

Original Paper

Preoperative Visceral Adiposity and Muscularity Predict Poor Outcomes after Hepatectomy for Hepatocellular Carcinoma

Yuhei Hamaguchi Toshimi Kaido Shinya Okumura Atsushi Kobayashi
Hisaya Shirai Siyuan Yao Shintaro Yagi Naoko Kamo Satoru Seo
Kojiro Taura Hideaki Okajima Shinji Uemoto

Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery,
Graduate School of Medicine, Kyoto University, Kyoto, Japan

Keywords

Hepatocellular carcinoma · Intramuscular adipose tissue content · Sarcopenia · Skeletal muscle mass index · Visceral adiposity · Visceral-to-subcutaneous adipose tissue area ratio

Abstract

Objective: Visceral adiposity, defined as a high visceral-to-subcutaneous adipose tissue area ratio (VSR), has been shown to be associated with poor outcomes in several cancers. However, in the surgical field, the significance of visceral adiposity remains controversial. The present study investigated the impact of visceral adiposity as well as sarcopenic factors (low muscularity) on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma (HCC). **Patients and Methods:** This retrospective study analyzed data from 606 patients undergoing hepatectomy for HCC at our institution between April 2005 and March 2016. Using preoperative plain computed tomography imaging at the level of the third lumbar vertebra, visceral adiposity, skeletal muscle mass, and muscle quality were evaluated by the VSR, skeletal muscle mass index (SMI), and intramuscular adipose tissue content (IMAC), respectively. The impact of these parameters on outcomes after hepatectomy for HCC was analyzed. **Results:** The overall survival rate was significantly lower among patients with a high VSR ($p < 0.001$) than among patients with a normal VSR. Similarly, the recurrence-free survival rate was significantly lower among patients with a high VSR ($p = 0.016$). A high VSR, low SMI, and high IMAC contributed to an increased risk of death ($p < 0.001$) and HCC recurrence ($p < 0.001$) in an additive manner. Multivariate analysis showed that not only preoperative low muscularity but also visceral adiposity was a significant risk factor for mortality (hazard ratio [HR] = 1.566, $p < 0.001$) and HCC recurrence (HR = 1.329, $p = 0.020$) after hepatectomy for HCC. **Conclusions:** Preoperative visceral adiposity, as well as low muscularity, was closely related to poor

Toshimi Kaido, MD, PhD
Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of
Surgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin
Sakyo-ku, Kyoto 606-8507 (Japan)
E-Mail kaido@kuhp.kyoto-u.ac.jp

outcomes after hepatectomy for HCC. It is crucial to establish a new strategy including perioperative nutritional interventions with rehabilitation for better outcomes after hepatectomy for HCC.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common human cancers, and it is the third leading cause of cancer-related death because of its highly malignant potential, characterized by rapid progression, frequent tumor recurrence, and metastasis [1, 2]. Today, surgical treatment, including hepatectomy and liver transplantation, is the only effective treatment for HCC, because there is no successful systemic chemotherapy for patients with advanced HCC [2–4]. Although advances in preoperative diagnosis, surgical technique and devices, and perioperative management have dramatically improved overall survival (OS) after partial hepatectomy for HCC, the HCC recurrence rate remains high even in patients with curative resection, with a 5-year recurrence rate as high as 70% [5–7].

Obesity has been well documented as a risk factor for various diseases, including type 2 diabetes mellitus, hypertension, cardiovascular disease, and nonalcoholic fatty liver disease [8, 9]. In addition, prospective studies and meta-analyses have also demonstrated that obese individuals are at increased risk of many types of cancer and have a poor prognosis [10–12]. On the other hand, several recent studies showed that patients with a higher body mass index (BMI) survive longer than normal-weight patients [13–16]. These contradictory results, the so-called obesity paradox, might occur because the BMI cannot account for differences in fat distribution because it is an indirect measure of adipose tissue.

In recent studies of body composition assessment, skeletal muscle and adipose tissue were directly evaluated using several imaging techniques such as dual-energy X-ray absorptiometry, computed tomography (CT), magnetic resonance imaging, and bioimpedance analysis. Especially on CT analysis, the areas of skeletal muscle and adipose tissue can be automatically quantified by the CT values peculiar to these tissues, and this has been shown to be a precise and reliable method to evaluate adipose tissue distribution [17–19]. Using this method, visceral adiposity can be easily calculated as the visceral-to-subcutaneous adipose tissue area ratio (VSR), and a high VSR has been reported to be a useful predictor of poor prognosis in various kinds of disease, including several cancers [20–24]. Although one study demonstrated the significance of visceral adiposity for patients with HCC, its impact on outcomes in patients undergoing hepatectomy for HCC remains unclear [20].

The present study retrospectively evaluated preoperative visceral adiposity, in addition to muscularity (skeletal muscle mass and muscle quality), and it aimed to investigate the impact of preoperative visceral adiposity and muscularity on outcomes after hepatectomy for HCC.

Patients and Methods

Patients

Between April 2005 and March 2016, a total of 622 patients were admitted to Kyoto University Hospital for hepatectomy for HCC. Sixteen patients who did not undergo preoperative plain CT were excluded from the analysis. This retrospective study therefore analyzed data from 606 patients (484 men, 122 women). The median duration of follow-up for these patients was 42.6 months (interquartile range [IQR] 19.7–71.7). Details about the surgical procedures of hepatectomy, pathological examination, and follow-up after hepatectomy have been described previously [25, 26].

