Original Article

A single center analysis of long-term outcomes and survival related risk factors in liver retransplantation

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Background: Liver retransplant is the only option to save a patient with liver graft failure. However, it is controversial due to its poor survival outcome compared to primary transplantation. Insufficient deceased organ donation in Taiwan leads to high waitlist mortality. Hence, living-donor grafts offer a valuable alternative for retransplantation. This study aims to analyze the single center's outcome in living donor liver retransplantation (re-LDLT) and deceased donor liver retransplantation (re-DDLT) as well as the survival related confounding risk factors.

Methods: This is a single center retrospective study including 32 adults who underwent liver retransplantation (re-LT) from June 2002 to April 2020. The cohort was divided into a re-LDLT and a re-DDLT group and survival outcomes were analyzed. Patient outcomes over different periods, the effect of timing on survival, and multivariate analysis for risk factors were also demonstrated

Results: Of the 32 retransplantations, the re-LDLT group (n=11) received grafts from younger donors (31.3 *vs.* 43.75 years, P=0.016), with lower graft weights (688 *vs.* 1,457.2 g, P<0.001) and shorter cold ischemia time (CIT) (45 *vs.* 313 min, P<0.001). The 5-year survival was significantly better in the re-LDLT group than in the re-DDLT group (100% *vs.* 70.8%, P=0.02). This difference was adjusted when only retransplantation after 2010 was analyzed. Further analysis showed that the timing of retransplantation (early *vs.* late) did not affect patient survival. Multivariate analysis revealed that prolonged warm ischemia time (WIT) and intraoperative blood transfusion were related to poor long-term survival.

Conclusions: Retransplantation with living donor graft demonstrated good long-term outcomes with acceptable complications to both recipient and donor. It may serve as a choice in areas lacking deceased donors. The timing of retransplantation did not affect the long-term survival. Further effort should be made to reduce WIT and massive blood transfusion as they contributed to poor survival after retransplantation.

Keywords: Retransplantation; living donor liver retransplantation (re-LDLT); deceased donor liver retransplantation (re-DDLT); timing of retransplantation; long-term outcome

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Introduction

For patients with end-stage liver disease, liver transplantation (LT) is the definitive treatment with 3-year overall survival rate of 91% in our center in Taiwan (1). When complications arise and liver allograft fails, liver retransplantation (re-LT) is the only effective treatment. However, re-LT has caused some controversy in the face of organ supply shortage, as it poses a higher surgical risk with less favorable outcomes compared with primary transplantation (2-4). 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. Similar outcomes were observed in the Australian and New Zealand Registry with an overall 1-year graft survival of 88% for primary LT and 79% for re-LT (5,6).

The influence of cultural and religious beliefs in Taiwan has contributed to the shortage of deceased donors (12.3 per million in 2016) (7,8). Therefore living donor liver transplantation (LDLT) has been more widely accepted (1). Most patients requiring re-LT are often in a very critical condition due to acute decompensated graft function and it is difficult for them to get a suitable donor graft while on the waitlist. Therefore, in our center, retransplantation was not only carried out with deceased-donor grafts but also with living-donor grafts to facilitate timely re-LT of patients on the waitlist. It is technically more demanding since it provides only a partial graft requiring anastomosis with smaller and shorter arteries and bile ducts. However, living donor liver retransplantation (re-LDLT) reduces the waiting time and allows sufficient time to prepare the recipient (4,9), but the outcome of re-LDLT is seldomly discussed in the literature due to the limited number of cases (10-12). We aim to investigate the long-term retransplant patient survival in our center following re-LDLT or deceased donor liver retransplantation (re-DDLT) and to elucidate the possible effect of timing and other risk factors on the outcome of retransplantation. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-178/rc).

Highlight box

Key findings

- In comparison to deceased donor liver retransplantation, patients who receive a living donor liver graft demonstrate significantly better long-term survival rates.

What is known and what is new?

- The timing of retransplantation (early *vs.* late) did not affect long-term patient survival.
- Prolonged warm ischemia time (WIT) and intraoperative blood transfusion were related to poor long-term survival.

What is the implication, and what should change now?

- While retransplantation continues to pose a formidable surgical challenge, a living donor graft in the hands of an experienced surgical team, employing improved standardized techniques, combined with efforts to minimize WIT and intraoperative blood transfusion, can lead to the attainment of outstanding long-term survival.

Methods

This is a retrospective cohort analysis that included 32 adult patients (≥18 years) who underwent re-LT at Kaohsiung Chang Gung Memorial Hospital from June 2002 till April 2020. Retransplant cases involving ABO incompatibility were excluded. All living-donor grafts were donated from living relatives in compliance with the Organ Transplant Act of Taiwan: age above 18 years old; relationship within five degrees of consanguinity with the recipient. Deceased donor grafts were all from donation after brain death donors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our institutional ethical committee (Kaohsiung Chang Gung Memorial Hospital) (IRB No. 202200073B0). The requirement for informed consent was waived by the review board because anonymous and de-identified information was used for the analysis.

Surgical techniques

For recipient hepatectomy, the hilar structures were dissected and cut intrahepatically up to a third-order branch because extrahepatic tissues were more likely to have dense adhesions and were easily damaged. With this, a longer bile duct can be preserved with sufficient blood supply and tension-free anastomosis can be carried out.

For living donors without fatty liver, the minimum standardized future liver remnant (sFLR) was 30%. For the high model for end-stage liver disease (MELD) recipients, the minimum graft-to-recipient weight ratio (GRWR) of the donor graft was 0.8. The living donor right lobe graft in our center was procured without the middle hepatic vein (MHV) while the living donor left lobe graft always included the MHV. To prevent congestion of

the right living donor graft, outflow other than the right hepatic vein would be reconstructed at the back table according to the following criteria: Segment V und VIII tributaries >5 mm, a small graft <40% of recipient's total liver volume, a large portion of graft drained by MHV tributaries examined by simultaneous clamping of right hepatic artery and the tributary during donor hepatectomy, severe portal hypertension and high MELD patients (13). The most common graft used in our center for outflow reconstruction is cryopreserved vascular grafts followed by polytetrafluoroethylene graft.

Deceased donor graft may be transplanted as a whole liver lobe or split liver lobe and the split was usually carried out *in situ*. Classic piggyback was used in living donor re-LT while modified piggyback was used in most cases involving deceased donor re-LT. For the modified piggyback technique, the upper end and lower end of the inferior vena cava were closed and a 5-cm opening was made on the cava for side-to-side anastomosis (14). The portal anastomosis was accomplished in an end-to-end fashion with a growth factor of 10 mm.

