Original Basic Science—Liver

Impact of Skeletal Muscle Mass Index, Intramuscular Adipose Tissue Content, and Visceral to Subcutaneous Adipose Tissue Area Ratio on Early Mortality of Living Donor Liver Transplantation

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Background. Skeletal muscle depletion has been shown to be an independent risk factor for poor survival in various diseases. However, in surgery, the significance of other body components including visceral and subcutaneous adipose tissue remains unclear. **Methods.** This retrospective study included 250 adult patients undergoing living donor liver transplantation (LDLT) between January 2008 and April 2015. Using preoperative plain computed tomography imaging at the third lumbar vertebra level, skeletal muscle mass, muscle quality, and visceral adiposity were evaluated by the skeletal muscle mass index (SMI), intramuscular adipose tissue content (IMAC), and visceral to subcutaneous adipose tissue area ratio (VSR), respectively. The cutoff values of these parameters were determined for men and women separately using the data of 657 healthy donors for LDLT between 2005 and 2016. Impact of these parameters on outcomes after LDLT was analyzed. **Results.** VSR was significantly correlated with patient age ($P = 0.041$), neutrophil-lymphocyte ratio ($P < 0.001$), body mass index ($P < 0.001$), and SMI ($P = 0.001$). The overall survival probability was significantly lower in patients with low SMI ($P < 0.001$), high IMAC ($P < 0.001$), and high VSR ($P < 0.001$) than in each respective normal group. On multivariate analysis, low SMI (hazard ratio [HR], 2.367, $P = 0.002$), high IMAC (HR, 2.096, $P = 0.004$), and high VSR (HR, 2.213, $P = 0.003$) were identified as independent risk factors for death after LDLT. **Conclusions.** Preoperative visceral adiposity, as well as low muscularity, was closely involved with posttransplant mortality.

(*Transplantation* 2017;101: 565–574)

Sarcopenia is an age-related progressive and generalized decline of skeletal muscle mass and muscle strength that has been accepted worldwide as a new geriatric syndrome.[1] Recent evidence has shown a significant association between sarcopenia and poor outcomes in various diseases.[2-7] In the field of liver transplantation (LT), pretransplant low skeletal muscle mass was shown to be strongly correlated with poor outcomes after LT.[8,9] Furthermore, we recently reported that both pretransplant skeletal muscle mass and low skeletal muscle quality (muscle steatosis) are independent risk factors for death after living donor LT (LDLT).[10] These findings demonstrate that preoperative low muscularity is closely involved with posttransplant mortality.

Obesity is a risk factor for various health disorders, including type 2 diabetes mellitus, hypertension, cardiovascular disease, and nonalcoholic steatohepatitis.[11,12] Obesity is generally evaluated using body mass index (BMI). However, as BMI is an indirect measurement of adipose tissue, it cannot account for differences in fat distribution. Moreover, BMI is usually overestimated due to massive ascites and systemic edema in patients with end-stage liver disease requiring LT. Therefore, adiposity has been directly measured using computed tomography (CT) imaging, which can distinguish between visceral and subcutaneous adipose tissue area.[13] A recent study showed that visceral adiposity, defined as a high visceral to subcutaneous adipose tissue area ratio (VSR), was associated with poor outcomes in patients with several kinds of cancers, including hepatocellular carcinoma (HCC), metastatic melanoma, and esophageal cancer.[13-15] Also in LT, several studies reported

Received 1 July 2016. Revision received 25 October 2016.

Accepted 31 October 2016.

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The authors declare no funding or conflicts of interest.

All authors participated in final approval of the article.

Y.H., T.K., and S.U. participated in the conception and design. Y.H., S.O., A.K., H.S., S.Y., N.K., and H.O. participated in the acquisition of data. Y.H. and T.K. participated in the analysis and interpretation of data. Y.H. and T.K. participated in the drafting of manuscript. S.O., A.K., H.S., S.Y., N.K., H.O., and S.U. participated in the revision of the article.

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Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

ISSN: 0041-1337/17/10103-565

DOI: 10.1097/TP.0000000000001587

that visceral adipose fat mass was significantly correlated with posttransplant outcome.[16,17] However, the impact of visceral adiposity indicated by VSR in LDLT has not been fully investigated.

In the present study, pretransplant visceral adiposity, in addition to muscularity (muscle mass and muscle quality), was retrospectively evaluated, and the impact of these measures of body composition on outcomes in patients undergoing LDLT was evaluated.

MATERIALS AND METHODS

Patients

A total of 274 adult (age ≥ 18 years) patients underwent LDLT at Kyoto University Hospital between January 2008 and April 2015; of these, 24 were excluded because they did not have preoperative plain CT imaging at the third lumbar vertebra (L3) level. Therefore, 250 patients (122 men, 128 women) were enrolled in the study. The selection criteria for the recipients, the surgical procedures for the donor and recipient, and the immunosuppressive regimen have been described previously.[18-20] The study was approved by the Ethics Committee of Kyoto University (R0061) and conducted in accordance with the principles laid down in the Declaration of Helsinki of 1996.

Image Analysis

All preoperative CT imaging was obtained with a multidetector CT scanner (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan). The technical parameters used for CT were: 120 kV tube voltage, 0.5 mm × 64 rows detector configuration, tube current modulation, 0.5 s/rotation (gantry rotation), and 7 mm reconstruction thickness.

