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ORIGINAL ARTICLE

Effect of pre-transplant sarcopenia on the estimation of standard liver volume in living-donor liver transplant candidates: risk factor for post-transplant small-for-size syndrome? A retrospective study

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SUMMARY

The aim of the present study was to investigate whether LT candidates with sarcopenia are at an increased risk of receiving an inappropriate standard liver volume (SLV) estimation by standard body weight (BW)-derived SLV formula. Non-BW-SLV estimation formulas were tested in 262 LDLT donors and compared to a standard BW-SLV formula. The anthropometric parameters used were the thoracic width (TW-SLV) and thoracoabdominal circumference (TAC-SLV). Subsequently, sarcopenic and non-sarcopenic LDLT candidates (total, 217 patients) were compared in terms of estimated BW-SLV (routine method) and non-BW-SLV. In donors, TW-SLV showed comparable concordance with CT scan measured total liver volume as BW-SLV. The performance of TAC-SLV was low. In recipients, the prevalence of pre-LT sarcopenia was 30.4%. Sarcopenic patients were attributed a significantly lower BW-SLV than non-sarcopenic (sarcopenia vs no-sarcopenia, 1063.8 ml [1004.1–1118.4] vs. 1220.7 ml [1115.0–1306.6], $P < 0.001$), despite comparable TW-SLV, age, body height, and gender prevalence. As a result, sarcopenic patients received a graft with a statistically lower weight at organ procurement and developed more frequently a small-for-size syndrome (SFSS) according to the Dahm *et al.* (27.7% vs. 6.8%, $P < 0.01$) and Kyushu (28.7% vs. 9.2%, $P < 0.01$) definition. Therefore, In sarcopenic patients, BW-SLV formulas are affected by an high risk of SLV underestimation, thus exposing them to an increased risk of post-LT SFSS.

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Key words
living-donor liver transplantation, sarcopenia, skeletal muscle mass index, small-for-size syndrome, standard liver volume, thoracic width

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Introduction

In living-donor liver transplantation (LDLT), the measurement of the standard liver volume (SLV) is of pivotal importance since it represents the main criteria for graft selection [1]. A small-for-size graft may result in prolonged cholestasis, ascites, coagulopathy, and encephalopathy, while a large-for-size graft is associated

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with an increased risk of vascular complications, immunological impairments, and respiratory failure [1]. In recipients, the direct measurement of SLV on cross-sectional imaging cannot be performed since the liver has undergone cirrhotic degeneration. Therefore, mathematical estimation is needed to determine the graft volume required for transplantation to meet the metabolic and biosynthetic demand of the recipient. The equations most commonly used in clinical practice and validated in healthy individuals are body weight (BW)-based, either directly or indirectly by the body surface area (BSA) [2]. However, end-stage liver disease (ESLD) is complicated by a significant modification of the body mass composition with muscle mass loss, peripheral edema, and ascites, making the BW an unreliable anthropometric parameter for this patient category [1,3]. The confounding effect of ascites may at least partially be controlled by BW measurement after paracentesis or by quantitative ascites estimation with the conventional five-point method on computed tomography (CT) scan [4–6]. Conversely, the impact on the BW of the muscle mass loss is less predictable, considering the possible association between sarcopenia and even obesity. Recently, new equations not based on BW/BSA have been developed demonstrating good reliability for SLV estimation [1,3].

The new parameters comprise the thoracic width (TW) [3] at the level of the costophrenic angle and the thoracoabdominal circumference (TAC) [1] at the level of the confluence of the hepatic veins. Thus, the aim of the present study was to retrospectively investigate whether LT candidates with sarcopenia were at an increased risk of receiving an inappropriate SLV estimation by standard BW-based equations, compared to estimations by non-BW-based equations.

Methods

Computed tomography scan measurements

Computed tomography images were analyzed with SYNAPSE VINCENT (FUJIFILM, Tokyo, Japan). The total liver volume (TLV) in donors was measured using three-dimensional reconstruction as described elsewhere [7]. TW was defined and measured as the distance between the left and right costophrenic angle on a frontal image, as described elsewhere [3]. The TW-based formula for SLV estimation according to Kokudo *et al.* [3] was the following:

$$\mathrm{TW-SLV} = 203.3 - (3.61 * \mathrm{age}) + (58.7 * \mathrm{TW}) - (463.7 * \mathrm{race}\,[1 = \mathrm{Asian}, 0 = \mathrm{Caucasian}])$$

