Changes in Liver Volume from Birth to Adulthood: A Meta-Analysis

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A diversity of equations is available for the estimation of liver volume (LV), derived from studies in populations of ethnically homogeneous individuals and using a variety of methods of measurement. The aim of this study was to integrate all published pediatric data and to define a general equation for estimating LV from birth onward. Data were collated from 5,036 subjects (birth to 18 yr old). Equations were developed based on simple regression against body surface area (BSA) and multiple regression of LV with weight, height, BSA, age, gender, race, methodology, and year of publication as covariates. These equations, together with those reported in the literature, were compared for accuracy of prediction of LV from birth to 18 yr old. The most parsimonious equation to describe LV was selected according to the Akaike information criteria (AIC), precision and bias and following visual inspection of residual errors and observed vs. predicted plots: LV = 0.722 * BSA$^{1.176}$. The multiple regression models indicated that Japanese have up to 19% larger livers compared to Caucasians for a given body weight. Radiographic and ultrasonic measurements were associated with up to 8% lower estimates of liver size compared to measurements made at autopsy. There was no evidence that gender or the year in which a study was published (1933-1999) influenced the estimation of LV. The general equation was also applied to predict adult LV, and its precision and accuracy was found to be superior to those of 10/11 published adult models. In conclusion, we have developed a more general model to predict LV in pediatric populations and young adults, and have investigated a range of covariates. (*Liver Transpl 2005;12:1481-1493.*)

Knowledge of liver volume (LV) is of clinical relevance when determining graft size for transplantation[1,2] and organ viability after resection.[3,4] It is also important to know this value and its variance in different populations when predicting hepatic drug clearance using physiologically-based pharmacokinetic models.[5,6] Early efforts at estimating LV indicate a linear but disproportional (nonzero intercept) relationship to body surface area (BSA) in adults,[7] although this does not appear to hold in the presence of liver disease.[8] Moreover, these linear models did not account for variation in liver size for a given BSA related to additional covariates (e.g., age, gender, and ethnicity). A survey of the literature indicated a number of other studies in both adults and children that derived a diversity of equations based on age, weight, height or BSA to predict LV (Table 1). There has been no attempt to describe a full-variance model for liver size using multiple regression analysis that accounts for a larger set of possible covariates.

Using computed tomography, Urata et al.[9] defined a simple linear relationship between LV and BSA in 96 Japanese children and adults without liver abnormalities. A similar relationship was determined, using magnetic resonance imaging, in a study of 16 North American children.[10] However, on applying the Urata equation to data from a large German population (n = 1,365; 4-80 yr old) in whom LV was measured at autopsy, Heinemann et al.[11] found that the model underestimated the observed LV. Hence, they derived a revised linear BSA equation. A recent multicenter study of 292 North Americans/North Europeans by Vauthey et al.[12] (14-90 yr old) using computed tomography indicated underestimation of LV the Urata equation and slight overestimation by the Heinemann equation. The authors developed new linear models, based on BSA, that included additional effects of age (Table 1). Yoshizumi et al.[13] formulated another set of linear equations based on 1,353 autopsy samples. Their model, which was derived from 60 subjects with BSA < 1 m^2, accounted for additional effects of age, apart from those defined by BSA, by assigning a pediatric correction factor (Table 1). Application of the Urata and Heinemann equations to the adult data of Yoshizumi et

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Abbreviations: LV, liver volume; BSA, body surface area.

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Table 1. Published Models of Liver Size in Adults and Children

Study	Population	No of subjects	Age range	Male/female separation	Methodology	Model*
DeLand and North (1968)[7]	North American	550	Adults (45 to 99 kg)	Y	Autopsy	LW(kg) = 1.02*BSA−0.22 (BSA > $1m^2$)
Haddad et al. (2001)[20]	North American		Birth to 18 years	Y	Data of Altman and Dittmer (1962)[19]	LW(g) = 0.0072(Age)^5−0.3975(Age)^4 + 7.9052(Age)^3−65.624(Age)^2 + 262.02(Age) + 157.52 (Males) LW(g) = 0.0057(Age)^5−0.3396(Age)^4 + 7.0134(Age)^3−59.539(Age)^2 + 251.9(Age) + 139.65 (Females)
Heinemann et al. (1999)[11]	German	1,365	4 to 80 years	Y	Autopsy	LV(L) = 1.0728*BSA−0.3457
Kanamori et al. (2002)[30]	North American		0 to 18 years	N	ICRP data[18]; Coppoletta and Wolbach (1933)[21]	LW(g) = 67.3(Age) + 229.8
Mt. Sinai Hospital[14]	North American	550	Adults	N	Autopsy	LW(g) = 13.2276*WT + 4*Age + 350
Murry et al. (1995)[10]	North American	16	3.3 to 18.8 years	N	Autopsy	LV(L) = 0.71*BSA
Noda et al. (1997)[16]	Japanese	54	10 days to 22 years	N	Computer tomography	LV(L) = 0.1126*Age$^{0.401}$ LV(L) = 0.05012*BW$^{0.78}$
Ogiu et al. (1997)[15]	Japanese	485	Birth to 19 years	Y	Autopsy	LW(g) = 576.9*HT + 8.9*BW−159.7(Males)
		1624	20 to 95 years			LW(g) = 674.3*HT + 6.5*BW−214.5 (Females)
Takahashi et al. (2000)[41]	Japanese	113	1−18	N	Autopsy data of Tanaka et al[42]	LW(g) = 15*(4.6*Age + 19.8)
		368	30−40			LW(g) = 15*(0.31*Age + 97.8)
		859	>40 years			LW(g) = 15*(−0.91*Age + 149)
Urata et al. (1995)[9]	Japanese	96	1 months to 27 years	Y	Computer tomography	LV(L) = 0.7062*BSA + 0.0024
		19	5 months to 15 years		Computer tomography and posttransplant liver weight	LV (L) = 0.006293*BW$^{0.426}$*HT$^{0.682}$
Vauthey et al. (2002)[12]	North American/ North European	292	14 to 90	N	Computer tomography	LV(L) = −0.79441 + 1.267*BSA LV(L) = −0.69581 + 1.27938*BSA−0.00226*Age
Yoshizumi et al. (2003)[13]	North American	1,413	Birth to 87 years	Y	Autopsy	LV (L) = (0.772*BSA−0.038)/1.08 if < $1m^2$ or LV (L) = (0.772*BSA)/1.08

