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A Formula to Calculate Standard Liver Volume Using Thoracoabdominal Circumference

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Background. With the use of split liver grafts as well as living donor liver transplantation (LDLT) it is imperative to know the minimum graft volume to avoid complications. Most current formulas to predict standard liver volume (SLV) rely on weight-based measures that are likely inaccurate in the setting of cirrhosis. Therefore, we sought to create a formula for estimating SLV without weight-based covariates. **Methods.** LDLT donors underwent computed tomography scan volumetric evaluation of their livers. An optimal formula for calculating SLV using the anthropomorphic measure thoracoabdominal circumference (TAC) was determined using leave-one-out cross-validation. The ability of this formula to correctly predict liver volume was checked against other existing formulas by analysis of variance. The ability of the formula to predict small grafts in LDLT was evaluated by exact logistic regression. **Results.** The optimal formula using TAC was determined to be SLV = (TAC × 3.5816) – (Age × 3.9844) – (Sex × 109.7386) – 934.5949. When compared to historic formulas, the current formula was the only one which was not significantly different than computed tomography determined liver volumes when compared by analysis of variance with Dunnett posttest. When evaluating the ability of the formula to predict small for size syndrome, many (10/16) of the formulas tested had significant results by exact logistic regression, with our formula predicting small for size syndrome with an odds ratio of 7.94 (95% confidence interval, 1.23-91.36; $P = 0.025$). **Conclusion.** We report a formula for calculating SLV that does not rely on weight-based variables that has good ability to predict SLV and identify patients with potentially small grafts.

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With respect to liver transplantation, an ideal liver volume should meet the metabolic demands of the recipient while fitting into the abdominal cavity. Understanding the minimum graft size requirement for a given recipient is critical, as small grafts are associated with multiple complications including small for size syndrome (SFSS). This is especially important in the context of living donor liver transplant (LDLT) as the donor risk has been reported to be higher with right versus left hepatectomy.[1-3]

Donor liver volume is typically estimated using volumetrics from cross sectional imaging such as computed tomography (CT) scan. The volume of the proposed LDLT recipient graft is then estimated by segmentation of the donor liver volume. Because the recipient liver is typically cirrhotic, mathematical estimates are needed to determine the volume of graft required by a given recipient. The majority of equations used to estimate liver volume have been height- and weight-based, using regression equations with recipient parameters such as body mass index or body surface area (BSA).[4-17] Though these calculations have been well validated in specific patient populations, complications associated with liver disease, including obesity, edema, and ascites, often contribute to overestimation of body weight. Some have sought to correct for this by using a measurement of the portal vein to correct the weight-based formula by Urata[18]; however, there may be issues in patients with advanced liver disease and portal vein thrombosis. Recently, Kokudo et al[19] used chest diameter as a single anthropomorphic characteristic to estimate liver volume size, and although race specific, they were able to accurately predict standard liver volume.

The purpose of this study was to use a heterogeneous cohort and cross-sectional imaging to develop a non–weight-based

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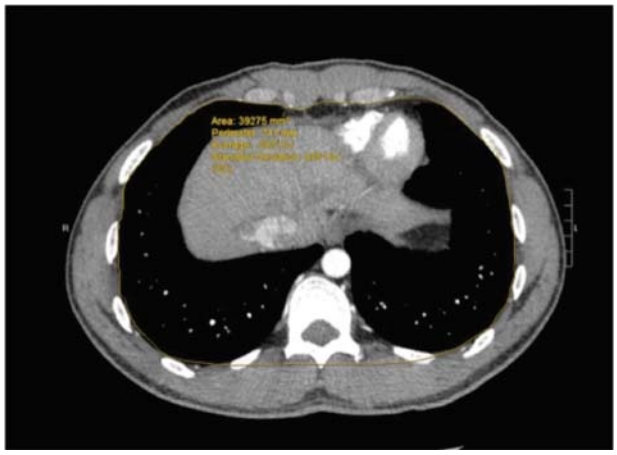

FIGURE 1. Representative CT scan demonstrating measurement of TAC by measuring the circumference of the body at the level of the dome of the liver.

formula to estimate an ideal liver volume for a potential recipient. The cohort population consisted of living liver donors at our institution from January 2003 to September 2016. Once validated, we used the model to predict the minimal necessary liver volume required by our LDLT recipients over the last 2 years (2014–2016) and analyzed patient outcomes after LDLT with reference to this prediction.

