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Low utilization of adult-to-adult LDLT in Western countries despite excellent outcomes: International multicenter analysis of the US, the UK, and Canada

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Research Article
Liver Transplantation

JOURNAL
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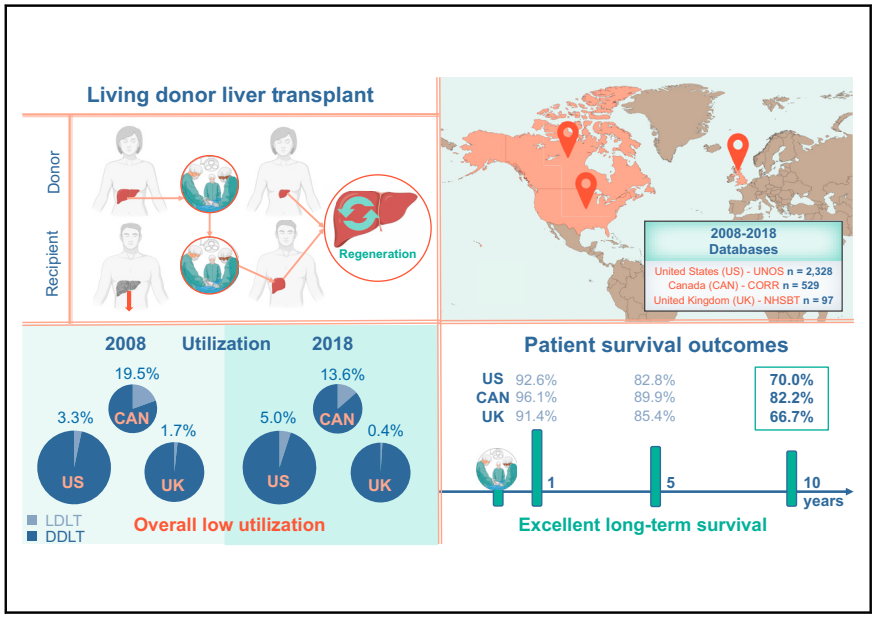
Graphical abstract



Highlights

- Living donor liver transplantation use is low in Western countries.
- Despite this, long-term survival after living donor liver transplantation is excellent.
- Continued efforts to increase use of living donor liver transplantation are warranted.

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Lay summary

This multicenter international comparative analysis of living donor liver transplantation in the United States, the United Kingdom, and Canada demonstrates that despite low use of the procedure, the long-term outcomes are excellent. In addition, the mortality risk is not statistically significantly different between the evaluated countries. However, the incidence and risk of retransplantation differs between the countries, being the highest in the United Kingdom and lowest in the United States.

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Low utilization of adult-to-adult LDLT in Western countries despite excellent outcomes: International multicenter analysis of the US, the UK, and Canada

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Background & Aims: Adult-to-adult living donor liver transplantation (LDLT) offers an opportunity to decrease the liver transplant waitlist and reduce waitlist mortality. We sought to compare donor and recipient characteristics and post-transplant outcomes after LDLT in the US, the UK, and Canada.

Methods: This is a retrospective multicenter cohort-study of adults (≥18-years) who underwent primary LDLT between Jan-2008 and Dec-2018 from three national liver transplantation registries: United Network for Organ Sharing (US), National Health Service Blood and Transplantation (UK), and the Canadian Organ Replacement Registry (Canada). Patients undergoing retransplantation or multi-organ transplantation were excluded. Post-transplant survival was evaluated using the Kaplan-Meier method, and multivariable adjustments were performed using Cox proportional-hazards models with mixed-effect modeling.

Results: A total of 2,954 living donor liver transplants were performed (US: n = 2,328; Canada: n = 529; UK: n = 97). Canada has maintained the highest proportion of LDLT utilization over time (proportion of LDLT in 2008 – US: 3.3%; Canada: 19.5%; UK: 1.7%; p <0.001 – in 2018 – US: 5.0%; Canada: 13.6%; UK: 0.4%; p <0.001). The 1-, 5-, and 10-year patient survival was 92.6%, 82.8%, and 70.0% in the US *vs.* 96.1%, 89.9%, and 82.2% in Canada *vs.* 91.4%, 85.4%, and 66.7% in the UK. After adjustment for characteristics of donors, recipients, transplant year, and treating transplant center as a random effect, all countries had a non-statistically significantly different mortality hazard post-LDLT (Ref US: Canada hazard ratio 0.53, 95% CI 0.28–1.01, p = 0.05; UK hazard ratio 1.09, 95% CI 0.59–2.02, p = 0.78).

Conclusions: The use of LDLT has remained low in the US, the UK and Canada. Despite this, long-term survival is excellent. Continued efforts to increase LDLT utilization in these countries may be warranted due to the growing waitlist and differences in allocation that may disadvantage patients currently awaiting liver transplantation.

Lay summary: This multicenter international comparative analysis of living donor liver transplantation in the United States, the United Kingdom, and Canada demonstrates that despite low use of the procedure, the long-term outcomes are excellent. In addition, the mortality risk is not statistically significantly different between the evaluated countries. However, the incidence and risk of retransplantation differs between the countries, being the highest in the United Kingdom and lowest in the United States.

Introduction

Living donor liver transplantation (LDLT) remains relatively uncommon in Western countries compared to those in the East.[1–3] Increasing LDLT in countries that perform mostly deceased donor liver transplantation (DDLT) provides an opportunity to reduce the imbalance between organ supply and demand and as a result offers waitlist candidates the possibility of earlier transplantation and decreased waitlist mortality.[4]

Recently, two international surveys evaluated LDLT practice patterns in 41 countries, which included donor selection and

Keywords: liver transplantation; living donor liver transplantation; LDLT; CORR; Canada; UK; NHSBT; US; UNOS; STAR.
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evaluation, graft type and donor characteristics, and acceptable graft-recipient-weight-ratio (GRWR).[5,6] These studies demonstrated that despite the availability of consensus guidelines, a wide range of practice patterns persists with the impact of the differences remaining unclear.[7,8]

A large-scale comparison of trends in LDLT and an examination of donor and recipient characteristics across countries has yet to be performed. Identifying differences in outcomes and other transplant characteristics may help identify areas for healthcare improvement and clarify whether expansion of LDLT can be justified in countries that rely primarily on DDLT.

We thus sought to compare recipient and donor characteristics, temporal trends, and post-LDLT outcomes between the US, Canada, and the UK using three respective national liver transplant registries. In addition, we sought to compare outcomes for LDLT with those of DDLT within each of the countries.

