11-2-2022

Long-term outcomes of retransplantation after live donor liver transplantation: A Western experience

Tommy Ivanics
Henry Ford Health, tivanic1@hfhs.org

Ashley Limkemann

Madhukar S. Patel

Marco P. A. W. Claasen

Luckshi Rajendran

See next page for additional authors

Recommended Citation

Ivanics T, Limkemann A, Patel MS, Claasen M, Rajendran L, Choi WJ, Shwaartz C, Selzner N, Lilly L, Bhat M, Tsien C, Selzner M, McGilvray I, Sayed B, Reichman T, Cattral M, Ghanekar A, and Sapisochin G. Long-term outcomes of retransplantation after live donor liver transplantation: A Western experience. Surgery 2022.

Authors

Tommy Ivanics, Ashley Limkemann, Madhukar S. Patel, Marco P. A. W. Claasen, Luckshi Rajendran, Woo JIn Choi, Chaya Shwaartz, Nazia Selzner, Les Lilly, Mamatha Bhat, Cynthia Tsien, Markus Selzner, Ian McGilvray, Blayne Sayed, Trevor Reichman, Mark Cattral, Anand Ghanekar, and Gonzalo Sapisochin

Surgery xxx (2022) 1–8

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Long-term outcomes of retransplantation after live donor liver transplantation: A Western experience

Tommy Ivanics, MD, MPH[a,b,c], Ashley Limkemann, MD, MPH[d], Madhukar S. Patel, MD, MBA, ScM[e], Marco P.A.W. Claasen, MD[a,f], Luckshi Rajendran, MD[g], Woo JIn Choi, MD[g], Chaya Shwaartz, MD[a], Nazia Selzner, MD, PhD[a,h,i], Les Lilly, MSc, MD, FRCPC[a,h,i], Mamatha Bhat, MD, MSc, PhD, FRCPC[a,h,i], Cynthia Tsien, MD, MPH, FRCPC[a,h,i], Markus Selzner, MD[a], Ian McGilvray, PhD, MD, FRCSC[a], Blayne Sayed, MD, PhD[a], Trevor Reichman, MD, PhD[a], Mark Cattral, BMedSci, MSc, MD, FRCSC[a], Anand Ghanekar, MD, PhD, FRCSC[a,j], Gonzalo Sapisochin, MD, PhD, MSc[a,g,*]

[a] *Multi Organ Transplant Program, University Health Network, Toronto, Canada*
[b] *Department of Surgery, Henry Ford Hospital, Detroit, MI*
[c] *Department of Surgical Sciences, Akademiska sjukhuset, Uppsala University, Sweden*
[d] *Division of Transplantation, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH*
[e] *Division of Surgical Transplantation, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[f] *Division of Hepatopancreatobiliary and Transplant Surgery, Department of Surgery, Erasmus MC Transplant Institute, University Medical Centre Rotterdam, the Netherlands*
[g] *Division of General Surgery, Toronto General Hospital, University of Toronto, Canada*
[h] *Division of Gastroenterology, Department of Medicine, University of Toronto, Canada*
[i] *Toronto General Hospital Research Institute, Toronto, Canada*
[j] *Transplant and Regenerative Medicine Centre, The Hospital for Sick Children, Toronto, Canada*

ARTICLE INFO

Article history:
Accepted 16 September 2022
Available online xxx

ABSTRACT

Background: Despite most liver transplants in North America being from deceased donors, the number of living donor liver transplants has increased over the last decade. Although outcomes of liver retransplantation after deceased donor liver transplantation have been widely published, outcomes of retransplant after living donor liver transplant need to be further elucidated.

Method: We aimed to compare waitlist outcomes and survival post-retransplant in recipients of initial living or deceased donor grafts. Adult liver recipients relisted at University Health Network between April 2000 and October 2020 were retrospectively identified and grouped according to their initial graft: living donor liver transplants or deceased donor liver transplant. A competing risk multivariable model evaluated the association between graft type at first transplant and outcomes after relisting. Survival after retransplant waitlisting (intention-to-treat) and after retransplant (per protocol) were also assessed. Multivariable Cox regression evaluated the effect of initial graft type on survival after retransplant.

Author contributions: T.I.: conception of project, literature review, data analysis, interpretation of results, and write up of the manuscript; A.L.: conception of project, literature review, interpretation of results, and write up of the manuscript; M.C.P.: interpretation of results and write up of the manuscript; M.P.A.W.C: interpretation of results and write up of the manuscript; L.R.: interpretation of results and write up of the manuscript; W.J.C.: interpretation of results and write up of the manuscript; C.S.: interpretation of results and write up of the manuscript; N.S.: interpretation of results and write up of the manuscript; L.L.: interpretation of results and write up of the manuscript; M.B.: interpretation of results and write up of the manuscript; C.T.: interpretation of results and write up of the manuscript; M.S.: interpretation of results and write up of the manuscript; I.M.: interpretation of results and write up of the manuscript; B.S.: interpretation of results and write up of the manuscript; T.R.: interpretation of results and write up of the manuscript; M.C.: interpretation of results and write up of the manuscript; A.G.: interpretation of results and write up of the manuscript; and G.S.: conception of project, literature review, interpretation of results, and write up of the manuscript. All authors have given final approval for this manuscript to be submitted to *Surgery*.

