Research Article

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A new formula for calculating standard liver volume for living donor liver transplantation without using body weight

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Background & Aims: The standard liver volume (SLV) is widely used in liver surgery, especially for living donor liver transplantation (LDLT). All the reported formulas for SLV use body surface area or body weight, which can be influenced strongly by the general condition of the patient.

Methods: We analyzed the liver volumes of 180 Japanese donor candidates and 160 Swiss patients with normal livers to develop a new formula. The dataset was randomly divided into two subsets, the test and validation sample, stratified by race. The new formula was validated using 50 LDLT recipients.

Results: Without using body weight-related variables, age, thoracic width measured using computed tomography, and race independently predicted the total liver volume (TLV). A new formula: $203.3 - (3.61 \times \text{age}) + (58.7 \times \text{thoracic width}) - (463.7 \times \text{race}\ [1 = \text{Asian}, 0 = \text{Caucasian}])$, most accurately predicted the TLV in the validation dataset as compared with any other formulas. The graft volume for LDLT was correlated with the postoperative prothrombin time, and the graft volume/SLV ratio calculated using the new formula was significantly better correlated with the postoperative prothrombin time than the graft volume/SLV ratio calculated using the other formulas or the graft volume/body weight ratio.

Conclusions: The new formula derived using the age, thoracic width and race predicted both the TLV in the healthy patient group and the SLV in LDLT recipients more accurately than any other previously reported formulas.

Keywords: Standard liver volume; Body surface area; Thoracic width; Living donor liver transplantation.

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Abbreviations: SLV, standard liver volume; LDLT, living donor liver transplantation; TLV, total liver volume; BSA, body surface area; CT, computed tomography; PT, prothrombin time; BMI, body mass index; PT-INR, international normalized ratio of prothrombin time; LOOCV, leave-one-out cross-validation; PRESS, predicted residual sum of squares; ICC, intra-class correlation; GV/BW, graft volume/body weight ratio; GV/SLV, graft volume/standard liver volume ratio; BH, Body height; BW, Body weight.

Introduction

The standard liver volume (SLV) has been widely used in living donor liver transplantation (LDLT) to estimate the required liver volume for the recipient [1–3]. Recently, the use of SLV has been reported as a substitute for the total liver volume (TLV) when estimating the risk of hepatic insufficiency after hepatectomy [4]. These reports underscore the importance of precise SLV estimations before liver surgery, especially for transplantations.

Based on autopsy data, DeLand *et al.* [5] first reported a correlation between body surface area (BSA) and liver volume. Then Urata *et al.* [6] reported a formula for calculating the SLV based on the BSA after an analysis of 96 Japanese children and adult patients using computed tomography (CT) scans to measure the TLV. Since these reports, more than 10 different formulas have been proposed for estimating the SLV [7].

All the reported formulas for SLV use BSA or body weight as a major variable [7]. However, the BSA depends on the body weight, which can be significantly influenced by a patient's condition. When applying the SLV for an LDLT recipient with liver failure, body weight is likely to be strongly influenced by the presence of ascites or edema. In these settings, paracentesis or diuretic administration may artificially decrease the body weight, thereby reducing the required graft volume calculated using formulas based on the BSA. This does not make sense, since the body weight, that is the most physiological and reliable for estimating the required graft volume, is unknown. When introducing the concept of SLV to liver resection for the treatment of malignant diseases, a similar dilemma occurs, as a loss of body weight is a typical symptom of patients with malignant disease or patients who are receiving chemotherapy [8,9]. These conditions highlight the need for a new formula that does not use body weight. Here we report a new formula for calculating the SLV that fulfills this condition and discuss its efficacy in LDLT.