On cross-sectional CT imaging at the L3 level, skeletal muscle and adipose tissue area were examined using the Aquarius iNtuition (TeraRecon, Inc, San Mateo, CA). Skeletal muscle areas including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis were identified and quantified using −29 to 150 Hounsfield units (HU) (Figure 1A).[20] The skeletal muscle mass index (SMI) was calculated by normalizing these skeletal muscle areas for height (cm^2/m^2). Similarly, subcutaneous and visceral adipose tissue areas were quantified using −190 to −30 HU (Figure 1B) and −150 to −50 HU (Figure 1C), respectively.[21,22] VSR, which indicates visceral adiposity, was calculated by dividing visceral adipose tissue area by subcutaneous adipose tissue area.[13] In addition, the quality of skeletal muscle was examined by intramuscular adipose tissue content (IMAC) at the L3 level. IMAC was calculated by dividing the CT value of the multifidus muscles (HU) with the CT value of subcutaneous fat (HU) (Figure 1D).[10] Higher IMAC indicates a greater amount of adipose tissue in skeletal muscle, and hence, a lower quality of skeletal muscle.

The cutoff values of SMI, IMAC, and VSR were determined for men and women separately using the data of 657 healthy donors for LDLT between 2005 and 2016. Low SMI was defined as less than the 2 standard deviation of the mean, and high IMAC and high VSR as more than the 2 standard deviations of the respective means.

Analyzed Parameters

First, the correlations of VSR with other factors, such as patient age, total lymphocyte count, prealbumin, cholinesterase, branched-chain amino acids, neutrophil-lymphocyte ratio (NLR), Prognostic Nutritional Index (PNI), the Model for End-stage Liver Disease (MELD) score, MELD-Na score,

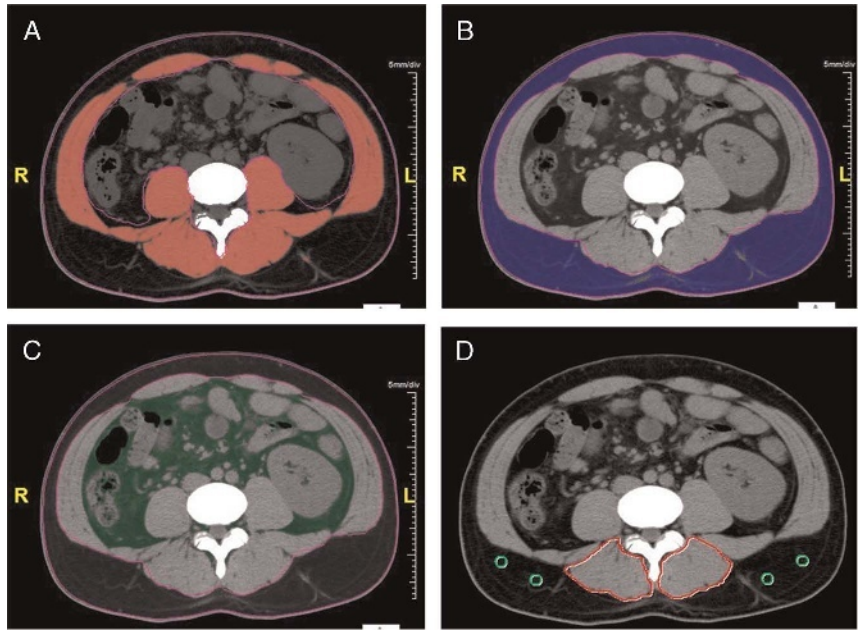


FIGURE 1. Cross-sectional computed tomographic images at the third lumbar vertebra level. A, Skeletal muscle areas including the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis were identified and quantified using −29 to 150 HU. B, Subcutaneous adipose tissue areas were quantified using −190 to −30 HU. C, Visceral adipose tissue areas were quantified using −150 to −50 HU. D, CT values of subfascial muscular tissue in the multifidus muscle and subcutaneous fat (4 small circles) were examined to calculate IMAC. HU, Hounsfield units.

Child-Pugh score, BMI, SMI, and IMAC were analyzed. PNI was calculated as 10 × albumin (g/dL) + 0.005 × total lymphocyte count (/μL).[23] MELD-Na was calculated as follows: MELD-Na = MELD – Na – [0.025 × MELD × (140 – Na)] + 140.[24] Second, the overall survival probability after LDLT was investigated in patients classified according to SMI, IMAC, and VSR. Finally, the prognostic factors were analyzed on the basis of the following variables: age of recipient (≥50 years vs < 50 years), age of donor (≥50 years vs < 50 years), sex (male vs female), original disease, period of LDLT (2008-2010 vs 2011-2015), ABO compatibility (identical/compatible vs incompatible), MELD score (≥20 vs < 20), Child-Pugh classification (A/B vs C), graft type (right vs left), graft-to-recipient body weight ratio (GRWR) (≥0.8% vs < 0.8%), splenectomy (with vs without), portal venous pressure (PVP) after portal pressure modulation (≥15 mm Hg vs < 15 mm Hg), duration of surgery (≥12 hours vs < 12 hours), estimated blood loss (≥10 L vs < 10 L), 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 median (interquartile range [IQR]). Continuous variables were nonparametrically analyzed using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test, as appropriate. Correlations between the continuous variables were assessed using Pearson correlation coefficient. Cumulative overall survival rates were calculated using Kaplan-Meier methods, and differences between curves were evaluated using the log-rank test. Any variable identified as significant ($P < 0.05$) or with P less than 0.10 on univariate analyses was considered a candidate for multivariate Cox regression analysis, and the results are shown as hazard ratios (HRs) with 95% confidence interval. A P value less than 0.05 was considered significant. All statistical data were generated using JMP Pro 12 (SAS Institute, Cary, NC) and Prism 6 (GraphPad Software, Inc., La Jolla, CA).

