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Living Donor Liver Transplantation in the United States: Evolution of Frequency, Outcomes, Center Volumes, and Factors Associated With Outcomes

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Recent modifications in organ allocation policies and increases in chronic liver diseases may have resulted in important changes in living donor liver transplantation (LDLT) in the United States. We examined the trends, outcomes, and factors associated with outcomes in adult LDLT. United Network for Organ Sharing data on 2566 adult LDLT recipients who received transplants from January 1, 2010, through December 31, 2019, were analyzed. LDLT graft and patient survival rates were compared with propensity score–matched deceased donor liver transplantation recipients by the Kaplan-Meier curve estimator. The association between preceding LDLT frequency and subsequent outcomes were assessed by Cox proportional hazards mixed effects modeling. After a stable annual frequency of LDLTs from 2010 to 2014 (~200 per year), the number of LDLTs doubled to 440 in 2019. The 1-year and 5-year graft survival rates for LDLT recipients were 88.4% and 78.1%, respectively, compared with 92.5% and 80.7% in the propensity score–matched donation after brain death recipients ($P = 0.005$), respectively. Older donor age and recipient diabetes mellitus and life support requirement were significantly associated with graft failure among LDLT recipients (P values <0.05). Average preceding LDLT frequencies of <3 per year, 3 to 20 per year, and >20 per year resulted in 1-year graft survival rates of 82%, 88% to 89%, and 93%, respectively (P values <0.05). There were 3 living donor deaths (0.12%). The frequency of LDLTs has doubled during the past decade, with good outcomes and acceptable donor safety profiles. However, there appear to be varying threshold transplant frequencies (volume/unit time) associated with acceptable (88%-89%) and aspirational (93%) 1-year graft survival rates. These data should be reassuring and encourage LDLT practice as efforts continue to expand the donor pool.

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Living donor liver transplantation (LDLT) increases the likelihood of patients on the waiting list receiving a prime donor liver who would otherwise be unlikely to be allocated a deceased donor organ in an expeditious fashion from the Model for End-Stage Liver Disease (MELD) score organ allocation system.[1,2] There have been more than 4600 adult LDLTs performed in the United States through 2015, representing <5% of the annual liver transplantations (LTs).[3]

In early 2019, the organ allocation policy was modified, with MELD exception scores capping at 3 points less than the median MELD score at transplant (MMaT-3) in the recipient's geographic region after a mandatory 6-month waiting period. In addition, acuity circles were introduced in lieu of United Network for Organ Sharing (UNOS) regions for

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplant Cohort Study; ALD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; DBD, donation after brain death; DC, decompensated cirrhosis; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HLA, human leukocyte antigen; HR, hazard ratio; ICU, intensive care unit; LDLT, living donor liver transplantation; LOS, length of stay; LT, liver transplantation; MELD, Model for End-Stage

organ allocation.[4] These combined changes aimed to decrease disparities in access to deceased donor organs between geographic areas by undoing the advantage patients with HCC had over patients with physiologic MELD scores. As a result, patients with HCC may now have inadvertent increases in LT wait times. In tandem, the number of patients on the waiting list has also been increasing disproportionately compared with the number of LTs performed, which has been driven in part by the ongoing nonalcoholic steatohepatitis (NASH) and alcohol-related liver disease (ALD) epidemics.[3,5-7] Furthermore, more LT candidates may have static uncompetitive MELD scores owing to the efficacy of direct-acting antivirals or alcohol cessation. The net impact of these factors is likely to include an increasing appeal of LDLT, with many centers expected to embrace LDLT to expand the donor pool.

The survival benefit of LDLT rather than waiting for a deceased donor LT (DDLT) has been demonstrated,[8] although the most recent study using the US national transplant database suggests that the survival benefit for LDLT had gradually disappeared by 2015.[3] How LDLT grafts compare with optimal DDLT grafts is unknown given the conflicting results and heterogenous analysis used in the literature. A single center has reported a statistically superior graft survival for LDLT[9]; however, this was a largely unadjusted analysis. There have been no prior studies comparing LDLT outcomes with optimally matched DDLTs for attributes affecting graft survival (eg, cold ischemia time and donor age).

Significant resource use and surgical expertise are needed for LDLT.[2,10] The landmark multicenter Adult-to-Adult Living Donor Liver Transplant Cohort Study (A2ALL) showed an overall 1-year graft survival rate of 81% and identified a significant learning curve for adult LDLTs of 15 to 20 LDLTs.[11,12] This was also demonstrated by other studies in which the learning curve leveled off after 20 LDLTs.[13-15] Given that the number of LDLTs in the United States has markedly increased, in conjunction with improved surgical techniques and perioperative management, an updated assessment of how center experience affects outcomes is needed to guide new centers both from programmatic planning and patient safety standpoints. Although the aforementioned studies showed a threshold for the cumulative total number of LDLTs, it is not known how the frequency (volume/unit of time) of LDLTs affects outcomes (eg, the association of graft survival with number of LDLTs performed during the preceding 24 months).

The ethical principle of minimizing the risk of harm to the donors also needs consideration.[16] Although the adoption of the MELD score organ allocation system in 2002 may have resulted in the subsequent decrease observed in LDLTs, a widely publicized donor death in New York may also have contributed.[17] Updated donor safety is needed to reassure LDLT centers and the public that living donation continues to be safe despite the likely increased practice that could conceivably lead to variability in outcomes. In addition, there also appears to be a rise in Good Samaritan/altruistic donors who are unrelated to the recipient.[18] Unrelated donors reduce the likelihood of overly close human leukocyte antigen (HLA) types and associated complications, such as graft-versus-host disease, potentially resulting in improved outcomes (versus related donors).[19] It remains to be elucidated whether the potential advantage of unrelated donation has translated to improved LDLT outcomes.

Given the expected increase in LDLT practice and the shortcomings in the existing literature, our study objectives were to (1) examine the trends and outcomes

Liver Disease; NASH, nonalcoholic steatohepatitis; OPTN, Organ Procurement and Transplantation Network; PSC, primary sclerosing cholangitis; TRR, transplant recipient registration; UNOS, United Network for Organ Sharing.

