Original Article

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Computed tomography donor liver volumetry before liver transplantation in infants ≤10 kg: does the estimated graft diameter affect the outcome?

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Abstract

Aim of the study: Living donor liver transplantation (LDLT) is regularly performed in small-sized infants. Computed tomography (CT)-based donor liver volumetry is used to estimate the graft size. The aim of our study was to assess the results of CT liver volumetry and their impact on the clinical outcome after LDLT in extremely small-sized infants.

Patients and methods: In this study, we included all patients with a body weight of ≤10 kg who underwent living related liver transplantation at our centre between January 2004 and December 2014. In all cases of LDLT, a preoperative CT scan of the donor liver was performed, and the total liver and graft volumes were calculated. The graft shape was estimated by measuring the ventro-dorsal (thickness), cranio-caudal, and transversal (width) diameter of segment II/III. We assessed the impact of CT donor liver volumetry and other risk factors on the outcome, defined as patient and graft survival.

Results: In the study period, a total of 48 living related liver transplantations were performed at our centre in infants ≤10 kg [20 male (42%), 28 female (58%)]. The mean weight was 7.3 kg (range 4.4–10 kg). Among the recipients, 33 (69%) received primary abdominal closure and 15 (31%) had temporary abdominal closure. The patient and graft survival rates were 85% and 81%, respectively. In CT volumetry, the mean estimated graft volume was 255 mL (range 140–485 mL) and the actual measured mean graft weight was 307 g (range 127–463 g). The mean ventro-dorsal diameter of segment II/III was 6.9 cm (range 4.3–11.2 cm), the mean cranio-caudal diameter was 9 cm (range 5–14 cm), and the mean width was 10.5 cm (range 6–14.7 cm). The mean graft-body weight ratio (GBWR) was 4.38% (range 1.41–8.04%). A high graft weight, a GBWR >4%, and a large ventro-dorsal diameter of segment II/III were risk factors for poorer patient survival.

Conclusion: Preoperative assessment of the graft size is a crucial investigation before LDLT. For extremely small-sized recipients, not only the graft weight but also the graft shape seems to affect the outcome.

Keywords: biliary complications; graft-body weight ratio; large-for-size-syndrome; living donor; paediatric surgery; temporary abdominal closure.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; GBWR, graft-body weight ratio; INR, international normalized ratio; LDLT, living donor liver transplantation; LLS, left lateral segment; LT, liver transplantation; MELD, model for end-stage liver disease; γGT, gamma-glutamyl-transpeptidase.

Introduction

Liver transplantation (LT) has become an established treatment for children with end-stage liver disease.

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Among the group of very small liver recipients, the most frequent disease leading to LT is biliary atresia, followed by several other chronic liver diseases [1, 2]. This special group of patients often requires transplantation before reaching a body weight of 10 kg. Therefore, performing LT in these patients remains a surgical challenge due to vascular complications, hypercoagulation, and, most important, size mismatching. Precise surgical planning including preoperative hepatic volumetry is required to avoid large-for-size grafts resulting in increased intra-abdominal pressure.

In addition, the organ supply from a deceased donor for infant recipients is much smaller than the actual demand, which makes it difficult to find adequate organs matching the small size of these patients and tightens the major problem of massive organ shortage in LT [1]. Besides new approaches like using ABO-incompatible or split grafts [3, 4], the most important possibility to overcome the organ shortage for infants and to avoid mortality while on the waiting list remains living donor LT (LDLT). In order to receive grafts that better match the size of small recipients, Kitajima et al. [5] recently reported on LDLT using reduced-thickness left lateral segment (LLS) grafts.

In order to assess the expected graft size, computed tomography (CT)-based volumetry of the donor liver has become an established examination prior to LDLT. Thus far, there are no reports investigating the clinical impact of the results of CT liver volumetry before LDLT in small-sized infants. As it is important to know aspects of volumetry that actually influence the course and the outcome of LDLT, in the present study, we investigated which parameters of pretransplant liver volumetry affect the outcome in extremely small recipients. The primary endpoint of our study was the outcome after LDLT; the secondary endpoints were identifying risk factors that influence the outcome after LDLT.

Materials and methods

The study design was reviewed and approved by the Local Research Ethical Committee (no. 17-7412-BO). In this study, we included all paediatric patients with a body weight ≤10 kg undergoing LDLT between January 2004 and December 2014 at one university transplant centre. The medical records of all recipients and donors were analysed retrospectively. Two patients were excluded from the study: one patient died during the operation, whereas another patient needed to be left anhepatic after the first LT and received a second LT on the same day.

The primary endpoint was the outcome, characterised by patient and graft survival. We focussed on those patients who received LDLT and evaluated the postoperative clinical course by identifying risk factors leading to a poorer outcome.

CT liver volumetry

In cases, the preoperative CT scans of the donor were evaluated and the diameter of segment II/III was assessed in all three dimensions: ventro-dorsal (thickness), cranio-caudal (length), and transversal (width) (Figure 1). The total liver volume was calculated after boundaries of the hepatic lobe were drawn manually on consecutive 5-mm-thick axial portal-venous phase CT images (no gap). Volumes were calculated by multiplying the slice thickness with the sum of all traced areas of the respective hepatic lobe. Manual measurement was favoured over automatic measurements, as automatic programs identify the left hepatic vein as the boundary whereas transplant surgeons choose their resection plane slightly moving into segment IV, so that automatic measurements would deliver too small values for the estimated graft volume.