Patients and methods

Study population

We included consecutive adults (≥18 years) who underwent LT between Jan-2008 and Dec-2018 from 3 national liver transplantation registries: United Network for Organ Sharing (UNOS; US), National Health Service Blood and Transplantation (NHSBT; UK), and the Canadian Organ Replacement Registry (CORR; Canada). These registries were chosen because they are well-maintained, validated, have sufficient granularity, have an acceptable degree of missing data, are publicly available, and represent a substantial proportion of liver transplants performed in the West. The three datasets were harmonized, a process of combining data from different sources to provide a comparable view of the data. Patients who underwent retransplantation, multi-organ transplantation, domino transplantation, had super-urgent transplant status, a diagnosis of acute liver failure, or had missing follow-up information were excluded. A Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)-compliant diagram of patients excluded and included is shown in Fig. 1. This study complies with the STROBE statement for retrospective studies.[9]

National transplant registries

UNOS STAR

Liver transplantation data from the United States was obtained from the Standard Transplant and Research (STAR) file from the Organ Procurement and Transplantation Network/UNOS. UNOS has collected data since 1987. Its STAR database captures information on donor, recipient, transplant center, waitlist characteristics, and post-LT outcomes for every organ donation and transplant event in the US.[10] The database undergoes serial audits for quality assurance and to minimize any discrepancies and inaccuracies in data reporting.[10]

CORR

CORR from the Canadian Institute for Health Information contains administrative data from all patients who underwent transplantation from 2000–2018 in Canada. It does not include listing information or waitlist outcomes. Patient and donor records from Quebec are not included in this database. Moreover, the Transplant Quebec registry data does not include recipient and post-transplant outcome information. As such, despite not representing a population-based dataset, CORR represents the largest scale transplant registry option available in Canada, covering 6 of the 7 transplant programs in Canada and representing the majority of centers in Canada.[11] The CORR dataset captures transplant information from 6 transplant centers in Canada (excluding Quebec), including B.C. Children's (British Columbia), Vancouver General (British Columbia), University of Alberta/AKC-North (Alberta), Hospital for Sick Children (Ontario), London Health Sciences Centre – University (Ontario),

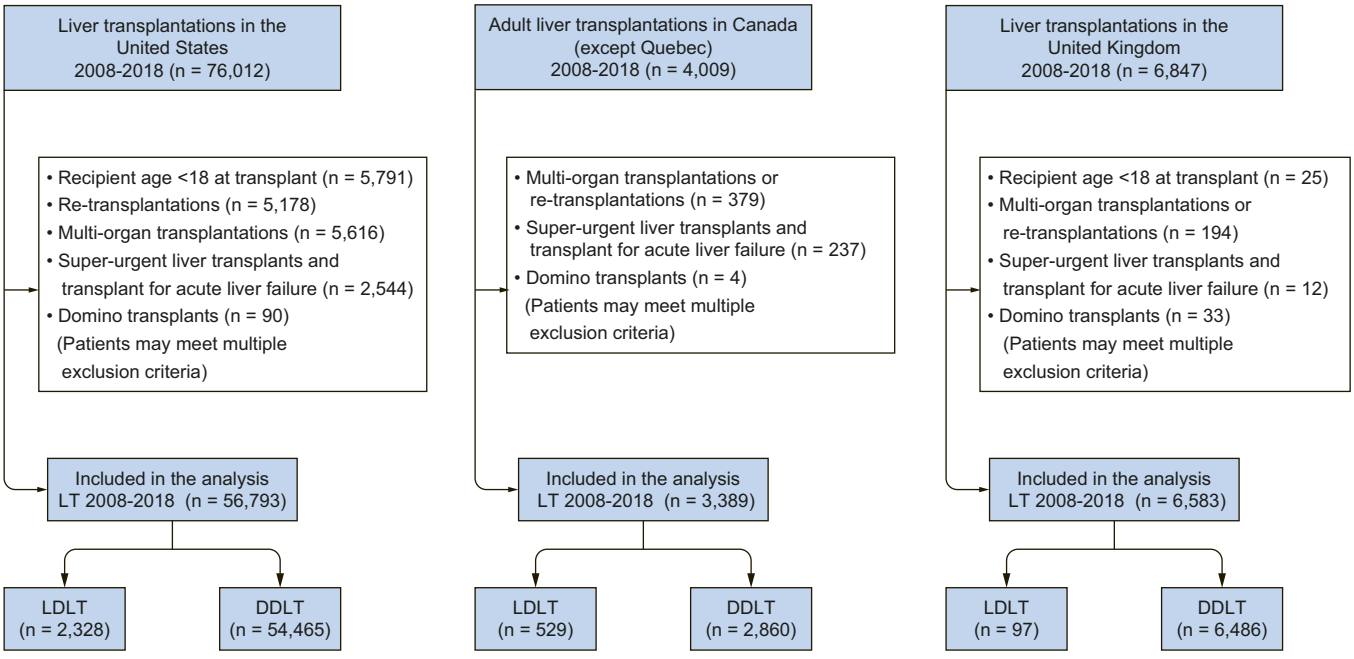

Fig. 1. STROBE-compliant diagrams of patient inclusion and exclusion for each registry. DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; LT, liver transplantation.

Toronto General Hospital (Ontario), and Queen Elizabeth (New Brunswick).[12]

NHSBT UK liver transplant registry

The Standard National Liver Transplant registry has collected detailed information on all liver transplants performed in the 7 liver transplant centers in the UK since 1984. The registry captures information on recipient characteristics, donor characteristics, and post-transplantation outcomes. The dataset undergoes regular audits to ensure that data completion exceeds 93% and data accuracy is upheld.[13]

Covariates

The sample was stratified according to country into the US, Canada, and the UK. Donor variables included age, BMI, allograft type (grouped as deceased donor transplant [including deceased after brain death and deceased after circulatory death [DCD] donors] and LDLT), graft laterality, and cold ischemia time (CIT) in minutes. We recorded recipient demographics (including sex, race, and age) and characteristics such as model for end-stage liver disease (MELD) score (calculated as MELD = 3.78*ln[serum bilirubin (mg/dl)] + 11.2*ln[INR] + 9.57*ln[serum creatinine (mg/dl)] + 6.43),[14] need for pre-liver transplant dialysis, functional status, ventilator requirement before liver transplant, waitlist time in days, BMI, and previous abdominal surgeries. Laboratory variables included creatinine (mg/dl), bilirubin (mg/dl), albumin (g/dl), internationalized normalized ratio (INR), recipient hepatitis C antibodies, blood group, ascites, encephalopathy, and recipient-donor blood group match status. Patients were grouped according to a liver disease classification system first adopted by Roberts *et al.*[15] In the case a patient has multiple diagnoses, patients are assigned to the diagnosis most likely to have influenced their prognosis at the time of LT. Disease classification was undertaken in a hierarchical order: cancer, HCV cirrhosis, primary sclerosing cholangitis, primary biliary cholangitis, alcohol-related liver disease, autoimmune disease, metabolic, and others. For instance, patients with a coded diagnosis of HCV and a diagnosis of hepatocellular carcinoma (HCC) would be assigned to the HCC category. A full description of disease etiology codes for this classification is provided in Table S1. For multivariable analyses, creatinine was set to 4.0 mg/dl for those with lower values who received renal replacement therapies immediately before transplantation. Implausible values of BMI (<10 or >100 kg/m^2), CIT (>40 hours), serum bilirubin (<0.1 mg/dl), and serum creatinine (0.1 or >15 mg/dl) were set to be missing.

Outcome measures

The primary outcome of the study was patient survival after LDLT. Patient survival was assessed from the transplant to death or last known time alive, regardless of any retransplants. The secondary outcomes were graft survival and the cumulative incidence of retransplantation after LDLT. Graft loss was defined as a) need for retransplantation or b) death. The date of graft loss was therefore defined as the date of retransplantation or the date of death if the date of death preceded retransplantation.