* Reprint requests: Gonzalo Sapisochin, MD, PhD, MSc, HBP & Multi Organ Transplant Program, Division of General Surgery, University of Toronto, University Health Network, 585 University Avenue, 11PMB184, Toronto, M5G 2N2, ON, Canada.
E-mail address: Gonzalo.sapisochin@uhn.ca (G. Sapisochin);
Twitter: @sapisochin

https://doi.org/10.1016/j.surg.2022.09.022

Results: A total of 201 recipients were relisted (living donor liver transplants, $n = 67$; donor liver transplants, $n = 134$) and 114 underwent retransplant (living donor liver transplants, $n = 48$; deceased donor liver transplants, $n = 66$). The waitlist mortality with an initial living donor liver transplant was not significantly different (hazard ratio = 0.51; 95% confidence interval, 0.23−1.10; $P = .08$). Both unadjusted and adjusted graft loss risks were similar post-retransplant. The risk-adjusted overall intention-to-treat survival after relisting (hazard ratio = 0.76; 95% confidence interval, 0.44−1.32; $P = .30$) and per protocol survival after retransplant (hazard ratio:1.51; 95% confidence interval, 0.54−4.19; $P = .40$) were equivalent in those who initially received a living donor liver transplant.
Conclusion: Patients requiring relisting and retransplant after either living donor liver transplants or deceased donor liver transplantation experience similar waitlist and survival outcomes.

Introduction

The incidence of liver retransplantation ranges from 5% to 22% of all liver transplants (LTs), as it remains the only curative option for recurrent liver failure.[1,2] Notwithstanding the opportunity cost to potential first-time transplant candidates on the waiting list, the outcomes after retransplant in recipients receiving a deceased donor liver graft during initial transplant are acceptable despite increased technical challenge, higher transfusion requirements, a more protracted postoperative course, and greater health care costs.[2–5]

Although a predominant majority of LTs performed in the West are deceased donor LTs (DDLTs), the use of living donor LTs (LDLTs) has increased in the last decade.[6,7] For recipients, results of LDLT are similar to outcomes using donation after brain death (DBD) and donation after circulatory death (DCD) grafts.[8–11] With regard to retransplantation, a registry study of the United States using data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) noted that short-term (1-year) outcomes for recipients who initially received LDLT are similar to retransplant after DDLT.[12] Currently, however, there remains a lack of granular data on outcomes after relisting for patients who have received an LDLT during their first transplant. Considering the relatively high rate of waitlist dropout for patients awaiting retransplant, waitlist outcomes as well as long-term outcomes after retransplant need to be clarified.

For recipients undergoing a primary LT with either an LDLT or DDLT allograft, we sought to evaluate and compare waitlist outcomes and survival, from intention-to-treat [ITT] (ie, after relisting for LT) and per protocol (ie, for those achieving retransplant) standpoints at a center performing a relatively high volume of both LDLTs and DDLTs. The intent for this information was to aid in counseling patients listed for retransplant. In considering sickness at the time of original transplant and etiologies for retransplant, it was hypothesized that waitlist and survival outcomes of retransplant after original LDLT would be superior to those after DDLT.

Methods

This study was approved by our institutional ethics review board (#19−5564), and a waiver of informed consent was obtained.

Study population

We assessed patients who were relisted for LT between April 2000 and October 2020 at our institution. The start date of the study period was chosen as to coincide with the start of the LDLT program at a North American center doing a high volume of both LDLTs and DDLTs. At the time of analysis, patient data were up to date as of January 23, 2021. Patients were grouped according to the type of graft received at initial LT: LDLT or DDLT. All retransplants except 1 were performed using grafts from deceased donors. Patients who were <18 years at their initial transplant ($n = 5$) received an initial LT at an outside institution ($n = 9$), underwent a multiorgan transplant at the time of the initial LT ($n = 2$), or underwent a multiorgan transplant at their retransplant ($n = 9$) were excluded. This study complies with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for retrospective studies.[13] Figure 1 is a STROBE-compliant diagram highlighting all patients who were included and excluded.

Covariates

We recorded sex; age, at relisting and retransplant; body mass index (BMI), at relisting and retransplant; blood group; etiology of liver disease (hepatitis C virus [HCV] and hepatitis B virus, cryptogenic cirrhosis, alcohol-related liver disease, primary sclerosing cholangitis/primary biliary cirrhosis/autoimmune hepatitis, nonalcoholic steatohepatitis, and other); laboratory Model for End-Stage Liver Disease (MELD) score (at initial LT, relisting, and retransplant); exception points at relisting; and time on the waitlist (from relisting). Donor variables included donor sex, age, and the relation of the donor to the recipient. Operative variables for both index and retransplant included details of the caval anastomosis (piggyback or caval replacement), biliary reconstruction, type and amount of blood products transfused (packed red blood cells [PRBCs], in milliliters; fresh frozen plasma [FFP], in milliliters; platelets, in milliliters; and cell saver, in milliliters), estimated blood loss, in milliliters; cold ischemia time (CIT), in minutes; warm ischemia time (WIT), in minutes; and graft type (including right or left lobe for LDLT, DCD, DBD, and split for DDLT). Postoperative variables for both index and retransplant included details about complications (biliary leak, stricture, or other biliary complication), vascular thrombosis (portal vein thrombosis and hepatic artery thrombosis), unplanned operations related to the LT itself, rejection, graft nonfunction, acute renal failure, need for dialysis, duration of postoperative dialysis in days, number of intensive care days, and length of stay in days. Reasons for graft failure included disease recurrence, graft nonfunction, vascular thrombosis (hepatic artery thrombosis [early (before 30 days) or late (after 30 days)] or portal vein thrombosis). When clinically relevant, data points were obtained at both the initial LT and relisting time points.