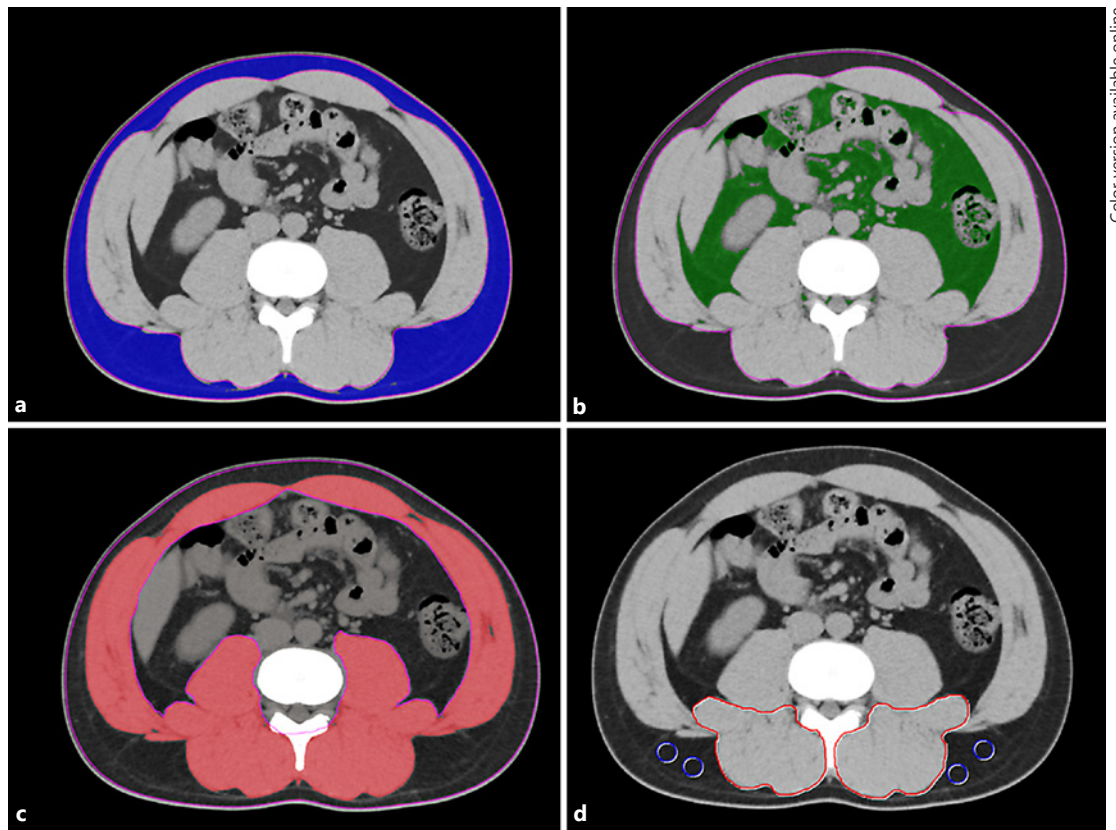


Fig. 1. Cross-sectional CT images at the level of the third lumbar vertebra. **a** Subcutaneous adipose tissue areas are identified and quantified using CT attenuation values of -190 to -30 HU. **b** Visceral adipose tissue areas are quantified using attenuation values of -150 to -50 HU. **c** Skeletal muscle areas are quantified using a CT attenuation value of -29 to 150 HU. **d** CT attenuation values of subfascial muscular tissue in the multifidus muscle and subcutaneous fat (4 small circles) are examined to calculate the intramuscular adipose tissue content. CT, computed tomography; HU, Hounsfield unit.

The indications for hepatectomy for HCC at our institution include Child-Pugh grade A or B and a future remnant liver volume $\geq 25\%$ of the whole liver. Hepatic resection is usually performed using the Cavitron Ultrasonic Surgical Aspirator and a bipolar cautery device equipped with a channel for water dripping, with an intermittent Pringle maneuver, or selective vascular clamping if necessary.

Image Analysis

All CT examinations were performed using a multidetector-row CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan). The technical parameters for CT were: tube voltage, 120 kV; detector configuration, $0.5 \text{ mm} \times 64$ rows; tube current modulation, 0.5 s/rotation (gantry rotation); and reconstruction thickness, 5 mm. Using a cross-sectional CT at the level of the third lumbar vertebra (L3), the adipose tissue area and skeletal muscle were examined using Aquarius iNtuition (TeraRecon, San Mateo, CA, USA). Aquarius iNtuition is an iNtuition client viewer with advanced visualization capabilities. With this software, visceral and subcutaneous adipose tissue and areas of skeletal muscle can be easily and automatically quantified using the CT attenuation values peculiar to these tissues. On the basis of previous reports, subcutaneous and visceral adipose tissue areas were quantified using attenuation values of -190 to -30 Hounsfield units (HU) (Fig. 1a) and -150 to -50 HU (Fig. 1b), respectively [17, 18]. Visceral adiposity was evaluated by the VSR, which was calculated as follows [20]: $\text{VSR} = \text{visceral adipose tissue area (cm}^2\text{)}/\text{subcutaneous adipose tissue area (cm}^2\text{)}$.

Similarly, skeletal muscle areas that include the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis were identified and quantified using attenuation values of -29 to 150 HU (Fig. 1c) [18]. The preoperative skeletal muscle mass was evaluated by the skeletal muscle mass index (SMI), calculated as follows: $\text{SMI} = \text{cross-sectional areas of skeletal muscle (cm}^2\text{)}/\text{patient's height}^2 \text{ (m}^2\text{)}$.

In addition, muscle quality was examined by intramuscular adipose tissue content (IMAC) at the L3 level. The IMAC was calculated as follows [24–26]: $\text{IMAC} = \text{CT attenuation value of the multifidus muscles (HU)}/\text{CT attenuation value of the subcutaneous fat (HU)}$ (Fig. 1d). A higher IMAC indicates a greater amount of adipose tissue within skeletal muscle, and thus a lower quality of skeletal muscle (muscle steatosis).

Cutoff Values for the VSR, SMI, and IMAC

The cutoff values for the VSR, SMI, and IMAC were determined for men and women separately using the data from 657 healthy donors for living donor liver transplantation between 2005 and 2016 [24]. A high VSR was defined as more than 2 standard deviations (SDs) above the mean VSR of younger donors (<50 years), resulting in cutoff values of 1.325 for males and 0.710 for females. A low SMI was defined as more than 2 SDs below the mean, resulting in cutoff values of 40.31 for males and 30.88 for females. Similarly, a high IMAC was defined as more than 2 SDs above the mean, resulting in cutoff values of -0.358 for males and -0.229 for females.

Analyzed Parameters

First, perioperative parameters were compared between patients with a high VSR and those with a normal VSR. The severity of complications was graded according to the Dindo-Clavien classification [27]. Major complications were defined as any complications of Clavien grade III or higher. Second, the OS and recurrence-free survival (RFS) rates after hepatectomy were investigated in the patients classified according to the VSR, SMI, or IMAC. Moreover, the prognostic factors were analyzed on the basis of the following variables: patient age (≥ 65 vs. <65 years), sex (male vs. female), etiology of HCC (HBV [hepatitis B virus] and/or HCV [hepatitis C virus]-related HCC vs. others), the presence of a treatment history for HCC before hepatectomy, the presence of obesity-related comorbidities (type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease), the period of hepatectomy (2005–2009 vs. 2010–2016), platelet count ($\geq 10 \times 10^4$ vs. $<10 \times 10^4/\text{mm}^3$), total lymphocyte count ($\geq 1,000$ vs. $<1,000/\text{mm}^3$), neutrophil-to-lymphocyte ratio (≥ 4.0 vs. <4.0), serum total bilirubin level (≥ 1.0 vs. <1.0 mg/dL), serum albumin level (≥ 3.5 vs. <3.5 g/dL), indocyanine green retention at 15 min (≥ 15 vs. $<15\%$), Child-Pugh class (A vs. B), serum α -fetoprotein (AFP) level (≥ 20 vs. <20 ng/dL), des- γ -carboxyprothrombin level (≥ 40 vs. <40 mAU/mL), liver histology (normal liver or chronic hepatitis vs. liver fibrosis or liver cirrhosis), tumor size (≥ 5.0 vs. <5.0 cm), number of tumors (solitary vs. multiple), microvascular invasion, tumor differentiation (well or moderately differentiated vs. poorly differentiated), pathological stage according to the Liver Cancer Study Group of Japan (I or II vs. III or IV), surgical procedure (lobectomy or more vs. less than segmentectomy), duration of surgery (≥ 360 vs. <360 min), estimated operative blood loss (≥ 500 vs. <500 mL), BMI (≥ 25 vs. <25), preoperative skeletal muscle mass (low SMI vs. normal SMI), skeletal muscle quality (high IMAC vs. normal IMAC), and visceral adiposity (high VSR vs. normal VSR).