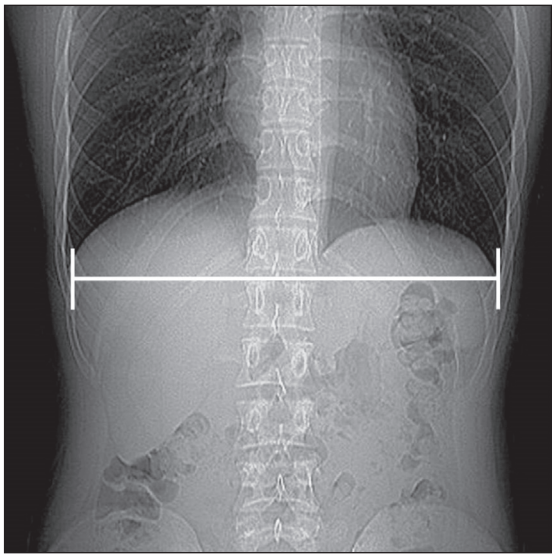

Fig. 1. Measurement of thoracic width using a scout image obtained during a computed tomography scan.

Patients and methods

Data sources

One hundred and eighty donor candidates examined at a tertiary care Japanese hospital between March 2006 and December 2013 and 160 patients who underwent CT for conditions unrelated to hepatobiliary disease at a tertiary care Swiss hospital between January 2001 and April 2014 were included in the analysis. Living donors were selected after considering their age (20–65 years old), blood type, graft size, and liver function. The detailed criteria for donor selection have been described previously [10,11]. Swiss patients who were admitted to the hospital for diseases unrelated to hepatobiliary or malignant diseases, such as appendicitis and diverticulitis, were included in the analysis. Patients with documented hepatic diseases (e.g., cirrhosis, fibrosis, or steatosis) were excluded. The patient age, sex, body height, and body weight were recorded. We also recorded the thoracic width, which was measured using a scout image obtained during a CT scan. All the CT scans were taken at full inspiration. The thoracic width was defined as the distance between the left and right costophrenic angle (Fig. 1). To validate this new formula in LDLT patients, 50 LDLT recipients treated at a tertiary care Japanese hospital between August 2010 and December 2013 were included in the analysis. The identification of the costophrenic angle was difficult in one patient with unilateral massive pleural effusion. The estimated costophrenic angle symmetric to the other side was used in this patient. One case of retransplantation and one case of temporary auxiliary partial orthotopic liver transplantation were excluded.

Assessment of TLV and calculation using previous formulas

Liver volume was measured using contrast-enhanced CT images with the region-growing method software Organs Volume Analysis (Hitachi Medico, Chiba, Japan) for the LDLT donor candidates and Synapse Vincent (Fujifilm Corporation, Tokyo, Japan) for the other analyses. The intrahepatic blood volume was excluded from the measured liver volume. For comparison, we calculated the estimated SLV according to previously reported formulas for adults [5,6,10,12–21]. Using these formulas, the BSA was calculated using the Dubois formula [22] as follows: BSA (m^2) = Body weight $(kg)^{0.425} \times$ Body height $(cm)^{0.725} \times$ 0.007184. For the formulas proposed by Vauthey *et al.* [14] and Yoshizumi *et al.* [15], the Mosteller's formula [23] was adopted: BSA = $\sqrt{}$(Body weight (kg) × Body height (cm)/3600).

Assessment of required graft volume after LDLT

To evaluate the application of the new formula for LDLT, we first tried to identify the variables correlated with the required graft volume of the recipient. Small-for-size syndrome is reportedly associated with a high bilirubin level, a low prothrombin time (PT), and encephalopathy [24]. Therefore, we hypothesized that these factors were likely to be predictors of the required graft volume. Since severe postoperative encephalopathy did not occur in our series, the analyzed variables were the postoperative day of bilirubin recovery (total bilirubin <2.0 mg/dl) and the postoperative day of PT recovery (international normalized ratio of PT [PT-INR] <1.15). Our surgical technique and basic perioperative care have been described previously [25,26]. The institutional criteria for fresh frozen plasma transfusion in LDLT is a PT of less than 30%. Post-transplant CT follow-up was performed at 1 month and at 3–4 months after transplantation.