Regarding the most challenging reconstruction of the artery and biliary duct, our center shifted from loupe reconstruction to microsurgical reconstruction. This procedure is performed by a plastic surgeon who is also part of the transplant team. The hepatic artery was reconstructed microscopically end-to-end, with a continuous running suture for the posterior wall and interrupted ties for the anterior wall (15). In cases of hepatic artery thrombosis (HAT) or dissection, alternative options such as the right gastroepiploic or left gastric artery can be utilized (16). For bile duct reconstruction, duct-to-duct anastomosis and Roux-en-Y hepaticojejunostomy were performed microscopically at the discretion of the surgeon. At times, ductoplasty was also performed, which was modified based on the size discrepancy and amount of duct, as described in previous literature (17).

Data analysis

Preoperative recipient variables were collected, including the patient's gender, age, body mass index (BMI), Unified Network for Organ Sharing (UNOS) staging, MELD score, Child-Turcotte-Pugh (CTP) score, the interval between transplants, indications of retransplantation. Liver donor information included the type of donor, gender, and age. Operative variables included cold ischemia time (CIT), warm ischemia time (WIT), blood loss, blood products transfused, and staged closure surgery. Complications such as hospital stay, infection rate, and Clavien-Dindo grading system were also collected.

Patients were classified into two groups according to the type of graft: living donor *vs.* deceased donor. The overall 30-day, 90-day, 1-, 3-, 5- and 10-year patient survival rates were calculated. Retransplant patients were classified as early (≤30 days) and late (>30 days) retransplantation according to the time interval between primary transplantation and retransplantation. Moreover, to study the effect of experience accumulation and implementation of staged surgery in re-LT, the study period was divided into two eras: before 2010 and after 2010. Different parameters predicting survival were also reviewed.

Statistical analysis

Categorical variables were compared with the Chi-square test. Continuous variables were expressed as the median with range and compared with the Mann-Whitney *U* test. Patients' long-term survival and hospital survival were calculated using Kaplan-Meier with the log-rank test. Univariate and multivariate analyses were examined using Cox Regression. The P value ≤0.05 was considered significant. SPSS Version 26 (Armonk, New York, USA) was used for data analysis.

Results

Re-LDLT vs. re-DDLT

From June 2002 to April 2020, our center performed LTs in 1,608 patients. Among them, 53 retransplantations (3.3%) were performed in 32 adults and 18 children (3 pediatric patients received 2nd re-transplantation). Of the 32 adult re-LT recipients, 11 (34%) received re-LDLT and 21 (66%) received re-DDLT. No adult retransplant recipients underwent a second retransplant. Demographic and pre-transplant characteristics of the recipients between the two groups are summarized in *Table 1*. Re-LDLT patients had a mean MELD score of 19.91 while re-DDLT patients had a mean MELD of 21.38 with insignificant differences. Both groups had similar distributions of early (20%) and late (80%) retransplant patients and there were no significant differences in their indications for retransplantation.

Donor graft characteristics and operative parameters

Table 2 illustrates the donor and graft characteristics as

Table 1 Demographic and pre-retransplant data of adult retransplant patients, grouping according to graft type

Variables	Re-LDLT (n=11)		Re-DDLT (n=21)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Age at retransplant (years)	49.29	47.34 [43.99–59.78]	46.9	48.3 [42.87–52.27]	0.463
Gender					0.519
Male		9 (81.8)		15 (71.4)	
Female		2 (18.2)		6 (28.6)	
BMI at retransplant (kg/m^2)	23.49	23.23 [20.2–27.28]	24.82	24.57 [21.57–27.47]	0.351
Indications for retransplant					0.603
Hepatic artery thrombosis		2 (18.2)		5 (23.8)	
Portal vein thrombosis		0		2 (9.5)	
Biliary complication		5 (45.5)		4 (19.0)	
Chronic rejection		3 (27.3)		5 (23.8)	
Sinusoidal obstruction syndrome		1 (9.1)		2 (9.5)	
Recurrent hepatitis					
HBV		0		1 (4.8)	
HCV		0		1 (4.8)	
Primary non-function		0		1 (4.8)	
Primary LT					0.371
LDLT		8 (72.7)		18 (85.7)	
DDLT		3 (27.3)		3 (14.3)	
MELD score—primary transplant	14.36	12 [8–19]	15.8	13.5 [11–21.5]	0.494
MELD score—pre-retransplant	19.91	17 [15–28]	21.38	21 [16.5–25]	0.647
CTP score—pre-retransplant	10	10 [8–11]	9.1	10 [7.5–10]	0.26
UNOS listing status for retransplant					0.623
1		2 (18.2)		3 (14.3)	
2a		2 (18.2)		3 (14.3)	
2b		7 (63.6)		12 (57.1)	
3		0		3 (14.3)	
Interval between primary transplant to retransplant (days)	2,152.09	939 [217–3,649]	1,128.67	673 [26–1,707.5]	0.393
Less than 7 days		2 (18.2)		4 (19.0)	
7–30 days		0		1 (4.8)	
31 days to 1 year		1 (9.1)		3 (14.3)	
More than 1 year		8 (72.7)		13 (61.9)	
Pre-retransplant blood test results					
Bilirubin (mg/dL)	20.21	15.8 [3.3–34.7]	17.39	11.7 [7.15–29.4]	0.953
Albumin (g/dL)	2.91	2.9 [2.5–3.3]	3.24	3.2 [2.8–3.77]	0.203
Creatinine (mg/dL)	0.9	0.98 [0.57–1.03]	0.97	0.9 [0.6–1.2]	0.874
INR	1.42	1.29 [1.25–1.53]	1.68	1.48 [1.17–1.87]	0.526
Platelet (/μL)	34,782	24,000 [4,900–70,000]	35,281	11,800 [4,550–29,050]	0.416

Re-LDLT, living donor liver retransplantation; Re-DDLT, deceased donor liver retransplantation; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; UNOS, United Network for Organ Sharing; INR, international normalized ratio.

well as the operative parameters between the two groups. The donor age in the re-LDLT group was significantly lower than that of the re-DDLT group (median 31.3 *vs.* 43.75, P=0.016). The re-LDLT group had also significantly lower graft weights (median 688 *vs.* 1,457.2 g, P<0.001), smaller graft-to-standard liver volume (GSLV) (median 61 *vs.* 125.09, P<0.001), and smaller GRWR (median 1.06 *vs.* 2.36, P<0.001). Graft CIT was also significantly shorter in the re-LDLT group compared to re-DDLT (median 45 *vs.* 313 min, P<0.001). In contrast, WIT, anhepatic time, operation time, blood loss, number of blood transfusions, and the necessity for staged biliary reconstruction and closure operation were not significantly different between re-LDLT and re-DDLT.

Post-operative complications of recipients and donors

Six patients (28.6%) in the re-DDLT group had early in-hospital mortality. On the other hand, there was no in-hospital mortality in the re-LDLT group. Furthermore, the re-LDLT group developed fewer high-grade complications (Clavien-Dindo grade III–V) compared to the re-DDLT group (18.2% *vs.* 57.1%, P=0.035). The two complications in the re-LDLT group consisted of portal vein stenosis managed with thrombectomy and stenting and another patient with prolonged mechanical ventilation requiring tracheostomy. The infection rate among the two groups, as well as the length of hospital stay, was comparable.