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in donors and recipients of adult LDLT using optimally matched DDLT controls, (2) study the effects of LDLT frequency on transplant center outcomes, and (3) analyze for factors associated with graft failure among LDLT recipients.

Patients and Methods

STUDY POPULATION AND DATA MANAGEMENT

National data were obtained from the UNOS database on adult patients (18 years of age or older) in the United States who underwent an LDLT from January 1, 2010, through December 31, 2019. These data are prospectively collected by the Organ Procurement and Transplantation Network (OPTN), under contract from UNOS, from transplant programs, organ procurement organizations, and histocompatibility laboratories and supplemented by the Centers for Medicare & Medicaid Services and the National Technical Information Service's Death Master File.[20] To ensure that the donor quality of DDLT recipients were as closely matched to LDLT recipients as possible, donation after circulatory death donors, cold ischemic times of 6 hours or greater, donor liver with ≥30% steatosis, and hepatitis C virus (HCV) antibody or HCV nucleic acid testing positive donors were excluded from the DDLT control group.[21,22] Moreover, acute liver failures, recipients who had previous LTs, and recipients who underwent multiorgan transplants or domino LTs were also excluded.

Data from both the liver donor transplant recipient and donor data sets were merged and analyzed concurrently. The clinical data analyzed included donor and recipient demographics; anthropometric measurements; comorbidities; laboratory values, including laboratory MELD scores; and diagnoses. Follow-up data included graft failure and mortality among transplant recipients and mortality and morbidity among the living donors. As per OPTN, graft failure was defined as the occurrence of either recipient death or removal of the transplanted organ. Transplant recipients were assigned primary listing indications in a stepwise approach, starting from the transplant recipient registration (TRR) form and next from the transplant candidate registration form if no diagnosis had been assigned from the TRR. HCC diagnoses were also assigned independently of chronic liver diseases.

COHORT ANALYSIS

Continuous variables were summarized by means and standard deviations or by medians and interquartile ranges, and frequencies and percentages were used for categorical variables. A comparative analysis between LDLT and DDLT recipients was performed. Comparison of continuous variables was based on the 2-sample *t* test for data with normal distribution, otherwise the 2-sample Wilcoxon rank test was used. The 2-sided chi-square test was used to compare categorical variables. Cox proportional hazards regression modeling was used to assess for variables associated with graft failure among LDLT recipients only. Multiple forms of the model were explored incorporating all available variables that have been associated with posttransplant graft failure in the medical literature. Schoenfeld residuals were examined to ensure that there was no violation of the proportional hazard assumption.

PROPENSITY SCORE–MATCHED ANALYSIS

Propensity score matching can be used to reduce bias in retrospective studies, including selection bias and other potential confounders. Propensity score matching simulates a randomized controlled trial–like situation where the treatment and the control groups are matched in terms of selected confounders.[23] The propensity score for each subject was estimated using a logistic regression model for LDLT recipients as a function of variables that are associated with graft failure in the literature. The donor variables that were used to generate the propensity score for each donor subject were age, race, and sex. The recipient variables that were used to generate the propensity score for each subject were age, race, sex, diabetes mellitus, body mass index (BMI), MELD score, HCC, etiology of liver disease (grouped as ALD, nonalcoholic fatty liver disease, HCV, cholestatic/autoimmune, and other), and transplant year. After estimation of the propensity score for each subject, we performed 1-to-1 matching using the nearest neighbor method with a caliper width of 0.15 of the standard deviation of the logit of the propensity score. All 2566 LDLT cases were matched. The balance of characteristics between the LDLT and DDLT groups in the matched sample was checked by examining standardized percentage bias (<10% was desirable) and performing formal comparative analysis between

covariates. Kaplan-Meier survival curve analysis with log-rank testing was used to estimate graft and patient survivals of the LDLT group compared with propensity score–matched DBD controls. These results are provided as hazard ratios (HRs) with confidence intervals (CIs).

TRANSPLANT VOLUME METRIC ANALYSIS

To assess how LDLT volume affected outcomes, individual patients were assigned the number of LDLTs performed at their respective transplant centers in the preceding 2 years before their transplant date. Preceding transplant volume assessment was adjudged to be more optimal means for assessing the true association between transplant volume and subsequent outcomes compared to previous methodology in the literature such as assessing total center volume and outcomes over a certain time period whereby outcomes are analyzed with respect to future volume (eg, a patient who received a transplant in 2011 in a low-volume LDLT center could be assigned to a high-volume LDLT center if an increase in LDLT practice occurred in later years). We chose 2 years rather than 1 year as we believed this would be a more accurate reflection of a transplant center's stability of volume. Cox proportional hazards regression modeling was used to assess the frequency of the preceding LDLT volume and 1-year graft failure rates. Possible clustering by individual transplant centers was assessed for using a shared frailty random effects Cox model. Additional analyses were performed on "new" LDLT centers during the study period, defined as no LDLT performed within the preceding 2 years.

The proportion of missing data was extremely low (<1%). A P value <0.05 was considered significant for the results. The statistical analyses were performed using the Stata statistical package (Stata Statistical Software, release 16 [StataCorp, College Station, TX]).

Results

FREQUENCY AND COMPARATIVE DEMOGRAPHICS

After merging the LDLT recipient and donor data sets, there were 2644 LDLTs observed during the study period. Of these, 78 were domino LTs and were excluded, leaving 2566 LDLTs in our final study cohort. Of the initial 64,041 adult DDLT recipients during the study period, 39,264 met the exclusion criteria, leaving 24,777 DBD LT recipients in the final control group. The study flow diagram detailing out cohort selection is shown in Supporting Fig. 1.

After a stable annual frequency of LDLTs from 2010 to 2014 (~200 per year), the number of LDLTs doubled to 440 in 2019 (Fig. 1). Overall, listing indications for NASH and ALD increased by more than 6-fold and 4-fold, respectively. Conversely, listing indications for HCV decreased by almost half, although HCV was still the number 1 chronic liver disease listing indication during the study period accounting for 501/2566 (19.5%) of LDLTs, whereas primary sclerosing cholangitis (PSC; 17.8%) was the second most common. Listing indications for HCC also increased from 76 in 2010 to 162 in 2019 and accounted for 966/2566 (37.6%) of LDLTs (Fig. 1). Of note, the increase in LDLTs occurred in the background of an increase in the DBD LT control group during the study time period, with the annual number of DBD LTs increasing from 1979 in 2010 to 3165 in 2019 using the study's patient selection criteria outlined in Supporting Fig. 1. LDLT now represents ~7% of all adult LTs in the United States.

