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Original article

Impact of sarcopenic obesity on outcomes in patients undergoing living donor liver transplantation

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SUMMARY

Background & aim: Sarcopenia is known to be a poor prognostic factor after liver transplantation (LT). However, the significance of obesity in combination with sarcopenia (sarcopenic obesity) remains unclear. This study examined the impact of sarcopenic obesity on outcomes after living donor LT (LDLT).
Methods: We retrospectively analyzed 277 adult patients who underwent LDLT at our center between January 2008 and June 2016. Body composition parameters including skeletal muscle mass index (SMI), intramuscular adipose tissue content (IMAC), visceral fat area (VFA), and visceral-to-subcutaneous adipose tissue area ratio (VSR) were evaluated by preoperative plain computed tomography imaging at the level of the third lumbar vertebra. This study defined sarcopenic obesity as a low SMI (male <40.31 cm^2/m^2; female <30.88 cm^2/m^2) with VFA ≥100 cm^2 or body mass index (BMI) ≥25 kg/m^2. We examined outcomes among four groups: nonsarcopenic/nonobesity (NN), nonsarcopenic/obesity (NO), sarcopenic/nonobesity (SN), and sarcopenic/obesity (SO) groups.
Results: On the basis of VFA, 1/5-year overall survival (OS) rates in patients of SN (n = 46, 59%/46%, P < 0.001) and SO (n = 9, 56%/56%, P = 0.338) groups were lower than those in patients of the NN group (86%/80%). On the other hand, on the basis of BMI, 1/5-year OS rates in patients of SN (n = 49, 59%/52%, P < 0.001) and SO (n = 6, 50%/17%, P = 0.002) groups were significantly lower than those in patients of the NN group (87%/81%). Multivariate analysis identified ABO incompatibility (P = 0.030), low SMI (P = 0.002), high IMAC (P = 0.002), and high VSR (P < 0.001) as independent risk factors for death after LT.
Conclusion: Patients with sarcopenic obesity showed worse survival after LDLT compared with nonsarcopenic/nonobesity patients.

1. Introduction

Sarcopenia, initially proposed by Rosenberg in 1989 as an age-related depletion of the skeletal muscle, is currently recognized as a syndrome with features of progressive and systemic loss of skeletal muscle mass and strength [1]. Some recent papers have revealed preoperative sarcopenia as strongly associated with poor outcomes after various kinds of surgeries including liver transplantation (LT) [2–7]. We have also reported that low pretransplant quality as well as the quantity of the skeletal muscle had a negative impact on outcomes after LT [8].

Obesity is an underlying condition that can lead to a variety of diseases and pathologies, including type 2 diabetes mellitus, abnormal lipid metabolism, hypertension, and nonalcoholic fatty liver disease, to the point of representing a risk factor for these disorders [9]. Moreover, a high body mass index (BMI) is considered as an important predictor of cancer risk [10,11]. Recent reports have shown visceral adiposity (i.e., abdominal fat distribution) as highly related to poor prognosis in patients with a number of diseases

Abbreviations: BMI, body mass index; CT, computed tomography; GRWR, graft-to-recipient body weight ratio; HU, Hounsfield units; IMAC, intramuscular adipose tissue content; LD, living donor; LT, liver transplantation; MELD, model for end-stage liver disease; NN, nonsarcopenic/nonobesity; NO, nonsarcopenic/obesity; PMI, psoas muscle index; SMI, skeletal muscle mass index; SN, sarcopenic/non-obesity; SO, sarcopenic/obesity; VFA, visceral fat area; VSR, visceral–to-subcutaneous adipose tissue area ratio.

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[12–15]. Furthermore, we have recently identified sarcopenic obesity, defined as the combination of low muscle mass and visceral obesity, as an independent risk factor for death after resection of hepatocellular carcinoma or pancreatic cancer [16,17]. However, the impact of preoperative sarcopenic obesity on outcomes in patients undergoing living donor LT (LDLT) is unclear. The present study therefore examined the impact of sarcopenic obesity on outcomes after LT.

2. Patients and methods

A total of 338 consecutive patients underwent adult-to-adult LDLT at Kyoto University Hospital between January 2008 and June 2016. Among them, 277 patients were enrolled in this retrospective study, after excluding 61 patients who underwent retransplantation or for whom no images were available from preoperative plain computed tomography (CT) at the level of the third lumbar vertebra (L3). The ethics committee at Kyoto University Hospital approved this study (R0061), which proceeded in accordance with the Declaration of Helsinki.

