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Impact of body composition in advanced hepatocellular carcinoma: A subanalysis of the SORAMIC trial

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Abbreviations: A1D, alpha-1 antitrypsin deficiency; AIH, autoimmune hepatitis; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FFM, fat-free mass; FM, fat mass; HC, hemochromatosis; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; LSMM, low skeletal muscle mass; NAT, nonalcoholic toxic; NS, not specified; OS, overall survival; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose tissue index; SMA, skeletal muscle area; SIRT, selective internal radiation therapy; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose tissue ratio.

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Abstract

Background: Body composition parameters have been reported to be prognostic factors in patients with oncologic diseases. However, the available data on patients with HCC are conflicting. The aim of this study was to assess the impact of body composition on survival in patients with HCC treated with sorafenib or selective internal radioembolization (SIRT) and sorafenib.

Methods: This is an exploratory subanalysis of the prospective, randomized controlled SORAMIC trial. Within the palliative arm of the study, patients were selected if a baseline abdominal CT was available. A broad set of skeletal muscle and adipose tissue parameters were measured at the L3 level. Low skeletal muscle mass (LSMM) and density parameters were defined using published cutoffs. The parameters were correlated with overall survival.

Results: Of 424 patients in the palliative study arm, 369 patients were included in the analysis. There were 192 patients in the combined sorafenib/SIRT and 177 patients in the sorafenib group. Median overall survival was 9.9 months for the entire cohort and 10.8 and 9.2 months for the SIRT/sorafenib and sorafenib groups, respectively. There was no relevant association of either body composition parameter with overall survival in either the overall cohort or in the SIRT/sorafenib or sorafenib subgroups.

Conclusions: This subanalysis of the prospective SORAMIC trial does not suggest a relevant influence of body composition parameters of survival in patients with advanced HCC. Body composition parameters therefore do not serve in patient allocation in this palliative treatment cohort.

INTRODUCTION

HCC is the most common primary liver cancer and one of the most common causes of cancer-related mortality worldwide.[1] Main causes are alcohol-associated liver cirrhosis, increasingly NASH, as well as viral hepatitis B and C, with regional variations.[2] Currently, staging and treatment algorithms are based on the Barcelona Clinic Liver Cancer (BCLC) classification. For patients with advanced-stage HCC, the multikinase inhibitor sorafenib has been the standard of care for the past decade, with new treatment regimens added only in recent years. Locoregional therapies such as transarterial chemoembolization and selective internal radiation therapy (SIRT) are treatment options for patients with unresectable HCC and may be used in addition to systemic therapy.[3,4] The multicenter SORAMIC trial (EudraCT 2009-012576-27, NCT01126645) has compared the efficacy of sorafenib and SIRT with Yttrium-90 (90Y) resin microspheres to sorafenib alone, without identifying significant improvements in overall survival (OS).[5]

In interventional procedures, patient selection remains pivotal. Multiple factors are known to influence survival in locoregional treatments. For patients treated with SIRT, the albumin-bilirubin ratio (ALBI) has been shown to be superior in predicting survival to the Child-Pugh classification.[6] The BCLC criteria themselves, while suitable for treatment allocation, are limited in their capacity to predict treatment outcomes and are unable to assess functional capacity.[7] In addition, the patient's performance status is not considered in these criteria.

In recent years, parameters of body composition such as skeletal muscle mass (SMM) and adipose tissue (AT) have emerged as possible biomarkers influencing clinical outcomes in patients with HCC. The use of CT-derived measurements of skeletal muscle and abdominal fat tissue allows quantification of different body composition parameters in routine clinical use. For SMM, measurements of paraspinal, abdominal wall, and psoas muscles are usually performed at the L3 level.[8] Published studies on the association between body composition parameters and OS in HCC have predominantly been conducted in Asia. Because of the scarcity of data, the influence of

TABLE 1A Clinical baseline characteristics of included patients

Characteristics	All patients (n = 369)	Sorafenib (n = 177)	Sorafenib + SIRT (n = 192)
Age, y, median (range)	66 (31–85)	66 (42–85)	66 (31–84)
Male/female, %	85.0/15.0	83.0/16.9	84.9/13.0
BCLC stage (%)	B: 28.2 C: 68.3	B: 28.2 C: 70.1	B: 28.1 C: 66.7
Cirrhosis, n (%)	369 (100)	177 (100)	192 (100)
Etiology, n (%)	AIH: 3 (2.4) Alcohol: 132 (35.8) Alcohol+viral: 19 (5.1) A1D: 1 (0.3) HBV: 26 (7.0) HCV: 70 (19.0) HC: 10 (2.7) NAFLD: 16 (4.3) NASH: 28 (7.6) NAT: 1 (0.3) NS: 21 (5.7) Cryptogenic: 41 (11.1) Steroid abuse: 1 (0.3)	AIH: 1 (0.6) Alcohol: 61 (34.5) Alcohol+viral: 10 (5.6) A1D: 1 (0.6) HBV: 15 (8.5) HCV: 31 (17.5) HC: 3 (1.7) NAFLD: 11 (6.2) NASH: 10 (5.6) NAT: 0 (0) NS: 9 (5.1) Cryptogenic: 24 (13.6) Steroid abuse: 1 (0.6)	AIH: 2 (1.0) Alcohol: 71 (37.0) Alcohol+viral: 9 (5.1) A1D: 1 (0.5) HBV: 11 (6.2) HCV: 39 (22.0) HC: 7 (3.6) NAFLD: 5 (2.6) NASH: 18 (10.2) NAT: 1 (0.5) NS: 12 (6.3) Cryptogenic: 17 (8.9) Steroid abuse: 0 (0)
ECOG, %	0: 65.6 1: 33.1 2: 1.4	0: 66.5 1: 33.0 2: 0.6	0: 64.7 1: 33.2 2: 2.2
OS, months	9.9	9.2	10.8

Abbreviations: A1D, alpha-1 antitrypsin deficiency; AIH, autoimmune hepatitis; HC, hemochromatosis; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; NAT, nonalcoholic toxic; NS, not specified.