Complications

Complications were recorded according to the Clavien-Dindo classification (excluding grade I complications) in various time intervals post-retransplant: complications to discharge, discharge to 3 months, 3 to 6 months, 6 to 12 months, and 12 to 24 months.[14] Transfusion was only recorded once within each time interval (ie, regardless of how many postoperative transfusions a patient

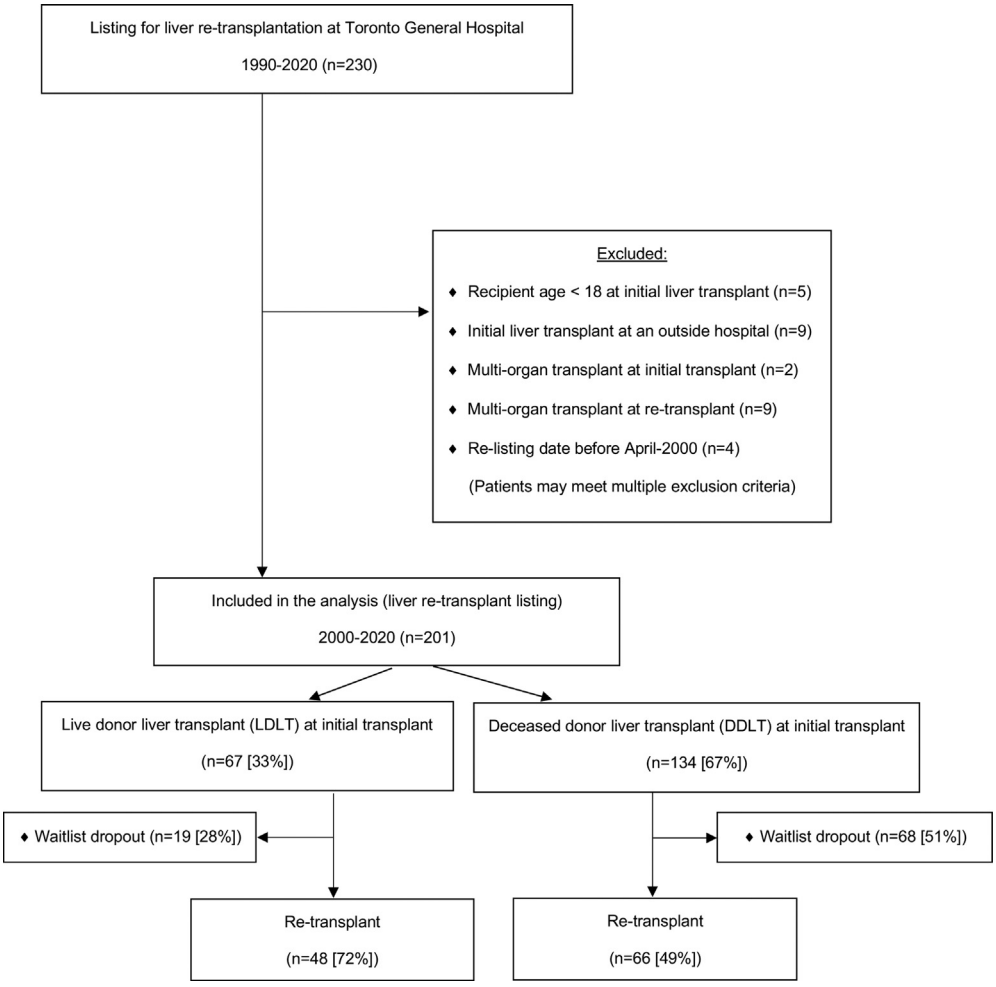

Figure 1. Strengthening the Reporting of Observational studies in Epidemiology diagram of cohorts, included and excluded.

received it was only captured once as a grade II complication within a given interval). At each time interval, a complication score according to the comprehensive complication index (CCI) was calculated.[15]

Listing criteria

Before December 2012 at our center, the allocation of organs was based on the CanWAIT approach, which prioritized patients according to their location (intensive care unit, hospital floor, or home) as well as the severity of their liver disease. After December 2012, the MELD-based allocation system was adopted.[16] Patients with a failed live donor/DCD graft (provided that they were transplanted within accepted criteria and graft failure occurred because of biliary and/or vascular complications) received MELD exception points. A baseline of 22 points were awarded, followed by a 3-point increase every 90 days up to $\leq$40 points.[17] Patients are deemed urgent status in cases of acute liver failure and retransplant for primary nonfunction of hepatic artery thrombosis $\leq$7 days of the first transplant (4F if intubated or 3F if not requiring mechanical ventilation[*]).[17] These patients receive first priority with national sharing of organs.[17,18]

Outcome measures

The 2 study groups, LDLT and DDLT, were based on the type of graft received at the initial transplant. The study's end points were waitlist mortality after relisting, patient survival after relisting for LT (ITT), patient and graft survival for those achieving retransplant (per protocol), and complications post-retransplant up to 24 months.

Waitlist mortality was defined as either death on the waitlist or dropout from the waitlist because of medical deterioration or unsuitability. Graft loss was defined as (1) need for repeat retransplant or (2) death due to liver failure. The date of graft loss was therefore defined as the date of the repeat retransplant or the date of death if the date of death was due to graft-related causes. Deaths from causes other than liver failure were not defined as graft failure. A sensitivity analysis for graft survival was also performed with death censoring (where graft loss was defined as retransplant or death due to any cause).

Statistical analysis

Descriptive data were expressed using medians and interquartile range (IQR) and compared using the Mann-Whitney *U* test.

[*] Candidates that urgently need an organ are designated as 4F or 3F in the Canadian organ allocation system (https://www.giftoflife.on.ca/resources/pdf/healthcare/TP-9-100.pdf).

