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ORIGINAL ARTICLE

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Meta-analysis and meta-regression of outcomes for adult living donor liver transplantation versus deceased donor liver transplantation

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Prior single center or registry studies have shown that living donor liver transplantation (LDLT) decreases waitlist mortality and offers superior patient survival over deceased donor liver transplantation (DDLT). The aim of this study was to compare outcomes for adult LDLT and DDLT via systematic review. A meta-analysis was conducted to examine patient survival and graft survival, MELD, waiting time, technical complications, and postoperative infections. Out of 8600 abstracts, 19 international studies comparing adult LDLT and DDLT published between 1/2005 and 12/2017 were included. U.S. outcomes were analyzed using registry data. Overall, 4571 LDLT and 66,826 DDLT patients were examined. LDLT was associated with lower mortality at 1, 3, and 5 years posttransplant (5-year HR 0.87 [95% CI 0.81–0.93], $p < .0001$), similar graft survival, lower MELD at transplant ($p < .04$), shorter waiting time ($p < .0001$), and lower risk of rejection ($p = .02$), with a higher risk of biliary complications (OR 2.14, $p < .0001$). No differences were observed in rates of hepatic artery thrombosis. In meta-regression analysis, MELD difference was significantly associated with posttransplant survival (R^2 0.56, $p = .02$). In conclusion, LDLT is associated with improved patient survival, less waiting time, and lower MELD at LT, despite posing a higher risk of biliary complications that did not affect survival posttransplant.

KEYWORDS
clinical research / practice, liver transplantation / hepatology, liver transplantation: living donor, meta-analysis

1 | INTRODUCTION

With an ongoing shortage of deceased donor organs, living donor liver transplantation (LDLT) has emerged as an option to reduce waitlist mortality and address the growing disparity between organ supply and demand. As programs have gained experience, LDLT has been shown to result in equivalent, and in some cases, superior recipient survival and long-term outcomes compared to deceased donor liver transplantation (DDLT), even following risk-adjustment.[1,2] LDLT also conveys the benefits of decreased mortality on the waitlist, reduced waiting time, and potential for transplantation at a lower Model for End-Stage Liver Disease (MELD) score.[1,3]

Despite the potential for good outcomes, LDLT has constituted less than 5% of all liver transplants performed in the U.S. and <30%

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Study; CI, confidence interval; DDLT, deceased donor liver transplantation; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HR, hazard ratio; LDLT, living donor liver transplantation; MD, mean difference; MELD, Model for End-Stage Liver Disease; OR, odds ratio; SRTR, Scientific Registry of Transplant Recipients.

of all liver transplants in the Americas and Europe.[4,5] Concerns regarding donation-related complications and outcomes following living liver donation may have slowed the expansion of LDLT in the Western hemisphere. Long-term follow-up of the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) cohort involving 740 donors showed that 40% experienced one or more complication, primarily Clavien-Dindo Grade 1 and 2, 95% of which resolved within the first-year postdonation.[6] In a recent Scientific Registry for Transplant Recipients (SRTR) analysis, among 105 non–directed living liver donors, only 15% experienced a postoperative complication or needed hospital readmission after donation, further demonstrating that the risk for living donors is generally low.[7]

In the early era of LDLT, technical complications including biliary stricture or leak, hepatic artery thrombosis (HAT), and small-for-size syndrome impacted posttransplant outcomes.[8-11] More recently, these early post-LDLT complications, while recognized to be higher than DDLT, have largely been mitigated by center experience and patient selection.[12-15] Generally, studies examining LDLT outcomes and complications, even in the contemporary era, have been limited to single center and/or national registry studies and have recognized limitations including differences in center experience, transplant recipient demographics, and duration of follow-up.[2,12,16]

Even in the contemporary era, the experience and outcomes of LDLT continue to be differentiated between lower volume, Western hemisphere countries and high-volume programs from the Middle East and Asia who rely on LDLT to overcome cultural and religious barriers to DDLT.[2,12,16,17] Previous meta-analyses have compared outcomes of LDLT and DDLT as it relates to biliary complications or hepatocellular carcinoma (HCC), focusing on patient survival and risk of disease recurrence.[18-22]

To date, a collective, global analysis of outcomes comparing LDLT and DDLT has not been completed. The aim of this study was to compare outcomes of LDLT to DDLT by performing a systematic review, meta-analysis, and meta-regression of patient survival, graft survival, and pretransplant and posttransplant outcomes.

2 | EXPERIMENTAL METHODS

2.1 | Literature search and study selection

This systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and as outlines in a predefined protocol (PROSPERO 2018: CRD42018104794).[23] A health sciences librarian developed the search strategy and searched the following databases on March 28, 2018: PubMed (coverage 1946-present), Embase and Embase Classic (coverage 1947-present), Cochrane Library (coverage 1898–present), Web of Science (coverage 1900-present), Clinicaltrials.gov, and Google Scholar. No filters were applied for date, study type, language, or any other limit. A combination of subject headings (when available) and keywords were used for the concepts living donor, deceased donor, and liver transplantation. See Table S1 for full search strategies and database details. Duplicated citations were removed in EndNote x9.2 using the Bramer method.[24] Cross-referencing and forward searches of articles fulfilling inclusion criteria were performed using Web of Science.

2.2 | Study selection

Screening was independently performed by two authors. Any conflict regarding study inclusion was resolved by the senior author. Studies were included if they were published between January 2005 and December 2017, available in full text, compared LDLT and DDLT cohorts, studied transplant recipients ≥18 years of age, and reported on the primary outcome of overall patient survival at ≥1-year posttransplant. A study was excluded if it was limited to <10 patients, did not include DDLT as a reference group, did not differentiate pediatric recipients from adults, did not report patient demographical information or pretransplant characteristics, or did not describe its methods of statistical analysis. Studies including multi-organ transplants, re-transplants, and those reporting only acute liver failure were also excluded.

At the outset, we anticipated that we would include A2ALL data. The most recent comprehensive analyses of A2ALL recipient outcomes include data from ~1000 LDLT and ~500 DDLT recipients from 11 U.S. centers and Toronto, performed between 1998 and 2010.[25,26] While both studies reported primary outcomes of graft and patient survival, neither included the majority of the secondary outcomes formatted for meta-analysis. Based on the *Cochrane Handbook for Systemic Review of Interventions*, we ultimately excluded the A2ALL papers and other U.S. single center papers and instead performed a larger, more contemporary SRTR analysis to represent U.S. outcomes, with 2750 LDLT and 58,120 DDLT performed between 2005 and 2017.[27] Two studies from the Toronto collectively describing 193 LDLT and 273 DDLT patients transplanted between 2001 and 2014 were also included, which reported both primary outcome measures and data related to all secondary outcomes.[28,29] Using this approach, we have captured all of the A2ALL centers in this meta-analysis.

2.3 | SRTR

A primary, up-to-date analysis of the U.S. SRTR registry data was completed to supplement what is presented in the annual data report, with the intent of including primary and secondary outcomes of interest.[5] For details on the SRTR data and analysis, please refer to Data S1. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

2.4 | Data extraction and outcome measures

Data extraction from eligible studies was independently conducted by two authors. For all studies, data regarding study design and characteristics (year of publication, first author, country), population characteristics (sample size for each patient cohort, recipients and donor demographics, MELD at transplant), and liver disease diagnosis were recorded when available. The primary study outcome was 1-, 3-, and 5-year patient survival. Secondary outcomes included 1-, 3-, and 5-year graft survival; preoperative variables (MELD score and time on waiting list); and postoperative variables (biliary complications, HAT, infection, rejection, and length of stay).