There was no living donor-related mortality, but two donors had grade-2 and grade-3a complications. One right lobe graft donor experienced postoperative ileus and required short-term total parenteral nutrition support. While another left lobe graft donor experienced a bile leak and had to undergo endoscopic retrograde cholangiography with temporary biliary stent placement.

Survival analysis of re-LDLT vs. re-DDLT

As shown in *Figure 1*, the re-LDLT group showed far superior long-term survival (P=0.02) and in-hospital survival (P=0.041) compared to the re-DDLT group. Long-term survival of the re-LDLT group was 100% at 30 days, 90 days, 1-, 3-, 5-, and 10-year respectively. Whereas patient survival rates in the re-DDLT group at 30 days, 90 days, 1-, 3-, 5-, and 10-year were 81%, 75.9%, 70.8%, 70.8%, 70.8%, and 42.5% respectively. The survival in the re-DDLT group was mostly affected in the first post-transplant year reflected by the in-hospital survival curve in *Figure 1B*.

When the incidence of retransplantation and survival were analyzed in two different periods (before 2010 and after 2010), it was discovered that the rate of re-LDLT increased from (n=1) 11.1% to (n=10) 43.5%. Retransplant patients' demographics and intraoperative parameters in general changed across both eras. Correlating to changes in the type of donor graft, in *Table 3* a reduction in graft weight, GSLV, GRWR, and CIT from the pre-2010 era to the post-2010 era was discovered. Decreases in operation time, WIT, and anhepatic time were noted in the post-2010 era with less intraoperative blood transfusion of leukocyte

Table 2 Intraoperative and postoperative data of adult retransplant patients, grouping according to graft type

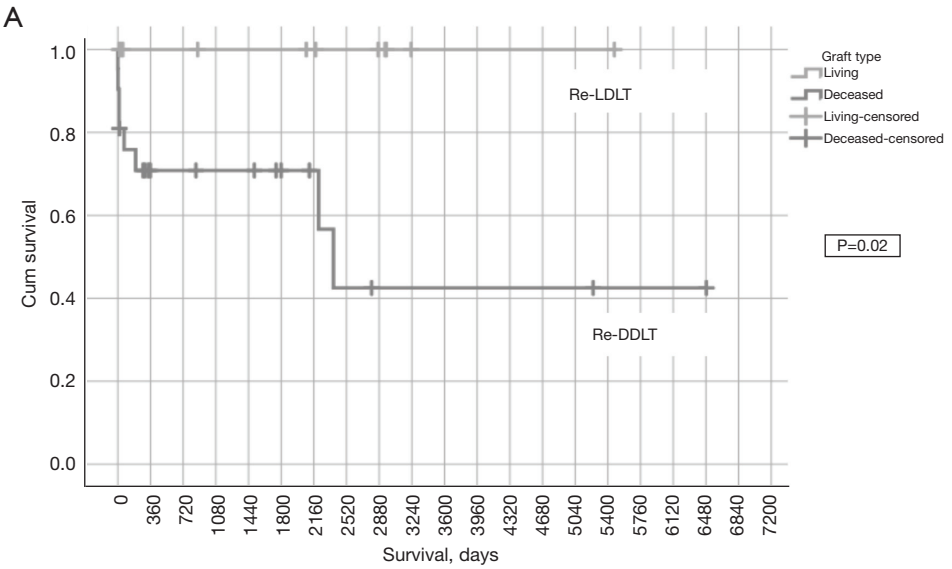
Variables	Re-LDLT (n=11)		Re-DDLT (n=21)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Donor age of retransplant (years)	32.22	31.3 [23.9–36.92]	43.01	43.75 [33.79–55.87]	0.016*
Donor gender of retransplant					0.453
Male		7 (63.6)		16 (76.2)	
Female		4 (36.4)		5 (23.8)	
Type of liver graft in retransplant					
Whole liver graft		0		19 (90.48)	
Right lobe graft		8 (72.73)		1 (4.76)	
Left lobe graft		3 (27.27)		1 (4.76)	

Table 2 (*continued*)

Table 2 (*continued*)

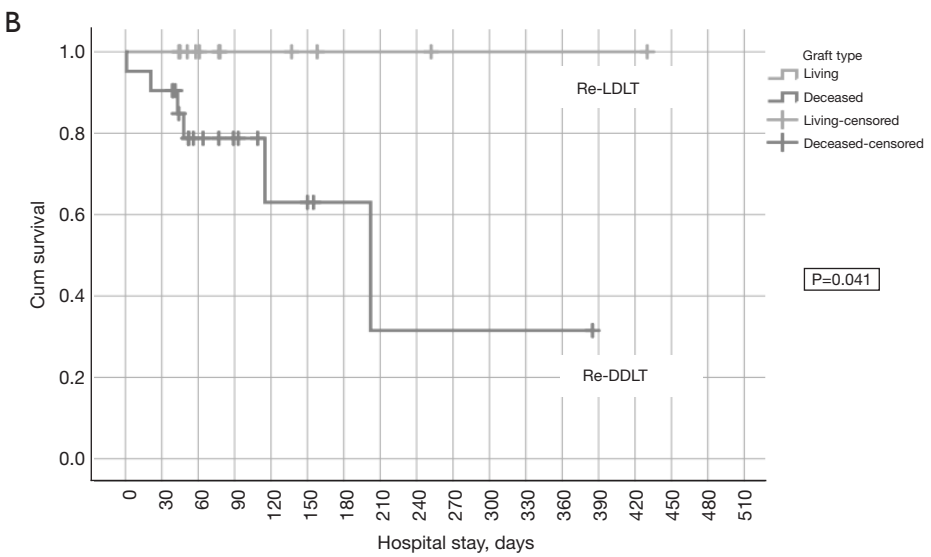
Variables	Re-LDLT (n=11)		Re-DDLT (n=21)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Actual graft weight (g)	670.82	688 [565–780]	1,520.75	1,457.2 [1,270–1,759]	<0.001*
GSLV (%)	56.12	61 [46–65.3]	121.62	125.09 [95.94–139.94]	<0.001*
GRWR	1.06	1.06 [0.87–1.27]	2.27	2.36 [1.63–2.65]	<0.001*
Cold ischemia time (min)	54	45 [24–86]	324	313 [240–394.5]	<0.001*
Warm ischemia time (min)	45.91	43 [36–50]	58.24	48 [42.5–65]	0.077
Anhepatic time (min)	112.55	111 [57–94]	125.05	113 [63–180]	0.552
HA reperfusion time (min)	73.45	70 [51–94]	90.1	76 [59–115.5]	0.578
Operation time (min)	628.09	650 [480–731]	538.24	514 [382.5–652.5]	0.071
Intraoperative ascites (mL)	1,090.91	400 [0–1,600]	769.05	0 [0–1,500]	0.289
Blood loss (mL)	17,822	8,000 [900–27,250]	12,369.05	5,500 [1,650–12,100]	0.706
Blood transfusion (U)					
LPR transfusion	43.27	24 [6–100]	45.52	32 [11–58.5]	0.634
FFP transfusion	15.09	16 [0–22]	16.43	16 [6–24.5]	0.779
Platelet transfusion	20.73	12 [0–24]	15.19	12 [6–24]	0.667
Cryoprecipitate	8.55	0 [0–12]	9.14	0 [0–18]	0.627
Albumin transfusion (mL)	2,727.27	2,800 [800–4,800]	3,019.05	1,600 [450–4,400]	0.75
Staged closure operation		6 (54.5)		8 (38.1)	0.373
Clavien-Dindo grade of early complication					
0–II (low grade)		9 (81.8)		9 (42.9)	0.035*
III–V (high grade)		2 (18.2)		12 (57.1)	
Infection					
Bacteremia		3 (27.3)		4 (19)	0.593
Pneumonia		3 (27.3)		7 (33.3)	0.725
Wound		2 (18.2)		3 (14.3)	0.773
Biliary tract		3 (27.3)		10 (47.6)	0.266
Urinary tract		2 (18.2)		7 (33.3)	0.365
Central venous catheter		1 (9.1)		2 (9.5)	0.968
Intraabdominal		7 (63.6)		11 (52.4)	0.542
Hospital stay (days)		77 [51–158]		56 [42–112]	0.226
Hospital mortality		0 (0.0)		6 (28.6)	0.049*
Current status—alive:dead (mortality)		11:0 (0.0%)		13:8 (38.1%)	0.018*
Survival time (days)	2,065	2,181 [55–2,960]	1,366.81	358 [43–2,161.5]	0.463