SMM and AT in patients with advanced HCC undergoing palliative locoregional therapies remains unclear. Most published studies in the palliative setting are of retrospective design and include only small patient numbers.

The present study is a subanalysis of the SORAMIC clinical trial. Using prospectively collected data, we aimed to assess the influence of baseline body composition parameters on OS in both treatment arms, using skeletal muscle and AT-derived parameters.

METHODS

Patient selection

This is an exploratory post hoc substudy of the SORAMIC trial, a prospective, randomized controlled, phase II trial conducted at 38 clinical sites in 12 countries in Europe and Turkey.[9] The present study was performed within the palliative part of SORAMIC, where patients were randomized to receive sorafenib monotherapy or SIRT and sorafenib.[9] In short, patients were eligible if they had preserved liver function (Child-Pugh $\leq$B7), an Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$2, and unresectable tumors not eligible for curative treatment or transarterial chemoembolization. The procedural details have been reported elsewhere.[5]

The study was approved by the local ethics committees. Study procedures were performed in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization-Good Clinical Practice. All patients provided written informed consent to participate in the study (ClinicalTrials.gov No. NCT01126645; EudraCT 2009-012576-27). Overall, there were 424 patients involved into the palliative part of SORAMIC. In 55 patients, no computed tomographic images within 30 days before the procedure were available, and they were excluded from the present analysis. Therefore, the final cohort comprised 369 patients. The sorafenib/SIRT treatment group comprised 192 patients, and the sorafenib group included 177 patients. There were 56 women (15.2%) and 313 men (84.8%), with a mean age of 67 $\pm$ 8.6 years, median age of 66 years, and age range from 31 to 85 years. Baseline patient characteristics are summarized in Table 1A.

Image analysis

For all patients, the last available CT scan at baseline before therapy was used. All measurements of body composition parameters were performed in a semi-automatic fashion on axial images at the level of the third lumbar vertebra (L3) with the freely available Software ImageJ (version 1.53, National Institute of Health, USA). The soft tissue window was used [45–250 Hounsfield Units (HU)]. Any necessary adjustments were made by an experienced radiologist (Alexey Surov), blinded to the clinical course of patients.

Acquired body composition parameters included the following: total adipose tissue, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intramuscular adipose tissue. The relative distribution of abdominal body fat was assessed by the VSR, which was calculated by dividing VAT by SAT. Thresholds for attenuation measurements were −190 to + 30 HU) for fat tissue and −29 to + 150 HU for muscle tissue.

Skeletal muscle area was defined as the cross-sectional muscle area, including the quadratus lumborum, psoas, rectus abdominus, and erector spinae muscles, and the internal transverse and external oblique muscles. Measurements of fat and muscle tissue were normalized for patients' body height in meters squared to attain the following indices: VAT index, subcutaneous adipose tissue index (SATI), total adipose tissue index (TATI), and skeletal muscle index (SMI).

Low skeletal muscle mass (LSMM) was defined as SMI <52.4 cm^2/m^2 for males and <38.5 cm^2/m^2 for females, using the thresholds defined by Prado et al.[10] High VAT and high SAT were defined as an area >100 cm^2. High VSR was defined as >1.1. In addition, radiodensity of the analyzed body compartments was measured. Finally, fat-free mass (FFM) and fat mass (FM) were calculated using the following formulae:[11]

$$\text{FFM (kg)} = 0.30 \times (\text{muscle L3 cross-sectional area}) + 6.06;$$

$$\text{FM (kg)} = 0.042 \times (\text{fat L3 cross-sectional area}) + 11.2.$$

Statistical analysis

SPSS Version 25 and R were used for statistical analysis. Mean and SD as well as median and interquartile range were calculated for continuous variables. To assess the impact of body composition