2.5 | Assessment of risk bias

The assessment for risk of bias was independently carried out by two authors. The NIH Quality Assessment Tool for Case-Control Studies was adopted to evaluate the quality of each included study. Based on the overall score, each study was classified as good (scored 9 or higher), fair (scored between 5 and 8), or poor (lower than 5) (Table S4).

2.6 | Statistical analysis

For the meta-analysis, percentage and total numbers were used to report categorical variables and mean with standard deviation (SD) for continuous variables. When included studies reported median and interquartile range, mean and SD were estimated according to established methods.[30] For pooled analyses, all variables reported in ≥5 studies were analyzed. Continuous variables were analyzed by mean difference (MD), whereas categorical variables were analyzed by odds ratio (OR), both with 95% confidence intervals (CI). Random effects model was adopted to balance intrinsic heterogeneity and effect size.[31] Heterogeneity was also assessed with chi-square statistic and I^2 statistic with $I^{2,}$>= 50% representing significant heterogeneity. The hazard ratio (HR) for time-to-event outcomes was estimated indirectly from other summary statistics or from data in published Kaplan-Meier curves.[32] The derived observed minus expected number of cases (O-E) and the variance for the single studies were then used to calculate individual and overall HR with the fixed-effect model to give a pooled HR for survival analyses.[33] Forest plots were created to display results. All data analyses were conducted using RevMan 5.3 according to published guidelines.[27] A random effects meta-regression analysis was conducted to better understand potential sources of heterogeneity of the primary outcome, specifically 1-year overall patient survival. The selection of covariates to include as moderator in the meta-regression model was based on their clinically likelihood to modify the outcome of interest and possible statistically significant different distributions between LDLT and DDLT patients that resulted from the meta-analysis. Meta-regression analysis was conducted using Metafor-package for R studio (version 3.6.3).

3 | RESULTS

3.1 | Systematic review

The literature review is summarized in a PRISMA diagram (Figure 1). After removal of duplications, 5364 abstracts were screened and 374 were selected for full-text review. A total of 19 studies from countries including Canada, China, France, Germany, South Korea, Italy, and Saudi Arabia were included in this meta-analysis (summarized in Table 1). Seventeen studies were from single centers and two included multi-center data. All studies but one were retrospective, while three had a matched-pair design and one was prospective. No randomized controlled studies were identified. The quality risk assessment for these studies determined that all met criteria for fair or good quality, and none showed poor design (Table S4).

3.2 | Meta-analysis

A total of 1821 LDLT and 8706 DDLT recipients were pooled from the published studies for inclusion in the meta-analysis; study and patient population characteristics are summarized in Table 1. When U.S. SRTR data were added, 4571 LDLT and 66,826 DDLT recipients were analyzed. For the entire study population, the mean age was 54.0 ± 9.9 years (51.2 ± 11.4 for LDLT vs 54.2 ± 9.7 for DDLT, $p < .001$) and 29.6% were female (33.8% of LDLT vs 28.9% of DDLT, $p < .001$). The most common etiology of liver disease was hepatocellular liver disease (autoimmune hepatitis, NASH or alcoholic liver disease; collectively 34.6%), followed by HCC (29.2%), viral hepatitis (26.3%), and cholestatic liver disease (7.7%).

Examination of our first primary outcome, patient survival, revealed superior overall patient survival for LDLT recipients when compared to the DDLT recipients ($p < .0001$, Figure 2). Specifically, LDLT recipients had a 17% reduction (95% CI 10–24) in the risk of mortality at 1-year posttransplant when compared to the DDLT group (HR 0.83 [95% CI 0.76–0.90]; $p < .0001$, Figure 2A). The survival benefit for LDLT recipients was also observed at both 3- and 5-years posttransplant (3 year: HR 0.85 [95% CI 0.79–0.92] and 5 year: HR 0.87 [95% CI 0.81–0.93], $p < .0001$ at both intervals, Figure 2B,C). Graft survival was studied as a secondary outcome. At all time points, graft survival was comparable between LDLT and DDLT recipients (1 year: HR 0.94 [95% CI 0.84–1.02], $p = .14$, 3 year: HR 0.96 [95% CI 0.89–1.03] $p = .25$, and 5 year: HR 0.95 [95% CI 0.88–1.01], $p = .12$) (Figure 3).

Next, secondary outcomes were analyzed among sub-cohorts of studies that included the specified variables. Two preoperative outcomes were studied: MELD score at transplant and waiting time (days). As shown in Figure 4A, MELD score at transplant was lower for LDLT recipients when compared to DDLT recipients (MD

