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ORIGINAL ARTICLE

A formula to calculate the standard liver volume in children and its application in pediatric liver transplantation

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Summary

Due to a lack of available size-matched liver grafts from children, most pediatric recipients are transplanted with technical variant grafts from adult donors. Size requirements for these grafts are not well defined, and consequences of mismatched graft sizes in pediatric liver transplantation are not known. Existing formulas for calculation of a standard liver volume are mostly derived from adults disregarding the age-related percentual liver weight changes in children. In this study, we aimed to establish a formula for general use in children to calculate the standard liver volume. In a second step, the formula was applied in pediatric patients undergoing liver transplantation at our institution between 2000 and 2010 (n = 377). Analysis of a large number (n = 388) of autopsy data from children by regression analysis revealed a best fit for two formulas: "Formula 1," children 0 to ≤1 year (n = 246): standard liver volume [ml] = −143.062973 + 4.274603051 * body length [cm] + 14.78817631 * body weight [kg]; "Formula 2," children >1 to <16 years (n = 142): standard liver volume [ml] = −20.2472281 + 3.339056437 * body length [cm] + 13.11312561 * body weight [kg]. In comparison with children receiving size-matched organs, we found an elevated risk of liver graft failure in children transplanted with a small-for-size graft, whereas large-for-size organs seem to have no negative impact.

Introduction

The normal standard liver weight in adults is about 2–3% of the body weight. In contrast, the estimation of the standard liver weight in children is more complex due to age-related changes in the percentual liver volume [1]. There are only few data available regarding the calculation of the standard liver volume in humans. Existing data are mainly based on small numbers of cases [2–4], and data concerning the standard liver volume in children are almost not available [2,5].

In pediatric liver transplantation, the availability of a size-matched donor represents an exceptional case. The majority of children undergoing liver transplantation will receive a technically modified graft from a deceased or living adult donor [6,7]. A left lateral graft consisting of segments 2 and 3 is considered suitable for infants and children up to 10 years. However, the use of left lateral grafts for this wide range of recipient age and size results in relatively large grafts in smaller children and relatively small grafts in older children. No evidence-based guidelines concerning size-matching in pediatric liver transplantation are available, and principally centers use their personal experience for judgment of the appropriateness of a graft.

Because of these limitations, we sought to develop a formula allowing calculation of the standard liver volume in children based on autopsy data collected in the Department of Forensic Medicine of the University Medical Center Hamburg-Eppendorf.

In a second step, this formula was applied to children undergoing liver transplantation at our institution. Based on these results, liver grafts were classified as size-matched or size-mismatched organs. The calculated standard liver volumes calculated by our new formula and the resulting classification in small-for-size/size-matched/large-for-size/extra large-for-size organs were compared to a categorization based on the graft-to-recipient-weight ratio (GRWR). Finally, the outcome following pediatric size-matched versus small-for-size and large-for-size LTX was analyzed using a prospective clinical database.

Methods

Development of a formula for calculation of a standard liver volume in children

Based on autopsy data of 388 Caucasian children under the age of 16 years, a formula to calculate the standard liver volume (SLV) in children was developed. Only children without known liver disease were included in this study. To avoid miscalculations due to autolysis, only corpses within 72 h after death were used without signs of putridity. A standardized harvesting procedure of the liver was applied with removal of attached soft tissue and weighing of the exsanguinous liver. The correlation between the SLV and the two independent variables body weight and body length was determined by multilinear regression analysis by means of a statistical fit-program (Table Curve 3D v3, SPSS Inc). The function of the fit is a simple linear equation SLV (body weight, body length) = $a + b$ * body length + c * body weight.

Application of the formulas in pediatric LTX recipients

Between January 2000 and December 2010, a total of 377 pediatric LTX were performed at the University Medical Center Hamburg-Eppendorf. Liver transplantation was performed using standard technique; details of the surgical technique for liver splitting used in our center have been described in detail previously [8]. All recipient and donor information as well as follow-up data were collected in a prospective database and retrospectively analyzed. A complete follow-up was available in 353 children.