Statistical Analysis

Continuous data are presented as medians (IQR); they were nonparametrically analyzed using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Correlations between continuous variables were assessed using Pearson's correlation coefficient. Cumulative OS and RFS rates were calculated using Kaplan-Meier methods, with differences between curves evaluated using the log-rank test. Among variables identified as significant ($p < 0.05$) or showing values of $p < 0.10$ on univariate analysis, candidates for a Cox proportional-hazards model were selected through a stepwise procedure using the minimum AICc method.

The results are shown as hazard ratios (HRs) with 95% CIs. The variation inflation factor and tolerance were calculated to assess multicollinearity before performing multivariate analysis, and multicollinear variables were excluded from the multivariate analysis. Especially, since tumor size, the number of tumors, and vascular invasion are factors constituting a pathological stage according to the Liver Cancer Study Group of Japan, these factors were not included in the multivariate analysis together with the pathological stage.

A p value <0.05 was considered significant. All statistical data were generated using JMP Pro 12 (SAS Institute, Cary, NC, USA) and Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

Table 1. Characteristics of the patients classified according to the VSR

Characteristic	Total (n = 606)	High VSR (n = 252)	Normal VSR (n = 354)	p value
Age, years	68 (61–75)	71 (64–80)	66 (59–77)	<0.001
Sex				
Male	484 (80)	191 (76)	293 (83)	0.040
Female	122 (20)	62 (24)	61 (17)	
Etiology				
HBV and/or HCV	392 (65)	129 (51)	263 (74)	<0.001
Others	214 (35)	123 (49)	91 (25)	
Previous treatment for HCC				
Yes	228 (38)	99 (39)	129 (36)	0.497
No	378 (62)	153 (61)	225 (64)	
Diabetes				
Yes	180 (30)	89 (35)	91 (26)	0.012
No	426 (70)	163 (65)	263 (74)	
Hypertension				
Yes	273 (45)	140 (56)	133 (38)	<0.001
No	333 (55)	112 (44)	221 (62)	
Dyslipidemia				
Yes	56 (9)	32 (13)	24 (7)	0.015
No	550 (91)	220 (87)	330 (93)	
Cardiovascular disease				
Yes	42 (7)	24 (10)	18 (5)	0.036
No	564 (93)	228 (90)	336 (95)	
Platelet count, ×10 ⁴ /mm ³	14.4 (10.5–19.1)	14.7 (10.6–19.5)	14.1 (10.4–18.9)	0.180
Total bilirubin, mg/dL	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.154
Albumin, g/dL	3.9 (3.6–4.2)	3.9 (3.6–4.2)	3.9 (3.6–4.3)	0.653
Total lymphocyte count, /mm ³	1,338 (994–1,756)	1,357 (982–1,721)	1,328 (1,006–1,778)	0.454
Neutrophil-to-lymphocyte ratio	1.9 (1.4–2.7)	2.1 (1.6–2.8)	1.8 (1.3–2.6)	0.046
ICG R15, %	15 (10–21)	15 (10–21)	15 (10–21)	0.680
Child-Pugh class				
A	555 (92)	229 (91)	326 (92)	0.657
B	51 (8)	23 (9)	28 (8)	
AFP, ng/mL	18.3 (5.3–204.1)	14.9 (5.0–167.5)	20.2 (5.4–223.7)	0.454
DCP, mAU/mL	142 (33–1,568)	215 (42–3,350)	97 (31.5–863)	0.019
Liver histology				
Normal liver + chronic hepatitis	305 (50)	132 (52)	173 (49)	0.411
Liver fibrosis + liver cirrhosis	301 (50)	120 (48)	181 (51)	
Tumor size, cm	3.5 (2.2–6.2)	4.0 (2.5–7.0)	3.0 (2.0–5.5)	0.001
Number of tumors				
Solitary	417 (69)	170 (67)	247 (70)	0.594
Multiple	189 (31)	82 (33)	107 (30)	
MVI				
Positive	196 (32)	87 (35)	109 (31)	0.334
Negative	410 (68)	165 (65)	245 (69)	
Differentiation of HCC				
Well	60 (10)	28 (11)	32 (9)	0.638
Moderate	364 (60)	146 (58)	218 (62)	
Poor	167 (28)	73 (29)	94 (27)	
Unknown	15 (2)	5 (2)	10 (3)	
TNM stage				
I + II	361 (60)	145 (58)	216 (61)	0.402
III + IV	245 (40)	107 (42)	138 (39)	
Surgical procedure				
Lobectomy or more	210 (35)	95 (38)	115 (33)	0.195
Less than segmentectomy	396 (65)	157 (62)	239 (67)	

Table 1 (continued)

Characteristic	Total (n = 606)	High VSR (n = 252)	Normal VSR (n = 354)	p value
Operative time, min	367 (277–459)	367 (283–463)	366 (270–454)	0.839
Operative blood loss, mL	720 (330–1,385)	800 (357–1,460)	607 (298–1,307)	0.651
Postoperative complications (Clavien-Dindo classification)				
Grade III or higher	132 (22)	64 (25)	68 (19)	0.073
Below grade III	474 (78)	188 (75)	286 (81)	
BMI	23.2 (21.1–25.1)	23.2 (21.2–25.6)	23.2 (21.0–24.9)	0.852
Preoperative SMI				
Normal	522 (86)	206 (81)	316 (89)	0.012
Low	84 (14)	46 (18)	38 (11)	
Preoperative IMAC				
Normal	348 (57)	131 (52)	216 (61)	0.025
High	258 (43)	121 (48)	137 (39)	
Preoperative VSR				
Males	1.203 (0.883–1.606)	1.713 (1.463–2.586)	0.967 (0.747–1.252)	<0.001
Females	0.709 (0.491–0.987)	0.984 (0.807–1.237)	0.494 (0.377–0.661)	<0.001

Values are presented as *n* (%) or median (IQR). Percentages might not add up to 100% because of rounding. VSR, visceral-to-subcutaneous adipose tissue area ratio; IQR, interquartile range; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; ICG R15, indocyanine green retention test at 15 min; AFP, α -fetoprotein; DCP, des- γ -carboxyprothrombin; MVI, microvascular invasion; TNM, tumour-node-metastasis (stage defined by the Liver Cancer Study Group of Japan); BMI, body mass index; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content.

Results

Patient Characteristics

The baseline characteristics and laboratory data of the 606 patients are shown in Table 1. The median patient age was 68 years (IQR 61–75). Two hundred and twenty-eight patients (38%) had a treatment history for HCC before hepatectomy, such as transcatheter arterial chemoembolization or radiofrequency ablation, while 378 patients (62%) underwent primary hepatectomy as the initial treatment for HCC. The Child-Pugh classes were A and B for 555 (92%) and 51 patients (8%), respectively. The median tumor size was 3.5 cm (IQR 2.2–6.2), and multiple HCCs were found in 189 patients (31%). The pathological stages according to the Liver Cancer Study Group of Japan were I, II, III, and IV for 166 (27%), 195 (32%), 157 (26%), and 88 patients (15%), respectively. Using the cutoff values described above, 252 patients (42%) had a high VSR (visceral adiposity) preoperatively, 84 patients (14%) had a low SMI (low muscle mass) preoperatively, and 258 patients (43%) had a high IMAC (low muscle quality).

