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Original Article

Association between Skeletal Muscle Depletion and Sorafenib Treatment in Male Patients with Hepatocellular Carcinoma: A Retrospective Cohort Study

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The effect of skeletal muscle mass (SMM) on the outcomes of sorafenib treatment for hepatocellular carcinoma (HCC) has not been established. We measured the SMM in HCC patients treated with sorafenib, evaluated the patients' survival, and evaluated the association between skeletal muscle depletion and sorafenib treatment. Of the 97 HCC patients treated with sorafenib at our institution in the period from July 2009 to February 2015, our study included 69 patients (51 males, 18 females) who had received sorafenib for ≥8 weeks and whose follow-up data were available. SMM was calculated from computed tomography images at the mid-L3 level (cm^2) and normalized to height (m^2) to yield the L3 skeletal muscle index (L3-SMI, cm^2/m^2). The median L3-SMI value was higher in the males (43 cm^2/m^2) compared to the females (36 cm^2/m^2). In the males only, the multivariate Cox regression identified an L3-SMI < 43 cm^2/m^2 as independently associated with higher mortality compared to an L3-SMI ≥ 43 cm^2/m^2 (hazard ratio 2.315, 95% confidence interval: 1.125-4.765, $p = 0.023$). Skeletal muscle depletion is a factor predicting poor prognosis for male patients with advanced HCC treated with sorafenib.

Key words: skeletal muscle depletion, hepatocellular carcinoma, sorafenib, L3 skeletal muscle index, prognostic factor

Hepatocellular carcinoma (HCC) is a common cancer with a high incidence and rate of mortality worldwide [1]. Although the majority of HCC cases occur in Asia and Africa, the incidence of HCC has increased even in developed nations. Several therapeutic options are available for the treatment of HCC; the selection of treatment is based on the stage of HCC, the patient's residual liver function and comorbidities, and the local clinical expertise. In Japan, sorafenib became the standard first-line therapy for the treatment of advanced HCC in 2009 based on the results and guidelines of the SHARP [2] and Asian-Pacific [3] studies, with evidence that sorafenib provides ≥3-month increase in survival. Important baseline predictors of

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the survival of patients with advanced HCC are the levels of alpha-fetoprotein (AFP) and vascular endothelial growth factor, the Child-Pugh score, and macrovascular invasion of the tumor have been identified as important baseline predictors of the survival of patients with advanced HCC [4].

Skeletal muscle depletion, also referred to as sarcopenia, has been identified as a factor predicting poor prognosis for patients undergoing chemotherapy for various carcinomas, including colorectal cancer [5], pancreatic cancer [6], and esophageal cancer [7]. The association between skeletal muscle depletion and prognosis in patients with HCC was evaluated by Iritani *et al*. [8], who reported that skeletal muscle depletion was an independent prognostic factor in HCC treatment outcomes. Two factors compelled us to further evaluate age-related sarcopenia in Japan in relation to the treatment of HCC. First, the population of elderly people in Japan already comprises a large segment of the general population, and it is growing rapidly. Secondly, due to the improved management of patients with chronic liver diseases, the mean age of patients with HCC has also been steadily rising [9]. In fact, for HCC patients with good liver function and good performance status, appropriate treatment can improve their chances of survival, even among extremely elderly patients [10]. The accurate evaluation of skeletal muscle mass (SMM) is therefore warranted in patients undergoing treatment for HCC.

Computed tomography (CT) imaging provides detailed anatomical information on specific muscles, adipose tissues and organs, and CT is useful for predicting whole-body composition [11]. Skeletal muscle depletion, estimated by the cross-sectional area of several muscles at the level of the third lumbar vertebra (L3), has been associated with a higher mortality rate in patients with liver cirrhosis, independent of Child-Pugh scores and Model for End stage Liver Disease (MELD) scores [12, 13]. To allow for between-subject comparisons, the measured muscle cross-sectional areas at L3 are normalized to the square of an individual's height (m^2) to yield the skeletal muscle index at L3 (L3-SMI, cm^2/m^2) [12].

Other techniques for evaluating body composition and providing a measure of SMM have been described in the literature and are used in research and practice, including bioelectrical impedance analysis, magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry, and ultrasonography [14, 15]. Due to the retrospective nature of our present study, we used a CT-based method to calculate the L3-SMI [16] and subsequently evaluated the association between L3-SMI and the prognosis of patients with HCC treated with sorafenib.

Although the association between skeletal muscle depletion and the prognosis of HCC patients treated with sorafenib has been examined, the precise association has not been established [17, 18]. There is a definite need to more completely evaluate the association between skeletal muscle depletion and outcomes of sorafenib therapy in HCC. We conducted this study to elucidate whether skeletal muscle depletion predicts survival in HCC patients treated with sorafenib.