RESULTS

Patient Characteristics

Table 1 shows the baseline characteristics and laboratory data of the 250 patients. The patients' median age was 54 years (IQR, 43-62 years). The indications for LDLT were HCC in 83 patients (33%), hepatitis B or C virus-associated liver cirrhosis (LC) in 49 (20%), progressive intrahepatic cholestatic diseases including primary biliary cirrhosis and primary sclerosing cholangitis in 42 (17%), biliary atresia in 21 (8%), acute liver failure with unknown etiology in 11 (4%), alcoholic LC in 12 (5%), metabolic liver diseases in 5 (2%), Budd-Chiari syndrome in 4 (2%), and other causes in 23 (9%). Seventy-three patients (29%) were ABO-incompatible, and 177 (71%) were identical or compatible. The median MELD score was 17 (IQR, 14-22). The Child-Pugh classifications were C, B, and A for 161 (64%), 73 (29%), and 16 patients (6%), respectively. Orthotopic LDLT was performed using a left lobe graft for 109 patients (44%), a right lobe graft for 133 patients (53%), a posterior segment graft for seven patients (3%), and a whole liver graft as a domino liver transplantation from a patient with familial amyloid polyneuropathy for 1 patient (0.4%). The median GRWR was 0.90 (IQR, 0.75-1.05).

Cutoff Values of SMI, IMAC, and VSR

The cutoff values for SMI were 40.31 cm^2/m^2 in men and 30.88 cm^2/m^2 in women. Similarly, the cutoff values for IMAC were –0.358 in men and –0.229 in women, whereas those for VSR were 1.325 in men and 0.710 in women. Then, there were 53 patients (21%) with preoperative low SMI (low muscle mass), 114 patients (46%) with high IMAC (low muscle quality), and 78 patients (31%) with high VSR (visceral adiposity). The perioperative parameters of patients classified according to SMI, IMAC, and VSR are outlined in Table 2.

Correlations Between Preoperative VSR and other Parameters

Although the correlations were weak, there were significant relationships between VSR and patient age ($r = 0.129$, $P = 0.041$; Figure 2A), NLR ($r = 0.216$, $P < 0.001$; Figure 2B), BMI ($r = –0.226$, $P < 0.001$; Figure 2C), and SMI ($r = –0.202$, $P = 0.001$; Figure 2D). No significant correlations were observed between VSR and other parameters, such as total lymphocyte count ($r = –0.106$, $P = 0.094$), prealbumin ($r = 0.076$, $P = 0.349$), cholinesterase ($r = –0.031$, $P = 0.636$), branched-chain amino acids ($r = –0.041$, $P = 0.531$), PNI ($r = 0.015$, $P = 0.814$), MELD score ($r = 0.015$, $P = 0.815$), MELD-Na score ($r = 0.083$, $P = 0.190$), Child-Pugh score ($r = –0.030$, $P = 0.632$), and IMAC ($r = 0.080$, $P = 0.209$) (data not shown).

Overall Survival Probability After LDLT

The overall survival probability after LDLT was significantly lower in patients with low SMI (n = 53) than in patients with normal SMI (n = 197; $P < 0.001$; Figure 3A). The 1- and 5-year survival probabilities in patients with low SMI and normal SMI were 55.4% and 45.3% versus 84.7% and 78.1%, respectively. Similarly, the survival probability was significantly lower in patients with high IMAC (n = 114) than in patients with normal IMAC (n = 136; $P < 0.001$; Figure 3B); the 1- and 5-year survival probabilities were 67.4% and 59.1% versus 88.1% and 81.3%, respectively. Moreover, the overall survival probability was significantly lower in patients with high VSR (n = 78) than in patients with normal VSR (n = 172; $P < 0.001$; Figure 3C). The 1- and 5-year survival probabilities in patients with high VSR and normal VSR were 60.1 % and 49.6% versus 87.1% and 81.2%, respectively. In addition, these 3 factors (low SMI, high IMAC, and high VSR) contributed to increase the risk for death after LDLT in an additive manner, which suggested that they are complementary predictors for poor prognosis in patients undergoing LDLT (Figure 4).

A total of 68 patients died in this follow-up period. The causes of death for 68 patients were sepsis (n = 23), pulmonary complications (n = 13), graft failure including antibody-mediated rejection and chronic rejection (n = 15), cerebral bleeding (n = 8), HCC recurrence (n = 2) and others (n = 7). Among 68 patients who died during follow-up, 41 patients (60%) had preoperative low SMI, 44 patients (65%) had high IMAC, and 38 patients (56%) had high VSR. Significantly more patients died from infectious complications, such as pneumonia, biliary infection, and sepsis in the low SMI ($P = 0.045$) and high VSR groups ($P = 0.027$) than in the corresponding normal groups. Patients with high IMAC

TABLE 1.