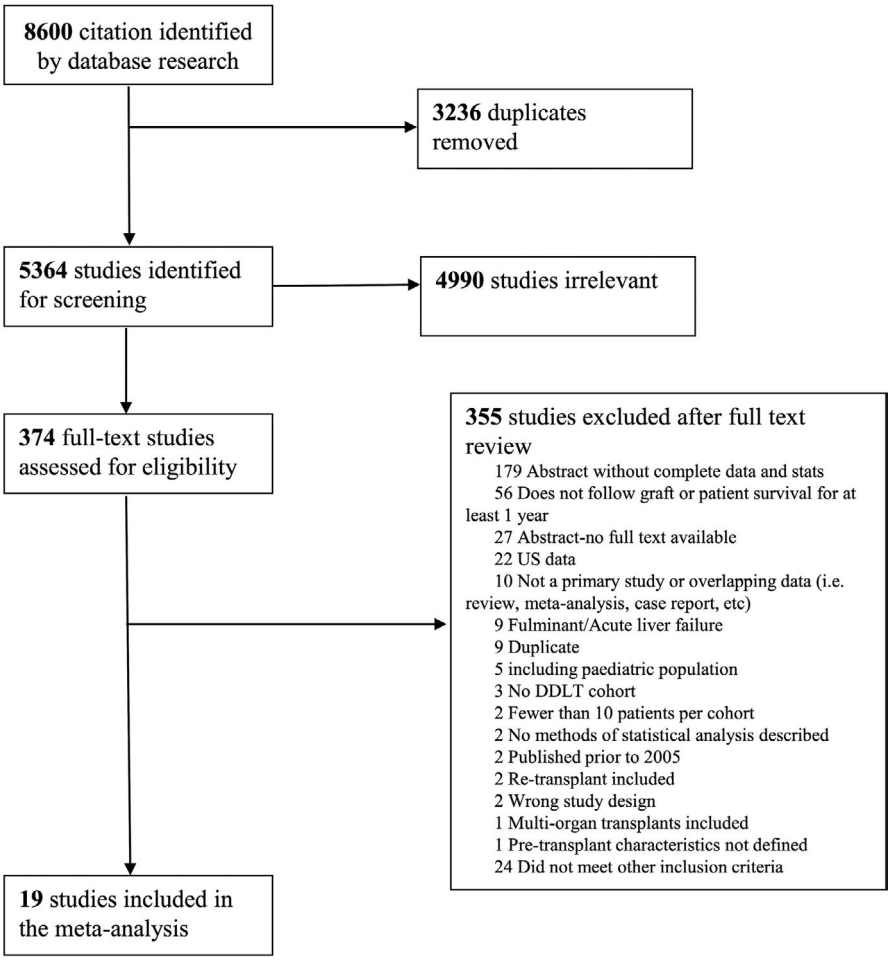


FIGURE 1 PRISMA diagram of systematic review

−2.54 [95% CI −5.02, −0.06] $p = .04$). LDLT recipients had a shorter waiting time when compared to DDLT recipients (MD −71.43 [95% CI −101.42, −41.44], $p < .0001$, Figure 4B). Post–operative technical complications including HAT and biliary complications were analyzed. While there was no difference between the two groups in the risk of HAT (OR 2.07 [95% CI 0.84–5.09], $p = 0.11$, Figure 5A), LDLT recipients experienced an approximately two-fold increase in the risk of biliary complications (OR 2.14 [95% CI 1.76–2.59], $p < .001$, Figure 5B). Pooled analysis for the risk of postoperative infection and length of hospital stay showed no difference between LDLT and DDLT recipients (OR 0.67 [95% CI 0.42–1.09], $p = .11$ [Figure 5C] and MD −3.80 [95% CI −8.36, 0.76], $p = .10$ [Figure 5D], respectively). Finally, LDLT recipients showed a lower risk of rejection when compared to DDLT recipients (OR 0.72 [95% CI 0.55–0.95], $p = .02$, Figure 5E).

3.3 | Meta-regression analysis

A meta-regression analysis was completed to explore potential relationships between MELD at transplant, time on waitlist and biliary complications and 1-year patient survival (Table 2). MELD score and time on waitlist were expressed as weighted mean differences between LDLT and DDLT means, whereas biliary complications were expressed as difference of rate of occurrence in the LDLT versus DDLT. MELD score at LT was the sole variable that demonstrated a relationship with 1-year patient survival (Figure 6). These data indicate that as MELD score difference increased, survival at 1-year post-LT decreased. Time on waitlist and biliary complications had no impact on 1-year patient survival. The inclusion of MELD score as a moderator in the meta-regression of 1-year patient survival explained most of the observed heterogeneity in the relative risk of death (R^2 0.56, $p = .02$, Figure 6).

4 | DISCUSSION

This meta-analysis identified and analyzed a global population of 4571 LDLT and 66,826 DDLT recipients across a broad range of liver disease diagnoses, programs, and countries. The results confirm that LDLT recipients experience superior patient survival at 1-, 3-, and 5-years posttransplant when compared to DDLT recipients. LDLT resulted in equivalent graft survival when compared to DDLT at all time points. Preoperative MELD and waiting time favored

TABLE 1 Characteristics of included studies and patient populations stratified by donor type

Studies: Author, year, country	Study design	Arms	Sample size	Age, years (mean ± SD)	Sex, no. female (%)	MELD at transplant (mean ± SD)	Diagnosis				
							HCC	NASH	HCV/ -HBV	ALD	PSC/-PBC/ -AIH
Barbas, 2017, Canada[28]	Retrospective study	LDLT	48	54.7 ± 9.4	13 (27)	17.8 ± 8.7	8	48	—	—	—
		DDLT	128	56.7 ± 9.3	41 (32)	21.8 ± 10.3	42	128	—	—	—
Reichman, 2013, Canada[29]	Matched cohort study	LDLT	145	54.2 ± 7.5	28 (19.3)	14.4 ± 3.8	55	4	99	26	16
		DDLT	145	53.9 ± 7.7	28 (19.3)	14 ± 6.8	80	4	99	26	16
Chen, 2015, China[63]	Retrospective study	LDLT	66	45.8 ± 7.7	6 (9.1)	11.1 ± 4.5	66				
		DDLT	163	47.9 ± 9.5	19 (11.7)	12 ± 6.4	163				
Lei, 2013, China[64]	Retrospective study	LDLT	31	44.4 ± 9.7	13 (41.9)	9.3 ± 6.1	31		28		
		DDLT	52	44 ± 8.2	21 (40.4)	9.1 ± 5.8	52		45		
Li, 2011, China[34]	Retrospective study	LDLT	128	43 ± 8.6	20 (15.6)	19.5 ± 10.7			116	2	1
		DDLT	221	44.5 ± 9.7	42 (19)	18.2 ± 9.6			209	5	5
Chok, 2017, China[65] *	Retrospective study	LDLT	54	51 ± 12	12 (22.2)	40 ± 1.3	1		43		1
		DDLT	40	51 ± 10.8	6 (15)	39 ± 1.3	3		36		
Liu, 2006, China[43] *	Prospective study	LDLT	124	47.5 ± 8.3	27 (21.8)	21 ± 6.5	36		111	1	3
		DDLT	56	48 ± 9.8	12 (21.4)	19 ± 10.8	11		49	0	1
Wan, 2014, China[37]	Matched cohort study	LDLT	40	48.6 ± 9.7	6 (15)		40		39		
		DDLT	80	49.5 ± 8.9	12 (15)		80		77	1	1
Chen, 2014, China[66]	Matched cohort study	LDLT	47		3 (6.4)		47				
		DDLT	94		6 (6.4)		94				
Hu et al, 2015, China[38]	Multi-center Retrospective study	LDLT	389	48.1 ± 8.7	29 (7.5)		389				
		DDLT	6471	50.1 ± 9.4	652 (10.1)		6471				
Bhangui, 2011, France[36]	Retrospective study	LDLT	36	54 ± 7	4 (11.1)	13.5 ± 5.9	36		28	6	
		DDLT	120	56 ± 8	20 (14.7)	14.5 ± 5.9	120		88	26	
Schmeding, 2007, Germany[67]	Retrospective study	LDLT	20	55.7 ± 8.9	7 (35)		11		20		
		DDLT	269	51.4 ± 9.8	105 (39)		73		269		
Kim, 2014, Korea[68]	Retrospective study	LDLT	21	53.1 ± 10.3	7 (33.3)	13.1 ± 5.4	17		18	3	0
		DDLT	29	51.3 ± 9.2	14 (48.3)	24.9 ± 11.6	11		14	6	3
E. Kim, 2017, Korea[69]	Retrospective study	LDLT	109	52 ± 8.5	28 (26.6)	12.5 ± 8.3	68		93	19	1
		DDLT	76	53.2 ± 11	26 (34.2)	24.9 ± 11.7	16		40	21	4
J.M. Kim, 2017, Korea[70] *	Multi-center retrospective study	LDLT	146	57 ± 6.3	42 (28.8)	15 ± 5.7	73		146		
		DDLT	35	53 ± 8.8	11 (31.4)	21 ± 10.5	11		35		

(Continues)

TABLE 1 (Continued)

Studies: Author, year, country	Study design	Arms	Sample size	Age, years (mean ± SD)	Sex, no. female (%)	MELD at transplant (mean ± SD)	Diagnosis				
							HCC	NASH	HCV/ -HBV	ALD	PSC/-PBC/ -AIH
Lee, 2012, Korea[41]	Retrospective study	LDLT	48	50 ± 7.8	8 (16.7)	24.5 ± 4.4	12		42	4	
		DDLT	23	48 ± 12.9	10 (43.5)	23 ± 3	6		16	2	
Vigano', 2008, Italy[71]	Retrospective study	LDLT	77				24		57		
		DDLT	244				75		143		
Al Sebayel, 2015, Saudi Arabia[72] *	Retrospective Study	LDLT	222	53 ± 10.8	83 (37.4)	18	45		120		24
		DDLT	269	52 ± 10.2	116 (52.3)	16	48		139		32
Jiang, 2013, China[73] *	Retrospective study	LDLT	70	40.3 ± 8.2	8 (11.4)	23.9 ± 11.1			70		
		DDLT	191	44.1 ± 9.3	29 (15.2)	21.7 ± 9.9			191		
SRTR, 2017, USA	Retrospective study	LDLT	2750	51.9 ± 12.3	1200 (43.6)	15 ± 5.3	340		611		
		DDLT	58120	54.8 ± 9.6	18120 (31.2)	21 ± 9.9	12163		15673		

*Denotes median to mean conversion or calculated SD.

