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ORIGINAL ARTICLE

Skeletal muscle mass is associated with toxicity, treatment tolerability, and additional or subsequent therapies in patients with hepatocellular carcinoma receiving sorafenib treatment

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Key words
additional and subsequent therapies, duration of treatment, hepatocellular carcinoma, skeletal muscle, sorafenib, visceral to subcutaneous adipose tissue area ratio.

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Abstract

Background and Aim: Several reports have demonstrated that skeletal muscle mass influences mortality in patients with hepatocellular carcinoma (HCC) receiving sorafenib treatment; however, there is still controversy with regard to whether skeletal muscle and adipose tissue are associated with the prognosis in HCC patients. We examined the relationship between body composition and prognosis in HCC patients.

Methods: We retrospectively analyzed 82 patients with unresectable HCC receiving sorafenib treatment. The skeletal muscle area and adipose tissue area were measured by computed tomography. Patients with low skeletal muscle index (male ≤36.2 cm^2/m^2, female ≤29.6 cm^2/m^2) and high visceral to subcutaneous adipose tissue area ratio (VSR) (male ≥ 1.33, female ≥ 0.93) were diagnosed as low skeletal muscle mass (LSMM) and high VSR, respectively.

Results: A total of 16 and 34 patients were classified as LSMM and high VSR, respectively. LSMM patients frequently experienced serious adverse events (SAEs) and thus had a shorter duration of sorafenib treatment than non-LSMM patients. High VSR was a significant factor for progression-free survival. LSMM patients less frequently received additional/subsequent therapies combined with sorafenib than non-LSMM patients. Multivariate Cox hazard analysis demonstrated that LSMM was a significant factor for the duration of sorafenib treatment. The treatment duration and receiving of additional/subsequent therapies were significantly associated with overall survival (OS) but not with LSMM or high VSR.

Conclusion: LSMM was associated with the frequency of SAEs, treatment tolerability, and treatment duration. LSMM patients were less likely to receive additional/subsequent therapies than non-LSMM patients. Thus, LSMM could identify a subgroup of patients with poor OS.

Introduction

Sorafenib is the first multikinase inhibitor that can improve overall survival (OS) in patients with unresectable hepatocellular carcinoma (HCC).[1] The recent Barcelona Clinic Liver Classification (BCLC), which is the staging system for HCC, recommends systemic treatments, including sorafenib, for BCLC stage C.[2] In addition, the efficacy of sorafenib conversion from transcatheter arterial chemoembolization (TACE) in TACE-refractory patients with intermediate-stage HCC in Japan has been reported.[3]

Body mass index (BMI) is usually used as a simple index of obesity that can be easily calculated using a patient's height and weight; however, body composition such as skeletal muscle mass and adipose tissue mass is not exactly reflected by BMI. In terms of prognosis, the effects of BMI are controversial in patients with HCC receiving sorafenib treatment.[4–6] Sarcopenia, which is defined as both loss of skeletal muscle mass and function, is classified as primary sarcopenia (age-related) and secondary sarcopenia (activity-, disease-, or nutrition-related) by the European Working Group on Sarcopenia in Older People (EWGSOP).[7] The EWGSOP also suggests a conceptual staging, presarcopenia, which is characterized by low muscle mass without impact on muscle strength or physical performance.[7] Some studies have demonstrated that skeletal muscle loss due to various malignancies, such as pancreatic cancer,[8] colorectal cancer,[9] breast cancer,[10] diffuse large B cell lymphoma,[11] lung cancer,[12] and HCC,[13] impairs OS. In addition to skeletal muscle mass loss, intramuscular fat and visceral adiposity independently predicted mortality in patients with various stages of HCC in Japan.[14]

Several reports have recently demonstrated that skeletal muscle loss is associated with prognosis in patients with unresectable HCC receiving sorafenib treatment.[6,15–20] However, only one report indicated that high visceral fat area (VFA) predicted survival in patients with HCC treated with tyrosine kinase inhibitors.[5] Therefore, there is still controversy with regard to whether the correlation between skeletal muscle mass and adipose tissue mass influences the prognosis in HCC patients treated with sorafenib.

In the present study, we measured body composition, such as skeletal muscle mass and adipose tissue mass, based on computed tomography (CT) imaging before sorafenib treatment and investigated the association between body composition and prognosis in patients with unresectable HCC who received sorafenib treatment. In addition, we also evaluated the association between simple indexes, such as BMI and body weight (BW), and prognosis in HCC patients.