Characteristics of patients undergoing living donor liver transplantation

Characteristics	
Recipient age, y	
Median (IQR)	54 (43-62)
Donor age, y	
Median (IQR)	45 (33-55)
Sex, n (%)	
Male	122 (51)
Female	128 (49)
Original disease, n (%)	
HCC	83 (33)
HBV or HCV-associated LC	49 (20)
PBC or PSC	42 (17)
Others	76 (30)
Period of LDLT, n (%)	
2008-2010	130 (52)
2011-2015	120 (48)
ABO compatibility, n (%)	
Identical	125 (50)
Compatible	52 (21)
Incompatible	73 (29)
MELD score	
Median (IQR)	17 (14-22)
Child-Pugh classification, n (%)	
A	16 (6)
B	73 (29)
C	161 (64)
GRWR (%)	
Median (IQR)	0.90 (0.75-1.05)
Graft, n (%)	
Whole liver	1 (0.4)
Right lobe	133 (53)
Posterior segment	7 (3)
Left lobe	109 (44)
Splenectomy, n (%)	
Yes	161 (64)
No	89 (36)
PVP, mm Hg	
Median (IQR)	13 (11-14)
Operative time, min	
Median (IQR)	840 (738-954)
Operative blood loss, mL	
Median (IQR)	6600 (3628-11388)
BMI, kg/m^2	
Median (IQR)	22.7 (20.6-25.5)
Pretransplant SMI, cm^2/m^2	
Males	
Median (IQR)	46.570 (41.488-52.025)
Females	
Median (IQR)	35.506 (31.476-41.024)
Pretransplant IMAC	
Males	
Median (IQR)	−0.383 (−0.482-0.297)
Females	
Median (IQR)	−0.239 (−0.367 to −0.107)
Pretransplant VSR	
Males	
Median (IQR)	0.858 (0.597-1.235)
Females	
Median (IQR)	0.587 (0.395-1.015)

HBV, hepatitis B virus; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

tended to die from infectious complications than patients with normal IMAC ($P = 0.089$).

Risk Factors for Poor Survival in Patients Undergoing LDLT

Univariate Cox regression analysis showed that ABO-incompatible case ($P = 0.049$), left lobe graft ($P = 0.015$), preoperative low SMI ($P < 0.001$), high IMAC ($P < 0.001$), and high VSR ($P < 0.001$) were significant risk factors for death after LDLT (Table 3). On multivariate analysis, preoperative low SMI (HR, 2.367; $P = 0.002$), high IMAC (HR, 2.096; $P = 0.004$) and high VSR (HR, 2.213; $P = 0.003$) were identified as poor prognostic factors after LDLT (Table 3).

DISCUSSION

In 2010, the European Working Group on Sarcopenia in Older People defined sarcopenia as a syndrome characterized by a progressive and generalized loss of skeletal muscle mass and strength.[1] Since then, low skeletal muscle mass, 1 of the components of sarcopenia, has been shown to be an independent risk factor for lower overall and disease-free survival in various kinds of diseases.[2-9] Recently, we focused on muscle quality indicated by intramuscular adipose tissue, and we found that muscle steatosis was a significant risk factor for poor outcomes after LDLT, hepatectomy for HCC, and resection of pancreatic and biliary cancer.[10,25-27] Today, adipose tissue, as well as skeletal muscle, is recognized as a secretory organ that produces proinflammatory and anti-inflammatory cytokines and adipokines, and the interconnection between adipokines and myokines plays an important role in various physiological processes such as insulin resistance, lipid metabolism, and prevention of obesity-related low-level chronic inflammation.[28-30] Although we have evaluated only the pretransplant sarcopenia and shown that low muscularity (muscle mass and muscle quality) was a significant risk factor for death after LDLT, the impact of adipose tissue in LDLT has not been fully investigated. Therefore, the present study newly focused on pretransplant adipose tissue distribution and investigated its impact on posttransplant outcomes.

In evaluating adiposity, BMI is generally used because it can be calculated easily from height and body weight. However, in patients requiring LT, anthropometric parameters, including BMI and waist circumference, are usually overestimated due to massive ascites and systemic edema. Today, body composition, including skeletal muscle and adipose tissue, can be directly evaluated using several imaging techniques, such as dual energy X-ray absorptiometry, magnetic resonance imaging, bioimpedance analysis, and CT. Of these methods, CT is commonly used in the surgical field to evaluate body composition, because CT images are normally acquired for preoperative diagnoses and follow-up. The areas of skeletal muscle and subcutaneous and visceral adipose

TABLE 2.