In all children, the standard liver volume was calculated depending on the recipient age by one of two formulas mentioned above.

For classification of the children into groups of size-matched versus size-mismatched organs, we correlated the actual weight of the transplanted liver graft with the calculated standard liver weight of the transplanted child. The pediatric liver transplant recipients were divided into four groups depending on the ratio graft to recipient standard liver weight.

Small-for-size grafts	≤0.5
Size-matched grafts	>0.5 to ≤1.5
Large-for-size grafts	>1.5 to ≤2
Extra large-for-size grafts	>2

Additionally, the GRWR was calculated and children were likewise classified into four groups.

Small-for-size grafts	<1%
Size-matched grafts	≥1% to <3%
Large-for-size grafts	≥3% to <4%
Extra large-for-size grafts	≥4%

Finally, the outcome of children undergoing size-matched LTX in comparison with small-for-size, large-for-size, or extra large-for-size LTX with special regard to early liver graft failure and overall graft and patient survival was compared.

Statistics

Continuous data were expressed as median/range and analyzed by Kruskal–Wallis test, and categorical variables were expressed as number/percentage and analyzed by chi-square test. Graft and patient survival were assessed by Kaplan–Meier survival curves using log rank test and additionally by Cox proportional hazards models, where we included the relative deviation from standard liver weight as predictor. Since we assumed that upward and downward deviations are both risk factors, but possibly not of the same magnitude, we introduced two slope terms using indicator functions. All statistics were performed using the SPSS 20.0 software (IBM, Munich, Germany). Significance levels were set at a P-value of ≤0.05.

Results

Formula for calculation of a standard liver volume in children

Regression analysis of the autopsy data showed the best correlation using two formulas and separation of children into two age groups with a cut-off point at 1 year.

"Formula 1," children 0 to ≤1 year (n = 246)

Standard liver volume [ml] = −143.062973 + 4.274603051 * body length [cm] + 14.78817631 * body weight [kg].

Data ranges:

Body mass: 0.9–14 [kg], body length: 35–81 [cm], BMI: 7.35–21.34 [kg/m^2], regression analysis: Coef det r^2 = 0.74; Std Err = 32.73.

"Formula 2," children >1 to <16 years (n = 142)

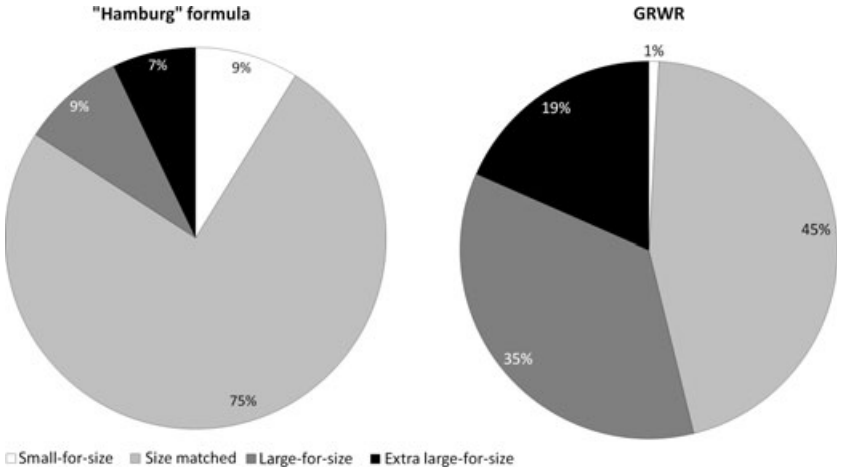

Figure 1 Classification of size-matched versus size-mismatched organs based on the new "Hamburg" formula in comparison with the GRWR. The standard liver volume in our children underwent LTX was calculated by the "Hamburg" formula and correlated to the transplanted liver graft weight. Based on the graft weight to standard liver volume ratio, LTX were divided into size-matched versus small-for-size and large-for-size/extra large-for-size organs. Additionally, LTX were divided on the basis of the GRWR into size matched versus size mismatched LTX. Classification of the LTX in the different groups was compared between the new "Hamburg" formula and the GRWR.