TAC was defined and measured as the circumference taken along the pleural surface at the level of the confluence of the hepatic veins on a transverse image, as described elsewhere [1]. The TAC-based formula for SLV estimation according to Shaw *et al.* [1] was the following:

$$\mathrm{TAC-SLV} = (\mathrm{TAC} * 3.5816) - (\mathrm{Age} * 3.9844) - (\mathrm{Sex} * 109.7386) - (934.5949)$$

To evaluate the presence and severity of sarcopenia, the skeletal muscle index at the lower end plate of the L3 body (L3-SMI) was used, as previously reported [8]. The L3 SMI was expressed as cross-sectional muscle area/height^2, and the cutoff for the diagnosis of low muscle mass was L3-SMI < 42 cm^2/m^2 for men and L3-SMI < 38 cm^2/m^2 for women, as determined by the Japanese Society of Hepatology guidelines [9]. Accordingly, two study groups were created as follows: sarcopenia group vs no-sarcopenia group.

Patient characteristics

From January 2002 to February 2019, a total of 262 patients underwent LDLT at the Nagasaki University Hospital. To confirm the reliability of TW-SLV and TAC-SLV formulas, a preliminary SLV calculation and confront with TLV was performed in the donors. BW-SLV estimation was based on the Urata *et al.* formula [10] as routinely used in the clinical setting of our Department:

$$\mathrm{BW-SLV} = (706.2 * \mathrm{body\,surface\,area}) + 2.4,$$

where the body surface area (BSA) was calculated using the Dubois formula = BW(kg)$^{0.4253}$*height (cm)$^{0.725}$*0.007184.

Among recipients, pediatric and re-transplantation cases as well as patients with a CT scan over 1 month before LT were excluded. The recipient's BW was measured on the day before LT, and it was corrected by subtracting the kg/l of ascites drained intraoperatively on opening the abdomen at LDLT. Significant ascites at LT was defined in presence of ascites volumes larger than 1000 ml at LDLT. Splenectomy for portal vein pressure modulation was not performed in any case at LT. The graft selection policy was based on the following criteria [11]: An extended left lobe graft was the first option and was selected if the estimated graft volume (GV)-to-

recipient's SLV was over 30%; if GV/SLV was below 30%, a right lobe graft was chosen if that the donor future liver remnant was over 35%; otherwise, a right posterior segment was considered if GV/SLV was over 30%.

To investigate the prevalence of small-for-size syndrome (SFSS) after LT, the two most frequently reported definitions were used [12]:

1. Dahm *et al.* [13] definition: presence of two of the following on 3 consecutive days after exclusion of any vascular or biliary complication as well as any infection or episode of rejection: bilirubin >100 μmol/l (5.85 mg/dl), international normalized ratio (INR) > 2, encephalopathy grade 3 or 4, during the first postoperative week;
2. Kyushu [14] definition: presence of both total bilirubin >10 mg/dl at postoperative day 14 without any other definitive cause for cholestasis and a daily production of ascites of >1000 ml at postoperative day (POD) 14, or > 500 ml at POD 28.

The following postoperative complications within POD 14 were considered and compared between the two study groups:

1. Acute cellular rejection: biopsy proven, treated with steroid pulse.
2. Blood stream infection: hemoculture proven.
3. Infected ascites: surgical drain liquid with positive culture (no cases of intra-abdominal abscess were recorded).
4. Need of continuous hemodiafiltration (CHDF): decided according to serum creatinine, blood urea nitrogen, potassium serum levels, and urinary output.
5. Major bleeding: intraoperative poorly controlled bleeding requiring intra-abdominal packing or continuous postoperative bleeding causing hemodynamic instability.
6. Vascular complications: stenosis or thrombosis of portal vein, hepatic artery or hepatic vein, splenic vein steal, managed with reoperation on interventional radiology procedures.
7. Biliary complication: biliary leak or stricture, managed either conservatively or with reoperation.
8. Re-laparotomy: urgent or planned reoperation for any underlying cause.

The present study was approved by the local Institutional Review Board.

Statistical analysis

Categorical variables were expressed as frequencies and percentage, while continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range IQR], as appropriate. In donor analysis, the concordance between TLV and BW-SLV, TW-SLV, and TAC-SLV, respectively, was explored using the Lin's concordance correlation coefficient and the Bland–Altman agreement analysis. For Bland–Altman analysis, the $\log_{10}$ values of TLV, BW-SLV, TW-SLV, and TAC-SLV were used because a relationship between difference and magnitude of liver volumes was noted [15]. In recipient analysis, the comparison between sarcopenia and no-sarcopenia group was performed with chi-square or Fisher's exact test for categorical variables and Student's t test or Mann–Whitney test for continuous variables.