Characteristics of patients classified according to SMI, IMAC, and VSR

	SMI			IMAC			VSR		
	Low (n = 53)	Normal (n = 197)	*P*	High (n = 114)	Normal (n = 136)	*P*	High (n = 78)	Normal (n = 172)	*P*
Recipient age, y									
Median	52	56	0.075	58	52	<0.001	58	54	0.169
(IQR)	(34-60)	(46-62)		(52-63)	(36-59)		(45-63)	(42-61)	
Donor age, y									
Median	49	44	0.208	45	45	0.652	48	43	0.132
(IQR)	(36-57)	(32-55)		(33-55)	(33-55)		(35-56)	(32-55)	
Sex, n (%)									
Male	23 (43)	99 (50)	0.440	52 (46)	70 (51)	0.376	25 (32)	97 (56)	<0.001
Female	30 (57)	98 (50)		62 (54)	66 (49)		53 (68)	75 (44)	
Original disease, n (%)									
HCC	15 (28)	68 (35)	0.417	42 (37)	41 (30)	0.283	22 (28)	61 (35)	0.311
Others	38 (72)	129 (65)		72 (63)	95 (70)		56 (72)	111 (65)	
Period of LDLT, n (%)									
2008-2010	29 (55)	101 (51)	0.757	61 (54)	69 (51)	0.704	40 (51)	90 (52)	0.892
2011-2015	24 (45)	96 (49)		53 (46)	67 (49)		38 (49)	82 (48)	
ABO compatibility, n (%)									
Identical	26 (49)	99 (50)	0.932	56 (49)	69 (51)	0.506	36 (46)	89 (52)	0.705
Compatible	12 (23)	40 (20)		21 (18)	31 (23)		17 (22)	35 (20)	
Incompatible	15 (28)	58 (29)		37 (32)	36 (26)		25 (32)	48 (28)	
MELD score									
Median	18	17	0.584	18	18	0.559	19	17	0.239
(IQR)	(14-26)	(14-22)		(14-22)	(14-22)		(14-26)	(14-21)	
Child-Pugh classification, n (%)									
A, B	17 (32)	72 (37)	0.629	38 (33)	51 (38)	0.510	31 (40)	58 (34)	0.393
C	36 (68)	125 (63)		76 (67)	85 (63)		47 (60)	114 (66)	
GRWR (%)									
Median	0.89	0.90	0.991	0.87	0.91	0.239	0.91	0.90	0.371
(IQR)	(0.76-1.04)	(0.75-1.07)		(0.73-1.03)	(0.78-1.07)		(0.79-1.05)	(0.73-1.07)	
Graft, n (%)									
Right lobe	18 (34)	123 (62)	<0.001	60 (53)	81 (60)	0.306	33 (42)	108 (63)	<0.001
Left lobe	35 (66)	74 (38)		54 (47)	55 (40)		45 (58)	64 (37)	
Splenectomy, n (%)									
Yes	35 (66)	126 (64)	0.872	74 (65)	87 (64)	0.895	49 (63)	112 (65)	0.776
No	18 (4)	71 (36)		40 (35)	49 (36)		29 (37)	60 (35)	
PVP, mm Hg									
Median	13	13	0.408	13	13	0.153	13	13	0.990
(IQR)	(12-14)	(10-14)		(11-15)	(10-14)		(11-15)	(11-14)	
Operative time, min									
Median	783	850	0.023	827	848	0.920	843	840	0.773
(IQR)	(706-908)	(757-973)		(743-953)	(727-958)		(741-928)	(729-961)	
Operative blood loss, mL									
Median	6910	6340	0.120	7147	5855	0.073	8199	5750	0.002
(IQR)	(5560-12 965)	(3360-10 860)		(3910-12 105)	(3255-11 005)		(5488-12 911)	(3355-10 438)	
BMI, kg/m^2									
Median	20.3	23.4	<0.001	23.3	22.5	0.023	21.4	23.2	<0.001
(IQR)	(17.4-21.7)	(21.6-26.0)		(20.9-26.6)	(20.0-24.5)		(19.7-23.4)	(21.2-26.0)	

tissues can be easily and automatically quantified using the CT values peculiar to these tissues, and this method has been shown to be precise and reliable to evaluate adipose tissue distribution.[21,22,31] Visceral adiposity indicated by VSR is calculated with the ratio of subcutaneous and visceral adipose tissue areas, and it has been reported that a high VSR is a useful predictor of poor outcomes in several cancers.[13-15] In the field of LT, Terjimanian et al[16] measured only visceral fat area, not subcutaneous fat area, and showed the significant association between visceral fat area and mortality after LT. On the other hand, Itoh et al[17] evaluated the skeletal muscle mass-to visceral fat area ratio (SVR), and investigated its impact on outcomes after LDLT only in HCC patients. In the present study, we showed not only low muscularity but high VSR was an independent risk factor for death after LDLT.

As shown in Table 2, although there was a significantly higher proportion of left lobe grafts in patients with low SMI and high VSR, the GRWR in those groups was almost

