Estimation of Liver Size for Liver Transplantation: The Impact of Age and Gender

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In general, the liver is considered to be larger in males than in females. In the present study, data on liver weight from 728 legal autopsies were analyzed with respect to gender, age, body height (BH), body weight (BW), body mass index (BMI), and body surface area (BSA). Descriptive statistics revealed that liver weight increases with age, reaching maximum values between 41 and 50 years in men and between 51 and 60 years in women. Thereafter, liver weight decreases again. Because this loss in liver weight starts earlier in men while liver weight continues to rise in women, the difference in liver weight between men and women is lost above the age of 50. Thus, this age defines a threshold value below which gender is expected to be a critical factor in the calculation of liver weight. When demographic data mentioned above were subjected to multiple stepwise linear regression analysis, liver weight (LW) was best predicted in younger people (16-50 years) by body weight, age, and gender: LW (g) = 452 + $16.34 \times BW + 11.85 \times age - 166 \times gender (r^2 = 0.381;$ "gender": 1 = female, 0 = male). In contrast, in elderly people (51-70 years) LW was best predicted by BW and age only. Gender was not a significant factor. LW (g) = $1390 + 15.94 \times BW - 12.86 \times age (r^2 = 0.35)$. When these formulas were applied to demographic data from 97 organ donors and compared to published formulas (which, however, do not consider the age-dependent effects of gender), the new formulas best predicted male to female liver weight ratios in younger and elderly donors. In conclusion, the new formulas might better predict liver weight in organ donors and transplant recipients to avoid liver size mismatch. (Liver Transpl 2004;10:678-685.)

S uccessful liver transplantation is the result of a large spectrum of factors, including optimal match of donors and recipients with respect to acute physical state,¹

Abbreviations: BH, body height; BMI, body mass index; BSA, body surface area; BW, body weight; LV, liver volume; LW, liver weight; SD, standard deviation; UNOS, United Network for Organ Sharing.

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poor nutritional state or hypermetabolism prior to liver transplantation, 1,3,4,5 donor weight above 100 kg,3 female donor gender,6 total ischemia time,1 and ABO compatibility. The important role of gender was first addressed by Marino et al.6 and revealed the worst outcome when female donor grafts were transplanted in male recipients. However, for the estimation of donor liver graft size, in most studies body weight alone⁷ or body weight in combination with body height (for calculation also of body surface area)7-12 were used, while surprisingly the role of gender¹¹ or age⁷ is still a matter of debate. This situation could result from the performance of regression analyses on data from quite different and hardly representative populations. For instance, Urata et al. used young Japanese pediatric patients9 while Vauthey et al.7 and Yoshizumi et al.11 used patients with ages ranging from adolescence to very old individuals (>80 years). Moreover, there is also substantial variation in the methods used to determine liver size, including autopsies, 12 back table weighing of donor grafts,11 computed tomography,7 and sonography.15

In conclusion, in the present study we analyzed data on liver weight from 728 legal autopsies with respect to gender, age, body height, body weight (BW), body mass index (BMI), and body surface area (BSA). Multiple stepwise linear regression analyses allowed us to calculate new formulas that predict liver weight in a gender- and age-dependent fashion. As compared with equations published so far, the new formulas described here for adult humans may be superior in the prediction of liver weight of organ donors and transplant recipients to avoid liver size mismatch, especially in younger or elderly males and females. For scheduled living-related liver transplantation, however, additional preoperative examinations should be considered to further increase the accuracy of the estimation of liver size.

Materials and Methods

Autopsy Protocols

In a retrospective study, the autopsy protocols of the Institute of Legal Medicine, Ludwig-Maximilians University, Munich, Germany, were reviewed over 18 months between 2001 and 2002. From 1410 autopsies, 682 subjects were excluded from