Standard selection criteria for recipients, surgical procedures for both donor and recipient operations, and perioperative management including nutritional therapy have been described in detail elsewhere [18,19].

All preoperative plain CT images were acquired from patients using a multidetector-row CT scanner (Aquilion 64; Toshiba Medical Systems, Tochigi, Japan) within 1 month before surgery. Cross-sectional CT images at the L3 level were evaluated using Aquarius iNtuition Server (TeraRecon, San Mateo, CA) to identify skeletal muscle as areas of −29 to 150 Hounsfield units (HU) (Fig. 1A). Skeletal muscle mass index (SMI) was calculated by normalizing all areas of the skeletal muscle for height (cm^2/m^2). In the same way, skeletal muscle quality was evaluated by intramuscular adipose tissue content (IMAC), calculated by dividing the CT value of the multifidus muscles by the CT value of subcutaneous fat (Fig. 1B) at the L3 level. Visceral adiposity was then evaluated as the visceral-to-subcutaneous adipose tissue area ratio (VSR). Visceral and subcutaneous adipose tissue areas were calculated as areas of −150 to −50 HU (Fig. 1C) and −190 to −30 HU (Fig. 1D), respectively. Optimal cutoff values of SMI, IMAC, and VSR for males and females were determined separately based on data from a large number of healthy LDLT donors [15,20]. Visceral fat area (VFA) $\geq$100 cm^2 in males and females at the L3 level or BMI $\geq$25 kg/m^2 was recognized as obesity in accordance with the guidelines of the Japan Society for the Study of Obesity [21]. This study defined sarcopenic obesity as the combination of low SMI (male, <40.31 cm^2/m^2; female, <30.88 cm^2/m^2) and either VFA $\geq$100 cm^2 or BMI $\geq$25 kg/m^2. Using these definitions, we divided all patients into four groups according to SMI and VFA or BMI: nonsarcopenic/nonobesity (NN); nonsarcopenic/obesity (NO); sarcopenic/nonobesity (SN); and sarcopenic/obesity (SO) groups.

The following variables were compared between groups: age, sex, body weight, BMI, positivity for hepatitis C virus, ABO compatibility, SMI, IMAC, VSR, VFA, underlying liver disease, Child-Pugh classification, model for end-stage liver disease (MELD) score, and surgical data (including graft type, graft/recipient body weight ratio (GRWR), operation time, and blood loss). Overall survival (OS) rates after LT were compared among the four groups. Factors independently associated with OS after LT were also analyzed.

2.1. Statistical analysis

Consecutive variables are expressed as median and range. Patient characteristics were compared between groups by the χ^2 test or Fisher's exact test for categorical variables, and the Mann–Whitney U test or Kruskal–Wallis test for continuous variables. Cumulative OS rates were calculated by the Kaplan–Meier method, and differences between curves were evaluated by the logrank test. Any variable identified as significant (P < 0.05) or showing values of P < 0.10 in univariate analyses was considered as a candidate for multivariate Cox proportional hazard modeling. We considered values of P < 0.05 as significant. All data were statistically analyzed using JMP Pro, version 12 (SAS Institute, Cary, NC).