Correlations of the Preoperative VSR with Other Parameters

The perioperative parameters of the patients classified according to their VSR are shown in Table 1. The median age was significantly higher among the patients with a high VSR than in the patients with a normal VSR ($p < 0.001$). The patients with a normal VSR showed more HBV- or HCV-related HCC than those with a high VSR ($p < 0.001$). In addition, more patients had obesity-related comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease, in the high-VSR group than in the normal-VSR group ($p = 0.012$, $p < 0.001$, $p = 0.015$, and $p = 0.036$, respectively). Although the median tumor size was significantly larger among the patients with a high VSR ($p = 0.001$), the TNM stage was not significantly different between the two groups ($p = 0.402$). The operative factors, such as surgical

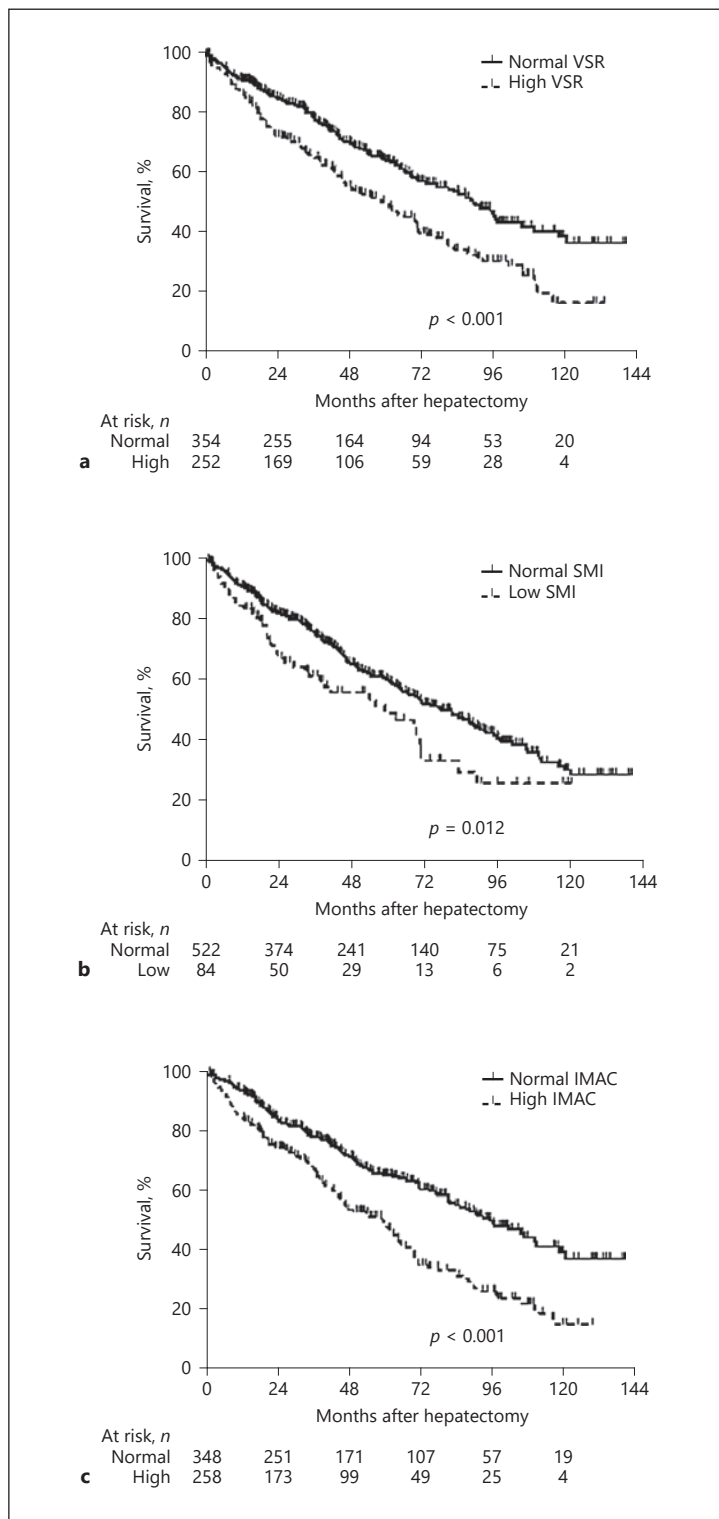


Fig. 2. OS rates among patients classified according to body composition variables. **a** The OS rate after hepatectomy for hepatocellular carcinoma was significantly lower among the patients with a high VSR ($n = 252$) than among the patients with a normal VSR ($n = 354$; $p < 0.001$). **b** The OS rate was significantly lower among the patients with a low SMI ($n = 84$) than among the patients with a normal SMI ($n = 522$; $p = 0.012$). **c** The OS rate was significantly lower among the patients with a high IMAC ($n = 258$) than among the patients with a normal IMAC ($n = 348$; $p < 0.001$). OS, overall survival; VSR, visceral-to-subcutaneous adipose tissue area ratio; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content.

procedure, operative time, and blood loss, were similar between the two groups. Among 252 patients with a high VSR, there were significantly more subjects with a low SMI ($p = 0.012$) and a high IMAC ($p = 0.025$). However, there were only weak correlations between VSR and SMI ($r = 0.076$), and between VSR and IMAC ($r = 0.056$) (data not shown).

OS and RFS Rates after Hepatectomy for HCC

The OS rate after hepatectomy for HCC was significantly lower among the patients with a high VSR ($n = 252$) than among those with a normal VSR ($n = 354$; $p < 0.001$; Fig. 2a). The 1-, 3-, and 5-year OS rates among the patients with a high VSR versus those with a normal VSR were 87.9, 65.3, and 50.5% versus 91.4, 79.4, and 64.9%, respectively. Similarly, the OS rate was significantly lower among the patients with a low SMI ($n = 84$) than among those with a normal SMI ($n = 522$; $p = 0.012$; Fig. 2b). Moreover, the OS rate was significantly lower among the patients with a high IMAC ($n = 258$) than among those with a normal IMAC ($n = 348$; $p < 0.001$; Fig. 2c).

The RFS rate after hepatectomy for HCC was significantly lower among the patients with a high VSR than among those with a normal VSR ($p = 0.016$; Fig. 3a). The 1-, 3-, and 5-year RFS rates among the patients with a high VSR versus those with a normal VSR were 56.5, 33.0, and 20.9% versus 67.6, 41.8, and 32.8%, respectively. The RFS rate was significantly lower among the patients with a low SMI than among those with a normal SMI ($p = 0.009$; Fig. 3b). Similarly, the RFS rate was significantly lower among the patients with a high IMAC than among those with a normal IMAC ($p = 0.047$; Fig. 3c).

In addition, these three factors (high VSR, low SMI, and high IMAC) contributed to an increased risk of death ($p < 0.001$; Fig. 4a) and HCC recurrence ($p < 0.001$; Fig. 4b) after hepatectomy for HCC in an additive manner, which suggests that they are complementary predictors of a poor prognosis in patients undergoing hepatectomy for HCC.