Methods

Patients. We retrospectively analyzed 82 Japanese patients with unresectable HCC who were treated with sorafenib at Asahikawa Medical University and Asahikawa Kosei General Hospital, Asahikawa, Japan from June 2009 to February 2016. HCC was diagnosed by ultrasound sonography, dynamic CT, and dynamic magnetic resonance imaging. The stage of HCC was classified by the BCLC staging system.[2]

Sorafenib treatment was initiated after obtaining informed consent when extrahepatic metastasis or portal vein tumor thrombosis was confirmed or when TACE was considered to be refractory. We assessed the discontinuation rate of sorafenib treatment by adverse effects (AEs), progression-free survival (PFS), and OS. Disease progression was according to the Response Evaluation Criteria in Solid Tumors criteria.[21] This study was approved by the Institutional Review Board of Asahikawa Medical University and Asahikawa Kosei General Hospital.

Analysis of CT images. Image analyses were performed using CT before sorafenib treatment was initiated. The skeletal muscle area was evaluated at the level of the third lumbar vertebra.[14] The VFA and subcutaneous fat area (SFA) were measured at the level of the umbilicus level,[5] and the visceral to subcutaneous adipose tissue area ratio (VSR) was evaluated. The skeletal muscle mass was normalized by height in meters squared as the skeletal muscle index (SMI, cm^2/m^2). Using the volume analyzer SYNAPSE VINCENT (Fujifilm, Tokyo, Japan), differential tissue areas were calculated in Hounsfield units (HU).[22] The skeletal muscle mass was evaluated within an HU range of −20 to 100 HU[23] that was modified in a previous report to exclude vasculature and areas of fatty infiltration.[24,25] The VFA and SFA were calculated within an HU range of −200 to −50 HU. Patients with massive ascites were excluded because the VFA could not be exactly calculated.

As previously reported, patients with low SMI (male ≤ 36.2 cm^2/m^2, female ≤ 29.6 cm^2/m^2)[14] were diagnosed with low skeletal muscle mass (LSMM). In addition, we classified the patients into two groups based on the criteria for Japanese patients: high VFA (≥100 cm^2)[26] and high VSR (male ≥ 1.33, female ≥ 0.93).[14] BMI was classified into three categories (<20.0, 20.0–24.9, and ≥25.0),[14] and BW was classified into two categories, namely, high BW (≥60 kg) and low BW (<60 kg).[27]

Statistical analysis. The results are expressed as mean and standard deviation. Statistical analyses were carried out using a log-rank test, Student's *t* test, Fischer's exact test, Pearson's test, the χ^2 test, and the chi-square test for trend. Possible risk factors for the duration of sorafenib treatment, PFS, and OS were evaluated using the Cox proportional hazard model. Each factor, including gender, age ≥ 65 years,[16] Child-Pugh score ≥ 7,[5] platelet count ≥ $10 \times 10^4/\mu L$,[16] serum α-fetoprotein (AFP) level ≥ 100 ng/mL,[16] BCLC stage C,[16] additional or subsequent therapies,[28,29] LSMM,[14] extrahepatic metastasis,[16] positive invasion of hepatic vessels,[16] VFA ≥ 100 cm,[2,26] VSR ≥ 1.33 (male),[14] and VSR ≥ 0.93 (female),[14] were analyzed by univariate Cox hazard analysis. All cut-off levels except for the VFA were based on previous reports that investigated prognosis in patients with HCC. The cut-off level for the VFA was based on the criteria for obesity in Japan. Factors with values of $P < 0.05$ in the univariate Cox hazard analysis were additionally analyzed in multivariate Cox hazard analysis. A P value <0.05 was considered statistically significant. All statistical analyses were performed using the free software EZR version 1.35 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing , Vienna, Austria).[30]

Results

Clinical features of the patients. Of 82 patients, 16 patients were diagnosed with LSMM, and 66 patients were diagnosed with non-LSMM; 34 patients were classified as having high VSR, and 7 patients were classified as having both LSMM and high VSR. The clinical features are described in Table 1. BMI and BW were correlated with the SMI, VFA, and VSR (Fig. S1, Supporting information). Thirty-five patients received additional or subsequent therapies, such as oral chemotherapy, TACE, hepatic arterial infusion chemotherapy (HAIC), radiation therapy, ablation, surgery, or a combination of several treatments after initial sorafenib treatment (Table S1). Non-LSMM patients frequently received additional or subsequent therapies (Table 1, $P = 0.009$).