		7	Table 1. Age Interv	als			
Age Intervals, yr ("Young")	>1	6-30	31-	-40	41–50		
Gender	Male Female		Male Female		Male Female		
n	92	28	107	27	114	50	
Age, years	23.46 (3.84)	23.93 (4.43) n.s.	35.93 (3.14)	35.44 (2.91) n.s.	45.92 (3.20)	46.20 (2.78) n.s	
Body weight, kg	78.99 (16.36)	60.36 (13.06)*	78.38 (14.14)	58.33 (15.49)*	79.60 (17.67)	68.47 (16.74)*	
Body height, cm	177.08 (6.76)	165.71 (6.75)*	174.87 (7.95)	162.67 (7.49)*	175.09 (6.55)	163.02 (5.98)*	
BMI, kg \times m ⁻²	25.18 (4.91)	21.91 (4.22)*	25.61 (4.28)	21.85 (4.81)*	25.91 (5.48)	25.67 (5.70) n.s	
BSA, m ²	1.95 (0.19)	1.66 (0.18)*	1.93 (0.19)	1.61 (0.22)*	1.94 (0.21)	1.73 (0.20)*	
Liver weight, g	1834.84 (524.24)	1404.25 (356.85)*	2003.89 (539.09)	1529.81 (388.55)*	2107.35 (552.79)	1768.92 (548.09)*	
Age Intervals, yr ("Elderly")	51-60		61-70		Overall Age Range >16-70		
Gender	Male	Female	Male	Female	Male	Female	
n	115	46	101	48	529	199	
Age, years	55.63 (2.97)	55.33 (2.76) n.s.	65.30 (2.97)	65.46 (3.05) n.s.	45.81 (14.53)	48.36 (14.15)	
Body weight, kg	80.25 (15.88)	68.33 (15.66)*	80.03 (17.21)	68.48 (15.49) n.s.	79.47 (16.25)	65.91 (15.93)	
Body height, cm	172.89 (6.01)	161.35 (10.38)*	172.20 (6.32)	160.2 (6.89)*	174.36 (6.92)	162.29 (7.86)	
BMI, kg \times m ⁻²	26.78 (4.83)	26.24 (5.49) n.s.	26.89 (5.20)	26.67 (5.73) n.s.	26.09 (4.89)	24.99 (5.66)	
BSA, m ²	1.93 (0.19)	1.72 (0.22)*	1.92 (0.21)	1.71 (0.19)*	1.94 (0.20)	1.70 (0.20)	
Liver weight, g	1925.07 (467.14)	1879.02 (496.52) n.s.	1832.23 (452.02)	1581.81 (381.12) n.s.	. 1946.60 (517.1)	1664.41 (478.41)	

NOTE. Data were tested for normal distribution by 1 sample Kolmogorov-Smirnov test and are expressed as mean values (± SD). Abbreviations: n.s., not significant; BMI, body mass index; BSA, body surface area.

analyses because of (a) putrification; (b) major abdominal and liver trauma; (c) jaundice, macroscopic liver steatosis, and cirrhosis; and (d) age younger or older than 16 or 70 years, respectively. Moreover, the population studied by autopsy mostly covers demographic characteristics of potential cadaveric organ donors because of the typically younger age and the reasons of their death (e.g., intracerebral bleeding, suicide, accident). A total of 728 data files were finally included. In these autopsies the following variables were determined: gender, age, body weight, body height, calculated body mass index (BMI), body surface area (BSA), and native liver weight measured ex situ. For routine legal necropsy, the abdomen was opened and inspected and abdominal organs were removed separately. Resection of livers was performed by surgical explantation and, in contrast to pathological sections, by cutting the liver veins at the inferior caval vein and the portal vessel. The liver was weighed on a balance.

Data Analyses

After testing for normal distribution (Kolmogorov-Smirnov test), descriptive statistics were calculated and data expressed as means \pm SD for age (year), body weight (kg), body height (BH in cm), body mass index [BMI = body weight (BW) in kg / body height (BH) in m]², body surface area (BSA according to DuBois:

$$[m^2] = BW (kg)^{0.425} \times BH (cm)^{0.725} \times 0.007184$$

and liver weight, separately for males and females. Demographic data are also presented for males and females classified by decades of age as it is generally done in the presentation of age-dependent variables in the field of pathology. Comparison of age-classified data between males and females was performed by two-sided unpaired t test (P<0.05). Stepwise multiple linear regression analysis was used to test for effects of independent variables (Table 1) on the dependent variable (measured liver weight), with $y = a + b_1c_1 + b_2c_2 + b_3c_3 + b_3c_4$... [y = liver weight; a = constant; b1 = unstandardized coefficient1; c1 = entered variable 1 (e.g., age); b2 = unstandardized coefficient 2; c2 = entered variable 2 (e.g., body weight...)], and so on. The new equations were tested for the prediction of the donor liver graft size of 97 human donors randomly recruited from the university's liver transplant database and compared to the values obtained by the equations published previously. To eliminate methodological differences in the determination of absolute liver weight, relative changes were expressed in percent of mean female size according to (mean male liver size mean female liver size) × 100 / mean female liver size. The reference values of age- and gender-dependent differences of the liver weight were calculated using directly measured liver weights from the autopsy data files (n = 728). All statistical analyses were performed by SPPS V10.0 program (SPSS, Chicago, IL).