TABLE 1B Baseline characteristics of body parameters of included patients

Characteristic	All patients (n = 369)	Sorafenib (n = 177)	Sorafenib + SIRT (n = 192)
Muscle area, cm^2	146.4 (80.0–225.3)	150.3 (80.6–211.8)	142.7 (80.0–225.3)
SMI, cm^2/m^2	48.7 (29.5–73.6)	49.7 (29.5–68.8)	47.9 (31.4–73.6)
LSMM, n (%)	206 (55.8)	92 (52.0)	114 (59.4)
Muscle density, HU	38.4 (1.7–74.8)	39.3 (16.0–74.8)	37.1 (1.7–60.0)
High VAT, n (%)	242 (65.6)	120 (67.8)	122 (63.5)
High SAT, n (%)	286 (77.5)	134 (75.7)	152 (79.2)
High VSR, n (%)	133 (36.0)	67 (37.9)	66 (23.4)
TAT, cm^2	329.5 (5.3–929.8)	334.4 (23.0–841.3)	324.4 (5.3–929.8)
VAT, cm^2	149.3 (1.1–522.2)	156.2 (1.1–437.6)	147.5 (1.4–522.2)
SAT, cm^2	150.1 (1.4–601.7)	151.9 (14.6–593.3)	147.9 (1.4–601.7)
IMAT, cm^2	12.3 (0.5–111.2)	12.4 (1.4–51.7)	12.3 (0.5–111.2)
SAT HU	−95.0 (−113.6 to −53.2)	−96.7 (−113.6 to −53.2)	−93.4 (−108.0 to −57.1)
VAT HU	−87.9 (−108.6 to −62.0)	−88.7 (−108.6 to −62.0)	−87.1 (−103.5 to −63.0)
TAT HU	329.5 (5.3–929.8)	334.4 (23.0–841.3)	324.4 (5.3–929.8)
IMAT HU	−61.1 (−77.4 to −42.9)	−61.5 (−76.1 to −45.5)	−60.8 (−77.4 to −42.9)
TATI	110.3 (1.9–363.2)	111.8 (7.3–281.6)	110.1 (1.9–363.2)
VATI	50.3 (0.4–164.8)	52.2 (0.4–147.9)	48.6 (0.4–164.8)
SATI	50.8 (0.5–235.0)	52.7 (4.6–205.3)	49.8 (0.5–235.0)
IMATI	4.1 (0.1–40.8)	4.1 (0.4–17.3)	4.1 (0.1–40.8)
SMI/TAT	0.1 (0.1–6.9)	0.1 (0.1–2.1)	0.2 (0.1–6.9)
SMA/TAT	0.4 (0.1–19.6)	0.4 (0.2–6.5)	0.5 (0.1–19.6)
FFM	50.0 (30.1–73.6)	51.2 (30.2–69.6)	48.9 (30.1–73.6)
FM	25.0 (11.4–50.3)	25.2 (12.2–46.5)	24.8 (11.4–50.3)
VSR	0.9 (0.03–4.6)	0.9 (0.03–3.5)	0.9 (0.1–4.6)

Abbreviations: FFM, fat-free mass; FM, fat mass; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose tissue ratio.

values on clinical variables and OS, univariable Cox regression model was used. The proportional hazards assumption was checked using graphical diagnostics based on the scaled Schoenfeld residuals using the function *ggcoxzph* in the *survminer* R package. No major departures were found. To detect nonlinearity, the martingale residuals against continuous covariates were used to assess the functional form. Visual inspection of the graphs using the R function *ggcoxfunctional* in the *survminer* R package do not indicate major violations of the linearity. HR are presented together with 95% CI. The resulting *p*-values were interpreted in an exploratory sense.

Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Kaplan-Meier curves were used for survival analysis.

RESULTS

Pooled OS

Baseline body composition results are shown in Table 1B. Median OS in the overall group was 9.9 months. LSMM was present in 206 (55.8%) patients. There was no relevant difference in OS between groups when stratified by SMI, VAT, SAT, or VSR (shown in Figure 1). Male patients showed a slightly higher SAT HU than female patients ($p = 0.007$, Supplemental Table S3, http://links.lww.com/HC9/A297). No relevant differences in body composition parameters were observed for stage BCLC B and stage BCLC C patients (Supplemental Table S4, http://links.lww.com/HC9/A297) or between patients aged below 60 and above 60 years (Supplemental Table S5, http://links.lww.com/HC9/A297). For etiology, patients with liver cirrhosis due to alcohol abuse or NAFLD/NASH