*, P<0.05. Re-LDLT, living donor liver retransplantation; Re-DDLT, deceased donor liver retransplantation; GSLV, graft-to-standard liver volume; GRWR, graft-to-recipient weight ratio; HA, hepatic artery; LPR, leukocyte poor red blood cell; FFP, fresh frozen plasma.



Survival rate (%)	1 month	3 months	1 year	3 years	5 years	10 years
Re-LDLT	100	100	100	100	100	100
Re-DDLT	81	75.9	70.8	70.8	70.8	42.5

No. at risk	Initial	1 month	3 months	1 year	3 years	5 years	10 years
Re-LDLT	11	10	8	8	7	7	1
Re-DDLT	21	16	15	10	9	6	2



Hospital survival (%)	30 days	60 days	90 days	120 days	150 days	180 days	210 days	240 days
Re-LDLT	100	100	100	100	100	100	100	100
Re-DDLT	90.5	78.8	78.8	63	63	63	31.5	31.5

No. at risk	Initial	30 days	60 days	90 days	120 days	150 days	180 days	210 days	240 days
Re-LDLT	11	10	7	4	4	3	2	2	2
Re-DDLT	21	19	10	7	4	3	2	1	1

Figure 1 Survival curve between re-LDLT group and re-DDLT group. (A) Long-term patient survival between re-LDLT group and re-DDLT group; (B) hospital survival between re-LDLT group and re-DDLT group. Re-LDLT, living donor liver retransplantation; Re-DDLT, deceased donor liver retransplantation.

Table 3 Demographic and data of adult retransplant patients, grouping according to era

Variables	Before 2010 (n=9)		After 2010 (n=23)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Age at retransplant (years)	45.33	46.61 [37.47–54.43]	48.66	49.39 [43.99–57.6]	0.346
Gender					0.82
Male		7 (77.8)		17 (73.9)	
Female		2 (22.2)		6 (26.1)	
BMI at retransplant (kg/m^2)	23.42	22.72 [20.74–25.12]	24.73	24.33 [20.28–27.48]	0.438
Indications for retransplant					0.933
Hepatic artery thrombosis		2 (22.2)		5 (21.7)	
Portal vein thrombosis		0		2 (8.7)	
Biliary complication		3 (33.3)		6 (26.1)	
Chronic rejection		2 (22.2)		6 (26.1)	
Veno-occlusive disease		1 (11.1)		2 (8.7)	
Recurrent hepatitis		1 (11.1)		1 (4.3)	
Graft primary non-function		0		1 (4.3)	
Primary LT					0.083
LDLT		8 (88.9)		18 (78.3)	
DDLT		1 (11.1)		5 (21.7)	
MELD score—primary transplant	19	20 [12.5–22]	13.77	12 [8.75–16.75]	0.04*
MELD score—retransplant	20.78	21 [15–24.5]	20.91	21 [15–28]	0.966
CTP score—retransplant	9.11	9 [7.5–10]	9.52	10 [8–11]	0.444
UNOS listing status for retransplant					0.218
1		1 (11.1)		4 (17.4)	
2a		0		5 (21.7)	
2b		6 (66.7)		13 (56.5)	
3		2 (22.2)		1 (4.3)	
Donor type					0.083
Living donor		1 (11.1)		10 (43.5)	
Deceased donor		8 (88.9)		13 (56.5)	
Interval between primary transplant to retransplant (days)	667.67	673 [192.5–997.5]	1,798.52	724 [8–2,812]	0.571
Pre-retransplant blood test results					
Bilirubin (mg/dL)	16.23	11 [4.7–30.65]	19.19	14.4 [4.7–33.1]	0.785
Albumin (g/dL)	3.28	3.2 [2.8–4]	3.06	3.02 [2.7–3.4]	0.488
Creatinine (mg/dL)	1	1 [0.86–1.25]	0.92	0.84 [0.55–1.03]	0.193
INR	1.34	1.19 [1–1.53]	1.69	1.48 [1.28–1.78]	0.024*
Platelet (/μL)	94,000	73,000 [37,500–161,000]	451,700	240,000 [5–660,000]	0.09