There were 56 transplant centers who performed at least 1 LDLT during the past decade. The number of transplant centers performing LDLTs has increased from 28 in 2010 to 43 in 2019 (Supporting Table 1). All 11 UNOS regions (as designated before the implementation of acuity circles) performed LDLTs in 2019, except region 6 (Fig. 2). There was a 13-fold difference in the frequency of LDLTs between the highest and lowest volume UNOS regions. LDLT recipients were younger (median = 56 years), received younger donors (median = 36 years), and had lower MELD scores (median = 15) and longer waitlist times (median = 150 days) compared with recipients of DBD donors (all P values <0.001; Table 1).

PATIENT AND GRAFT SURVIVAL RATES

There were 2566 DBD controls propensity score–matched to the 2566 LDLTs (Table 1). The covariate balancing is presented in Supporting Fig. 2. The 1-year and 5-year patient survival rates for LDLT recipients were 93.4% and 83.8%, respectively, compared with 94.6% and 83.0% in the propensity score–matched DBD recipients (P = 0.973), respectively (Fig. 3). The 1-year and 5-year graft survival rates for LDLT recipients were

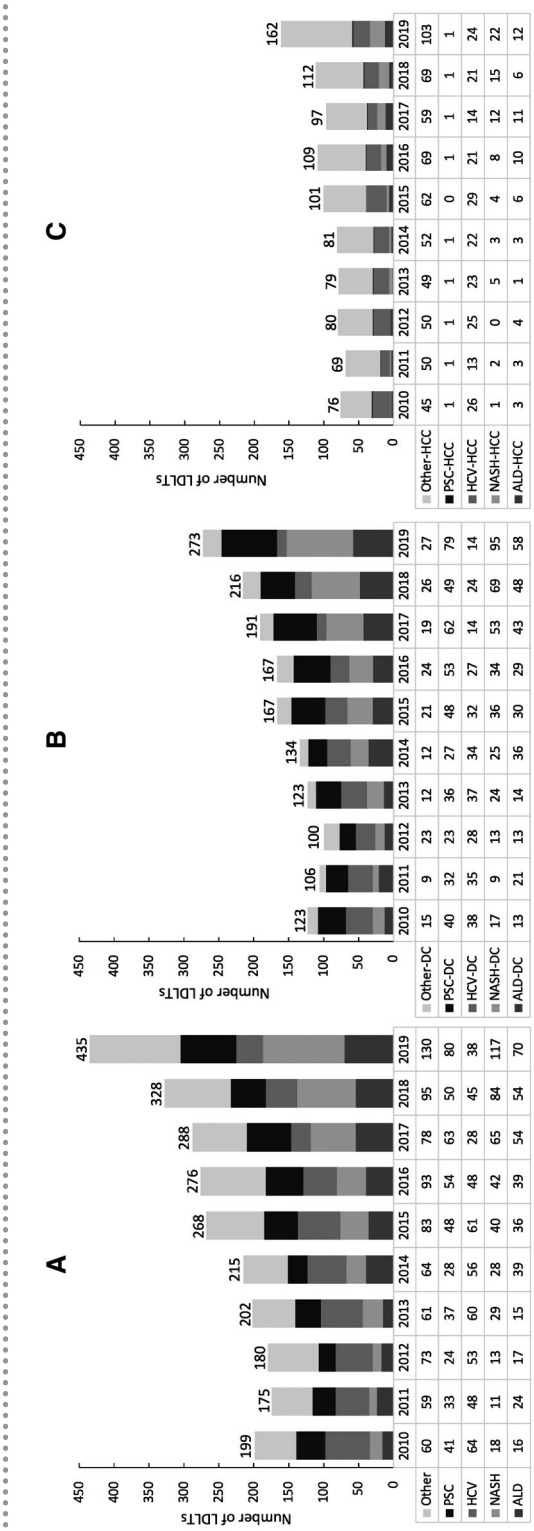

FIG. 1. Number of LDLTs in the United States from 2010 to 2019 stratified by etiology of liver disease and substratified by (A) overall, (B) DC, and (C) HCC.

