Effect of Sarcopenic Obesity on Outcomes of Living-Donor Liver Transplantation for Hepatocellular Carcinoma

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Abstract. *Background/Aim: We aimed to evaluate the effect of body composition on the outcome of living-donor liver transplantation (LDLT) in patients with hepatocellular carcinoma (HCC). Patients and Methods: We performed LDLT in 153 patients with HCC and divided the patients into two groups based on skeletal muscle mass-to-visceral fat area ratio (SVR), as assessed by computed tomography (CT) measurement, namely a low-SVR group (n=38) and a not-low SVR group (n=112). We compared surgical outcomes between the two groups. Results: A low SVR was significantly correlated with a higher body mass index and male sex. No differences were found between the two groups in terms of other factors. The patients in the low-SVR group had a significantly poorer prognosis than those in the not-low SVR group in terms of recurrence-free (p=0.01) and overall (p=0.03) survival. The results of the multivariate analysis showed low SVR to be an independent and prognostic indicator for patients with HCC who had undergone LDLT. Conclusion: Pre-transplant body composition measured by CT is a major determinant of prognosis in LDLT for HCC in Japan.*

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm worldwide and a major cause of death in many countries, especially in Japan (1, 2). Hepatic resection is an effective treatment of HCC (3, 4). However, the postoperative recurrence rate remains high even if curative resection is performed, although surgical techniques have recently been improved (5). Liver transplantation is an established therapy for unresectable HCC in patients with poor liver dysfunction (6). Recently, expanded criteria for the selection of candidates for liver transplantation among patients with HCC have been proposed (7-9).

Several body composition features have been associated with the incidence, etiology, and therapeutic outcomes of cancer. Obesity, as one example, has been implicated in the etiology and prognosis of various cancer types (10) and numerous chronic health conditions (11). Body mass index (BMI) has been widely used as an indicator of obesity. However, compared to BMI, measures of visceral fat area (VFA) allow for the possibility of redefining obesity. Computed tomographic (CT) measurements of body composition, such as an increased amount of VFA (central obesity) and depletion of skeletal muscle (sarcopenia), have been associated with poorer survival from cancer (12-15). Of interest is sarcopenic obesity, which is characterized by simultaneous severe obesity and low skeletal muscle mass. This body composition type might be of clinical importance. However, no such data are available for patients undergoing living-donor liver transplantation (LDLT) for HCC. The purpose of this study was to examine the association of body composition by using skeletal muscle mass and VFA measured by using CT with outcomes of LDLT in patients with HCC.

Patients and Methods

Patients. One hundred and fifty-three recipients with HCC underwent LDLT because of end-stage liver disease at the Kyushu University Hospital between July 2001 and November 2012. All patients underwent preoperative CT. The selection criteria for patients with HCC to undergo LDLT were as follows: (a) no modality, except LDLT, available to treat patients with HCC and end-stage liver disease; (b) no extrahepatic metastasis; and (c) no major vascular infiltration such as of the portal or hepatic vein. Only patients with a des-gamma-carboxyprothrombin level >300 mAU/ml and a maximum tumor size >5 cm were contraindicated, as previously reported (8, 9). The study protocol was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the Institutional Review Board. (no. 27-147).

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Table I. *Variables for patients with hepatocellular carcinoma who had undergone living-donor liver transplantation.*

Variable	Not-low SVR (n=115)	Low SVR (n=38)	*p*-Value
Age (years)	58 (21-73)	57 (47-67)	0.508
Gender, male/female	56/59	30/8	0.001
BMI (kg/m^2)	23.1 (16.5-36.3)	26.5 (20.7-37.1)	<0.001
HCV-Ab-positive	82 (71.3%)	28 (73.6%)	0.777
Child-Pugh class C	63 (54.7%)	22 (57.8%)	0.737
MELD score ≥15	35 (30.4%)	13 (34.2%)	0.663
Number of tumors ≥4	35 (30.4%)	11(28.9%)	0.862
Tumor size >5 cm	4 (3.4%)	2 (5.2%)	0.638
Met the Milan criteria	73 (63.4%)	23 (60.5%)	0.744
AFP ≥300 ng/ml	23 (20.0%)	5 (13.1%)	0.469
DCP ≥300 mAU/ml	20 (17.3%)	7 (18.4%)	0.885
Ncutrophil-to-lymphocyte ratio >4	18 (15.6%)	7 (18.4%)	0.689
CNI: CyA/TAC	62/50	19/16	0.911
Age of donor ≥40 years	31 (26.9%)	8 (21.0%)	0.436
GV/SLV <35%	26 (22.6%)	9 (23.6%)	0.952