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Before 2010 (n=9)		After 2010 (n=23)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Donor age (years)	40.48	43.75 [33.45–50.87]	38.84	34.3 [30.61–49.04]	0.516
Actual graft weight (g)	1,535.91	1,457.2 [1,292.5–1,688]	1,108.33	823 [644–1,728]	0.051
GSLV (%)	128.77	125.09 [112.35–133.28]	87.5	72 [53–135.96]	0.038*
GRWR	2.48	2.36 [2.14–2.58]	1.61	1.5 [0.96–2.4]	0.022*
Cold ischemia time (min)	350.78	357 [301.5–436.5]	184.39	193 [45–253]	0.006*
Warm ischemia time (min)	74.67	70 [47.5–98.5]	45.9	43 [36–50]	0.003*
Anhepatic time (min)	158.56	160 [115.5–183.5]	105.96	95 [48–136]	0.017*
HA reperfusion time (min)	102.11	98 [61–136.5]	77.43	70 [59–90]	0.142
Operation time (min)	678.89	640 [604.5–735.5]	526.17	480 [390–665]	0.051
Intraoperative ascites (mL)	927.78	400 [0–2,350]	860.87	0 [0–1,000]	0.407
Blood loss (mL)	18,727.78	13,600 [5,250–26,175]	12,489.13	4,900 [800–10,600]	0.068
Blood transfusion (U)					
LPR transfusion	75.11	63 [36–120]	32.87	24 [6–42]	0.004*
FFP transfusion	24.33	25 [19–29.5]	12.7	12 [0–16]	0.004*
Platelet transfusion	17.22	12 [12–24]	17.04	12 [0–24]	0.634
Cryoprecipitate	4	0 [0–6]	10.87	12 [0–24]	0.136
Albumin transfusion (mL)	5,455.56	4,000 [3,000–5,600]	1,926.09	1,200 [400–3,200]	0.005*
Staged closure operation		2 (22.2)		12 (52.2)	0.125
Clavien-Dindo grade of early complication					0.102
0–II (low grade)		3 (33.3)		15 (65.2)	
III–V (high grade)		6 (66.7)		8 (34.8)	
Infection					
Bacteremia		2 (22.2)		5 (21.7)	0.976
Pneumonia		2 (22.2)		8 (34.8)	0.491
Wound		2 (22.2)		3 (13.0)	0.52
Biliary tract		6 (66.7)		7 (30.4)	0.061
Urinary tract		4 (44.4)		5 (21.7)	0.199
Central venous catheter		2 (22.2)		1 (4.3)	0.119
Intraabdominal		5 (55.6)		13 (56.5)	0.96
Hospital stay (days)	100.78	115 [41–156.5]	102.57	61 [48–93]	0.883
Hospital mortality		4 (44.4)		2 (8.7)	0.02*
Current status—alive:dead (mortality)		3:6 (66.7%)		21:2 (8.7%)	0.001*
Survival time (days)	2,451.11	2,212 [40–5,355]	1,276.48	880 [55–2,181]	0.516

*, P<0.05. BMI, body mass index; LT, liver transplantation; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; UNOS, United Network for Organ Sharing; INR, international normalized ratio; GSLV, graft-to-standard liver volume; GRWR, graft-to-recipient weight ratio; HA, hepatic artery; LPR, leukocyte poor red blood cell; FFP, fresh frozen plasma.

poor red blood cells (LPRs) and fresh frozen plasma (FFP). The long-term survival analysis stratified by the era in *Figure 2A* showed a significant difference (P=0.008): before 2010, all retransplant patient survival rates at 1-, 3- and 5-year were 55.6% which improved to 91.3% after 2010. The long-term survival of re-LDLT and re-DDLT patients before and after 2010 was further compared. However, there was only 1 re-LDLT in the pre-2010 era, therefore further analysis could not be carried out. But in the post-2010 era, a comparable outcome was demonstrated between both groups. After 2010, the 1-year survival in the re-LDLT group was 100% while 1-year survival in the re-DDLT group was 84.6% (P=0.206) as shown in *Figure 2B*.

Early retransplant vs. late retransplant

When the timing of retransplantation was analyzed, it was found that there were some significant differences between early (n=7) and late retransplant (n=25) groups. *Table 4* demonstrates the differences in retransplant indications between early and late retransplant patients as the main indication of early re-LT was HAT (71.4%) while the main indications for late re-LT were biliary complication (36%) and chronic rejection (32%).

The proportion of living and deceased donor grafts being utilized in early and late retransplant patients was similar (P=0.715) with 28.6% *vs.* 71.4% in the early re-LT group and 36% *vs.* 64% in the late re-LT group. The late retransplant group has longer anhepatic time (median 120 *vs.* 45 min, P=0.002) and operation time (median 620 *vs.* 375 min, P=0.018) with greater blood loss (median 9,500 *vs.* 450 mL, P<0.001), more LPR transfusion (median 36 *vs.* 4 U, P<0.001), more FFP transfusion (median 16 *vs.* 0 U, P=0.002), more albumin transfusion (median 3,200 *vs.* 1,000 mL, P=0.03) intraoperatively. Due to prolonged operation time, increased blood loss with massive transfusion, hemodynamic instability, and other adverse factors, there were more staged biliary reconstruction and closure operations in late retransplant patients (56% *vs.* 0%, P=0.008). Late retransplant patients had a significantly higher incidence of biliary tract infection (52% *vs.* 0%, P=0.013) and intraabdominal infection (68% *vs.* 14.3%, P=0.011). However, both early and late retransplant patients had similar lengths of hospital stay (52 *vs.* 77 days) and hospital mortality (14.3% *vs.* 20%). The long-term survival between early and late retransplant patients shown in *Figure 3* was 85.7% *vs.* 78.7% at 1, 3, and 5 years respectively with no significant difference (P=0.422).

Univariate and multivariate analysis

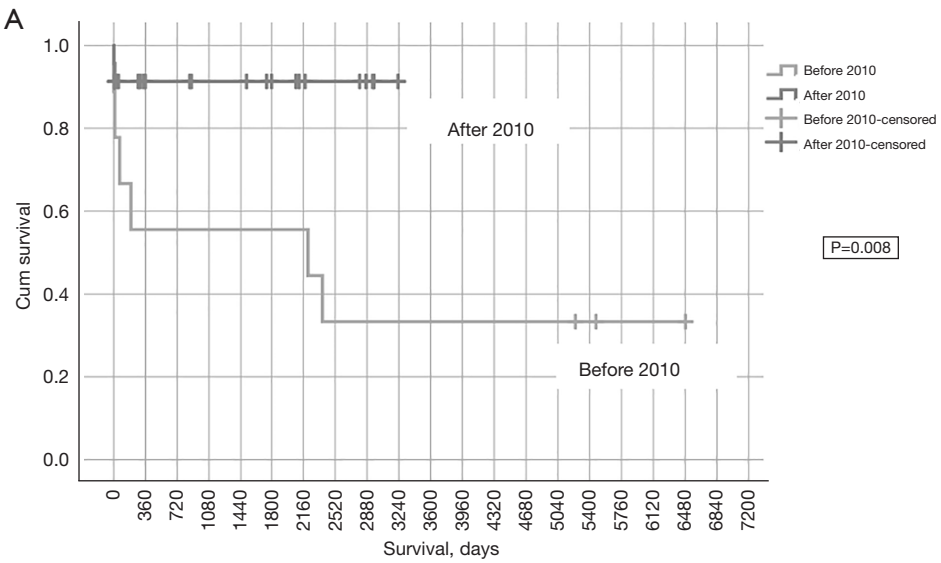
Univariate analysis was performed to identify factors predicting long-term survival. As shown in *Table 5*, various factors affected the long-term survival of adult patients who underwent retransplantation surgery, including the period during which the surgery was carried out (before 2010 *vs.* after 2010) (P=0.021), INR (P=0.048), WIT (P=0.014), anhepatic time (P=0.007), blood loss (P=0.048), LPR transfusion (P=0.005), FFP transfusion (P=0.038), albumin transfusion (P=0.005). CIT (P=0.054) and central venous catheter infection rate (P=0.054) also showed a trend of significance toward long-term survival.