LDLT recipients, and lower MELD at transplant was strongly associated with posttransplant survival on meta-regression. Moreover, despite a higher rate of biliary complications, LDLT recipients had a similar rate of HAT, risk of postoperative infection, and overall length of hospital stay and less rejection when compared to DDLT. Collectively, these data suggest that LDLT can offer several advantages when compared to DDLT.

The primary outcome of this meta-analysis, overall patient survival, identified a reduced risk of mortality of 17%, 15%, and 13% at 1, 3, and 5 years posttransplant respectively for LDLT recipients (Figure 2). Prior single center or consortium studies have also suggested that LDLT confers an overall survival advantage.[34-38] This finding is likely multifactorial, as shown by analysis of secondary outcomes, specifically preoperative variables indicating that LDLT recipients experience a shorter waiting time and are transplanted at a lower MELD (Figure 4). Indeed, meta-regression examining the correlation between MELD at transplant and patient survival confirmed a strong relationship exists (Figure 6). Other factors that likely contribute to superior outcomes for LDLT were not studied in this analysis. Generally, LDLT is an elective surgery and thus programs have the opportunity to screen and choose an ideal donor, schedule the procedure for the daytime with a highly specialized team, plan for anatomic variants, and optimize a recipient for surgery. Furthermore, a living donor allograft is not exposed to brain death, which may negatively affect both graft and patient survival.[39,40]

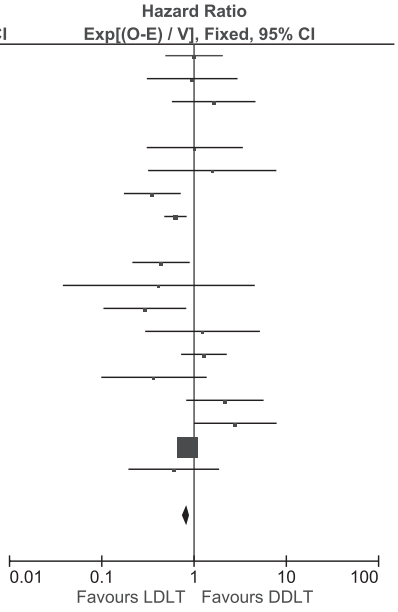
Analysis of the first secondary outcome, overall graft survival, demonstrated that graft survival is comparable between LDLT and DDLT for all time points (Figure 3). This is an important finding, as it suggests that the risk for early graft loss for DDLT and LDLT are equivalent. That being said, the risk profile for each type of donor is different. LDLT is a highly technical procedure, and as a consequence, poses a greater risk for procedure-related complications including vascular complications, biliary stricture or leak, early allograft dysfunction, or ultimately early graft loss requiring re-transplant. In countries with a predominant LDLT experience and thus lower rate overall rate of technical complications, such as Japan or Korea, national registry data have shown that 1-year graft survival modestly favors DDLT over LDLT.[12,16] Prior studies have reported variable outcomes for graft survival, ranging from equivalence between LDLT and DDLT, to improved graft survival for LDLT when compared to DDLT.[13,29,38,41-43]

Our analysis established that LDLT recipients had a lower MELD at transplant when compared to DDLT recipients, and this was associated with improved survival rates on meta-regression. This is consistent with the North American A2ALL cohort, which reported a lower MELD at transplant for LDLT recipients, with only 16% of LDLT recipients with MELD >20 at the time of transplant compared to 43% of DDLT recipients.[2] While LDLT candidates benefit from being transplanted at a lower MELD, studies have reported acceptable outcomes following LDLT even for higher MELD patients. A prior study comparing LDLT and DDLT with MELD >30 showed an improved overall patient survival for LDLT, even for patients with hepatorenal syndrome.[41] Similarly, single center studies from Taiwan

(A) 1 Year Patient Survival

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Al Sebayel, 2015	14	222	16	269	0	7.46	1.4%	1.00 [0.49, 2.05]
Barbas, 2017	4	48	12	128	-0.139	3	0.6%	0.95 [0.31, 2.96]
Bhangui, 2011	5	36	12	120	1.73	3.53	0.7%	1.63 [0.58, 4.63]
Chen, 2014	0	0	0	0	0	0		Not estimable
Chen, 2015	4	34	8	72	0.049	2.67	0.5%	1.02 [0.31, 3.38]
Chok, 2017	6	54	2	40	0.68	1.5	0.3%	1.57 [0.32, 7.80]
E. Kim, 2017	12	109	21	76	-7.96	7.64	1.4%	0.35 [0.17, 0.72]
Hu, 2016	51	389	1670	6470	-23	49.49	9.2%	0.63 [0.48, 0.83]
Jiang, 2013	0	0	0	0	0	0		Not estimable
Kim JM, 2017	20	146	12	35	-6.18	7.5	1.4%	0.44 [0.21, 0.90]
Kim, 2014	1	21	2	29	-0.589	0.67	0.1%	0.42 [0.04, 4.55]
Lee, 2012	6	48	9	23	-4.42	3.6	0.7%	0.29 [0.10, 0.82]
Lei, 2013	3	31	5	52	0.397	1.875	0.3%	1.24 [0.30, 5.17]
Li, 2011	20	128	29	221	2.92	11.84	2.2%	1.28 [0.72, 2.26]
Liu, 2006	4	124	5	56	-2.22	2.22	0.4%	0.37 [0.10, 1.37]
Reichman, 2013	10	145	7	145	3.17	4.12	0.8%	2.16 [0.82, 5.67]
Schmeding, 2007	4	17	38	269	3.73	3.62	0.7%	2.80 [1.00, 7.85]
SRTR 2005-2017	440	2750	13368	58120	-67.49	426	78.9%	0.85 [0.78, 0.94]
Wan, 2014	4	40	12	80	-1.52	3	0.6%	0.60 [0.19, 1.87]
Total (95% CI)		**4342**		**66205**			**100.0%**	**0.83 [0.76, 0.90]**
Total events	608		15228					

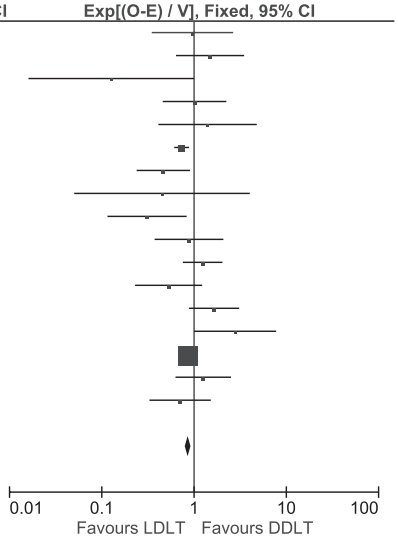
Heterogeneity: Chi² = 33.11, df = 16 (P = 0.007); I² = 52%
Test for overall effect: Z = 4.34 (P < 0.0001)