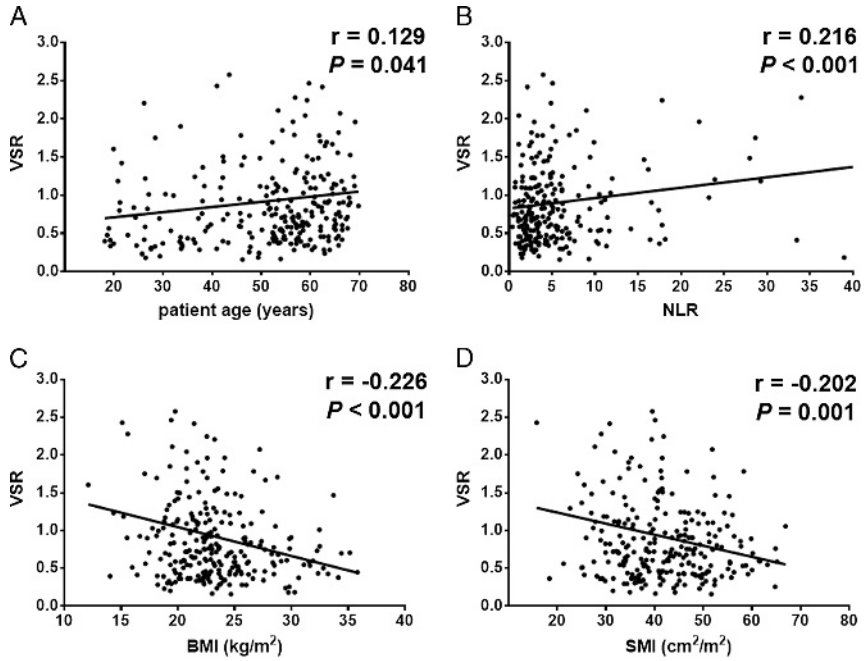


FIGURE 2. The correlations between VSR and perioperative factors. A, A significantly positive relationship is observed between VSR and patient age ($r = 0.129$, $P = 0.041$). B, Similarly, a significantly positive relationship is observed between VSR and NLR ($r = 0.216$, $P < 0.001$). C, On the other hand, there is a significantly negative correlation between VSR and BMI ($r = -0.226$, $P < 0.001$). D, Similarly, a significantly negative relationship is observed between VSR and SMI ($r = -0.202$, $P = 0.001$).

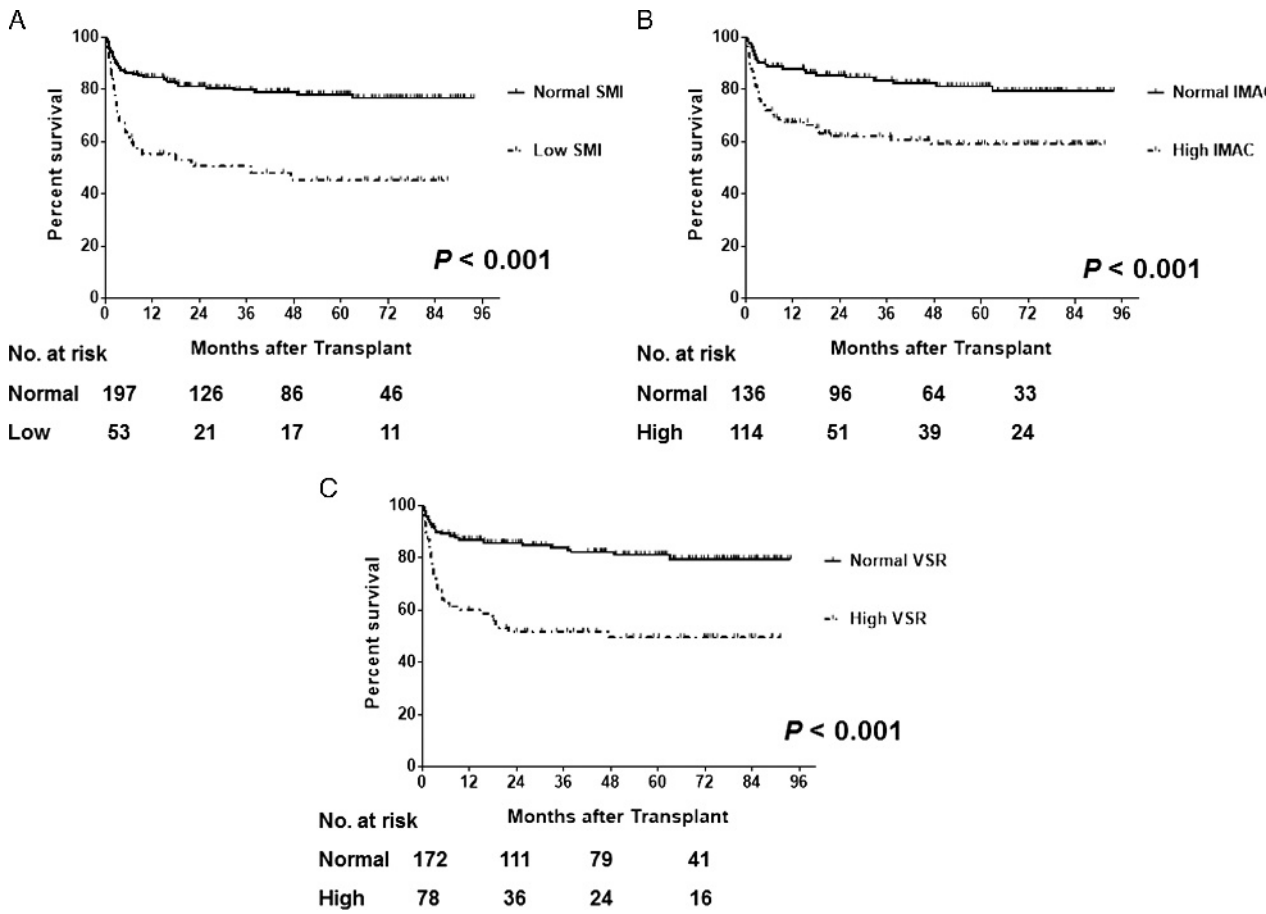
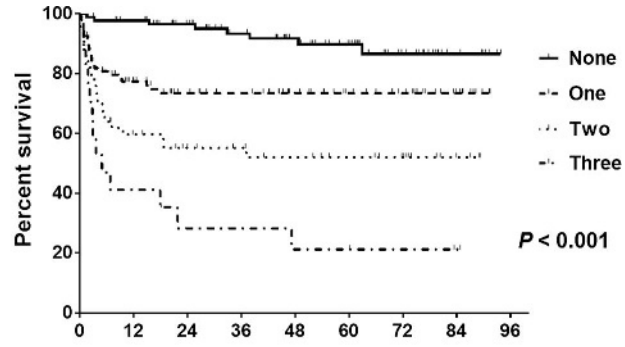


FIGURE 3. Overall survival rates in patients classified by body composition variables. A, The overall survival rate after LDLT is significantly lower in patients with low SMI (n = 53) than in patients with normal SMI (n = 197; $P < 0.001$). B, The overall survival rate is significantly lower in patients with high IMAC (n = 114) than in patients with normal IMAC (n = 136; $P < 0.001$). C, The overall survival rate is significantly lower in patients with high VSR (n = 78) than in patients with normal VSR (n = 172; $P < 0.001$).