^{*} Unpaired t test, P < .05 vs. male.

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Results and Discussion

Descriptive Analyses of Subjects' Characteristics

To establish a relationship between liver weight and demographic data, analyses by legal autopsies may serve as a gold standard, especially because autopsies are performed under standardized conditions. The data on 728 human autopsies are given in Table 1. The mean age was 46.5 years (range 16-70 years) and was normally distributed as was body mass index, which describes the ratio between weight and height. Approximately 70% of males and females had normal body mass index (BMI 18.5-24.9 kg \times m⁻²) or moderate overweight (BMI 25–29.9 kg \times m⁻²). Obesity (30 kg \times m⁻² < BMI < 40 kg \times m⁻²) was observed in less than one-fifth of the subjects (data not shown) according to the definition of overweight and obesity by BMI $(kg \times m^{-2})$. Thus, the population studied by autopsy fairly represents the North American (NHANES III Surveys)13 and the European population (MONICA Project, MONItor trends in CArdiovascular diseases¹⁴) with an obesity rate less than 25%.

Changes of body height and weight, body mass index (BMI), body surface area (BSA), and liver weight in males and females in dependence upon aging was analyzed in five age intervals, which include young (16–30, 31–40, 41–50 years) and elderly individuals (51–60, 61–70 years), respectively. Mean ages of males and females within each interval and over the entire range of 16–70 years did not differ significantly. In these 529 males, aging did not result in significant changes of body weight, while body height tended to decrease upon the fourth life decade. In females both body weight and body height increased or decreased, respectively, which resulted in a rise in BMI upon the fourth decade.

Weight of livers was significantly higher in young males (16–30 years) than in young females (Figure 1). Irrespective of gender, liver weight increased with age, reaching maximum values for males in the fifth (41–50 years) and for females in the sixth (51–60 years) decade. Thereafter, liver weight decreased again. Because this loss in liver weight started earlier in men, while weight of the liver still continued to rise in women, the difference between the higher liver weight in men and the lower liver weight of women was lost above the age of 50 years.

Interestingly, this relation between age and gender appears to be independent from body size. In order to test the hypothesis that men and women of the same body size/weight have livers of still different sizes, liver

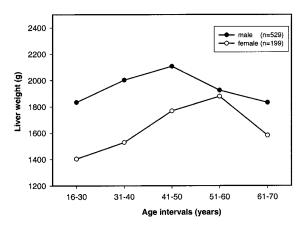


Figure 1. Changes of mean liver weight upon aging in men (filled circles) and women (open circles) from 728 autopsies. Because gender-specific differences are lost beyond the fifth decade, data were analysed separately for two groups of "young" (16–50 years) or "elderly" (51–70 years) people.

weights of men and women of the same body mass index and age were compared. Table 2 shows genderand age-dependent liver weights for four major classes of body mass index [BMI <18.4 kg \times m² (underweight), $18.5 - 24.9 \text{ kg} \times \text{m}^2$, $25 - 29.9 \text{ kg} \times \text{m}^2$, $30-39.9 \text{ kg} \times \text{m}^2 \text{ (obesity)}$]. Concerning data of individuals with BMI in the two middle categories (ranges $18.5 - 24.9 \text{ kg} \times \text{m}^2 \text{ and } 25 - 29.9 \text{ kg} \times \text{m}^2$), which compromise approximately 70% of humans of the western population, liver weight of women was always significantly lower than that of men in the younger groups (16-50 years) but not in the older groups (51-70 years). For individuals with underweight or obesity a similar trend could be observed but level of significance was not obtained as a result of too few cases in these extreme groups.

Thus, the age of 50 might define a threshold value below which gender could be a critical factor in the calculation of liver weight in younger people (16–50 years) but not in elderly (51–70 years) people.