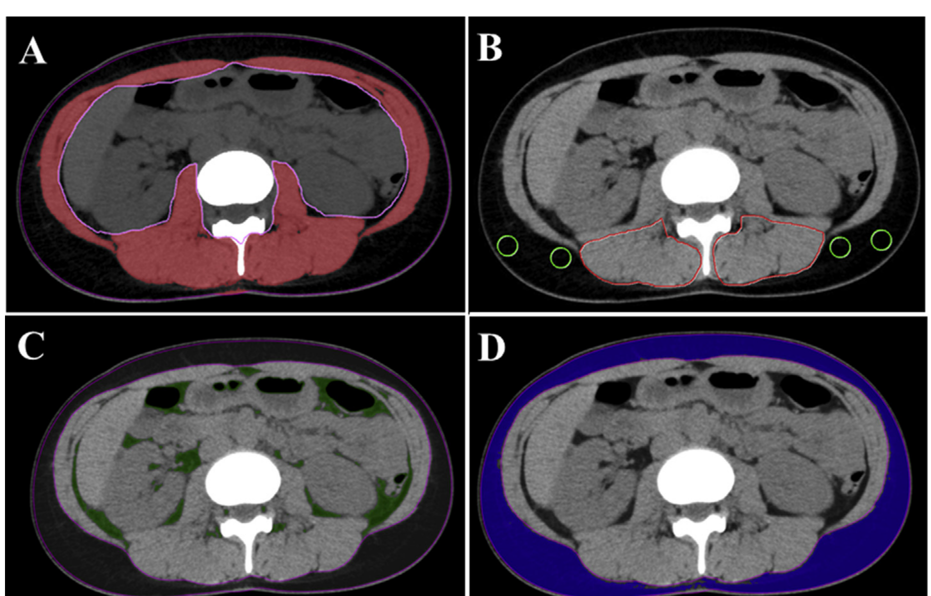

Fig. 1. Cross-sectional CT images at the L3 level. Skeletal muscle areas are calculated as areas of −29 to 150 HU (A). IMAC is calculated by dividing the CT value of the multifidus muscle with that of subcutaneous fat (B). Visceral and subcutaneous adipose tissue areas are calculated as areas of −150 to −50 HU (C) and −190 to −30 HU (D), respectively. CT, computed tomography; HU, Hounsfield units; IMAC, intramuscular adipose tissue content.

3. Results

3.1. Patient characteristics and OS rates according to VFA or BMI

Patient characteristics are summarized in Table 1. A total of 277 patients were assigned to either the visceral obesity group (n = 64) or the nonvisceral obesity group (n = 213) according to their VFA. Patient characteristics and surgical variables according to VFA are shown in Table 2. Recipient age and body weight were significantly higher in the visceral obesity group than in the nonvisceral obesity group ($P = 0.005$ and $P = 0.024$, respectively). Proportions of males and right lobe grafts were significantly higher in the visceral obesity group than in the nonvisceral obesity group ($P < 0.001$ each). Operation time was significantly longer and the volume of blood loss was significantly higher in the visceral obesity group than in the nonvisceral obesity group ($P = 0.001$ and $P = 0.016$, respectively). OS rates did not differ significantly between visceral obesity and nonvisceral obesity groups ($P = 0.934$) (Fig. 2A).

Patient characteristics and surgical variables for the BMI ≥25 kg/m^2 group (n = 49) and BMI <25 kg/m^2 group (n = 228) are shown in Table 3. Recipient age and body weight were significantly higher in the BMI ≥25 kg/m^2 group than in the BMI <25 kg/m^2 group ($P < 0.001$ each). Proportions of females and positivity for hepatitis C virus were significantly higher in the BMI ≥25 kg/m^2 group than in the BMI <25 kg/m^2 group ($P < 0.001$ each). Operation time was significantly shorter in the BMI ≥25 kg/m^2 group than in the BMI <25 kg/m^2 group ($P = 0.016$). OS rates did not differ significantly between BMI ≥25 kg/m^2 and <25 kg/m^2 groups ($P = 0.080$) (Fig. 2B).

Table 1
Patients characteristics undergoing living donor liver transplantation.

Characteristics	n = 277
Recipient Age (years)	54 [18–69]
Sex (male/female)	134/143
Body weight (kg)	56.1 [18.1–111.7]
BMI (kg/m^2)	20.9 [6.4–36.4]
Underlying disease	
Hepatocellular carcinoma	74
Hepatitis B/C-related cirrhosis	60
Cholestatic disease	56
Others	87
Child Pugh (A,B/C)	91/186
MELD	17 [4–55]
Hepatitis C virus positivity	93 (34%)
Ascites	189 (68%)
ABO compatibility	
Identical, compatible/Incompatible	200/77
Graft type (Right/Others)	148/129
GRWR (%)	0.89 [0.53–1.46]
Operation time (min)	843 [294–1360]
Blood loss (mL)	6475 [290–100,000]
SMI (cm^2/m^2)	
Male	47.006 [25.564–66.920]
Female	35.764 [15.786–59.181]
IMAC	
Male	−0.392 [−0.900 to −0.003]
Female	−0.262 [−1.096–0.574]
VSR	
Male	0.809 [0.209–4.741]
Female	0.586 [0.154–5.435]
VFA	66.1 [1.96–259]
Sarcopenic obesity (VFA/BMI)	9 (3%)/6 (2%)

BMI, body mass index; GRWR, graft/recipient body weight ratio; IMAC, intramuscular adipose tissue content; MELD, model for end-stage liver disease; SMI, skeletal muscle mass index; VFA, visceral fat area; VSR, visceral to subctaneous adipose tissue area ratio.