*LW can be converted to LV by dividing by 1.08 (Heinemann et al.[11]). Published equations for liver volume in adults and children are presented as in the original publications with the exception of the Mt. Sinai formula, which has been converted to metric units for body weight.

Table 2. Summary of In Vivo Pediatric Liver Size Data Stratified by Age Bands

	n	Age range (year)	Weight range (kg)	Height range (cm)	BSA range (m^2)	LV range (L)
Neonates	576	0.001–0.083	3.4–3.75	50.5–52	0.22–0.24	0.072–0.16
Infants	1,518	0.015–1	4.1–10.1	53–80.4	0.25–0.47	0.123–0.375
Young child	1,535	1.16–6	9.65–21.9	74–119	0.45–0.85	0.22–0.66
Older child	649	6.45–12	21.2–45	113–153	0.78–1.38	0.52–1.1
Adolescent	758	12.2–18	39.3–73.7	144–179	1.25–1.92	0.81–1.7

NOTE. All age bands contain data from both sexes, mixed races, different measurement methods, and study years. The full database is available in Appendix A.

al.[13] again was associated with underestimation and overestimation of LV, respectively. However, for pediatric subjects (BSA < 1 m^2) the Urata equation performed well, while the Heinemann equation underestimated LV. Yoshizumi et al.[13] also applied a number of other equations[7,14] to their data, with inconsistent results. Ogiu et al.[15] used the liver weights of 2,109 Japanese to derive separate liver weight equations for males and females based on height and weight. Another Japanese study[16] of 54 subjects (10 days-22 yr old), using computed tomography, derived a power function of body weight to predict LV, which was subsequently reported to give similar predictions to the equation of Ogiu et al.[15] in children and of Heinemann et al.[11] in adults.[17]

Physiologically-based pharmacokinetic models tend to use autopsy values of LV from the International Commission on Radiological Protection report on "reference man"[18] or from the publication by Altman and Dittmer.[19] Data from the latter source were recently used to derive a polynomial function relating LV to age.[20] The inconsistencies found when applying the above models might be related to differences in population covariates (e.g., gender, age, and ethnicity) or different measurement techniques (see Tables 1 and 2).

None of the published equations for predicting LV or liver weight have been based on multiple regression analysis, such that the effects of all potential covariates could be explored. We have now analyzed all of the published data on liver size in children and young adults available to us, with the aim of deriving a more comprehensive liver-size model, especially for the pediatric age range, that includes a range of covariates.

Methods

Compilation of a Database (Birth to 18 Yr Old) to Develop LV Models

Data on liver size as a function of age in healthy children and young adults were extracted from the literature, initially using the National Library of Medicine's online bibliographic database (MEDLINE) and their Excerpta Medica database (EMBASE), then by scrutinizing the recovered reports for additional references not covered by the electronic search. A summary of these data is shown in Table 2, and a full version of the database is given in Appendix A. A total of 5,036 liver size measurements in subjects from birth to 18 yr old, from 9 different reference sources[9-11,15,16,18,19,21,22] were included in our analysis. In the majority of cases the individual data and associated covariates were not reported, only mean values

Table 3. Models Fitted to the Database (Birth to 18 Years)

Analysis	Dependent variable	Independent variable
1a	LV	BSA only
1b	LV	BSA, Sex, Age, Race, Time, Method, Height, Weight
2a	Log LV	Log BSA only
2b	Log LV	Log BSA, Log age, Log time, Log height, Log weight, Sex, Race, Method
3	$\sqrt[3]{LV}$	$\sqrt{BSA}$ only

NOTE. All data were weighted by 1/variance. Parameters were coded in the SPSS analysis as follows: Gender, −1 (female), 1 (male), 0 (unknown); Age, age in years; Race, 0 (Japanese), 1 (North American/North European); Time, year study completed (e.g., 1975 = 75); Method, 0 (autopsy), 1 (other method); Height, height in cm; Weight, weight in kg.