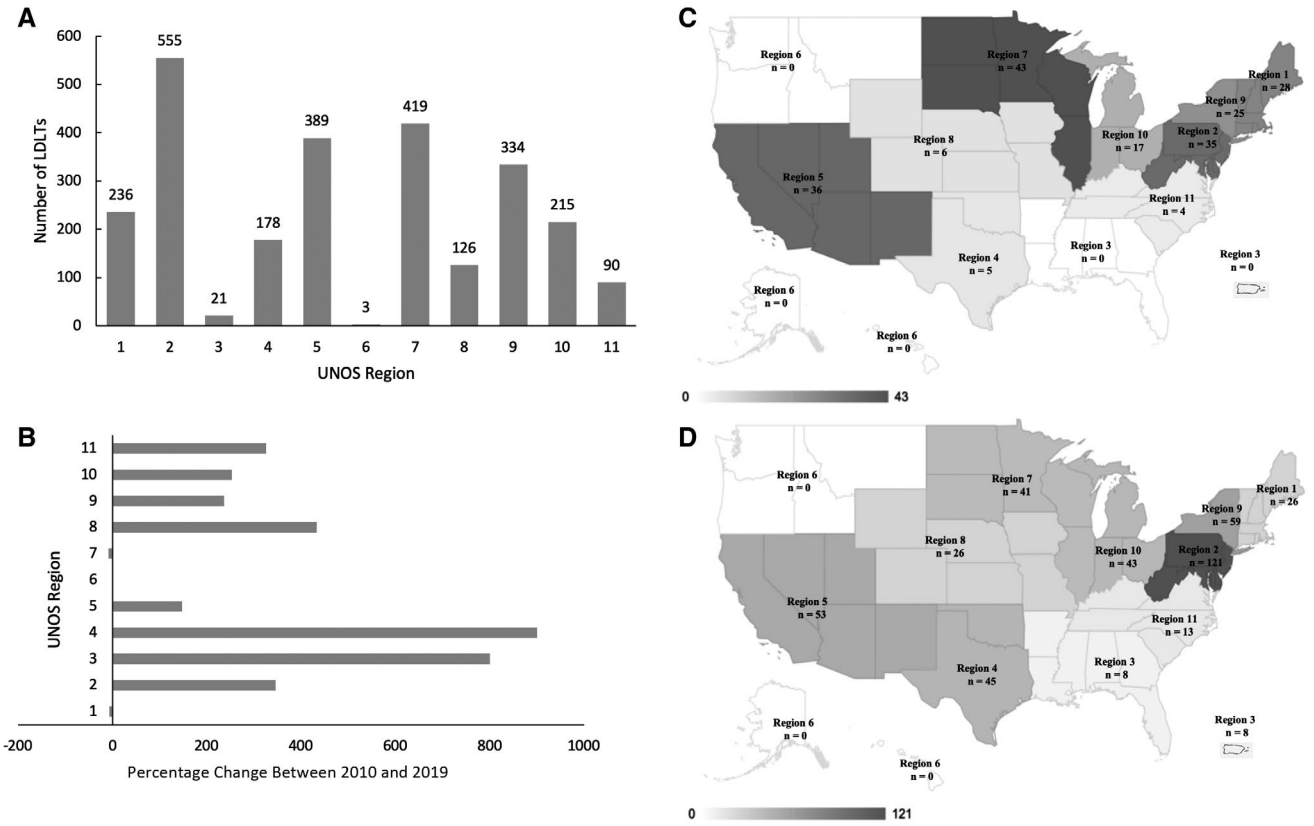

FIG. 2. Geographic variation of LDLTs in the United States from 2010 to 2019 stratified by UNOS region. The bar charts display the (A) overall number and (B) percentage change between 2010 and 2019, whereas the maps show the number of LDLTs performed in respective UNOS regions in (C) 2010 and (D) 2019.

88.4% and 78.1%, respectively, compared with 92.5% and 80.7% in propensity score–matched DBD recipients ($P = 0.005$), respectively (Fig. 3). The 1-year and 5-year cumulative probabilities of liver retransplantation were 5.3% and 7.3% in the LDLT group compared with 2.3% and 3.4% in the DBD LT control group, respectively ($P < 0.001$). To assess how retransplantation rates have changed over time, the cohorts were divided into the following 2 periods: 2010 to 2014 (n = 1941) and 2015 to 2019 (n = 3191). LDLT recipient retransplantation risk (versus the DBD controls) decreased from an HR of 2.26 (95% CI, 1.54-3.30) during the 2010 to 2014 period to an HR of 1.91 (95% CI, 1.27-2.85) during the 2015 to 2019 period. In addition, among LDLT recipients, those who were transplanted in the 2015 to 2019 period had a reduced risk of being retransplanted compared with those transplanted in the 2010 to 2014 period (HR, 0.70; 95% CI, 0.53-0.92).

Among the LDLT recipients, graft failure was associated with increased donor age (HR, 1.02; 95% CI, 1.01-1.03), recipient diabetes mellitus (HR, 1.38; 95% CI, 1.10-1.69), lower recipient BMI (HR, 0.97; 95% CI, 0.95-0.99), and recipient life support requirement (HR, 3.08; 95% CI, 1.50-6.30; Table 2). Recipient age was not associated with graft failure (HR, 1.00; 95% CI, 1.00-1.01). MELD score was also not associated with graft failure during the Cox model building stages and was omitted from the final model as it did not improve the model. Within the same Cox model, donor age was also incorporated as an ordinal variable (18-29, 30-39, 40-49, ≥50 years) instead of a continuous variable (Table 2). The donor age of 18 to 29 years had the best graft outcomes.

At 1 year, there were 266 (10.4%) graft failures among the LDLT group compared with 227 (8.9%) in the DDLT control group. Among the graft failures, there was a higher rate of vascular thrombosis (1.9% versus 0.9%; $P = 0.350$) and biliary complications (0.8% versus 0.4%; $P = 0.658$) in the LDLT group; however, "other/unknown" reasons comprised most of the graft failures in both groups (61.7% in LDLTs versus 48.5% in DDLTs; $P = 0.002$).

TABLE 1. Baseline Characteristics of LT Recipients in the United States Who Received Transplants Between January 1, 2010, and December 31, 2019