Overall survival (OS) was defined as the time (expressed as months) from LT to either death or to the last follow-up visit. Cox regression was used to estimate the prognostic value of pre-LT sarcopenia and SFSS for OS, after the assumption of the proportional hazard was verified. The proportional hazard assumption was tested using the Schoenfeld residual test. Statistical significance was accepted at $P < 0.05$.

Results

SLV assessment in donors

The median donor age was 38 [29–51] years with a male-to-female ratio of 146:116 and a median BMI of 22.3 [20.5–23.8]. The median TLV was 1188.3 [1055.6–1354.5] ml.

The BW-SLV and TW-SLV showed a comparably moderate-high concordance with the TLV measured at predonation CT scan with a rho value of 0.68 and 0.62, respectively (Figure 1) (Table 1). In the Bland–Altman plot analysis (Figure 2), despite the logarithmic transformation of the liver volume values, the BW formula tended to overestimate SLV for small liver volumes and to underestimate for larger ones. Such trend was not evident for TW-SLV. Overall, the BW-SLV and TW-SLV estimations were 0.97 [0.78–1.20] and 0.93 [0.73–1.18] times the TLV measure, respectively (Table 1). TAC-SLV showed a low performance (rho 0.35), with significant overestimation of TLV that increased for smaller liver volumes. In 95% of the cases, TAC-SLV value was between 0.96 and 1.62 times the TLV measure. Thus, it was decided not to use TAC-SLV in the subsequent analysis in the recipients.

SLV assessment in recipients and SFSS development after LT

Two hundred and seventeen recipients were included in the study. Their demographic and clinical

Transplant International 2020; 33: 1282–1290

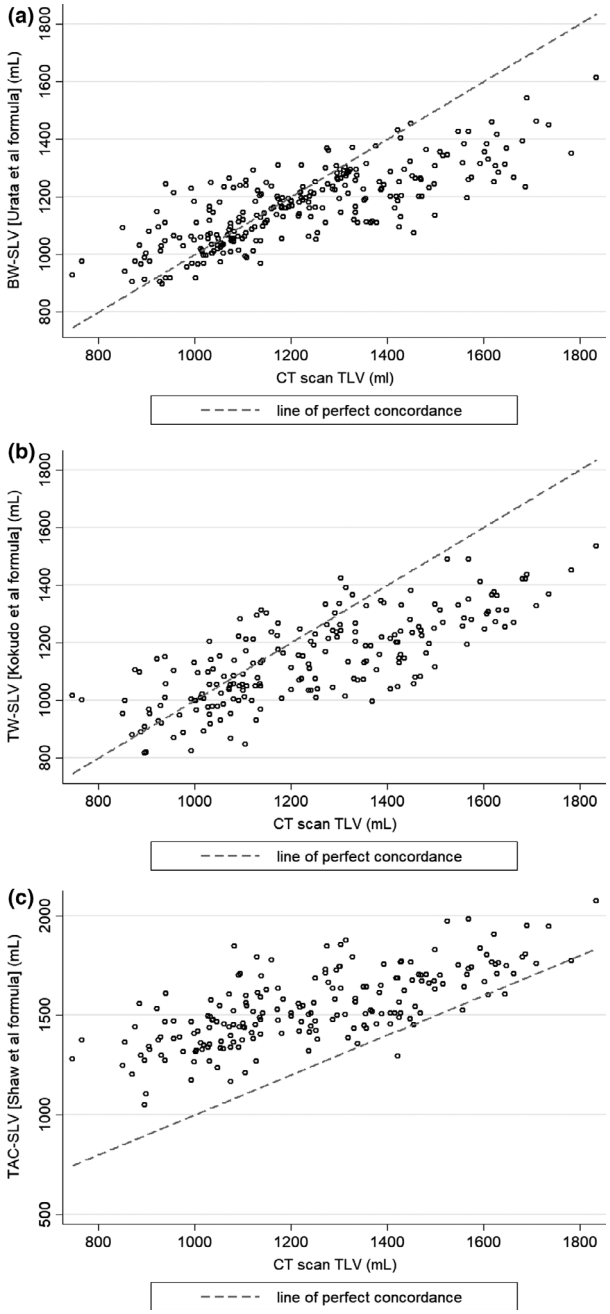

Figure 1 Graphic representation of the concordance between CT scan TLV and BW-SLV (a), TW-SLV (b), and TAC-SLV (c), respectively, in LDLT donors. CT, computed tomography; TW, thoracic width; TAC, thoracoabdominal circumference; TLV, total liver volume; SLV, standard liver volume.

characteristics are summarized in Table 2. The prevalence of pre-transplant sarcopenia was 30.4%, and the affected patients showed a significantly lower BW, BMI, and BSA, while the body height, age, and sex distribution were comparable. The prevalence of significant ascites on opening the abdomen at LT and

Table 1. Concordance analysis between CT scan TLV and BW-SLV, TW-SLV, and TAC-SLV, respectively, in donors of LDLT.