MATERIALS AND METHODS

Population and Data Collection

To create the model, we conducted a retrospective chart review of donors involved in adult-to-adult LDLT at our institution between January 2003 and September 2016. All donors had preoperative CT scans with volumetric calculations of liver size (CTLV). Living donors had no medical contraindications to donation, normal liver function tests, and no indication of liver disease on imaging. We measured the thoracoabdominal circumference (TAC) at the level of the confluence of the hepatic veins. Measurements were taken along the pleural surface, using the CT scan, as demonstrated in Figure 1.

For recipients, we evaluated graft function at postoperative days (POD) 7 and 14 (as determined by an International Normalized Ratio [INR] > 1.5 and/or bilirubin >10), length of hospital stay, date of INR normalization, biliary complications requiring IR or operative intervention, need for additional surgery and whether portal inflow modulation was required. Model of End Stage Liver Disease-Sodium (MELD) and transplant indication for recipients was also tallied. Finally, we obtained TAC using the same method as for donors allowing us to estimate the standard liver volume (SLV).

Model Creation

To create a model for prediction of SLV, we used the donors' CTLV as our dependent variable. Independent variables included in model selection were TAC, age, sex, and the interaction of sex and TAC. Linear regression was performed using standard methods. Model goodness of fit was assessed by adjusted R^2 and leave-one-out-cross-validation with calculation of the root mean predicted residual sum of squares (rmPRESS) as previously described.[20] All donor data were used in the creation of the model as there was a relatively smaller number of patients.

Model Comparison

The current model was compared to multiple historical formulas using multiple methods. The distributions of SLV estimates were plotted along with actual CTLV. Values were compared with the CTLV estimations and tested for statistical difference by analysis of variance followed by Dunnett posttest to compare to CTLV. The root mean standard error (RMSE) was also calculated for each equation in comparison to the CTLV. These analyses were repeated using the current formula defined only on a "Training" data set, representing n = 95 (~70%) of the total data and a "Testing" data set of n = 38 (~30%) of the data, redefining coefficients using only the "Training" data set to prevent overfitting.

Prediction of Recipient Outcomes

First, we compared the outcomes of individuals that were classified as having a "Small Graft" by the current (TAC 2017) formula to those with adequate graft volumes (GVs) for certain clinical outcomes. A "Small Graft" was defined as GV/SLV less than 0.33 (with SLV estimated by TAC 2017). The value of 1/3 (or 0.33) was chosen as many texts define a small graft as between 30% and 40%.[21] The SLV as estimated by all formulas was compared to the actual GV used for LDLT. Exact logistic regression was used to calculate an odds ratio (OR) for developing SFSS given a "Small Graft." SFSS was defined as "dysfunction or nonfunction of the graft, characterized by signs of hepatic dysfunction, such as cholestasis, ascites, coagulopathy, and encephalopathy, during the first postoperative week after exclusion of other causes" including an INR greater than 1.5 or bilirubin greater than 10 on POD 7.[22] A categorical variable with a

TABLE 1.

Characteristics of donors and recipients

Characteristics	Donors (n = 133)	Recipients (n = 43)	*P*
Age: med (range), y	35 (18-58)	55 (23-73)	< 0.0001
Sex, female, n (%)	69 (52)	23 (54)	0.863
Race/ethnicity, n (%)			0.253
Asian	5 (4)	2 (5)	
Black	4 (3)	2 (5)	
Latino	26 (20)	14 (33)	
White	86 (66)	20 (48)	
Other	10 (7)	4 (9)	
TAC: median (IQR), mm	741 (705-790)	778 (746-838)	< 0.0001
CTLV: median (IQR), mm^3	1495 (1352-1721)	N/A	N/A
MELD at transplant: median (IQR)	N/A	17 (11–21)	N/A
Indications for transplant, n (%)	N/A		N/A
Autoimmune		9 (21)	
HBV/HCV		10 (24)	
HCC		7 (17)	
NASH		3 (7)	
Alcoholic liver disease		9 (21)	
Other		4 (10)	

Age and TAC compared by Wilcoxon rank sum test, sex compared by Fisher exact test.