	All Patients (n = 27,343)			Propensity Score–Matched Patients (n = 5124)		
Variable	LDLT (n = 2566)	DBD LT (n = 24,777)	*P* Value	LDLT (n = 2566)	DBD LT (n = 2566)	*P* Value
Donor						
Age, years	36.0 (28.0-45.0)	44.0 (29.0-56.0)	<0.001	*36.0 (28.0-45.0)*	*33.0 (22.0-48.0)*	*<0.001*
BMI, kg/m^2	26.2 (23.5-28.7)	27.0 (23.5-31.3)	<0.001	26.2 (23.5-28.7)	26.1 (22.5-30.6)	0.120
Male sex	1214 (47.3)	14,447 (58.3)	<0.001	*1214 (47.3)*	*1276 (49.7)*	*0.083*
Caucasian	2088 (81.4)	15,780 (63.7)	<0.001	*2088 (81.4)*	*2031 (79.2)*	*0.050*
Cold ischemia time, hours	1.5 (1.0-2.1)	4.7 (4.0-5.4)	<0.001	1.5 (1.0-2.1)	4.7 (3.9-5.5)	<0.001
Recipient						
Age, years	56.0 (46.0-63.0)	58.0 (51.0-63.0)	<0.001	*56.0 (46.0-63.0)*	*56.0 (47.0-63.0)*	*0.850*
Male sex	1401 (54.6)	16,275 (65.7)	<0.001	*1401 (54.6)*	*1425 (55.5)*	*0.500*
Caucasian	2087 (81.3)	17,965 (72.5)	<0.001	*2087 (81.3)*	*2005 (78.1)*	*0.004*
BMI, kg/m^2	26.3 (23.3-30.0)	28.1 (24.6-32.3)	<0.001	*26.3 (23.3-30.0)*	*26.0 (23.2-29.9)*	*0.440*
Posttransplant LOS, days	10.0 (8.0-16.0)	9.0 (6.0-15.0)	<0.001	10.0 (8.0-16.5)	8.0 (6.0-12.0)	<0.001
Waitlist time, days	150.0 (78.0-302.0)	96.0 (18.0-284.0)	<0.001	150.0 (78.0-302.0)	163.5 (48.0-351.0)	0.079
Diabetes mellitus	607 (23.7)	6627 (26.7)	<0.001	*608 (23.7)*	*621 (24.2)*	*0.920*
Serum creatinine, mg/dL	0.8 (0.7-1.1)	1.0 (0.8-1.6)	<0.001	0.8 (0.7-1.1)	0.9 (0.7-1.1)	<0.001
Serum total bilirubin, mg/dL	2.7 (1.4-4.8)	3.9 (1.7-10.9)	<0.001	2.7 (1.4-4.8)	2.0 (1.0-4.3)	<0.001
MELD score	15.0 (11.0-20.0)	21.0 (13.0-30.0)	<0.001	*15.0 (11.0-20.0)*	*14.0 (1.0-20.0)*	*0.004*
Life support requirement	20 (0.8)	1515 (6.1)	<0.001	20 (0.8)	42 (1.6)	0.005
ICU	32 (1.2)	2739 (11.1)	<0.001	32 (1.2)	70 (2.7)	<0.001
Dialysis requirement	16 (0.6)	2374 (9.6)	<0.001	16 (0.6)	40 (1.6)	0.001
Ascites, mild or worse	1628 (63.4)	18,518 (74.7)	<0.001	1628 (63.4)	1607 (62.6)	0.540
Hepatic encephalopathy, grade 1 or worse	1285 (50.1)	15,565 (62.8)	<0.001	1285 (50.1)	1306 (50.9)	0.560
Portal vein thrombosis	295 (11.5)	3092 (12.5)	0.150	295 (11.5)	295 (11.5)	0.280
HCC	450 (17.5)	8326 (33.6)	<0.001	*450 (17.5)*	*520 (20.3)*	*0.013*

NOTE: Values are presented as n (percentage) or median (interquartile range). There are 10 propensity score–matched variables presented in *italics* in this table. In addition, recipients were also matched on transplant year and etiology of liver disease.

ASSOCIATION OF PRECEDING TRANSPLANT CENTER VOLUME ON GRAFT SURVIVAL

The 2566 LDLT recipients were divided into the following 5 groups on the basis of the preceding 2 years of transplant volume: 0 to 5 (n = 267), 6 to 15 (n = 616), 16 to 25 (n = 722), 26 to 40 (n = 566), and >40 (n = 395). The 1-year graft survival rates were 82.7%, 88.1%, 88.5%, 88.5%, and 92.7% in the 0 to 5, 6 to 15, 16 to 25, 26 to 40, and >40 volume groups, respectively (Fig. 4). The lowest volume group (0-5 in the preceding 2 years, or an average or less than 3 annually) had statistically inferior outcomes to all other groups (all *P* values <0.05), whereas the highest volume group (>40 in the prior 2 years, or an average of >20 LDLTs annually) had statistically superior outcomes to all other groups (all *P* values <0.05). A similar trend in outcomes was observed in the Cox proportional hazards mixed effects model that adjusted for ages of the donor and recipient and recipient sex, diabetes mellitus, and life support requirement, with individual transplant centers included as a random effect to account for possible clustering by individual transplant center (Table 3). The random effect was not statistically significant (*P* = 0.073).

OUTCOMES OF "NEW" LDLT TRANSPLANT CENTERS

There were 37 "new" LDLT transplant centers during the study period (Supporting Table 2). The 1-year