Table 4. Published Studies on Liver Size in Normal Adults

Study	Population/Race and (number)	Age year mean or (median)	Age range (or SD)	Weight (kg)	Weight range (or SD)	Height (cm)	Height range (or SD)	BSA (m^2)	Liver volume (L) mean or (median)	Liver volume range (or SD)
Heinemann et al. (1999)[11]	German (1,365)	50.6	18.9 (SD)	71.1	11.9 (SD)	170.7	10.1 (SD)	1.83*	1.596	0.9–2.25
Wynne et al.[43]	British	54*		62*		168*		1.7*		
	(20)		24–40						1.3725	(0.358)
	(23)		40–64						1.3265	(0.335)
	(22)		65–91						1.0365	(0.28)
Urata et al. (1995)[9]	Japanese (31)	21	16–27 (4 SD)	57	(9 SD)	164.8		1.613	1.149	(0.142)
Tanaka et al. (1970)[42]†	Japanese		16–25						1.223	
Ogiu et al.[15]	Japanese (1,333)	34.5	20–50	55.92	49.2–62.7	160.6	152.7–169.1	1.58*	1.269	1.180–1.377
Urata et al. (2000)[44]	Japanese (92)	36	(10 SD)	57	(9 SD)	164[a]		1.62	1.147	(0.193)
Vauthey et al. (2002)[12]	North American and European (292)	54	14–90	72	43–165	169	118–192	1.84	1.531 (1.487)	0.649–3.558
Yoshizumi et al. (2003)[13]	North American (1,413)	41.94	0–87	69.54	4.1–158.9	167.7	50.8–213.4	1.788	1.277	0.138–2.6
	White (986)							1.80	1.312	0.33
	Black (237)							1.785	1.200	0.35
	Hispanic (166)							1.702	1.195	0.325
	Other (24)							1.643	1.1284	0.27
ICRP (1975)[18]	North American/ Western European (150)	35*	20–50	64.4*		168.5*		1.73*	(1.6148)	1.3–2.129

*Values derived from national demographic data or calculated from other parameters.
†Data not used in this study.

Table 5. Final LV Models

Analysis	Covariates*	Covariates dropped	Final Model
1a	BSA	–	LV = (0.728*BSA)−0.035
2a	Log BSA	–	$LV = 0.722*BSA^{1.176}$
1b	Age; race; method; BSA	Height; weight; sex; time	LV = −0.088 + BSA*0.98 +Age*0.017 −0.036 (if NA/NE) −0.072 (for radiographic/ultrasonic method)
2b	Log weight; race; Method	Log BSA; Log time; Log age; Log height; sex	$LV = 0.0437*Weight^{0.9}$ *1.19 (if Japanese) *0.92 (if radiological/ultrasonic method)
3	BSA	–	$LV = (\sqrt{BSA}*0.72 + 0.171)^3$

NOTE. Height in cm, weight in kg, and age in years.
Abbreviation: NA/NE, North American/North European populations.
*Statistically significant covariates remaining in the models.

(and variability) stratified for age groups. The small amount (2.5%) of individual data from the studies of Heinemann et al.,[11] Murry et al.,[10] and Urata et al.[9] was grouped into age bands ($n \geq 3$), with variability, to reduce bias from such data in the generation of residual values. The data and associated covariates were entered into our analysis using a weighting factor of 1/variance. This weighting factor accounts for both the different number of subjects generating each mean value and the variability around these values. When liver size was expressed as weight, the corresponding LV was calculated using a value of 1.08 kg/L for liver density.[11] For cases in which complete information (e.g., on body height and body weight) for stratified age groups was not provided, these data were derived from standard growth charts for the corresponding ethnic population,[23,24] and are indicated in the full version of the database (Appendix A). Body surface area (BSA) was calculated using the Dubois and Dubois[25] equation if body weight was greater than 15 kg, and using the Haycock et al.[26] equation if body weight was less than 15 kg. Other covariables recorded were ethnicity, age, gender, study publication year, and method used to assess liver size (e.g., autopsy, radiography). The complete dataset was placed in study order and every fourth subject was extracted to generate a training set comprising 3,594 subjects (75%) and a validation set of 1,442 subjects (25%). This approach ensured a representative spread of age, gender, and data from specific studies in each dataset.

Data Analysis and Modeling

The training dataset used to construct equations to predict LV was analyzed by multiple regression (stepwise inclusion method) using SPSS (version 12 for Windows; SPSS, Chicago, IL). The observed values of LV were weighted by 1/variance. In addition to multiple regressions, a simple regression of LV against BSA was carried out to enable direct comparison of our integrated data with the simpler linear BSA models reported in the literature (Table 1). Simple regression was also performed using log-transformed values of LV and BSA and square and cube root-transformed values of BSA and LV, respectively. A summary of the analyses and the dependent and independent variables is shown in Table 3.

Model Comparisons

Using the validation dataset, the LV models derived in this study were compared with published models (Table 1) to predict changes in liver volume from birth to 18 yr old. This was done using the Akaike information criteria (AIC)[27] (Eq. 1) implemented in Microsoft Excel (Microsoft, Redmond, WA) according to the following equation:

$$AIC = N_{OBS} * \ln(WRSS) + 2 * N_{PAR} \quad (1)$$

where N_{OBS} is the number of observations, WRSS is the weighted residual sum of squares, and N_{PAR} is the number of parameters. WRSS values were based on squared residual errors weighted for 1/variance. The distributions of residuals against BSA were also examined visually for any systematic deviation in model predictions. Observed vs. predicted plots were also examined for agreement. In addition, the root mean squared prediction error (rmse) and mean prediction error (me) were calculated as measures of precision and bias, respectively, for each of the models using Equations 2-4.[28]

$$mse = \frac{1}{N} * \sum_{1=1}^{N} pe^2 \quad (2)$$

where pe is the prediction error ($LV - L_{prd}$).