Standard liver volume [ml] = −20.2472281 + 3.339056437 * body length [cm] + 13.11312561 * body weight [kg].

Data ranges:

Body mass: 4–93.5 [kg], body length: 53–193 [cm], BMI: 14.24–25.10 [kg/m^2].

Regression analysis: Coef det r^2 = 0.88; Std Err = 136.35.

Standard liver volume in pediatric liver transplant recipients

Between 2000 and 2010, a total number of 377 pediatric LTX were performed, with a complete follow-up being available in 353 children. 132 (37%) children were younger than 1 year, and 221 (63%) children were aged between 1 and <16 years. The standard liver volume was calculated by the two formulas ("formula 1" for children 0 to ≤1 year and "formula 2" for children >1 to <16 years) based on autopsy data of about 400 children mentioned before. In the children until 1 year of age with a median body weight of 5.6 kg (range 2–11 kg), the median calculated standard liver volume was 201 ml (range 70–360 ml). In children older than 1 and younger than 16 years, the median calculated standard liver volume was 533 ml (range 264–1354 ml).

Because of the widespread use of the GRWR also in children, regardless of the overall higher percentual liver weight with age-related changes in this patient group, we additionally calculated the GRWR in all children undergoing LTX. Based on the classification described before, children were divided into recipient groups of size-matched organs versus small-for-size, large-for-size, or extra large-for-size organs.

Comparison of the classification of the children into recipients of size-matched versus mismatched organs based on the different formulas used for calculation of the standard liver volume and the GRWR is shown in Fig. 1.

Size-matched versus small-for-size and large-for-size/extra large-for-size LTX

Applying our formula ("formula 1 + 2") to the whole study population of 377 pediatric LTX recipients led to classification of 266 LTX as size-matched in contrast to 31 small-for-size LTX, 31 large-for-size LTX, and 25 extra large-for-size LTX. The corresponding mean GRWR in the four groups was 3.1% (range 1.3–12%) in the group of size-matched organs, 1.3% (range 0.7–2%) in the small-for-size group, 6% (range 4.1–7.9%) in the large-for-size group, and 7.6% (range 4.6–12.5%) in the extra large-for-size group.

Patient and donor characteristics

Comparison of the recipient age, weight, and height between the four groups showed a significant difference (all *P*-value 0.000) with older, heavier, and larger children assigned to the small-for-size group and younger, lighter, and smaller children assigned to the large-for-size and extra large-for-size groups compared with children receiving size-matched organs. As expected, the

GRWR was significantly lower in children undergoing small-for-size LTX and significantly higher in children undergoing large-for-size and extra large-for-size LTX in contrast to size-matched LTX ($P = 0.000$). However, there was no significant difference in the distribution of whole organs versus technical variant grafts between the four groups. Likewise, we found no significant difference in recipient diagnosis, ratio of elective to high-urgent LTX, cold and warm ischemic time, or donor age between the groups. Detailed patient and donor characteristics are given in Table 1.

Comparison of the children with liver disease undergoing LTX with the children included in the regression analysis (autopsy data), showed a comparable age distribution with a maximum of younger children in both. However, there was a trend to a lower body weight in the children undergoing LTX despite similar age (Fig. 2).

Graft survival

In a first step, we analyzed the graft survival between four groups (small-for-size organs, size-matched organs, large-for-size organs, and extra large-for-size organs) by log rank test and illustrated by Kaplan–Meier survival curves. Although not statistically significant ($P = 0.292$) by the log rank test, survival curves showed a clear trend toward a reduced graft survival in children undergoing small-for-size LTX in contrast to size-matched or oversized LTX (Fig. 3). 1- and 5- year graft survival according to size-match was 80.6/49.8% (small-for-size), 84.3/73.6% (size-matched), 80.6/67.1% (large-for-size), and 87.5/82.9% (extra large-for-size) in the children analyzed. To avoid overlooking significant differences using a cut-off statistic for arbitrarily defined categorizations which are commonly used in the literature for the description of graft recipient size-matching, we additionally performed a Cox regression analysis.