		Concordance analysis			Agreement analysis*
CT scan TLV (ml)	1188.4 [1055.6–1354.5]	Rho value	95% confidence interval	Mean ratio between SLV estimation and CT scan TLV	95% agreement interval
BW-SLV (mL) [Urata *et al.* formula]	1167.6 [1061.7–1258.2]	0.670	0.619–0.721	0.97	0.78–1.20
TW-SLV (mL) [Kokudo *et al.* formula]	1138.7 [1035.2–1251.0]	0.615	0.537–0.673	0.93	0.73–1.18
TAC-SLV (mL) [Shaw *et al.* formula]	1511.0 [1410.8–1676.8]	0.346	0.284–0.408	1.25	0.96–1.62

BW, body weight; CT, computed tomography; LDLT, living-donor liver transplantation; SLV, standard liver volume; TAC, thoracoabdominal circumference; TLV, total liver volume; TW, thoracic width.
*The values reported were re-transformed taking the anti-log.

Table 2. Demographic and clinical data of LDLT candidates.

	Total (n = 217)	No-sarcopenia group (n = 151)	Sarcopenia group (n = 66)	P-value
Age (years)	57 [52–62]	57 [52-63]	57 [48-62]	0.268
Sex (M:F)	123:94	88:63	35:31	0.473
Body weight (kg)	61.9 [52.4–72.9]	67.4 [58.8-75.4]	51.9 [48.5-58]	**<0.001**
Body weight corrected for ascites (kg)	60.9 [50.8–72.2]	67.3 [57.9–74.4]	49.9 [46.6–53.2]	**<0.001**
Significant ascites at LT (%)	75 (39.6%)	39 (25.8%)	36 (54.5%)	**<0.001**
Pre-LT renal replacement therapy (%)	15 (6.9%)	8 (5.3%)	7 (10.6%)	0.156
Body height (cm)	162 [154–169]	163 [155–170]	161 [151–168]	0.132
BMI (kg/m^2)	23.8 [24.1–26.6]	25.3 [22.6–27.7]	20.7 [18.7–22.5]	**<0.001**
BSA (m^2)	1.64 [1.49–1.80]	1.72 [1.57–1.84]	1.50 [1.42–1.58]	**<0.001**
Pre-LT SMI (cm^2/m^2)				
Men	47.6 [41.9–55.8]	51.8 [47.3–58.1]	39.9 [35.2–41.1]	**<0.001**
Women	41.6 [36.7–46.6]	44.5 [41.5–48.9]	34.5 [32.7–36.3]	**<0.001**
MELD	15 [12–22]	15 [11–20]	19 [14–25]	**0.002**
Pre-transplant total bilirubin (mg/dl)	3.2 [1.6–6.7]	3 [1.6–4.9]	4.6 [1.6–9.8]	0.128
Pre-transplant PT-INR	1.45 [1.28–1.75]	1.44 [1.24–1.77]	1.49 [1.31–1.66]	0.471
HCV infection (%)	78 (35.9%)	59 (39.0%)	19 (28.7%)	0.146
HCC diagnosis (%)	89 (41.0%)	68 (45.0%)	21 (31.8%)	0.069
Pre-transplant ICU admission (%)	15 (6.9%)	10 (6.6%)	5 (7.5%)	0.797
BW-SLV (ml)	1162.6 [1060.4–1276.5]	1220.7 [1115.0–1306.6]	1063.8 [1004.1–1118.4]	**<0.001**
TW-SLV (ml)	1145.4 [1041.5–1236.1]	1160.3 [1019.4–1263.7]	1126.6 [1063.4–1194.9]	0.202
GV (ml)	515 [435–628]	533 [448–655]	485 [417–573]	**0.008**
Graft weight (g)	454 [380–565]	472 [400–603]	429 [353–532]	**0.020**
GV/SLV*	44.5% [37.2–53.4]	44.5% [37.2–52.8]	44.5% [37.2–53.7]	0.833
GV/SLV* <30% (%)	6 (2.76%)	4 (2.65%)	2 (3.17%)	>0.99
Graft type				**0.02**
Right lobe	69 (31.8%)	55 (36.4%)	14 (21.2%)	
Right posterior sector	10 (4.6%)	9 (5.9%)	1 (1.5%)	
Extended left lobe	138 (63.6%)	87 (57.7%)	51 (77.3%)	
Donor age (years)	39 [30–53]	38 [31–53]	39 [30–50]	0.868

Bold indicates statistical significance values.