3.2. Patient characteristics and OS rates after LT among four subgroups

All patients were divided into four groups according to SMI and VFA or BMI: NN (n = 167 (60%)/n = 179 (65%)); NO (n = 55 (20%)/n = 43 (15%)), SN (n = 46 (17%)/n = 49 (18%)), and SO (n = 9 (3%)/n = 6 (2%)). Patient characteristics and surgical variables among these four groups are shown in Tables 4 and 5. On the basis of VFA, significant differences were seen among the four groups for recipient age ($P = 0.001$), sex ($P < 0.001$), body weight ($P = 0.016$), BMI ($P = 0.031$), underlying disease ($P = 0.005$), graft type ($P < 0.001$), operation time ($P < 0.001$), and blood loss ($P = 0.006$). On the other hand, on the basis of BMI, significant differences were apparent among the four groups for recipient age ($P < 0.001$), sex ($P < 0.001$), body weight ($P < 0.001$), BMI ($P < 0.001$), underlying disease ($P < 0.001$), Child-Pugh ($P = 0.042$), hepatitis C virus positivity ($P = 0.004$), graft type (0.002), and operation time ($P = 0.003$).

One- and 5-year OS rates after LT in NN, NO, SN, and SO groups on the basis of VFA were 86%/80%, 84%/75%, 59%/46%, and 56%/56%, respectively (P < 0.001; Fig. 3A). OS rates after LT were significantly lower in the SN group than in the NN group ($P < 0.001$). No differences were seen between patients with NN and SO ($P = 0.338$).

Table 2
Clinical and surgical characteristics classified by visceral fat area.

	Non-visceral obesity (n = 213)	Visceral obesity (n = 64)	P
Recipient Age (years)	53 [18–69]	57 [22–68]	0.005
Sex (male/female)	89/124	45/19	<0.001
Body weight (kg)	54.7 [18.1–98.0]	58.2 [27.1–111.7]	0.024
BMI (kg/m^2)	20.8 [6.4–32.8]	21.2 [11.6–36.4]	0.509
Underlying disease			0.003
Hepatocellular carcinoma	47	27	
Hepatitis B/C-related cirrhosis	44	16	
Cholestatic disease	40	9	
Others	82	12	
Child Pugh (A,B/C)	66/147	25/39	0.228
MELD	18 [4–48]	16 [6–55]	0.211
Hepatitis C virus positivity	67 (31%)	26 (41%)	0.178
ABO compatibility			0.181
Identical, compatible/Incompatible	158/55	42/22	
Graft type (Right/Others)	100/113	48/16	<0.001
GRWR (%)	0.90 [0.53–1.46]	0.85 [0.54–1.39]	0.088
Operation time (min)	500 [294–1,353]	913 [487–1,360]	0.001
Blood loss (mL)	5885 [290–100,000]	8204 [1,300–67,230]	0.016

BMI, body mass index; MELD, model for end-stage liver disease; GRWR, graft/recipient body weight ratio.

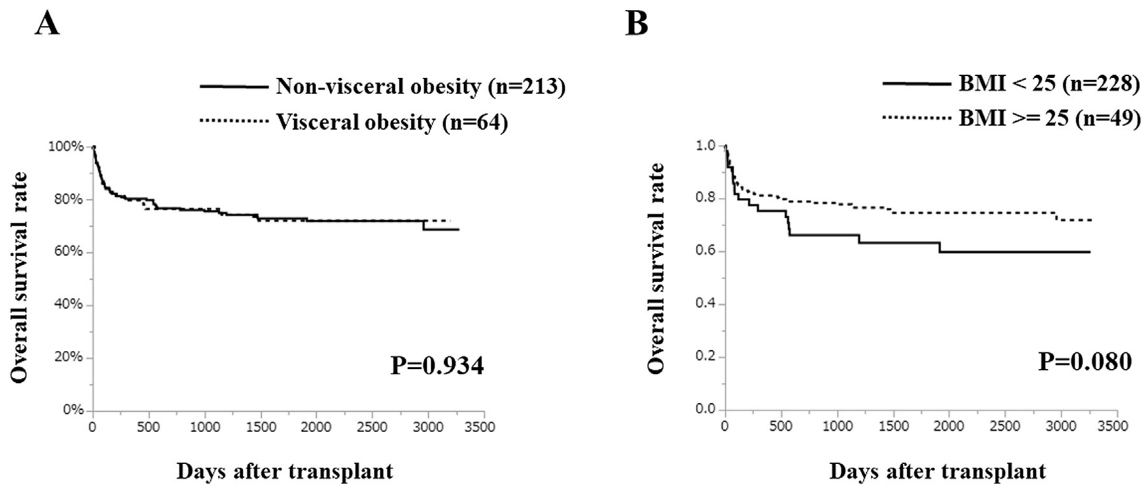

Fig. 2. Overall survival rates after LT classified by obesity. Overall survival rates after LT classified by nonvisceral and visceral obesity (A), or BMI <25 kg/m^2 and BMI ≥25 kg/m^2 (B). LT, liver transplantation; BMI, body mass index.