Table 1. Patient and donor characteristics. The table gives an overview about the patient and donor characteristics of all pediatric LTX divided into the different groups of size-matched versus size-mismatched organs.

	Size-matched organs $n = 266$	Small-for-size organs $n = 31$	Large-for-size organs $n = 31$	Extra large-for-size organs $n = 25$	Statistic
Recipient age [years]; median (range)	2.2 (0–16)	7.4 (0.8–15.3)	0.6 (0–6.8)	0.4 (0–15.2)	$P = 0.000$
Recipient weight [kg]; median (range)	10 (2.6–61)	22 (7–62)	5.2 (3.1–18)	4.9 (2–31)	$P = 0.000$
Recipient height [cm]; median (range)	80 (49–177)	120 (67–175)	60 (44–105)	55 (38–130)	$P = 0.000$
Graft weight [g]; median (range)	313 (125–1570)	290 (106–566)	346 (186–880)	340 (250–1900)	$P = 0.044$
GRWR [%]; median (range)	3.1 (1.3–12)	1.3 (0.7–2)	6 (4.1–7.9)	7.6 (4.6–12.5)	$P = 0.000$
Graft type [*n* (%)]					
Whole organ	45 (16.9)	1 (3.2)	7 (22.6)	3 (12)	$P = 0.175$
Reduced organ	26 (9.8)	0 (0)	4 (12.9)	2 (8)	
Split organ	129 (48.5)	21 (67.7)	12 (38.7)	16 (64)	
Living donation	66 (24.8)	9 (29)	8 (25.8)	4 (16)	
Recipient diagnosis [*n* (%)]					
Cholestatic liver disease	125 (47)	9 (29)	18 (58.1)	16 (64)	$P = 0.816$
Metabolic liver disease	43 (16.2)	7 (22.6)	4 (12.9)	4 (16)	
Alagille-syndrome	18 (6.8)	2 (6.5)	2 (6.5)	1 (4)	
Acute hepatic failure	22 (8.3)	3 (9.7)	2 (6.5)	1 (4)	
Hepatic tumor	8 (3)	1 (3.2)	1 (3.2)	0 (0)	
Other	50 (18.8)	9 (29)	4 (12.9)	3 (12)	
Elective/high-urgent LTX [*n* (%)]	202/64 (75.9/24.1)	27/4 (87.1/12.9)	23/8 (74.2/25.8)	18/7 (72/28)	$P = 0.502$
Primary LTX	204 (76.7)	22 (71)	28 (90.3)	21 (84)	$P = 0.635$
Re-LTX; *n* (%)					
First	46 (17.3)	7 (22.6)	2 (6.5)	3 (12)	
Second	14 (5.3)	1 (3.2)	1 (3.2)	1 (4)	
Third	2 (0.8)	1 (3.2)	0 (0)	0 (0)	
PELD score; median (range)	39 (18–80)	37 (26–55)	50 (23–60)	43 (36–67)	
Cold ischemic time [min]; median (range)	535 (122–1034)	574 (157–967)	570 (182–848)	538 (227–755)	$P = 0.808$
Warm ischemic time [min]; median (range)	34 (10–85)	34 (14–60)	40 (19–72)	36 (15–95)	$P = 0.781$
Donor age [years], median (range)	28.8 (0–59.5)	25.1 (1–50.6)	20.8 (1–59.8)	23.2 (1.3–53)	$P = 0.339$
Donor risk index, median (range)	0.77 (0.01–1.57)	0.54 (0.03–1.07)	0.89 (0.27–1.40)	0.94 (0.11–1.63)	$P = 0.296$