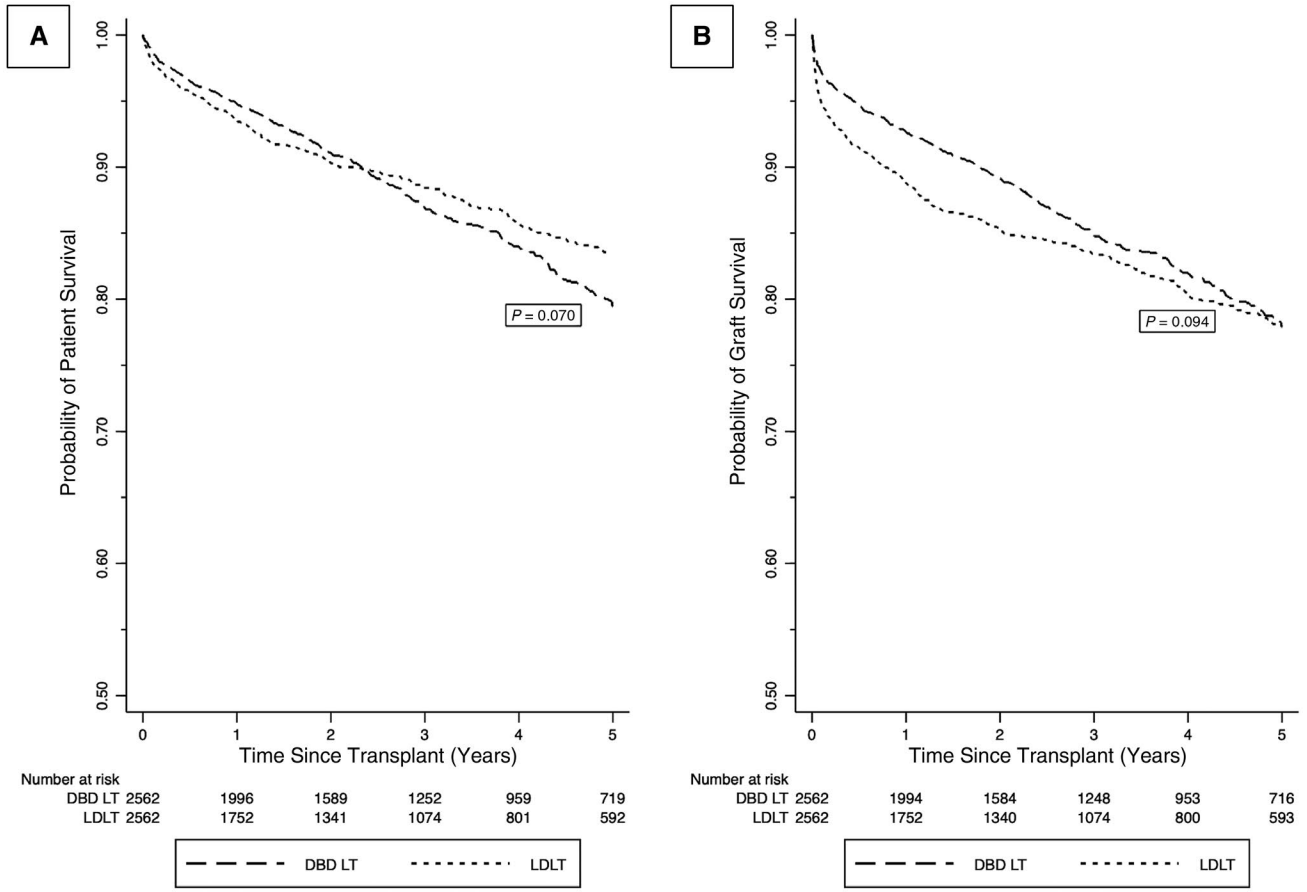

FIG. 3. (A) Patient survival rates and (B) graft survival rates for LDLT recipients in the United States who received transplants from January 1, 2010, to December 31, 2019, versus propensity score–matched DBD recipients.

graft survival outcomes were analyzed among these centers in incremental blocks of 5 LDLTs. After the cumulative transplant numbers reached 25, the outcomes appeared to plateau (Supporting Table 3).

TOTAL TRANSPLANT VOLUME AND OUTCOMES

The relationship between total transplant volume and 1-year graft survival was also assessed. Low-volume centers who performed 1 to 25 LDLTs in 10 years had significantly inferior outcomes compared with larger total volume centers ($P < 0.05$; Supporting Table 4).

RELATIONSHIP STATUS OF DONORS TO RECIPIENTS

Among the 2566 LDLT donors, 1590 (62%) were relatives of the recipients with 935/1590 (62%) being offspring. Unrelated liver donation tripled during the study time period from 70 in 2010 (representing 35.2% of 2010 LDLTs) to 205 in 2019 (representing 47% of

TABLE 2. Multivariate Cox Proportional Hazards Model of Associations With Graft Failure in LDLT Recipients Who Received Transplants From 2010 to 2019 (n = 2566)

Covariate	HR (95% CI)	*P* Value
Donor		
Age (reference: 18-29 years)		
30-39 years	1.35 (1.05-1.73)	0.016
40-49 years	1.49 (1.15-1.92)	0.002
≥50 years	1.70 (1.27-2.27)	<0.001
Recipient		
Age	1.00 (1.00-1.01)	0.258
Diabetes mellitus	1.38 (1.10-1.69)	0.003
BMI	0.97 (0.95-0.99)	0.003
Life support requirement	3.08 (1.50-6.30)	0.002

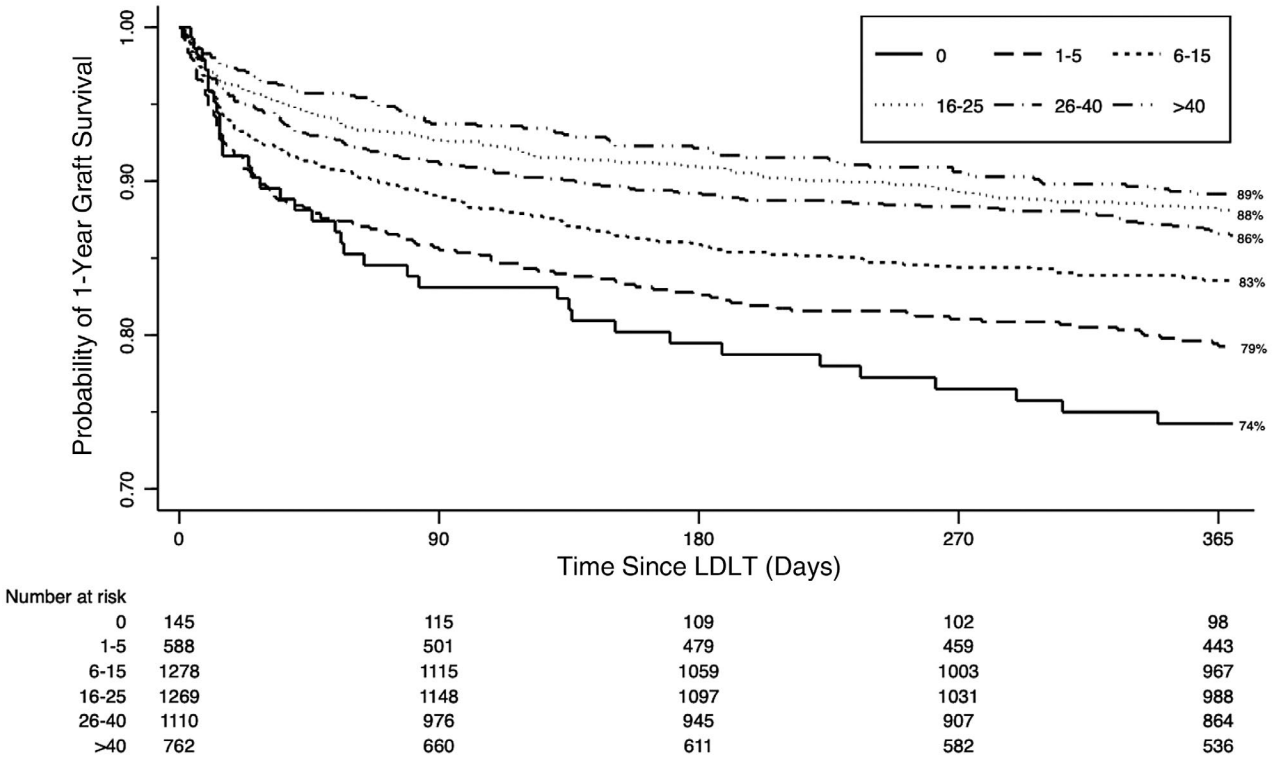

FIG. 4. The 1-year graft survival rates for LDLTs in the United States from 1996 to 2019, stratified by the number of LDLTs performed in the combined 2 years preceding the transplant date for each individual recipient at the respective transplant centers. A volume effect was observed, with an incremental statistically significant improvement up to the 16 to 25 LDLTs group, after which the volume effect appeared to stabilize with no statistically significant difference among the higher volume groups. The pairwise comparisons are also provided.