Correlations between one-dimensional measurements and volumes were analysed.

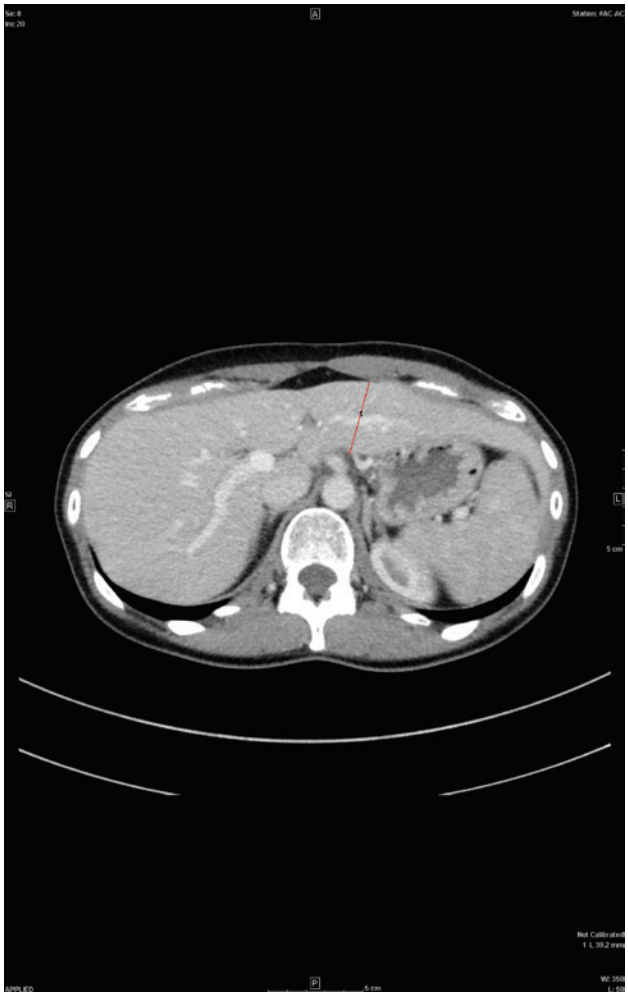

Figure 1: CT of the liver.
Axial portal-venous phase CT image with the ventro-dorsal diameter of a female donor liver.

Surgical technique

The surgical technique for the donor and recipient operation followed previously described principles [1, 6–8]. All LTs were carried out via an open transverse laparotomy. The graft was anastomosed to the recipients' inferior vena cava by using the piggy-back technique. Anastomoses of the portal vein and hepatic artery were performed by using the end-to-end technique. The bile flow was maintained by performing a bileo-enteric anastomosis. Immediately after vascular anastomosis, intraoperative duplex ultrasound was performed, and portal venous, hepatic artery, and venous outflow were measured.

Primary abdominal closure was performed when the muscular abdominal wall could be well adapted. If, however, the portal venous or arterial flow was impaired upon approximation and the portal venous flow was <10 mL/min, the abdomen was left open and a silicon foil was inserted, as described before [9]. Therefore, duplex ultrasound was repeatedly performed before and after abdominal wall closure. The decision for temporary abdominal closure was also made according to the surgeons' evaluation in case of limited intra-abdominal space when the muscular abdominal wall could not be adapted after the surgery. Heparin (50 IE/kg) was administered postoperatively for a minimum of 7 days in uncomplicated cases and then replaced by acetylsalicylic acid (50 mg 3×/week).

Statistical analysis

Statistical analysis was performed using Fisher's exact test and unpaired Student's t-test with significance assumed at $p < 0.05$. The correlation between two variables was determined by calculating the Pearson product-moment correlation coefficient. Laboratory data of donors and recipients as well as demographic data are given as mean and range.

Results

LDLT: recipient and donor characteristics

In the study period, 48 infants with a body weight of ≤10 kg [20 male (42%), 28 female (58%)] underwent LDLT in a single university transplant centre. The mean body weight of the 48 paediatric recipients was 7.3 kg (range 4.4–10 kg). The underlying diseases for the LDLT were extrahepatic biliary atresia in 38 cases; hepatoblastoma in three cases; progressive familial intrahepatic cholestasis type 2 in two cases; primary hyperoxaluria in two cases; and Alagille syndrome, toxic liver failure, and cholestatic liver disease of unknown origin in one case each. These patients spent a mean time of 40 days (range 1–345 days) on the waiting list for LT. The mean model for end-stage liver disease score was 15 (range 6–35), and the mean paediatric end-stage liver disease score was 28 (range 22–40). In three cases (6.3%), an ABO-incompatible LDLT was performed.

One donor for LDLT was the grandmother, whereas all other donors were parents of the recipients [fathers 16 (33%), mothers 31 (65%)], with one mother being an unrelated adoptive mother. The mean age of the donors was 31.8 years (range 22.1–48.3 years), and their mean body mass index was 24.4 (range 18–33.4). The mean graft-body weight ratio (GBWR) was 4.38% (range 1.41–8.04%). The mean donor weight-graft weight ratio was 9.9 (range 5.2–15.3).

LDLT: CT volumetry

In all cases, a CT-based volumetry of the donor liver was performed prior to LDLT. The mean estimated total liver volume of the donor was 1579 cm^3 (range 865–3060 cm^3). As we regularly use the LLS for LDLT, in all cases, liver segment II/III of the donor was measured to estimate the graft volume and diameters. The mean ventro-dorsal diameter of segment II/III was 6.9 cm (range 4.3–11.2 cm); the mean cranio-caudal diameter was 9 cm (range 5–14 cm). The mean transversal diameter, describing the width of the graft, was 10.5 cm (range 6–14.7 cm). The grafts from male donors had a significantly larger thickness (ventro-dorsal diameter, $p < 0.005$) than those from female donors.