(B) 3 Year Patient Survival

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Barbas, 2017	4	48	18	128	-0.15	3.72	0.5%	0.96 [0.35, 2.65]
Bhangui, 2011	7	36	22	120	2.12	5.31	0.8%	1.49 [0.64, 3.49]
Chen, 2014	1	26	9	52	-1.86	0.9	0.1%	0.13 [0.02, 1.00]
Chen, 2015	9	34	19	72	0.07	6.1	0.9%	1.01 [0.46, 2.24]
Chok, 2017	7	54	4	40	0.86	2.55	0.4%	1.40 [0.41, 4.78]
Hu, 2016	116	389	2963	6471	-34.55	111.62	15.9%	0.73 [0.61, 0.88]
Kim JM, 2017	26	146	13	35	-6.65	8.67	1.2%	0.46 [0.24, 0.90]
Kim, 2014	1	21	4	29	-0.64	0.8	0.1%	0.45 [0.05, 4.02]
Lee, 2012	7	48	9	23	-4.62	3.94	0.6%	0.31 [0.12, 0.83]
Lei, 2013	8	31	15	52	-0.66	5.22	0.7%	0.88 [0.37, 2.08]
Li, 2011	27	128	38	221	3.38	15.78	2.2%	1.24 [0.76, 2.03]
Liu, 2006	14	124	9	56	-3.48	5.48	0.8%	0.53 [0.23, 1.22]
Reichman, 2013	25	145	16	145	4.87	9.76	1.4%	1.65 [0.88, 3.08]
Schmeding, 2007	5	17	54	269	3.75	3.66	0.5%	2.79 [1.00, 7.76]
SRTR 2005-2017	523	2750	13368	58120	-73.36	503.3	71.8%	0.86 [0.79, 0.94]
Vigano, 2008	12	77	24	244	1.84	8	1.1%	1.26 [0.63, 2.52]
Wan, 2014	9	40	24	80	-2.28	6.55	0.9%	0.71 [0.33, 1.52]
Total (95% CI)		**4114**		**66157**			**100.0%**	**0.85 [0.79, 0.92]**
Total events	801		16609					

Heterogeneity: Chi² = 30.23, df = 16 (P = 0.02); I² = 47%
Test for overall effect: Z = 4.20 (P < 0.0001)



(C) 5 Year Patient Survival

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Barbas, 2017	6	48	24	128	-0.175	4.8	0.6%	0.96 [0.39, 2.36]
Bhangui, 2011	10	36	22	120	2.41	6.875	0.8%	1.42 [0.67, 3.00]
Chen, 2014	3	26	10	52	-2.97	2.3	0.3%	0.27 [0.08, 1.00]
Chen, 2015	11	34	22	72	0.08	7.33	0.9%	1.01 [0.49, 2.09]
Chok, 2017	8	54	7	40	-1.08	3.73	0.4%	0.75 [0.27, 2.07]
Hu, 2016	131	389	3432	6471	-36.73	126.18	15.0%	0.75 [0.63, 0.89]
Kim JM, 2017	30	146	13	35	-6.81	9.07	1.1%	0.47 [0.25, 0.90]
Lee, 2012	9	48	9	23	-4.94	4.5	0.5%	0.33 [0.13, 0.84]
Lei, 2013	9	31	17	52	-0.703	5.88	0.7%	0.89 [0.40, 1.99]
Li, 2011	35	128	42	221	3.67	19.09	2.3%	1.21 [0.77, 1.90]
Reichman, 2013	33	145	22	145	5.67	13.2	1.6%	1.54 [0.90, 2.64]
Schmeding, 2007	6	17	67	269	4.6	5.51	0.7%	2.30 [1.00, 5.31]
SRTR 2005-2017	605	2750	16274	58120	-81.86	626.7	74.4%	0.88 [0.81, 0.95]
Wan, 2014	10	40	27	80	-2.4	7.29	0.9%	0.72 [0.35, 1.49]
Total (95% CI)		**3892**		**65828**			**100.0%**	**0.87 [0.81, 0.93]**
Total events	906		19988					

Heterogeneity: Chi² = 27.33, df = 13 (P = 0.01); I² = 52%
Test for overall effect: Z = 4.18 (P < 0.0001)

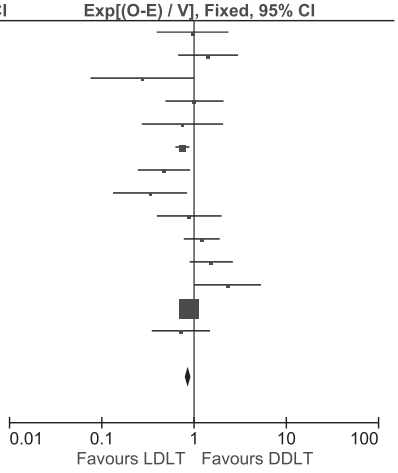


FIGURE 2 Forest plot of hazard ratios for overall patient survival at 1 year (A), 3 years (B), and 5 years (C) posttransplant. LDLT favored patient survival when compared to DDLT at all time points