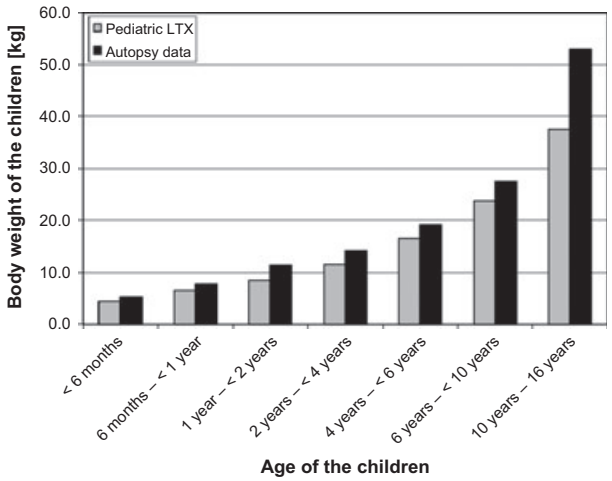

Figure 2 Comparison of the body weight of the children included the regression analysis and of the children undergoing LTX. The figure compares the body weight of the children, whose autopsy data are included in the regression analysis to develop the formula for the standard liver volume and the body weight of the children undergoing liver transplantation. Body weight is given a mean value for each age group.

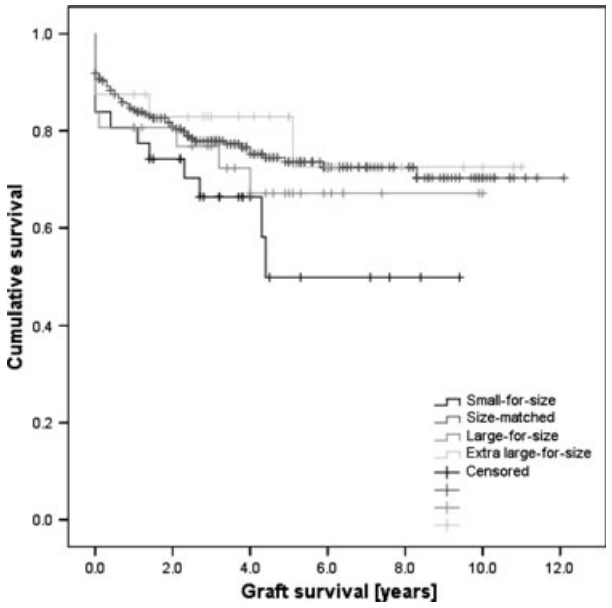

Figure 3 Graft survival. The figure shows the Kaplan–Meier graft survival curves for the four groups. Statistical analysis by log rank test showed no significant difference in the graft survival between the groups ($P = 0.292$).

Separate analyses were carried out to investigate a possible negative impact of both small-for-size and large-for-size organs, respectively. Cox regression analysis identified a significant elevated risk of graft failure in children receiving very small organs ($P = 0.029$). In detail, 10% reduction in the calculated standard volume resulted in an increase of 12.8% for liver graft failure and 50% reduction corresponds to an increase of 83% for liver graft failure. Cox regression analysis for oversized organs did not show a significantly elevated risk of liver graft failure ($P = 392$).

To identify possible differences in the organ quality between living and deceased donors (e.g., brain death, longer preservation time), a separate analysis for both types of donor grafts ($n = 266$ vs. 87) regarding the outcome depending on the liver graft size was performed. Overall, no significant difference in the graft survival, neither in children receiving living donor grafts ($P = 0.361$), nor in children receiving deceased donor grafts ($P = 0.633$), was evident when comparing size-matched versus size-mismatched organs. However, there was a clear trend to a reduced graft survival in children receiving a small-for-size organ from both types – living or deceased – of donors. Also multivariate analysis including the factor deceased versus living donation in the Cox regression analysis revealed a significant negative impact of small-for-size organs ($P = 0.031$) and no negative impact of large-for-size organs ($P = 0.396$) both independent of the kind of donation.