The mean estimated graft volume was 255 mL (range 140–485 mL). There was no difference between male and female donors concerning the estimated graft weight. The actual measured mean graft weight at transplantation was 307 g (range 127–463 g). There was no significant difference between the estimated graft volume and the actual measured graft weight. However, the ratio describing the accuracy of the estimated graft volume by CT volumetry (mean estimated graft volume/actual graft weight) was 85% (range 48–168%), indicating that CT volumetry estimated a graft volume that was lower than the actual measured graft weight.

By analysing correlations between one-dimensional measurement, we found the following formulas for estimating the graft volume:

- Male donors: graft volume (mL) = 83.1 + 2.2 ∗ ventro-dorsal diameter (deviation ± 23% (10/90-quantile: –22.8%/18.1%)
- Female donors: graft volume (mL) = 116.76 + 0.23 ∗ cranio-caudal diameter ∗ ventro-dorsal diameter [deviation ± 50/61% (10/90-quantile: –39%/26%].

A formula for the accurate estimation of the graft volume including all three dimensions of segment II/III (ventro-dorsal, cranio-caudal, and transversal) could not be identified.

LDLT: outcome

The mean operation duration for LDLT was 426 min (range 281–1273 min). The mean cold ischaemic time was 92 min (range 6–298 min), whereas the mean warm ischemic time was 45 min (range 15–123 min). After LDLT, 33 recipients (69%) received primary abdominal closure and 15 (31%) received temporary abdominal closure. The serum activities of liver enzymes, bilirubin, and coagulation parameters before and 6 months after transplantation are shown in Table 1. Surgical complications included pleural effusion (n = 21), hepatic artery thrombosis (n = 12), portal vein thrombosis (n = 9), biliary leakage (n = 7), chylascites (n = 7), biliary stenosis (n = 6), intra-abdominal bleeding (n = 5), and gastrointestinal bleeding (n = 4). After LDLT, the patient and graft survival rates were 85% and 81%, respectively.

Overall, there were five cases of graft loss secondary to vascular complications. The graft loss was caused by hepatic arterial thrombosis in four cases and by hepatic vein thrombosis in one case. In two of these five cases, there was a large-for-size situation with a GBWR >4%. The other three cases had a GBWR <4%, and none had a GBWR >6%.

Table 1: Serum levels of different liver markers preoperatively and 6 months after LT.

	Mean (range)	
	Preoperatively	**6 Months post-LT**
Bilirubin (mg/dL)		
Whole cohort	12.4 (0.1–44)	2.1 (0.1–34.3)
LDLT	14 (0.2–44)	1.4 (0.1–21.1)
Prothrombin time (quick%)		
Whole cohort	61 (10–120)	83 (26–114)
LDLT	64 (16–120)	85 (28–114)
PTT (s)		
Whole cohort	55 (21–170)	38 (21–160)
LDLT	56 (23–160)	40 (21–160)
INR		
Whole cohort	1.57 (0.86–4.78)	1.07 (0.95–1.33)
LDLT	1.45 (0.86–3.81)	1.06 (0.95–1.33)
γGT (U/L)		
Whole cohort	171 (10–1829)	113 (4–2207)
LDLT	162 (10–1829)	102 (7–2207)
ALT (U/L)		
Whole cohort	290 (15–4946)	185 (9–2894)
LDLT	166 (23–1874)	143 (13–2109)
AST (U/L)		
Whole cohort	475 (26–8197)	529 (20–14253)
LDLT	230 (26–811)	239 (20–5132)

LT, Liver transplantation; LDLT, living donor liver transplantation; PTT, partial thromboplastin time; INR, international normalised ratio; γGT, gamma-glutamyl-transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

LDLT: risk factors

In statistical analysis, we identified several clinical and biochemical parameters as risk factors for a poorer patient or graft survival in the group who received LDLT (Table 2). The characteristics of the graft affecting patient survival were a high graft weight, a GBWR of >4%, and a large ventro-dorsal diameter of segment II/III (graft thickness), measured using CT volumetry (Figure 2). A GBWR of >4%

Table 2: Risk factors for poorer patient and graft survival (univariate analysis).

Risk factor	Patient survival (p-value)	Graft survival (p-value)
Vascular thrombosis	Yes (0.007)[a]	Yes (0.017)[a]
MELD	Yes (0.05)[a]	–
Graft weight	Yes (0.006)[a]	–
GBWR >4%	Yes (0.03)	Yes (0.04)[a]
Recipient age at LT	Yes (0.08)	–
Donor age	–	Yes (0.04)
AP diameter of segment II/III	Yes (0.045)	–
Temporary abdominal closure	Yes (0.04)	–
Days at waiting list	Yes (0.05)	Yes (0.06)

MELD, Model for end-stage liver disease; GBWR, graft-body weight ratio; LT, liver transplantation; AP, anteroposterior. [a]Independent risk factor (multivariable analysis).