Statistical analysis

A multiple linear regression analysis was used to predict the TLV. Since thoracic width, body mass index (BMI) and BSA showed high correlations among each other, we chose age, sex, body measures (any of the thoracic width, BMI or BSA), square of each body measure and interaction between race and each body measure to develop the new formula. The dataset was randomly divided into two subsets, the test and validation sample, stratified by race. In a test sample data, leave-one-out cross-validation (LOOCV) method was used to prevent the selected model from over-fitting and to ensure the predictive ability for future observations. The LOOCV was repeated under each model with all combinations of explanatory variables (best subset selection method). The root of the mean predicted residual sum of squares (PRESS) was calculated for each model. The selected model was applied to the validation sample, and the root of the mean PRESS and intra-class correlation (ICC) were calculated. The Spearman rank correlation coefficient was used to estimate the correlations between graft volumes and variables predicting the required liver volume. Categorical variables were analyzed using the X^2 test, and continuous variables were analyzed using the Mann-Whitney U test. All the statistical analyses were two-tailed, and p values less than 0.05 were considered to indicate statistical significance. The SAS software, version 9.3 (SAS Institute Inc., Cary, NC), was used for the multiple linear regression analysis using the LOOCV method and calculating the PRESS and ICC. For other analyses, the JMP 11 software (SAS Institute Inc., Cary, NC) was used.

Results

Differences in patient characteristics between Asian and Caucasian populations

The patient characteristics of the Japanese donor candidates (Asian population) and the Swiss patients (Caucasian population) are shown in Table 1. Significant differences in all the variables were observed between the two groups, with the exception of sex. The difference in age was probably caused by the inclusion criteria (20–65 years old) for the LDLT donor candidates [11]. The other differences imply that the physical frame differs between races, with larger TLVs observed in the Caucasian population. These results led us to include race difference as a possible variable in subsequent analyses.

New formula for estimating liver volume that does not use body weight or BSA

To develop a new formula for the prediction of liver volume, we hypothesized that the liver volume would be correlated with the size of other organs. We initially examined the kidney volume but found that this parameter was not correlated with the liver volume (data not shown). The size of the lung or thoracic cavity was another possible substitute for body weight. Since measurements of the lung or thoracic cavity volume are technically difficult, we instead measured the width of the thoracic cavity using a scout image obtained from a CT scan, as shown in Fig. 1. Since the BMI, BSA and thoracic width were highly correlated with each other, we developed three formulas using one of these body measures through a multiple linear regression analysis, as shown in

Table 1. Comparison of patient characteristics between Asian and Caucasian populations.

	Asian (n = 180)	Caucasian (n = 160)	*p* value
Age (years)*	39.4 (20-65)	56.5 (19-90)	p <0.001
Sex (male/female)	78/102	71/89	p = 0.847
Body weight (kg)	58.5 (38-85)	73.3 (40-105)	p <0.001
Body height (cm)	164 (146-184)	169 (146-189)	p <0.001
Body surface area (m^2)**	1.63 (1.24-2.03)	1.83 (1.37-2.30)	p <0.001
Body mass index (kg/m^2)	21.5 (16.7-34.2)	25.6 (13.7-38.8)	p <0.001
Thoracic width (cm)	25.4 (21.1-30.8)	27.5 (20.8-33.6)	p <0.001
Total liver volume (cm^3)	1092 (667-1629)	1622 (888-2438)	p <0.001

*Mean (Range).
**Dubois formula [22]: Body surface area (m^2) = Body weight $(kg)^{0.425}$ × Body height $(cm)^{0.725}$ × 0.007184.

Table 2. Results of the multiple linear regression analysis performed to predict the total liver volume using each of the body anthropometric measures.

Body measures	Formula	Root of the mean PRESS
Thoracic width	203.3 - 3.61 × age + 58.7 × thoracic width - 463.7 × race	200.5
BSA*	2670.1 - 1.95 × age + 70.8 × sex - 1940.5 × BSA + 761.2 × BSA^2 - 420.1 × race	201.6
BMI	1222.1 - 3.24 × age + 210.7 × sex + 18.8 × BMI - 505.8 × race	218.6

*Dubois formula [22]: BSA (m^2) = Body weight $(kg)^{0.425}$ × Body height $(cm)^{0.725}$ × 0.007184.
Race; 1 = Asian, 0 = Caucasian, Sex; 1 = Male, 0 = Female.
BSA, body surface area, BMI, body mass index, PRESS, predicted residual sum of squares.