All these factors underwent stepwise logistic regression analysis with forward selection however only WIT [odds ratio (OR): 1.034, 95% CI: 1.011–1.058, P=0.003] and LPR transfusion (OR: 1.032, 95% CI: 1.010–1.054, P=0.003) reached statistical significance (Table S1).

Discussion

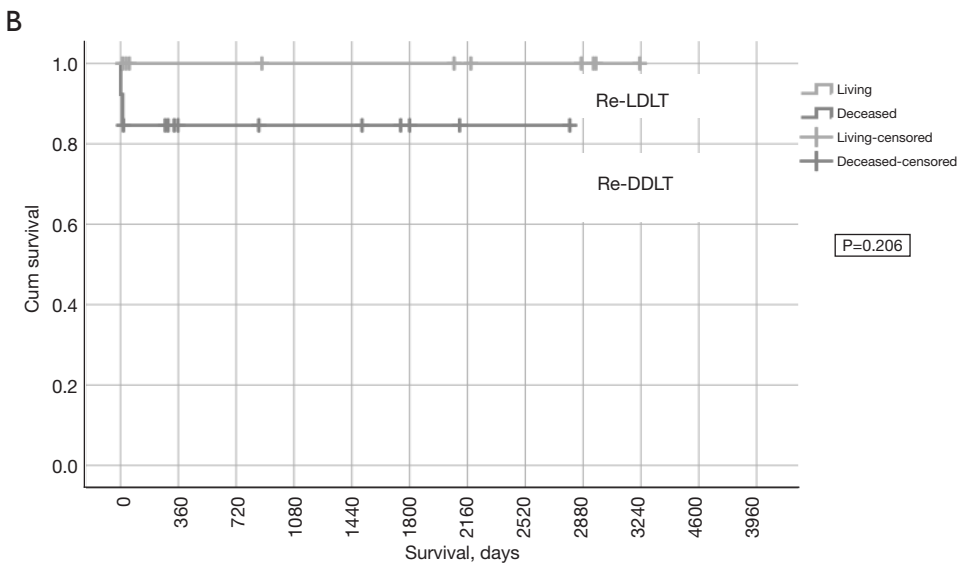
This retrospective study presents the perspective of a single Taiwanese center on re-LT and offers three main findings. Re-LDLT offers a valuable alternative to re-DDLT with comparable overall survival. Late retransplantation (>30 days after primary LT) is associated with higher blood loss and need for blood transfusion resulting in longer operation time compared to early retransplantation, however, the timing of retransplantation does not affect long-term survival. Instead, WIT and massive blood transfusion are risk factors for poor long-term survival.

Our center is a high-volume LDLT center in Taiwan where deceased donation is scarce and living donation predominates. The incidence of re-LT is relatively low at 3.3% compared to other centers (3% to 22%) (18-23). The high expertise in LDLT built within the last two decades led to excellent graft- and patient survival where the need for retransplantation was rare. 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.



Survival rate (%)	1 month	3 months	1 year	3 years	5 years	10 years
Before 2010	77.8	66.7	55.6	55.6	55.6	33.3
After 2010	91.3	91.3	91.3	91.3	91.3	–

No. at risk	Initial	1 month	3 months	1 year	3 years	5 years	10 years
Before 2010	9	7	6	5	5	5	3
After 2010	23	19	17	13	11	8	0



Survival rate (%)	1 month	3 months	1 year	3 years	5 years
Re-LDLT after 2010	100	100	100	100	100
Re-DDLT after 2010	84.6	84.6	84.6	84.6	84.6

No. at risk	Initial	1 month	3 months	1 year	3 years	5 years
Re-LDLT after 2010	9	9	7	7	6	6
Re-DDLT after 2010	13	10	10	6	5	2

Figure 2 Survival curve of retransplant patients between different time period. (A) Long-term survival of all retransplant patients before 2010 and after 2010; (B) long-term survival between re-LDLT group and re-DDLT group after 2010. Re-LDLT, living donor liver retransplantation; Re-DDLT, deceased donor liver retransplantation.

Table 4 Demographic data, intraoperative and postoperative data of adult retransplant patients, grouping according to early retransplant versus late retransplant

Variables	Early retransplant (n=7)		Late retransplant (n=25)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
Interval (days)	4.3	3 [2–8]	1,893.8	950 [44–7,497]	0.32
Age at retransplant (years)	50.5	50.18 [44.22–58.95]	46.95	47.34 [42.87–54.56]	0.48
Gender					
Male		5 (71.4)		19 (76.0)	0.805
Female		2 (28.6)		6 (24.0)	
BMI at retransplant (kg/m^2)	27.57	28.08 [23.31–30.82]	23.46	23.23 [20.24–25.76]	0.024*
Indication for retransplant					0.002*
Hepatic artery thrombosis		5 (71.4)		2 (8.0)	
Portal vein thrombosis		1 (14.3)		1 (4.0)	
Biliary complication		0		9 (36.0)	
Chronic rejection		0		8 (32.0)	
Sinusoidal obstruction syndrome		0		3 (12.0)	
Recurrent hepatitis		0		2 (8.0)	
Graft primary non-function		1 (14.3)		0	
MELD score—primary transplant	15.57	11 [9–23]	15.21	13.5 [11–19]	0.887
MELD score—pre-retransplant	18.14	22 [10–25]	21.64	21 [15.5–26.5]	0.437
CTP score—pre-retransplant	8.86	9 [6–11]	9.56	10 [8–11]	0.517
UNOS listing status for retransplant					<0.001*
1		5 (71.4)		0	
2a		1 (14.3)		4 (16.0)	
2b		1 (14.3)		18 (72.0)	
3		0		3 (12.0)	
Donor type					0.715
Living donor		2 (28.6)		9 (36.0)	
Deceased donor		5 (71.4)		16 (64.0)	
GSLV (%)	91.85	96.74 [53–125.09]	101.14	95.14 [61.32–135.43]	0.698
GRWR	1.64	1.63 [0.9–2.22]	1.92	1.63 [1.08–2.5]	0.6
Cold ischemia time (min)	263.57	240 [91–386]	222.12	240 [54.5–352]	0.715
Warm ischemia time (min)	54.86	43 [36–76]	53.76	48 (41.5–55)	0.855
Anhepatic time (min)	62.57	45 [43–88]	137.04	120 [98.5–180]	0.002*
HA reperfusion time (min)	66.86	70 [51–80]	89.28	81 [59–111]	0.236
Operation time (min)	428.43	375 [320–469]	608.52	620 [472.5–707.5]	0.018*
Intraoperative ascites (mL)	0	0 [0–0]	1,126	400 [0–2,250]	0.006*
Blood loss (mL)	1,121.43	450 [300–800]	17,918	9,500 [4,450–23,050]	<0.001*
Blood transfusion (U)					