LSMM is associated with the discontinuation rate of sorafenib due to adverse events. The median duration of sorafenib treatment was 138 (7–1757) days. All grade AEs are described in Tables S2–S4 (some AEs were overlapping). Twenty-seven patients discontinued sorafenib treatment because of serious AEs (SAEs), such as pancreatitis, hand and foot skin reaction, hepatic failure, loss of appetite, thrombocytopenia, liver injury, erythema multiforme, pancytopenia, renal dysfunction, melena, and sudden death. The frequencies of both grade 3/4 AEs and SAEs were significantly higher in patients with LSMM than in non-LSMM patients (Table S2). Although BMI did not contribute to the frequencies of grade 3/4 AEs and SAEs, these frequencies were higher in patients with low BW than in those with high BW (Tables S3 and S4). BMI and BW were not associated with the duration of sorafenib treatment (Fig. 1a,b); however, the median duration of sorafenib treatment

Table 1 Clinical features of patients with hepatocellular carcinoma treated with sorafenib

	Total (n = 82)	LSMM (n = 16)	Non-LSMM (n = 66)	P value
Age (years)	69.0 ± 9.1	73.2 ± 9.4	68.0 ± 8.8	0.038
Gender (male/female)	67/15	14/2	53/13	0.723
Etiology (HBV/HCV/HBV + HCV/NBNC)	21/41/1/19	3/10/0/3	18/31/1/16	0.843
Child-Pugh score	6.0 ± 1.1	6.3 ± 1.1	6.0 ± 1.1	0.32
Body mass index (kg/m^2)	22.7 ± 3.4	19.7 ± 2.0	23.4 ± 3.3	<0.001
Body weight (kg)	58.6 ± 10.1	51.3 ± 7.7	60.3 ± 9.9	0.001
BCLC stage A/B/C	8/35/39	3/4/9	5/31/30	0.153
Positive invasion of hepatic vessels (%)	22 (26.8)	3 (18.8)	19 (28.8)	0.539
Extrahepatic metastasis (%)	21 (25.6)	6 (37.5)	15 (22.7)	0.337
Additional/subsequent therapies (%)	35 (43.9)	2 (12.5)	33 (50.0)	0.009
SMI (cm^2/m^2)	43.3 ± 8.7	32.5 ± 4.1	46.0 ± 7.3	<0.001
VFA (cm^2)	114.5 ± 71.7	79.2 ± 60.4	123.0 ± 72.0	0.027
VSR	1.32 ± 0.85	1.64 ± 1.41	1.24 ± 0.64	0.085
Initial dose of sorafenib per day (mg)	546.3 ± 198.9	500.0 ± 206.6	557.6 ± 196.9	0.302
Serious adverse events	27	10	17	0.008
Platelet counts (×10^4/μL)	14.5 ± 11.4	15.9 ± 11.6	14.2 ± 11.5	0.578
Total bilirubin (mg/dL)	1.09 ± 0.66	0.93 ± 0.65	1.12 ± 0.66	0.298
Albumin (g/dL)	3.4 ± 0.5	3.1 ± 0.5	3.5 ± 0.5	0.027
Aspartate aminotransferase (U/L)	67.0 ± 48.5	87.6 ± 80.9	62.0 ± 35.9	0.057
Alanine transaminase (U/L)	46.6 ± 34.4	47.3 ± 36.5	46.5 ± 34.2	0.929
γ glutamyl transpeptidase (U/L)	145.9 ± 178.5	107.6 ± 116.1	155.1 ± 190.1	0.343
Prothrombin time (%)	82.0 ± 15.1	84.0 ± 15.4	81.6 ± 15.1	0.571
AFP (ng/mL)	27 016.7 ± 167 149.6	14 921.5 ± 28 379.8	299 489 ± 185 972.2	0.749

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Classification; HBV, hepatitis B virus; HCV, hepatitis C virus; LSMM, low skeletal muscle mass; NBNC, Non-B Non-C; SMI, skeletal muscle index; VFA, visceral fat area; VSR, visceral to subcutaneous adipose tissue area ratio.