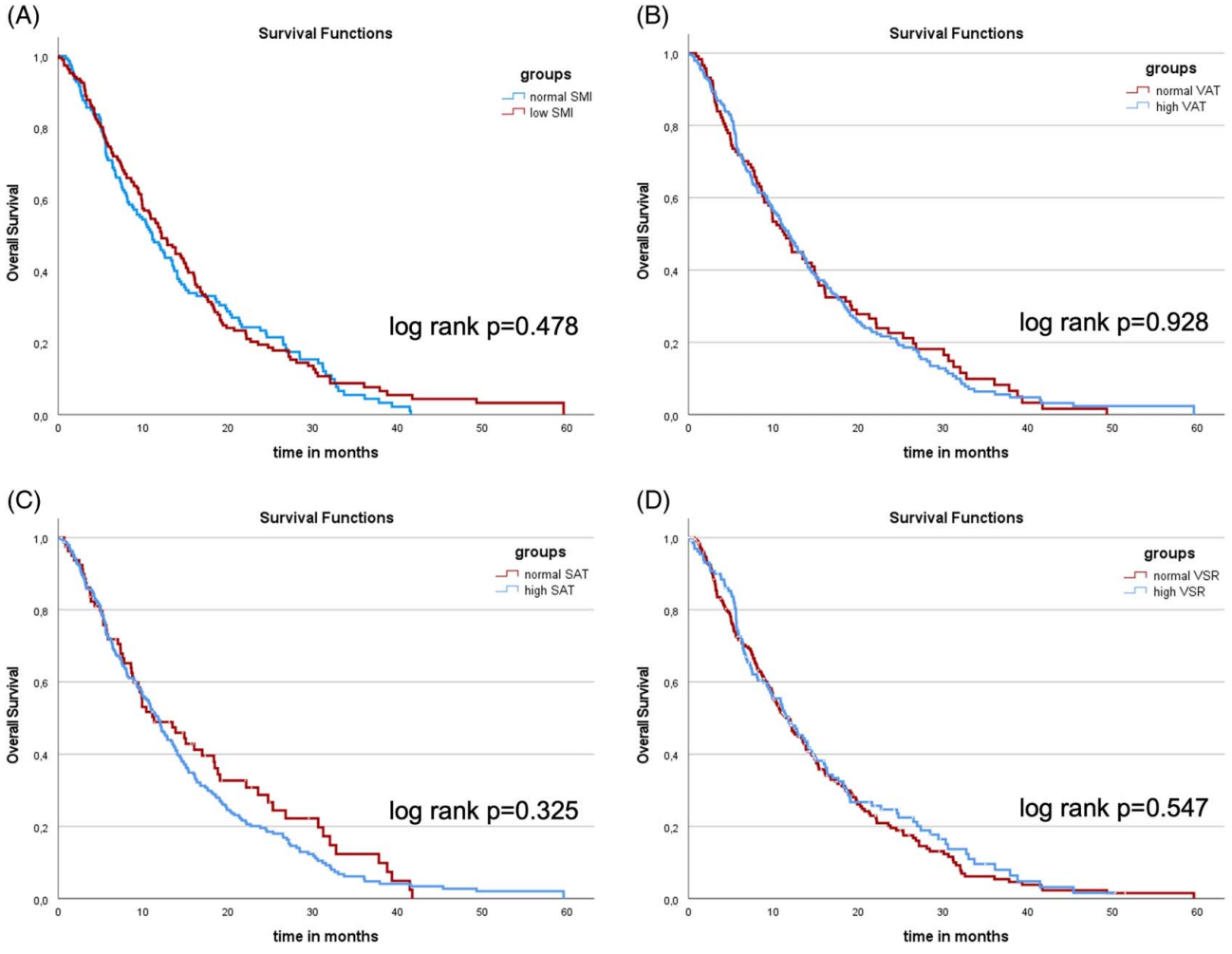

FIGURE 1 Kaplan-Meier curves for overall survival in the entire cohort for (A) the LSMM (median OS 12.2 mo, 95% CI, 10.1; 14,3) and non-LSMM group (median OS 11.1 mo, 95% CI, 8.9; 13.3), (B) the high VAT (median OS 11.8 mo, 95% CI, 10.0; 13.5) and normal VAT group (median OS 11.3 mo, 95% CI, 9.3; 13.2), (C) the high SAT (median OS 11.8 mo, 95% CI, 10.3; 13.2), and normal SAT group (median OS 11.3 mo, 95% CI, 6.3; 16.3), and (D) the high VSR (median OS 11.7 mo, 95% CI, 8.9; 14.6) and normal VSR group (median OS 11.8 mo, 95% CI, 9.9; 13.7). Abbreviations: LSMM, low skeletal muscle mass; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VSR, visceral-to-subcutaneous tissue ratio.

TABLE 2 Regression analysis results for OS for the entire cohort and subcohorts

	Overall cohort		Sorafenib only		SIRT/sorafenib	
Variables	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***
SMA	1.002 (0.997; 1.006)	0.446	1.002 (0.995; 1.008)	0.607	1.002 (0.996; 1.008)	0.465
SMI	1.005 (0.992; 1.019)	0.446	1.005 (0.986; 1.025)	0.583	1.006 (0.987; 1.026)	0.513
Muscle area	1.002 (0.997; 1.006)	0.446	1.002 (0.995; 1.008)	0.607	1.002 (0.996; 1.008)	0.465
Muscle HU	1.005 (0.992; 1.018)	0.445	1.004 (0.985; 1.024)	0.681	1.009 (0.990; 1.028)	0.360
VAT	1.000 (0.999; 1.001)	0.804	1.000 (0.998; 1.002)	0.911	1.000 (0.999; 1.001)	0.977
SAT	1.001 (0.999; 1.002)	0.245	1.001 (0.999; 1.003)	0.248	1.000 (0.998; 1.002)	0.815
TAT	1.000 (1.000; 1.001)	0.503	1.000 (0.999; 1.001)	0.542	1.000 (0.999; 1.001)	0.913
IMAT	0.997 (0.987; 1.007)	0.552	0.994 (0.978; 1.010)	0.483	0.999 (0.985; 1.012)	0.829
VSR	0.983 (0.825; 1.170)	0.846	0.911 (0.676; 1.228)	0.541	1.021 (0.825; 1.263)	0.849
VATI	1.001 (0.998; 1.004)	0.620	1.001 (0.996; 1.006)	0.674	1.000 (0.996; 1.004)	0.929
SATI	1.002 (0.998; 1.006)	0.235	1.003 (0.997; 1.008)	0.296	1.001 (0.996; 1.007)	0.670
TATI	1.001 (0.999; 1.003)	0.385	1.001 (0.998; 1.004)	0.434	1.000 (0.998; 1.003)	0.811
IMAT HU	0.999 (0.980; 1,017)	0.877	0.996 (0.969; 1,023)	0.768	1.002 (0.976; 1,029)	0.875
VAT HU	0.992 (0.978; 1.005)	0.233	0.993 (0.972; 1.014)	0.510	0.993 (0.974; 1.011)	0.430
SAT HU	0.992 (0.981; 1.003)	0.171	0.992 (0.977; 1.007)	0.315	0.994 (0.978; 1.010)	0.437
SMI/VATI	0.997 (0.984; 1.010)	0.633	1.001 (0.982; 1.021)	0.894	0.994 (0.978; 1.011)	0.512
SMI/TATI	0.936 (0.787; 1.113)	0.452	1.038 (0.780; 1.381)	0.798	0.897 (0.714; 1.126)	0.348
FFM	1.006 (0.991; 1.020)	0.446	1.006 (0.984; 1.027)	0.607	1.007 (0.988; 1.027)	0.465
FM	1.005 (0.990; 1.021)	0.503	1.007 (0.984; 1.030)	0.542	1.001 (0.980; 1.023)	0.913
SMI (low vs. high)	0.918 (0.726; 1.162)	0.478	0.997 (0.705; 1.409)	0.985	0.828 (0.597; 1.148)	0.258
VAT (high vs. low)	1.011 (0.793; 1.290)	0.929	0.971 (0.680; 1.386)	0.870	1.031 (0.737; 1.442)	0.858
SAT (high vs. low)	1.151 (0.870; 1.522)	0.325	1.062 (0.714; 1.579)	0.768	1.206 (0.808; 1.800)	0.358
VSR (high vs. low)	0.930 (0.732; 1.180)	0.548	0.948 (0.670; 1.341)	0.761	0.950 (0.651; 1.258)	0.552