Table 3
Clinical and surgical characteristics classified by BMI.

	BMI < 25 (n = 228)	BMI ≥ 25 (n = 49)	P
Recipient Age (years)	52 [18–69]	63 [48–69]	<0.001
Sex (male/female)	127/101	7/42	<0.001
Body weight (kg)	53.5 [18.1–73.3]	64.8 [53.1–111.7]	<0.001
BMI (kg/m^2)	19.7 [6.4–24.9]	27.4 [25.1–36.4]	<0.001
Underlying disease			<0.001
Hepatocellular carcinoma	52	22	
Hepatitis B/C-related cirrhosis	50	10	
Cholestatic disease	38	11	
Others	88	6	
Child Pugh (A,B/C)	72/156	19/30	0.336
MELD	18 [4–55]	16 [6–36]	0.077
Hepatitis C virus positivity	66 (29%)	27 (55%)	<0.001
Ascites	157 (69%)	32 (65%)	0.630
ABO compatibility			0.894
Identical, compatible/Incompatible	165/63	35/14	
Graft type (Right/Others)	126/102	22/27	0.187
GRWR (%)	0.89 [0.53–1.46]	0.95 [0.56–1.39]	0.699
Operation time (min)	853 [294–1,353]	790 [535–1,280]	0.016
Blood loss (mL)	6,600 [290–100,000]	5,749 [904–39,126]	0.282

BMI, body mass index; MELD, model for end-stage liver disease; GRWR, graft/recipient body weight ratio.

Table 4
Clinical and surgical characteristics classified by SMI and VFA.

	NN (n = 167)	NO (n = 55)	SN (n = 46)	SO (n = 9)	P
Age (years)	54 [18–69]	57 [27–69]	52 [19–68]	59 [37–66]	0.001
Sex (male/female)	70/97	40/15	19/27	5/4	<0.001
Body weight (kg)	56.3 [18.1–98.0]	58.0 [27.1–111.7]	52.2 [19.2–68.1]	59.4 [37.9–65.8]	0.016
BMI (kg/m^2)	21.8 [6.4–31.8]	21.2 [11.6–36.4]	19.0 [7.0–32.8]	21.4 [12.2–29.3]	0.031
Underlying disease					<0.001
Hepatocellular carcinoma	40	24	7	3	
Hepatitis B/C-related cirrhosis	36	14	8	2	
Cholestatic disease	26	5	14	4	
Others	65	12	17	0	
Child Pugh (A,B/C)	53/114	21/34	13/33	4/5	0.617
MELD	18 [4–48]	17 [6–55]	19 [7–46]	14 [10–22]	0.159
Hepatitis C virus positivity	56 (34%)	22 (40%)	11 (24%)	4 (44%)	0.322
ABO compatibility					0.188
Identical,compatible/Incompatible	125/42	34/21	33/13	8/1	
Graft type (Right/Others)	88/79	42/13	12/34	6/3	<0.001
GRWR (%)	0.91 [0.53–1.46]	0.85 [0.54–1.39]	0.87 [0.55–1.33]	0.95 [0.75–1.31]	0.213
Operation time (min)	837 [294–1353]	953 [638–1359]	789 [482–1292]	735 [487–1360]	<0.001
Blood loss (mL)	5352 [290–100,000]	8752 [1300–67,230]	7110 [340–23,920]	5749 [1529–17,615]	0.006

BMI, body mass index; GRWR, graft/recipient body weight ratio; MELD, model for end-stage liver disease; NN, non-sarcopenic/non-obesity; NO, non-sarcopenic/obesity; SMI, skeletal muscle mass index; SN, sarcopenic/non-obesity; SO, sarcopenic/obesity; VFA, visceral fat area.

Table 5
Clinical and surgical characteristics classified by SMI and BMI.