According to the two different formulas, we analyzed the graft survival divided into children ≤1 year ($n = 132$; small-for-size $n = 1$, size-matched $n = 82$, large-for-size $n = 26$, extra large-for-size $n = 23$) and children >1 to <16 years ($n = 221$; small-for-size $n = 30$, size-matched $n = 184$, large-for-size $n = 5$, extra large-for-size $n = 2$). Overall, we found no significant difference in the outcome between children receiving size-matched organs versus size-mismatched organs in both age groups analyzed separately (P-values 0.188 and 0.696).

Early liver graft failure, small-for-size, and large-for-size syndrome

Seven children died within 30 days after liver transplantation due to cardiopulmonary failure ($n = 3$), infectious complications ($n = 2$), or hypoxic brain death ($n = 2$) with a functioning liver graft. Another 33 (9.3%) children developed liver graft failure within 30 days after liver transplantation and underwent re-LTX. Causes of early liver graft failure in these children were primary liver graft nonfunction in 18 children and hepatic artery thrombosis in 15 children. Rate of early liver graft failure was 7.9% (21/266) in children receiving a size-matched graft and 16.1% (5/31), 16.1% (5/31), and 8% (2/25) in children with small-for-size, large-for-size, and extra large-for-size grafts, respectively.

In addition to the children with early liver graft failure mentioned previously, there were no other children presenting with the symptoms and signs of primary poor or delayed liver graft function. In particular, none of the children exhibited signs of a small-for-size syndrome

including ascites, prolonged cholestasis, and persistent coagulopathy. Also, no children presented with classic symptoms of a large-for-size syndrome including inadequate liver perfusion due to inadequate liver size or respiratory problems due to elevated abdominal pressure. In case of clinically elevated intra-abdominal pressure or impaired doppler ultrasound parameters, an elastic patch was used for temporarily abdominal wall closure (extra large-for-size group 89%, large-for-size group 62%, size-matched group 33%, small-for-size group 12%). These children underwent operative revision with stepwise reduction in the patch twice a week until definitive closure, in all children the patch could be removed successful after 1–6 re-operations.

Discussion

Pediatric liver transplantation has always been accompanied by a shortage of age- and size-matched organs explained by the epidemiology of pediatric liver disease with the highest demand of liver transplantation in children <2 years of age. In the past, transplantation of reduced liver grafts from adult donors has substantially decreased mortality on the pediatric waiting list, however, at the price of a reduced number of available organs for adults. The development of techniques to split a liver allows transplantation a child and a second (adult) patient, and nowadays, a left lateral lobe (segments 2 and 3) derived from a deceased or living donor represents the liver graft most commonly used in pediatric recipients. The degree of freedom to tailor a split liver graft according to the size requirements of the recipient, though, is limited due to anatomical reasons, especially in living donors. Studies investigating size-matching in liver transplantation mostly address the issue small-for-size grafts in the setting of adult to adult living donor liver transplantation [9], while data regarding the outcome following small-for-size and also large-for-size LTX in children are almost not available.

Most formulas available for calculation of the standard liver weight in humans were developed based on the data from adults or from a very limited number of and mostly older children. A recent review comparing the variability of standard liver volume estimation found 16 different formulas worldwide, thereof only four formulas that also included data from younger children [10]. One of the best known and most cited formula to calculate the standard liver volume was published in 1995 by Urata *et al.* [2], which was based on CT scan data including 96 patients including 65 pediatric subjects. Another formula to calculate the standard liver volume based on CT scan data was developed by Noda *et al.* in 1997 based on 54 children and adolescents [5]. Main limitations of both formulas arise from the small number of cases studied. Further, as pointed out in a recent publication, a transcription error in the equation for calculation of the body surface area used in the "Urata" formula for children under 15 kg leads to an systematic bias in a number of publications using this formula [11]. In our study, the formula developed to calculate the standard liver volume is based on autopsy data from a large number ($n = 388$) of liver healthy children. The age distribution in the autopsy data and the cohort of children who underwent LTX at our institution was similar spanning a range from the day of birth up to 16 years. However, for similar age groups, the body weight of children undergoing LTX was lower compared to children analyzed in the autopsy study. Most likely this observation can be explained by the presence of chronic underlying illness, for example cholestatic or metabolic liver disease with retardation of growth in the pediatric liver transplant recipients. Nevertheless, a correct estimation of the standard liver volume will be predicted by our formula as it is based on body weight and height instead of patient age.