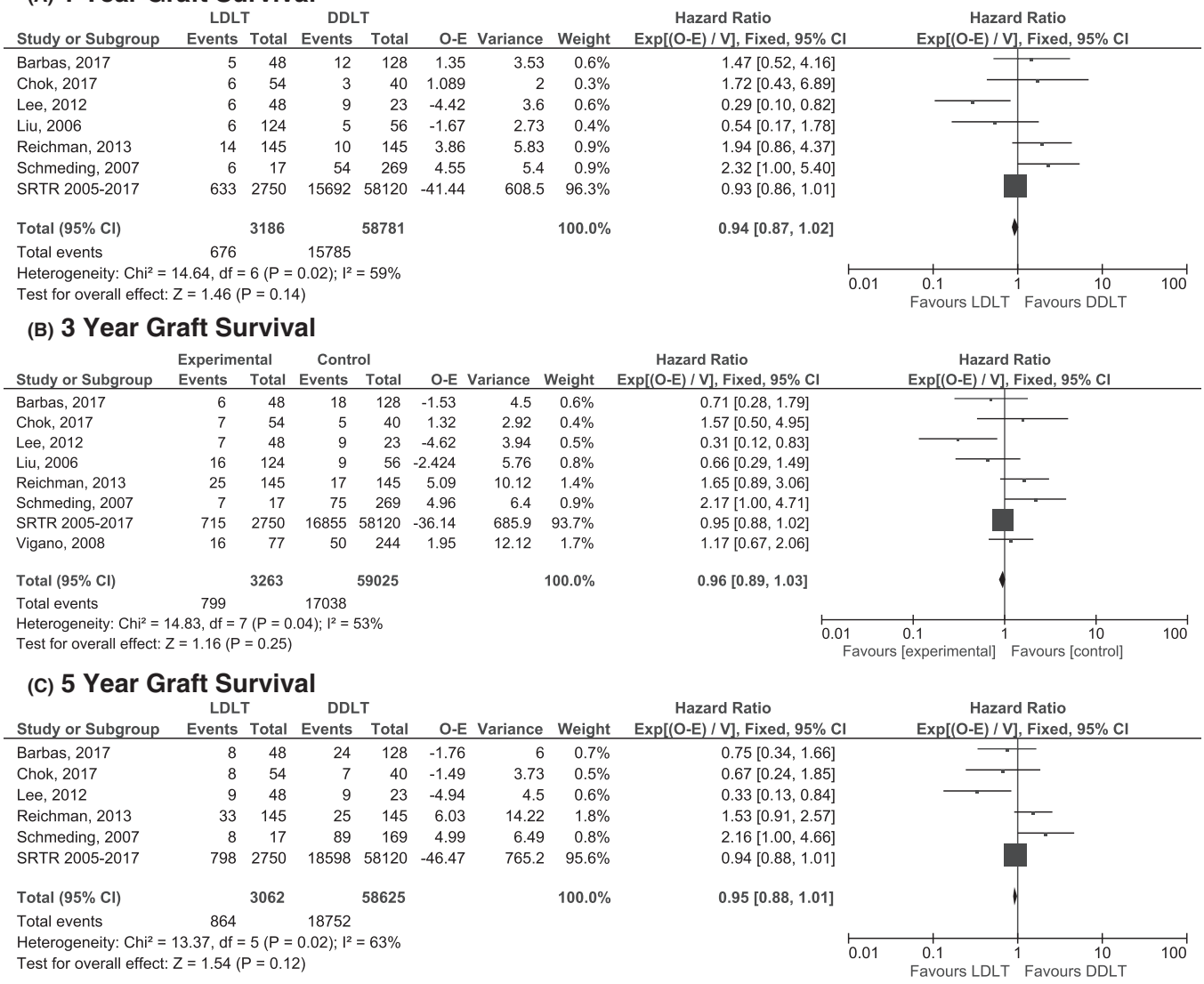


FIGURE 3 Forest plot of hazard ratios for overall graft survival at 1 year (A), 3 years (B), and 5 years (C) posttransplant. LDLT and DDLT had equivalent graft survival at 1, 3, and 5 years posttransplant

and India have demonstrated that 5-year overall survival for LDLT with MELD >30 is comparable to the outcome in patients with MELD <30.[44,45]

A second preoperative variable that may influence patient survival is time on the waiting list. Even when including U.S. data, which showed a modestly longer waiting time for LDLT recipients, our comprehensive meta-analysis confirmed an overall shorter waiting time for LDLT recipients, which was not associated with overall survival on meta-regression (Figure 4; Table 2). Specific factors contributing to longer waiting time for LDLT recipients in the U.S. were beyond the scope of our study, but it is likely that variable local access to LDLT in different states and additional time for LDLT referral and donor evaluation are involved. Shorter waiting time for LDLT recipients may specifically benefit patient populations that may be disadvantaged in current allocation schemes: children, women, and patients with HCC.[46-48]

LDLT was associated with an increased incidence of arterial complications in the early era.[49,50] However, in this meta-analysis, no difference in risk of HAT was observed between LDLT and DDLT recipients. Studies from high-volume centers have confirmed this finding, as the rate of vascular complications has decreased over time, presumably as surgeons have gained experience and in some cases considered microvascular reconstruction.[13,15,51-53] A single center analysis of risk factors associated with HAT identified prolonged anastomosis time, perioperative blood transfusion, and graft to recipient weight ratio >1.15% as risk factors for early HAT.[54] One shortcoming of our analysis was the inability to effectively track HAT in the SRTR, and thus U.S. data were not included in examination of this variable.

Even with experience, early biliary complications are the recognized 'Achille's heel' in LDLT. Our meta-analysis confirmed that the risk of biliary complication was approximately two-fold higher in the LDLT group; however, there was no difference in graft survival between LDLT and DDLT and biliary complications did not negatively impact survival on meta-regression. A recent study from an

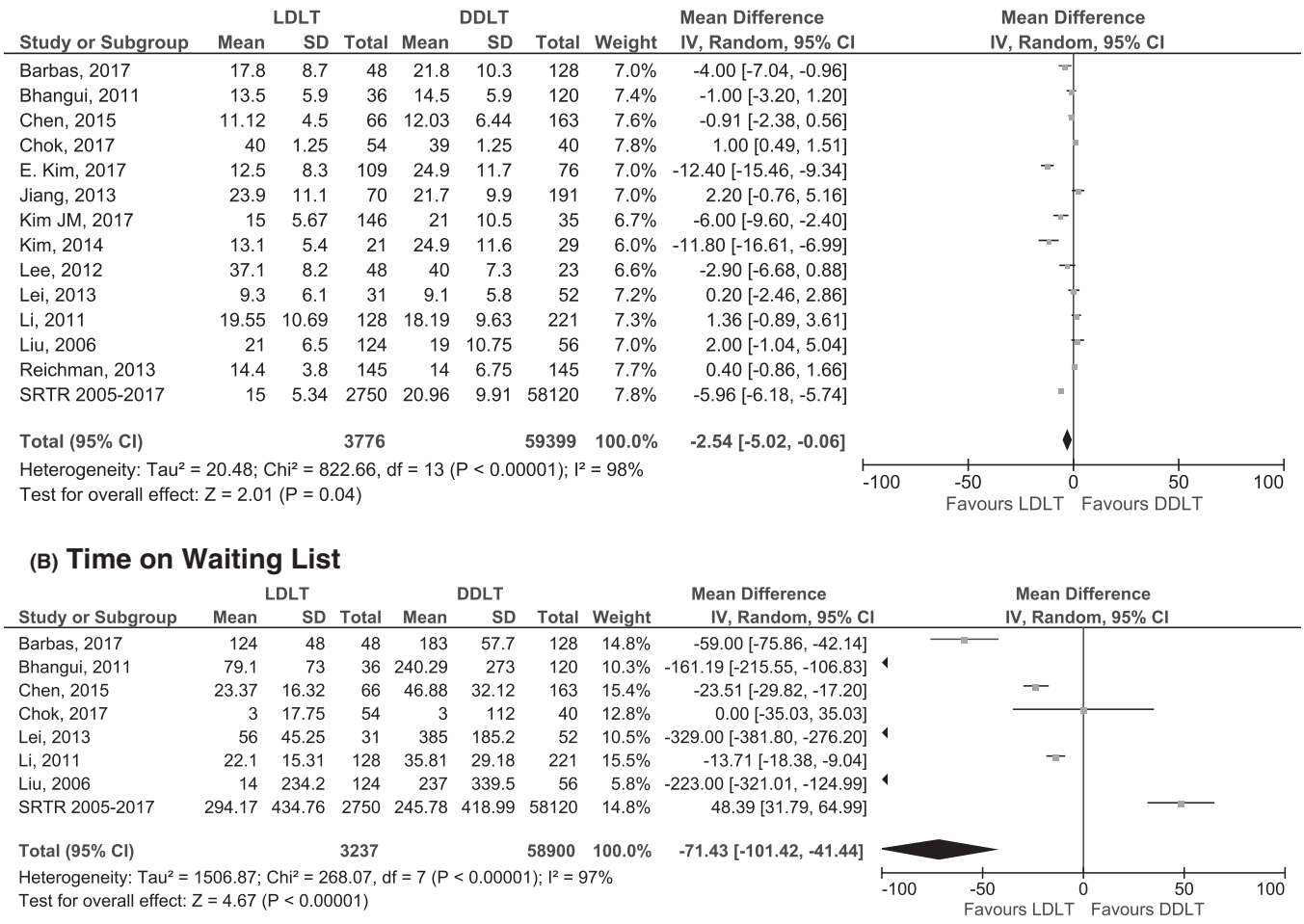


FIGURE 4 Forest plot of preoperative variables. (A) MELD at transplant and (B) time on waiting list. LDLT favored lower MELD at transplant and less time on the waiting list

experienced Japanese program reported a rate of biliary complications in LDLT of 17.3% and observed that multiple bile duct anastomoses and recurrent cholangitis prior to transplant were risk factors for biliary stricture or leak.[9] Our results are supported by a prior systematic review of biliary complications following LT, which identified MELD ≥35, multiple bile ducts, prolonged cold ischemic time, post–operative bile leak, and HAT as risk factors for biliary stricture for LDLT recipients on multivariable analysis.[19]