Categorical variables were expressed using numbers and percentages and compared using the χ^2 and Fischer exact test. Multivariable Poisson regression with robust variance and linear regression models were constructed to evaluate the association of graft type with Clavien-Dindo grade ≥IIIb and the CCI from retransplant up to 3 months, respectively. To assess waitlist outcomes, instead of the Kaplan-Meier method, which censors for the competing event of transplant, a cumulative incidence approach was used to account for the presence of a competing risk of transplant with waitlist mortality.[19] The cumulative incidence was estimated using sub-distribution estimates for each cause. To assess the effect of the exposure (graft type at initial LT), a cause-specific competing-risk multivariable model was constructed for hazard of waitlist mortality and retransplant. Similarly, for the evaluation of graft failure, causes of death due to causes other than those related to the graft itself were considered competing events for graft loss (need for re-retransplant or death due to liver failure). Graft-related reasons included portal vein thrombosis, liver failure, graft failure: other, recurrent disease, recurrent HCV, graft failure: hepatitis, hepatic artery thrombosis, cirrhosis, and graft failure: primary. Non–graft-related reasons included hepatocellular carcinoma recurrence, multisystem organ failure, cerebral bleed, myocardial infarction, unknown, sepsis, cardiac arrest, respiratory failure, de novo cancers, ischemic small bowel, cancer, hemorrhagic shock, cardiac arrest, acute respiratory distress syndrome, and renal failure. These were also analyzed using cause-specific Cox models. ITT patient survival was evaluated from the time of relisting to death or last known follow-up. On the per protocol analysis, patient and graft survival was evaluated in those who received retransplant. All survival estimates used the Kaplan Meier method, and group comparisons were made with log-rank tests. Additional sensitivity analyses were performed stratifying by graft type at initial transplant and receipt of exception points at relisting and a separate analysis separating the DDLT group into deceased after circulatory death and deceased after brain death donation.

Multivariable Cox regression was performed to evaluate the association between graft type at the initial transplant and mortality after re-listing for LT. Variables included in the model for ITT survival included etiology of primary liver disease; reason for graft failure after the initial LT; recipient sex, age, BMI, dialysis requirement, MELD score, and exception points, all at relisting; time between the first LT and relisting; and year of first listing. Variables included in the multivariable model for the sub-distribution hazard of waitlist mortality and transplantation were the same as those included in the ITT model. The variables included in the model for graft failure included etiology of primary liver disease; reason of graft failure after the initial LT; recipient sex, age, BMI, dialysis requirement, MELD score, and exception points, all at retransplant; CIT; WIT; time between primary LT and relisting; and year of first listing. Variables included in the model for per protocol survival were the same as those included in the graft failure model.

Statistical analyses were performed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). The competing risk analysis with the cumulative incidence function was performed using the package cmprsk, version 2.2-10.[20] Robust error variance for the Poisson model was computed using the package, sandwich, version 3.0-1,[21,22] which were applied to the marginal Wald tests using the package, lmtest, version 0.9-38.[23]

Results

Study population and index liver transplantation

A total of 201 recipients relisted for transplant met the study inclusion criteria (graft at first transplant LDLT, $n = 67$, and DDLT, $n = 134$; Figure 1). Of the 721 total primary LDLTs in the study period, 67 (9%) were relisted and of the 1,957 total primary DDLTs in the study period, 134 (7%) were relisted. Upon relisting, 48 underwent retransplant in the initial LDLT group and 66 underwent retransplant in the initial DDLT group. Five of the patients included who received a retransplant were also retransplanted at a later stage (ie, repeat retransplant) and received a total of 3 grafts ($n = 2$ in the LDLT group and $n = 3$ in the DDLT group). The LDLT group had lower biologic MELD scores at the first LT (median [IQR] LDLT = 16 [12–21] vs DDLT = 19 [13–26]; $P = .048$) and a higher proportion of Roux-en-Y biliary reconstructions (LDLT = 45 [67%] vs DDLT = 35 (27%); $P < .001$). Biliary complications ($n = 23$ [34%]) and early (<30 days) hepatic artery thrombosis ($n = 20$ [30%]) were the most common reasons for graft failure after LDLT and were more common in these patients than in the initial DDLT group ($P < .001$). The most common cause of DDLT graft failure was disease recurrence ($n = 33$ [25%]) and rejection ($n = 26$ [19%]; Table S1). Retransplant and relisting characteristics are shown in Table 1 and Table S2, respectively.

Waitlist outcomes after relisting

The cumulative incidence of waitlist mortality at both 90 days (LDLT = 3.0% [95% confidence interval {CI}, 0.6–9.3] vs DDLT = 17.2% [95% CI, 11.3–24.0]; $P = .004$) and 1 year (LDLT = 9.0% [95% CI, 3.6–17.4] vs DDLT = 28.4% [95% CI, 21.0–36.2]; $P = .002$) post-relisting was lower in the LDLT group (Figure 2A). After multivariable adjustment, patients initially receiving a DDLT had a similar of waitlist mortality (reference [ref]: DDLT, LDLT cause-specific hazard ratio [HR] = 0.51; 95% CI, 0.23–1.10; $P = .08$) (Table 2).

The cumulative incidence of LT after relisting was similar between the groups at 90 days (LDLT = 38.8% [95% CI, 27.1–50.3] vs DDLT = 29.1% [95% CI, 21.6–37.0]; $P = .11$) and 1 year (LDLT = 55.2% [95% CI, 42.4–66.3] vs DDLT = 43.3% [95% CI, 34.7–51.5]; $P = .08$) (Figure 2B). After multivariable adjustment, initially receiving an LDLT was not associated with an increased incidence of retransplant after relisting (ref: DDLT, LDLT cause-specific HR = 1.44; 95% CI, 0.94–2.20; $P = .10$) (Table 2).

Intention-to-treat survival from relisting

The median ITT survival was 4.3 years in the DDLT group and 7.2 years in the LDLT group. The ITT survival was higher in the LDLT group at 1 year (DDLT = 64.0% [95% CI, 56.4–72.7] vs LDLT = 82.7% [95% CI, 73.9–92.6]; $P = .005$) (Figure 3, Figure S1, and Table S3). After multivariable adjustment, the ITT mortality hazard was not statistically significantly different between the groups (ref: DDLT; LDLT HR = 0.76, 95% CI, 0.44–1.32; $P = .30$]) (Table 3).