Risk Factors for Poor Outcomes in Patients Undergoing Hepatectomy for HCC

The results of the univariate and multivariate analyses of OS among patients undergoing hepatectomy for HCC are shown in Table 2. The multivariate analysis identified a low serum albumin level (HR = 1.501, $p = 0.015$), high serum AFP level (HR = 1.590, $p < 0.001$), advanced TNM stage (HR = 1.969, $p < 0.001$), preoperative low SMI (HR = 1.333, $p = 0.045$), high IMAC (HR = 1.774, $p < 0.001$), and high VSR (HR = 1.566, $p = 0.001$) as independent risk factors for mortality after hepatectomy (Table 2).

Table 3 shows the results of the univariate and multivariate analyses of RFS. The multivariate analysis showed that a high serum AFP level (HR = 1.370, $p = 0.004$), advanced TNM stage (HR = 2.198, $p < 0.001$), preoperative low SMI (HR = 1.447, $p = 0.016$), high IMAC (HR = 1.234, $p = 0.049$), and high VSR (HR = 1.329, $p = 0.020$) were independent risk factors for HCC recurrence (Table 3).

Discussion

The European Working Group on Sarcopenia in Older People in 2010 defined sarcopenia as a syndrome that is characterized by a progressive and generalized loss of skeletal muscle mass and strength [28], and the Asian and Japanese working groups have recently established their own sarcopenia assessment criteria [29, 30]. On the basis of these definitions, low muscularity has been shown to be an independent risk factor for lower overall and disease-free survival with various kinds of diseases [31–38]. Today, not only skeletal muscle mass but also adipose tissue is recognized as a secretory organ that produces pro- and anti-inflammatory cytokines and adipokines, and the balance between these cytokines plays an important role in various physiological processes such as insulin resistance, lipid metabolism, and obesity-related low-level chronic inflammation [39–41]. In recent studies, the VSR, which accounts for differences in fat distribution, has been reported to be associated with poor outcomes in several cancers [20–24]. Therefore, this study newly focused on preoperative adipose tissue distribution, and the impact of visceral adiposity on outcomes after hepa-

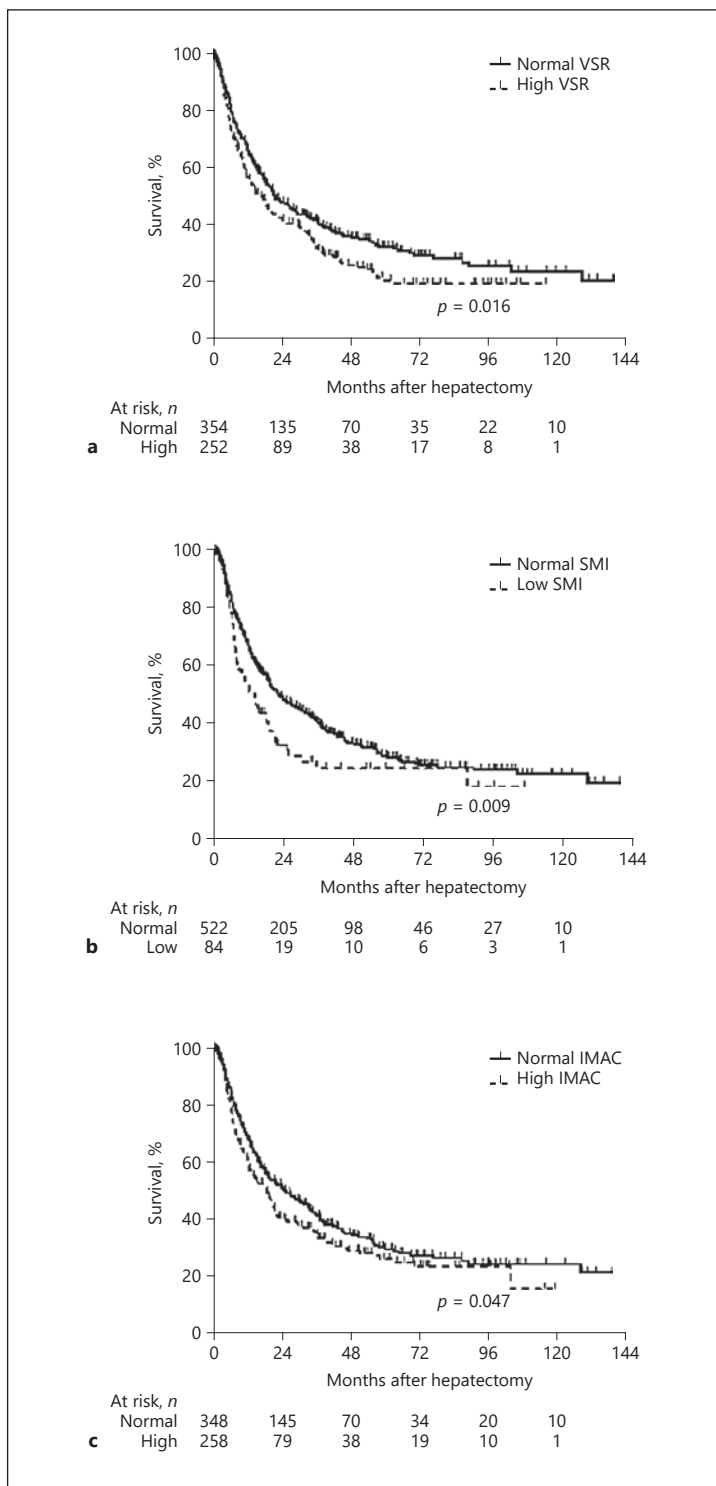


Fig. 3. RFS rates among patients classified according to body composition variables. **a** The RFS rate after hepatectomy for hepatocellular carcinoma was significantly lower among the patients with a high VSR than among the patients with a normal VSR ($p = 0.016$). **b** The RFS rate was significantly lower among the patients with a low SMI than among the patients with a normal SMI ($p = 0.009$). **c** The RFS rate was significantly lower among the patients with a high IMAC than among the patients with a normal IMAC ($p = 0.047$). RFS, recurrence-free survival; VSR, visceral-to-subcutaneous adipose tissue area ratio; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content.

tectomy for HCC was investigated. As far as we know, this is the first and largest study to show that preoperative visceral adiposity, as well as low muscularity, is a predictor of poor prognosis after hepatectomy for HCC.

In evaluating obesity or adiposity, the BMI is generally used because it can be easily calculated from body weight and height. However, the BMI cannot directly reflect differences in fat