Patients and Methods

Patient characteristics and follow-up method. Sorafenib was administered to 97 patients with HCC at our hospital in the period from July 2009 to February 2015. Of this group, 69 patients who had received sorafenib for > 8 weeks and whose follow-up data were available formed our study population; 51 males and 18 females (mean age 70.7 ± 8.8 years old). The clinical stage of HCC was determined using the staging system of the Japanese Liver Cancer Study Group (JLCSG) [19]. The clinical indications for treatment using sorafenib were based on the 2013 Clinical Practice Guidelines for Hepatocellular Carcinoma of the Japan Society of Hepatology (available from: http://www.jsh.or.jp/English/examination_en, accessed Mar. 2017) [20]. The patient's responses to treatment were evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines [21]. Clinical images were obtained by dynamic CT and MRI. Overall survival (OS) was calculated as the period from the date at which sorafenib therapy was initiated to the date of death or until March 2015 for surviving patients.

Image evaluation of SMM. Each patient's SMM was calculated using CT images obtained prior to the initiation of sorafenib therapy. The cross-sectional area of the following skeletal muscles was measured at the mid-L3 level: psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. The cross-sectional areas were calculated using commercial segmentation software (Synapse Vincent, Fujifilm, Tokyo, Japan)

[16, 22]. Calculated cross-sectional areas (cm^2) were normalized by the square of the individual's height (m^2) to obtain the normalized L3-SMI (cm^2/m^2) [8]. The total visceral fat area at the mid-L3 level (L3-fat) was measured using the same technique. Based on the difference in body mass composition for men and women, we performed separate analyses for the 2 genders.

Statistical analysis. Categorical data were compared using Fisher's exact test, and continuous data using Wilcoxon's test. Survival was evaluated using the Kaplan-Meier method, with differences examined using the log-rank test. Survival was also evaluated using a multivariate analysis with the Cox proportional hazards regression model. Although the univariate analyses did not show significant differences in the tested factors (except for L3-SMI) among the male patients, we analyzed the Child-Pugh score, clinical stage, and AFP (which are common prognostic factors) in a multivariate analysis. *P*-values < 0.05 were considered significant. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences software ver. 21 (SPSS 21, IBM, NY, USA).

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by our institutional ethics review committee. The participants' informed consent was not required, due to the retrospective nature of our study.

Results

Patient background. The distribution of the underlying etiology of HCC among the 69 patients was as follows: hepatitis B (6/69, 9%), hepatitis C (44/69, 64%), excessive alcohol use (7/69, 10%), and other conditions such as non-alcoholic steatohepatitis (2/69, 3%) and primary biliary cirrhosis (1/69, 1%), which were regrouped into one category of "other" (12/69, 17%). In terms of the clinical stage of the disease, 62 patients were classified as Child-Pugh grade A, and the other seven patients were classified as grade B.

The impact of HCC on the patients' daily functioning was evaluated using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale and criteria. The distribution of ECOG PS grades was as follows: 51 patients had the ECOG PS grade of 0 (*i.e.*, fully active, able to carry on all pre-disease activities without restriction); 15 had the ECOG PS grade of 1 (*i.e.*, restricted from physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature); and the remaining 3 patients had the ECOG PS grade of 2 (ambulatory, up and about > 50% of waking hours, and capable of all self-care, but unable to carry out any work activities). The classification of the clinical stage using the JLCSG system was confirmed: 0 patients at stage I; seven at stage II; 34 at stage III; 13 at stage IV-A; and 15 at stage IV-B. The median L3-SMI was 42 cm^2/m^2, and the median L3-fat index was 78 cm^2/m^2. The median initial dose of sorafenib was 400 mg/day (Table 1).

L3-SMI level-based comparison of background characteristics. We divided the 69 patients into two groups using the median L3-SMI (42 cm^2/m^2) as a cut-off, and we compared background characteristics between the low L3-SMI (< 42 cm^2/m^2) group ($n = 35$) and the high L3-SMI group (≥ 42 cm^2/m^2; $n = 34$) (Table 2). There were significantly fewer women in the high L3-SMI group compared to the low L3-SMI group. Based on this difference, we decided to analyze the prognostic factors for sorafenib treatment separately for the men and the women.

Regardless of gender, there were no significant differences between the low and high L3-SMI groups in terms of the Child-Pugh score, previous treatment for HCC, clinical stage using the JLCSG classification system, level of AFP, levels of proteins induced by vitamin K absence (PIVKA-II), or the initial dose of sorafenib. The patients' age, body mass index (BMI), and L3-fat index values were higher in the high L3-SMI group compared to the low L3-SMI group.

Patient outcomes of sorafenib treatment. Of the 51 males in our patient population, 38 died due to tumor progression and hepatic failure. The median survival time (MST) was 12 months, with 1- and 2-year survival rates of 50.6% and 25.4%, respectively. Among the 18 female patients, 12 died due to tumor progression and hepatic failure. The MST of the female patients was 14.8 months, with 1-, and 2-year survival rates of 71.1% and 39.1%, respectively. Although the MST was better for the women, this between-sex difference was not significant. There was also no significant difference between the low L3-SMI (< 42 cm^2/m^2) and the high L3-SMI (≥ 42 cm^2/m^2) groups in terms of the OS (log-rank test, $p = 0.466$; Fig. 1A).