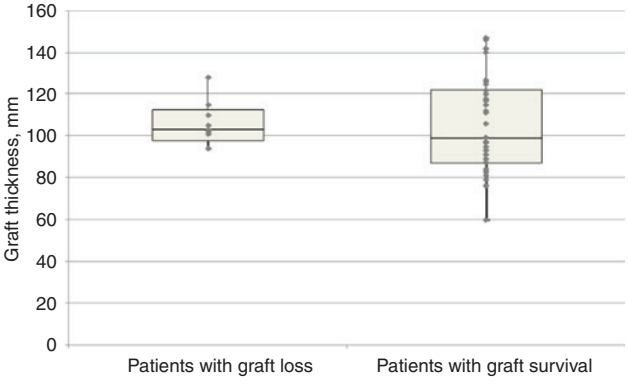

Figure 2: Boxplot showing the correlation between graft thickness and graft survival.
Left box: Patients with graft loss (n = 9). Graft loss median graft thickness: 103 mm. Graft loss 25 quartile: 98 mm. Graft loss 75 quartile: 113 mm. Right box: Patients with graft survival (n = 39). Graft survival median graft thickness: 99 mm. Graft survival 25 quartile: 87 mm. Graft survival 75 quartile: 122 mm.

affected both patient survival and graft survival. There was no correlation between any other parameter concerning the donor liver measured in CT volumetry and the outcome. However, the occurrence of vascular thrombosis, including hepatic artery and portal vein thrombosis, was identified in multivariable analysis as an independent risk factor for both poorer patient survival and graft survival. There was no correlation between the occurrence of thrombosis and any of the estimated graft diameters.

Discussion

Preoperative imaging of the liver donor with estimation of the graft size has become a crucial investigation prior to LT. According to Lim et al. [10], imaging-based volumetry of the liver is vital in the preoperative planning for LT, as the liver volume is one key factor in the selection of the appropriate individual for LDLT. Especially in LDLT, precise assessment of the donor liver volume is crucial in determining whether the donor is suitable for LDLT, to ensure safety for both donor and recipient [10]. In addition, preoperative imaging is required to ensure that there is no underlying focal or diffuse liver disease that may make transplantation unsuitable, such as steatosis, cirrhosis, and focal benign or malignant neoplasms.

Currently, the preferred means of imaging-based liver and graft size estimation is CT volumetry, which generally provides good correlation of the estimated volume with the graft weight obtained [10, 11]. Yoon et al. [12] used the actual graft weight as a standard of reference in living liver donors for determination of the accuracy, reproducibility, and improvement in the clinical workflow of a semi-automatic CT virtual surgical planning program in estimating graft volume. The authors reviewed the liver CTs of 105 liver donor candidates, and found a strong correlation between the predicted volumes of the hepatic graft and the actual graft weight. Furthermore, the mean processing time of hepatic volumetry, segmentation, and surgical planning using software was significantly shorter than using manual volumetry.

An actual clinical impact of preoperative imaging before LDLT was first described by Ringe et al. [13]. In a study on the significance of CT in the donor selection process, the authors found that almost one-third of the donor candidates were rejected because of CT findings. The authors concluded that CT can help reduce the risk for donors and recipients by excluding unsuitable donor livers.

However, these studies did not exclusively address liver donors for infants. One critical challenge in extremely small-sized infants receiving LDLT is the increased risk for developing large-for-size syndrome. In the past, several authors described different approaches, trying to avoid a large-for-size situation in small-sized liver recipients: Ogawa et al. [14] used reduced monosegmental grafts for LDLT in nine extremely small-sized infants, and reported a patient and graft survival at 1 year of 66.7%. They concluded that reduced monosegmental LDLT represents a feasible option for neonates and extremely small infants with liver failure.

Another approach to avoid a large-for-size situation was recently published by Yamada et al. [15]. The group reported on their graft selection strategy being based on preoperative CT volumetry for recipients ≤6 kg. The group's strategy for graft selection among those patients depended on the GBWR, based on the donor preoperative CT volumetry for the LLS graft. When the predictive GBWR of the LLS graft was ≤5%, they selected the LLS as the liver graft. When the predictive GRWR of the LLS graft was >5%, they selected the S2 monosegment as the liver graft. When the actual GRWR was >4%, they performed partial graft hepatectomy *ex vivo* to reduce the GRWR to ≤4%. The authors concluded that their graft selection strategy based on the preoperative CT volumetry value is highly useful in patients weighing ≤6 kg. They stated that the use of S2 monosegment grafts is effective and safe in very small infants and particularly in neonates. Recently, Kitajima et al. [5] reported on their experience with reducing the thickness of the LLS and stated that LDLT using reduced LLS is a feasible option with better outcomes when compared with non-reduced grafts.

In contrast to these studies, the study by Schulze et al. [3] showed that using exclusively left lateral grafts from living donors or split grafts for extremely small paediatric liver recipients leads to an excellent outcome without the need for reduction of the grafts or the use of monosegments. The group used temporary abdominal closure in a high proportion of their patients, in 28% of the whole cohort and in 39% of the large-for-size group, and stated that the use of a patch is one possibility to avoid large-for-size syndrome. However, recently, our group found that LDLT is possible without reduction and without the necessity of a patch in some cases of a high GBWR [9]. According to this strategy, our group performed all LDLTs using the LLS without any form of a further graft reduction.

Another key factor in avoiding a large-for-size situation in extremely small-sized liver recipients is CT-based graft size estimation, which is a precise estimation of the graft size. Thus far, there have been no reports on the outcome after LDLT depending on the results of preoperative CT liver

volumetry. As this investigation has become a standard procedure, it is important to know which aspects of volumetry actually have clinical relevance, and whether they influence the course and the outcome after LDLT.