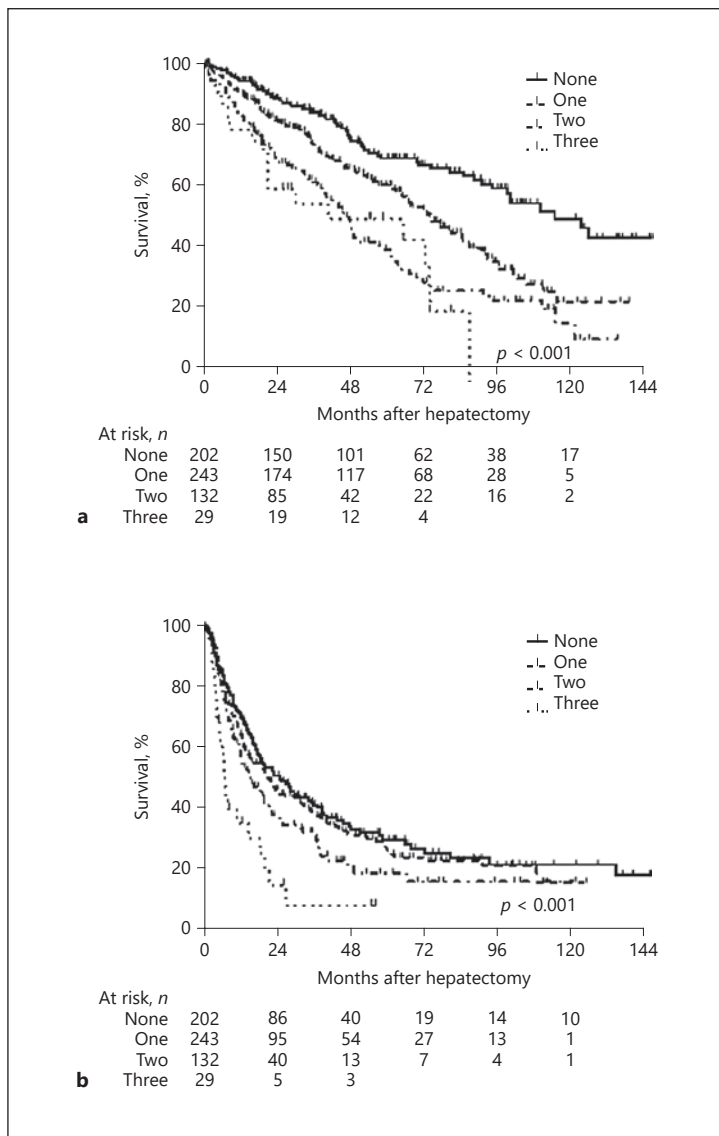


Fig. 4. OS and RFS rates among patients classified by the number of body composition variables. The OS (**a**) and RFS (**b**) rates after hepatectomy for hepatocellular carcinoma decreased significantly with an increasing number of prognostic body composition factors (high visceral-to-subcutaneous adipose tissue area ratio, low skeletal muscle mass index, and high intramuscular adipose tissue content) ($p < 0.001$ and $p < 0.001$, respectively). OS, overall survival; RFS, recurrence-free survival.

distribution. In the present study, a high BMI (>25) was not a significant risk factor for postoperative death or HCC recurrence. Nowadays, body composition, including adipose tissue and skeletal muscle, can be directly evaluated using CT imaging, especially in the surgical field. Although recent studies have shown that a higher visceral fat area (VFA) evaluated using CT imaging was significantly associated with poor survival in several cancers [42–46], the association between VFA and prognosis remains controversial [47–49]. Our previous study also evaluated the VFA for a definition of visceral obesity, and obesity was considered present when the VFA was $\geq 100 \text{ cm}^2$ in both males and females [50]. Although the OS and RFS rates among the patients with sarcopenic obesity were significantly lower than among the patients with nonsarcopenic nonobesity, there were no significant differences in OS and RFS rates between the sarcopenic nonobese and the sarcopenic obese group, or between the nonsarcopenic nonobese and the nonsarcopenic obese group. These results suggested that the VFA had no impact on postoperative outcomes in HCC patients. Also in the present study, a higher VFA had no impact on OS ($p = 0.284$; online suppl. Fig. 1a; for all online suppl. material,

Table 2. Prognostic factors for overall survival on univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age						
≥65 years (<i>n</i> = 395)	1.232	0.961–1.592	0.101			
<65 years (<i>n</i> = 211)	1.000	(referent)				
Sex						
Male (<i>n</i> = 484)	1.003	0.752–1.364	0.982			
Female (<i>n</i> = 122)	1.000	(referent)				
Etiology of HCC						
HBV and/or HCV (<i>n</i> = 392)	0.967	0.757–1.242	0.788			
Others (<i>n</i> = 214)	1.000	(referent)				
Previous treatment for HCC						
Yes (<i>n</i> = 228)	1.331	1.048–1.688	0.019			
No (<i>n</i> = 378)	1.000	(referent)				
Obesity-related comorbidities						
Yes (<i>n</i> = 361)	1.003	0.790–1.278	0.978			
No (<i>n</i> = 245)	1.000	(referent)				
Period of hepatectomy						
2005–2009 (<i>n</i> = 302)	0.905	0.696–1.181	0.459			
2010–2016 (<i>n</i> = 304)	1.000	(referent)				
Platelet count						
<10 × 10 ⁴ /mm ³ (<i>n</i> = 128)	1.410	1.071–1.835	0.015	1.199	0.895–1.589	0.220
≥10 × 10 ⁴ /mm ³ (<i>n</i> = 478)	1.000	(referent)		1.000	(referent)	
Total lymphocyte count						
<1,000/mm ³ (<i>n</i> = 156)	1.279	0.975–1.660	0.075			
≥1,000/mm ³ (<i>n</i> = 450)	1.000	(referent)				
Neutrophil-to-lymphocyte ratio						
<4.0 (<i>n</i> = 547)	0.750	0.514–1.143	0.174			
≥4.0 (<i>n</i> = 59)	1.000	(referent)				
Total bilirubin						
≥1.0 mg/dL (<i>n</i> = 187)	1.123	0.868–1.442	0.371			
<1.0 mg/dL (<i>n</i> = 419)	1.000	(referent)				
Albumin						
<3.5 g/dL (<i>n</i> = 100)	1.799	1.329–2.398	<0.001	1.501	1.084–2.045	0.015
≥3.5 g/dL (<i>n</i> = 506)	1.000	(referent)		1.000	(referent)	
ICG R15						
≥15% (<i>n</i> = 312)	1.195	0.944–1.516	0.139			
<15% (<i>n</i> = 294)	1.000	(referent)				
Child-Pugh class						
A (<i>n</i> = 555)	0.746	0.508–1.144	0.172			
B (<i>n</i> = 51)	1.000	(referent)				
AFP						
≥20 ng/dL (<i>n</i> = 294)	1.792	1.412–2.282	<0.001	1.590	1.236–2.050	<0.001
<20 ng/dL (<i>n</i> = 312)	1.000	(referent)		1.000	(referent)	
DCP						
≥40 mAU/mL (<i>n</i> = 428)	1.239	0.955–1.625	0.108			
<40 mAU/mL (<i>n</i> = 178)	1.000	(referent)				
Liver histology						
Normal liver or chronic hepatitis (<i>n</i> = 305)	0.899	0.709–1.138	0.376			
Liver fibrosis or liver cirrhosis (<i>n</i> = 301)	1.000	(referent)				
Tumor size						
≥5.0 cm (<i>n</i> = 209)	1.609	1.265–2.041	<0.001			
<5.0 cm (<i>n</i> = 397)	1.000	(referent)				