In the second part of our study, we applied our newly developed formula to a cohort of pediatric patients transplanted at our center. The risk of graft failure was analyzed (i) after classification of pediatric recipients into different size-matching groups defined by the ratio graft to recipient standard liver weight and (ii) by Cox regression analyses divided into increasing and decreasing liver volume. In the small-for-size setting, our data showed significant elevated risk of liver graft failure in children receiving very small organs. Large-for-size or even extra large-for-size organs had no impact on the graft survival. Separate analysis with regard to donor type – deceased or living related – revealed similar results.

Review of the existing literature on the other hand allows no conclusive statement about the impact of small-for-size or large-for-size liver grafts in pediatric LTX. Data regarding the impact of small-for-size organs in pediatric LTX are sparse and frequently compromised by methodological problems. Often, results were obtained from a mixture of pediatric and adult transplantations without further differentiation, almost all studies are based on living-related LTX, and calculations to define small-for-size liver graft were based on the formula by "Urata" with its equation error [12–14] or based on GRWR. Application of GRWR, however, as commonly applied in the adult situation seems to be an inappropriate tool in pediatric liver transplantation. The normal standard liver weight in adults depends on race, gender, and body mass index, but overall is constant about 2–3% of the body weight [15]. In contrast to adults, the liver weight in children is age-related with a maximum relative liver weight of about 5% of the body

weight at the age of 1 year [1]. This became clearly apparent when we applied our newly developed formula to all transplanted children and divided the pediatric recipients based on the liver graft weight to standard liver volume ratio in four groups (small-for-size, size-matched, large-for-size, and extra large-for-size). Additional application of the GRWR and the traditional classification in size-matched versus size-mismatched organs (small-for-size GRWR <1%, size-matched GRWR ≥1% to ≤3%, large-for-size >3% to ≤4%, extra large-for-size >4%) showed a clear shift to large-for-size and extra large-for-size grafts in our children, whereas small-for-size organs do almost not exist.

Kiuchi *et al.* [16], for example, analyzed 276 pediatric and adult recipients of liver grafts from living donation concerning outcome divided by the GRWR regarding small-for-size and large-for-size organs. Children were classified regardless of differences in the age-related liver volume in the same classes as the adult recipients, which means newborns with a GRWR of more than 3% were classified as large-for-size graft recipients, although the normal percentual liver weight in this age group is about 5% of the body weight. These data clearly underline the fact that the GRWR is not suitable to predict the optimal liver volume in children.

Large-for-size transplantation had no negative impact on graft survival in our study. This result that goes along with a recent analysis of a small number of pediatric large-for-size LTX showed a comparable outcome to size-matched LTX [17]. Thus, it might be speculated that further reductions in left lateral liver grafts or the use of monosegments with the aim to avoid a large-for-size situation in very small children with its associated increase in complication rate [18,19] might not be necessary.

In summary, a correct estimation of the standard liver volume is essential to compare the outcome of size-matched versus small-for-size or oversized organs in children.

Our formula allows an improved calculation of the standard liver volume in pediatric liver transplant recipients. Application of the formula to our large pediatric liver transplant database revealed that small-for-size transplantations were associated with an impaired graft survival, whereas large-for-size liver grafts had no negative impact.

These findings might have implications for further development of allocations rules for pediatric liver transplant recipients in a sense that small children and infants are well served with left lateral graft even in large-for-size situations, whereas small-for-size situations that especially occur in larger children weighing 25–50 kg should be avoided (i.e., by allocation of whole organs from pediatric donors instead of smaller left lateral grafts from adults).

Authorship

UH collected and analyzed data and wrote the article. FW: collected and analyzed data. AH and BN: designed the study. RG: analyzed data. EG: collected data. EV: analyzed data (statistic analysis). LF: designed the study and wrote the article.

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