major limitation of our analysis is that it was based on a retrospective study, although in our study, there were no repeat skeletal muscle area measurements using serial CT imaging. As a result, it could not be demonstrated whether correcting sarcopenia could improve survival in patients with cirrhosis. Further studies are necessary to clarify the beneficial effects of correcting sarcopenia on long-term survival. Also, there is a possibility that the association between sarcopenia and survival in patients with advanced decompensated cirrhosis could have been underestimated, because of relatively small number of patients. Therefore, further prospective research should be performed to clarify the impact of sarcopenia in patients with advanced decompensated cirrhosis. We were unable to collect data on muscle function (strength or performance). Recent consensus recommends using the presence of both low muscle mass and low muscle function for defining sarcopenia[32–34]; however, we analysed the prognostic value of low skeletal muscle mass only. Although sarcopenia is already a widely recognized term, an accurate and universal definition is needed. Another limitation of our study is that we used a definition of sarcopenia based on cut-off values validated in a population of individuals with cancer because predefined values for sarcopenia in patients with cirrhosis are still lacking. Recently, a large cohort study validated the MELD–sarcopenia score and showed that survival was different between patients with and without sarcopeniaM but not between patients with and without sarcopeniaC.[35] This result is interesting because it is contrasting to the results of the present study. The reason for this is that BMI of Asians is lower than that of individuals in the western region; thus, sarcopenia could be underestimated in male patients when the criteria established by Martin *et al*. (sarcopeniaM) is used. Therefore, it is considered that further validation study for estimating the cut-off value of sarcopenia is needed for the application of MELD–sarcopenia score in Asian population with BMI-specific threshold values (sarcopeniaM).

In conclusion, the results of this study suggest that sarcopenia measured at the L3 SMI is an attractive and

readily available parameter that may be predictive of mortality in patients with cirrhosis. Interestingly, using sarcopenia along with conventional prognostic factors showed patients with early decompensated cirrhosis had worse prognosis than those with advanced decompensated if they had sarcopenia. These results reiterate that the maintenance of an adequate nutritional status seems to have greater effect, when achieved in patients having better liver function. Although the MELD score, CTP class, and HVPG are known to be important conventional prognostic factors in patients with cirrhosis, their ability to assess prognosis was reduced in patients with severe sarcopenia in our study. Therefore, incorporating sarcopenia in the conventional prognostic factors, such as the MELD score, CTP score, and HVPG, had added value in predicting mortality, especially in compensated and early decompensated cirrhosis. The association of sarcopenia with conventional prognostic factors may provide insights into the new subclassification of prognostic factors according to sarcopenia to assess the prognosis of cirrhosis.

## Acknowledgement

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.[36]

## Conflict of interest

The authors do not have any conflict of interest to disclose.

## Funding

This work was supported by the National Research Foundation of Korea grant funded by the Korea government (2017R1A2B4009199, 2017R1A5A2015369 and 2018R1C1B5044890).

## Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Causes of death in patients with and without sarcopenia.
**Table S2.** Prevalence of sarcopenia according to MELD score, Child-Turcotte-Pugh class, and HVPG.
**Table S3.** The prognostic value of MELD score, Child-Turcotte-Pugh class, and HVPG according skeletal mass index in male patients.
**Table S4.** The prognostic value of MELD score, Child-Turcotte-Pugh class, and HVPG according skeletal mass index in female patients.
**Figure S1.** Kaplan–Meier estimates of overall survival according to the presence of sarcopeniaC (A) and sarcopeniaM (B). Kaplan–Meier survival curves in patients with sarcopenia C/M compared with those without sarcopenia C/M. Log-rank test $P < 0.001$.
**Figure S2.** Prognostic value of sarcopeniaC according to severity of liver cirrhosis. (A) Kaplan–Meier survival curves according to sarcopeniaC and the Model for End-Stage Liver Disease (MELD) score. The impact of sarcopeniaC was significant in patients with low MELD scores ($< 15$) but not in patients with high MELD scores ($\geq 15$). (B) Kaplan–Meier survival curves according to sarcopeniaC and the Child–Turcotte–Pugh (CTP) class. The impact of sarcopeniaC was significant in patients with CTP A/B class but not in patients with a CTP C class. (C) Kaplan–Meier survival curves according to sarcopeniaC and the hepatic venous pressure gradient (HVPG). The impact of sarcopeniaC was significant in patients with low and moderate HVPG ($< 20$ mmHg) but not in patients with high HVPG ($\geq 20$ mmHg). *$P < 0.05$

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