

Reviewer Assessment

Nagoud Schukfeh*, Maren Schulze, Anna Charlotte Holland, Jens Dingemann, Dieter P. Hoyer, Andreas Paul and Jens M. Theysohn

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

<https://doi.org/10.1515/iss-2017-0047>

Received November 26, 2017; accepted June 18, 2018

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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 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?
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:
Overall Reviewer Manuscript Rating:

Reject
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. nicotine 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 provide 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 important 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 < 10 kg?

Answer of the authors: The mean weight of the 48 pediatric recipients was 7,3 kg (range 4,4 to 10 kg). 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 highlighted 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 duplex 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 [References 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 inquiring of this very interesting 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 preoperatively 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 Introduction 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. nicotine 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 of the criticized 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 believe that is of potential interest to the reader not to have only information about the technical 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 manuscript 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 is 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:
Overall Reviewer Manuscript Rating:

Accept with Minor Revision
N/A

Custom Review Questions

Is the subject area appropriate for you?

Response
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].