Table 2. The new formula using the thoracic width for calculation of the SLV was as follows: SLV (cm^3) = 203.3 − (3.61 × age [years]) + (58.7 × thoracic width [cm]) − (463.7 × race [1 = Asian, 0 = Caucasian]). The calculated roots of the mean PRESS for the thoracic width, BSA and BMI were 200.5, 201.6, and 218.6, respectively, indicating that the formula derived using the thoracic width was well correlated with the TLV, being comparable to the formula derived using the BSA and superior to the formula derived using the BMI.

Comparisons between the new formula and previously reported formulas

We analyzed the differences between the results obtained using other previously reported formulas and the new formula in the validation patients group [5,6,10,12–21]. The new formula derived using the thoracic width showed the lowest root of the mean PRESS (171.8) and the highest ICC (0.87) as compared to any other previously reported formula (Table 3). Next to the new formula, the formula proposed by Vauthey *et al.* [14] predicted the TLV relatively well. These results indicate that the new formula is the most accurate to predict the TLV in the healthy patient group as compared with any other formula.

Thoracic width does not change according to the intra-abdominal or general condition of the patients

To further apply this new formula under various conditions, it was necessary to confirm that the thoracic width does not change according to variations in the patients' intra-abdominal or general conditions, such as the presence of ascites, body edema, or liver volume. LDLT recipients were a suitable subject population for this analysis, since the size of the liver differs significantly before and after transplantation and the presence of ascites or body edema decreases significantly after transplantation. We measured the thoracic width of 20 LDLT recipients before and after transplantation. The median difference was 0.482 cm (range; −0.882 to +1.288). We considered this difference to be negligible and conducted a further analysis in which the patients' intra-abdominal or general conditions were not equivalent.

PT is strongly correlated with graft size in LDLT

The patient characteristics of 50 LDLT recipients are shown in Table 4. To predict the required liver volume in LDLT recipients, we first analyzed the correlation between graft volume and variables related to small-for-size syndrome; i.e., total bilirubin and PT [24]. The correlation between graft volume and the postoperative day of PT recovery ($\rho = -0.462$, p <0.001) were statistically significant (Fig. 2). Therefore, we used the postoperative PT as a predictor of the required graft volume for LDLT recipients in subsequent analyses.

Correlation between the new formula using thoracic width and the postoperative PT of LDLT recipients

The graft volume/standard liver volume ratio (GV/SLV) using Urata's formula and the graft volume/body weight ratio (GV/BW) are widely used for the estimation of the required liver volume [10,24]. Therefore, we compared these two indices to the GV/SLV using the present formula in LDLT recipients. We used the previously reported value of 40% as the cut-off value for GV/SLV and 0.8% as the cut-off value for GV/BW [3,24]. Since Urata's formula generally overestimate the SLV, compared with the new formula (Fig. 3), we divided the patients into three groups as follows: group A, GV/SLV new ⩾40% and GV/SLV Urata ⩾40% (n = 31); group B, GV/SLV new ⩾40% and GV/SLV Urata <40% (n = 7); and group C, GV/SLV new <40% and GV/SLV Urata <40% (n = 12). The postoperative day of PT recovery after LDLT was significantly later in group C (p = 0.034) than in groups A and B (Fig. 4A). Concerning the GV/BW, the GV/SLV calculated using the new formula was also significantly better correlated with the postoperative PT recovery (Fig. 4B). These results indicate that the new formula is better at predicting the required graft volume of LDLT recipients than the GV/SLV of Urata's formula or the GV/BW. Furthermore, formulas based on BSA or body weight generally overestimate the SLV in LDLT recipients, which could lead to errant volumetric restrictions for the donor candidates.

Table 3. Differences between the actual liver volume and standard liver volume calculated using previously reported formulas in the validation patient group.