$$rmse = \sqrt{mse} \quad (3)$$

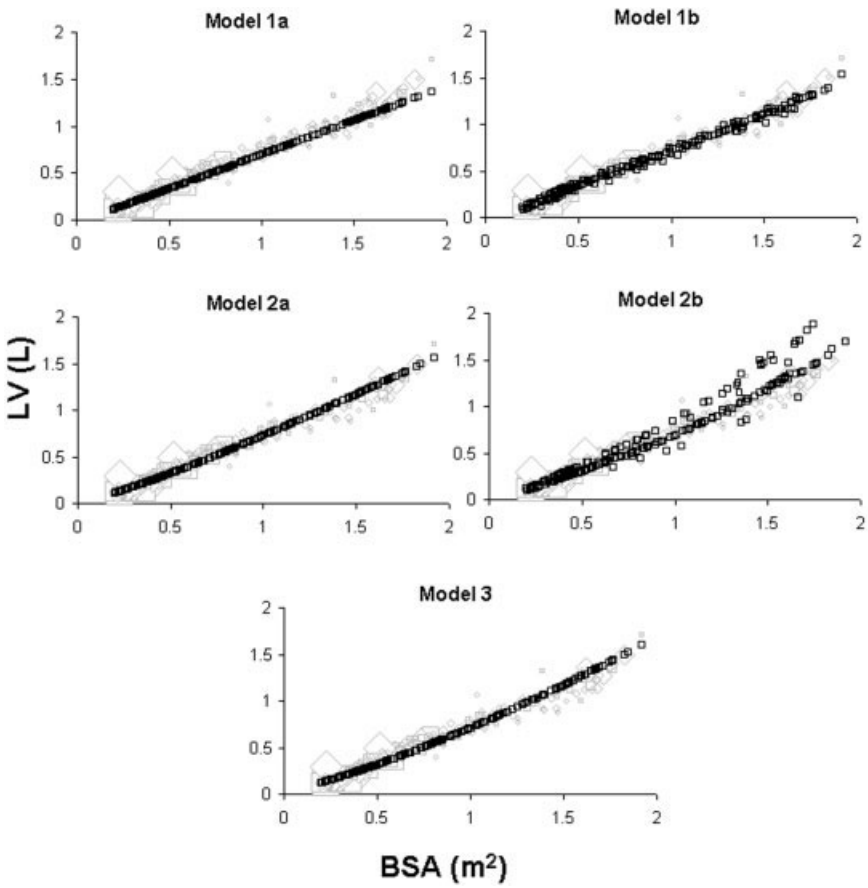

Figure 1. The relationship between liver volume and BSA. Observed data are indicated by gray diamonds (training data) and squares (validation data), the sizes of which are proportional to the number of subjects from which the data were derived; the black squares are values predicted by the equations developed from the training database (birth to 18 yr old).

$$me = \frac{1}{N} * \sum_{i=1}^{N} pe \quad (4)$$

Compilation of an Adult Database to Test Extended Application of the LV Model

The predictive power of the LV model based on data from birth to 18 yr old was tested with an extended data base of LV values in adult populations. Details of the latter are shown in Table 4. Data from individuals with liver disease were excluded from the analysis. In a small number of studies, the demographic data (body height and weight) required for our model were not available. In these cases mean population values for the corresponding age, gender, and ethnic groups were used. Age, height, and weight were compared between the ethnic groups to investigate statistical differences (2-tailed, non-paired *t*-test) in these background data.

The overall means and standard deviations of LV values were estimated separately for North American/Northern European adults and Japanese adults. Overall means (WX) were calculated using Equation 5.

$$W\bar{X} = \frac{\sum_{j=1}^{J} n_j \cdot \bar{x}_j}{\sum_{j=1}^{J} n_j} \quad (5)$$

where n_j is the number of subjects in the jth study and x_j is the mean value from that study. Overall standard deviation (sd) was calculated using Equations 6 and 7:

$$\text{Overall Sum of Squares} = \sum_{j=1}^{J} [[(sd_j)^2 + (\bar{x}_j)^2] \times n_j] - N \cdot (WX)^2 \quad (6)$$

where sd_j is the standard deviation from the jth study and N is the number of subjects in all studies.