Abbreviations: BMI, body mass index; FFM, fat-free mass; FM, fat mass; HU, Hounsfield unit; IMAT, intramuscular adipose tissue; IMATI, intramuscular adipose tissue index; SAT, subcutaneous adipose tissue; SATI, subcutaneous adipose index; SMA, skeletal muscle area; SMI, skeletal muscle index; TAT, total adipose tissue; TATI, total adipose tissue index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; VSR, visceral-to-adipose-tissue ratio.

showed higher values of skeletal muscle area, SMI, and VAT than patients with viral etiology of cirrhosis. Patients with NAFLD/NASH had higher values of AT than other etiologies. Both FM and FFM were highest in the NAFLD/NASH group (Supplemental Table S6, http://links.lww.com/HC9/A297).

In the univariable cox regression analysis, neither muscle parameter [SMI (HR 1.005, 95% CI, 0.992; 1.019, $p = 0.446$)] nor AT parameter showed a relevant association with OS. There was also no relevant association of LSMM with OS [SMI (HR 0.918, 95% CI, 0.726; 1.162, $p = 0.478$), high VAT (HR 1.011, 95% CI, 0.793; 1.290, $p = 0.929$)]. Regression results are shown in Table 2. Stratified analysis by ECOG Status (Supplemental Table S2A, B, http://links.lww.com/HC9/A297) or BCLC Status (Supplemental Table S2C, D Supplement, http://links.lww.com/HC9/A297) did not reveal a relevant association between body composition and OS.

OS in sorafenib group

Median OS in the sorafenib group was 9.2 months. The prevalence of LSMM was 52.0% (92/177 patients). Median OS for the low SMI group was 12.2 months (95% CI, 10.1; 14,3), and median OS for the normal SMI group was 11.1 months (95% CI, 8.9; 13.3; $p = 0.478$). There was no relevant difference in survival between the groups when stratified by body composition parameters (Figure 2). There was nearly no association with either muscle parameter [SMI (HR 1.005, 95% CI, 0.986; 1.025; $p = 0.583$)] or AT parameter [VAT (HR 1.000, 95% CI, 0.998; 1.002, $p = 0.911$)] and OS. LSMM and high VAT did not show a relevant influence on OS (HR 0.997, 95% CI, 0.705; 1.409, $p = 0.985$; HR 0.971, 95% CI, 0.680; 1.386, $p = 0.870$) (Table 2).

OS in the SIRT/sorafenib group

Median OS in the SIRT/sorafenib group was 10.8 months. A total of 114 patients had LSMM (59.4%). No relevant differences in survival were found when stratified by body composition parameters (Figure 3). No important association between either analyzed body composition parameter and OS was

found in the SIRT/sorafenib group. There was no relevant influence of SMI (HR 1.006, 95% CI, 0.987; 1.026, $p = 0.513$) nor VAT (HR 1.000, 95% CI, 0.999; 1.001, $p = 0.977$) or LSMM (HR 0.828, 95% CI, 0.597; 1.148, $p = 0.258$) on OS (Table 2).

DISCUSSION

Our study investigated the influence of different body composition parameters on outcome in patients with HCC undergoing either sorafenib alone or SIRT and sorafenib for advanced HCC, applying a comprehensive range of body composition parameters. Neither skeletal muscle nor AT parameters showed the capability to predict OS in our cohort. The results of our study suggest that the pattern of body composition is not a relevant factor impacting survival in our palliative cohort with patients with compensated cirrhosis. To the best of our knowledge, this is the first study evaluating the association between sarcopenia and OS in HCC in distinct palliative treatment arms.

Sarcopenia is a complex syndrome that has been linked to adverse outcomes in oncologic and non-oncologic diseases. In clinical routine, it can be measured on CT imaging by the proxy parameter LSMM. Sarcopenia is common in patients with cirrhosis and HCC, with a prevalence of around 40%, and has been linked to adverse outcomes.[12,13–16] In a recent meta-analysis including patients with HCC, around 39% of patients were affected by LSMM, with associations with worse OS and lower recurrence-free survival.[12]

A meta-analysis with patients with HCC found an association between LSMM and OS both in the curative as well as in the palliative setting. Treatments in the 2 included studies with palliative patients included systemic chemotherapy with sorafenib in one and intra-arterial chemoembolization or radiofrequency ablation in the other study, with cohort sizes of 116 and 93 patients, respectively.[17] Studies focusing on patients with advanced HCC undergoing sorafenib therapy are still scarce, based on relatively small cohorts, and retrospective in nature, with the literature showing conflicting results regarding the influence of LSMM on OS.[15,18,19] For example, Nault and colleagues[18] and Labeur and colleagues[19] did not find an association between SMI and OS, whereas Imai et[20] Hiraoka[15] and colleagues found an influence of the SMI and PMI, respectively. A comprehensive overview of the current evidence can be found in Labeur et al.[19]

