

Peer Review File

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Reviewer A:

Nicely written, original paper

SOME MINOR REVISIONS are necessary

Page 2 line 51 better to replace reported by revealed (avoid repetition of words report)

Reply: We have modified our text as advised (Changes highlighted)

Changes in the text: The United States annual data report in 2013 **revealed** a 1-year graft-survival of approximately 90% for primary LT and 80% for re-LT.

Page 3 Line 65 are better than were

Reply: We have modified our text as advised

Changes in the text: But the outcomes of re-LDLT **are** seldomly discussed in the literature

74 eliminate children ...it is already stated that only adult cohorts were analyzed

Reply: We have modified our text as advised

Changes in the text: Retransplant cases involving ABO incompatibility were excluded.

87 explain for the reader what means modified piggy-back

Reply: We have added in description of modified piggyback technique.

Changes in the text: For modified piggyback technique, upper end and lower end of inferior vena cava was being closed and a 5cm opening was being made on the cava for side to side anastomosis.

91 replace facilitated by used

Reply: We have modified our text as advised

Changes in the text: For cases with hepatic artery thrombosis, right gastroepiploic artery is being **used**.

Page 4 111 before with minor capital

Reply: We have modified our text as advised

Changes in the text: ...was divided into two eras: **before** 2010 and after 2010.

Page 5 125 re-transplantation is better that retransplant

Reply: We have modified our text as advised

Changes in the text: 3 pediatric patients received 2nd **retransplantation**

135 Table 2 illustrates

Reply: We have modified our text as advised

Changes in the text: Table 2 **illustrates** the donor and graft characteristics

Page 6 160 cholangiography

Reply: We have modified our text as advised

Changes in the text: ...endoscopic retrograde **cholangiography** with temporary...

Page 7 188...and elsewhere ...better to drop the word “we” ...It was found, observed etc

(PS I do not like the we form in papers)

Reply: We have dropped all the word we and changed it into passive form.

Changes in the text: was analysed, **it was** found that ...

195...grafts with s

Reply: We have modified our text as advised

Changes in the text: ..deceased donor **grafts** being utilized...

202-203 ...rephrase a bit the sentence

Try to use uniform tenses ...simple present or simple past ...avoid mixing in some paragraphs the tenses

Reply: We have rephrased the sentence and make correction of the tenses.

Changes in the text: **Due to prolonged operation time, increased blood loss with massive transfusion, hemodynamic instability and other adverse factors, there was more staged biliary reconstruction and closure operation in late retransplant patients.**

Page 8 214 time period during which the ...

Reply: We have modified our text as advised

Changes in the text: ..including the time period **during which the** surgery was carried..

Page 9

233 ...mention how many patients died on WL for RELT due to lack of DD or LD .This is an important argument in favor of LDLT and would even show a wider discrepancy in the curves of FIG 1...and so be a strong argument to opt in EXPERIENCED centres for re-LDLT, Proposal to include this ‘intention-to-treat’ element in the paper ...is important and in fact represents the main problem in DDLT especially in the late setting of re-LT

Reply: We thank the reviewer for his valuable input regarding the waitlist mortality. We already know for primary liver transplantation that LDLT can reduce waitlist mortality by shortening the waiting time. Although it’s logical to assume the same is true for retransplantation, no study exists to illustrate this. To do so, one needs to analyze the mortality of patients remaining on the waitlist and not receiving re-LDLT, and those who received re-LDLT. Unfortunately, we do not have the data of all patients on the waitlist from 2002 until 2020 to answer the reviewer’s specific question. In our

study, we focused on the outcome of retransplant recipients rather than those patients on the waitlist. However, we agree with the reviewer that it is a very important question which we would like to answer in a follow-up study.

236 donors with s

Reply: We have modified our text as advised

Changes in the text: ... the scarcity of deceased **donors** in our country...

237 avoid use of two times retransplant

Reply: We have modified our text as advised

Changes in the text: ..our patients requiring retransplant, regardless of **the timing**, ..

241 stenting

Reply: We have modified our text as advised

Changes in the text: ...or portal vein **stenting**.

251 split LT should here also be addressed shortly

Reply: We have mentioned split LT in this context as well.