No. at risk		Months after Transplant		
None	89	70	47	22
One	94	52	37	23
Two	50	22	17	11
Three	17	5	4	3

FIGURE 4. Overall survival rates in patients classified by the number of the body composition variables. The overall survival rates after LDLT significantly decreased based on the increase in the number of prognostic body composition (low SMI, high IMAC, and high VSR) ($P < 0.001$).

same compared with each respective normal group. This result might indicate that even when the graft volume appeared to be sufficient, the grafts used in patients with low SMI and high VSR were actually small for size for them because their weight might be less due to the pretransplant malnourished state. Then, we investigated the impact of this relative small for size on posttransplant outcomes among low SMI and high VSR groups. However, the graft type or GRWR did not have any impact on posttransplant infectious complications both in low SMI ($P = 0.392$, $P = 0.249$, respectively) and high VSR groups ($P = 0.746$, $P = 0.742$, respectively). In addition, there was no significant difference in the risk of death in patients with low SMI and high VSR classified according to graft type ($P = 0.420$; see **Figure S1A**, $P = 0.149$; **Figure S1B**, respectively, SDC http://links.lww.com/TP/B377) or GRWR ($P = 0.350$; see **Figure S1C**, $P = 0.865$; **Figure S1D**, respectively SDC, http://links.lww.com/TP/B377). These results suggest that the different mechanisms from graft type or volume would affect posttransplant morbidity and mortality in patients with low muscularity and visceral adiposity.

Adipose tissue is known to generally shift away from subcutaneous to visceral adipose depots and ectopic sites such as intermuscular and intramuscular sites during the aging process.[32] To evaluate what kind of state of recipients the VSR reflected, we investigated relationships between VSR and other factors showing nutritional status or the severity of liver disease. There were no significant relationships between VSR and total lymphocyte count, prealbumin, cholinesterase, branched-chain amino acids, PNI, IMAC, MELD score, MELD-Na score, and Child-Pugh score, which indicated that VSR was independent of such factors related to pretransplant nutritional status and the severity of liver disease. Interestingly, VSR was significantly correlated with NLR ($r = 0.216$, $P < 0.001$), which is a well-known marker of systemic inflammation. Conversely, there was no significant correlation between NLR and SMI ($r = -0.086$, $P = 0.131$) or IMAC ($r = 0.003$, $P = 0.965$) (data not shown). Excessive adipose tissue is associated with chronic low-grade inflammation caused by the abnormal secretion of cytokines from adipocytes and resident macrophages, followed by the activation of pro-inflammatory signaling pathways.[29] Previous studies showed that visceral adipose tissue was different from subcutaneous adipose tissue in the cytokine production profile; pro-inflammatory cytokines, such as TNF-α and IL-6 are mainly secreted from visceral adipocytes, while adiponectin, 1 of the anti-inflammatory cytokines, is secreted from subcutaneous adipocytes.[33,34] Currently, we are conducting a prospective investigation of pretransplant proinflammatory and anti-inflammatory cytokine profiles including TNF-α, IL-1, IL-6, leptin, and adiponectin, which could reveal the relationship between visceral adiposity and pretransplant inflammatory status.

The mechanism by which low muscularity and visceral adiposity adversely affect postoperative morbidity and mortality remains incompletely understood. As shown in Figure 3, the overall survival probability was significantly lower in patients with low muscularity or visceral adiposity than in each respective group. However, we found that the risk of death was not significantly higher in low SMI ($P = 0.204$; **Figure S2A, SDC**, http://links.lww.com/TP/B377), high IMAC ($P = 0.456$; **Figure S2B, SDC**, http://links.lww.com/TP/B377), and high VSR groups ($P = 0.056$; **Figure S2C, SDC**, http://links.lww.com/TP/B377) than in the corresponding normal groups when we investigated among patients who have survived the first year after LDLT. These results indicated that pretransplant low muscularity and visceral adiposity had impact on early mortality after LDLT. Skeletal muscle loss with increasing inter- and intra-muscular adipose tissue leads to the synthesis and secretion of various kinds of pro-inflammatory adipokines and the decline of myokines.[35] A previous study showed that this imbalance between adipokines and myokines in the aged or sarcopenic population resulted in immune senescence, especially of natural killer lymphocytes involved in innate immunity.[36] Montano-Loza et al[37] demonstrated that the presence of sarcopenia increases the risk of sepsis-related death in patients with cirrhosis, probably due to impaired immunity. On the other hand, although excessive adipose tissue, especially visceral adiposity, activates various kinds of immune cells through the increase in leptin and the decrease in adiponectin, visceral adiposity paradoxically impairs immune function by altering

TABLE 3.