	Formula for estimating SLV	Root of the mean PRESS	ICC
DeLand [5] (1968)	1020 × BSA - 220	309.2	0.51
Urata [6] (1995)	706.2 × BSA + 2.4	291.3	0.47
Lin [12] (1998)	13 × BH + 12 × BW - 1530	254.9	0.68
Heinemann [13] (1999)	1072.8 × BSA - 345.7	287.3	0.58
Vauthey [14] (2002)§	1267.28 × BSA - 794.41	239.0	0.73
Yoshizumi [15] (2003)§	772 × BSA	251.7	0.60
Yu [16] (2004)	$21.585 \times BW^{0.732} \times BH^{0.225}$	253.2	0.67
Choukèr [17] (2004)	[16-50 years] 452 + 16.34 x BW + 11.85 × age - 166 × sex (1 = female, 0 = male) [51-70 years] 1390 + 15.94 × BW - 12.86 × age	484.5	0.21
Hashimoto [10] (2006)	961.3 × BSA - 404.8	261.0	0.61
Chan [18] (2006)	218 + BW × 12.3 + sex × 51 (0 = female, 1 = male)	393.5	0.27
Yuan [19] (2008)	949.7 × BSA - 247.4 - 48.3 x age factor (1; <40; 2; 41-60; 3; >60)	256.1	0.61
Fu-Gui [20] (2009)	11.508 × BW + 334.024	367.3	0.29
Poovathumkadavil [21] (2010)	12.26 × BW + 555.65	251.2	0.60
Present (2015)	203.3 - 3.61 × age + 58.7 × thoracic width - 463.7 × race (1 = Asian, 0 = Caucasian)	171.8	0.87

§Mosteller's formula [23] was adopted for BSA: $\sqrt{(BW \times BH/3600)}$. In the other formulas, the Dubois formula [22] was adopted for BSA: $BW^{0.425} \times BH^{0.725} \times 0.007184$.
PRESS, predicted residual sum of squares; ICC, intra-class correlation; CT, Computed tomography; BSA, Body surface area; BW, Body weight; BH, Body height; SLV, Standard liver volume.

Table 4. Patient characteristics of the living donor liver transplantation recipients.

	n = 50
Age (years)*	53.2 (18-65)
Sex (male/female)	22/28
Body weight (kg)	60.8 (39.8-105)
Body height (cm)	163 (146-185)
Body surface area (m^2)**	1.65 (1.31-2.23)
Body mass index (kg/m^2)	22.8 (17.2-32.7)
Thoracic width (cm)	26.8 (22.2-31.9)
Model for end-stage liver disease (MELD) score	16.1 (6-38)
Child-Pugh classification B/C	17/33
SLV calculated using Urata's formula (cm^3)	1167 (924-1578)
SLV calculated using present formula (cm^3)	1081 (749-1391)
Graft volume (g)	515 (337-775)
Hospital stay (days)	54.0 (27-183)
Mortality within 90 days after transplantation	None

*Mean (Range).
**Dubois formula [22]: Body surface area (m^2) = Body weight $(kg)^{0.425}$ × Body height $(cm)^{0.725}$ × 0.007184.
SLV, Standard liver volume.

Discussion

The current study revealed that, without using body weight-related variables, age, thoracic width measured using CT, and race (Asian *vs.* Caucasian) were independent predictors of the TLV. A new formula devised using these three variables most accurately predicted the TLV compared with other existing formulas based on body weight or BSA. In pathological settings, this new formula was better at predicting the required graft volume of LDLT recipients compared with the other existing formulas.

Thoracic width was a new variable analyzed in this study. We initially decided to investigate this variable after hypothesizing that the liver volume was likely to be correlated with the volumes of other organs, such as the kidney or lung. Since measurements of the lung volume or the volume of the thoracic cavity are technically difficult, we instead used the thoracic width measured using scout CT images. Other possible variables, such as chest circumference, might be correlated with body weight, BSA, and subsequently the TLV. This issue will require further investigation in a prospective study.