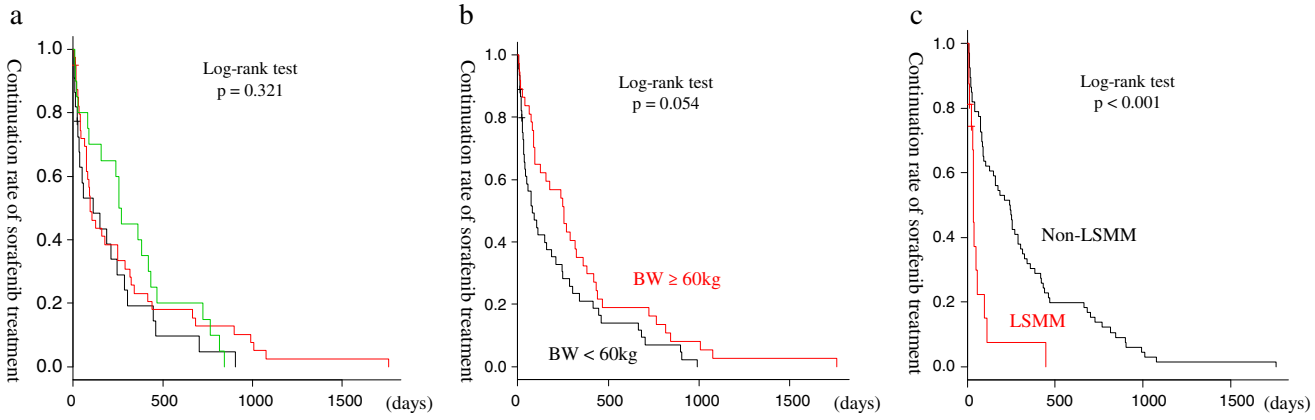

Figure 1 Continuation rate of sorafenib treatment. (a, b) Body mass index (BMI) and body weight (BW) were not associated with the duration of sorafenib treatment. (c) The median periods of sorafenib treatment were significantly shorter in patients with low skeletal muscle mass (LSMM) than in non-LSMM patients (34.0 *vs* 243.0 days, P < 0.001, log-rank test). (a): (——), BMI < 20; (——), 20 ≤ BMI < 25; (——), BMI ≥ 25.

was significantly shorter in patients with LSMM than in non-LSMM patients (34.0 *vs* 243.0 days, P < 0.001, Fig. 1c). Multivariate Cox hazard analysis demonstrated that LSMM most potently contributed to the discontinuation rate of sorafenib treatment (Table 2).

Possible factors related to PFS in patients with HCC treated with sorafenib. Next, we analyzed possible factors for PFS. The median PFS was significantly shorter in patients with LSMM than in non-LSMM patients (46.5 *vs* 122.0 days, P = 0.036, Fig. 2a); however, BMI and BW did not contribute to PFS (Fig. 2b,c). In patients with high VSR, the median PFS was significantly shorter than in those with low VSR (100.5 *vs* 109.5 days, P = 0.010, Fig. 2d). Moreover, both LSMM and high VSR significantly exacerbated PFS in an additive manner (Fig. 2e). Multivariate Cox hazard analysis demonstrated that the duration of sorafenib treatment (hazard ratio (HR), 0.9998; 95% confidence interval (CI), 0.997–0.999,

Table 2 Univariate and multivariate Cox hazard analyses of factors related to the discontinuation rate of sorafenib treatment in patients with hepatocellular carcinoma

	Univariate Cox hazard analysis			Multivariate Cox hazard analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender (male)	0.642	0.364–1.133	0.126	—	—	—
Age ≥ 65 years	1.168	0.717–1.901	0.533	—	—	—
Child-Pugh score ≥ 7	1.518	0.914–2.523	0.107	—	—	—
Platelet count ≥ 10 × 10^4/μL	1.031	0.661–1.608	0.894	—	—	—
AFP ≥ 100 ng/mL	1.582	1.009–2.481	0.046	1.690	1.063–2.688	0.027
BCLC stage C	1.392	0.886–2.187	0.152	—	—	—
Additional/subsequent therapies	0.608	0.384–0.960	0.033	0.828	0.491–1.391	0.480
Low skeletal muscle mass	3.185	1.713–5.922	<0.001	3.396	1.731–6.664	<0.001
Extrahepatic metastasis	0.992	0.581–1.694	0.977	—	—	—
Positive invasion of hepatic vessels	2.08	1.242–3.482	0.005	2.192	1.258–3.818	0.006
VFA ≥ 100 cm^2	0.967	0.616–1.517	0.882	—	—	—
VSR ≥ 1.33 (male)	1.448	0.901–2.329	0.127	—	—	—
VSR ≥ 0.93 (female)	—	—	—	—	—	—

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Classification; CI, confidence interval; HR, hazard ratio; VFA, visceral fat area; VSR, visceral to subcutaneous adipose tissue area ratio.