Univariate and multivariate analyses of prognostic factors for posttransplant survival

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Recipient age, y						
<50 (n = 84)	1.000	(referent)				
≥50 (n = 166)	0.720	0.445-1.183	0.191			
Donor age, y						
<50 (n = 147)	1.000	(referent)				
≥50 (n = 103)	1.224	0.755-1.971	0.410			
Sex						
Male (n = 122)	1.000	(referent)				
Female (n = 128)	1.256	0.780-2.042	0.349			
Original disease						
HCC (n = 83)	1.000	(referent)				
HBV or HCV-associated LC (n = 49)	0.998	0.501-1.917	0.996			
PBC or PSC (n = 42)	1.454	0.743-2.762	0.267			
Others (n = 83)	0.737	0.382-1.386	0.345			
Period of LDLT						
2008-2010	1.000	(referent)				
2011-2015	0.925	0.566-1.503	0.754			
ABO compatibility						
Identical/compatible (n = 177)	1.000	(referent)		1.000	(referent)	
Incompatible (n = 73)	1.652	1.001-2.677	0.049	1.650	0.989-2.703	0.055
MELD score						
<20 (n = 160)	1.000	(referent)		1.000	(referent)	
≥20 (n = 90)	1.530	0.941-2.464	0.086	1.397	0.843-2.295	0.193
Child-Pugh classification						
A, B (n = 89)	1.000	(referent)				
C (n = 161)	1.056	0.648-1.763	0.829			
GRWR (%)						
<0.8 (n = 76)	1.000	(referent)				
≥0.8 (n = 174)	0.923	0.536-1.531	0.763			
Graft type						
Right (n = 141)	1.000	(referent)		1.000	(referent)	
Left (n = 109)	1.810	1.124-2.942	0.015	1.161	0.697-1.944	0.567
Splenectomy						
Yes (n = 161)	1.000	(referent)				
No (n = 89)	1.126	0.546-1.475	0.639			
PVP, mm Hg						
<15 (n = 203)	1.000	(referent)		1.000	(referent)	
≥15 (n = 47)	1.714	0.974-2.882	0.061	1.704	0.953-2.919	0.071
Operative time, h						
<12 (n = 52)	1.000	(referent)				
≥12 (n = 198)	0.711	0.423-1.251	0.227			
Operative blood loss, L						
<10 (n = 173)	1.000	(referent)				
≥10 (n = 77)	0.700	0.393-1.187	0.191			
Preoperative SMI						
Normal (n = 197)	1.000	(referent)		1.000	(referent)	
Low (n = 53)	3.086	1.876-4.995	<0.001	2.367	1.399-3.957	0.002
Preoperative IMAC						
Normal (n = 136)	1.000	(referent)		1.000	(referent)	
High (n = 114)	2.566	1.574-4.285	<0.001	2.096	1.271-3.536	0.004
Preoperative VSR						
Normal (n = 172)	1.000	(referent)		1.000	(referent)	
High (n = 78)	3.395	2.106-5.521	<0.001	2.213	1.324-3.726	0.003

CI, confidence interval.

leucocyte counts, as well as cell-mediated immune responses.[38] The present study showed that the incidence of death from infectious complications was significantly higher in the low SMI ($P = 0.045$) and high VSR groups ($P = 0.027$), and tended to be higher in the high IMAC group ($P = 0.089$) than in the corresponding normal groups. These results indicate that low muscularity and visceral adiposity would induce an inflammatory microenvironment by the imbalance in adipokines and other cytokines, which could impair immune function and increase mortality risk. Further investigations into the relationships among muscularity, adiposity, and immunological status are needed.

At present, we do not intend to directly incorporate pretransplant muscularity or visceral adiposity in our selection criteria for LT because the present study was retrospective and conducted in a single institution. Preoperative short-term nutritional intervention might not improve the nutritional status in patients undergoing LDLT. However, our previous study showed that perioperative nutritional intervention could improve the overall survival in patients with preoperative low skeletal muscle mass.[9] Therefore, although it remains unclear whether pretransplant nutritional therapy and rehabilitation could change the muscularity (SMI, IMAC) and visceral adiposity (VSR), preoperative intervention could improve posttransplant outcomes in patients with low muscularity or high visceral adiposity. To establish the new selection criteria for LT, prospective and larger multicenter studies are needed.

The findings of this study should be considered in light of several limitations. First, the present study was retrospective and conducted in a single institution. Larger multicenter studies are needed to confirm the results in this study. Second, the possibility of selection bias exists in terms of patient inclusion in the study group, because 24 patients (8.8%) were excluded from the present analysis. However, these 24 patients were excluded only because they had not undergone preoperative CT imaging at the L3 level. Indeed, patient characteristics such as age, sex, indications for LDLT, MELD score, Child-Pugh classification, and other perioperative parameters in this excluded population were essentially similar to those of the study group. Therefore, there was likely little to no selection bias in the present study.

In conclusion, pretransplant visceral adiposity, as well as low muscularity, was found to be closely involved with posttransplant mortality. We are investigating whether perioperative interventions, including nutritional therapy and rehabilitation, could have an impact on body composition and improve posttransplant outcomes. To improve outcomes after LDLT, it is essential to clarify the relationships among sarcopenia, visceral adiposity, and peritransplant nutritional and immunological status.

ACKNOWLEDGMENTS

The authors would like to thank Ms. Mayumi Kawashima for her help with collecting the data for this study.

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