The males were dichotomized based on the group median L3-SMI of 43 cm^2/m^2 and the MST compared between the high and low L3-SMI groups. For men in

Table 1 Patient characteristics

Characteristics	Parameter	Patients *n* (%)
No. of patients		69 (100)
Gender		
	Male	51 (74)
	Female	18 (26)
Age, year		
	Median	72
	Range	49-87
Etiology		
	HCV	44 (64)
	HBV	6 (9)
	Alcohol	7 (10)
	Others	12 (17)
Child-Pugh grade		
	A	62 (90)
	B	7 (10)
ECOG PS		
	0	51 (74)
	1	15 (22)
	2	3 (4)
Previous treatment		
	TACE	44 (64)
	HAIC	24 (35)
	RFA	9 (13)
	Surgery	9 (13)
	Radiation	1 (1)
	None	7 (10)
Clinical stage of JLCSG		
	II	7 (10)
	III	34 (49)
	IV-A	13 (19)
	IV-B	15 (22)
AFP (ng/ml)		
	Median	95
	Range	2-104410
PIVKA-II (mAU/ml)		
	Median	155
	Range	10-53500
BMI (kg/m^2)		
	Median	24
	Range	16-35
L3-SMI (cm^2/m^2)		
all patients	Median	42
	Range	27-60
L3-SMI of male	Median	43
	Range	31-60
L3-SMI of female	Median	36
	Range	27-55
L3-fat (cm^2/m^2)		
	Median	78
	Range	12-215
Initial dose of sorafenib (mg)		
	100	10 (15)
	200	21 (30)
	300	1 (1)
	400	27 (39)
	600	1 (1)
	800	9 (14)

HCV, hepatitis C virus; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; RFA, radiofrequency ablation; JLCSG, Japanese Liver Cancer Study Group; AFP, alpha fetprotein; PIVKA-II, Proteins induced by vitamin K absence; BMI, body mass index; L3-SMI, L3-Skeletal muscle index.

Table 2 Background of patients according to the L3-SMI level

Characteristics	L3-SMI <42	L3-SMI ≥ 42	*P* value
Number of patient	35	34	
Gender (male/female)	21/14	30/4	0.008
Age (yr)	73.8 ± 7.4 (60–87)	67.6 ± 9.1 (49–86)	0.005
Child-Pugh score	5.4 ± 0.8	5.4 ± 0.7	0.623
Previous treatment (−/+)	4/31	3/31	0.720
Clinical stage of JLCSG (II, III/IV)	21/14	20/14	0.921
AFP (ng/ml)	$5,689 \pm 18,078$ (2–104410)	$783 \pm 1,935$ (2.8–9883)	0.139
PIVKA-II (mAU/ml)	$6,238 \pm 14,653$ (10–53500)	$1,471 \pm 3,314$ (19–17700)	0.415
BMI (kg/m^2)	21.6 ± 2.7 (16.1–27.2)	26.2 ± 3.8 (19.7–35.5)	<0.001
L3-SMI (cm^2/m^2)	35.7 ± 4.2 (27.1–42.9)	49.8 ± 4.7 (43.1–60.1)	<0.001
L3-fat (cm^2/m^2)	60.2 ± 30.0 (11.5–119.6)	109.2 ± 43.4 (37.9–215.5)	<0.001
Initial dose of sorafenib (mg)			0.711
<400	17	15	
≥ 400	18	19	

JLCSG, Japanese Liver Cancer Study Group; AFP, alpha fetprotein; PIVKA-II, proteins induced by vitamin K absence; BMI, body mass index; L3-SMI, L3-Skeletal muscle index. Data were revealed as the mean value ± standard deviation. Ranges were shown in each parentheses. Wilcoxon's test was used to compare the medians of each variables between the 2 groups. Categorical data were compared using Fisher's exact test.

the high L3-SMI group, the MST was 13.5 months, with 1-, and 2-year survival rates of 57.6% and 36.0%, respectively. By comparison, for men in the low L3-SMI group, the MST was 7.6 months, with 1-, and 2-year survival rates of 39.7% and 11.3%, respectively. The OS was therefore significantly longer for the men with an L3-SMI ≥ 43 cm^2/m^2 compared to those with an L3-SMI <43 cm^2/m^2 (log-rank test, $p=0.044$; Fig. 1B).

We also divided the female patients into 2 groups by the median L3-SMI among women (36 cm^2/m^2). There was no significant difference in OS between the low L3-SMI (<36 cm^2/m^2) and high L3-SMI (≥ 36 cm^2/m^2) female groups (log-rank test, $p=0.675$; Fig. 1C).