Causes of death were categorized into malignancy, sepsis, graft failure/liver-related, hemorrhage, pulmonary failure, renal failure, cardiovascular failure, gastrointestinal failure, infection, cerebrovascular accident, and other. The coding used for this classification harmonization is shown in Table S2. Because multiple causes of death are possible for a patient, each cause was dichotomized. Comparisons of causes of death between countries were only performed for patients whose cause was neither missing nor unknown. Causes of graft failure were categorized as acute rejection, chronic rejection, primary non-function, vascular occlusion, recurrent disease, biliary complications, and other. The coding used for this classification harmonization is shown in Table S3. Because multiple causes can contribute to graft failure (*i.e.*, overlap), each cause was dichotomized. Comparisons of causes of graft failure between countries were only performed for patients whose cause of graft failure was neither missing nor unknown.

Statistical analysis

Descriptive data were expressed as medians (IQR) for non-normally distributed variables. These were compared using the Mann-Whitney *U* tests. Normally distributed continuous variables were expressed as means (SD) and compared using independent sample *t* tests. Categorical variables were expressed using n (%) and compared using the Chi-square test. To evaluate the temporal trend in the proportion of LDLT transplanted, a Cochran-Armitage Test for trend was performed. This entails testing a 2-sided null hypothesis of no trend, meaning that the binomial proportion (LDLT) is the same for all levels of the explanatory variable (year of transplant). A sensitivity analysis was performed to evaluate the temporal trends in the use of right lobe grafts across the countries according to a similar methodology. Follow-up data were available for the US until 3-Mar-2020, Canada until 31-Dec-2018, and the UK until 22-Apr-2020. Overall patient and graft survival were estimated using the Kaplan-Meier method and groups compared with log-rank tests. Multiple pairwise comparisons between groups with corrections for multiple testing were performed using the Benjamini-Hochberg method. The cumulative incidence of retransplantation was performed with death considered as a competing risk using the cumulative incidence function.[16] A Gray's modified log-rank test was used to compared unadjusted cumulate incidence estimates.[17] We used mixed-effects Cox regression to evaluate the effect of each country on survival. In addition, Fine-Gray subdistribution hazard ratios were presented for the hazard of retransplantation for completeness. All multivariable models were analyzed using complete-case analyses. Separate models were constructed. In the first model, hazard ratios (HRs) comparing post-transplant survival in liver transplant recipients were estimated without adjustment for the donor or recipient characteristics. In the final model, HRs were estimated after adjustment for both donor and recipient factors. Similar models were constructed to evaluate the effect of LDLT relative to DDLT for patient and graft survival within each country. However, in these models, no adjustments for donor characteristics were performed except for age, as favorable donor characteristics (such as shorter CIT) may be present in the causal pathway of a survival benefit with LDLT, instead of representing potential confounders requiring adjustment in multivariable models.[18,19] In the models, transplant center was treated as a random effect. The cumulative incidence of retransplantation after LDLT for each country were calculated, with death preceding retransplantation considered as a competing event.[16] A mixed-effects competing-risk multivariable model was constructed to evaluate the cause-specific hazard of the UK and Canada relative to the US for retransplantation after LDLT, with adjustment for recipient factors (age, etiology of liver disease, BMI, laboratory parameters at LDLT [bilirubin, INR, and creatinine], donor age,

and transplant characteristics (CIT and year of transplant), with transplant center treated as a random effect. In Canada, due to the structure of the dataset, only 2 center groupings could be performed: University Health Network (UHN) and non-UHN. Additional sensitivity analyses were performed between DDLT and LDLT within each country, between different graft types (left lobe and right lobe), and by HCC status. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R Core Team (2013) R (R Foundation for Statistical Computing v4.1.1, 2021-08-10, Vienna, Austria URL http://www.R-project.org/). Mixed-effects cox regression was performed using the package 'survival' version 3.2.11 and 'coxme' version 2.2-16. Competing-risk models were constructed using the package 'cmprsk' version 2.2-10. This study was approved by our institutional ethics review board (REB) (REB#19-5835), and a waiver of informed consent was obtained.

Results

Country-specific LDLT utilization (2008-2018)

A total of 2,954 living donor liver transplants (LDLTs) were identified in the three registries (US n = 2,328, Canada n = 529, UK n = 97) (Fig. 1). The annual proportion of LDLT was highest in Canada (11.6–19.5%) and lowest in the UK (0.4–1.8%). Over the duration of the study period, the proportion of LDLTs was largely stable in each country, with a modest steady increase over time in the US (2008 *vs.* 2018: US 3.3% *vs.* 5.0%; Canada 19.5% *vs.* 13.6%; UK 1.7% *vs.* 0.4%) (Fig. 2). There was a statistically significant trend in the proportion of LDLTs performed over the study period in all countries (Cochran-Armitage Test: US increasing p <0.001; Canada decreasing p <0.001; UK decreasing p = 0.02). There was also a statistically significant trend in the proportion of right lobe LDLTs performed over the study period in all countries except the UK where the use remained stable (Cochran-Armitage Test: US increasing p = 0.04; Canada increasing 0.002; UK neither increasing nor decreasing p = 0.87) (Fig. S1).

Donor characteristics

Compared to Canada and the UK, donors in the US were older (median years [IQR]: US 36 [28–45] *vs.* Canada 35 [27–46] *vs.* UK 33 [25–40]; p = 0.009). The CIT was longest in the UK (median minutes [IQR]: US 84 [56–120] *vs.* Canada 88 [58–128] *vs.* UK 110 [72–162]; p = 0.002) (Table 1).

Recipient characteristics

There was no significant difference between recipient sex between countries. At the time of LT, recipients in the US were older (years [IQR]: US 56 [47–62] *vs.* Canada 54 [45–61] *vs.* UK 53 [35–61]; p <0.001), and had longer waitlist times (days [IQR]: US 150 [80–307] *vs.* Canada 123 [68–230] *vs.* UK 92 [7–202]; p <0.001) (Table 2). Cancer represented the highest proportion of LDLTs performed in Canada (US 18% *vs.* Canada 20% *vs.* UK 18%; p <0.001). There was a higher proportion of HCV LDLTs in the US (US 17% *vs.* Canada 12% *vs.* UK 10%; p <0.001), whereas primary sclerosing cholangitis was the most common etiology of liver disease in the UK (US 16% *vs.* Canada 19% *vs.* 20%; p <0.001) (Table 2). In the US, the largest 5 centers performed 9.7%, 7.7%, 7.5%, 5.8%, and 5.7% of all the LDLTs during the study period. In Canada, the majority of LDLTs were performed at UHN (421 [76%]). In the UK, 2 centers performed over 70% of the LDLTs (33% and 40%).