Changes in the text: This is however different from split graft in DDLT which is also small in size but with a longer cold ischemia time. Split DDLT graft have other influencing factors such donor condition, flushing of perfusion fluid, storage condition, machine perfusion. We have two split DDLT graft in this study but due to insufficient case number we could not further analyse its influence on outcome but there was a study showing that LDLT is associated with better allograft and patient survival than split DDLT graft in primary transplantation.

266 ...findings are ...

Reply: We have modified our text and rephrase.

271 skip IN

Reply: We have modified our text and rephrase

274-75 numbers beneath 10 should be written out

Reply: We have modified our text as advised

Changes in the text: two re-DDLT patients died due to perioperative hemorrhagic and circulatory shock while three succumbed to sepsis during the same hospital stay.

277...avoid to repeat "our team"...

Reply: We have modified our text as advised

Changes in the text: After accumulating more experience in re-LT, the learning curve and difficulties were overcome by the development and refinement of standardized techniques which were described in "Surgical Techniques"

290 has and skip survival

Reply: We have modified our text as advised

Changes in the text: .. the outcome has tremendously improved...

Page 10 299 I propose to use everywhere re-LT instead of retransplant

Reply: We have modified our text as advised

Page 11 Line 304 grafts with s

Reply: We have modified our text as advised

Changes in the text: ..the distribution of living donor grafts in early and late..

318 rates with s

Reply: We have modified our text.

319 are in line with ...better that agreed with

Reply: We have modified our text as advised

Changes in the text: This is in line with the observations of other studies

330 also add renal function

Reply: We have modified our text as advised

Changes in the text: ..., creatinine, renal function, albumin....

Page 12

337 ...of note : Starzl already claimed that long warm ischaemis time is an important risk factor for failure in LT an reLT

SEE Book EXPERIENCE IN HEPATIC TRANSPLANTATION ...PAGE 70 should be referred to

Reply: We have added in this reference as advised.

Changes in the text: See Reference 48

Page 12

365 single center cohort is NOT a limitation ...in contrary! Proposal to just keep the retrospective nature of the study as a limiting factor

Reply: We have modified our text as advised.

Changes in the text: In conclusion, although the retrospective nature and small cohort are limiting factors, it is safe to say that retransplantation...

REFERENCE SECTION ADD

Ref Mattos et al 2015 Hepatogastroenterology 4-center study about predictors of success in re-LT

Lerut J et al 1999 Acta chir Belgica : reLT in DDLT

Starzl Book – see above

Reply : We have added in references as being advised.

Changes in the text: See References 23, 47

TABLE SECTION

Table 1

Recurrence hepatitis ..specify type HBV..HCV...other

Reply: We have modified our table as advised.

Changes in the text: We added HBV and HCV as subgroup in recurrent hepatitis.

Skip graft ...PNF is ok

Reply: We have modified our text as advised. See Table 1

Changes in the text: Primary non function

Reviewer B:

The manuscript entitled "Outcomes of Living Donor and Deceased Donor Liver Retransplantation: A Single-Center Retrospective Study" reports on the long-term outcomes and risk factors associated with living donor liver retransplantation (re-LDLT) and deceased donor liver retransplantation (re-DDLT) in a single center. The authors have attempted to address an important issue regarding the use of living-donor grafts as an alternative approach for retransplantation due to the deficiencies in deceased organ donation in Taiwan, which are valuable for clinicians who work with patients requiring liver retransplantation. However, there are some minor issues that should be addressed before publication.

Firstly, it would have been better if this study could be conducted as a multi-center study with an expanded sample size to increase the generalizability of the findings. Secondly, it would be helpful if the authors could provide more detail on the inclusion criteria for the study, such as what were the factors considered in determining whether a patient received a re-LDLT or a re-DDLT.

Lastly, It is recommended to add the surgical difficulties and challenges of re-liver transplantation to the discussion section, along with the corresponding technical strategies.

Reply:

- 1. Thanks a lot for the suggestion regarding multicenter study. This would be our next plan in mind as well. However, we think that it is also important to share the finding of our single center study because in this setting, the patients are being operated by the same team and being handled with the same protocol. With our excellent long-term outcome, it is an invaluable experience to share with the world. On the other hand, multicenter study can recruit a higher number of case number and improve the generalizability of the findings, but the heterogeneities between centers are big regarding operation style, perioperative management and postoperative immunosuppressant use. Nevertheless, we agree that in the future a multicenter study is required to examine the applicability of this result all over the world.