Prognostic factors for patients with advanced HCC. We first identified prognostic factors of survival for male HCC patients treated with sorafenib by using the Cox proportional hazards model. Among the 8 variables identified in Table 3a, only L3-SMI <43 cm^2/m^2 was significantly associated with OS in the univariate

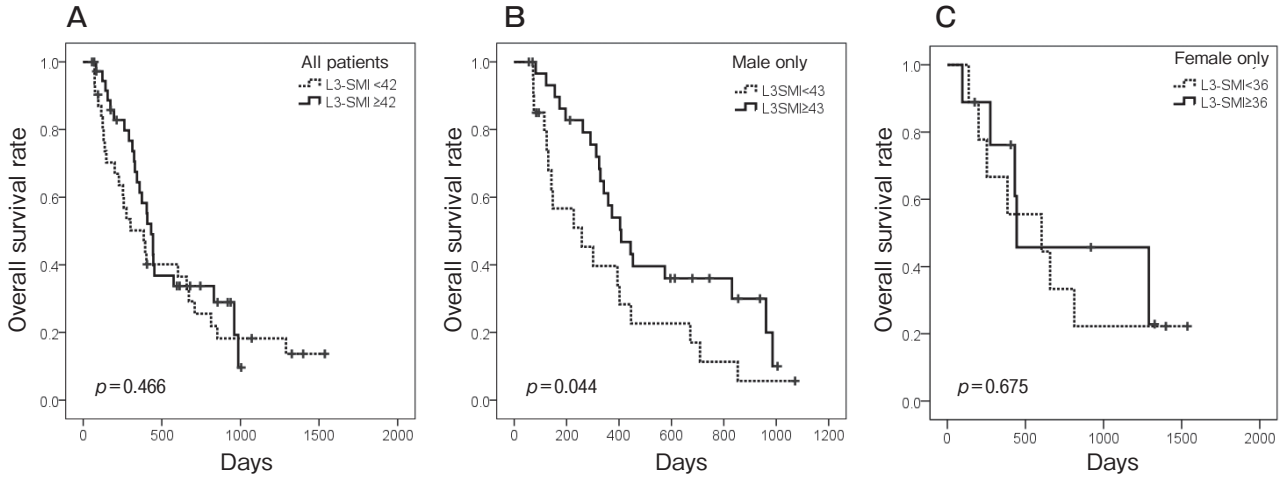

Fig. 1 Kaplan-Meier curves for overall survival (OS) in all patients, the males only, and the females only. Each group was divided into 2 arms based on their respective L3 skeletal muscle index (L3-SMI) median. (**A**) Subgroup comparison based on the L3-SMI among all patients. There was no difference between the L3-SMI < 42 cm^2/m^2 and L3-SMI ≥ 42 cm^2/m^2 groups in the OS period (log-rank test, $p = 0.466$). (**B**) The male patients only. The OS period was significantly longer for the male patients in the L3-SMI ≥ 43 cm^2/m^2 group compared to those in the L3-SMI < 43 cm^2/m^2 group (log-rank test, $p = 0.044$). (**C**) The female patients only. There was no significant difference in the OS period between the L3-SMI < 36 cm^2/m^2 and L3-SMI ≥ 36 cm^2/m^2 groups (log-rank test, $p = 0.675$).

analysis, with a hazard ratio (HR) of 1.916 and 95% confidence interval (CI) of 1.008-3.642 ($p = 0.047$). In addition, L3-SMI < 43 cm^2/m^2 was an independent prognostic factor for male HCC patients treated with sorafenib in our multivariate analysis (HR 2.315, 95% CI: 1.125-4.765, $p = 0.023$). The patients in the low SMM group (L3-SMI < 43 cm^2/m^2) had a poor survival rate (Fig. 1B).

We next attempted to identify the prognostic factors of survival for female HCC patients treated with sorafenib using the Cox proportional hazards model. Among the eight variables listed in Table 3b, L3-fat (HR 0.273, 95% CI: 0.080-0.932, $p = 0.038$) and the initial dose of sorafenib (HR 0.073, 95% CI: 0.009-0.601, $p = 0.015$) were significantly associated with OS in the univariate analyses. However, no prognostic factors for the female HCC patients treated with sorafenib were identified in the multivariate analysis (Table 3b).

Adverse effects in male HCC patients. Over the study period, 13 of the 51 males were forced to discontinue the sorafenib treatment due to adverse effects, with sorafenib discontinued in another 25 due to disease progression. The adverse effects included the following: abnormal levels of alanine aminotransferase (n = 3), hepatic coma (n = 2), cerebral hemorrhage (n = 1), cerebral infarction (n = 1), gastrointestinal bleeding (n = 1), sepsis (n = 1), intestinal pneumonitis (n = 1), general fatigue (n = 1), abdominal pain (n = 1), and diarrhea (n = 1).