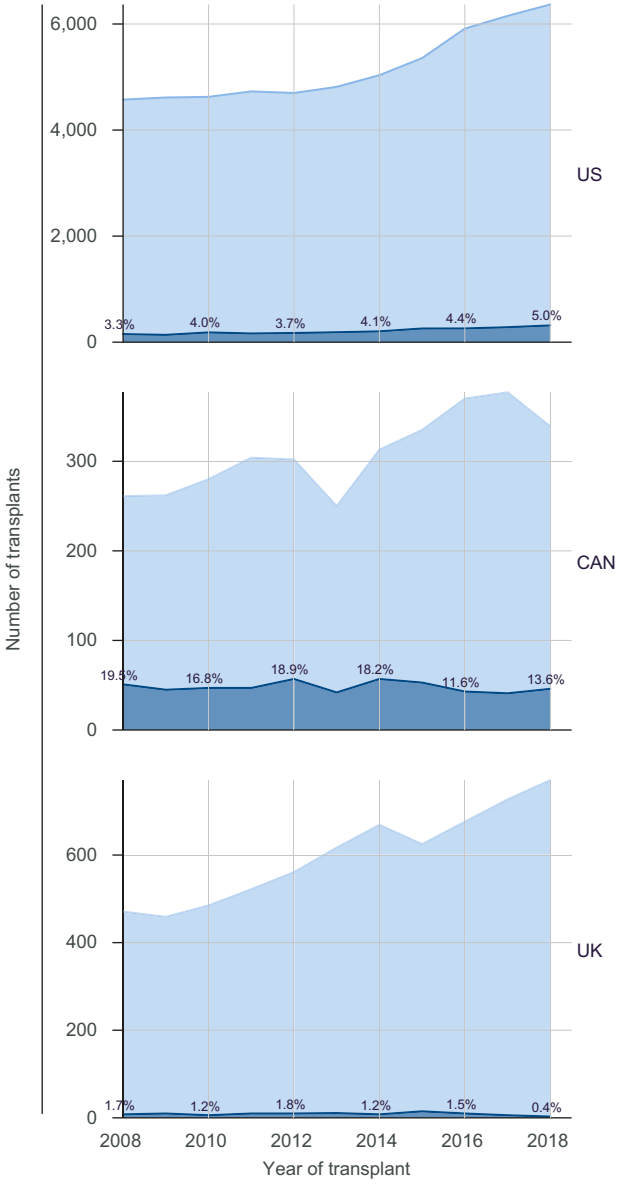

Fig. 2. Proportion of LDLTs performed over time per country (the light color are all primary LTs and the dark shaded color the LDLTs). LDLT, living donor liver transplants; LT, liver transplants.

Post-transplant patient survival

The median follow-up time after LDLT was longest in Canada (US, 3.9 years, IQR, 1.8–6.5; Canada 4.8 years, IQR, 2.4–7.6; UK 3.2 years, IQR, 1.2–5.5; p <0.001). The overall post-LDLT patient survival was significantly higher in Canada compared to the US (p <0.001), but not significantly different from the UK (p = 0.19), which in turn was similar to the US (p = 0.73) (Fig. 3). The 1-, 3-, 5-, and 10-year patient survival was 92.6% 87.6% 82.8%, and 70.0% in the US *vs.* 96.1%, 92.3%, 89.9%, and 82.7% in Canada, *vs.* 91.4%, 90.0%, 85.4%, and 66.7%, in the UK (p values: 1-year p = 0.02; 3-year p = 0.01; 5-year p = 0.002; 10-year p <0.001) (Table S4). A sensitivity analysis stratified by HCC status overall and by country is shown in Fig. S2 and Fig. S3 along with estimates of patient and graft survival in Table S5 and Table S6. An additional sensitivity analysis stratified by graft type overall and by country

Table 1. Donor characteristics.

	US (n = 2,328)	Canada (n = 529)	UK (n = 97)	*p* value
Sex, n (%)				<0.001[2]
Female	1,229 (53%)	231 (44%)	35 (36%)	
Male	1,099 (47%)	298 (56%)	62 (64%)	
Age, years				0.009[1]
Median (Q1, Q3)	36 (28, 45)	35 (27, 46)	33 (25, 40)	
BMI				
Median (Q1, Q3)	26 (24, 29)	25 (23, 28)	n.a.	
Graft laterality, n (%)				
Missing	21	0	0	<0.001[2]
Left lobe	309 (13%)	34 (6%)	23 (24%)	
Right lobe	1,998 (87%)	495 (94%)	74 (76%)	
CIT, minutes				0.002[1]
Median (Q1, Q3)	84 (56, 120)	88 (58, 128)	110 (72, 162)	

CIT, cold ischemia time.
[1]Kruskal-Wallis rank sum test.
[2]Pearson's Chi-square test.

is shown in Fig. S4 and Fig. S5 along with estimates of patient and graft survival in Table S7 and Table S8. These demonstrated largely equivalent patient survival between graft types within the different countries.

Post-transplant graft survival

The overall post-LDLT graft survival was not statistically significant different in Canada compared to the US ($p = 0.10$), but was higher than in the UK ($p = 0.04$), which in turn was not statistically significantly different from the US ($p = 0.10$) (Fig. S6). The 1-, 3-, 5-, and 10-year graft survival rates were 90.5%, 85.3%, 79.9%, and 66.5% in the US *vs.* 92.3%, 87.4%, 83.8%, and 72.0% in Canada, *vs.* 82.9%, 80.2%, 75.4%, and 54.4%, in the UK (p values: 1-year $p = 0.02$; 3-year $p = 0.01$; 5-year $p = 0.002$; 10-year $p < 0.001$) (Table S4).

Risk-adjusted analysis

Compared to the US, the unadjusted Cox proportional-hazards model demonstrated a 42% lower mortality hazard in Canada

Table 2. Recipient characteristics.

	US (n = 2,328)	Canada (n = 529)	UK (n = 97)	*p* value
Sex, n (%)				0.16[1]
Female	1,021 (44%)	231 (44%)	52 (54%)	
Male	1,307 (56%)	298 (56%)	45 (46%)	
Age				<0.001[2]
Median (IQR)	56 (47–62)	54 (45–61)	53 (35–61)	
BMI				<0.001[2]
Median (IQR)	26 (23–30)	26 (23–29)	24 (22–28)	
Race, n (%)				<0.001[1]
White	1,915 (82%)	123 (22%)	51 (53%)	
Black	72 (3%)	1 (0%)	1 (1%)	
Other	361 (15.0%)	432 (78%)	45 (46%)	
MELD				0.003[2]
Median (IQR)	13 (9, 17)	15 (10, 18)	11 (8, 16)	
Renal support, n (%)				<0.001[1]
N-Missing	5	0	0	
Pre-transplant support	13 (1%)	7 (1%)	9 (9%)	
Functional status, n (%)*				
N-Missing	31	529	1	
High	711 (31%)	0	12 (13%)	
Intermediate	1,202 (52%)	0	36 (38%)	
Low	384 (17%)	0	48 (50%)	
Ventilatory status, n (%)				
N-Missing	0	529	1	
Ventilated	6 (0%)	0	0 (0%)	
Waitlist time, days				<0.001[2]
Median (IQR)	150 (80–307)	123 (68–230)	92 (7–202)	
Previous abdominal surgery, n (%)				
N-Missing	35	529	1	
Yes	1,146 (50%)	0	18 (19%)	
Creatinine pre-transplant (mg/dl)				0.36[2]
Median (IQR)	0.86 (0.70–1.10)	0.82 (0.71–1.10)	0.80 (0.58–1.07)	
Bilirubin pre-transplant (mg/dl)				<0.001[2]
Median (IQR)	2.70 (1.40–4.80)	3.68 (1.93–6.96)	2.49 (1.35–4.50)	
Albumin pre-transplant (g/dl)				
Median (IQR)	3.10 (2.70–3.60)	NA	3.20 (2.68–3.82)	