Values are numbers (percentages) or median (range). SVR, Skeletal muscle mass-to-visceral fat area ratio; BMI, body mass index; HCV-Ab, hepatitis C virus antibody; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin; CNI, calcineurin inhibitor; CyA, cyclosporine A; TAC, tacrolimus; GV/SLV, graft volume-to-standard liver volume ratio.

The degree of proportional visceral adiposity and skeletal muscle mass were measured from the patients' preoperative CT images. VFA was measured from a single axial slice at the level of the umbilicus (16, 17). VFA was calculated by measuring pixels with densities ranging from −190 to −30 Hounsfield units (HU). A transverse CT image at the third lumbar vertebra (L3) in the inferior direction was assessed from each scan (18, 19). Skeletal muscle was identified and quantified by HU thresholds ranging from −29 to 150 (water is defined as 0 HU; and air, as 1000 HU). Multiple muscles were quantified, including the psoas, *erector spinae*, *quadratus lumborum*, *transversus abdominis*, external and internal oblique abdominal, and *rectus abdominis* muscles. CT measurements were calibrated with water and air at fixed intervals. VFA and skeletal muscle mass were measured by manual outlining on CT images, and the measurements were checked by the radiologist.

Details of the transplant procedures for both the donors and recipients have been reported previously (20). The basic immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids, gradually tapered to calcineurin monotherapy within 1 year of LDLT (21).

The clinical follow-up of the patients who received transplantation for HCC followed a strict protocol, which did not change during the study period. The patients were seen biweekly for the first month and then screened monthly for 6 months for tumor markers such as alpha-fetoprotein (AFP) and des-gamma-carboxyprothrombin (DCP). The patients underwent ultrasonography and enhanced CT at 6-month intervals. An angiographic examination was performed after admission when disease recurrence was strongly suspected.

Statistical analysis. Continuous variables were compared by using the Mann-Whitney *U*-test. Categorical variables were compared by using the χ^2 test or Fisher's exact test. The univariate Cox proportional hazards model was performed by using survival data. Covariates that were significant at $p<0.05$ were included in the multivariate Cox proportional hazards model. The overall and disease-free survival rates were calculated by using the product limit method of the Kaplan–Meier method and compared by using the log-rank test. Differences were considered significant at $p<0.05$. All statistical analyses were performed by using the JMP statistical software package (SAS Institute, Inc., Cary, NC, USA).

Results

The median follow-up was 5.2 years (range=0.0-12.8 years). During the follow-up, 23 patients (21.8%) developed recurrence. Firstly, the patients were divided into quartiles according to the skeletal muscle mass-to-VFA ratio (SVR), which was normalized for stature by weight. We defined the quartile with the lowest SVR as the low-SVR group and the other quartiles as the not-low SVR group.

The clinicopathological characteristics of patients in the low-SVR group (n=38) and not-low SVR group (n=115) are compared in Table I. The BMI in the low-SVR group was significantly lower than that in the not-low SVR group ($p<0.001$). The percentage of male patients in the low-SVR group was significantly higher than that in the not-low SVR group ($p=0.001$). No differences were noted between the two groups in terms of other host-related factors.

Figure 1 exhibits the recurrence-free and overall survival curves after LDLT for the two groups. The 1-, 3- and 5-year recurrence-free survival rates were 95.5%, 88.8% and 87.4%, respectively, in the not-low SVR group and 85.7%, 73.4% and 73.4% in the low-SVR group, respectively. The 1-, 3-, 5- and 10-year overall survival rates were 93.9%, 88.3%, 85.3% and 78.8%, respectively, in the not-low SVR group and 86.8%, 78.6%, 72.2% and 67.0% in the low-SVR group,