In the Cox proportional hazards model, we searched for prognostic factors of sorafenib discontinuation in male patients. Among the nine variables listed in Table 4, no prognostic factor was significantly associated with the discontinuation of sorafenib treatment in our univariate analysis. The initial dose of sorafenib (< 800 vs. 800 mg) was associated with a nonsignificant trend toward sorafenib discontinuation (HR 3.676, 95% CI: 0.976-13.846, $p = 0.054$; Table 4).

Discussion

Sorafenib is an oral small-molecule inhibitor of intracellular tyrosine and serine/threonine protein kinases, with anti-proliferative and anti-angiogenic activities. Sorafenib has been approved worldwide as a first-line therapy for patients with advanced HCC who are ineligible for surgical resection, locoregional ablation, and transarterial embolization [2,3]. The identification of prognostic factors for the effective use of sorafenib is clinically important to optimize treatment outcomes.

Table 3 Prognostic factors for overall survival in patients with advanced HCC

(a) male

Prognostic factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*P* value	Hazard ratio	95%CI	*P* value
Age (< 70 year vs. ≥70)	0.950	0.500–1.803	0.950			
Child-Pugh score (5 vs. ≥6)	1.614	0.799–3.261	0.182	1.927	0.856–4.338	0.113
Clinical stage (II, III vs. IV)	1.425	0.753–2.696	0.276	1.894	0.937–3.828	0.075
AFP (< 400 vs. ≥400 ng/ml)	1.213	0.630–2.338	0.563	1.082	0.482–2.428	0.849
BMI (< 24 vs. ≥24 kg/m^2)	0.937	0.491–1.791	0.845			
L3-SMI (≥43 vs. < 43 cm^2/m^2)	1.916	1.008–3.642	0.047	2.315	1.125–4.765	0.023
L3-fat (< 85 vs. ≥85 cm^2/m^2)	1.059	0.554–2.025	0.862			
Initial dose of sorafenib (< 400 vs. ≥400 mg)	1.119	0.575–2.177	0.741			

AFP, alpha fetprotein; BMI, body mass index; L3-SMI, L3-Skeletal muscle index.

(b) female

Prognostic factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*P* value	Hazard ratio	95%CI	*P* value
Age (< 70 year vs. ≥70)	3.135	0.819–11.999	0.095	0.960	0.148–6.216	0.966
Child-Pugh score (5 vs. ≥6)	2.856	0.794–10.272	0.108	0.422	0.054–3.318	0.412
Clinical stage (II, III vs. IV)	0.610	0.174–2.141	0.440			
AFP (< 400 vs. ≥400 ng/ml)	0.492	0.106–2.287	0.366			
BMI (< 24 vs. ≥24 kg/m^2)	1.582	0.504–4.964	0.432			
L3-SMI (≥36 vs. < 36 cm^2/m^2)	1.279	0.404–4.045	0.675	1.835	0.372–9.040	0.456
L3-fat (< 61 vs. ≥61 cm^2/m^2)	0.273	0.080–0.932	0.038	0.338	0.070–1.638	0.178
Initial dose of sorafenib (< 400 vs. ≥400 mg)	0.073	0.009–0.601	0.015	0.063	0.004–1.010	0.051

AFP, alpha fetprotein; BMI, body mass index; L3-SMI, L3-Skeletal muscle index.

Table 4 Univariate analysis for discontinuation risk of sorafenib due to its toxicity in male patients by Cox proportional hazards model

Prognostic factors	Univariate analysis		
	Hazard ratio	95%CI	*P* value
Age (< 70 year vs. ≥70)	0.703	0.226–2.188	0.543
Child-Pugh score (5 vs. ≥6)	1.423	0.419–4.862	0.574
Clinical stage (II, III vs. IV)	1.425	0.457–4.444	0.541
AFP (< 400 vs. ≥400 ng/ml)	1.173	0.350–3.927	0.796
BMI (< 24 vs. ≥24 kg/m^2)	1.408	0.442–4.483	0.562
L3-SMI (≥43 vs. < 43 cm^2/m^2)	1.610	0.516–5.019	0.412
L3-fat (< 85 vs. ≥85 cm^2/m^2)	0.606	0.182–2.018	0.415
Initial dose of			
sorafenib (< 400 vs. ≥400 mg)	1.504	0.449–5.035	0.508
sorafenib (< 800 vs. 800 mg)	3.676	0.976–13.846	0.054

AFP, alpha fetprotein; BMI, body mass index; L3-SMI, L3-Skeletal muscle index.

Llovet *et al.* reported that angioprotein 2 (a biomarker of angiogenesis) and vascular endothelial growth factor are independent predictors of survival in patients with advanced HCC [23]. However, the measurement of angiogenesis biomarkers is difficult in practice. In our multivariate analysis, we identified the L3 skeletal muscle index as an independent negative prognostic factor of OS in male HCC patients being treated with sorafenib (Table 3a). This finding is not completely surprising based on emerging evidence of

the negative impact of age-related sarcopenia on the health outcomes of elderly individuals. Sarcopenia is defined as an age-related involuntary loss of SMM and strength [24], and sarcopenia has been associated with a high risk for infections, longer hospitalization, greater need for rehabilitation care after hospital discharge, and higher mortality rate for various diseases [25].