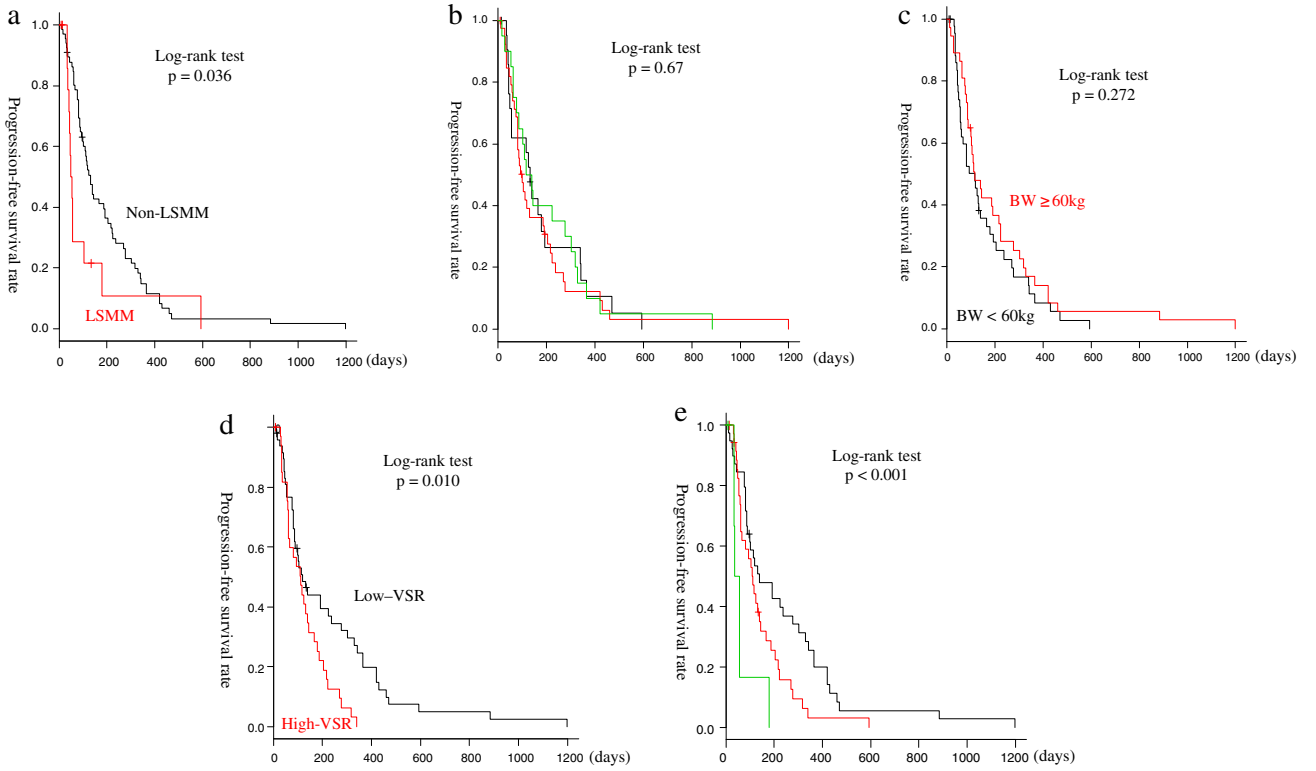

Figure 2 Kaplan–Meier curves for progression-free survival (PFS). (a) The median PFS was significantly shorter in patients with low skeletal muscle mass (LSMM) (46.5 days) than in non-LSMM patients (122.0 days) (log-rank test, $P = 0.036$). (b, c) Body mass index (BMI) and body weight (BW) did not contribute to PFS. (d) The median PFS was significantly shorter in patients with high visceral to subcutaneous adipose tissue area ratio (VSR) (100.5 days) than in those with low VSR (109.5 days) (log-rank test, $P = 0.010$). (e) Both LSMM and high VSR contributed a worse median PFS in an additive manner (log-rank test, $P < 0.01$). (b): (——), BMI < 20; (——), 20 ≤ BMI < 25; (——), BMI ≥ 25. (e): (——), Non-LSMM and low-VSR; (——), LSMM or high-VSR; (——), LSMM and high-VSR.

$P < 0.001$) and high VSR (HR, 1.643; 95% CI, 1.001–2.699, $P = 0.049$) were associated with PFS (Table 3); however, LSMM was not identified as an independent factor for PFS.

Possible factors related to the OS in patients with HCC treated with sorafenib. Finally, we analyzed possible factors for OS. The median OS was 344.5 (9–1851) days.

Table 3 Univariate and multivariate Cox hazard analyses of factors related to progression-free survival

	Univariate Cox hazard analysis			Multivariate Cox hazard analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender (male)	0.96	0.535–1.724	0.891	—	—	—
Age ≥ 65 years	0.946	0.584–1.533	0.822	—	—	—
Child-Pugh score ≥ 7	1.316	0.768–2.255	0.644	—	—	—
Platelet count ≥ 10 × 10^4/μL	0.952	0.601–1.509	0.833	—	—	—
AFP ≥ 100 ng/mL	1.572	0.988–2.501	0.056	—	—	—
BCLC stage C	1.185	0.743–1.892	0.477	—	—	—
Additional/subsequent therapies	0.941	0.593–1.494	0.756	—	—	—
Low skeletal muscle mass	1.899	1.029–3.506	0.04	1.233	0.653–2.327	0.519
Extrahepatic metastasis	1.171	0.678–2.021	0.571	—	—	—
Positive invasion of hepatic vessels	1.125	0.723–2.075	0.45	—	—	—
Duration of sorafenib treatment	0.997	0.996–0.999	<0.001	0.998	0.996–0.999	<0.001
VFA ≥ 100 cm^2	1.014	0.641–1.605	0.951	—	—	—
VSR ≥ 1.33 (male)	1.9	1.154–3.127	0.012	1.643	1.001–2.699	0.049
VSR ≥ 0.93 (female)	—	—	—	—	—	—

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Classification; CI, confidence interval; HR, hazard ratio; VFA, visceral fat area; VSR, visceral to subcutaneous adipose tissue area ratio.