Table 2 (continued)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Number of tumors						
Multiple (<i>n</i> = 189)	1.542	1.206–1.962	0.001			
Solitary (<i>n</i> = 417)	1.000	(referent)				
MVI						
Positive (<i>n</i> = 196)	1.891	1.485–2.400	<0.001			
Negative (<i>n</i> = 410)	1.000	(referent)				
Tumor differentiation						
Well or moderate (<i>n</i> = 424)	0.551	0.427–0.718	<0.001	0.739	0.537–1.040	0.081
Poor (<i>n</i> = 167)	1.000	(referent)		1.000	(referent)	
TNM stage						
I or II (<i>n</i> = 361)	0.454	0.357–0.575	<0.001	0.508	0.391–0.659	<0.001
III or IV (<i>n</i> = 245)	1.000	(referent)		1.000	(referent)	
Surgical procedure						
Lobectomy or more (<i>n</i> = 210)	1.536	1.205–1.950	0.001			
Less than segmentectomy (<i>n</i> = 396)	1.000	(referent)				
Operative time						
≥360 min (<i>n</i> = 318)	1.495	1.179–1.899	0.001			
<360 min (<i>n</i> = 288)	1.000	(referent)				
Operative blood loss						
≥500 mL (<i>n</i> = 378)	1.644	1.269–2.151	<0.001	1.012	0.758–1.362	0.936
<500 mL (<i>n</i> = 228)	1.000	(referent)		1.000	(referent)	
BMI						
≥25 (<i>n</i> = 157)	0.994	0.753–1.296	0.964			
<25 (<i>n</i> = 449)	1.000	(referent)				
Preoperative SMI						
Low (<i>n</i> = 84)	1.506	1.077–2.058	0.018	1.333	1.007–1.752	0.045
Normal (<i>n</i> = 522)	1.000	(referent)		1.000	(referent)	
Preoperative IMAC						
High (<i>n</i> = 258)	1.918	1.500–2.468	<0.001	1.774	1.375–2.302	<0.001
Normal (<i>n</i> = 348)	1.000	(referent)		1.000	(referent)	
Preoperative VSR						
High (<i>n</i> = 252)	1.656	1.308–2.099	<0.001	1.566	1.222–2.008	<0.001
Normal (<i>n</i> = 354)	1.000	(referent)		1.000	(referent)	

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG R15, indocyanine green retention test at 15 min; AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; MVI, microvascular invasion; TNM, Tumour-Node-Metastasis (stage defined by the Liver Cancer Study Group of Japan); BMI, body mass index; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content; VSR, visceral-to-subcutaneous adipose tissue area ratio.

see www.karger.com/doi/10.1159/000488779) or RFS (*p* = 0.719; online suppl. Fig. 1b) after hepatectomy for HCC. On the other hand, visceral adiposity as evaluated by the VSR itself was an independent risk factor for death and HCC recurrence after hepatectomy for HCC. In fact, even among the 84 patients with a low SMI, the OS (online suppl. Fig. 2a) and RFS rates (online suppl. Fig. 2b) were significantly lower in the group of patients with a high VSR (*n* = 46) than in the group with a normal VSR (*n* = 38; *p* = 0.048 and *p* = 0.023, respectively). Similarly, among the 258 patients with a high IMAC, the OS (online suppl. Fig. 3a) and RFS rates (online suppl. Fig. 3b) were significantly lower in the group of patients with a high VSR (*n* = 121) than in the group with a normal VSR (*n* = 137; *p* = 0.027 and *p* = 0.023, respectively). On the basis of these findings, we consider that the VSR is independent of the SMI and IMAC, and

has an added impact on outcomes after hepatectomy for HCC. Previous studies have shown that there are significant differences in the cytokine production profile between visceral and subcutaneous adipose tissue: proinflammatory cytokines such as tumor necrosis factor- α and interleukin-6 are mainly secreted from visceral adipocytes, while adiponectin, one of the anti-inflammatory cytokines, is secreted from subcutaneous adipocytes [51, 52]. These results suggest that the balance between visceral and subcutaneous adipose tissue would be more important than the VFA alone.

The mechanism by which visceral adiposity adversely affects postoperative morbidity and mortality remains unclear. As shown in Table 1, a significantly higher proportion had type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease in the high-VSR group as compared to the normal-VSR group. However, there were no significant relationships between each comorbidity and poor outcomes after hepatectomy for HCC (Tables 2, 3). In addition, the following six factors were significantly different between the high-VSR and the normal-VSR group: patient age, sex, serum des- γ -carboxyprothrombin level, tumor size, SMI, and IMAC. In order to exclude any effect of these confounding factors on the two groups, we made adjustments for these six variables using a propensity score matching analysis. Even after adjusting for these factors, the OS (online suppl. Fig. 4a) and RFS rates (online suppl. Fig. 4b) were lower among the patients with a high VSR ($n = 219$) than among the patients with a normal VSR ($n = 219$; $p = 0.001$ and $p = 0.083$, respectively). This result might suggest that any differences in these variables between the two groups could not affect the postoperative outcomes in the HCC patients. A shift of adipose tissue away from subcutaneous to visceral adipose sites with skeletal muscle loss during the aging process leads to an imbalance between proinflammatory adipokines and myokines [53, 54]. This imbalance in the cytokine profile in elderly or sarcopenic populations has been shown to lead to immunosenescence, particularly of the natural killer lymphocytes involved in innate immunity [55]. On the other hand, visceral adiposity paradoxically impairs immune function by altering leukocyte counts, as well as cell-mediated immune responses, although excessive adipose tissue, especially visceral adiposity, activates various kinds of immune cells through an increase in leptin and a decrease in adiponectin [56]. Moreover, several studies have shown an effect of adiponectin and leptin on tumor cells; adiponectin inhibits the oncogenic actions of leptin by blocking Stat 3 and Akt phosphorylation, while leptin promotes the growth and proliferation of tumor cells via activation of various signaling pathways [40, 57]. These results indicate that visceral adiposity with low muscularity would decrease immune function for oncogenesis due to an imbalance in adipokines and other cytokines, which could lead to an increased risk of death and HCC recurrence. Further investigations into the associations between the cytokine profile and visceral adiposity or low muscularity are needed.

There are several limitations to this study. First, it is retrospective and was conducted at a single institution. Larger, multicenter studies are needed to confirm the results of the present study. Second, it is necessary to consider whether the use of the cutoff values for body composition parameters that we had previously investigated was adequate in this study. In our previous studies [23, 25, 26, 37], the cutoff values for body composition parameters had been determined based on receiver operating characteristic curves. Although the use of receiver operating characteristic curves provides a more accurate and objective method than the use of SDs for designing cutoff levels, these values differ markedly between study populations. Therefore, in order to avoid this potential problem, we have established optimal cutoffs that could be universally applied to other research into body composition [24]. A previous study defined sex-specific cutoff levels for low skeletal muscle mass as >2 SDs below the means of young adults [58]. In addition, the Asian Working Group for Sarcopenia has also recommended using 2 SDs below the mean muscle mass of a young reference group or the lower quintile when determining cutoffs [29]. We therefore decided to define donors <50