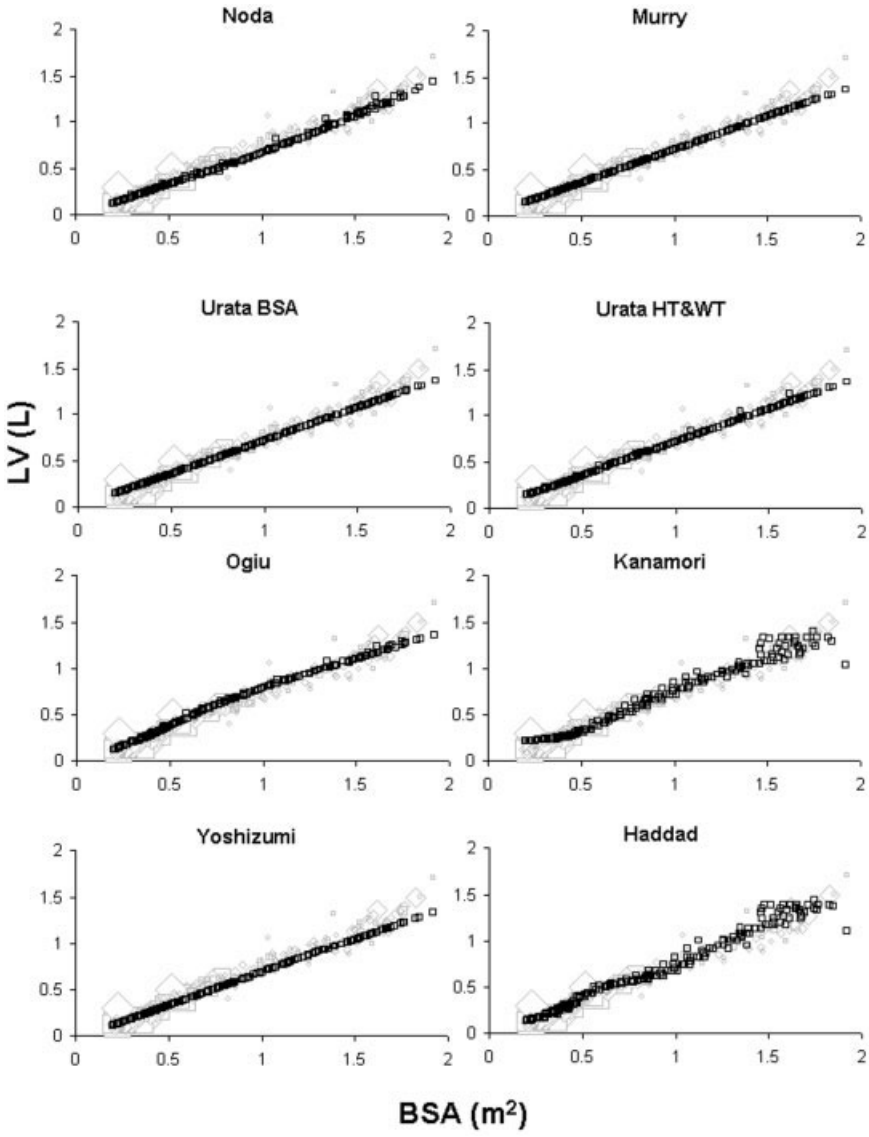

Figure 2. The relationship between liver volume and BSA. Observed data are indicated by gray diamonds (training data) and squares (validation data), the sizes of which are proportional to the number of subjects from which the data were derived; the black squares are values predicted by published pediatric models.

$$\text{Overall SD} = \sqrt{\frac{\text{Overall Sum of Squares}}{N}} \quad (7)$$

In turn, geometric mean or median values (assuming log-normal distributions) were calculated using Equations 8, 9, and 10.

$$\sigma = \sqrt{\ln(1 + CV^2)} \quad (8)$$

where CV is the standard deviation divided by the mean;

$$\mu = \ln \bar{X} - (0.5^*\sigma^2) \quad (9)$$

$$\text{Median} = e^{\mu} \quad (10)$$

Interquartile values and 95% confidence intervals for likely observations were calculated around the geometric mean values using Equations 11 and 12, respectively (adapted from Armitage and Berry).[29]

$$\text{Interquartile value} = e^{\mu \pm (0.67^*\sigma)} \quad (11)$$

$$95\% \text{ Confidence Interval} = e^{\mu \pm (1.96^*\sigma)} \quad (12)$$

The LV equations determined in this study from the birth to 18 yr old database were compared with reported equations based on adult data for both North Americans/Europeans and Japanese. In applying models 1b and 2b to the adult data, it