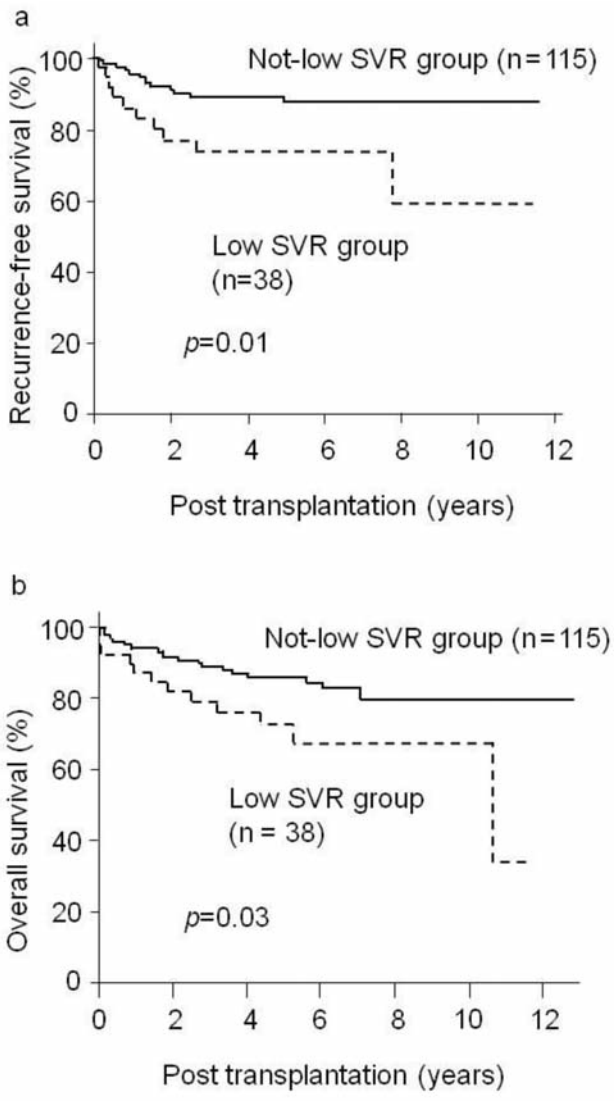

Figure 1. *Comparison of the recurrence-free (a) and overall (b) survival curves after living-donor liver transplantation in patients with hepatocellular carcinoma between the group with low skeletal muscle mass-to-visceral fat area ratio (SVR) and the not-low SVR. p-Values were derived from the log-rank test.*

respectively. Patients in the low-SVR group had a significantly worse prognosis than those in the not-low SVR group in terms of both recurrence-free (p=0.01) and overall (p=0.03) survival.

In the univariate analysis, the significant prognostic factors for poor recurrence-free survival were low SVR, number of tumors ≥4, tumor size >5 cm, not meeting the Milan criteria, AFP level ≥300 ng/ml, DCP level ≥300 mAU/ml, neutrophil-to-lymphocyte ratio (NLR) >4, and age of donor ≥40 years (Table II). The significant prognostic factors for overall survival were low SVR, number of tumors ≥4, not meeting the Milan criteria, AFP level ≥300 ng/ml, and DCP level ≥300 mAU/ml (Table III). The multivariate analysis identified four factors indicative of poor prognosis (low SVR, number of tumors ≥4, AFP level ≥300 ng/ml, and DCP level ≥300 mAU/ml) that influenced recurrence-free survival and one (low SVR) that influenced overall survival (Tables II and III).

Discussion

In this retrospective single-institution study, we found that a low SVR was an independent predictor of recurrence-free and overall survival in patients with HCC who had undergone LDLT. This is the first clinical study to compare body composition and cancer outcomes after LDLT in patients with HCC.

Changes in body composition, especially depletion of skeletal muscle mass (sarcopenia), have been reported for various kinds of diseases (14, 22). We previously reported that sarcopenia was a prognostic indicator for patients with HCC who had undergone hepatic resection (15, 18) and an independent predictor of mortality and sepsis after LDLT (23). Hence, in this study, we focused on the outcomes of LDLT for HCC in terms of an increased amount of body fat, which is another change in body composition, in addition to sarcopenia. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and function in the diagnosis of sarcopenia (24). However, muscle function is difficult to evaluate; thus, low muscle mass was investigated in the present study. CT is the gold-standard tool for quantifying skeletal muscle mass and VFA and hence constitutes a good resource for objective and detailed nutritional and metabolic assessments of patients. Moreover, a CT scan is generally available for review, especially in patients with HCC, and constitutes an important tool for diagnosis, staging, and suitability to undergo LDLT.