The possibility of differences in liver volume among races has been reported, and the variety of formulas reported by different countries support such a difference [27,28]. The body frame differs significantly between Asian and Caucasian populations [29]. Indeed, all the variables including body weight, body height, BSA, and BMI differed between the Asian and Caucasian populations in this study. Consequently, the TLV also differed significantly (Table 1). These facts led us to include race as a possible variable. In a multiple linear regression analysis, this variable was independently correlated with the TLV. This finding suggests that the formulas used for Eastern and Western populations should differ. The superior predictive power of the new formula for TLV in the validation group as compared to previously reported formulas can be explained by the fact that we added race as a variable for predicting the TLV. Concerning the numerous formulas developed in each country (such as China, Korea, or Germany), the liver volume may differ even for populations with relatively small ethnic differences [7]. Therefore, our formula should be validated in an international database consisting of a large number of patients from several countries.

Age was an independent variable in our patient group, and several studies have reported similar results [14,17,19]. However, most of the proposed formulas do not include age as

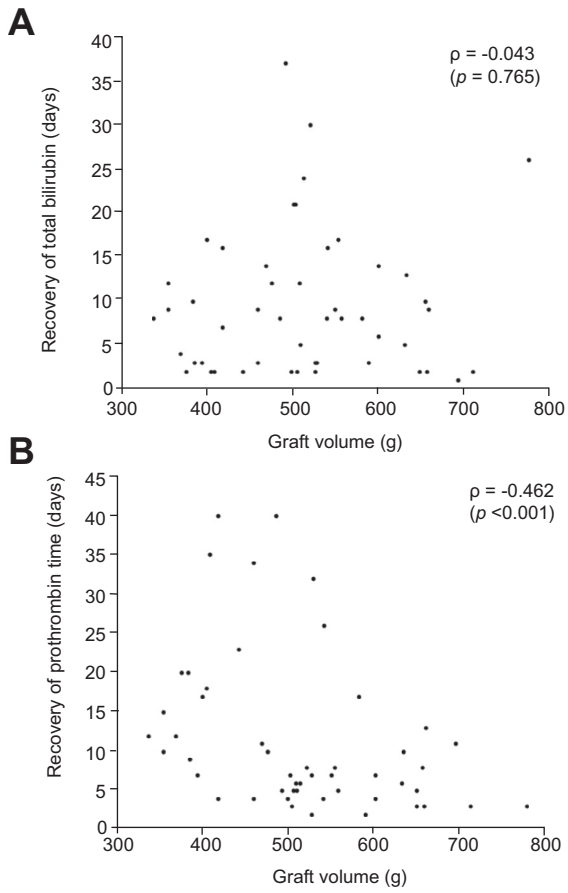

Fig. 2. Scatter plot and correlation with graft volume in living donor liver transplantation recipients. (A) Postoperative day of total bilirubin recovery (<2.0 mg/dl). (B) Postoperative day of prothrombin time recovery (international normalized ratio of prothrombin time [PT-INR] <1.15). ρ: Spearman rank correlation coefficient.

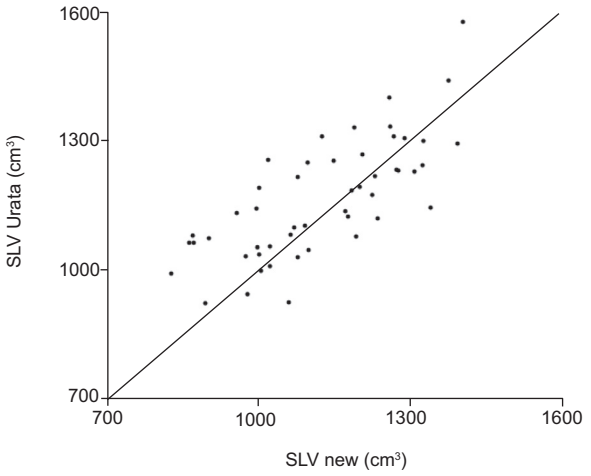

Fig. 3. Scatter plots showing the correlation between standard liver volume calculated using Urata's formula and the present formula in living donor liver transplantation recipients. SLV Urata: standard liver volume calculated using Urata's formula [6], SLVnew: standard liver volume calculated using the present formula.