Postoperative infections and length of stay were similar among LDLT and DDLT in this meta-analysis. Prior single center studies have reported a higher incidence of bacterial infection in DDLT when compared to LDLT.[37,38,55] A Korean study identified receipt of a deceased donor allograft as an independent risk factor for postoperative infection (OR 5.5 [95% CI: 2.4–12.3]).[56] Length of stay is a difficult metric to study across different geographic regions, as practice patterns vary considerably. Even with regional variation, LDLT has been reported to be associated with a shorter length of stay in Canada (19 vs. 22 days), the U.S. (11 vs. 13 days), and China (42 vs. 45 days).[13,29,38]

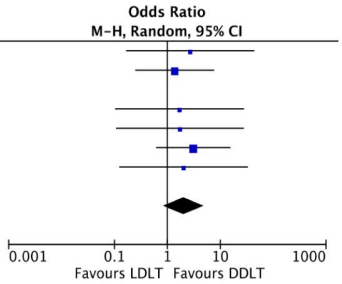
This meta-analysis confirms that LDLT recipients have a lower risk of rejection when compared to DDLT (Figure 5E). Single center studies have shown that LDLT recipients experience a lower rate of biopsy-proven rejection at 24 months post-LT compared to DDLT recipients.[57,58] It has been postulated that prolonged cold ischemic time and exposure to the physiology of brain death can lead to inflammatory cell recruitment into the allograft, thereby disrupting liver immune homeostasis, a phenomenon that is reduced in LDLT.[59] A more recent study analyzing both A2ALL and OPTN data reported a lower risk of biopsy-proven acute rejection among biologically related LDLT when compared to non–biologically related LDLT and DDLT recipients, and more importantly, acute rejection was associated with increased risk of graft failure and death.[60] Thus, an additional factor that may relate to superior patient survival over time following LDLT is the lower rate of rejection episodes.

There are limitations to our study. By design, we required that eligible studies included a comparison cohort. As a consequence, studies from centers that exclusively performed either LDLT or DDLT were not included. While all available studies reporting outcomes of LDLT versus DDLT were included, data were screened by center to exclude studies that may have contained overlapping patient cohorts. The majority of the included studies were retrospective, and no randomized

(A) Hepatic Artery Thrombosis

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	Weight	Odds Ratio M-H, Random, 95% CI
Barbas 2017	1	48	1	128	10.4%	2.70 [0.17, 44.08]
Jiang 2013	2	70	4	191	27.4%	1.38 [0.25, 7.68]
Kim 2017 B	0	21	0	29		Not estimable
Lei 2013	1	31	1	52	10.3%	1.70 [0.10, 28.19]
Li 2011	1	128	1	221	10.5%	1.73 [0.11, 27.93]
Reichman 2013	6	145	2	145	31.0%	3.09 [0.61, 15.55]
Wan 2014	1	40	1	80	10.4%	2.03 [0.12, 33.25]
Total (95% CI)		**483**		**846**	**100.0%**	**2.07 [0.84, 5.09]**
Total events	12		10			

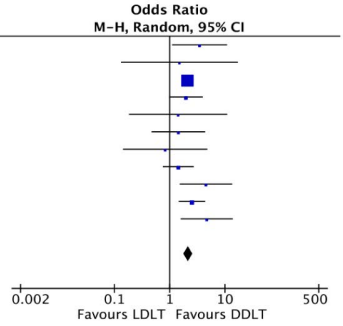
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 5 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.58 (P = 0.11)



(B) Biliary Complications

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	Weight	Odds Ratio M-H, Random, 95% CI
Barbas 2017	7	48	6	128	2.8%	3.47 [1.10, 10.92]
Chok 2017	2	54	1	40	0.6%	1.50 [0.13, 17.14]
Hu 2016	81	389	721	6471	56.4%	2.10 [1.62, 2.71]
Jiang 2013	16	70	25	191	7.6%	1.97 [0.98, 3.96]
Kim 2014	2	21	2	29	0.9%	1.42 [0.18, 10.99]
Kim 2017 B	10	109	5	76	3.0%	1.43 [0.47, 4.38]
Lei 2013	2	31	4	52	1.2%	0.83 [0.14, 4.80]
Li 2011	19	128	24	221	8.9%	1.43 [0.75, 2.73]
Liu 2006	32	124	4	56	3.1%	4.52 [1.51, 13.50]
Reichman 2013	50	145	25	145	12.3%	2.53 [1.46, 4.38]
Wan 2014	11	40	6	80	3.2%	4.68 [1.58, 13.82]
Total (95% CI)		**1159**		**7489**	**100.0%**	**2.14 [1.76, 2.59]**
Total events	232		823			

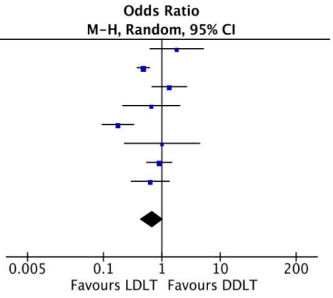
Heterogeneity: Tau² = 0.00; Chi² = 8.27, df = 10 (P = 0.60); I² = 0%
Test for overall effect: Z = 7.73 (P < 0.00001)



(C) Risk of Infection

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	Weight	Odds Ratio M-H, Random, 95% CI
Chok 2017	13	54	6	40	9.8%	1.80 [0.62, 5.23]
Hu 2016	72	389	2073	6471	18.1%	0.48 [0.37, 0.63]
Jiang 2013	14	70	30	191	13.6%	1.34 [0.66, 2.71]
Kim 2014	8	21	14	29	9.2%	0.66 [0.21, 2.07]
Kim 2017	33	109	54	76	14.2%	0.18 [0.09, 0.34]
Lei 2013	3	31	5	52	6.6%	1.01 [0.22, 4.54]
Reichman 2013	39	145	42	145	15.7%	0.90 [0.54, 1.51]
Wan 2014	16	40	41	80	12.8%	0.63 [0.29, 1.37]
Total (95% CI)		**859**		**7084**	**100.0%**	**0.67 [0.42, 1.09]**
Total events	198		2265			

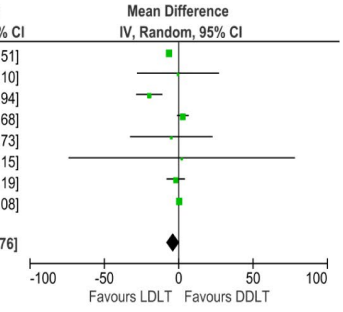
Heterogeneity: Tau² = 0.32; Chi² = 28.23, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 1.60 (P = 0.11)



(D) Length of stay

Study or Subgroup	LDLT Mean	LDLT SD	LDLT Total	DDLT Mean	DDLT SD	DDLT Total	Weight	Mean Difference IV, Random, 95% CI
Barbas, 2017	12.5	2.5	48	19	4	128	23.1%	-6.50 [-7.49, -5.51]
Chok, 2017	24	99.25	54	24.5	25.25	40	2.4%	-0.50 [-28.10, 27.10]
E. Kim, 2017	32.3	20.7	109	52.1	35.4	76	12.4%	-19.80 [-28.66, -10.94]
Hu, 2016	45.67	37.07	389	42.97	62.02	6471	19.8%	2.70 [-1.28, 6.68]
Kim, 2014	21	35.5	21	26	63.75	29	2.4%	-5.00 [-32.73, 22.73]
Liu, 2006	19	17.8	124	17	290.5	56	0.4%	2.00 [-74.15, 78.15]
Reichman, 2013	19.8	27.4	145	21.8	26.4	145	16.3%	-2.00 [-8.19, 4.19]
SRTR 2005-2017	15.44	20.16	2750	15.13	20.22	58120	23.2%	0.31 [-0.46, 1.08]
Total (95% CI)			**3640**			**65065**	**100.0%**	**-3.80 [-8.36, 0.76]**