Our study is the first to investigate the association between body composition and the combination of SIRT and sorafenib in HCC. The available data on the influence of body composition in patients treated with SIRT are sparse. High VAT density was significantly associated with increased mortality and more adverse events in a Canadian study with 101 patients. There was no influence of SMI or LSMM on survival.[7] The prevalence of LSMM was 56%, with similar median values for body composition parameters compared with our cohort. However, our cohorts vary significantly: the rate of alcohol-associated cirrhosis was only 14%, whereas it was 35% in our cohort. Moreover, the rate of BCLC stage C patients was 68% in our cohort and only 25% in the cohort by Ebadi and colleagues, potentially accounting for differences in outcome. Sarcopenia as defined by FFM area measured in MRI predicted increased mortality in 2 studies including patients undergoing Y90-SIRT.[21,22] However, with a sample size of 82 and 56 patients, respectively, the analyzed cohorts were relatively small.

In contrast to skeletal muscles, analysis of AT in patients with HCC was performed in only few studies, and the results are heterogeneous. With regard to AT, Ohki et al. have shown that baseline visceral fat are was an independent factor for recurrence in non-viral HCC after radiofrequency ablation.[23] A study with a Swiss and UK cohort with patients with HCC at different stages found an association between SAT density and OS.[24] In a study by Montano-Loza et al[25], a high VATI was identified as a risk factor for HCC and HCC recurrence after liver transplantation. Parikh et al[26] showed that high VAT radiodensity was linked with shorter OS in patients with HCC undergoing trans-arterial chemoembolization. In patients receiving sorafenib, Nault et al[18] reported an association between VATI and OS in a small cohort of 52 patients.

While screening for body composition is pivotal to improve patients' functional capacity, our study does not suggest that LSMM or AT measurements can serve treatment decisions in palliative treatment arms in advanced HCC. There are several possible explanations for our findings. First, given the indications for radioembolization and study inclusion criteria, patients were suffering from advanced tumor stages and high tumor burden. Hepatic tumor burden, macrovascular invasion, and the presence of extrahepatic metastases are known factors for adverse outcomes in HCC.[27] Advanced-stage BCLC C patients are a heterogenous patient group. Gianni et al[28] have shown significant differences in OS in patients with stage BCLC C when stratified by performance status and tumor characteristics. In a study with patients with HCC with extrahepatic spread under sorafenib therapy, liver function according to Child-Pugh class and microvascular invasion were identified as prognostic factors for OS.[29] Other prognostic factors associated with OS are new extrahepatic lesions and new vascular invasion.[30] All patients in our cohort had compensated cirrhosis. These factors may diminish the influence of body composition.

Second, OS in our cohort may be too short to account for influences of LSMM or AT. It has been reported that in patients with aggressive tumor characteristics and short OS, the effect of body composition