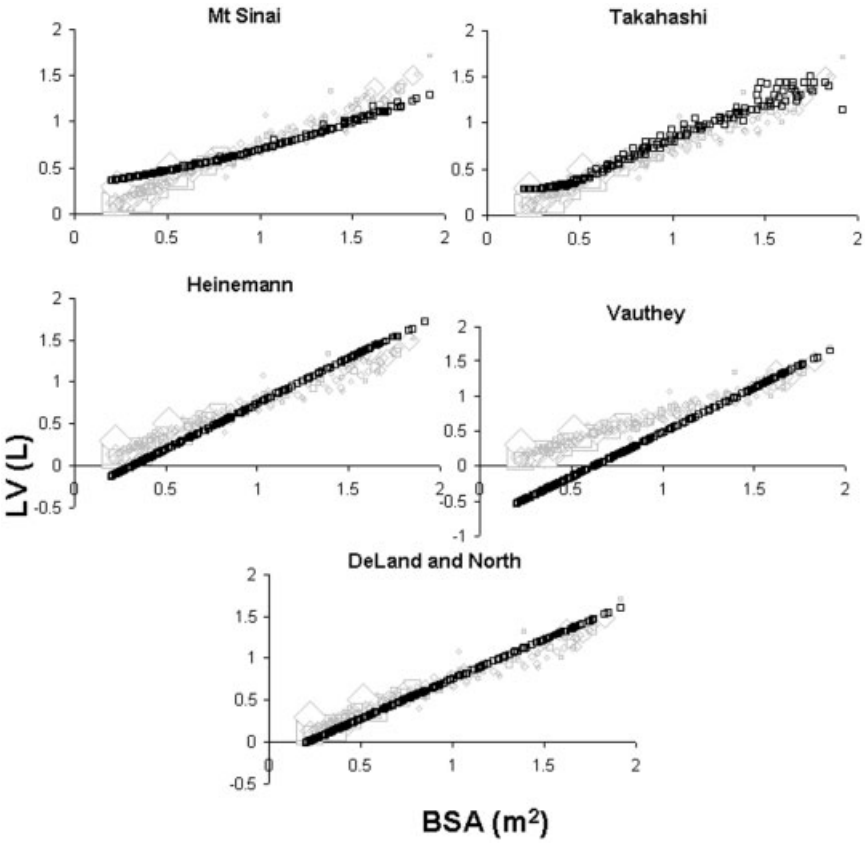

Figure 3. The relationship between liver volume and BSA. Observed data are indicated by gray diamonds (training data) and squares (validation data), the sizes of which are proportional to the number of subjects from which the data were derived; the black squares are values predicted by published adult models.

was necessary to incorporate bivariate inputs for measurement technique (0 = autopsy, 1 = radiology). These values were calculated according to the proportional representation of each element in the overall population (North American/North European = 0.11 and Japanese = 0.08).

The values for variables rmse and me were calculated as measures of precision and bias, respectively (Eq. 2-4) for each of the models.

Results

Equations for LV in Pediatric and Young Adult Subjects

A summary of the results of our analysis with details of the derived LV equations is shown in Table 5. Observed (birth-18 yr old, combined North American/Northern European/Japanese database) and predicted values of LV are plotted as a function of BSA in Figures 1-3. Figure 1 shows predictions of the 5 sets of equations developed from the training dataset, Figure 2 indicates predictions of published pediatric models, and Figure 3 indicates predictions of published adult models. The AIC, precision, and bias for each equation are shown in Table 6, indicating that model 2a provided the best fit (lowest AIC, highest precision, and second-least bias). Residual plots for the 5 equations fitted to the birth to 18 yr old database indicate that the error is scattered randomly around zero for all of the models (data not shown). The observed vs. predicted plots for the derived models 2a and 2b are shown in Figure 4; the R^2 values were 0.97 and 0.92, respectively (the plots for models 1a and 1b are very similar to 2a and are not shown). Although model 2b appears accurate up to a LV of 1 L, there is wide variation in observed vs. predicted values after this point.

Of the published pediatric equations, those of Ogiu et al.,[15] Yoshizumi et al.,[13] and Noda et al.[16] gave the best predictions, while those of Murry et al.[10] and Urata et al.[9] (HT and WT) tended to slightly over predict LV at BSA values less than 0.5 m^2. The equations based on age tended to perform less well; the Haddad et al.[20]

Table 6. Rank Order of Best-Fit of Models to Database (Birth-18 Years) According to Akaike criterion values

Rank order	Description	Akaike information criterion value	Precision	Bias
1	Model 2a	176	0.13	−0.064
2	Model 1a	180	0.137	−0.081
3	Model 1b	183	0.133	−0.12
4	Model 3	184	0.141	−0.026
1	Ogiu et al. model[15]	186	0.142	0.31
2	Yoshizumi et al. model[13]	189	0.149	−0.16
3	Noda et al. model[16]	194	0.155	−0.098
4	Urata et al. model H&W[9]	199	0.154	0.21
5	Murry et al. model[10]	200	0.164	0.27
6	Haddad et al. model[20]	201	0.16	0.21
	Urata et al. BSA[9]	202	0.17	0.28
	Model 2b	240	0.23	−0.097
7	Kanamori et al. model[30]	254	0.27	0.52
8	Deland and North model[7]	286	0.37	−1.08
9	Takahashi et al. model[39]	306	0.44	1.36
10	Heinemann et al. model[11]	356	0.70	−2.21
11	Mt. Sinai model[14]	365	0.72	2.17
12	Vauthey et al. model[12]	470	2	−6.94

NOTE. The precision and bias of the various models are also shown.

model gave reasonable predictions up to about 1.2 m^2 BSA, and the Kanamori et al.[30] model only predicted LV accurately between 0.5 and 1.2 m^2. The adult equations predicted LV in children poorly. The Heinemann et al.[11] and Vauthey et al.[12] models predicted negative LV in individuals with BSA of less than 0.3 and 0.7 m^2, respectively.

Application of the Models to Adult Data

The overall mean, standard deviation, median, and 95% confidence intervals for adult LV in North American/North European and Japanese populations are shown in Figure 5. There was no statistically significant difference in age ($P = 0.16$), weight ($P = 0.06$), or height ($P = 0.12$) between the 2 groups, although, as expected, the Japanese were generally smaller and lighter. The overall mean LV/BSA values were 0.802 and 0.798 for North American/North European and Japanese, respectively. The precision and bias of the various models (models 1a-3, based on the birth-18 yr old database, and literature models) in predicting median LV in these adult populations are shown in Figure 6. Models 2a and 3 gave the greatest precision, followed by those of DeLand and North[7] and Vauthey et al.[12] The Vauthey et al.[12] BSA model showed the least bias, closely followed by model 3. Thus, the simple regression models derived from pediatric data (0-18 yr old) performed well in predicting the adult data.