Heterogeneity: Tau² = 23.22; Chi² = 134.19, df = 7 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.63 (P = 0.10)



(E) Rejection

Study or Subgroup	LDLT Events	LDLT Total	DDLT Events	DDLT Total	Weight	Odds Ratio M-H, Random, 95% CI
Al Sebayel, 2015	3	244	1	269	1.4%	3.34 [0.34, 32.29]
E. Kim, 2017	21	109	15	76	13.6%	0.97 [0.46, 2.03]
Hu, 2016	7	389	166	6471	12.7%	0.70 [0.32, 1.49]
Jiang, 2013	10	70	29	191	12.3%	0.93 [0.43, 2.03]
Kim JM, 2017	32	146	7	35	8.8%	1.12 [0.45, 2.81]
Kim, 2014	2	21	4	29	2.3%	0.66 [0.11, 3.98]
Lei, 2013	0	31	1	52	0.7%	0.54 [0.02, 13.79]
Reichman, 2013	30	145	53	145	26.9%	0.45 [0.27, 0.77]
Schmeding, 2007	9	20	127	289	8.9%	1.04 [0.42, 2.60]
Vigano, 2008	8	77	39	244	11.4%	0.61 [0.27, 1.37]
Wan, 2014	0	40	5	80	0.9%	0.17 [0.01, 3.14]
Total (95% CI)		**1292**		**7881**	**100.0%**	**0.72 [0.55, 0.95]**
Total events	122		447			

Heterogeneity: Tau² = 0.00; Chi² = 8.49, df = 10 (P = 0.58); I² = 0%
Test for overall effect: Z = 2.35 (P = 0.02)

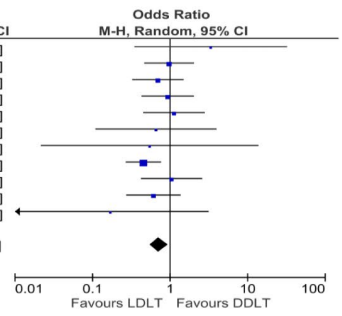


FIGURE 5 Forest plot of postoperative variables. (A) Hepatic artery thrombosis, (B) biliary complications, (C) risk of infection, (D) length of stay, (E) rejection rate. LDLT was equivalent to DDLT for rates of postoperative HAT (A), infections, and length of stay (D). LDLT were more likely to have biliary complications (B) and had a lower risk of rejection when compared to DDLT (E)

TABLE 2 Results of meta-regression analysis of MELD difference, waiting time, and post-LT biliary complications on 1-year overall patient survival. Residual τ^2 indicates whether, after including each moderator, heterogeneity exists due to the covariate being examined

Outcome measure	Relative risk [95% CI]	Residual τ^2	*p*-value
1-year patient survival			
MELD difference −5.5	0.67 [0.51, 0.87]	0.0515	.02
Time on Waitlist	0.94 [0.55,1.61]	0.0321	.9
Biliary complications	0.83 [0.58,1.20]	0.0976	.21

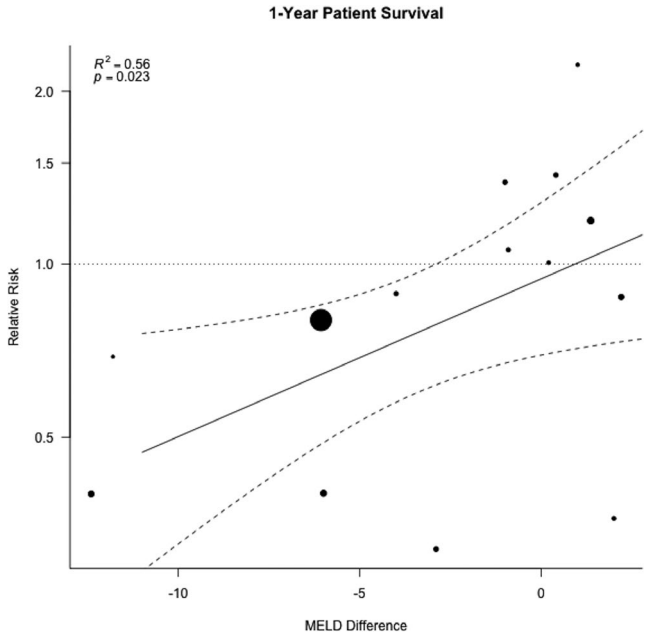


FIGURE 6 Random effects meta-regression showing how results of meta-analysis examining 1-year patient survival are influenced by the difference in MELD score between LDLT and DDLT. Each dot represents an individual study, the solid line represents the regression prediction, and the dotted lines the 95% confidence intervals

controlled studies were available. While 20 studies representing four continents were included, the U.S. data represent >50% of the LDLT and DDLT cohorts, which may have impacted some of the results. There were also inherent differences between LDLT and DDLT recipients in terms of age, sex, and etiology of underlying liver disease, that may have impacted our findings. Neither the SRTR analysis nor all studies examined reported on each of the secondary outcomes, potentially introducing bias and affecting the analysis. In particular, rejection, biliary and vascular complication are not consistently reported in the SRTR, limiting the possibility of including those data on analysis of secondary outcomes in this study. Additionally, there was heterogeneity among the studies, reflecting the differences in practice, protocols, and possibly in outcomes. Lastly, as per our study design, some outcomes were not considered, such as graft size or volume, technical details including anatomic variants, or the recurrence of disease and its impact on patient outcome.

5 | CONCLUSION

In summary, this meta-analysis and meta-regression confirms that LDLT provides superior overall patient survival when compared to DDLT, regardless of region of practice, spanning patients from both the East and the West. LDLT recipients are usually transplanted with a lower MELD, spend less time on the waiting list, have a lower risk of rejection, and have a comparable risk of postoperative vascular complications and infections with an equivalent length of stay when compared to DDLT. LDLT is associated with a higher rate of biliary complications, but this does not impact overall survival.

Recently, there has been renewed interest and growth in LDLT in the U.S. However, the overall proportion continues to be well below 10% of all adult LT, and only 20 states had LDLT activity in 2019.[61] As the proportion of financially vulnerable LT candidates continues to grow, a greater proportion of patients will be covered by public health insurance, which can further limit ability to travel to an out-of-state LDLT center.[62] This meta-analysis supports the continued expansion of LDLT for patients with end-stage liver disease who have access to a suitable living donor, even in regions where DDLT predominates, as LDLT allows for transplant at a lower MELD score, in patients with less deteriorated health condition, and can optimize posttransplant outcomes.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

Involved in the conception or design of the work: JE, CT, MK, and HS; literature screening and review: JE, CT, MK, AA, and AB; data acquisition and statistical analysis: AB, CT, and MA; analysis and interpretation of data: AB and JE; drafted the article: AB, CT, and JE; critically revised the article: all contributing authors. Finally approved the version to be published: All contributing authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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