a predictor of SLV [21]. This situation can probably be explained by the fact that most formulas are based on young, healthy populations. Indeed, if only the Japanese donor candidates were analyzed, age was not a significant variable [10]. Vauthey *et al.* [14] conducted a multicenter analysis and found that age was an independent predictor with a coefficient of −2.26/year, which was similar to our result (−3.61/year). However, they concluded that the effect of this variable was negligible and did not include it in their final formula. Although a coefficient of −3.61/year has only a small effect, if we compare healthy patients in their twenties to patients in their eighties, for example, the difference in the SLV can be as large as 200 cm^3. Since LDLT is usually performed in young adults, this difference does not necessarily need to be considered [25,26]. However, if we apply this formula for liver resection, this difference is not negligible. As a result of recent advances, liver resection has become a reasonably safe treatment, and aggressive surgical resection has been proposed for cases with advanced disease [30–32]. Consequently, the age of patients undergoing liver resection has recently been increasing [33,34]. This situation indicates the emerging need for a formula that includes age in predictions of the SLV [4].

Since small-for-size syndrome is affected by various conditions, including operative procedures, the exact required graft volume of LDLT recipients can be difficult to estimate [24–26]. The TLV of recipients after LDLT cannot be used to estimate the required graft volume because it can be affected by viral infection, and we previously reported that the liver does not regenerate to 100% of the TLV based on an analysis of liver regeneration in LDLT donors [35]. In the present study, we found that the postoperative PT can be a predictor of the required graft volume of LDLT recipients. On the other hand, the postoperative serum bilirubin level, well known as a predictor of postoperative liver failure in patients undergoing liver resection, was not correlated with the graft volume. This is probably due to the fact that the serum bilirubin level after LDLT can also be strongly affected by other factors such as acute rejection, stenosis of the biliary anastomosis and viral hepatitis.

We found that the PT was more strongly correlated with the GV/SLV calculated using the present formula, compared with the GV/SLV calculated using Urata's formula or the GV/BW. As expected, Urata's formula and the criteria based on body weight generally overestimate the required liver volumes of the LDLT recipients. LDLT recipients suffer from ascites or edema leading to an increased body weight; thus, the BSA is generally estimated to be larger, and as a result, the estimated required graft volume calculated using the BSA or body weight is generally larger. These results indicate that the new formula is more strongly correlated with the required graft volume and may expand the volumetric indications of LDLT donors.

Although the postoperative PT was correlated with the graft size, the correlation did not have a high degree of predictive power. This is probably due to the fact that the liver functional reserve after LDLT is dependent on multiple surgical and biological variables that are not measured. However, other than in the case of small-for-size syndrome, we found that the postoperative PT was correlated with the graft volume. Although the correlation does not have a high predictive power, postoperative PT is certainly useful to evaluate the required graft volume in LDLT.

The paradigm shift in the present study is that while body weight is useful for calculating the SLV in healthy populations, it is not necessarily reliable under pathological conditions.