Percentage Liver Size With Age

Analysis of all of the data used in this study was performed to determine age-related changes in liver weight as a percentage of body weight. For individuals from 0 to 2 yr of age, the median value was 3.5% (range 2.1-4.7%), and for individuals of 18 yr old and over the value was 2.2% (range 1.8-2.8%).

Discussion

The accurate estimation of liver volume has a number of clinical and scientific applications. Liver grafts that are too small for the recipient can compromise the results of transplantation. Graft volume-to-standard liver volume values of 40% or less and graft weight-to-body weight ratios less than 0.8 are associated with increased morbidity and impaired graft survival after transplant.[2] Since the liver is the main organ of elimination for most drugs and xenobiotics, liver size is an important determinant of the capacity of an individual to clear such compounds. Accordingly, an accurate model of liver size is an essential component of physiologically-based pharmacokinetic models. To date many of these models have relied on published equations for liver size[31,32] that do not account for covariates such as ethnicity and gender. The main aim of the current analysis was to define a more universal and accurate liver-size model for pediatric and young adult subjects,

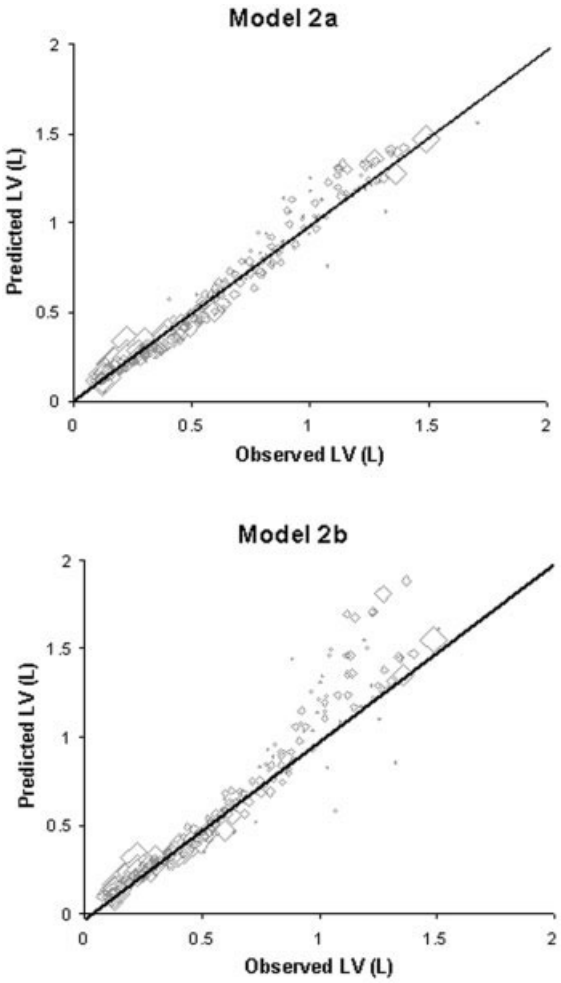

Figure 4. Relationship between predicted and observed liver volumes for Equations 2a and 2b developed from the data base (birth to 18 yr old). The observed data are indicated by diamonds (all data), the sizes of which are proportional to the number of subjects from which the data were derived. The black line is the line of unity.

by combining all published data on liver volume and weight.

The simple linear regression models (1a, 2a, and 3) provided high correlations between LV and BSA, in agreement with previous studies.[7,9,11] Statistically, these models were superior to the multiple regression models (1b and 2b). However, they fail to account for the variability observed in LV at given values of BSA (Fig. 1). Moreover, they do not give any information on other potentially significant covariates.

Height and weight were dropped from model 1b in favor of BSA, and age was detected as a minor covariate. Model 1b was not based on log values. Hence, the effects of measurement method and race as covariates were defined as constant values regardless of liver size (e.g., 0.072 L smaller in North American/Northern European subjects, whether for a small pediatric liver or a liver from an 18-yr-old). Overall, model 1b appears to provide a good fit to the observed data. However, its precision and bias are poor for the reason given above. Natural logarithmic transformation of LV (and BSA, age, height, and weight) in the regression analysis created model 2b, in which the covariate effects could be defined as proportional deviations from the corresponding average values of other parameters.

Model 2b indicated a major influence of weight (explaining 92% of the variability). However, as with model 1b, race and method were required as additional covariates to improve it. Overall, model 2b performed poorly as judged by AIC values, precision, and bias, and by visual inspection of the observed vs. predicted plot. The model is especially poor in estimating the size of livers over 1 L in volume. Overall, the effects of race and measurement method appear to be overestimated by this model.

Based on models 1b and 2b, radiologic and sonographic assessments were associated with up to 8% lower estimates of LV compared to those based on autopsy measurements. Because liver volumes or weights measured at autopsy would not include intrahepatic blood, higher estimates might have been expected. The discrepancy between methods may be due to measurement errors. In the case of radiographic/ultrasonic methods this may be due to operator error.