BMI, body mass index; BSA, body surface area; BW, body weight; TW, thoracic width; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; PT-INR, prothrombin time international normalized ratio; SLV, standard liver volume; SMI, skeletal muscle mass index.

*The SLV estimation was calculated based on the Urata et al formula, using the candidate BW not corrected for ascites, as routinely performed at our Department.

the MELD score value were significantly higher in sarcopenic patients. The prevalence of HCC diagnosis was lower at nearly significant level. Conversely, the prevalence of HCV infection and pre-transplant admission to intensive care unit were homogeneous between the groups.

The TW-SLV estimation showed no statistically significant difference between sarcopenic and non-sarcopenic patients. However when the BW-SLV formula was used, sarcopenic patients were attributed a significantly lower SLV value, by 13% of the estimated SLV in the no-sarcopenia group (Table 2). A significant underestimation remained even when the BW was not corrected for the ascites volume (BW-SLV - sarcopenia group versus no-sarcopenia group, 1092.4 ml [1015.4–1140.9] vs. 1224.1 ml [1116.6–1309.8], $P < 0.001$).

Pre-LT graft selection policy did not differ between sarcopenic and non-sarcopenic LDLT candidates (Table 3). As a matter of fact, the median donor age, the graft volume-to-SLV ratio (GVSLV), and the prevalence of GVSLV < 30% cases were comparable between the study groups. Nonetheless, the estimated GV on pre-donation CT scan volumetry and the actual graft weight (GW) at procurement were significantly lower for sarcopenic patients. As a result, during the postoperative course, a significantly higher prevalence of SFSS, according to both the definitions used, was recorded in the sarcopenia group compared to no-sarcopenia group

Table 3. Postoperative trend of liver graft function and prevalence of SFSS.

	Total (n = 215)	No-sarcopenia group (n = 150)	Sarcopenia group (n = 65)	P-value
Acute cellular rejection episode*	13 (5.9%)	10 (6.6%)	3 (4.5%)	0.758
Blood stream infection*	16 (7.4%)	11 (7.3%)	5 (7.5%)	0.971
Infected ascites*	27 (12.4%)	18 (11.9%)	9 (13.6%)	0.764
Need of continuous hemodiafiltration (CHDF)*	30 (13.8%)	19 (12.6%)	11 (16.6%)	0.456
Re-laparotomy*	45 (20.7%)	32 (21.2%)	13 (19.7%)	0.750
Major bleeding*	20 (9.2%)	14 (9.3%)	6 (9.1%)	0.863
Vascular complications*	18 (8.3%)	12 (7.9%)	6 (9.1%)	0.811
Biliary complications*	2 (0.9%)	1 (0.6%)	1 (1.5%)	0.517
Clavien–Dindo classification grade ≥ 3*	52 (23.9%)	37 (24.5%)	15 (22.7%)	0.627
Peak bilirubin serum level, within POD 7 (mg/dL)	8.1 [5.1–11.1]	6.7 [5.0–10.8]	9.3 [6.1–11.6]	**0.041**
Peak PT-INR, within POD 7	2.02 [1.57–2.59]	2 [1.57–2.56]	2.35 [1.6–2.75]	0.536
Significant ascites on POD 7†	97 (45.3%)	57 (38.5%)	40 (60.6%)	**0.003**
Dahm-SFSS [13] (%)	29 (13.7%)	10 (6.8%)	18 (27.7%)	**<0.001**
Bilirubin serum level >10mg/ml on POD 14	63 (29.3%)	36 (24.1%)	27 (40.9%)	**0.013**
Significant ascites on POD 14†	92 (42.6%)	58 (38.6%)	34 (51.5%)	0.071
Kyushu-SFSS [14] (%)	33 (15.2%)	14 (9.33%)	19 (29.2%)	**<0.001**

Bold indicates statistical significance values.

BMI, body mass index; BSA, body surface area; BW, body weight; TW, thoracic width; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; PT-INR, prothrombin time international normalized ratio; SLV, standard liver volume; SMI, skeletal muscle mass index.

*Within POD 14.

†Significant ascites defined as ascites >1000 ml.