2019 LDLTs). The unadjusted 1-year and 5-year graft survival rates for LDLT recipients with related donors were 88.0% and 78.1% respectively, compared with 89.0% and 76.7%, respectively, in those who received unrelated donor livers ($P = 0.710$; Fig. 5). There was no difference in graft survival rates between related and unrelated LDLTs when adjusted for donor age; cold ischemic time; and recipient age, diabetes mellitus, BMI, MELD score, and life support requirement (HR, 1.04; 95% CI, 0.85-1.27; $P = 0.726$). The unadjusted 1-year and 5-year graft survival rates for LDLT recipients whose donors were offspring were 88.2% and 78.7%, respectively, compared with 88.5% and 77.0%, respectively, in those who received nonoffspring donor livers ($P = 0.542$; Fig. 4). There was no difference in graft failure rates between offspring and nonoffspring LDLT recipients when adjusted for the same variables described previously (HR, 1.03; 95% CI, 0.81, 1.31; $P = 0.825$).

DONOR OUTCOMES

Among the 2566 living donors during the 10-year study period, there were 3 donor deaths (0.12%; 1 per 833). In 2010, 2 donors, a 56-year-old man and a 34-year-old man, died from cardiorespiratory arrests within 4 days of surgery. In 2016, a 50-year-old woman died as a result of a cardiac arrest secondary to a venous air embolism. In addition, there was 1 donor who developed acute liver failure requiring LT. Of the living donors, 159/2566 (6%) were rehospitalized; 318/2566 (12.4%) had a documented postsurgical complication, with biliary complications (81/2566; 3.2%) being the most common (Supporting Table 5).

Discussion

LDLT has been shown to have comparable outcomes to optimal DDLTs, with implied but only partly fulfilled

potential to reduce waitlist mortality by expanding the donor pool.[9,12] Our study has several important findings. First, although LDLT remains comparatively underused in the United States, the practice has undergone notable expansion in recent years, with preservation of acceptable graft and patient outcomes. An important novel finding of our study is that not only is center LDLT experience (total number of LDLT procedures performed) an important predictor of outcomes but that the frequency of LDLT volume is also important.

TABLE 3. Multivariate* Cox Proportional Hazards Regression of 1-Year Graft Failure in LDLT Recipients Stratified by Preceding Transplant Volume (n = 2566)

Covariate	HR (95% CI)	*P* Value
Transplant volume† (reference: 0-5 group)		
6-15 group	0.69 (0.47-1.02)	0.063
16-25 group	0.62 (0.42-0.92)	0.018
26-40 group	0.61 (0.41-0.94)	0.024
>40 group	0.36 (0.21-0.62)	<0.001

*Adjusted for donor age, recipient age, sex, diabetes mellitus, and life support requirement and includes individual transplant centers as a random effect ($\Theta = 0.04$, likelihood ratio test of $\Theta = 0$: $P = 0.073$) in a shared frailty model.
†In the preceding 2 years at each respective transplant center for individual patients.

Recent changes in organ allocation policies and an increasingly competitive transplant environment may have resulted in increased appeal and advantage of LDLT.[24] The acuity circles allocation system has facilitated a national distribution of organs to the patients with the highest MELD scores while consequently reducing organ access for patients with lower MELD scores, prompting centers to look for ways to increase organ accessibility for patients relatively disadvantaged in a MELD-based organ allocation system. We observed a doubling of the annual rate of LDLT in 2019 to 440 cases from the baseline annual rate of