Table 3. Prognostic factors for recurrence-free survival on univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age						
≥65 years (<i>n</i> = 395)	0.994	0.807–1.229	0.955			
<65 years (<i>n</i> = 211)	1.000	(referent)				
Sex						
Male (<i>n</i> = 484)	1.047	0.817–1.359	0.721			
Female (<i>n</i> = 122)	1.000	(referent)				
Etiology of HCC						
HBV and/or HCV (<i>n</i> = 392)	1.111	0.900–1.378	0.330			
Others (<i>n</i> = 214)	1.000	(referent)				
Previous treatment for HCC						
Yes (<i>n</i> = 228)	1.377	1.122–1.687	0.002			
No (<i>n</i> = 378)	1.000	(referent)				
Obesity-related comorbidities						
Yes (<i>n</i> = 361)	0.867	0.709–1.064	0.172			
No (<i>n</i> = 245)	1.000	(referent)				
Period of hepatectomy						
2005–2009 (<i>n</i> = 302)	1.319	1.074–1.626	0.008			
2010–2016 (<i>n</i> = 304)	1.000	(referent)				
Platelet count						
<10 × 10 ⁴ /mm ³ (<i>n</i> = 128)	1.194	0.930–1.516	0.162			
≥10 × 10 ⁴ /mm ³ (<i>n</i> = 478)	1.000	(referent)				
Total lymphocyte count						
<1,000/mm ³ (<i>n</i> = 156)	1.056	0.835–1.330	0.633			
≥1,000/mm ³ (<i>n</i> = 450)	1.000	(referent)				
Neutrophil-to-lymphocyte ratio						
<4.0 (<i>n</i> = 547)	0.942	0.675–1.357	0.737			
≥4.0 (<i>n</i> = 59)	1.000	(referent)				
Total bilirubin						
≥1.0 mg/dL (<i>n</i> = 187)	1.252	1.008–1.548	0.042			
<1.0 mg/dL (<i>n</i> = 419)	1.000	(referent)				
Albumin						
<3.5 g/dL (<i>n</i> = 100)	1.244	0.939–1.622	0.126			
≥3.5 g/dL (<i>n</i> = 506)	1.000	(referent)				
ICG R15						
≥15% (<i>n</i> = 312)	1.172	0.957–1.435	0.124			
<15% (<i>n</i> = 294)	1.000	(referent)				
Child-Pugh class						
A (<i>n</i> = 555)	0.873	0.615–1.287	0.479			
B (<i>n</i> = 51)	1.000	(referent)				
AFP						
≥20 ng/dL (<i>n</i> = 294)	1.431	1.169–1.751	0.001	1.370	1.109–1.695	0.004
<20 ng/dL (<i>n</i> = 312)	1.000	(referent)		1.000	(referent)	
DCP						
≥40 mAU/mL (<i>n</i> = 428)	1.418	1.134–1.787	0.002			
<40 mAU/mL (<i>n</i> = 178)	1.000	(referent)				
Liver histology						
Normal liver or chronic hepatitis (<i>n</i> = 305)	0.898	0.734–1.098	0.295			
Liver fibrosis or liver cirrhosis (<i>n</i> = 301)	1.000	(referent)				
Tumor size						
≥5.0 cm (<i>n</i> = 209)	1.549	1.254–1.905	<0.001			
<5.0 cm (<i>n</i> = 397)	1.000	(referent)				

Table 3 (continued)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Number of tumors						
Multiple (<i>n</i> = 189)	1.731	1.402–2.130	<0.001			
Solitary (<i>n</i> = 417)	1.000	(referent)				
MVI						
Positive (<i>n</i> = 196)	1.934	1.566–2.380	<0.001			
Negative (<i>n</i> = 410)	1.000	(referent)				
Tumor differentiation						
Well or moderate (<i>n</i> = 424)	0.707	0.566–0.889	0.003	0.851	0.673–1.082	0.186
Poor (<i>n</i> = 167)	1.000	(referent)		1.000	(referent)	
TNM stage						
I or II (<i>n</i> = 361)	0.461	0.377–0.565	<0.001	0.455	0.366–0.566	<0.001
III or IV (<i>n</i> = 245)	1.000	(referent)		1.000	(referent)	
Surgical procedure						
Lobectomy or more (<i>n</i> = 210)	1.469	1.190–1.806	<0.001			
Less than segmentectomy (<i>n</i> = 396)	1.000	(referent)				
Operative time						
≥360 min (<i>n</i> = 318)	1.169	0.956–1.431	0.128			
<360 min (<i>n</i> = 288)	1.000	(referent)				
Operative blood loss						
≥500 mL (<i>n</i> = 378)	1.318	1.069–1.631	0.010	0.962	0.767–1.211	0.739
<500 mL (<i>n</i> = 228)	1.000	(referent)		1.000	(referent)	
BMI						
≥25 (<i>n</i> = 157)	1.000	0.793–1.250	0.999			
<25 (<i>n</i> = 449)	1.000	(referent)				
Preoperative SMI						
Low (<i>n</i> = 84)	1.456	1.087–1.914	0.013	1.447	1.074–1.913	0.016
Normal (<i>n</i> = 522)	1.000	(referent)		1.000	(referent)	
Preoperative IMAC						
High (<i>n</i> = 258)	1.205	1.013–1.497	0.044	1.234	1.001–1.493	0.049
Normal (<i>n</i> = 348)	1.000	(referent)		1.000	(referent)	0.049
Preoperative VSR						
High (<i>n</i> = 252)	1.283	1.047–1.571	0.017	1.329	1.047–1.685	0.020
Normal (<i>n</i> = 354)	1.000	(referent)		1.000	(referent)	

HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG R15, indocyanine green retention test at 15 min; AFP, α -fetoprotein; DCP, des- γ -carboxyprothrombin; MVI, microvascular invasion; TNM, Tumour-Node-Metastasis (stage defined by the Liver Cancer Study Group of Japan); BMI, body mass index; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content; VSR, visceral-to-subcutaneous adipose tissue area ratio.

years old as the reference group, and to use these values to determine cutoff levels. Finally, although the preoperative body composition was shown to be significant, it remains unclear whether pre- and postoperative interventions such as nutritional therapy and rehabilitation could change adiposity or muscularity and improve postoperative outcomes. Our previous study had shown that perioperative nutritional therapy, including an immunomodulating diet enriched with hydrolyzed whey peptide, branched-chain amino acid nutrients, and synbiotics, significantly reduced posttransplant mortality among sarcopenic recipients of a liver transplantation [35]. We consider that it would take a long time to improve visceral adiposity and the sarcopenic status by preoperative nutritional intervention and rehabilitation. However, there is the dilemma that the duration of preoperative interventions for cancer

patients should be limited because of the progression of the disease during these interventions. Therefore, we now start the preoperative intervention as early as possible after patients have consulted us at our institution, without extension of the period to operation. Further prospective investigations are needed to reveal whether this preoperative “short-term” nutritional intervention and rehabilitation improves body composition and results in better outcomes after hepatectomy for HCC. In addition, because the risk of postoperative death and HCC recurrence was significantly higher among the patients showing all three factors (high VSR, low SMI, and high IMAC), new selection criteria for hepatectomy that take into account preoperative body composition need to be established.

In conclusion, preoperative visceral adiposity, as well as low muscularity, was closely related to postoperative death and HCC recurrence after hepatectomy for HCC. It would be crucial to establish a new strategy for hepatectomy that takes both preoperative body composition and tumor factors into account. Such a strategy could lead to better outcomes after hepatectomy for HCC.

Statement of Ethics

All study protocols were approved by the Ethics Committee of Kyoto University (approval No. R0061) and were conducted in accordance with the 1996 revision of the Declaration of Helsinki.

Disclosure Statement

The authors declare no conflict of interest.

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