2. There is no specific selection criteria in choosing living or deceased donor graft. It all depends on the availability of donor except in cases where the recipient has portal vein thrombosis or hepatic artery thrombosis which may require a long vascular graft or a high MELD score recipient requiring a graft with a minimum GRWR of 0.8

Changes in Text: Nevertheless, patients who require re-LT were always advised to opt for both options (re-LDLT and re-DDLT). The waiting time for a deceased donor graft is typically long. However, since most patients are LDLT recipients, it is also hard for them to find a second living donor in the family. In addition, patients with extensive portal vein thrombosis, other vascular complications, or a high MELD score requiring a graft with a minimum GRWR of 0.8 are not ideal candidates for re-LDLT. Hence, our center cannot simply choose re-LDLT over re-DDLT, unless a suitable donor is found.

3. We thank you for your recommendation to add in surgical difficulties and challenges of retransplant. We address the technique of recipient hepatectomy, donor graft outflow reconstruction, artery and biliary reconstruction in Patient and Method” Surgical techniques” section. We also mentioned temporary abdominal closure and staged biliary reconstruction in discussion as a corresponding strategy for critical and hemodynamically unstable retransplant patient.

Reviewer C:

I carefully reviewed the manuscript entitled “A single center analysis of long-term outcomes and survival related risk factors in liver retransplantation”. My comments are below.

This paper has two main objectives: one is to analyze the single center's outcomes in re-LDLT and re-DDLT, and the other is to identify survival related confounding risk factors. The biggest problem is that the number of patients for the latter analysis is insufficient. It is understandable that the number of patients with re-LDLT and re-DDLT is not very high at any transplant center. However, the 32-patient sample was too small to perform statistical analyses, including multivariate analysis, which could lead to erroneous statistical results. The other result of single center's outcome in re-LDLT and re-DDLT seems simply introducing the results of a single institution, and does not seem to be useful new knowledge for readers. In order to be published in Hepatobiliary Surgery and Nutrition, it is necessary to actively write in the manuscript what is new and useful for readers.

Reply:

- Regarding the multivariate analysis, we know that the small sample size is a limiting factor however we already cross examined our results with several

multivariate analysis with different conditions. The tables presented below are the raw data of statistics used in this article and have not been published previously.

- First, we choose variables with $p < 0.05$ in univariate analysis as below: INR, warm ischemia time, anhepatic time, blood loss, pRBC transfusion during OP, plasma transfusion during OP, Albumin transfusion during OP and run multivariate analysis using enter method and the result is as below

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
INR	0.864	0.510	2.871	1	0.090	2.372	0.873	6.444
warm_ischemia	0.050	0.023	4.759	1	0.029	1.051	1.005	1.099
anhepatic	0.013	0.017	0.609	1	0.435	1.014	0.980	1.049
blood_loss	0.000	0.000	1.669	1	0.196	1.000	1.000	1.000
blood_transfusion	0.062	0.024	6.960	1	0.008	1.064	1.016	1.115
plasma_transfusion	-0.122	0.083	2.147	1	0.143	0.885	0.752	1.042
albumin	0.000	0.000	0.532	1	0.466	1.000	1.000	1.001

- Then we run a similar multivariate analysis using stepwise method and the result is as below.

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Step 1 blood_transfusion	0.023	0.008	7.731	1	0.005	1.023	1.007	1.040
Step 2 warm_ischemia	0.034	0.012	8.622	1	0.003	1.034	1.011	1.058
blood_transfusion	0.032	0.011	8.533	1	0.003	1.032	1.010	1.054

- We then choose only variables with $p < 0.01$ in univariate analysis as below, anhepatic time, pRBC transfusion during OP and albumin transfusion during OP and run multivariate analysis using enter method and the result is as below.

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
anhepatic	0.010	0.007	1.988	1	0.159	1.010	0.996	1.024
blood_transfusion	0.017	0.010	2.487	1	0.115	1.017	0.996	1.038
albumin	0.000	0.000	0.014	1	0.905	1.000	0.999	1.001

- We then choose 4 variables with the least p in univariate analysis as below, warm ischemia time, anhepatic time, pRBC transfusion during OP and albumin transfusion during OP and run multivariate analysis using enter method and the result is as below.