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

TABLE 2.
Model creation

Model terms	Adjusted R^2	rmPRESS
TAC, age, sex	0.464	208.8
TAC, age, sex × TAC	0.463	209.14
TAC, age, sex, sex × TAC	0.462	210.03
TAC, sex	0.451	210.38
TAC, sex × TAC	0.45	210.56
TAC, age	0.448	210.87
TAC	0.444	210.88
TAC, sex, sex × TAC	0.447	211.84

Models arranged by goodness of fit as assessed by the rmPRESS.

value of 1 when the GV/SLV was less than 0.33, and a value of 0 when greater than 0.33, was generated to use as the independent variable in this exact logistic regression.

Leave-one-out cross-validation and the rmPRESS were performed in R v.3.3.1 (Vienna, Austria). All other statistical tests were performed using STATA v.13.1 (College Station, TX).

RESULTS

Demographics and Model Creation

The demographic and anthropomorphic characteristics of recipients and donors are described in Table 1. Donors were significantly younger than recipients and had a smaller TAC. Additionally, there was a wide, but similar, variation in race/ethnicity in both of the groups. The median MELD at transplant was 17 and most common indication for transplant was hepatitis B virus and hepatitis C virus caused cirrhosis.

Of the models created using donor data, the equation including TAC, age, and sex had the highest adjusted R^2 and lowest rmPRESS with values of 0.46 and 208.80, respectively (see Table 2) and yielded the following equation:

$$SLV = (TAC \times 3.58) - (Age \times 3.98) - (Sex \times 109.74) - 934.59$$

TAC is in mm, age is age in years, and sex = 0 for female patients and sex = 1 for male patients.

Model Comparison

The model was then compared with previous equations that predicted SLV. Table 3 presents all of the formulas evaluated by RMSE. The current (TAC 2017) formula performed best on this data set. This was repeated for the "testing" and "training" data set as described above with similar results (not shown).

In Figure 2, the CTLV is graphed along with predictions of SLV as determined by the current and historical formulas. Using a repeated-measures analysis of variance with a Dunnett posttest to compare SLV, it was demonstrated that all distributions except for the current formula (TAC 2017) were statistically and significantly different than the SLV. When restricting the analysis to the "testing" data and using a TAC-based formula generated by the "training" data, similar results are obtained. In this case, the formulas from Lin 1998, Vauthey 2002, and Yu 2004 were also not statistically different than the CTLV.

Prediction of SLV for LDLT Recipients and Clinical Outcomes

Information from individuals who underwent LDLT was then used to predict SLV for the LDLT recipients. This SLV was compared to the actual GV obtained at time of

TABLE 3.
Historical formula comparison

Source	Formula	RMSE
Deland 1968[10a]	1020 × BSA_D – 220	251.62
Urata 1995[8a]	706.2 × BSA_D + 2.4	304.74
Lin 1998[15]	13 × height + 12 × weight – 1530	229.40
Heinemann 1999[7a]	1072.8 × BSA_D – 354.7	233.51
Vauthey 2002—formula 1[16]	18.51 × weight + 191.8	213.29
Vauthey 2002—formula 2[16b]	1267.28 × BSA_M – 793.41	221.11
Yoshizumi 2003[6b]	772 × BSA_M	220.39
Yu 2004[4]	21.585 × (weight$^{0.732}$) × (height$^{0.225}$)	218.32
Chouker 2004[5c]	16.434 × weight + 11.85 × age – 166 × Sex + 452	544.93
Hashimoto 2006[17a]	961.3 × BSA_D-404.8	251.11
Chan 2006[9d]	12.29 × weight + 50.74 × sex	631.73
Yuan 2008[13a,e]	949.7 × BSA_D-48.3 × age factor – 247.4	218.23
Fu-Gui 2009[11]	11.508 × weight + 334.024	400.71
Poovathumkadavil 2010[12]	12.26 × weight + 555.65	212.22
Um 2015[14b]	893.485 × BSA – 439.169	358.15
Kokudo 2015[19f]	58.7 × thoracic width – 463.7 × race – 3.61 × Age + 203.3	295.14
Current (TA circum 2017)[c]	TAC × 3.58 + 4.40 × height – age × 3.98 – sex × 109.74 – 934.59	203.8