(*continued on next page*)

Table 2. (*continued*)

	US (n = 2,328)	Canada (n = 529)	UK (n = 97)	*p* value
INR pre-transplant				0.11[2]
Median (IQR)	1.40 (1.20–1.60)	1.41 (1.20–1.70)	1.40 (1.20–1.90)	
Anti HCV antibodies, n (%)				0.40[1]
N-Missing	75	108	0	
Positive	545 (24%)	91 (22%)	20 (21%)	
Blood group, n (%)				<0.001[1]
N-Missing	0	1	0	
0	1,067 (46%)	227 (43%)	47 (49%)	
A	1,003 (43%)	193 (37%)	21 (22%)	
AB	29 (1%)	24 (5%)	2 (2%)	
B	229 (10%)	84 (16%)	27 (28%)	
Ascites, n (%)				
N-Missing	0	529	0	
Ascites	1,506 (65%)	0	44 (45%)	
Encephalopathy, n (%)				
N-Missing	0	529	3	
Encephalopathic	1,191 (51%)	0	22 (23%)	
Blood group match, n (%)				
N-Missing	0	529	2	
Compatible	518 (22%)	0	21 (22%)	
Identical	1,796 (77%)	0	73 (77%)	
Incompatible	14 (1%)	0	1 (1%)	
Liver disease etiology, n (%)				<0.001[1]
Cancer	421 (18%)	108 (20%)	17 (18%)	
HCV	393 (17%)	62 (12%)	10 (10%)	
PSC	378 (16%)	100 (19%)	19 (20%)	
HBV	101 (4%)	9 (2%)	4 (4%)	
PBC	191 (8%)	55 (10%)	10 (10%)	
ALD	252 (11%)	60 (11%)	6 (6%)	
AID	203 (9%)	37 (7%)	8 (8%)	
Metabolic	347 (15%)	52 (10%)	10 (10%)	
Other	42 (2%)	52 (10%)	13 (13%)	
Retransplantation, n (%)	85 (4%)	41 (8%)	10 (10%)	<0.001[1]

AID, autoimmune disease; ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; UHN, University Health Network.
*Harmonized according to FUNC_STAT_TRR (Karnofsky score) (US) and RLIFE (Lifestyle activity score). Low activity was considered as a Karnofsky score 10-40% and a lifestyle that was either only capable of limited self-care (confined mostly to bed or chair) or completely reliant on nursing/medical care). Intermediate was considered as a Karnofsky score of 50-70% or the ability to move freely (capable of self-care; unable to do any form of work). High was considered as a Karnofsky score of 80-100% or a lifestyle that is only restricted in physically strenuous activity or the ability to carry out normal activity without restriction.
[1]Pearson's Chi-square test.
[2]Kruskal-Wallis rank sum test.

(HR 0.58, 95% CI 0.44–0.76; p <0.001), and a non-statistically significantly different hazard in the UK (HR 0.91, 95% CI 0.52–1.58; p = 0.74). After adjustment for both recipient and donor characteristics, both Canada and the UK had a non-statistically significantly different post-LDLT mortality hazard as the US (Canada adjusted HR [aHR] 0.53, 95% CI 0.28–1.01, p = 0.05; UK aHR 1.09, 95% CI 0.59–2.02, p = 0.78) (Table S9) Similar trends were noted when comparing the hazard of graft loss after LDLT across countries, except for a higher graft loss hazard in the UK when adjusted for recipient and donor characteristics (aHR 1.72; 95% CI 1.08–2.76; p = 0.02) (Table S10).

Country-specific LDLT *vs.* DDLT

Post-transplant survival

In the US, the unadjusted 1-, 3-, 5-, and 10-year survival was 92.6%, 87.6%, 82.8%, and 70.0% for LDLT *vs.* 91.3%, 83.8%, 77.7%, and 62.4% for DDLT (p values: 1-year p = 0.04; 3-year p <0.001; 5-year p <0.001; 10-year p <0.001) (Table S11). The median survival in the US was 12.0 years for DDLT and was not reached for LDLT. In Canada, the unadjusted 1-, 3-, 5-, and 10-year survival was 96.1%, 92.3%, 89.9%, and 82.2% for LDLT *vs.* 92.0%, 86.7%, 82.7%, and 75.0% for DDLT (p values: 1-year p = 0.001; 3-year p <0.001; 5-year p <0.001; 10-year p <0.001) (Table S11). The median survival in Canada was not reached for either LDLT or DDLT. In the UK, the unadjusted 1-, 3-, 5-, and 10-year survival was 91.4%,

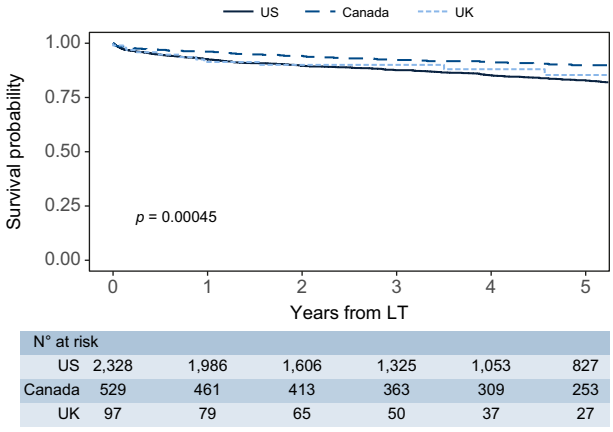

Fig. 3. Post-transplant survival after living donor LT stratified by country (Kaplan-Meier method and log-rank test). LT, liver transplantation.

90.0%, 85.4%, and 66.7% for LDLT *vs.* 93.2%, 87.7%, 82.2%, and 69.4% for DDLT (*p* values: 1-year $p = 0.52$; 3-year $p = 0.69$; 5-year $p = 0.63$; 10-year $p = 0.69$) (Table S11). The median survival in the UK was 11.9 years for DDLT and not reached for LDLT (Fig. 4). There was no statistically significant difference in the causes of death between the countries where the cause of death was known (Table S12).

Risk-adjusted analysis comparing outcomes for LDLT and DDLT

Compared to DDLT, the unadjusted Cox proportional-hazards model demonstrated a 25% lower mortality hazard for LDLT in the US (HR 0.75; 95% CI 0.68–0.83; $p < 0.001$), a 39% lower hazard in Canada (HR 0.61; 95% CI 0.47–0.80; $p < 0.001$), and a non-statistically significantly different hazard in the UK (HR 0.89; 95% CI 0.52–1.54; $p = 0.69$). Finally, after adjustment for both recipient and donor characteristics, LDLT was associated with a non-statistically significantly different post-LT mortality hazard as DDLT in all countries (US aHR 1.00, 95% CI 0.90–1.12, $p = 0.96$; Canada aHR 0.70, 95% CI 0.46–1.08, $p = 0.10$; UK aHR 1.28, 95% CI 0.71–2.31, $p = 0.41$) (Table S13).