	NN (n = 179)	NO (n = 43)	SN (n = 49)	SO (n = 6)	P
Age (years)	53 [18–69]	63 [47–69]	51 [19–66]	64 [53–68]	<0.001
Sex (male/female)	103/76	7/36	24/25	0/6	<0.001
Body weight (kg)	56.0 [18.1–73.3]	68.9 [57.5–111.7]	53.0 [19.2–66.9]	64.7 [53.1–68.1]	<0.001
BMI (kg/m^2)	20.1 [6.4–24.9]	27.2 [25.4–36.4]	18.1 [7.0–24.2]	28.7 [26.1–32.8]	<0.001
Underlying disease					<0.001
Hepatocellular carcinoma	44	20	8	2	
Hepatitis B/C-related cirrhosis	43	7	7	3	
Cholestatic disease	22	9	17	1	
Others	70	7	17	0	
Child Pugh (A,B/C)	60/119	14/29	12/37	5/1	0.042
MELD	18 [4–55]	16 [6–36]	19 [7–46]	13 [12–20]	0.164
Hepatitis C virus positivity	55 (31%)	23 (53%)	11 (22%)	4 (67%)	0.004
ABO compatibility					0.939
Identical,compatible/Incompatible	128/51	31/12	37/12	4/2	
Graft type (Right/Others)	110/69	20/23	16/33	2/4	0.002
GRWR (%)	0.89 [0.53–1.46]	0.95 [0.56–1.39]	0.87 [0.55–1.33]	0.91 [0.72–1.32]	0.922
Operation time (min)	869 [294–1359]	790 [535–1280]	783 [482–1360]	787 [684–961]	0.003
Blood loss (mL)	6570 [750–100,000]	4220 [904–39,126]	6800 [340–23,920]	7560 [5749–17,800]	0.329

BMI, body mass index; GRWR, graft/recipient body weight ratio; MELD, model for end-stage liver disease; NN, non-sarcopenic/non-obesity; NO, non-sarcopenic/obesity; SMI, skeletal muscle mass index; SN, sarcopenic/non-obesity; SO, sarcopenic/obesity.

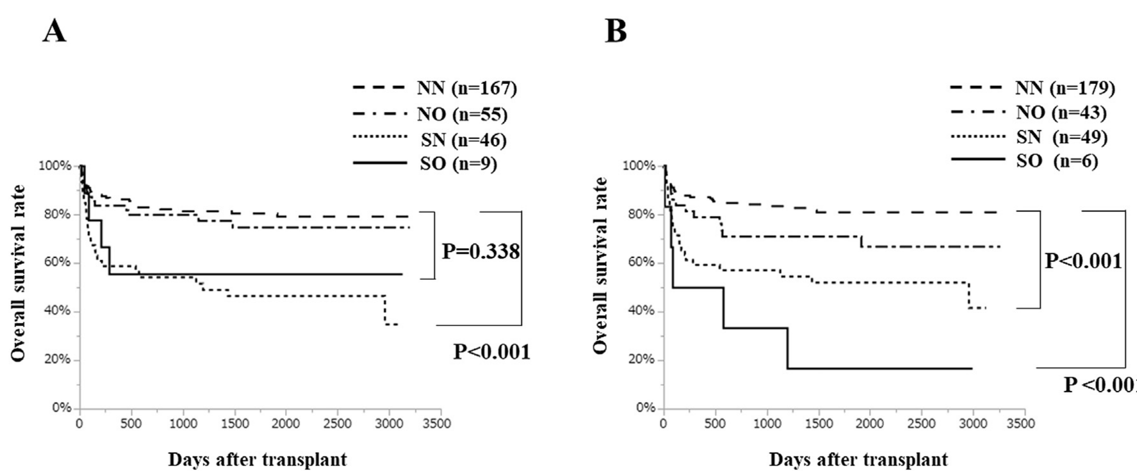

Fig. 3. Overall survival rates after LT according to SMI and obesity. Overall survival rates after LT according to the four body composition categories classified by SMI and VFA (A), or SMI and BMI (B). LT, liver transplantation; SMI, skeletal muscle mass index; VFA, visceral fat area; BMI, body mass index; NN, nonsarcopenic/nonobesity; NO, nonsarcopenic/obesity; SN, sarcopenic/nonobesity; SO, sarcopenic/obesity.

On the other hand, on the basis of BMI, 1- and 5-year OS rates after LT in NN, NO, SN, and SO groups were 87%/81%, 79%/71%, 59%/52%, and 50%/17%, respectively (P < 0.001, Fig. 3B). OS rates after LT were significantly lower in the SN and SO groups than in the NN group ($P < 0.001$ each).

3.3. Risk factors for mortality after LT

Univariate analysis identified BMI ≥25 kg/m^2, ABO incompatibility, graft type other than right graft, operation time <12 h, low SMI, high IMAC, and high VSR as significant risk factors for death after LT (P = 0.097, 0.036, 0.008, 0.096, <0.001, <0.001, and <0.001, respectively; Table 6). On multivariate analysis, ABO incompatibility (P = 0.030), low SMI (P = 0.002), high IMAC (P = 0.002), and high VSR ($P < 0.001$) were identified as independent risk factors for death after LT.