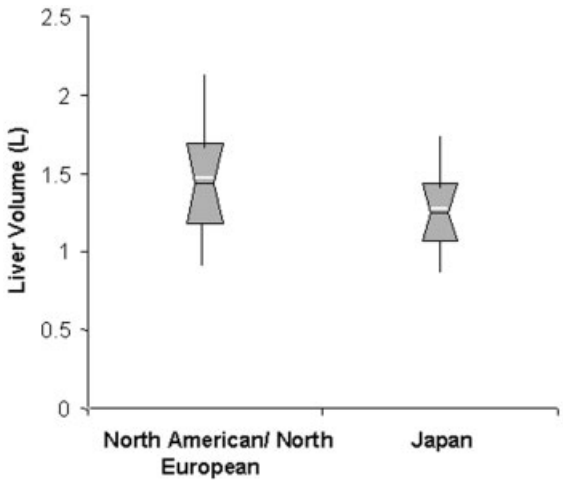

Figure 5. Box-whisker plots of liver volume in adult North American/European and Japanese populations. The boxes encompass the median and upper and lower quartiles, the error bars represent 95% confidence intervals and the white line is the mean.

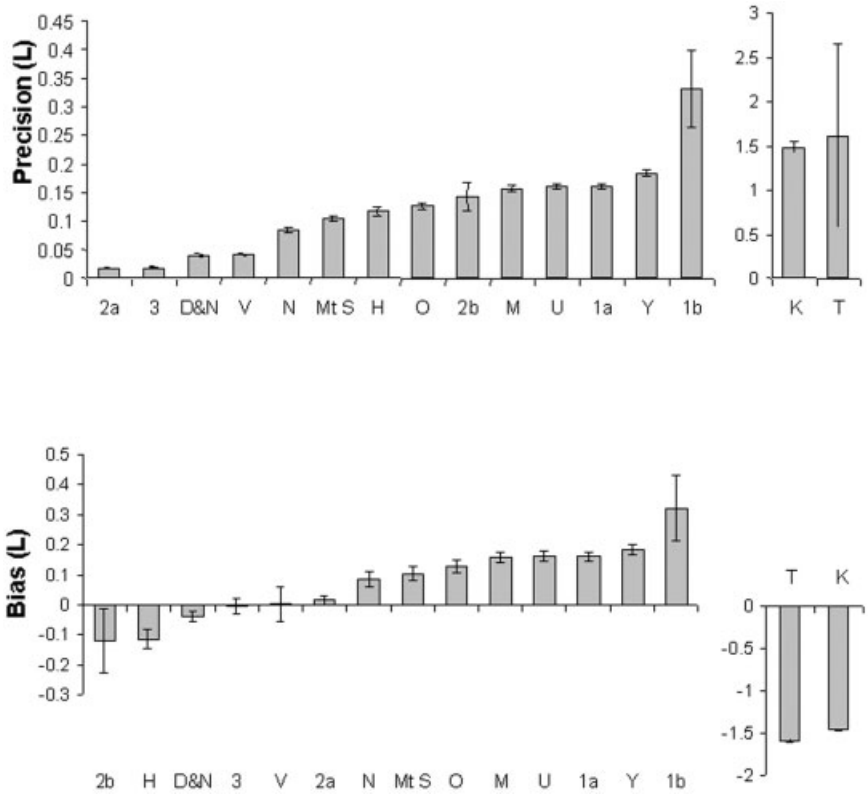

Figure 6. Precision and bias of estimates of median adult liver volume predicted by different models. Models 1a, 1b, 2a, 2b, and 3 were derived in this study; D&N, DeLand and North[7]; V, Vauthey et al.[12]; N, Noda et al.[16]; MtS, Mount Sinai[14]; H, Heinemann et al.[11]; O, Ogiu et al.[15]; M, Murry et al.[10]; U, Urata et al.[9]; Y, Yoshizumi et al.[13]; K, Kanamori et al.[30]; and T, Takahashi et al.[41]. Error bars are 95% confidence intervals.

With regard to autopsy measurements, changes in liver volume can occur during the survival period,[11] but the data required to account for this were not available to this study. Previous reports indicate that the measurement of liver volume by ultrasound or computed tomography correlates well with measurements taken at autopsy or after transplantation.[9,33-37] Schiano et al.[34] showed that small livers tend to be overestimated by computed tomography, while large ones are underestimated. We found no evidence that the year in which a study was carried out (1933-1999) influenced the estimation of LV.

Based on models 1b and 2b from the pediatric data, Japanese have up to 19% larger livers for a given body size, age, gender, and measurement technique compared to Caucasians. Previous data suggest that, when normalized to BSA, LV is smaller in Japanese compared to Caucasians.[11,12] However, these studies only compared data from Caucasians with the 96 Japanese subjects from the study by Urata et al.[9] Inclusion of data from the 485 pediatric subjects in the study of Ogiu et al.[15] reversed this trend. In contrast, based on the combined adult data in this study there was no difference in LV normalized for BSA between Japanese and Caucasians.

The relationship between LV and BSA has been considered to be the same for males and females.[7,13] This is confirmed by the results of the present study.

The current findings also confirm those from previous studies that have suggested a liver weight of about 4% of body weight in infants compared to 2 to 2.7% in adults.[16] This difference is reflected in the faster clearance of hepatically metabolized drugs in infants following the development of drug metabolizing enzymes to adult capacity after about 1 yr of age.[38-40]

Overall, the simple models predict liver volume well for both clinical purposes and for in silico simulations in the context of physiologically-based pharmacokinetic modeling. Physiological variability can be incorporated into the LV values for the latter purpose by incorporating changes in the CV with age and by using a log-normal distribution.

In conclusion, we recommend that model 2a be used to predict LV up to the age of 18 yr. Beyond this age, either Equation 3 or that of Vauthey et al.[12] (BSA model) are recommended.

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