The cumulative incidence of retransplantation

For patients who underwent LDLT, the cumulative incidence of retransplantation was highest in the UK and lowest in the US (5-year cumulative incidence: US 3.7%, Canada 6.5%, UK 9.7%; $p < 0.001$) (Fig. S7). Stacked cumulative incidence curves for retransplantation with the competing event of death for each country are shown in Fig. S8. Compared to the US, after adjustment for recipient, donor, and transplant characteristics, the UK was associated with a higher cause-specific hazard of retransplantation after LDLT (Canada adjusted cause-specific HR 1.79, 95% CI 0.83–3.86, $p = 0.13$ and UK adjusted cause-specific HR 3.92, 95% CI 1.82–8.45, $p < 0.001$) (Table S14). The Fine-Gray subdistribution HRs had a similar pattern for these estimates (Table S14). A sensitivity analysis of the cumulative incidence of retransplantion by graft type stratified by country both overall and by country is shown in Fig. S9 and Fig. S10. All but 2 retransplantations (both in the US) after LDLT were performed using deceased donor grafts. The causes of graft failure are shown in Table S15.

Discussion

This study represents the largest international cohort describing trends, characteristics, and outcomes of LDLT between three nations – the US, Canada, and the UK. With the exception of Canada, these represent population-based data and are therefore representative of the respective countries' LDLT practices and outcomes. Of the three nations, Canada has the highest proportion of LDLT use, whereas the UK has the lowest. Overall, the trends of LDLT use have been consistent in each nation, except for a modest, steady increase in the US. Survival outcomes are excellent for all three countries, with 5-year survival exceeding 82% and 10-year survival 66%. The overall risk-adjusted mortality post-LDLT, after adjustment for both recipient and donor characteristics, considering the transplant center as a random effect, was not statistically significantly different between the countries. While Canada was associated with a non-statistically significantly different hazard of graft loss from the US, the hazard of graft loss for the UK was higher relative to the US. No statistically significant difference in risk-adjusted post-transplant mortality was noted when comparing outcome between DDLT and LDLT. This was the case for each country. The cumulative incidence of retransplantation after LDLT was highest in the UK and lowest in the US. Compared to the US, the risk-adjusted cause-specific hazard of retransplantation was not statistically significantly different for Canada but was higher in the UK.

The trends of LDLT use have been low and stable in each country, compared to many centers in the East, such as Taiwan, Japan, South Korea, India, and Turkey, where LDLT comprises the majority of grafts used for LT.[20–22] There are several explanations for the high LDLT utilization in the East, including cultural preferences and issues regarding care coordination and logistics of DDLT.[23–26] The low use of LDLT grafts in the West is explained by early series demonstrating higher biliary and vascular complications,[1,27] higher HCC recurrence rates,[28] higher inpatient costs and hospitalization rates, and inherent living donor risk in the context of a deceased donor option.[29] More recent studies have provided evidence that is more favorable for LDLT. A meta-analysis by Barbetta *et al.*, including studies between 2005-2017, found LDLT to be associated with a higher odds of biliary complications but not hepatic artery thrombosis.[30] Regarding patients with HCC, survival benefit has been demonstrated for patients undergoing LDLT from an intention-to-treat standpoint, primarily driven by lower dropout and shorter waitlist time, with similar recurrence rates post-LT despite more advanced tumors.[31–33] Regarding costs and hospitalization times, high-volume institutions such as University Health Network (Canada) and the University of Pittsburgh (US) have demonstrated that by being able to offer LT sooner, LDLT can achieve a more rapid postoperative recovery and shorter hospital length of stay, which are associated with lower hospital costs and improved resource utilization.[34,35] Though rare, the risk of donor mortality (1.7 per 1,000 donors) represents a significant impediment to more widespread adoption of LDLT, especially in the US, where such events have been highly publicized.[36]

To the best of our knowledge, this study represents the first and largest evaluation of LDLT outcomes between three large nations in the West. Based on a recent analysis of the Korean national liver transplant registry, a country where LDLT accounts for over 75% of all liver transplants, the survival rate for LDLT in 2019 was 90.4% at 1-year and 81.0% at 5-years.[21] This compares favorably to the survival noted in each country in our analysis (1-year US 92.6%, Canada 96.1%, UK 91.4%; 5-year US 82.8%, Canada 89.9%, UK 85.4%). Whether these differences are statistically and clinically different remains unclear, as donor and recipient selection criteria are likely different with the latter being potentially more aggressive in the East where LDLT remains the primary source of organs for transplantation.[6,20] Nonetheless, it offers an optimistic view that LDLT outcomes do not differ dramatically between low- and high-volume LDLT countries.

There was a trend towards increased use of LDLT in the US, with more recent data from UNOS demonstrating a continued increase in the numbers of LDLT performed.[37,38] There are 56 transplant centers in the US that have performed at least 1 LDLT in the last decade, while the majority of LDLTs are performed in a cluster of approximately 5 centers.[37,38] University of Pittsburgh represents the highest volume LDLT center in the US, with LDLT comprising 60% of their annual total adult LT volume.[35,39] The significant increase in their use of LDLT has been attributed to a change in practice, preferentially considering LDLT whenever possible, establishing a Champions program to help recipients identify donors, use of paired exchanged, ABO-incompatible