Complications after retransplant

There was no difference in the proportions of dialysis requirement, machine ventilation, or intensive care location at re-LT between the groups (Table 1). There was no difference in intensive care unit stay, total length of hospital stay, need for post-retransplant dialysis, or duration of dialysis post-retransplant between the groups. Moreover, the total complication scores (CCIs) and the proportion of Clavien-Dindo grade ≥IIIb were overall similar between the groups after retransplant, with the exception of a higher proportion of Clavien-Dindo grade ≥IIIb after retransplant between 6 and 12 months in the group that had undergone an initial transplant with an LDLT graft (0 vs 17%; $P < .001$) (Tables S4 and S5).

Table I
Retransplant characteristics

	DDLT ($n = 66$)	LDLT ($n = 48$)	*P* value
Age at re-LT, y, median (IQR)	54 (45–59)	53 (43–60)	.98
BMI at re-LT, median (IQR)	24.6 (21.7–27.3)	24.8 (22.7–27.7)	.60
Blood type, *n* (%)			.18
A	27 (41)	24 (50)	
B	12 (18)	12 (25)	
AB	4 (6)	0 (0)	
O	23 (35)	12 (25)	
MELD at re-LT, median (IQR)	25 (18–32)	20 (16–24)	.003
Receipt of exception points at relisting, *n* (%)	5 (8)	21 (44)	< .001
Dialysis at re-LT, *n* (%)	11 (20)	6 (15)	.56
Machine ventilation at re-LT, *n* (%)	10 (15)	9 (19)	.60
Intensive care unit at re-LT, *n* (%)	15 (23)	17 (35)	.15
Graft type at re-LT, *n* (%)			.33
DCD	2 (3)	0	
LDLT	1 (2)	0 (0)	
NDD	63 (96)	48 (100)	
Donor age, y, median (IQR)	39 (22–50)	39 (23–52)	.65
Donor age ≥60, *n* (%)	9 (14)	7 (15%)	.89
PRBC transfusion intraoperatively, mL, median (IQR)	1,500 (1,000–2,500)	1,000 (500–2,125)	.02
FFP transfusion intraoperatively, mL, median (IQR)	1,800 (900–3,600)	1,200 (350–2,000)	.01
PLT transfusion intraoperatively, mL, median (IQR)	200 (0–509)	64 (0–320)	.45
Cell saver transfusion intraoperatively, mL, median (IQR)	500 (233–1,555)	460 (208–750)	.26
EBL, mL, median (IQR)	2,500 (2000–5,000)	2,100 (1,450–4,100)	.37
Roux-en-Y biliary reconstruction, *n* (%)	44 (68)	36 (77)	.30
Piggyback technique, *n* (%)	6 (13)	7 (17)	.54
CIT at re-LT, min, median (IQR)	472 (373– 570)	381 (311–491)	.01
CIT ≥6 and <12 h at re-LT, *n* (%)	45 (68)	26 (57)	.21
CIT ≥12 h at re-LT, *n* (%)	5 (8)	2 (4)	.49
WIT at re-LT, min, median (IQR)	46 (40–53)	45 (39–52)	.51

BMI, body mass index; *CIT*, cold ischemia time; *DCD*, deceased after circulatory death donation; *DDLT*, deceased donor liver transplant; *EBL*, estimated blood loss; *FFP*, fresh frozen plasma; *IQR*, interquartile range; *LDLT*, living donor liver transplant; *MELD*, Model for End-Stage Liver Disease; *NDD*, donor after neurologic determination of death; *PLT*, platelet; *PRBC*, packed red blood cell; *re-LT*, retransplant; *WIT*, warm ischemia time.

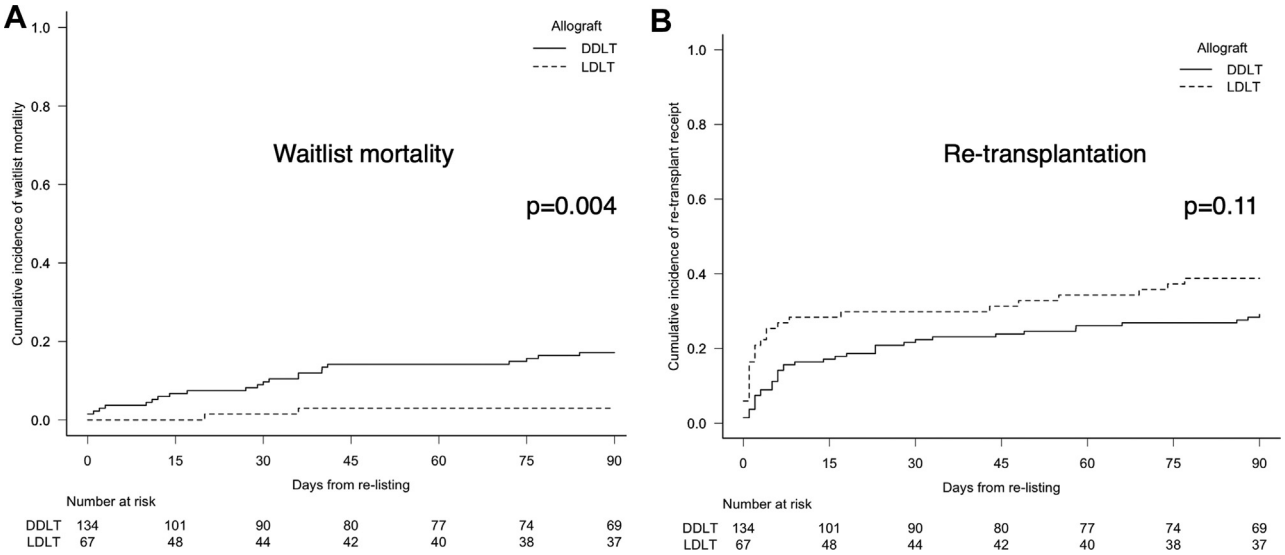

Figure 2. The 90-day cumulative incidence of *(A)* waitlist mortality and *(B)* retransplant from relisting by graft type at first transplant.