In the present study, we provide, for the first time, different diameters of the estimated graft size for recipients ≤10 kg, combining them with clinical data and their impact on the outcome. We found that not only the graft weight but also the estimated thickness of the graft, characterised by the ventro-dorsal diameter of segment II/III, significantly influenced patient survival, whereas the total volume of the donor liver and the volume of the graft had no influence. This goes along with the findings of Schulze et al., who noted that the ventro-dorsal diameter of the graft appeared to be more relevant to potential graft necrosis than the actual graft size [3]. One possible explanation could be the mismatch between the vessels of the graft and the small-sized ones of the neonatal recipient. The difference in the vessel size might rather be a limiting factor in the transplantation procedure than the actual volume of the graft. This clinically relevant aspect in preoperative CT liver volumetry is new and might be beneficial in finding the appropriate graft for extremely small-sized recipients. However, the present study has limitations. We did not differentiate between biliary atresia patients who often show hypoplastic portal veins and cirrhotic livers and therefore might require different surgical strategies as opposed to patients with non-cirrhotic liver diseases. Also, donor-associated factors such as comorbidities or alcohol consumption could have influenced the outcome. The study is also limited by its retrospective nature, and a further prospective study is needed to verify our results. Should the influence of the segment II/III ventro-dorsal diameter on the outcome be confirmed, possibly a cut-off diameter of segment II/III of the donor liver could be recommended before LDLT in extremely small-sized infants to reduce the risk of large-for-size syndrome. However, it is important to note that graft function and survival are not only influenced by graft size but are also affected by other factors. In our present study, the number of days the recipients spent on the waiting list for transplantation, a GBWR >4%, and the occurrence of vascular thrombosis were risk factors for both poorer patient and graft survival, which agrees with the results of previously published studies on parameters affecting the outcome after LT [16–18].

Conclusion

Preoperative assessment of the graft size is a crucial investigation before LDLT. We identified larger graft thickness, estimated by measuring the ventro-dorsal diameter of segment II/III in CT donor liver volumetry, as a risk factor for a poorer patient survival. This new aspect might be helpful in finding more grafts for extremely small-sized recipients despite high donor volumes of segment II/III when its configuration is slim.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable. Ethical approval: The research related to human use complied with all the relevant national regulations and institutional policies, and was performed in accordance to the tenets of the Helsinki Declaration. The study design was reviewed and approved by the Local Research Ethical Committee (no. 17-7412-BO).

Author Contributions

Nagoud Schukfeh: conceptualization; data curation; writing – original draft. Maren Schulze: conceptualization; data curation. Anna-Charlotte Tabea Holland: data curation; investigation; methodology. Jens Dingemann: writing – review & editing. Dieter P. Hoyer: formal analysis; methodology. Andreas Paul: supervision; writing – review & editing. Jens M. Theysohn: conceptualization; data curation; investigation; project administration; software; supervision; writing – review & editing.

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Supplementary Material: The article (https://doi.org/10.1515/iss-2017-0047) offers reviewer assessments as supplementary material.

Reviewer Assessment

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Nov 27, 2017

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	70

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	4
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	3
Please rate the practical significance.	4
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	1 - Low/No
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

Thanks for sharing your experience with pediatric liver transplantation, especially the problem of large-for-size syndrome in very small infant transplantation.
Overall, we find your article interesting and worthwhile to be published.
Criticism:
1. there is no diagram showing the correlation between graft thickness and graft survival. Instead, you provide a graph pointing out the correlation between vascular thrombosis and graft survival which is not new.
2. As you try to highlight and discuss risk factors of graft survival in a large-for-size setting, would it be worthwile studying in the same intention the correlation between portal vein flow relative to graft size and thickness to assess Portal hypoperfusion as a potential risk factor?
3. was there any influence of the underlying disease or indication to transplantation on graft survival?

Reviewer 2: anonymous

Feb 20, 2018

Reviewer Recommendation Term:	Reject
Overall Reviewer Manuscript Rating:	N/A

Custom Review Questions	**Response**
Is the subject area appropriate for you?	3
Does the title clearly reflect the paper's content?	3
Does the abstract clearly reflect the paper's content?	3
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	2
How adequate is the data presentation?	2
Are units and terminology used correctly?	N/A
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	3
Please rate the practical significance.	2
Please rate the accuracy of methods.	2
Please rate the statistical evaluation and quality control.	2
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	2
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

The concepts that GBWR > 4 % and large ventro-dorsal diameter of the graft do represent a risk factors for large for size syndrome are already known. What is really original and innovative in your paper?
For example, It would be great if you could report a sort of cut off formula regarding the ventro-dorsal diameter in relation to depth of the abdominal cavity of the recipient
Which was the mean weight of the 48 pediatric recipients < 10 Kg?
Why did you measure the volume manually? Actually, there are different programs doing it automatically? Did you try it? How was your experience at this regard? Not reliable? If so, this should be reported too.
Did you measure the intraoperative flows only by doplex US or did you use also other flowmeter devices?
Did you never perform a graft size reduction? If yes, how?
The list of postoperative medication is confusing and not useful in this context
Which is your center policy regarding GBWR ? Do you have any cut off over that you do not perform any LDLT or above that you reduce the graft?
How many of your vascular complication and consequent graft loss were secondary to large for size syndrome?
Minor comment: use LDLT instead of LRLT

Reviewer 3: Ulrich Baumann

Feb 26, 2018

Reviewer Recommendation Term:	Revise with Major Modification
Overall Reviewer Manuscript Rating:	40