Formulas and root mean standard error (RMSE) for all formulas used in this article.

[a] BSA calculated using Du-Bois formula.

[b] BSA calculated using Mosteller formula.

[c] For sex, female = 1, male = 0.

[d] For sex, male = 1, female = 0.

[e] Age factor is age < 40 = 0, 40-60 = 1, >60 = 2.

[f] Race = 1 for Asian, race = 0 for non-Asian.

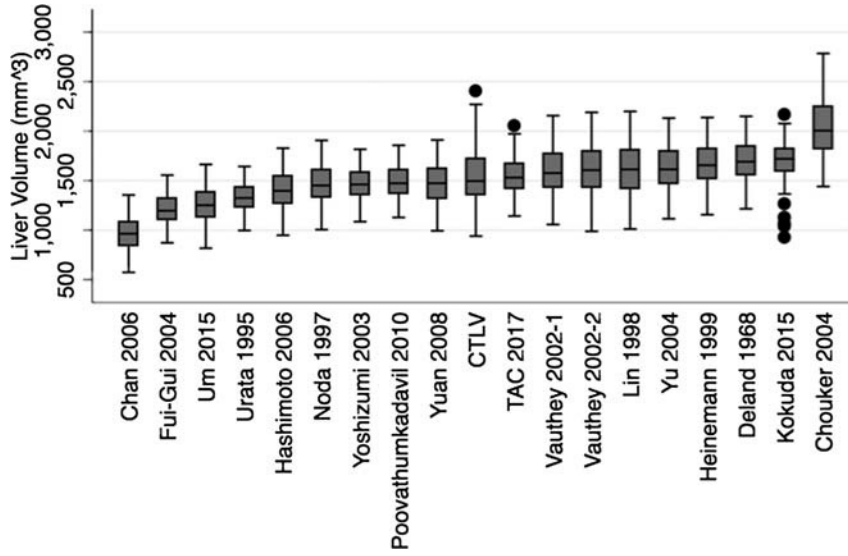

FIGURE 2. All data plotted as box plots with the middle line representing the median, the box representing the inter-quartile range, the whiskers representing the upper and lower adjacent values, and all dots representing outliers. Boxes are ordered from least to greatest.

implantation. In Table 4, certain clinical outcomes of interest are listed, first for all patients (all data column) as well as for patients assessed to have a "small" or "adequate" graft (defined as a GV/SLV less than or greater than 0.33, respectively, where SLV was defined by the current TAC 2017 formula). These data highlight that individuals with a "small graft" generally had more adverse outcomes with higher point estimate prevalence of need for inflow modification, need for additional surgery, and graft dysfunction at POD 7 and POD 14. This difference was statistically significant when comparing the prevalence of SFSS between "small" and "adequate" graft recipients as defined by the TAC 2017 formula. Additionally, these "Small Graft" recipients had statistically significantly later normalization of INR but not length of stay (LOS).

Predicting SFSS

To assess the clinical utility of the TAC formula in LDLT recipients, we conducted an exact logistic regression using GV/SLV less than 0.33 or greater than 0.33 as our independent variable and diagnosis of SFSS as our dependent variable. Using this model, we obtain an OR of 7.94 (95% confidence interval [CI], 1.23-91.36, $P = 0.025$). ORs for all other formulas are shown in Table 5. The highest OR was for the Lin and Vauthey formulas at 10.60(95% CI, 1.61-124.6, $P = 0.009$).