Depending on the cause of onset, sarcopenia can be classified as being either primary or secondary. Primary sarcopenia is considered age-related when no underlying cause is evident other than aging itself. Secondary sarcopenia, in contrast, is considered when one or more other causes are evident, such as decreased physical activity, disease, or poor nutrition [26]. Ishii *et al.* estimated the prevalence of sarcopenia in functionally independent, community-dwelling Japanese adults ≥ 65 years old as 14.2% in men and 22.1% in women [27].

Patients with chronic liver disease are at risk for sarcopenia, with rapid skeletal muscle wasting being predictive of poor survival in patients with liver cirrhosis [28]. The normalized L3-SMI, as we used in the present study, has been reported before and used in research. However, we identified significant sex differences in the L3-SMI. Based on these differences, we judged that it was not appropriate to evaluate prognostic factors for men and women combined, as was done in the previous studies [17, 18]. Rather, we evaluated prognostic factors separately for men and women. Thus, the present study is the first to analyze the sex-specific association between SMM and sorafenib treatment for HCC.

Although a low L3-SMI level ($< 43\ cm^2/m^2$) was associated with a poor prognosis for our male patients with advanced HCC and treated with sorafenib, no prognostic factors for the female patients were identified in the multivariate analysis. In addition, we analyzed the OS in all patients, the men only, and the women only using the Kaplan-Meier method and the log-rank test. We divided these three groups into 2 arms using their respective L3-SMI medians. Although the OS of the low and high L3-SMI arms did not differ in the OS period among all patients and among the women-only groups, the male patients in the high L3-SMI arm showed significantly better OS compared to the male patients in the low L3-SMI arm, similar to the results of the multivariate analyses. The small number of patients in the female group (n = 18) could have contributed to the lack of significant prognostic factors in women. Future studies should examine a sufficiently large number of patients with HCC of both sexes to evaluate possible sex-specific differences in prognostic factors without bias.

We also performed an L3-SMI level-based comparison of the patients' background characteristics. The ratio of females, age, BMI, and L3-fat were higher in the high L3-SMI group compared to the low L3-SMI group. In our multivariate analyses, BMI and L3-fat were not significant prognostic factors for the men or the women. Overall, these results suggest that aspects of body compositions such as the SMM and fat should be assessed in HCC patients to better predict their prognosis.

Mir *et al.* reported associations among sarcopenia and sorafenib-related toxicities, the need to reduce the dosage, and the discontinuation of sorafenib [29]. However, we did not identify an association between L3-SMI and sorafenib discontinuation in our study (Table 4), which confirms findings reported by Imai *et al.* [17]. Our use of a lower dose than the standard initial dose of 800 mg/day may explain this result. In particular, the dose was ≤ 400 mg/day in 44 of our 51 male patients (86%) (Table 1). These low doses of sorafenib might improve patients' adherence to therapy, possibly by lowering the incidence of adverse effects.

Morimoto *et al.* reported that use of an initial half-dose of sorafenib (*i.e.*, 400 mg/day) led to fewer severe adverse effects and a comparable survival benefit, compared with a full dose in selected patients with HCC, particularly for those of advanced age [30]. In our study, the use of high-dose sorafenib (*i.e.*, 800 mg vs. < 800 mg) was associated with a tendency toward early discontinuation of the therapy (HR 3.676, 95% CI: 0.976-13.846, $p = 0.054$; Table 4).

Our study adds to previous evidence of a positive effect of maintaining SMM on the prognosis of HCC patients. It was reported that sarcopenia significantly increases the risk for mortality in patients with liver cirrhosis, with evidence of a benefit of branched chain amino acid (BCAA) supplementation for improving survival in these patients [13]. Two randomized controlled trials from Italy and Japan confirmed the benefits of BCAA supplementation in reducing the duration of cirrhosis-related hospitalization, as well as cirrhosis-related deaths [31, 32].

A recent multicenter retrospective cohort study by Imanaka *et al.* showed that BCAA improved the sur-

vival prognosis in HCC patients treated with sorafenib [33]. BCAA supplementation may improve adherence to sorafenib by maintaining liver function and SMM, and by improving the patients' general health status, resulting in a longer-term administration of sorafenib and a prolonged OS.