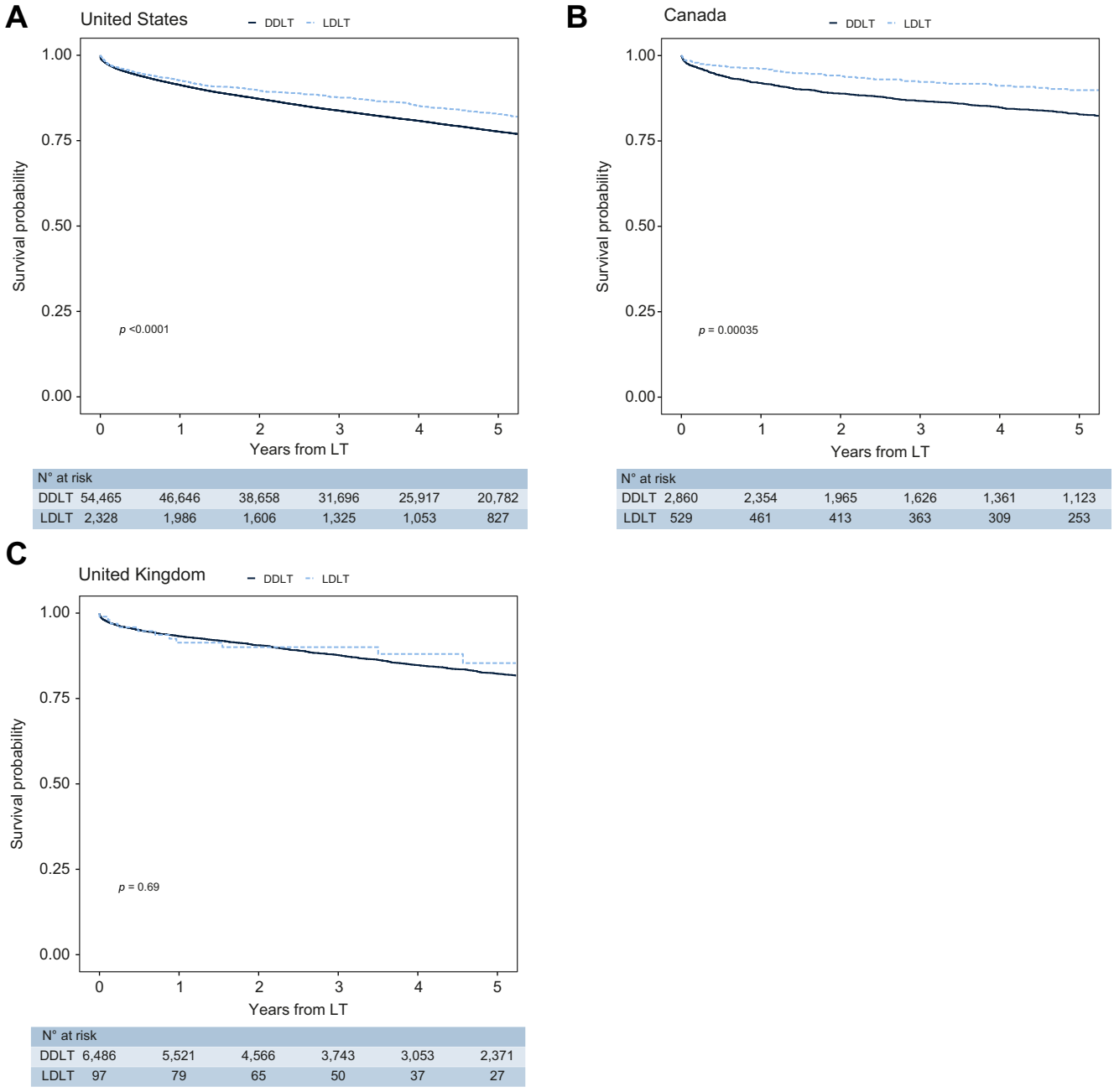

Fig. 4. Comparison of post-transplant survival between DDLT and LDLT. (A) Post-transplant survival after LT by graft type (US); (B) Post-transplant survival after LT by graft type (Canada); (C) Post-transplant survival after LT by graft type (UK) (Kaplan-Meier method and log-rank test). DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; LT, liver transplantation.

transplants, non-directed donors, and disregard for traditional MELD cut-offs for recipient selection.[40] Moreover, their donor acceptance rate is 70%, with very few donors being excluded solely based on GRWR being less than 0.8%.[40]

Canada had the highest proportion of LDLT of all the countries. The CORR dataset comprises six transplant centers in Canada (not including Quebec). Of these, the UHN (which includes Toronto General Hospital) is responsible for performing the most liver transplants, and the majority of the LDLTs in the country. Specifically, LDLT accounts for approximately 25–40% of all adult liver transplants in Toronto.[41,42] Further, the high proportion of LDLTs seen in Canada is primarily driven by this one institution, representing over three-quarters of the LDLTs. Drivers for the high use of LDLT in Toronto include a deceased donor organ shortage that is more pronounced than in the US, a high hepatobiliary surgical volume, surgical and center experience, and a high proportion of patients with HCC meeting traditional and expanded transplant oncology indications.[42,43]

In the UK, the use of LDLT has been stably low. It has been overshadowed by a high use (approximately 20% in the last couple of years) of DCD grafts which have been associated with more than acceptable outcomes, and a survival advantage

compared to waiting for a deceased after brain death donor graft.[44,45] Compared to the US, the incidence and risk of graft loss after LDLT was higher in the UK, which is in turn was similar to Canada. The underlying reason for this is not clear but may possibly be related to unmeasured confounding. The UK also had a higher rate of retransplantation than the US and Canada, which may reflect a more effective system of prioritization for retransplantation, but also the fact that volumes are low and this has been shown to impact outcomes, though future explorative analyses are needed to further understand this finding.[46] Notwithstanding this, it is critical to note that despite differences in graft survival and risk of retransplantation, the overall risk-adjusted mortality with LDLT is not different between the countries. While there are seven transplant centers in the UK, most LDLTs in the UK are performed in three centers (King's College Hospital in London, Queen Elizabeth Hospital in Birmingham, and St James's University Hospital in Leeds – coincidentally, these are also the only centers that perform pediatric liver transplantation in the UK). These centers maintain the recommended standard of patient survival of at least 50% at 5 years.[7,47,48] Moreover, the historical practice of LT has relied on DDLT which may be difficult to change. The recently implemented Transplant Benefit Score in 2018 is expected to increase the number of life-years gained from transplanted livers and reduce the number of waiting list deaths.[49] As a result, this may further reduce the incentive to expand LDLT practices. Moreover, the full impact of the recently adopted 'opt-out' policy, which came into effect in 2020, is not clear.[50] It may result in a higher availability of better quality deceased donors, further potentially reducing the pressure on the waitlist. Lastly, the increased use of normothermic machine perfusion, which can lead to reduced organ discard rates and therein result in a greater transplant rate and better outcomes, may impede future LDLT expansion.[51,52] Despite clear guidelines in place along with demonstrated excellent outcomes with LDLT, the exact reason for the low proportion of LDLTs performed in the UK is likely multifactorial and related to many of the reasons discussed above.[7]

Within each of the US and Canada, though LDLT was associated with a predominantly better unadjusted survival, the risk-adjusted mortality hazard was similar for LDLT and DDLT. In general, LDLT is utilized for recipients who may be less sick, and thus disadvantaged by the "sickest-first" allocation policy. This is likely reflected in the better unadjusted survival rates, with a group difference in hazard of death that diminishes after adjusting for potential confounders. Several previous reports comparing the two types of transplant have found either equivalent survival between the groups[41] or improved post-LT survival with LDLT.[30,35] Nonetheless, the survival advantage of LDLT primarily stems from receiving a transplant earlier and decreasing the chance of waitlist dropout.[32,53] In the US, waitlist mortality ranged between 18-20% between 2008 and 2019.[54–56] In Canada, waitlist mortality averaged 20% between 2010-2019.[12] In the UK, the 6-month, 1-year, and 2-year waitlist mortality rates were 7-8%, 9-10%, and 10-11%, respectively, for new elective liver only registrants between April 2013 and March 2017.[57–59] It is also possible that some heterogeneity in post-LT survival outcomes seen between LDLT and DDLT may be related to learning curves and center experience.[1,35,60] Consequently, it is conceivable that in addition to offering improved waitlist outcomes, post-LT outcomes have the potential to improve as experience grows. Though not the main aim of the study, LDLT was associated with similar post-LT mortality as DDLT in each of the countries after risk adjustment; it should be noted that this represents a relative hazard from the time of LT.

The benefit of LDLT is primarily the ability to undergo a transplant earlier, therein minimizing the chance for deterioration and potential waitlist dropout. Both patients with and without HCC derive a survival benefit with LDLT compared to waiting for a DDLT.[32,53,61] Consequently, a demonstrable survival benefit for LDLT and appropriate risk adjustment should occur when the decision of listing is made, thus requiring an intention-to-treat analysis. Unfortunately, an evaluation of waitlist outcomes for patients with a potential LDLT is currently not possible with the registry data used for this study and would require more granular data sources. As randomized controlled trials are unable to evaluate this, lower-level evidence, with accompanying potential for selection bias and unmeasured confounding, will need to suffice to form the basis for comparative evidence between LDLT and DDLT. Notwithstanding this, herein, we demonstrate that LDLT is at least associated with similar survival as DDLT when evaluating outcomes from the time of transplantation.