Custom Review Questions	**Response**
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	3
Do the keywords clearly reflect the paper's content?	3
Does the introduction present the problem clearly?	2
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	2
How adequate is the data presentation?	3
Are units and terminology used correctly?	4
Is the number of cases adequate?	2
Are the experimental methods/clinical studies adequate?	2
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	2
Please rate the practical significance.	4
Please rate the accuracy of methods.	2
Please rate the statistical evaluation and quality control.	2
Please rate the appropriateness of the figures and tables.	2
Please rate the appropriateness of the references.	2
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
This manuscript touches on the important problem of graft selection in LRLT. The CT imaging of a cohort of 48 live donors is analysed and correlated to transplant outcomes. The authors identify graft thickness as a key determinant of graft outcome. The manuscript is appropriately structured and is using fluent language, however I see a number of open questions:
1. The introduction is not quoting appropriate references: The fact that thickness of a left lateral graft impact on comorbidity and graft outcome is well recognised amongst tx surgeons.
2. Clearly defined objectives are missing.
3. Donor and recipient cohorts are not well described, i.e. the manuscript does not point out the hypoplastic portal veins and arterialised (cirrhotic) livers of patients with BA which require different surgical strategies as opposed to i.e. patients with metabolic (non cirrhotic) or malignant liver disease. Recipient weight variability is not taken into account. Equally donor basic characteristics are missing. Donor variability in i.e. nicotin or alcohol consumption, age, comorbidity are confounding factors they have not been taken into account.
4. Overall the manuscript is lacking some streamline and would benefit from focussing on 1-2 key messages. Currently the ms often drifts away from the focus on CT imaging.
5. In my opinion the figures do not support the text very well.
I am not convinced the manuscript in it´s current format is focussed sufficiently to add much to our current understanding. However in principle and with more focus this work is of potential interest.

Authors' Response to Reviewer Comments

Apr 28, 2018

Dear editor, dear reviewers,
we would like to thank you for your time and effort evaluating our paper and for your constructive comments. In the following we address each point that was remarked.

Reviewer 1:

Thanks for sharing your experience with pediatric liver transplantation, especially the problem of large-for-size syndrome in very small infant transplantation. Overall, we find your article interesting and worthwhile to be published.

Answer of the authors: We appreciate the positive response of the referee regarding our manuscript. Nonetheless he pointed out some shortcomings and had several suggestions. We revised our manuscript according to the reviewer`s suggestions.

1. There is no diagram showing the correlation between graft thickness and graft survival. Instead, you provide a graph pointing out the correlation between vascular thrombosis and graft survival which is not new.

Answer of the authors: We are aware the Figure 1 describes survival depending on vascular complications which are not the main issue of this manuscript. To better focus on our main message, we removed Figure 1 from the manuscript.

We appreciate the suggestion of the reviewer to provided a diagram showing the correlation between graft thickness and graft survival. This is an important figure and we therefore created a boxplot, (new Figure 1) illustrating this important information.

2. As you try to highlight and discuss risk factors of graft survival in a large-for-size setting, would it be worthwhile studying in the same intention the correlation between portal vein flow relative to graft size and thickness to assess portal hypoperfusion as a potential risk factor?

Answer of the authors: We thank the reviewer for pointing out this important aspect. We agree that portal hypoperfusion might be discussed as a potential risk factor. However, in our present work, we measured portal vein flow intraoperatively to assess a potential abdominal compartment. In our univariate analysis we found no significant correlation between thrombosis and any graft diameter. As suggested by the reviewer, we added this importan issue into our manuscript and highlighted the changes in yellow (Results section page 8).

3. Was there any influence of the underlying disease or indication to transplantation on graft survival?

Answer of the authors: We appreciate this question of the reviewer. It would be interesting to know whether the underlying disease influences the graft survival, In our present study, the underlying diseases for the LRLT were extrahepatic biliary atresia in 38 cases, hepatoblastoma in 3, progressive familial intrahepatic cholestasis type 2 in 2, primary hyperoxaluria in 2, alagille syndrome, toxic liver failure and cholestatic liver disease of unknown origin in one case respectively. The rare incidences of diagnoses other than biliary atresia makes it difficult to make a statement about statistically significant differences.

Reviewer 2:

1. The concepts that GBWR>4% and large ventro-dorsal diameter of the graft do represent a risk factors for large for size syndrome are already known. What is really original and innovative in your paper? For example, it would be great if you could report a sort of cut off formula regarding the ventro-dorsal diameter in relation to depth of the abdominal cavity of the recipient

Answer of the authors: We thank the reviewer for this interesting suggestion to report a sort of cut off formula regarding the ventro dorsal diameter in relation to the depth of the abdominal cavity of the recipient. In our present cohort, we did not measure the depth of the abdominal cavity of the recipient and a CT was only regularly performed for the donors. However, we will consider this very interesting aspect for future studies.

2. Which was the mean weight of the 48 pediatric recipients <10kg?

Answer of the authors: The mean weight of the 48 pediatric recipients was 7,3kg (range 4,4 to 10kg). We thank the reviewer for asking this important question and added the information into our Abstract as well as into the Results section (page 6) of our manuscript and hightlighted the additional information in yellow.

3. Why did you measure the volume manually? Actually, there are different programs doing it automatically? Did you try it? How was your experience at this regard? Not reliable? If so, this should be reported too.