(sarcopenia vs no-sarcopenia, Dahm-SFSS: 27.7% vs. 6.8%, $P < 0.01$; Kyushu-SFSS: 28.7% vs. 9.2%, $P < 0.01$). Two patients died within POD 14: one sarcopenic patient (1.51%), due to graft failure for suspected rejection, and one non-sarcopenic (0.66%) due to massive bleeding. The prevalence of the other investigated complications within POD 14 was comparable between the two study groups (Table 3). The patient overall survival at 1, 3, and 5 years was 81.2%, 75.2%, and 69.1%, respectively. In line with our previous results [8], pre-LT sarcopenia was not found as a significant prognostic factor for post-LT patient's survival (HR 1.103, 95% CI 0.663–1.834, $P = 0.705$), while SFSS was identified as a significant risk factor for mortality (Dahm-SFSS: HR 2.725, 95% CI 1.551–4.788, $P < 0.001$, Kyushu-SFSS: HR 3.135, 95% CI 1.855–5.296, $P < 0.001$). Thirty-two patients developed a graft failure at a median follow-up time of 4.7 months [1.3–11.6]. Kyushu-SFSS was identified as a significant predictor of graft failure (HR 3.686, 95% CI 1.773–7.663, $P < 0.001$) while Dahm-SFSS did not (HR 2.061, 95% CI .845-5.027, $P = 0.112$). Pre-LT sarcopenia was not identified as a significant risk factor (HR 0.745, 95% CI 0.335–1.660, $P = 0.473$).

Discussion

Pre-transplant sarcopenia has been extensively recognized as a severe negative prognostic factor for LT outcome. It has been associated with longer ICU stay, longer hospitalization, increased postoperative complications, and overall increased LT morbidity and mortality [9]. The underlying pathogenesis is complex and multifactorial, comprising immunologic, metabolic, endocrine, and inflammatory factors. It has been demonstrated that sarcopenic patients have an increased risk of sepsis and infections after LT [9,16] and liver regeneration may be impaired due to the insufficient availability of energy resources and metabolic substrates [17]. Moreover, muscle mass loss may significantly compromise the respiratory function, increasing the risk of post-transplant respiratory failure [18], and it may be associated with an increased risk of left ventricular systolic dysfunction [19]. Nonetheless, several other unknown pathogenic mechanisms may exist to determine the increased risk of poor LT outcome associated with pre-LT sarcopenia. In the present study, it was demonstrated that sarcopenia is associated with a significant underestimation of the SLV when calculated with

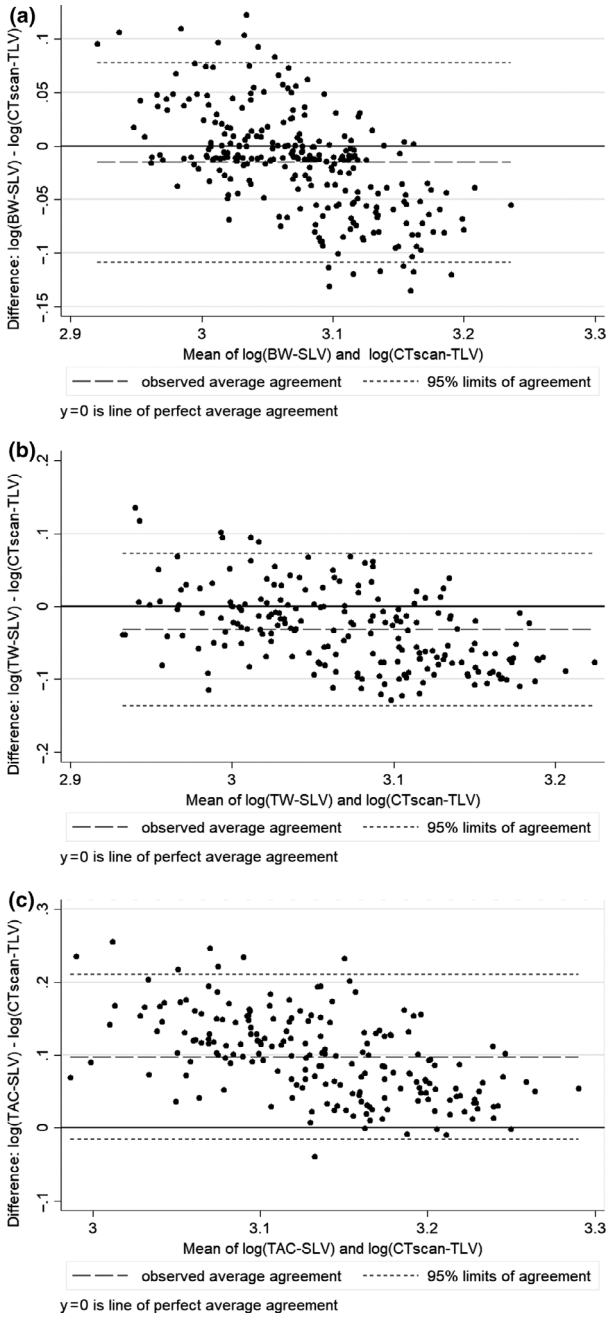

Figure 2 Bland–Altman agreement plots analysis of $\log_{10}$ values of CT scan TLV and BW-SLV (a), TW-SLV (b), and TAC-SLV (c), respectively, in LDLT donors. CT, computed tomography; TW, thoracic width; TAC, thoracoabdominal circumference; TLV, total liver volume; SLV, standard liver volume.