Per protocol survival after retransplant

The median per protocol survival was not reached in either the DDLT group or the LDLT group. The 90-day and 1-, 3-, 5-, and 10-year per protocol survival was not statistically significantly different between the groups (Figure S2 and Table S6). After multivariable adjustment, the per protocol mortality hazard was not statistically significantly different between the groups (ref: DDLT; LDLT HR = 1.51; 95% CI, 0.54–4.19; $P = .40$]) (Table 3).

Graft failure after retransplant

The cumulative incidence of graft failure after retransplant was similar between the LDLT and DDLT groups (Figure S3). Similarly, the cumulative incidence of death due to non–graft-related

Table II
Effect of graft type at first transplant (live donor liver transplant versus deceased donor liver transplant) on waitlist outcomes after relisting

Outcome (cause-specific hazard)	Overall (reference: DDLT)	
	Cause-specific HR (95% CI)	*P* value
Waitlist mortality*		
LDLT	0.51 (0.23–1.10)	.08
Transplant*		
LDLT	1.44 (0.94–2.20)	.10

CI, confidence interval; *DDLT*, deceased donor liver transplant; *HR*, hazard ratio; *LDLT*, live donor liver transplant; *LT*, liver transplant; *MELD*, Model for End-Stage Liver Disease.
* Adjusted for time between primary transplant and relisting, reason of graft failure after initial LT, age at relisting, MELD score at relisting, exception points awarded at relisting, and year of relisting.

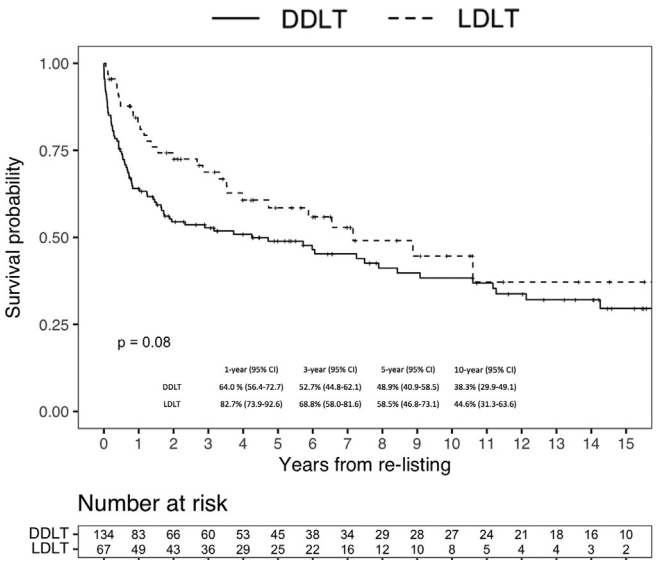

Figure 3. Intention-to-treat survival from relisting stratified by graft type at the first transplant.

reasons was similar between the LDLT and DDLT groups (Figure S4). On sensitivity analysis, death-censored graft survival post-retransplant was similar between the groups ($P = .50$) (Figure S5). After risk-adjustment, there was no statistically significant difference in graft loss (ref: DDLT; LDLT cause-specific HR = 1.33; 95% CI, 0.32–5.47; $P = .69$) or death due to non–graft-related reasons (ref: DDLT; LDLT cause-specific HR = 0.91; 95% CI, 0.34–2.42; $P = .85$) between the groups (Table S7).

Sensitivity analyses

Survival and waitlist outcomes based on initial graft type and receipt of exception points are shown in Figures S6–S11.

Discussion

After relisting for LT, the waitlist outcomes are similar in patients undergoing an LDLT at their first transplant compared with those who had received a DDLT. Specifically, on both ITT survival from relisting and per protocol survival (from retransplant), similar outcomes were noted between groups. Additionally, the risk of graft loss after retransplant was noted to be equivalent between patients who received either an LDLT or DDLT as their first transplant.

Table III
Effect of graft type at first transplant (LDLT *v* DDLT) on intention-to-treat and per protocol survival from relisting and retransplant, respectively

Outcome	Reference: DDLT	*P* value
	Overall	
	HR (95% CI)	
Intention to treat*		
LDLT	0.76 (0.44–1.32)	.30
Per protocol†		
LDLT	1.51 (0.54–4.19)	.40

BMI, body mass index; *CI*, confidence interval; *CIT*, cold ischemia time; *DDLT*, deceased-donor liver transplant; *HR*, hazard ratio; *LDLT*, live donor liver transplant; *LT*, liver transplant; *MELD*; Model for End-Stage Liver Disease; *WIT*, warm ischemia time.
* Adjusted for etiology of liver disease, reason of graft failure after the initial LT, recipient sex, age at relisting, BMI at relisting, MELD score at relisting, dialysis requirement at relisting, exception points awarded at relisting, time between primary transplant and relisting, and year of first listing.
† Adjusted for etiology of liver disease, reason of graft failure after the initial LT, BMI at re-LT, recipient age at re-LT, MELD at re-LT, exception points awarded at relisting, CIT, WIT, packed red blood cell transfusion (in milliliters), dialysis requirement at relisting, time between primary LT and relisting, and year of re-LT.