This study is limited by its retrospective non-randomized study design, with the potential for misclassification and selection bias. The registries do not contain outcomes for donors, though previous studies have demonstrated favorable outcomes, with increasing center volume being associated with lower rates of postoperative complications.[62] Moreover, certain variables such as GRWR are not recorded in any of the examined registries, which may represent a source of unmeasured confounding. In a recent systematic review by Patel *et al.*, an expert panel recommended that GRWR ≥0.8% is compatible with enhanced recovery of the recipient, but those <0.8% can be used in select LDLT recipients provided that optimal donor-recipient selection, surgical technique, and perioperative management can be ensured.[63] Specific thresholds depend on center experience, donor age, donor steatosis, degree of recipient hyperdynamic circulation, recipient illness severity, and the need for portal flow modulation – all factors that are often not collected as a part of national registry data. Similarly, while donor safety remains paramount, meta-analyses of single center series have reported a wide range of overall complications ranging from 20%-50%, wherein major complication rate (often defined as the proportion of severe (≥Clavien-Dindo III) constitute 1%-65%.[64] Though the number of missing variables is low in the NHSBT and UNOS, they are relatively high in CORR. Moreover, data validity in each database depends on data entry by certified clinical reviewers, non-quantifiable differences in measurement, and variable interpretation between countries. With regard to Canadian data, the Quebec organ transplant dataset is not included in the dataset from CORR. Though CORR collects data from transplant programs, organ procurement organizations, and independent health facilities, data reporting to CORR is voluntary, and compliance is not monitored or required. For analyses, despite covariate adjustments in the multivariable analyses, there remains the potential for residual confounding. Lastly, survival is evaluated from the time of transplant, as waitlist outcomes for patients receiving LDLTs were unavailable in the datasets, precluding the performance of an intention-to-treat analysis. Notwithstanding these limitations, this represents the largest multi-institutional international comparison of post-transplant survival after LDLT to date.

This study highlights that LDLT outcomes are excellent in the US, Canada, and the UK, despite differences in donor and recipient characteristics. This study offers support for further expansion of LDLT use in the West, which can provide several advantages as mentioned above, including the potential to alleviate the increasing demand for transplantation and the unacceptably high mortality on the waitlist.[12] Such expansion of LDLT practices should only be done while ensuring that short- and long-term outcomes are maintained for both donors and recipients. Moreover, there is no ideal proportion of LDLTs any center or country should achieve as this is contingent on several factors, including the quality and outcomes of other graft types (*e.g.*, DCD), the different liver disease etiologies on the waitlist (as some patients may be disadvantaged by the MELD-based allocation system), the overall number of available deceased donor grafts (including national policies surrounding organ donations like opt-out *vs.* opt-in), and region/center wait times as well as waitlist mortality. Nonetheless, with this data, in regions where mortality on the waiting list is high, an expanded use of LDLT should be pursued. Moreover, in regions where the waitlist dropout rate is low, LDLT may offer significant potential to expand evolving indications, such as within the transplant oncology realm.[65]

The barriers to increasing LDLT are thus unlikely to stem from an unwillingness to recognize its potential advantages but rather from obstacles related to culture and logistics. Donor morbidity is relatively common at roughly 24-30%, with no significant difference between right and left liver graft donors.[62,66] Though donor mortality is fortunately rare (0.2-0.4%), it is not zero.[35] An intolerance of non-zero mortality and a perception of inflated donor risks will continue to hinder the expansion of LDLT and thus require further education and a culture change in the transplant community.[39] Moreover, though safe expansion of LDLT requires clear guidelines to ensure that donor selection is optimal and post-LT outcomes are not compromised, they should not be viewed in a vacuum. Instead, it should be recognized that with increased center experience, acceptable outcomes can be achieved even with more marginal donors (older, higher BMI, lower GRWR) and sicker recipients (acute liver failure and high MELD).[35,67–70] As mentioned previously, an increase in LDLT volume can also be achieved through paired exchanges, ABO-incompatible donors, non-directed donors, and the establishment of Champion programs which can alleviate the burden on recipients of identifying a potential donor.[40] Creating an effective and sustainable LDLT framework within the LT workflow is necessary as successful implementation necessitates active involvement from a multidisciplinary team. Therefore, it is more feasible that LDLT expansion takes place within high-volume LT centers that also have significant expertise in liver resections.

LDLT use has remained stably low in the US, Canada, and the UK. Despite this, long-term survival post-LDLT is excellent in each of the examined nations. Moreover, LDLT is associated with a similar risk of post-LT mortality as DDLT in the US, Canada, and the UK. Continued efforts to increase LDLT in these countries are thus warranted due to the growing waitlist and differences in allocation that may disadvantage patients currently awaiting LT.

Abbreviations

aHR, adjusted hazard ratio; CIT, cold ischemia time; CORR, Canadian Organ Replacement Registry; DCD, deceased after circulatory death; DDLT, deceased donor liver transplantation; GRWR, graft-recipient weight ratio; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; LDLT, living donor liver transplantation; LDLTs, living donor liver transplants; MELD, model for end-stage liver disease; STAR, Standard Transplant and Research; UHN, University Health Network; UNOS, United Network for Organ Sharing.

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Conflict of interest

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

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

TI: Conception of project, literature review, interpretation of results, write up of the manuscript. DW: Conception of project, literature review, interpretation of results, write up of the manuscript. MPAWC: Interpretation of results, write up of the manuscript. MSP: Interpretation of results, write up of the manuscript. RB: Interpretation of results, write up of the manuscript. CS: Interpretation of results, write up of the manuscript. AP: Interpretation of results, write up of the manuscript, manuscript review. PS: Interpretation of results, write up of the manuscript, manuscript review. WJ: Interpretation of results, write up of the manuscript, manuscript review. NH: Interpretation of results, write up of the manuscript, manuscript review. GM: Interpretation of results, write up of the manuscript. NM: Interpretation of results, write up of the manuscript. AM: Interpretation of results, write up of the manuscript. JvdM: Interpretation of results, write up of the manuscript. DS: Interpretation of results, write up of the manuscript. GS: Literature review, interpretation of results and write up of the manuscript. All authors have given final approval for this manuscript to be submitted to *Journal of Hepatology.*

Data availability statement

The data that support the findings of this study are available from Organ Procurement and Transplantation Network (OPTN), the UK Liver Transplant Registry, and the Canadian Organ Replacement Registry. Restrictions apply to the availability of these data, which were used under license for this study. Data are available OPTN at https://optn.transplant.hrsa.gov/data/request-data/ with the permission of OPTN and United Network of Organ Sharing (UNOS), at https://www.odt.nhs.uk/statistics-and-reports/access-data/ with the permission of the NHBST Blood and Transplant, and at https://www.cihi.ca/en/access-data-and-reports/data-holdings/make-a-data-request. Any statistical analytical files are available upon request.

Disclaimer

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Supplementary data

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Author names in bold designate shared co-first authorship

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