4. Discussion

This retrospective study is the first to examine the impact of sarcopenic obesity as defined by the combination of low SMI and either high VFA or high BMI on outcomes after LDLT. Patients with sarcopenic obesity as defined by low SMI and high BMI showed significantly worse survival after LDLT compared with non-sarcopenic/nonobesity patients.

Regarding the impact of pretransplant obesity on LDLT, some investigators have reported that obesity alone as defined by BMI was not associated with low post-transplant survival [22,23]. Those studies used BMI as a parameter of obesity. In patients undergoing LT, BMI does not correctly mean obesity because BMI is overestimated due to the presence of the ascites and edema usually associated with decompensated liver cirrhosis in these patients. The present study therefore examined the impact on outcomes using two different definitions of obesity: BMI ≥25 kg/m^2 and VFA ≥100 cm^2. Strictly speaking, obesity should be defined not as BMI ≥25 kg/m^2 but rather as BMI ≥30 kg/m^2. In general, Japanese people have a smaller physique than Western individuals. In fact, only five of the 277 patients in the present analysis had BMI ≥30 kg/m^2. We therefore defined obesity as BMI ≥25 kg/m^2 in this study.

In the present study, OS rates after LT displayed no significant differences between nonvisceral obesity and visceral obesity or

Table 6
Univariate and multivariate analysis of prognostic factors for posttransplant survival.

Variable	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Recipient Age						
<50 (n = 97)	1.000					
≥50 (n = 180)	0.939	0.644–1.234	0.644			
Gender						
Male (n = 134)	1.000					
Female (n = 143)	1.198	0.759–1.906	0.439			
Body weight (kg)						
<52 (n = 96)	1.000					
≥52 (n = 181)	0.732	0.462–1.171	0.190			
BMI (kg/m^2)						
<25 (n = 228)	1.000			1.000		
≥25 (n = 49)	1.600	0.915–2.665	0.097	1.120	0.621–1.939	0.697
Underlying disease						
Hepatocellular carcinoma (n = 74)	1.000					
Hepatitis B/C-related cirrhosis (n = 60)	1.295	0.682–2.460	0.426			
Cholestatic disease (n = 49)	1.431	0.727–2.784	0.294			
Others (n = 94)	0.837	0.445–1.579	0.579			
Child-Pugh classification						
A, B (n = 91)	1.000					
C (n = 186)	0.927	0.580–1.514	0.756			
MELD score						
<25 (n = 217)	1.000					
≥25 (n = 60)	1.447	0.846–2.378	0.171			
Hepatitis C virus positivity						
Negative (n = 184)	1.000					
Positive (n = 93)	1.134	0.701–1.802	0.602			
ABO incompatibility						
identical/compatible (n = 200)	1.000			1.000		
incompatible (n = 77)	1.678	1.037–2.666	0.036	1.730	1.057–2.783	0.030
Graft type						
right graft (n = 148)	1.000			1.000		
others (n = 129)	1.866	1.178–2.995	0.0078	1.290	0.800–2.109	0.298
GRWR						
<0.8 (n = 87)	1.000					
≥0.8 (n = 190)	0.996	0.616–1.660	0.987			
Operation time (min)						
<12 h (n = 55)	1.000			1.000		
≥12 h (n = 222)	0.641	0.392–1.087	0.096	0.624	0.378–1.063	0.081
Blood loss (ml)						
<10,000 (n = 192)	1.000					
≥10,000 (n = 85)	0.828	0.488–1.360	0.465			
SMI						
Normal (n = 222)	1.000			1.000		
Low (n = 55)	3.109	1.928–4.930	<0.001	2.316	1.379–3.837	0.002
IMAC						
Normal (n = 156)	1.000			1.000		
High (n = 121)	2.599	1.631–4.224	<0.001	2.181	1.340–3.616	0.002
VSR						
Normal (n = 194)	1.000			1.000		
High (n = 83)	3.377	2.138–5.365	<0.001	2.363	1.444–3.881	<0.001
VFA						
<100 (n = 213)	1.000					
≥100 (n = 64)	0.977	0.552–1.642	0.934			

BMI, body mass index; GRWR, graft/recipient body weight ratio; IMAC, intramuscular adipose tissue content; MELD, model for end-stage liver disease; SMI, skeletal muscle mass index; VFA, visceral fat area; VSR, visceral to subcutaneous adipose tissue area ratio.