The etiology of sarcopenia in the elderly is multi-factorial in nature, and the prevention of sarcopenia during the prehospitalization stage would be important to improve the prognosis of patients with HCC. Wakabayashi *et al*. proposed a comprehensive approach to sarcopenia treatment in elderly patients, including pharmaceutical therapies for age-related sarcopenia and comorbid chronic diseases, resistance training, speed walking, nutrition management, protein and amino acid supplementation, and support for cessation of smoking, as needed [26]. Although such a comprehensive program can be successfully implemented on an in-patient basis, it may be difficult to sustain over the longer term, even for elderly individuals who are facing health problems related to sarcopenia. As a solution, Yamada *et al*. provided evidence of the benefits of a 6-month mall-based walking program in combination with nutritional supplementation for preventing sarcopenia in community-dwelling older adults [34]. This community-based approach is promising and could be useful as a large population-based approach for the prevention of sarcopenia and frailty among community-dwelling elderly people.

The limitations of our study should be acknowledged in the interpretation and application of our results. Foremost, we were unable to evaluate prognostic factors in the female HCC patients treated with sorafenib due to their low number (n = 18). In addition, we only evaluated L3-SMI as a variable of skeletal muscle, with no evaluation of the quality of the strength of skeletal muscles. The consensus report of the Asian Working Group for Sarcopenia recommends that sarcopenia be defined through a combined measure of SMM and muscle quality, evaluated by handgrip strength or usual gait speed [24]. It is possible that an evaluation of both SMM and muscle quality could identify more accurate prognostic factors.

In conclusion, the quantification of SMM using CT imaging at the mid-L3 level could provide a useful technique for predicting the prognosis of patients with HCC, including those treated with sorafenib. As skeletal muscle depletion was identified as a factor predicting poor prognosis among patients with advanced HCC, the prevention of skeletal muscle depletion may be an important component of therapeutic interventions to improve survival prognosis in male HCC patients. Prospective studies are needed to confirm the relationship between skeletal muscle depletion and prognosis, as well as to investigate prognostic factors in female patients with advanced HCC treated with sorafenib.

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References

1. Bruix J and Sherman M: Management of hepatocellular carcinoma: an update. Hepatology (2011) 53: 1020–1022.
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, de Oliveira AC, Santoro A, Raoul J-L, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz J-F, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D and Bruix J: Sorafenib in Advanced Hepatocellular Carcinoma. N Engl J Med (2008) 359: 378–390.
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D and Guan Z: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol (2009) 10: 25–34.
4. Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Saito T, Motoyama T, Suzuki E, Tawada A, Kanai F and Yokosuka O: Sorafenib treatment in Child-Pugh A and B patients with advanced hepatocellular carcinoma: safety, efficacy and prognostic factors. Invest New Drugs (2015) 33: 729–39.
5. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, Hiyoshi Y, Iwagami S, Yoshida N, Watanabe M and Baba H: Negative Impact of Skeletal Muscle Loss after Systemic Chemotherapy in Patients with Unresectable Colorectal Cancer. PLoS One (2015) 10: e0129742.
6. Choi Y, Oh DY, Kim TY, Lee KH, Han SW, Im SA, Kim TY and Bang YJ: Skeletal Muscle Depletion Predicts the Prognosis of Patients with Advanced Pancreatic Cancer Undergoing Palliative Chemotherapy, Independent of Body Mass Index. PLoS One (2015) 10: e0139749.
7. Harada K, Ida S, Baba Y, Ishimoto T, Kosumi K, Tokunaga R, Izumi D, Ohuchi M, Nakamura K, Kiyozumi Y, Imamura Y, Iwatsuki M, Iwagami S, Miyamoto Y, Sakamoto Y, Yoshida N, Watanabe M and Baba H: Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma. Dis Esophagus (2016) 29: 627–633.
8. Iritani S, Imai K, Takai K, Hanai T, Ideta T, Miyazaki T, Suetsugu A, Shiraki M, Shimizu M and Moriwaki H: Skeletal muscle depletion is an independent prognostic factor for hepatocellular carcinoma. J Gastroenterol (2015) 50: 323–332.
9. Dohmen K, Shirahama M, Shigematsu H, Irie K and Ishibashi H: Optimal treatment strategy for elderly patients with hepatocellular carcinoma. J Gastroenterol Hepatol (2004) 19: 859–865.
10. Tsukioka G, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H,