Clinical Correlates of SFSS

The presence of ascites (defined as high drain output at least 7 days after surgery), date of INR normalization, hepatic encephalopathy, and cholestasis (defined as an elevated bilirubin greater than 10 on POD 7 or a failure of the bilirubin to downtrend within the first 10 days after surgery) were used to compare the spectrum of SFSS symptoms between groups of different GVs. These data are shown in Table 6 and demonstrate a higher proportion of individuals with these symptoms in the "small graft" group (as defined by the TAC, Lin, and Vauthey formulas, our best performing formulas) and in the SFSS-defined group.

DISCUSSION

In the current study, we propose a formula, based on a heterogeneous cohort, for the prediction of SLV using a single anthropomorphic measurement: TAC. This formula compares

TABLE 4.

Prediction of adverse outcomes by formula

Characteristics	All recipients (n = 43)	TAC 2017—small graft, GV/SLV <0.33 (n = 17)	TAC2017—adequate graft, GV/SLV >0.33 (n = 26)	*P*
Inflow modification, n (%)	12 (28)	7 (41)	5 (19)	0.17
All biliary complications, n (%)	18 (42)	5 (29)	13 (50)	0.22
Need for reoperation, n (%)	8 (19)	5 (29)	3 (12)	0.23
Graft dysfunction, POD 7, n (%)	17 (40)	10 (59)	7 (26)	0.057
Graft dysfunction, POD 14, n (%)	9 (21)	6 (35)	3 (12)	0.12
SFSS: n (%)	9 (21)	7 (41)	2 (8)	0.018
Day of INR normalization: median (IQR)	4 (3-7)	7 (6-10)	3 (3-4.5)	< 0.000
LOS: median (IQR), d	9 (8-13)	9 (7-17)	9 (8-12)	0.87

The top row (all data) shows certain clinical outcomes in the overall population a total of n = 43 patients. Below are the outcomes for those estimated by the TAC (current) formula to have a "small graft" (ie, GV/SLV < 0.33) and for those with a "large graft" (ie, GV/SLV > 0.33) with SLV defined by the current formula (TAC 2017). All statistical tests are between the TAC 2017—small and TAC 2017—adequate GV columns. All categorical comparisons by Fisher exact test. Day of INR normalization and LOS compared by Wilcoxon rank sum test.

TABLE 5.

Exact logistic regression comparison

Formula	Exact logistic regression, OR (95% CI)	*P*
Deland 1968	7.94 (1.23-91.37)	0.024
Urata 1995	5.66 (0.79-43.17)	0.092
Lin 1998	10.60 (1.61-124.6)	0.009
Heinemann 1999	9.13 (1.40-106.41)	0.016
Vauthey 2002—formula 1	10.60 (1.61-124.60)	0.009
Vauthey 2002—formula 2	10.60 (1.61-124.60)	0.009
Yoshizumi 2003	7.25 (1.21-56.74)	0.028
Yu 2004	7.94 (1.23-91.37)	0.025
Chouker 2004	2.82 (0.30-141.78)	0.62
Hashimoto 2006	5.53 (0.91-37.85)	0.068
Chan 2006	N/A	N/A
Yuan 2008	6.81 (1.07-49.14)	0.041
Fui-Gui 2009	10.05 (0.75-Inf)	0.080
Poovathumkadavil 2010	7.25 (1.20-56.74)	0.028
Um 2015	3.94 (0.05-333.23)	0.76
Kokudo 2015	6.09 (1.09-79.47)	0.04
Current (TACircum, 2017)	7.94 (1.23-91.36)	0.025

Each formula was assessed for its ability to predict SFSS by Exact logistic regression with ORs, 95% CIs, and *P* values presented for each regression.

Inf, infinity; N/A, not applicable.

well with other previously described formulae in terms of both RMSE and percent difference from CTLV. The formula was modeled on a diverse set of patients undergoing abdominal imaging during the process of living liver donation. Living liver donation requires the donor to be in ideal health thus providing an excellent study population for mathematical modeling of an ideal liver size.