Linear Regression

In consequence, necropsy data were subjected to stepwise multiple linear regression analyses separately for younger (16–50 years, n = 418) and elderly (51–70 years, n = 310) subjects (Table 3). In younger subjects, liver weight (LW) was best predicted by body weight, age, and gender: LW (g) = $452 + 16.34 \times BW + 11.85 \times age - 166 \times gender$ (r² = 0.381; "gender": 1 = female, 0 = male). In contrast, in the elderly subjects (51–70 years) LW was best predicted by BW

	BMI $<$ 18.4 kg \times	m ⁻² (underweight)	BMI 18.5–24.9 kg \times m ⁻²		
	Male	Female	Male	Female	
Liver weight, g: 16–30 years	1310 ± (475)	1307 ± (389)	1742 ± (468)	1376 ± (354)	
	n=4	n=4	n = 47	n = 18	
Liver weight, g: 31–40 years	$1520 \pm (506)$	$1008 \pm (233)$	$1789 \pm (366)$	$1538 \pm (394)^*$	
	n = 3	n = 3	n = 44	n = 15	
Liver weight, g: 41–50 years	$1688 \pm (505)$	$1817 \pm (180)$	$1938 \pm (397)$	$1548 \pm (422)^*$	
	n = 7	n = 3	n = 42	n = 22	
Liver weight, g: 51–60 years	$1468 \pm (317)$	$1664 \pm (688)$	$1732 \pm (377)$	1665 ± (392) n.s.	
	n = 6	n = 3	n = 44	n = 14	
Liver weight, g: 61–70 years	$1076 \pm (248)$	$1001 \pm (232)$	$1594 \pm (365)$	$1357 \pm (335) \text{ n.s.}$	
	n=4	n = 3	n = 32	n = 16	
	BMI 25-2	BMI 25–29.9 kg \times m ⁻²		$kg \times m^{-2}$ (obesity)	
	Male	Female	Male	Female	
Liver weight, g: 16–30 years	$1839 \pm (474)$	1657 ± (413) n.s.	2211 ± (559)	$1340 \pm (28)$	
	n = 26	n=4	n = 14	n = 2	
Liver weight, g: 31–40 years	$2080 \pm (568)$	$1640 \pm (285)^*$	$2474 \pm (432)$	$2018 \pm (322)$	
	n = 46	n = 6	n = 12	n = 3	
Liver weight, g: 41–50 years	$2133 \pm (467)$	$1775 \pm (428)^*$	$2589 \pm (641)$	$2221 \pm (825)$ n.s.	
	n = 43	n = 16	n = 18	n = 7	
Liver weight, g: 51–60 years	$1990 \pm (377)$	$2054 \pm (353)$ n.s.	$2147 \pm (538)$	1971 ± (654) n.s	
	n = 39	n = 15	n = 27	n = 13	
Liver weight, g: 61–70 years	$1953 \pm (377)$	$1720 \pm (364)$ n.s.	$2042 \pm (432)$	$1825 \pm (264) \text{ n.s.}$	
	n = 34	n = 16	n = 29	n = 11	

and age only. Gender was not a significant factor. LW (g) = $1390 + 15.94 \times BW - 12.86 \times age (r^2 = 0.35)$. All other variables (body height, BMI, and BSA) were of no significant predictive value.

We also subjected the necropsy data of the present study to multiple stepwise linear regression analysis for all subjects over the entire range of age (males and females, 16-70 years). By doing this, liver weight was predicted best only by body weight according to the equation: LW (g) = $591.82 + 16.98 \times BW (r^2 = 10.98)$ 0.33). Listed in Table 3 are also equations for liver size that were published previously by others. The equation shown for Rasmussen was calculated by us using that study's published data.15 Comparison of these equations shows that the variables for liver size (liver weight or volume) and the methods used for their determination (autopsy, ultrasound, computed tomography) clearly differ. There are also substantial differences in the number of individuals and the range of ages of individuals studied (e.g., Urata et al.9 calculated liver volume in pediatric patients, mean age 11 years). Moreover, possible effects of gender were not considered in

these studies and even frequently were not assessed. Despite these obvious differences, these published formulas are used to estimate liver size of potential organ donors and transplant recipients to avoid mismatch. But how good are these different methods to correctly predict liver size or volume?