The definition of sarcopenia based on CT measurement has been set by using an unfounded cutoff level and has not been accurately determined as yet. We previously performed CT based on skeletal muscle mass, which was normalized for stature by using height, and defined sarcopenia as a skeletal muscle area <41.1 cm^2/m^2 for women and 43.75 cm^2/m^2 for men (15, 18). Meanwhile, in terms of body fat, the cutoff value for VFA was defined as 69 cm^2 for women and 103 cm^2 for men, which were recognized as measures of metabolic abnormalities in Japan (15, 25). However, these cutoff values were not suitable for patients with end-stage liver disease. Lim *et al*. reported that sarcopenia defined based on skeletal muscle mass, that was normalized for stature by using weight, is more closely associated with metabolic syndrome than that defined based on height (26). Therefore, we developed the SVR to evaluate body composition by using both skeletal muscle mass, normalized for stature by using weight, and VFA in patients with end-stage liver disease.

Table II. *Univariate and multivariate analyses of factors related to recurrence-free survival in the patients with hepatocellular carcinoma who had undergone living-donor liver transplantation (Cox proportional hazards analysis).*

	Univariate			Multivariate		
Variable	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Age (years)	0.99	0.94-1.05	0.939			
Gender: male	0.99	0.99-2.34	0.997			
Low SVR	2.81	1.19-6.41	0.018	5.26	2.03-13.8	<0.001
BMI ≥25 kg/m^2	0.83	0.33-1.91	0.669			
HCV-Ab-positive	1.40	0.55-4.24	0.491			
Child-Pugh class C	0.75	0.32-1.72	0.502			
MELD score ≥15	0.61	0.20-1.53	0.313			
Number of tumors ≥4	6.36	2.71-16.5	<0.001	5.70	1.09-10.5	0.036
Tumor size >5 cm	7.80	2.24-21.0	0.003	1.56	0.36-5.75	0.526
Not met the Milan criteria	5.56	2.30-15.4	<0.001	1.34	0.20-26.8	0.785
AFP ≥300 ng/ml	6.23	2.72-14.4	<0.001	4.32	1.59-11.7	0.004
DCP ≥300 mAU/ml	7.27	3.18-16.8	<0.001	3.42	1.22-9.54	0.019
NLR >4	2.92	1.12-6.88	0.029	122	0.43-3.16	0.683
CNI: TAC	0.66	0.26-1.52	0.335			
Age of donor ≥40 years	3.57	1.04-22.3	0.040	1.67	0.42-11.0	0.491
GV/SLV <35%	1.05	0.34-2.64	0.915			

CI, Confidence interval; SVR, skeletal muscle mass-to-visceral fat area ratio; BMI, body mass index; HCV-Ab, hepatitis C virus antibody; AFP, alpha-fetoprotcin; DCP, *des*-gamma carboxyprothrombin; NLR, neutrophil-to-lymphocyte ratio; CNI, calcineurin inhibitor; TAC, tacrolimus; GV/SLV, graft volume-to-standard liver volume ratio.

Table III. *Univariate and multivariate analyses of factors related to overall survival in the patients with hepatocellular carcinoma who had undergone living-donor liver transplantation (Cox proportional hazards analysis).*

	Univariate			Multivariate		
Variable	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Age (years)	0.99	0.94-1.04	0.839			
Gender: male	1.42	0.69-3.05	0.338			
Low SVR	2.14	1.01-4.34	0.045	2.58	1.17-5.52	0.019
BMI ≥25 kg/m^2	0.90	0.42-1.82	0.777			
HCV-Ab-positive	1.31	0.59-3.30	0.516			
Child-Pugh class C	0.73	0.36-1.46	0.375			
MELD score ≥15	1.10	0.49-2.28	0.793			
Number of tumors ≥4	4.57	2.24-9.83	<0.001	3.03	0.86-19.2	0.090
Tumor size >5 cm	2.27	0.53-6.53	0.231			
Not met the Milan criteria	4.29	2.05-9.80	<0.001	1.25	0.18-5.02	0.781
AFP ≥300 ng/ml	2.32	1.05-4.80	0.037	1.35	0.54-3.17	0.496
DCP ≥300 mAU/ml	3.69	1.78-7.43	<0.001	2.08	0.90-4.66	0.083
NLR >4	2.18	0.9M.69	0.076			
CNI: TAC	0.51	021-1.12	0.096			
Age of donor ≥40 years	1.67	0.77-3.40	0.182			
GV/SLV < 35%	1.49	0.65-3.11	0.325			