Answer of the authors: We thank the reviewer for his interest in our methods of measuring the volume. We are aware that there are programs that automatically measure the volume of the estimated graft. However, these programs follow the exact anatomical structures and would identify the left hepatic vein as the boundary. In contrast, transplant surgeons choose their resection plane slightly moving into segment IV. Therefore, an automatic program would deliver estimated volumes that would be systematically smaller than the actual volume of the graft. To avoid this bias, and get exacter values we chose to measure the volume manually.

As suggested by the reviewer, we added this information into our manuscript to make this point clearer to the reader (page 4, Patients and Methods, section Computed tomography liver volumetry) and highlighted it in yellow. It now reads: The manual measurement was favoured over automatic measurements, as automatic programs identify the left hepatic vein as the boundary whereas the transplant surgeons choose their resection plane slightly moving into segment IV, so that automatic measurements would deliver too small values for the estimated graft volume.

4. Did you measure the intraoperative flows only by doplex US or did you use also other flowmeter devices?
Answer of the authors: We thank the reviewer for their interest in this issue. We used solely duplex US for measuring the intraoperative blood flows.
5. Did you never perform a graft size reduction? If yes, how?
Answer of the authors: We thank the reviewer for asking this important question. As reported in our Methods section, we used left lateral segment (II and III) for liver transplantation in all cases. We actually never performed graft reduction. Previous data from our as well as from other groups [Refences 3 and 8 of our manuscript] have shown that there is no need for monosegmental or reduced size liver grafts for very small children if the optimal surgical technique is performed by an experienced liver transplant surgeon.
To emphasize this important point and make our operative strategy clearer to the reader, we added the following sentence into our Discussion section (page 10) and highlighted it in yellow:
„According to this strategy, our group performed all LDLT using the LLS without any form of a further graft reduction."
6. The list of postoperative medication is confusing and not useful in this context
Answer of the authors: We thank the reviewer for this suggestion and accordingly removed the section *Posttransplant protocol*. However, we believe that the postoperative anticoagulative therapy is of interest for reader regarding the incidence of vascular thrombosis. We therefore added the information about it into the Materials and Methods -> Surgical technique section (page 5) and highlighted it in yellow.
7. Which is your center policy regarding GBWR? Do you have any cut off over that you do not perform any LDLT or above that you reduce the graft?
Answer of the authors: We thank the reviewer for his interest in our center policy regarding GBWR. Actually, we do not have a cut off point of a calculated GBWR. As stated above, we do not reduce the graft, but we rather perform LDLT with secondary abdominal closure using a patch, when it seems clinically indicated. Our decision depends mainly on the maintenance of hepatic arterial and portal venous blood flow and is individually made by the performing surgeon. As stated above, we do not perform graft reduction, but rather chose a temporary abdominal closure using a patch in case of a size mismatch between the graft and the patients' abdominal cavity.
8. How many of your vascular complication and consequent graft loss were secondary to large for size syndrome?
Answer of the authors: Overall, we had 5 cases of graft loss secondary to vascular complications. In four of them the graft loss was caused by hepatic arterial and in one by hepatic vein thrombosis.
In two of these five cases, there was a large-for-size situation with a GBWR >4%. The other three cases had a GBWR <4%, and none had a GBWR >6%.
We thank the reviewer for inquring of this very intersting subject. We believe that these additional information may be of interest to the reader and therefore inserted it into our manuscript (page 8, Results, LDLT-Outcome section) and highlighted the changes in yellow.
9. Minor comment: use LDLT instead of LRLT
Answer of the authors: We thank the reviewer for this correction and accordingly replaced the term throughout the manuscript.

Reviewer 3:
This manuscript touches on the important problem of graft selection in LRLT. The CT imaging of a cohort of 48 live donors is analysed and correlated to transplant outcomes. The authors identify graft thickness as a key determinant of graft outcome. The manuscript is appropriately structured and is using fluent language; however I see a number of open questions.
Answer of the authors: We thank the referee for indicating that the topic of our manuscript is of interest for the reader. Nonetheless he pointed out some shortcomings and had several suggestions. We revised our manuscript according to the suggestions of the referee and thank the referee for helping us to improve our manuscript so that it is more relevant the reader of this esteemed Journal.

1. The introduction is not quoting appropriate references: The fact that thickness of a left lateral graft impact on comorbidity and graft outcome is well recognised amongst tx surgeons.
Answer of the authors: We thank the reviewer for pointing out that the fact that thickness of a left lateral graft impacts on the outcome is well recognized among transplant surgeons. Notwithstanding, there have been only few studies that investigate the subject of graft thickness and its impact on the outcome. The present study, for the first time shows a relationship between the preoperativel determined graft thickness and the outcome, which we believe makes the study worth publishing. Nevertheless, to better meet the expectation of the reviewer, we added the following studies to our referenced in the introduction (page 3) and highlighted it in yellow:
In order to receive grafts that better match the size of small recipients, Kitajima et al [5] recently reported on LDLT using reduced-thickness left lateral segment grafts.