Comparison of Different Formulas to Predict Liver Weight of Organ Donors

In order to answer this question, demographic data from organ donors documented in the liver transplant database of our clinic were taken to calculate liver size in males and females for the two groups of younger and elderly subjects separately, using our equations and those published by others. It was expected that calculated liver size was different when estimated by different formulas, especially because the equations published were derived by different methods (autopsies vs. back table vs. ultrasound vs. computed tomography) from different cohorts or races (e.g., "Caucasian,"12 "Asian"7). Moreover, underestimation of liver size by 682 Choukèr et al.

Table 3. Regression Formulas of Present and Previous Studies

		Previous Studies*		
	Equation 16-50	Equation 51-70	Equation 16-70	Equation Rasmussen ¹⁵ †
Data source	autopsies	autopsies	autopsies	ultrasound
	(legal medicine)	(legal medicine)	(legal medicine)	
Data files analysed (n)	418	310	728	78
Male (n) / female (n)	313 / 105	216 / 94	529 / 199	35 / 43
Age range (years)	16-50	51-70	16-70	20-80
Mean age (SD)	36.30 (9.78)	60.06 (5.71)	44.57 (14.45)	44.51 (16.24)
Regressors	BW, age, gender $(0 = m; 1 = f)$	BW and age	BW	age, BW
R^2	0.381	0.35	0.33	0.506
Regression formula	$LW = 452 + 16.34 \times BW + 11.85$	$LW = 1390 + 15.94 \times BW$	LW = 591.82 + 16.98	$LV = 577.43 + (-4.67 \times age)$
_	\times age + (-166.5 \times gender)	$+$ ($-12.86 \times age$)	\times BW	$+ 18.82 \times BW$

Abbreviations: LW, liver weight (g); LV, liver volume (ml); BMI, body mass index (kg \times m⁻²); BSA, body surface area (m²); BW, body weight (kg); SD, standard deviation; n.p., not published, data not cited in publications.

* "Previously published studies" refers to other reported equations from the literature to allow for liver size estimation.

computed tomography or ultrasonography might result from the weight of the gallbladder, attached ligaments, portal vessels, and hepatic vena cava vessels, which are not removed prior weighing during a legal postmortem section but are routinely excluded in size estimation by computed tomography. To circumvent such investigator-dependent and methodological errors, the difference between the mean value of the size of male and female livers was calculated and this difference was expressed in percent of the mean liver size of females (Table 4).

The group of organ donors was approximately normally distributed with respect to age, body height, body weight, body mass index, and body surface area. Distribution of these variables was not significantly different from those of the younger necropsy group (Table 3, mean age group 16-50 years: 36.3 years). Mean age of organ donors was $\sim\!40$ years (total n = 97; male n = 53, female n = 44) with 22% older than 50 years. The other demographic data were: body height (173.8 cm \pm 7.8), body weight (72.6 kg \pm 11.3), body mass index (BMI = 24 kg \times m⁻² \pm 2.8) and body surface

Donors					Presen	t Study			Previous	Studies
Gender	Age (yr)	n	LV equa. I Mean	16-50	LV equa. <u>'</u> Mean	51-70	LV equa. 1 Mean	6-70	LV equa. <mark>Ras</mark> Mean	mussen ¹⁵
Male	16-50 4	44	44 2153.83	226.91	_	_	1937.48	175.4	1908.56	191.7
	51-70	9	_	_	1884.75	107.17	1912.48	116.03	1770.66	126.5
Female	16-50	30	1754.5	181.09	_	_	1675.14	125.36	1610.06	141.0
	51-70	14	_	_	1726.17	141.22	1749.07	134.21	1580.07	149.6
Calculated difference in male and female liver size										
in % of female	16-50		22.7%				13.5%		18.5%	
liver size	51-70				9.1%		8.5%		12.0%	
Reference values from autopsies	16–50							23.7%	(n = 418)	
Difference in male and female liver size in % of										
female liver	51-70							9.1% (n = 310	

Abbreviations: LV, liver volume (ml); LW, liver weight (g).

NOTE. To eliminate differences between studies with respect to the methods used for liver size determination, the absolute difference between mean values of male and female liver size was calculated and this difference expressed in percent of mean female size according to ([mean male liver size – mean female liver size] \times 100) / mean female liver size). Reference values were calculated the same way but using directly measured liver weights from the autosy data files (n = 728). Absolute data on liver size are expressed as mean values \pm SD.