Table 4 (*continued*)

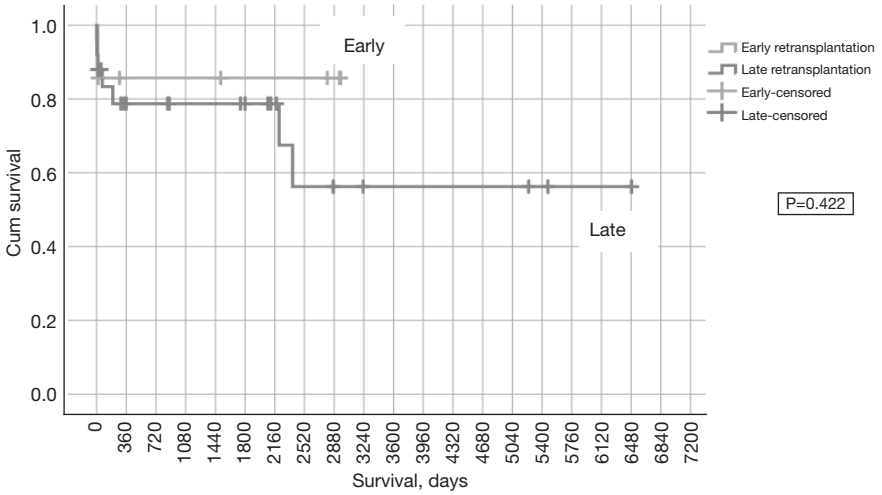
Table 4 (*continued*)

Variables	Early retransplant (n=7)		Late retransplant (n=25)		P
	Mean	Median [range] or n (%)	Mean	Median [range] or n (%)	
LPR transfusion	6.57	4 [2–8]	55.44	36 [24–93]	<0.001*
FFP transfusion	3.71	0 [0–6]	19.4	16 [12.5–26.5]	0.002*
Platelet transfusion	9.71	12 [0–20]	19.16	12 [12–24]	0.165
Cryoprecipitate	5.14	0 [0–12]	10	0 [0–18]	0.361
Albumin transfusion (mL)	871.43	1,000 [0–1,500]	3,492	3,200 [900–4,800]	0.03*
Staged closure operation		0		14 (56.0)	0.008*
Infection					
Bacteremia		1 (14.3)		6 (24.0)	0.583
Pneumonia		3 (42.9)		7 (28.0)	0.454
Wound		1 (14.3)		4 (16.0)	0.912
Biliary tract		0		13 (52.0)	0.013*
Urinary tract		4 (57.1)		5 (20.0)	0.053
Central venous catheter		0		3 (12.0)	0.336
Intraabdominal		1 (14.3)		17 (68.0)	0.011*
Hospital stay (days)	63.43	52 [43–93]	112.88	77 [46–152.5]	0.316
Hospital mortality		1 (14.3)		5 (20.0)	0.732
Current status—alive:dead (mortality)		6:1 (14.3%)		18:7 (28.0%)	0.459
Survival time (days)	1,502	1,504 [18–2,944]	1,636.2	880 [61.5–2,293.5]	0.909

*, P<0.05. BMI, body mass index; MELD, model for end-stage liver disease, CTP, Child-Turcotte-Pugh; UNOS, United Network for Organ Sharing; GSLV, graft-to-standard liver volume; GRWR, graft-to-recipient weight ratio; HA, hepatic artery; LPR, leukocyte poor red blood cell; FFP, fresh frozen plasma.

Under the above-mentioned circumstances of our center, the initial analysis arrived at a superior in-hospital and long-term survival outcome of re-LDLT (with a 5-year survival of 100%) compared to re-DDLT. This finding is novel and not consistent with previous studies where the long-term survival of re-LDLT and re-DDLT were comparable (10-12,24). Several factors must be considered before appreciating this finding. It is well-known that living donor graft quality is superior to cadaveric grafts. Living donor grafts are harvested from younger donors with a shorter CIT. Both factors are believed to influence the graft and patient survival (25-27). On the other hand, living donor grafts are partial grafts with a lower weight, smaller GSLV, and GRWR, compared to whole cadaveric grafts. Split grafts utilized in DDLT are also small in size but they experience a longer CIT and have other influencing factors such as donor condition, flushing of perfusion fluid, storage condition, and machine perfusion. We had two split DDLT grafts in this study but due to insufficient case numbers we could not further analyze their influence on the outcome. There was a study showing that LDLT is associated with better allograft and patient survival than split DDLT grafts in primary transplantation (28). Previous comparisons between primary LDLT and DDLT matching recipients for MELD score, age, and pretransplant patient status did not show any difference in survival (29,30). Hence it's questionable whether the superior LDLT graft function is solely responsible for our observation.

Another known advantage of LDLT is the shorter waiting time allowing patients to receive transplantation at a low MELD score and reducing the waitlist mortality. While the latter might be also true for patients waiting for retransplantation, both re-DDLT and re-LDLT recipients shared comparable preoperative characteristics, i.e., MELD score and timing of retransplantation. This might be due to the fact, that finding a second living donor takes a



Survival rate (%)	1 month	3 months	1 year	3 years	5 years	10 years
Early	85.7	85.7	85.7	85.7	85.7	–
Late	88	83.4	78.7	78.7	78.7	56.2

No. at risk	Initial	1 month	3 months	1 year	3 years	5 years	10 years
Early	7	5	5	4	4	3	0
Late	25	21	18	14	12	10	3

Figure 3 Long-term survival between early and late retransplant group.

Table 5 Univariate analysis of variables predicting outcome of liver retransplantation surgery

Variables	Odds ratio	95% CI	P value
Gender of recipient (male *vs.* female)	0.867	0.171–4.425	0.867
Age of recipient	0.974	0.909–1.043	0.443
BMI at retransplant (kg/m^2)	1.09	0.91–1.305	0.35
Interval between primary transplant to retransplant (days)	1	0.999–1	0.425
Era (before 2010 *vs.* after 2010)	6.74	1.337–33.975	0.021*
Type of liver donor (deceased *vs.* living)	48.592	0.132–17,947.94	0.198
Graft weight	1.001	1–1.002	0.1
Indications for retransplant			
Hepatic artery thrombosis	1.234	0.168–9.062	0.836
Portal vein thrombosis	0	0	0.996
Biliary complication	0.91	0.128–6.474	0.925
Chronic rejection	1.04	0.094–11.55	0.975
Veno-occlusive disease	0	0	0.993
Recurrent hepatitis	4.518	0.343–59.483	0.251
Graft primary non-function	–	–	–

Table 5 (*continued*)

Table 5 (*continued*)