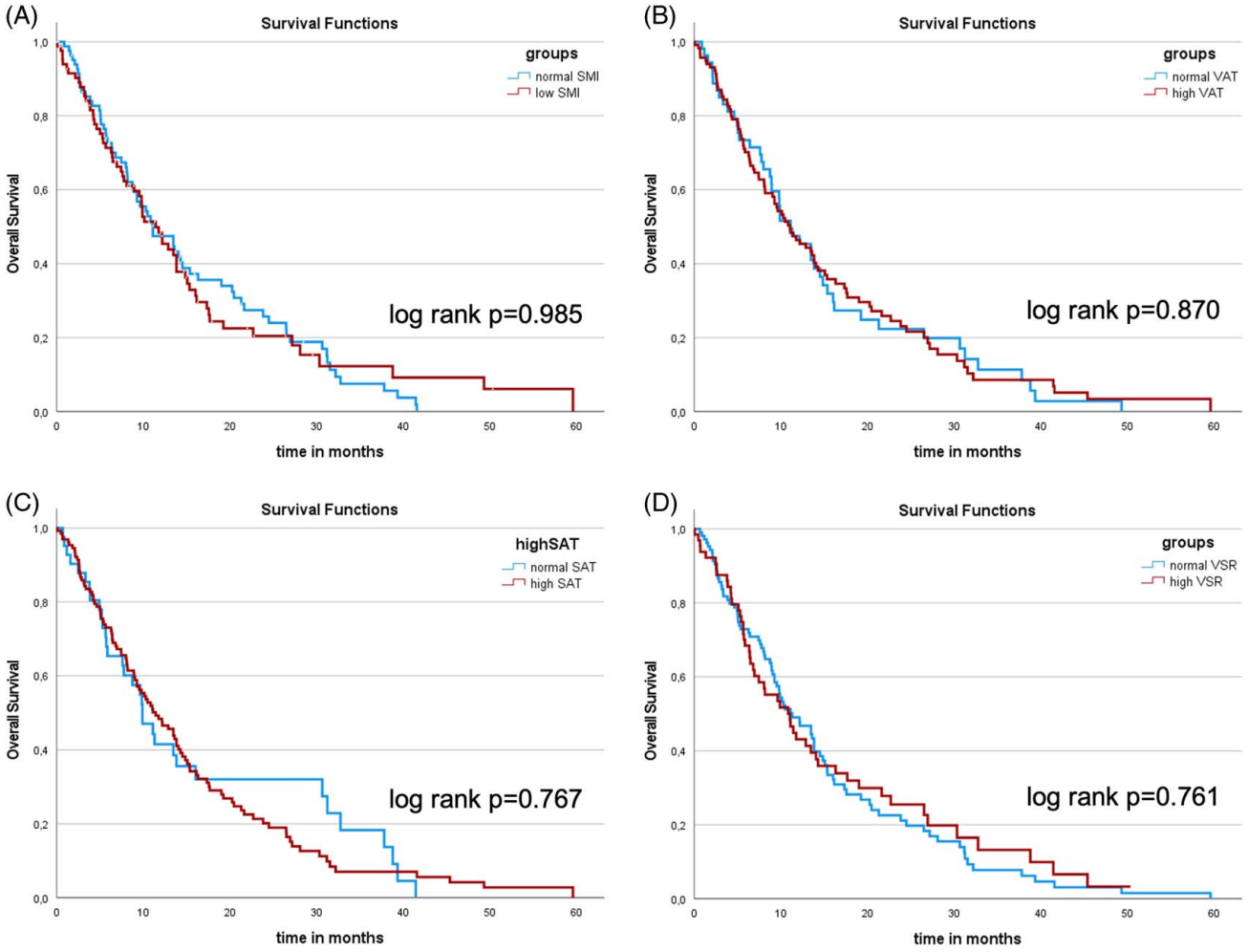

FIGURE 2 Kaplan-Meier curves for overall survival in the sorafenib-only cohort for (A) the LSMM (median OS 11.4 mo, 95% CI, 8.5; 14.4) and non-LSMM group (median OS 11.1 mo, 95% CI, 7.1; 15.0), (B) the high VAT (median OS 11.0 mo, 95% CI, 8.1; 13.9) and normal VAT group (median OS 11.1 mo, 95% CI, 7.7; 14.5), (C) the high SAT (median OS 11.4 mo, 95% CI, 8.6; 14.3) and normal SAT group (median OS 9.9 mo, 95% CI, 7.1; 12.7), and (D) the high VSR (median OS 11.0 mo, 95% CI, 7.0; 15.0) and normal VSR group (median OS 11.3 mo, 95% CI, 8.0; 14.6). Abbreviation: LSMM, low skeletal muscle mass; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VSR, visceral-to-subcutaneous tissue ratio.

parameters may not have a relevant influence on OS.[31] Our cohort does therefore not prove that there is no association between body composition on clinical outcomes. Yet patients in the selected treatment arms may not benefit from physical exercise and improved nutrition in terms of longer OS. Beyond survival time, multimodal interventions may yet improve quality of live or other functional parameters that we have not studied in our analysis.

Third, the prevalence of LSMM in our cohort is higher than reported in most studies with patients under sorafenib therapy. With the exception of the studies by Ebadi et al, Antonelli et al, and Labeur et al, the reported rate of LSMM ranges between 11% and 25%.[7,15,19,32,33] However, both Antonelli and colleagues and Labeur and colleagues, with a prevalence of sarcopenia of 49% and 52%, respectively, applied cutoff values by Martin et al[34] to their cohort, with an additional stratification according to BMI. Labeur and colleagues did not find an association between either single body composition parameter and OS. Ebadi used predefined cutoff values for patients with cirrhosis awaiting liver transplantation. For SMI, we applied fixed cutoff values by Prado et al.[10] We believe these to be best validated in various studies across different diseases. As the SMI has already been normalized by body height, we do not think an additional cutoff based on BMI is necessary. Sensitivity analysis may have provided different cohort-specific cutoff values at the cost of reproducibility. The SORAMIC trial included patients with liver-dominant disease and patients with pulmonary metastases were excluded, potentially leading to bias in our analysis.

A limitation is the exclusion of patients without baseline abdominal CT scan, which might lead to selection bias. Strengths of our study are the large sample size and the prospectively collected data within a clinical trial.

In conclusion, in this substudy of the multicentric SORAMIC trial, we did not find an association between