the standard BW-derived formula. Such effect might be masked by refractory ascites which is frequently associated with sarcopenia [20] and does inappropriately increase the measured BW. However, in the present study, sarcopenic patients were attributed a significantly underestimated SLV even when the BW was not corrected for the ascites volume. All these aspects support the suspicion that BW-SLV may be an unreliable parameter in cirrhotic patients. TW-SLV estimation according to the Kokudo *et al*. [3] formula showed good concordance with the TLV measured in donors, although a trend toward underestimation for larger TLV was noted. Conversely, TAC-SLV did not perform well, with a trend of significant TLV overestimation, probably due to ethnicity-related anthropometric differences between the study population used to create the formula [1] and the present one.

To the best of our knowledge, this is the first time that the cirrhosis-related changes of body mass composition are evaluated for their impact on SLV estimation. We focused specifically on pre-LT sarcopenia because it represents one of the most impactful features of pathologic alteration of the body mass composition caused by cirrhosis. Moreover, although it is evident that sarcopenia causes a significant BW decrease, it currently appears difficult to quantify the ideal BW associated with an appropriate muscle mass in sarcopenic patients. This is particularly evident when considering that obesity and fluid retention states can frequently coexist with sarcopenia [20,21]. The critical aspect of SLV estimation is that the related formulas are usually developed and validated in LDLT donors who are healthy, relatively young, lean, with normal muscle mass and no pathologic fluid retention. However, we currently do not know whether these formulas perform equally well when used in elderly, obese, sarcopenic, or severely edematous patients, as LDLT candidates generally are. The present investigation actually showed that BW-based SLV formula may be critically unreliable and the direct clinical implication of such finding was an increased risk of SFSS after LT. This is a new finding. Whether the SFSS in sarcopenic recipients is caused by a too small graft for the patient's anthropometric size or for the specific patient's metabolic status, it is an aspect that will require further studies. In liver resection setting, it has been already shown that sarcopenic patients require a greater future liver remnant as their liver functional reserve is significantly lower [22,23]. Under this perspective, the graft selection should possibly not be based only on the SLV but should ideally be individualized according to the severity of the pre-transplant clinical condition. For example, Marubashi *et al*. [24] have proposed a formula to estimate the minimum graft size to control the risk of small-for-size–associated graft loss, which is based not only on SLV but also on MELD score.

This study presents several limitations: (i) The investigation did not account for the presence of fluid

retention states which may act as confounders in the BW analysis; (ii) TW, as anthropometric parameter, may be equally influenced by the presence of sarcopenia; indeed, it has been demonstrated that sarcopenia is associated with a respiratory dysfunction [17]; and moreover, in donors, TW-SLV performance in estimating the TLV was lower than BW-SLV; (iii) the study population comprised just Japanese patients, and thus, the results may not apply for populations of other ethnicities.

Conclusions

Graft volume selection is a critical step in LDLT and currently mainly depends on the recipient's SLV estimation as well as on the donor's availability and characteristics. Sarcopenic patients were attributed a significantly lower SLV than non-sarcopenic when SLV was calculated with BW-derived formula, despite comparable age, body height, and gender prevalence. Conversely, SLV calculated using thoracic width as anthropometric measure did not appear to be affected by the pathologic changes of body mass composition associated with end-stage liver disease. As a result, sarcopenic patients were associated with an increased risk of SFSS after LT. New formula for SLV estimation or quantification of the appropriate graft size for sarcopenic LDLT candidates should be investigated in the future.

Authorship

RP, MH, UB, and SE: designed the study. RP, MH, SO, TK, AS, TA, TH, TH, and FP: collected the data. RP and MI: performed the statistical analysis. RP, UB, and MH: wrote the paper. AR and SE: supervised the research and reviewed the paper.

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Conflicts of interest

The authors have declared no conflicts of interest.