Abe T, Toyoda M, Katakai K, Kojima A, Yamazaki Y, Otsuka T, Matsuzaki Y, Makita F, Kanda D, Horiuchi K, Hamada T, Kaneko M, Suzuki H and Mori M: Hepatocellular carcinoma in extremely elderly patients: an analysis of clinical characteristics, prognosis and patient survival. World J Gastroenterol (2006) 12: 48–53.
11. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ and Baracos VE: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab (2008) 33: 997–1006.
12. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, Esfandiari N, Baracos V, Montano-Loza AJ and Myers RP: Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl. (2012) 18: 1209–1216.
13. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, Takai K, Shimizu M and Moriwaki H: Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition (2015) 31: 193–199.
14. Minetto MA, Caresio C, Menapace T, Hajdarevic A, Marchini A, Molinari F and Maffiuletti NA: Ultrasound-Based Detection of Low Muscle Mass for Diagnosis of Sarcopenia in Older Adults. PM R (2016) 8: 453–462.
15. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S and Baracos VE: Definition and classification of cancer cachexia: an international consensus. Lancet Oncol (2011) 12: 489–495.
16. Yoshizumi T, Shirabe K, Nakagawara H, Ikegami T, Harimoto N, Toshima T, Yamashita Y, Ikeda T, Soejima Y and Maehara Y: Skeletal muscle area correlates with body surface area in healthy adults. Hepatol Res (2014) 44: 313–318.
17. Imai K, Takai K, Hanai T, Ideta T, Miyazaki T, Kochi T, Suetsugu A, Shiraki M and Shimizu M: Skeletal muscle depletion predicts the prognosis of patients with hepatocellular carcinoma treated with sorafenib. Int J Mol Sci (2015) 16: 9612–9624.
18. Hiraoka A, Hirooka M, Koizumi Y, Izumoto H, Ueki H, Kaneto M, Kitahata S, Aibiki T, Tomida H, Miyamoto Y, Yamago H, Suga Y, Iwasaki R, Mori K, Miyata H, Tsubouchi E, Kishida M, Ninomiya T, Abe M, Matsuura B, Kawasaki H, Hiasa Y and Michitaka K: Muscle volume loss as a prognostic marker in hepatocellular carcinoma patients treated with sorafenib. Hepatol Res (2016) doi: 10.1111/hepr.12780.
19. Izumi N: Diagnostic and treatment algorithm of the Japanese society of hepatology: a consensus-based practice guideline. Oncology (2010) 78 Suppl 1: 78–86.
20. Japan Society of Hepatology: Clinical Practice Guidelines for Hepatocellular Carcinoma 2013. (2013).
21. Lencioni R and Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis (2010) 30: 52–60.
22. Lieffers JR, Mourtzakis M, Hall KD, McCargar LJ, Prado CM and Baracos VE: A viscerally driven cachexia syndrome in patients with advanced colorectal cancer: contributions of organ and tumor mass to whole-body energy demands. Am J Clin Nutr (2009) 89: 1173–1179.
23. Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G and Bruix J: Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res (2012) 18: 2290–2300.
24. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M and Arai H: Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc (2014) 15: 95–101.
25. Peterson SJ and Braunschweig CA: Prevalence of sarcopenia and associated outcomes in the clinical setting. Nutr Clin Pract (2016) 31: 40–48.
26. Wakabayashi H and Sakuma K: Comprehensive approach to sarcopenia treatment. Curr Clin Pharmacol (2014) 9: 171–180.
27. Ishii S, Tanaka T, Akishita M, Ouchi Y, Tuji T and Iijima K: Metabolic syndrome, sarcopenia and role of sex and age: cross-sectional analysis of Kashiwa cohort study. PLoS One (2014) 9: e112718.
28. Hanai T, Shiraki M, Ohnishi S, Miyazaki T, Ideta T, Kochi T, Imai K, Suetsugu A, Takai K, Moriwaki H and Shimizu M: Rapid skeletal muscle wasting predicts worse survival in patients with liver cirrhosis. Hepatol Res (2016) 46: 743–751.
29. Mir O, Coriat R, Blanchet B, Durand JP, Boudou-Rouquette P, Michels J, Ropert S, Vidal M, Pol S, Chaussade S and Goldwasser F: Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One (2012) 7: e37563.
30. Morimoto M, Numata K, Kondo M, Kobayashi S, Ohkawa S, Hidaka H, Nakazawa T, Okuwaki Y, Okuse C, Matsunaga K, Suzuki M, Morita S, Taguri M and Tanaka K: Field practice study of half-dose sorafenib treatment on safety and efficacy for hepatocellular carcinoma: A propensity score analysis. Hepatol Res (2015) 45: 279–287.
31. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F and Abbiati R: Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology (2003) 124: 1792–1801.
32. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S and Kumada H: Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol (2005) 3: 705–713.
33. Imanaka K, Ohkawa K, Tatsumi T, Katayama K, Inoue A, Imai Y, Oshita M, Iio S, Mita E, Fukui H, Yamada A, Nakanishi F, Inada M, Doi Y, Suzuki K, Kaneko A, Marubashi S, Ito Y, Fukui K, Sakamori R, Yakushijin T, Hiramatsu N, Hayashi N and Takehara T: Impact of branched-chain amino acid supplementation on survival in patients with advanced hepatocellular carcinoma treated with sorafenib: A multicenter retrospective cohort study. Hepatol Res (2016) 46: 1002–1010.
34. Yamada M, Nishiguchi S, Fukutani N, Aoyama T and Arai H: Mail-Based Intervention for Sarcopenia Prevention Increased Anabolic Hormone and Skeletal Muscle Mass in Community-Dwelling Japanese Older Adults: The INE (Intervention by Nutrition and Exercise) Study. J Am Med Dir Assoc (2015) 16: 654–660.