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
anhepatic	0.003	0.008	0.136	1	0.712	1.003	0.988	1.018
blood_transfusion	0.029	0.012	6.112	1	0.013	1.030	1.006	1.054
albumin	0.000	0.000	0.062	1	0.804	1.000	1.000	1.001
warm_ischemia	0.030	0.014	4.895	1	0.027	1.031	1.003	1.058

- We then repeat multivariate analysis with the 4 variables using stepwise method and the result is as below.

		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Step 1	blood_transfusion	0.023	0.008	7.731	1	0.005	1.023	1.007	1.040
Step 2	blood_transfusion	0.032	0.011	8.533	1	0.003	1.032	1.010	1.054
	warm_ischemia	0.034	0.012	8.622	1	0.003	1.034	1.011	1.058

In above 5 methods, only when we run the test with the variables ($p < 0.01$) in univariate analysis, is the result of multivariate analysis insignificant. **However, in all the other 4 methods, warm ischemia time and pRBC transfusion in operation showed significance.** Although our patient number is little, but we should not ignore the high possibility that these factors affect the long-term outcome in retransplant patients. We can also further examine the effect of these variables on long term patient survival in further multicenter study.

- We think that it is important to share the finding of our study because of our result renews the perception regarding the outcome of living donor graft in retransplant. Previous studies only showed similar long-term result between re-DDLT and re-LDLT in retransplant patients.
 - a. Ref 10: Comparable short- and long-term outcomes in deceased-donor and living-donor liver retransplantation
<https://doi.org/10.1007/s12072-017-9821-2>
 Re-LDLT and re-DDLT have similar survival outcomes ($p=0.467$) in patient survival and $p=0.102$ in graft survival.
 - b. Ref 11: Is It Justified to Use Liver Grafts From Living Donors for Retransplant? A Single-Center Experience, DOI: 10.6002/ect.2019.0262
 Re-LDLT 1-, 3-, and 5-year patient and graft survival rates were 81.3%, whereas in the re-DDLT these rates were 51.4% ($p = 0.08$).
 - c. Ref. 12: A Multicenter Japanese Survey Assessing the Long-term Outcomes of Liver Retransplantation Using Living Donor Grafts DOI: 10.1097/TP.0000000000002958. At retransplantation, 194 re-LDLT (73.2%) with respective 1-, 3-, and 5-year patient survival rates of 61.9%, 59.0%, and 56.3% and 64.4%, 60.1%, and 57.0% for re-DDLT($p= 0.92$).

There are only limited literature that involved the analysis of retransplantation of living donor graft and we think our paper will provide a new vision in this field. Our finding is a novel outcome, and we are the first center to show superior long term survival of living donor graft in retransplant patients when compared to deceased donor graft. We also managed to demonstrate that regardless of timing of retransplantation, living donor graft is always an optimal option and with good survival rate. We've also addressed some important technical issues in retransplantation and our ways of overcoming the difficulties.

Reviewer D

Liver re-transplantation, particularly beyond early post-transplant period, is a technically demanding procedure due to anatomical distortion and the presence of extensive and dense hilar and perihepatic adhesions.

Because hilar structures are highly vulnerable to injury during dissection, DDLT is generally recommended for re-transplantation given the advantage of being able to use a graft with longer vascular and biliary pedicles. Unfortunately, due to scarcity of deceased donors more specifically in this part of the world and the associated high waitlist mortality, this center has developed techniques and strategies to overcome this limitation such as microsurgical arterial and biliary anastomoses, staged biliary reconstruction and abdominal closure. Through decades of accumulated experience in technical refinements, the authors have achieved excellent long-term outcomes of 100% with re-LDLT, even superior to re-DDLT, and have demonstrated that LDLT for re-transplantation is a viable option.

Given the paucity of global experience and available literature on LDLT re-transplantation, I believe that after the authors have addressed the concerns raised by other reviewers, it will provide valuable insights regarding the role of LDLT in re-transplantation for the HBSN readership.

Reply: Thanks for your kind comment. We will make the adjustments accordingly.