CI, Confidence interval; SVR, skeletal muscle mass-to-visceral fat area ratio; BMI, body mass index: HCV-Ab, hepatitis C virus antibody; AFP, alpha-fetoprotein; DCP, *des*-gamma carboxyprothrombin; NLR, neutrophil-to-lymphocyte ratio; CNI, calcineurin inhibitor; TAC, tacrolimus; GV/SLV, graft volume-to-standard liver volume ratio.

Sarcopenic obesity has been shown to be a major determinant of cancer prognosis (12). Tan *et al*. reported that sarcopenic obesity was a factor indicating a poorer prognosis for patients with pancreatic cancer than sarcopenia or obesity (13). In this study, a low SVR represented increased VFA and reduced muscle mass, and might be thought to be related

to sarcopenic obesity, hence a low SVR could be of independent prognostic value.

The molecular mechanism of body composition for HCC progression is not known. Muscle wasting is a known complication associated with insulin resistance found commonly in obesity (27). Adipose tissue, especially visceral fat, synthesizes and secretes circulating hormones and adipokines that act as systemic inflammatory mediators and signals of nutritional status (28). These adipocyte factors such as tumor necrosis factor-alpha and interleukin-6 are thought to play a major role in the induction of insulin resistance in skeletal muscle, leading to an increase in muscle protein loss and shortening the survival of natural killer lymphocytes, which are innate immune cells that control intracellular infectious agents and cancer. Therefore, increased VFA is associated with a strong pro-inflammatory state that promotes sarcopenia and may inhibit natural killer lymphocytes (29). Further study is needed to clarify the molecular mechanism concerning muscle-fat cross-talk.

The study has the following limitations: (a) it is a single-institution and retrospective review; (b) it included a relatively small number of patients; and (c) the categorization in this study is controversial. These limitations will need to be overcome with multi-institutional reviews and possible clinical studies.

In conclusion, the present study found that a low SVR had a prognostic role in patients with HCC who had undergone LDLT. High skeletal muscle mass and low VFA might be advantageous for long-term survival after LDLT for HCC in Japan.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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References

1 Bruix J and Lovet JM: Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology *35*: 519-524, 2002.

2 Bosch FX, Ribes J, Díaz M and Cléries R: Primary liver cancer: worldwide incidence and trends. Gastroenterology *127*: S5-16, 2004.

3 Itoh S, Morita K, Ueda S, Sugimachi K, Yamashita Y, Gion T, Fukuzawa K, Wakasugi K, Taketomi A and Maehara Y: Long-term results of hepatic resection combined with intraoperative local ablation therapy for patients with multinodular hepatocellular carcinomas. Ann Surg Oncol *16*: 3299-3307, 2009.

4 Shirabe K, Takeishi K, Taketomi A, Uchiyama H, Kayashima H and Maehara Y: Improvement of long-term outcomes in hepatitis C virus antibody-positive patients with hepatocellular carcinoma after hepatectomy in the modern era. World J Surg *35*: 1072-1084, 2011.

5 Itoh S, Shirabe K, Taketomi A, Morita K, Harimoto N, Tsujita E, Sugimachi K, Yamashita Y, Gion T and Maehara Y: Zero mortality in more than 300 hepatic resections: validity of preoperative volumetric analysis. Surg Today *42*: 435-440, 2012.

6 Vitale A, Morales RR, Zanus G, Farinati F, Burra P, Angeli P, Frigo AC, Del Poggio P, Rapaccini G, Di Nolfo MA, Benvegnù L, Zoli M, Borzio F, Giannini EG, Caturelli E, Chiaramonte M, Trevisani F, Cillo U; Italian Liver Cancer group: Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. Lancet Oncol *12*: 654-662, 2011.

7 Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group: Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol *10*: 35-43, 2009.

8 Taketomi A, Sanefuji K, Soejima Y, Yoshizumi T, Uhciyama H, Ikegami T, Harada N, Yamashita Y, Sugimachi K, Kayashima H, Iguchi T and Maehara Y: Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. Transplantation *87*: 531-537, 2009.