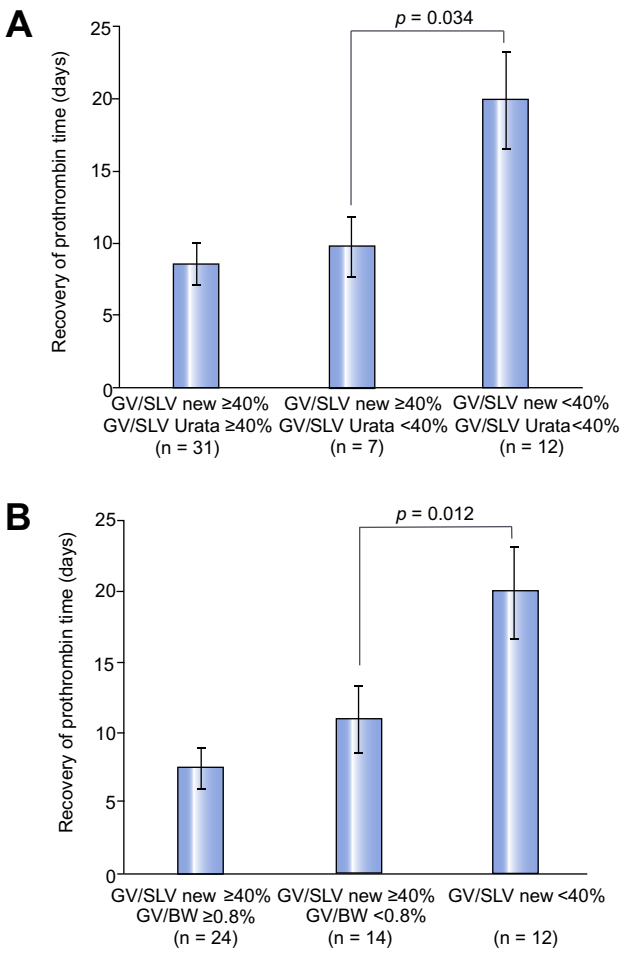

Fig. 4. Postoperative day of prothrombin time recovery (international normalized ratio of prothrombin time [PT-INR] <1.15) after living donor liver transplantation in the patient groups divided according to (A) the graft volume/standard liver volume ratio, and (B) the graft volume/body weight ratio. GV/SLV Urata: graft volume/standard liver volume ratio calculated using Urata's formula [6], GV/SLV new: graft volume/standard liver volume ratio calculated using the present formula, GV/BW: graft volume/ body weight ratio. The error bars show the standard errors of the mean.

Since the formulas for estimating BSA have also been developed based on healthy populations, this new concept may also be applicable to formulas for estimating the BSA [22,23]. Furthermore, the chest circumference is reportedly correlated with body weight in various species, and formulas for predicting BSA differ among species [36,37]. Thus this hypothesis may deserve further investigation.

One of the possible limits of our study is the presence of subclinical steatosis. Liver steatosis reportedly affects the liver volume, but a liver biopsy was not routinely performed in our patient group [38,39]. Liver biopsy itself is associated with a risk of complications and is not feasible in all patients. This issue requires further discussion through an analysis of the SLV in patients who have undergone a liver resection or through an analysis of liver volume in autopsy patients.

Although we showed that the thoracic width does not significantly change with the intra-abdominal condition through an analysis of LDLT recipients, a slight but statistically significant difference was observed. We think that this difference is small and negligible, as was the daily change in body weight. However, we have not evaluated this new formula in patients with large liver tumors or massive bilateral pleural effusions. This issue is one of the limitations of our study and will require further investigation in patients with various conditions.

In conclusion, we have reported a new formula for estimating the SLV based on age, thoracic width, and race. The new formula predicted both the TLV in the healthy patient group and the SLV in LDLT recipients more accurately than any other previously reported formulas. This new formula has the potential to be used worldwide in various settings in the place of existing formulas.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Author contributions

Takashi Kokudo: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript.
Kiyoshi Hasegawa: Study concept and design, Analysis and interpretation of data, Drafting of the manuscript, Critical revision.
Emilie Uldry: Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript.
Junichi Kaneko: Analysis and interpretation of data, Critical revision.
Nobuhisa Akamatsu: Analysis and interpretation of data, Critical revision.
Taku Aoki: Analysis and interpretation of data, Critical revision.
Yoshihiro Sakamoto: Analysis and interpretation of data, Critical revision.
Nicolas Demartines: Analysis and interpretation of data, Critical revision.
Yasuhiko Sugawara: Analysis and interpretation of data, Drafting of the manuscript, Critical revision.
Norihiro Kokudo: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript, Critical revision.
Nermin Halkic: Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript, Critical revision.
Yutaka Matsuyama: Study concept and design, Analysis and interpretation of data, Drafting of the manuscript, Critical revision.

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