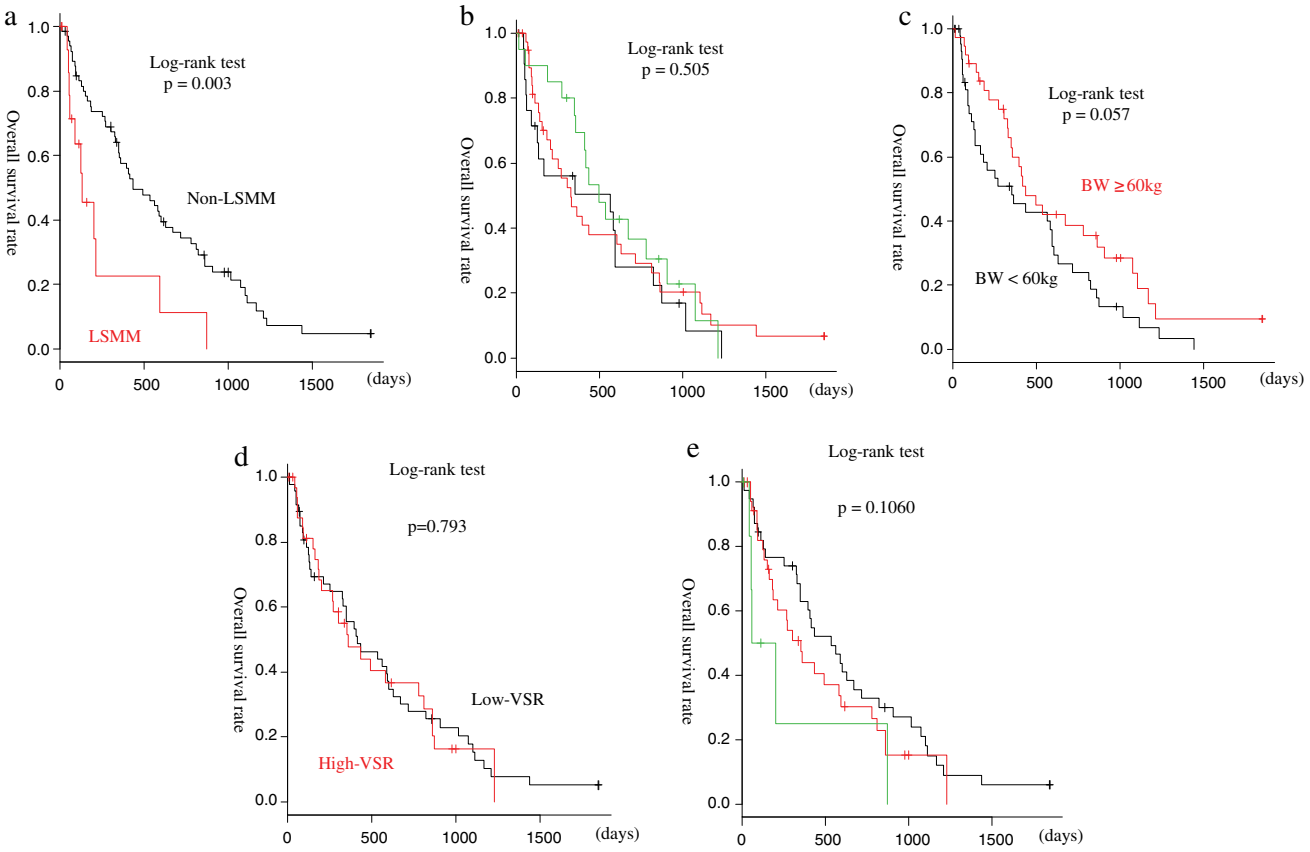

Figure 3 Kaplan–Meier curves for overall survival (OS). (a) The median OS was significantly lower in patients with low skeletal muscle mass (LSMM) (100.5 days) than in non-LSMM patients (413.0 days) (log-rank test, *P* = 0.003). (b–d) Body mass index (BMI), body weight (BW), and high visceral to subcutaneous adipose tissue area ratio (VSR) did not contribute to OS. (e) Both of LSMM and high VSR also did not contribute to OS. (b): (——), BMI < 20; (——), 20 ≤ BMI < 25; (——), BMI ≥ 25. (e): (——), Non-LSMM and low-VSR; (——), LSMM or high-VSR; (——), LSMM and high-VSR.