between BMI <25 kg/m^2 and BMI ≥25 kg/m^2. However, with the addition of sarcopenia as a factor to these groups, significant differences in OS after LT were seen among the four groups ($P < 0.001$). These findings suggest that the sarcopenic factor is much more important than the obesity factor. Moreover, in cases where we use VFA as an index of obesity, the OS rate after LT was significantly lower in the SN group than in the NN group ($P < 0.001$). On the other hand, no significant differences were apparent between patients with NN and SO ($P = 0.338$), possibly because the number of patients in the SO group was small (n = 9). Multivariate analysis also identified low SMI, but not VFA, as an independent risk factor for death after LT. By contrast, using BMI as the index of obesity, the OS rate after LT was significantly lower in the SO group than in the NN group, although the number of patients in the SO group was again quite small (n = 6). Although the exact reasons why the SO group showed worse survival after LDLT remain unclear, abnormal body compositions could contribute to poor survival. In fact, five of the six patients showed abnormalities in all three body composition parameters (low SMI, high IMAC, and high VSR). This finding is in line with our most recent report showing that the prognosis of patients with all three abnormal variables together was quite poor [24].

Liver, muscle, and adipose tissue are currently considered as the main target organs for insulin function [25]. Moreover, insulin resistance is associated with the physiological mechanisms of chronic inflammation and damage, which are widely associated with the development of both obesity and sarcopenia. Myokines secreted from myocytes and adipokines from adipocytes influence the immune system. Inflammation may be an important mediator to restrain myogenesis and/or to accelerate muscle protein degradation due to reactive oxygen species and other intermediates [26,27]. However, further investigations are needed to confirm the detailed mechanism in the future.

Among advanced nations, atherosclerotic disease has become a major cause of death. Some investigators have reported that sarcopenia is associated with increased visceral fat mass, thus leading to metabolic impairment including insulin resistance [28–30]. Kim et al. also revealed a correlation between metabolic syndrome and sarcopenic obesity [31]. In our case, comparison with the presence or absence of visceral obesity showed no significant differences in patients between visceral obesity and nonvisceral obesity groups ($P = 0.934$). However, adding sarcopenic factors demonstrated significant differences in patients among groups ($P < 0.001$), thus suggesting that the most important factor is the sarcopenic factor, not the obesity factor. This might be the reason why patients with SO according to VFA showed no significant difference in survival after LT. To date, we have already reported on the impact of perioperative nutritional and rehabilitation after LT in patients with sarcopenia [32,33].

Previously, we reported an impact of sarcopenic overweight on the outcomes after LDLT [34]. However, there are two major differences between this study and the previous one. First, in the previous report, the authors defined sarcopenia as a low psoas muscle index (PMI). On the other hand, we used SMI instead of PMI in the present study because SMI reflects skeletal muscle mass and is more popular than PMI. Second, we defined sarcopenic obesity on the basis of VFA or BMI in the present study, whereas the previous report defined sarcopenic obesity only on the basis of BMI.

Several limitations must be considered when interpreting the results of this study. First, the present study involved data from only a single center. A nationwide study is required to confirm the present findings. Second, the number of patients in each group in this retrospective study differed markedly. In particular, patient numbers in the SO group according to VFA or BMI were quite small ($n = 9$ and $n = 6$, respectively). Third, this was a retrospective study. Perioperative management and surgical techniques have changed during the 8-year study period. A prospective study is warranted to confirm the results of this study. Finally, we used VFA $\geq 100\ cm^2$ in males and females at the L3 level to define obesity, as suggested by the guidelines of the Japan Society for the Study of Obesity. If a different definition of obesity had been used, the results may well have differed.

In conclusion, patients with sarcopenic obesity showed worse survival after LDLT compared with nonsarcopenic/nonobesity patients. Abnormal body compositions including low skeletal muscle mass, a high degree of muscle steatosis, and visceral adiposity exert strong negative impacts on survival after LDLT.

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Statement of authorship

Naoko Kamo and Toshimi Kaido designed study. Naoko Kamo, Toshimi Kaido, Yuhei Hamaguchi, Shinya Okumura, Atsushi Kobayashi, Hisaya Shirai, Siyuan Yao, Shintaro Yagi, and Shinji Uemoto performed the study. Naoko Kamo collected the data. Naoko Kamo and Shinji Uemoto analyzed the data. Naoko Kamo and Toshimi Kaido wrote the paper. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest to disclose.

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