^{* &}quot;Previously published studies" refers to other reported equations from the literature to allow for liver size estimation † The formula "Rasmussen" was not published before and was calculated from raw data of Rasmussen¹⁵ by us.

		Previous Studies*		
Equation Vauthey ⁷	Equation Heinemann ¹²	Equation Urata ⁹	Equation Yoshizumi ¹¹	Equation DeLand
computed tomography	autopsies	computed tomography	cadavric liver donors	autopsies
292	1332	96	1413	625
n.p.	n.p.	61 / 35	851 / 562	n.p.
14-90	n.p.	1-27	0.18-87 years	n.p.
54	50.6 (18.9)	11.1 (8.8)	m 38.6 (20.6) f 47.0 (19.7)	n.p.
BSA	BSA	BSA	BSA	BSA
0.46 - 0.49	< 0.3	0.962 - 0.969	0.49	n.p.
LV = -794.4 + 1.27	LV = -345.7 + 1072.8	LV = 2.4 + 706.2	$LW = 772 \times BSA$	LW (kg) = -0.2
\times BSA	\times BSA	\times BSA		$+$ 1.02 \times BSA

area (BSA = $1.86 \text{ m}^2 \pm 0.17$). When these data of the organ donors were used in our new equations, calculated absolute mean liver weight was in younger males 2153 g and in younger females 1754 g. Accordingly, mean male liver weight was 22.7% higher than that of female livers. The same calculation procedure predicted a 9.1% higher mean weight of male livers than female livers in the group of elderly organ donors. As shown by the liver weights measured directly in our autopsy groups (reference values, Table 4), mean weight of livers of younger males (16–50 years) was \sim 23.7% higher

than that of younger females, while in older subjects (51-70 years) the value was 9.1%.

Thus, the values calculated above by our newly established gender-dependent and gender-independent equations for young and elderly subjects, respectively, were in good agreement with the reference values that were obtained by the direct measurement of liver weights in the younger and elderly autopsy groups.

In contrast, using those equations that do not consider the effect of gender in an age-dependent fashion, ours included (16-70 years), differences in

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male and female mean liver size as expressed in percent of mean female size greatly differed for younger and older individuals as compared with the reference values determined from our autopsy data. Taking into account that 80% of organ donors are under the age of 51 years, the best prediction of liver size was obtained by the equation of Vauthey et al.7 followed by Rasmussen. 15 Male liver size was usually underestimated in comparison to that of females by the other equations. In older subjects (51 – 70 years) male liver size was in general overestimated in relation to that of females. Such bias may contribute to mismatch of liver size between organ donors and recipients. For instance, if body surface area is taken as the sole criterion for liver size estimation (see DeLand and North,8 Yoshizumi et al.,11 Heinemann et al.,12 and Table 3), liver size is underestimated in a young male donor and overestimated in a young female. In other words, real weight of the male liver is higher than estimated, while real weight of the female liver is lower than calculated. Transplantation of such an organ from the man to the woman may hence cause the situation of "too-large-for-recipient." In this situation nutritional blood flow to the liver16 may be compromised and contribute to graft failure in up to 26% of patients after abdominal closure. 17 In contrast, liver size is overestimated in an elderly man and underestimated in an elderly woman. Transplantation of the organ from the elderly man into the elderly female may cause the situation of "too-smallfor-recipient." In this case, surgery might be easier but it is well known that a critical liver volume is required to avoid poor outcome.18 In addition, liver enlargement after transplantation was suspected to increase antigen expression by cell proliferation,19 thereby decreasing graft survival.^{20,21} The reverse situations are given, if transplantation takes place from women to men, resulting in the situations of "too small for recipient" and "too large for recipient" with both organ donors and recipients from the younger group and the older group, respectively. In this context it is worth emphasizing the clinical observation that the outcome of liver transplantation was bad when female donor grafts were transplanted in male recipients,6 possibly reflecting the importance of the "too small for recipient" situation, of course, besides gender-related unknown effects.

Because the formulas developed in the present study take into account the difference in liver size between adult males and females in an age-dependent fashion, the formulas might be quite useful in avoiding mismatch between donors and recipients in pre-transplant liver size estimation.

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