Table 4 Univariate and multivariate Cox hazard analyses of factors related to overall survival

	Univariate Cox hazard analysis			Multivariate Cox hazard analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Gender (male)	0.704	0.394–1.257	0.236	—	—	—
Age ≥ 65 years	1.198	1.188–4.392	0.013	1.301	0.724–2.339	0.379
Child-Pugh score ≥ 7	1.362	0.77–2.444	0.3	—	—	—
Platelet count ≥ $10 \times 10^4/\mu L$	1.017	0.626–1.653	0.946	—	—	—
AFP ≥ 100 ng/mL	1.672	1.020–2.742	0.042	1.554	0.878–2.748	0.130
BCLC stage C	1.885	1.156–3.074	0.011	2.551	1.065–6.113	0.036
Additional/subsequent therapies	0.375	0.225–0.623	<0.001	0.270	0.138–0.530	<0.001
Low skeletal muscle mass	2.629	1.341–5.154	0.004	1.153	0.538–2.474	0.715
Extrahepatic metastasis	1.392	0.778–2.492	0.265	—	—	—
Positive invasion of hepatic vessels	1.97	1.134–3.421	0.016	0.600	0.255–1.41	0.24
Duration of sorafenib treatment	0.998	0.997–0.999	<0.001	0.997	0.996–0.999	<0.001
VFA ≥ 100 cm^2	0.823	0.503–1.346	0.438	—	—	—
VSR ≥ 1.33 (male)	1.07	0.645–1.778	0.793	—	—	—
VSR ≥ 0.93 (female)	—	—	—	—	—	—

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Classification; CI, confidence interval; HR, hazard ratio; VFA, visceral fat area; VSR, visceral to subcutaneous adipose tissue area ratio.

The median OS was significantly shorter in patients with LSMM than in non-LSMM patients (100.5 *vs* 413.0 days, $P = 0.003$, Fig. 3a); however, BMI and BW did not contribute to OS as well as PFS (Fig. 3b,c). Although high VSR worsened PFS, this factor was not associated with OS (Fig. 3d,e). Multivariate Cox hazard analysis demonstrated that BCLC stage C (HR, 2.551; 95% CI, 1.065–6.113, $P = 0.036$), additional or subsequent therapies (HR, 0.270; 95% CI, 0.138–0.530, $P < 0.001$), and the duration of sorafenib treatment (HR, 0.997; 95% CI, 0.996–0.999, $P < 0.001$) (Table 4) were independent prognostic factors in patients with HCC receiving sorafenib treatment; however, LSMM was not identified as an independent factor for OS.

Discussion

In the present study, we demonstrated that patients with LSMM had a significant number of SAEs and were intolerant of sorafenib treatment and thus had a shorter duration of sorafenib treatment than non-LSMM patients. In addition, patients with LSMM were less likely to receive additional/subsequent therapies than non-LSMM patients. Therefore, LSMM could identify a subgroup of patients with poor OS due to the inability to receive sorafenib treatment and additional/subsequent therapies. In contrast, unlike previous studies, LSMM, VFA, and VSR were not associated with OS in our study.

In our study, the frequencies of both grade 3/4 AEs and SAEs were significantly higher in patients with LSMM than in non-LSMM patients. One study reported that patients with sarcopenia suffered grade 3 or 4 AEs,[18] and another reported that LSMM predicted early dose-limiting toxicities of treatment with sorafenib.[15] Others have indicated that high anticancer drug exposure in patients with LSMM may be correlated with increased chemotherapy toxicity, leading to early cessation and early progression in renal cell carcinoma, lung cancer, and HCC.[15,31,32] Previous studies have reported that the duration of sorafenib treatment is significantly shorter in patients with LSMM than in non-LSMM patients.[16–18] In contrast, others did not investigate the therapy duration.[6,20] These findings indicate that patients with LSMM are more likely to have a shorter duration of sorafenib treatment than non-LSMM patients; however, previous studies have indicated that LSMM was associated with survival without analyzing the duration of sorafenib treatment with Cox regression analysis. Only one study reported that the therapy duration in patients with presarcopenia did not differ from that in patients without presarcopenia.[19] The study indicated that presarcopenia is a significant prognostic factor in patients with two or less negative prognostic factors (serum albumin level ≤ 3.5 g/dL, AFP level ≥ 100 ng/mL, the presence of bilateral lesions, or the presence of major portal vein invasion). Regarding the association between treatment duration and survival, two previous studies have demonstrated that the duration of sorafenib treatment is an independent risk factor for survival.[33,34] These findings suggest that skeletal muscle mass seems to be associated with OS when there is no difference in the duration of sorafenib treatment. However, the duration of sorafenib treatment might be more important for OS than skeletal muscle mass if the duration of treatment differs between patients with LSMM and non-LSMM patients.