Variables	Odds ratio	95% CI	P value
MELD score—primary transplant	1.074	0.984–1.172	0.112
MELD score—pre-retransplant	1.077	0.981–1.183	0.119
CTP score—pre-retransplant	1.012	0.717–1.428	0.947
Pre-retransplant blood test results			
Bilirubin (mg/dL)	1.006	0.963–1.051	0.782
Albumin (g/dL)	0.718	0.206–2.503	0.603
Creatinine (mg/dL)	0.87	0.19–3.987	0.858
INR	2.129	1.007–4.503	0.048*
Platelet (/μL)	0.978	0.94–1.017	0.269
Age of donor (years)	1.006	0.954–1.06	0.834
Gender of donor (male *vs.* female)	0.909	0.182–4.523	0.907
Actual graft weight (g)	1.001	1–1.002	0.1
GSLV (%)	1.01	0.998–1.023	0.114
GRWR	1.63	0.86–3.09	0.134
Cold ischemia time (min)	1.004	1–1.008	0.054
Warm ischemia time (min)	1.023	1.005–1.042	0.014*
Anhepatic time (min)	1.015	1.004–1.027	0.007*
HA reperfusion time (min)	1.003	0.988–1.018	0.71
Operation time (min)	1.005	0.999–1.01	0.082
Intraoperative ascites (mL)	1	0.999–1	0.638
Blood loss (mL)	1	1–1	0.048*
Blood transfusion (U)			
LPR transfusion	1.023	1.007–1.04	0.005*
FFP transfusion	1.061	1.003–1.122	0.038*
Platelet transfusion	1.005	0.964–1.047	0.831
Cryoprecipitate	1.01	0.961–1.062	0.685
Albumin transfusion (mL)	1	1–1	0.005*
Staged closure operation	2.031	0.461–8.95	0.349
Infection			
Bacteremia	1.449	0.287–7.31	0.653
Pneumonia	0.853	0.166–4.39	0.849
Wound	1.791	0.359–8.919	0.477
Biliary tract	4.486	0.903–22.295	0.067
Urinary tract	2.442	0.608–9.803	0.208
Central venous catheter	5.395	0.973–29.908	0.054
Intraabdominal	0.89	0.217–3.649	0.871

*, P<0.05. BMI, body mass index; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; INR, international normalized ratio; GSLV, graft-to-standard liver volume; GRWR, graft-to-recipient weight ratio; LPR, leukocyte poor red blood cell; FFP, fresh frozen plasma; HA, hepatic artery; 95% CI, 95% confidence interval.

considerable amount of time. We do not believe that the superior re-LDLT survival is derived from a shorter waiting time.

The explanation is rather to be found in the difference of expertise in re-LT. Before 2010, 90% of retransplant in our study was performed using deceased donor graft, only one re-LDLT was performed. Due to the lack of expertise in handling retransplant patients, two re-DDLT patients died due to perioperative hemorrhagic and circulatory shock while three succumbed to sepsis during the same hospital stay. Among the mortalities of re-DDLT in our center, 75% happened in the pre-2010 era. 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" (31). These differences were reflected in the reduction of the operation time, WIT, and anhepatic time with less blood loss and intraoperative blood transfusion in the post-2010 era. Since 2010 our team has also adopted the strategy of perihepatic packing and temporary abdominal closure for critical patients with massive bleeding during LT surgery. This provided adequate time for coagulopathy to be corrected and for patients to be metabolically and hemodynamically stabilized (32). With the improvement of surgical techniques, preoperative evaluation, intraoperative monitoring/management, and postoperative care the outcome of re-LT has tremendously improved after 2010. Re-LDLT, mainly performed after 2010, profited from the accumulated experience of re-DDLT before 2010. In a high-volume LDLT center, non-inferior outcomes can be achieved with re-LDLT compared to re-DDLT.

Regarding the timing of re-LT, to our surprise, no outcome differences were observed despite significant differences in indication, intraoperative and postoperative parameters. Similar to other studies (33,34), the most frequent indication for early retransplant in our study was HAT while biliary complications and chronic rejection leading to graft failure were for late retransplant. The distribution of living donor grafts in early and late retransplant groups did not significantly differ, since preoperative evaluation of a living donor could be completed within 1–2 days. While early retransplant patients face the acute threat of HAT and graft failure, late retransplant patients bring the problem of dense adhesions and poor tissue integrity caused by long-term immunosuppressive regimens (9,20,35). All these factors contribute to significantly increased blood loss, massive blood transfusion, prolonged operation time, and hemodynamic instability. When biliary reconstruction was performed under these suboptimal conditions, it may lead to an increased risk of biliary complications. Therefore, the bail-out procedure of temporary abdominal closure with delayed biliary reconstruction in staged surgery was employed more frequently in late retransplant patients (32,36). As for the postoperative course, significantly higher rates of the biliary tract and intraabdominal infection had been recorded in the late retransplant group. Nevertheless, long-term survival was not affected by those negative impactors. This is in line with the observations of other studies demonstrating no significant difference in survival between early and late retransplantation (33,37-39). While there is also data suggesting early retransplantation to have poorer survival compared to late retransplantation (40-42).

This leaves the question of which risk factors affect the outcome of re-LT. Previous studies have reported a set of different factors including the urgency of retransplantation, etiology, recipient age, creatinine, renal function, albumin, preoperative mechanical ventilator, MELD score greater than 27, donor age, CIT, WIT, massive blood transfusion >30 units of PRBC during surgery, the interval between primary transplant and retransplant, multiple liver transplants (3,4,19,42-47). We identified WIT and intraoperative LPR transfusion to be independent risk factors of poor patient survival. WIT plays a significant role in graft and patient survival. The implantation time was shown to be independently associated with the transplant failure rate for deceased donor livers (48). Every 10-minute increase in WIT was comparable to the effect of a 1-hour increase in CIT with hazard ratio (HR) 1.03, P<0.001. Keeping WIT as close to the average implantation time within a given center, ideally below 45 minutes (43), is likely to reduce graft failure (49). High intraoperative blood transfusion reflects uncontrolled coagulopathy, one of the deadly triads, and is, therefore, a strong prognostic factor (50-52). In addition, a massive blood transfusion may be related to further immune modulation, higher risk of infection, and overload to the cardiovascular system (53).

Conclusions

In conclusion, although the retrospective nature and small cohort are limiting factors, it is safe to say that retransplantation is a challenging procedure, and a living donor graft, albeit with a smaller graft size, proved that, with meticulous planning and under the hands of an experienced surgical team, can provide excellent long-term outcome and serves as a chance of survival where the supply

of deceased donors is insufficient. Although the timing of retransplantation did not affect its long-term survival, further effort should be made to reduce WIT and blood transfusion intraoperatively as they may negatively impact the patient's long-term survival. A further multicenter study is essential to examine the outcome of living donor grafts in retransplant patients and the effect of the risk factors mentioned above on long-term patient survival across the continent.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-178/rc

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Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-178/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-178/coif). C.L.C. serves as an unpaid editorial board member of *Hepatobiliary Surgery and Nutrition*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by our institutional ethical committee (IRB No. 202200073B0). The requirement for informed consent was waived by the review board because anonymous and de-identified information was used for the analysis.

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