2. Clearly defined objectives are missing.
Answer of the authors: We thank the reviewer for suggesting the missing of clearly defined objectives. We now added this important information to the end of the Introducion section (page 5) and highlighted it in yellow. It now reads:
Primary endpoint of our study was the outcome after LDLT; secondary endpoints were identifying risk factors that influence the outcome after LDLT.
3. Donor and recipient cohorts are not well described, i.e. the manuscript does not point out the hypoplastic portal veins and arterialised (cirrhotic) livers of patients with BA which require different surgical strategies as opposed to i.e. patients with metabolic (non cirrhotic) or malignant liver disease. Recipient weight variability is not taken into account. Equally donor basic characteristics are missing. Donor variability in i.e. nicotin or alcohol consumption, age, comorbidity are confounding factors they have not been taken into account.
Answer of the authors: We thank the reviewer for pointing out these important limitations of our study. However, some oft he critized factors were actually taken into account, such as the donor age, that statistically had no influence on the outcome. In our Results section (Recipient and donor characteristics) we do mention the mean age as and the range of the donors. As we did not find a statistically significant correlation between donor age and the outcome, we did not mention this point additionally.
Nevertheless, to better meet the expectations of the reviewer, we highlighted this issue in our Discussion section (page 11). It now reads:
However, the present study has limitations. We did not differentiate between BA patients who often show hypoplastic portal veins and cirrhotic livers and therefore might require different surgical strategies as opposed to patients with non-cirrhotic liver diseases. Also donor associated factors such as comorbidity or alcohol consumption could have influenced the outcome. The study is also limited by its retrospective character, and a further, prospective study is needed to verify our results.
4. Overall the manuscript is lacking some streamline and would benefit from focussing on 1-2 key messages. Currently the ms often drifts away from the focus on CT imaging.
Answer of the authors: We appreciate this suggestion of the reviewer to better focus on few key messages. We see the focus of our manuscript not on CT imaging, but rather, as stated in the title of our manuscript, on the impact of the results of CT imaging on the outcome. We therefore belief that is of potential interest to the reader not to have only information about the techniqual part of the CT imaging, but also to provide information about the outcome and other risk factors that affect the outcome in this very special group of infant liver recipients, However, we restructured parts of the manscript to better focus on few key messages and hope that the reviewer is now better convinced of our study. In this purpose, we also removed the different ratios between graft weight and liver volumes from the Patients and Methods as well as from the Results section, as this aspect are not crucial for the message of our paper.
5. In my opinion the figures do not support the text very well.
Answer of the authors: We are aware the Figure 1 describes survival depending on vascular complications which are not the main issue of this manuscript. To better focus on our main message, we removed Figure 1 from the manuscript.
6. I am not convinced the manuscript in its current format is focused sufficiently to add much to our current understanding. However in principle and with more focus this work is of potential interest.
Answer of the authors: We understand the considerations of the reviewer concerning the focus of our manuscript on few key messages. However, after having revised the manuscript according to the suggestions of the reviewers, we think that these modifications helped to better point out the key messages and hope that our manuscript now better meets the expectations of the reviewer. We thank the reviewer for his comments that helped us to clearly improve our manuscript and hope that it now is worth being published in your esteemed Journal.

Reviewers' Comments to Revision

Reviewer 3: Ulrich Baumann

Apr 30, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	N/A
Custom Review Questions	**Response**
Is the subject area appropriate for you?	4

Does the title clearly reflect the paper's content?	3
Does the abstract clearly reflect the paper's content?	3
Do the keywords clearly reflect the paper's content?	3
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	3
How comprehensive and up-to-date is the subject matter presented?	3
How adequate is the data presentation?	3
Are units and terminology used correctly?	3
Is the number of cases adequate?	3
Are the experimental methods/clinical studies adequate?	3
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	3
Please rate the practical significance.	3
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	3
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
Much improved and could be published. There are still some typos in the text, i.e. Alagille is a name and needs to start with a capital A. Altogether clinical results do not seem overwhelmingly good, ie. high rate of arterial thrombosis, however it is reassuring to see such genuine and honest reporting.

Authors' Response to Reviewer Comments

Jun 17, 2018

Dear editor,
we would like to thank you again for your time and effort evaluating our paper and your positive approval. In the following we address each point that was remarked.

Reviewer #3:
Much improved and could be published.
Answer of the authors: We appreciate the positive response of the referee regarding our manuscript. Nonetheless he pointed out some shortcomings. We revised our manuscript according to the reviewer`s suggestions.

1. There are still some typos in the text, i.e. Alagille is a name and needs to start with a capital A.
Answer of the authors: We thank the reviewer for this indication. Accordingly, we corrected it and highlighted the correction in yellow (Results section 1 line 5).
2. Altogether clinical results do not seem overwhelmingly good, ie. high rate of arterial thrombosis, however it is reassuring to see such genuine and honest reporting.
Answer of the authors: We thank the reviewer for pointing out this important aspect and for his approval of our honest reporting. We agree that the high rate of arterial thrombosis seems somewhat high. However, our results are comparable to other reports of liver transplantation in biliary atresia patients in the literature [Tannuri AC et al. Living related donor liver transplantation in children. Transplant Proc. 2011;43:161-4.] In contrast to studies reporting on the outcome and complications after paediatric liver transplantation, we mainly report on small infants with the diagnosis of biliary atresia. In this special group of patients, the higher prevalence of vascular complications is explained by the fact that in our experience, paediatric patients with other diagnoses like PFIC or Alagille syndrome have less vascular complications than biliary atresia patients. Recently, Vasavada confirmed our observations by stating that vascular complications are frequently seen in liver transplantation for biliary atresia. Large for size grafts, weight less than 10 kg, age less than 1 year, and prolonged warm ischemia time were significantly associated with vascular complications [Vasavada B, Chen CL; Vascular complications in biliary atresia patients undergoing living donor liver transplantation: Analysis of 110 patients over 10 years. J Indian Assoc Pediatr Surg. 2015;20:121-6].