REFERENCES

1. Shaw BI, Burdine LJ, Braun HJ, Ascher NL, Roberts JP. A formula to calculate standard liver volume using thoracoabdominal circumference. *Transplant Direct* 2017; **3**: e225.
2. Um EH, Hwang S, Song GW, *et al.* Calculation of standard liver volume in Korean adults with analysis of confounding variables. *Korean J Hepatobiliary Pancreat Surg* 2015; **19**: 133.
3. Kokudo T, Hasegawa K, Uldry E, *et al.* A new formula for calculating standard liver volume for living donor liver transplantation without using body weight. *J Hepatol* 2015; **63**: 848.
4. Oriuchi N, Nakajima T, Mochiki E, *et al.* A new, accurate and conventional five-point method for quantitative evaluation of ascites using plain computed tomography in cancer patients. *Jpn J Clin Oncol* 2005; **35**: 386.
5. Sakaida I, Okita K. Correlation between changes in bodyweight and changes in ascites volume in liver cirrhosis patients with hepatic edema in short-term diuretic therapy. *Hepatol Res* 2014; **44**: 735.
6. Wang R, Qi X, Guo X. Quantification of ascites based on abdomino-pelvic computed tomography scans for predicting the in-hospital mortality of liver cirrhosis. *Exp Ther Med* 2017; **14**: 5733.
7. Pravisani R, Soyama A, Takatsuki M, *et al.* Impact of the inferior right hepatic veins on right liver lobe regeneration in living-donor liver transplant: 3-dimensional computed tomography scan analyses in donors and recipients. *Exp Clin Transplant* 2019; **17**: 768.
8. Pravisani R, Soyama A, Isola M, *et al.* Chronological changes in skeletal muscle mass following living-donor liver transplantation: an analysis of the predictive factors for long-term post-transplant low muscularity. *Clin Transplant* 2019; **33**: e13495.
9. Nishikawa H, Shiraki M, Hiramatsu A, Moriya K, Hino K, Nishiguchi S. Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): Recommendation from the working group for creation of sarcopenia assessment criteria. *Hepatol Res* 2016; **46**: 951.
10. Urata K, Kawasaki S, Matsunami H, *et al.* Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995; **21**: 1317.
11. Pravisani R, Soyama A, Takatsuki M, *et al.* Relationship between venous drainage patterns and regeneration of segments 5 and 8 in right lobe grafts in adult living-donor liver transplant recipients. *Exp Clin Transplant* 2019; **17**: 529.
12. Riddiough GE, Christophi C, Jones RM, Muralidharan V, Perini MV. A systematic review of small for size syndrome after major hepatectomy and liver transplantation. *HPB (Oxford)* 2019 **22**: 487.
13. Dahm F, Georgiev P, Clavien PA. Small-for-size syndrome after partial liver transplantation: definition, mechanisms of disease and clinical implications. *Am J Transplant* 2005; **5**: 2605.
14. Soejima Y, Taketomi A, Yoshizumi T, *et al.* Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single-center experience of 107 cases. *Am J Transplant* 2006; **6**(pt 1): 1004.
15. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999; **8**: 135.
16. Masuda T, Shirabe K, Ikegami T, *et al.* Sarcopenia is a prognostic factor in

living donor liver transplantation. *Liver Transpl* 2014; **20**: 401.
17. Pravisani R, Soyama A, Ono S, *et al*. Is there any correlation between liver graft regeneration and recipient's pretransplant skeletal muscle mass?—A study in extended left lobe graft living-donor liver transplantation. *HepatoBiliary Surg Nutr* 2020; **9**: 183.
18. Shirai H, Kaido T, Hamaguchi Y, *et al*. Preoperative low muscle mass has a strong negative effect on pulmonary function in patients undergoing living donor liver transplantation. *Nutrition* 2018; **45**: 1.
19. Mathew A, Halegoua-De Marzio D, Reddy S, *et al*. Pre-liver transplant muscle loss is a risk factor for post-liver transplantation left ventricular systolic dysfunction. *Ann Transplant* 2017; **22**: 759.
20. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol* 2016; **65**: 1232.
21. Eslamparast T, Montano-Loza AJ, Raman M, Tandon P. Sarcopenic obesity in cirrhosis-The confluence of 2 prognostic titans. *Liver Int* 2018; **38**: 1706.
22. Imai K, Takai K, Watanabe S, *et al*. Sarcopenia impairs prognosis of patients with hepatocellular carcinoma: the role of liver functional reserve and tumor-related factors in loss of skeletal muscle volume. *Nutrients* 2017; **9**: 1054.
23. Dello SA, Lodewick TM, van Dam RM, *et al*. Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB (Oxford)* 2013; **15**: 165.
24. Marubashi S, Nagano H, Eguchi H, *et al*. Minimum graft size calculated from preoperative recipient status in living donor liver transplantation. *Liver Transpl* 2016; **22**: 599.