When compared with other cohorts, our donor cohort has a fairly wide donor age range and is ethnically diverse.[7,11,12,14] Our formula also performed well in predicting donor liver volume as evidenced by the small percentage difference for the predictions versus the obtained CTLV. Additionally, the TAC formula predictions were not statistically different form the CTLV estimations, whereas most historical formulas were.

To test the current formula's ability to predict clinical outcomes of interest, recipients were stratified into those with "small" and "adequate" grafts, with "small" graft defined as GV/SLV < 0.33 where SLV was predicted by the TAC 2017 formula. Though the sample was small, there were significantly more patients with clinical SFSS in the "small graft" group as predicted by the current formula and these individuals had significantly later normalization of INR.

To compare the abilities of multiple formulas to predict SFSS, we used an exact logistic regression to determine an OR for each formula's ability to predict SFSS given a "small" graft (GV/SLV < 0.33). Ten of the formulas presented had statistically significant ORs to predict SFSS, including the present formula. Interestingly, multiple of the previous formulae outperformed our non–weight-based formula, though by a small margin with overlapping CIs. In fact the equations developed by Lin in 1998, and the 2 formulas by Vauthey had the greatest ability to predict SFSS despite being dependent only on height, weight, and BSA. Their strong performance, however, is unsurprising as they also were among the best of the historical formulas at predicting SLV in the donor cohort.

Another way to determine the formulas abilities to predict SFSS is to look at the spectrum of symptoms that are considered hallmarks of SFSS. We show that both the current formula, and the high performing Lin and Vauthey formulas do have higher point estimates of the symptoms associated with SFSS as well as slightly later dates of INR normalization.

Overall, the current formula adequately predicts SFSS and is generally more accurate than weight-based formulas at predicting SLV when compared with CT volumetrics measurement as the criterion standard. Continued investigation into the ability of our current formula's performance at predicting SFSS should be undertaken due to the small sample size represented in the present study.

Limitations to the current study include a relatively small sample size. However, the cross-validation techniques used aided in the creation of valid formula. Likewise, the small number of recipients limits our ability to make comparisons of outcomes, including SFSS, however we maximize our ability to observe differences by using exact logistic regression. Race was not a significant factor in our formula (data not shown). This may be because only 5% of our sample was Asian, and further study of the formula in a cohort with more Asian individuals is warranted. Finally, CT volumetric measurements of liver volume may overestimate actual liver volume by up to 10%.[23] However, this is likely due to intraoperative blood loss and therefore would not affect the performance of our formula.

CONCLUSIONS

In this study, we present a new formula constructed with a non–weight-based anthropomorphic measure that is able to accurately estimate SLV. The formula performs well across a number of races without adjustment and allows for broad clinical applications. We find this equation useful for not only estimating the minimal necessary liver volume of living donor recipients but also predicting what an ideal liver volume might be in a patient undergoing whole graft deceased donor

TABLE 6.

SFSS symptoms by patient group

Patient subset	Cholestasis, n (%)	Day of INR normalization, median (IQR)	Ascites, n (%)	Encephalopathy, n (%)
All recipients (n = 43)	19 (44)	4 (3-7)	17 (40)	3 (7)
TAC—small graft, GV/SLV <0.33 (n = 17)	10 (59)	7 (6-8)	10 (59)	3 (18)
Lin—small graft, GV/SLV < 0.33 (n = 15)	10 (66)	7.5 (6-9)	9 (60)	3 (20)
Vauthey—small graft, GV/SLV < 0.33 (n = 15)	10 (66)	8 (6-8)	9 (60)	3 (20)
SFSS clinical definition (n = 9)	7 (78)	8 (6-10)	8 (89)	2 (22)

Data show the prevalence of 4 cardinal symptoms of SFSS among (1) all patients, (2) those classified as small graft by the TAC formula, (3) those classified as small graft by Lin formula, (4) those classified as small graft by Vauthey formula.

liver transplant. Further refinement with a larger cohort of recipients to determine the optimal cutoff for determining a small graft using the current formula would be of use in predicting SFSS.

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