Similar to after DDLT, ~10% of LDLT recipients require retransplant.[24–26] Patient and graft survival after retransplant has historically been inferior to survival after primary LT, although outcomes for retransplant have improved over time.[5,25,27] These improvements result from progress in perioperative care, immunosuppression, and better treatment of HCV.[28,29] Another consideration of retransplant is the associated higher cost relative to primary LT.[30] Nonetheless, the present consensus does not consider previous receipt of a scarce medical resource, such as a graft, as a criterion for future distribution of the same resource.[31–34] Instead, organs are distributed based on the sickness of the patient and the likelihood of benefit they can derive from the transplant.[34,35]

Understanding the outcomes of waitlisted patients provides insight into whether the present allocation of organs effectively prioritizes certain groups of patients as well as clinically meaningful data that allow informed counseling of potential recipients on expected survival once relisted. A prior study evaluating waitlist mortality by Bitterman et al[12] noted similar outcomes between the retransplant groups (initial LDLT = 18.9% vs initial DDLT = 22.2%; $P = .192$). In the present report, the waitlist dropout due to death for the initial LDLT group was 15% (10/67) and for the DDLT group 37% (50/134). To further understand this, we evaluated survival from the time of relisting as an ITT analysis. The purpose of this analysis was to capture the survival of the cohort of patients who are unable to undergo a retransplant due to waitlist dropout. Compared with DDLT, the LDLT group had a similar 5-year, 10-year, and overall ITT survival. Although patients who develop graft failure after LDLT requiring retransplant received prioritization (assuming they were transplanted within accepted criteria and graft failure occurred because of biliary and/or vascular complications), the present system seems equitable in that outcomes between the 2 groups were equivalent. Furthermore, it should be taken into account that patients undergoing LDLT have not yet had a negative effect on the waiting list and in fact have increased organ availability for other patients awaiting their first transplant. After risk-adjustment, including adjustment for receipt of exception points at relisting, the LDLT group had a similar risk of waitlist mortality and transplant as the DDLT group. Although not explored explicitly in this study, it is feasible to perform retransplantation using living donor grafts, which we have previously described.[36] The option of retransplantation using LDLT may be an option in select patients, such as those with stable MELD scores with clear deterioration on the waitlist as manifested by progressive weight loss, sarcopenia,

need for frequent paracenteses, etc. Further, the potential donor should have an ideal graft (age <50, nonsteatotic, ABO-compatible, and with a graft-recipient weight ratio >1). Challenges around the use of living donor grafts for retransplantation include the higher potential risk associated with complex vascular reconstructions as well as concerns for small-for-size syndrome, the sequelae of which may be particularly detrimental for patients who are critically ill and have a relatively higher metabolic demand than primary LT recipients.

Patients who receive a primary LT with a living donor graft have distinct advantages over patients who receive a DDLT, as they are typically less sick and often more conditioned at the time of LT, experience shorter wait times, and have potential to receive a higher-quality graft.[37] They were, however, more frequently retransplanted for hepatic artery thrombosis and biliary complications. Compared with prior studies, 1- and 5-year survival outcomes were similar for retransplant after an initial LDLT (1-year University Health Network [UHN] = 86.7% vs Adult-to-Adult Living Donor Liver Transplantation Cohort Study [A2ALL] = 86%; 5-year UHN = 64.5% vs A2ALL = 64%).[24] In the OPTN/UNOS registry analysis by Bitterman et al,[12] the odds of 1-year mortality after retransplant was similar between patients with either an initial LDLT or DDLT (odds ratio = 0.74; 95% CI, 0.51–1.08). One of the strengths of this study is that it offers a longer-term follow-up (up to 10 years) of survival from retransplant for patients with initial LDLT and DDLT and reports that for patients who can undergo a second transplant, the survival from retransplant is similar.

This study is limited by its retrospective and nonrandomized study design, with the potential for selection and misclassification bias. We attempted to limit the potential effect of selection bias by analyzing the ITT outcomes from the time patients were relisted for a broad-spectrum view on relisted LDLT and DDLT patients. Nonetheless, as a result of the single-institutional study design, results may not be generalizable to other centers. However, a single-institutional study design can overcome some of the substantial differences and variability in listing/transplanting practices that multicenter/large database studies are more likely to be subject to. The high volume of both DDLTs and LDLTs performed at this single center in North America make the data distinct and well suited for addressing the study's aims. Lastly, although multivariable adjustment for potential confounders was performed, the potential for residual confounding and type I error remains.

In conclusion, patients who require relisting and retransplant after either LDLT or DDLT experience similar waitlist outcomes, ITT survival from relisting, per protocol survival from retransplant, complications after retransplant, and incidence of graft loss after retransplant.

Funding/Support

The authors have indicated that they have no funding regarding the content of this article.

Conflict of interest/Disclosure

Gonzalo Sapisochin discloses consultancy for AstraZeneca, Roche, Novartis, and Integra; has received financial compensation for talks for Roche, AstraZeneca, Chiesi, and Integra; and has received a grant from Roche. None of the other authors has any conflicts of interest to declare.

Acknowledgments

No preregistration exists for the studies reported in this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2022.09.022.