9 Shirabe K, Taketomi A, Morita K, Soejima Y, Uchiyama H, Kayashima H, Ninomiya M, Toshima T and Maehara Y: Comparative evaluation of expanded criteria for patients with hepatocellular carcinoma beyond the Milan criteria undergoing living-related donor liver transplantation. Clin Transplant *25*: E491-498, 2011.

10 Murthy NS, Mukherjee S, Ray G and Ray A: Dietary factors and cancer chemoprevention: an overview of obesity-related malignancies. J Postgrad Med *55*: 45-54, 2009.

11 Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, Narayan KM and Williamson DF: Secular trends in cardiovascular disease risk factors according to body mass index in US adults. JAMA *293*: 1868-1874, 2005.

12 Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L and Baracos VE: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol *9*: 629-635, 2008.

13 Tan BH, Birdsell LA, Martin L, Baracos VE and Fearon KC: Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res *15*: 6973-6979, 2009.

14 van Vledder MG, Levolger S, Ayez N, Verhoef C, TranTC and Ijzermans JN: Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg *99*: 550-557, 2012.

15 Itoh S, Shirabe K, Matsumoto Y, Yoshiya S, Muto J, Harimoto N, Yamashita Y-i, Ikegami T, Yoshizuimi T, Nishie A and Maehara Y: Effect of body composition on outcomes after hepatic resection for hepatocellular carcinoma. Ann Surg Oncol *21*: 3063-3068, 2014.

16 Kvist H, Chowdhury B, Sjöström L, Tylén U and Cederblad A: Adipose tissue volume determination in males by computed tomography and 40 K. Int J Obes *12*: 249-266, 1988.
17 Yoshizumi T, Nakamura T, Yamane M, Islam AH, Menju M, Yamasaki K, Arai T, Kotani K, Funahashi T, Yamashita S and Matsuzawa Y: Abdominal fat: standardized technique for measurement at CT. Radiology *211*: 283-286, 1999.
18 Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y, Nishie A and Yamanaka T: Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg *100*: 1523-1530, 2013.
19 Yoshizimi T, Shirabe K, Nakagawara H, Ikegami T, Harimoto N, Toshima T, Yamashita Y, Ikeda T, Soejima Y and Maehara Y: Skeletal muscle area correlates with body surface area in healthy adults. Hepatol Res *44*: 313-318, 2014.
20 Ikegami T, Bekki Y, Imai D, Yoshizimi T, Ninomiya M, Hayashi H, Yamashita Y-i, Uchiyama H, Shirabe K and Maehara Y: Clinical outcomes of living donor liver transplantation for patients 65 years old or older with preserved performance status. Liver Transpl *20*: 408-415, 2014.
21 Soejima Y, Shirabe K, Taketomi A, Yoshizumi T, Uchiyama H, Ikegami T, Ninomiya M, harada N, Ijichi H and Maehara Y: Left lobe living donor liver transplantation in adults. Am J Transplant *12*: 1877-1885, 2012.
22 Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, Holcombe SA, Wang SC, Segev DL and Sonnenday CJ: Sarcopenia and mortality after liver transplantation. J Am Coll Surg *211*: 271-278, 2010.
23 Masuda T, Shirabe K, Ikegami T, Harimoto N, Yoshizumi T, Soejima Y, Uchiyama H, Ikeda T, Baba H and Maehara Y: Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl *20*: 401-407, 2014.
24 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing *39*: 412-423, 2010.
25 Kashihara H, Lee JS, Kawakubo K, Tamura M and Akabayashi A: Criteria of waist circumference according to computed tomography- measured visceral fat area and the clustering of cardiovascular risk factors. Circ J *73*: 1881-1886, 2009.
26 Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, Kim KW, Lim JY, Park KS and Jang HC: Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care *33*: 1652-1654, 2010.
27 Wang X, Hu Z, Hu J, Du J and Mitch WE: Insulin resistance accelerates muscle protein degradation: activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology *147*: 4160-4168, 2006.
28 Shoelson SE, Herrero L and Naaz A: Obesity, inflammation, and insulin resistance. Gastroenterology *132*: 2169-2180, 2007.
29 Lutz CT and Quinn LS: Sarcopenia, obesity, and natural killer cell immune senescence in aging: altered cytokine levels as a common mechanism. Aging (Albany NY) *4*: 535-546, 2012.

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