A recent report showed that, in patients with HCC treated with tyrosine kinase inhibitors (sorafenib: 85%, brivanib: 15%), the VFA could predict survival.[5] In contrast, the present study demonstrated that the VSR but not the VFA was associated with PFS in HCC patients treated with sorafenib There were more obese patients in the previous study (BMI ≥ 25: 50%)[5] than in our study (BMI ≥ 25: 24.4%). The difference in the prevalence of the obese population might have influenced the incongruence of the results. Based on these findings, we suggest that an increased VSR, but not an increased VFA, might be a biomarker for progression of HCC in patients treated with sorafenib. Although we could not clarify the reason why high VSR but not high VFA was associated with PFS, the difference in the characteristics of visceral and subcutaneous adipose tissues might be related to the following reasons. Free fatty acids (FFAs) are released from excess visceral adipose tissue.[35] In contrast, subcutaneous adipose tissue can store excess FFAs and prevent FFA

flow into other organs, suggesting that subcutaneous adipose tissue can exert metabolically advantageous functions.[36] A recent report have suggested that de novo synthetized fatty acids and exogenous fatty acids broken down by lipoprotein lipase play an important role in HCC development in vivo and in vitro.[37] Thus, an imbalance in fat composition could play an important role in the progression of HCC possibly through the metabolism of FFAs.

In this study, 35 patients received additional therapy that was combined with sorafenib or subsequent therapy that was a second-line therapy without sorafenib. Among them, 30 patients received additional or subsequent TACE. Although several clinical trials have failed to show a combined effect of TACE and sorafenib,[38–40] a survival advantage of TACE combined with sorafenib was recently demonstrated in the final analysis of GIDEON.[27] Several meta-analyses[41,42] and propensity score-matching analyses[43,44] have demonstrated improvement in OS with combined TACE and sorafenib. Furthermore, after failure of sorafenib treatment, additional or subsequent treatment including TACE has been reported to contribute to prolonged survival postprogression and might prolong OS.[45] As these findings indicated that additional or subsequent treatment seems to be associated with OS, patients with LSMM who were less likely to receive additional or subsequent therapies had poor OS in the present study.

Several approaches, such as branched chain amino acid (BCAA) supplementation,[46,47] BCAA supplementation and walking exercise,[48] and L-carnitine treatment,[49] have been reported to prevent the development of skeletal muscle loss in patients with liver cirrhosis. In addition, previous studies have suggested that BCAA supplementation may be useful for maintaining hepatic functional reserve and may help to avoid early discontinuance of sorafenib therapy in patients with HCC receiving sorafenib treatment.[50,51] These findings suggest that BCAA supplementation, exercise, and L-carnitine treatment could improve skeletal muscle loss and subsequently prolong the duration of sorafenib treatment in patients with advanced HCC.

There are some limitations in the present study. First, this study is a retrospective cohort study with a relatively small sample size. Second, various cut-off values for LSMM have been reported.[6,14–17] In the present study, we defined LSMM by the previous criteria, which were generated based on a large number of HCC patients in Japan[14]; however, a specific cut-off value is still unknown. For the same reason, we diagnosed high VSR and high VFA based on the cut-off values for the VSR[14] and VFA[26] that were defined by Japanese criteria. Third, we did not elucidate muscle strength or physical performance. As we could not clearly classify sarcopenia or presarcopenia, we used the term "low skeletal muscle mass."

In conclusion, we demonstrated that LSMM was associated with SAEs, treatment tolerability, and the duration of sorafenib treatment. In addition, patients with LSMM received less frequent additional/subsequent therapies than non-LSMM patients. Therefore, LSMM could identify a subgroup of patients with poor OS due to the inability of receiving sorafenib treatment and additional/subsequent therapies. Further investigation is needed to determine whether prevention and treatment of LSMM could improve treatment tolerability and the duration of sorafenib treatment and allow patients with LSMM to receive additional/subsequent therapies.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1 Correlation between the simple indexes and body composition. (a, b) BMI was positively correlated with SMI ($r = 0.559$, $P < 0.001$) and VFA ($r = 0.631$, $P < 0.001$). (c) BMI was negatively correlated with VSR ($r = -0.226$, $P = 0.042$). (d, e) BW was positively correlated with SMI ($r = 0.601$, $P < 0.001$) and VFA ($r = 0.532$, $P < 0.001$). (f) BW was negatively correlated with VSR, but the correlation was not statistically significant ($r = -0.216$, $P = 0.051$). BMI, body mass

index; BW, body weight; SMI, skeletal muscle index; VFA, visceral fat area; VSR, visceral to adipose tissue area ratio.

Table S1 Patients treated with additional or subsequent therapies.

Table S2 Adverse events, classified according to skeletal muscle mass.

Table S3 Adverse events, classified according to body mass index.

Table S4 Adverse events, classified according to body weight.