References

1. Yao FY, Saab S, Bass NM, et al. Prediction of survival after liver retransplantation for late graft failure based on preoperative prognostic scores. *Hepatology*. 2004;39:230–238.
2. Onaca N, Levy MF, Ueno T, et al. An outcome comparison between primary liver transplantation and retransplantation based on the pretransplant MELD score. *Transpl Int*. 2006;19:282–287.
3. Hong JC, Kaldas FM, Kositamongkol P, et al. Predictive index for long-term survival after retransplantation of the liver in adult recipients: analysis of a 26-year experience in a single center. *Ann Surg*. 2011;254:444–449.
4. Maggi U, Andorno E, Rossi G, et al. Liver retransplantation in adults: the largest multicenter Italian study. *PLoS One*. 2012;7:e46643.
5. Jeffrey AW, Delriviere L, McCaughan G, et al. Excellent contemporary graft survival for adult liver retransplantation: an Australian and New Zealand Registry analysis from 1986 to 2017. *Transplant Direct*. 2019;5:e472.
6. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: liver. *Am J Transplant*. 2021;21(suppl 2):208–315.
7. Cotter TG, Minhem M, Wang J, et al. Living-donor liver transplantation in the United States: evolution of frequency, outcomes, center volumes and factors associated with outcomes. *Liver Transpl*. 2021;27:1019–1031.
8. Ninomiya M, Shirabe K, Facciuto ME, et al. Comparative study of living and deceased donor liver transplantation as a treatment for hepatocellular carcinoma. *J Am Coll Surg*. 2015;220:297–304.e3.
9. Muller X, Marcon F, Sapisochin G, et al. Defining benchmarks in liver transplantation. *Ann Surg*. 2018;267:419–425.
10. Ogawa K, Takada Y. Living vs. deceased-donor liver transplantation for patients with hepatocellular carcinoma. *Transl Gastroenterol Hepatol*. 2016;1:35.
11. Kollmann D, Sapisochin G, Goldaracena N, et al. Expanding the donor pool: donation after circulatory death and living liver donation do not compromise the results of liver transplantation. *Liver Transplant*. 2018;24:779–789.
12. Bittermann T, Shaked A, Goldberg DS. When living donor liver allografts fail: exploring the outcomes of retransplantation using deceased donors. *Am J Transplant*. 2017;17:1097–1102.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.
14. Dindo D, Demartines N, Clavien P. Classification of surgical complications. 2004;240:205–213.
15. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258:1–7.
16. Tschuor C, Ferrarese A, Kümmerli C, et al. Allocation of liver grafts worldwide is there a best system? *J Hepatol*. 2019;71:707–718.
17. Trillium Gift of Life Network. *Policies: Wait List, Organ Offers and Allocation*. Toronto: Ontario Health; 2019.
18. Canadian Blood Services. Liver Listing and Allocation Forum. https://professionaleducation.blood.ca/sites/msi/files/liver_listing_and_allocation_forum_report_-_final_en.pdf. Accessed May 9, 2022.
19. Varadhan R, Weiss CO, Segal JB, Wu AW, Scharfstein D, Boyd C. Evaluating health outcomes in the presence of competing risks: a review of statistical methods and clinical applications. *Med Care*. 2010;48(6 suppl):S96–S105.
20. Gray B. cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-10. 2020. https://CRAN.R-project.org/package=cmprsk. Accessed October 24, 2022.
21. Zeileis A, Köll S, Graham N. Various versatile variances: An object-oriented implementation of clustered covariances in R. *J Stat Softw*. 2020;95:1–36.
22. Zeileis A. Econometric computing with HC and HAC covariance matrix estimators. *J Stat Softw*. 2004;11:1–17.
23. Zeileis A, Hothorn T. Diagnostic checking in regression relationships. *R News*. 2002;2:7–10.
24. Braun HJ, Grab JD, Dodge JL, et al. Retransplantation after living donor liver transplantation: data from the Adult to Adult Living Donor Liver Transplantation Study. *Transplantation*. 2021;105:1297–1302.
25. Azoulay D, Linhares MM, Huguet E, et al. Decision for retransplantation of the liver: an experience- and cost-based analysis. *Ann Surg*. 2002;236:713–721;discussion 721.
26. Markmann JF, Markowitz JS, Yersiz H, et al. Long-term survival after retransplantation of the liver. *Ann Surg*. 1997;226:408–420.
27. Kitchens WH, Yeh H, Markmann JF. Hepatic retransplant: what have we learned? *Clin Liver Dis*. 2014;18:731–751.
28. Watt KDS, Lyden ER, McCashland TM. Poor survival after liver retransplantation: is hepatitis C to blame? *Liver Transpl*. 2003;9:1019–1024.

29. Ivanics T, Rizzari M, Moonka D, et al. Retransplantation outcomes for hepatitis C in the United States before and after direct-acting antiviral introduction. *Am J Transplant*. 2021;21:1100–1112.
30. Markmann JF, Gornbein J, Markowitz JS, et al. A simple model to estimate survival after retransplantation of the liver. *Transplantation*. 1999;67:422–430.
31. Ethical considerations in the allocation of organs and other scarce medical resources among patients. Council on Ethical and Judicial Affairs, American Medical Association. *Arch Intern Med*. 1995;155:29–40.
32. Ubel PA, Arnold RM, Caplan AL. Rationing failure. The ethical lessons of the retransplantation of scarce vital organs. *JAMA*. 1993;270:2469–2474.
33. Rivlin MM. Why the fair innings argument is not persuasive. *BMC Med Ethics*. 2000;1:E1.
34. Huesch MD. One and done? Equality of opportunity and repeated access to scarce, indivisible medical resources. *BMC Med Ethics*. 2012;13:11.
35. Tschuor C, Ferrarese A, Kuemmerli C, et al. Allocation of liver grafts worldwide – is there a best system? *J Hepatol*. 2019;71:707–718.
36. Patel MS, Ghanekar A, Sayed BA, et al. Liver retransplantation using living donor grafts: a western experience. *Liver Transpl*. 2022;28:887–890.
37. Humar A, Ganesh S, Jorgensen D, et al. Adult living donor versus deceased donor liver transplant (LDLT versus DDLT) at a single center: time to change our paradigm for liver transplant. *Ann Surg*. 2019;270:444–451.