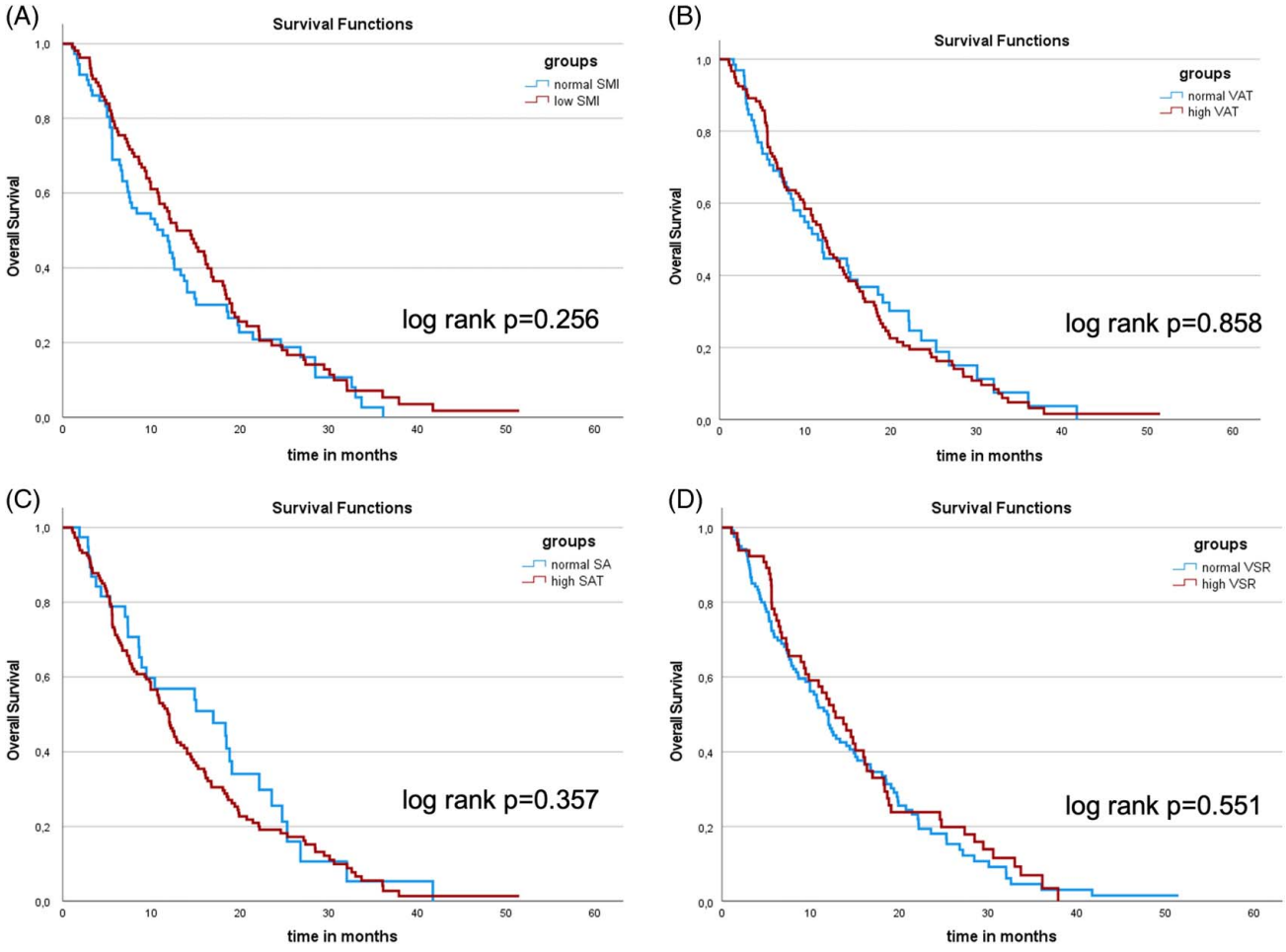

FIGURE 3 Kaplan-Meier curves for overall survival in the SIRT/sorafenib cohort for (A) the LSMM (median OS 12.9 mo, 95% CI, 9.7; 16.0) and non-LSMM group (median OS 11.3 mo, 95% CI, 7.0; 15.5), (B) the high VAT (median OS 12.4 mo, 95% CI, 10.3; 14.4) and normal VAT group (median OS 11.5 mo, 95% CI, 8.6; 14.4), (C) the high SAT (median OS 12.0 mo, 95% CI, 10.5; 13.5) and normal SAT group (median OS 17.0 mo, 95% CI, 6.5; 27.4), and (D) the high VSR (median OS 12.8 mo, 95% CI, 9.4; 16.2) and normal VSR group (median OS 11.8 mo, 95% CI, 10.0; 13.6). Abbreviations: LSMM, low skeletal muscle mass; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VSR, visceral-to-subcutaneous tissue ratio.

body composition parameters and OS. Body composition parameters therefore do not serve in patient allocation in this palliative treatment cohort.

AUTHOR CONTRIBUTIONS

Alexey Surov.: conception and design of the study; generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Maximilian Thormann: conception and design of the study; generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Osman Öcal, Kerstin Schütte, Christoph J. Zech, Christian Loewe, Otto van Delden, Vincent Vandecaveye, Chris Verslype, Bernhard Gebauer, Christian Sengel, Irene Bargellini, Roberto Iezzi, Thomas Berg, Heinz J. Klümpen, Julia Benckert, Antonio Gasbarrini, Holger Amthauer, Bruno Sangro, Peter Malfertheiner, and Mattes Hinnerichs: generation, collection, assembly, analysis, and/or interpretation of data and approval of the final version of the manuscript. Max Seidensticker: generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Ricarda Seidensticker: generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Jazan Omari: generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Andreas Wienke: generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Jens Ricke: generation, collection, assembly, analysis, and/or interpretation of data; drafting or revision of the manuscript; and approval of the final version of the manuscript. Maciej Pech: conception and design of the study; generation,

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CONFLICTS OF INTEREST

Max Seidensticker advises and received grants from Bayer. He received grants from Sirtex. Kerstin Schutte advises Bayer. Chris Verslype advises, is on the speakers' bureau, and received grants from Bayer. He consults for Ipsen and Roche. Bernhard Gebauer received grants from Sirtex. Thomas Berg advises and is on the speakers' bureau for Roche, Bayer, Eisai, and Sirtex. He is on the speakers' bureau for Ipsen. Antonio Gasbarrini consults for AbbVie, Alfasigma, Lion Health, Roche, Sanofi, and Takeda. Holger Amthauer consults and received grants from Sirtex. Bruno Sangro consults, advises, is on the speakers' bureau, and received grants from Bristol-Myers Squibb and Sirtex. He consults, advises, and is on the speakers' bureau for AstraZeneca, Bayer, Eisai, Eli Lilly, Incyte, Ipsen, Novartis, Roche, and Terumo. He consults and advises Boston Scientific. Peter Malfertheiner consults for Aboca and Bayer, advises Allergosan, is on the speakers' bureau for Biocodex and Malesci, and received grants from Menarini. Maciej Pech consults and is on the speakers' bureau for Sirtex. The remaining authors have no conflicts to report.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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