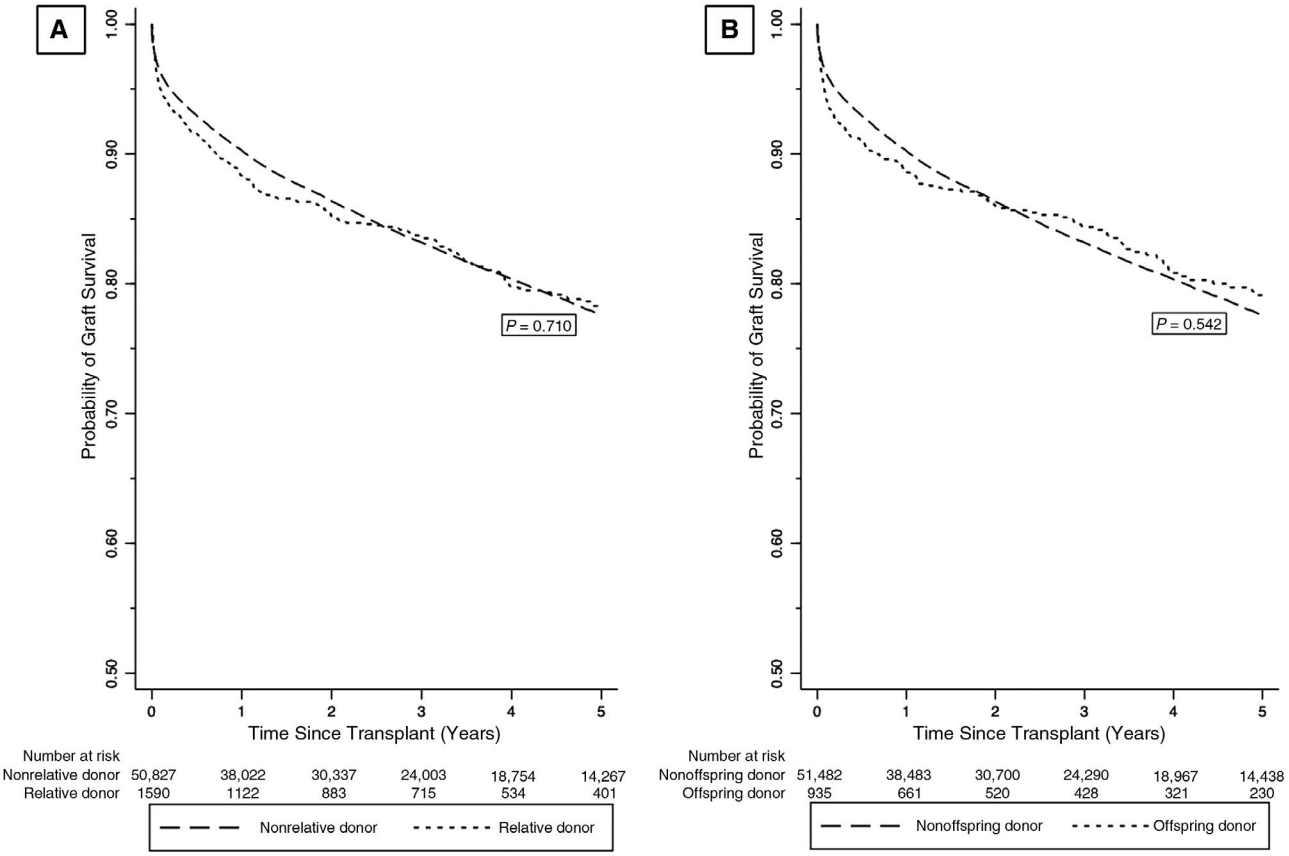

FIG. 5. Graft survival rates for LDLTs stratified by (A) relative versus nonrelative donors and (B) offspring versus nonoffspring donors in the United States.

~200 earlier in this decade, and a 45% increase in the proportion of transplant centers performing LDLTs. Both decompensated cirrhosis (DC) and HCC have increased substantially in 2019, coinciding with the organ allocation policy change (26% for DC and 45% for HCC between 2018 and 2019). The main listing indications that are driving this change are PSC, HCC, and NASH. LDLT now comprises 7% of all LT practice in the United States.

Some of the increase in LDLT practice has no doubt been driven by an expansion in Good Samaritan/altruistic donors, in which we observed a tripling of unrelated donors between 2010 and 2019. There are potential practical implications to this, including decreasing the need for suboptimal (eg, graft-to-weight ratio or age at the edge of acceptable) donor selection by increasing the donor pool. Although we failed to confirm our hypothesis that unrelated donor LDLT recipients may have superior outcomes compared with related donor recipients,[19] a trend toward improved outcomes was observed at 1 year and 2 years after transplant.[19] If this practice continues to expand in the future, it is possible that a statistically significant difference may be observed with improved outcomes in LDLT recipients who receive unrelated donors.

The 1-year graft survival rate among LDLT recipients during the past decade has been acceptable at 88.4% and illustrates the overall improvement over time when compared with the 81% 1-year graft survival rate in the seminal A2ALL report.[11] There was a 4% higher 1-year graft survival rate among propensity score–matched DBD LTs at 92.5%, likely reflective of the increased surgical complexity of LDLT and highlighting the careful planning needed when initiating a LDLT program. Interestingly, LDLT recipients had a higher rate of early graft failure, with LDLT recipients having a 3% higher rate of retransplantation at 1 year after transplant compared with DBD LT controls. To this end, we observed relatively higher proportions of vascular and biliary complications in the LDLT recipients, consistent with findings in the A2ALL cohort and in a meta-analysis,[11,25,26] emphasizing the technical challenges inherent to LDLT that programs need to focus on when striving to optimize outcomes. Promisingly, there was a trend toward decreased retransplantation rates among LDLT recipients between 2015 and 2019 compared with 2010 to 2014, possibly demonstrating early signals of improved outcomes as LDLT programs increase their experience.

As more transplant centers embrace LDLT practice, a clear understanding of the experience needed to achieve desired outcomes is important. It also allows patients to be fully informed when choosing their transplant program. A significant learning curve for adult LDLTs has been reported, with outcomes leveling off after 20 LDLTs.[11,13-15] In our updated study on LDLTs, we have similarly shown that 1-year graft survival rates continue to improve at "new" transplant centers with increasing center volumes until a slightly higher cumulative threshold is reached (after 25 LDLTs). Importantly, once LDLT centers achieve technical competency, regular LDLT practice is needed to maintain outcomes. An average preceding LDLT frequency of less than 3 per year is associated with subsequent inferior outcomes and a 1-year graft survival rate of 82%. There were acceptable outcomes (88%-89% 1-year graft survival rates) observed at an average preceding frequency of 3 to 20 LDLTs per year. While there were excellent outcomes (93% 1-year graft survival rate) observed at an average preceding frequency of 21 or more LDLTs per year. This could be considered as the aspirational goal of LDLT centers in the United States. Although >20 LDLTs per year may seem difficult to achieve, 5 LDLT centers in the United States achieved this number in 2019, and Asian LDLT centers regularly greatly surpass this metric.[27] This observation suggests that the recent frequency of LDLTs be added to the total number of procedures as an important predictor of post-LDLT outcomes. Of note, an increased risk of graft failure was associated with older donors (a 2% increased risk of graft failure for each increase in year, with recipients of donors aged 18-29 having the best outcomes), recipient diabetes mellitus (38% increased risk), and recipient life support requirement (308% increased risk). These donor and recipient factors should be considered when assessing LDLT candidates, particularly in centers with a recent LDLT frequency of less than 3 per year (eg, new LDLT transplant centers, in which a more conservative approach appears prudent).

LDLT has long been a source of immense ethical debate, beginning before the first LDLTs were performed,[28,29] largely centered on the principle of minimizing harm to the donors.[16] To this end, it is imperative that donor safety is considered in LDLT outcomes. A prior worldwide survey of LT centers estimated a low 0.2% donor mortality.[30] Donor hepatectomies have also been shown to be safe in all age groups, including the elderly aged ≥60 years.[31] Our

results show a slightly lower living donor death rate (0.12%; 1 per 833 LDLTs) during the past decade. With advances in minimally invasive surgery, laparoscopic donor hepatectomies for LDLT have now been safely performed and should make LDLT donation an even more attractive option for potential donors.[32] Of the living donors in our study, 6% (159/2566) were rehospitalized, with almost half having biliary complications, confirming the low recent donor morbidity in LDLT in the United States.

We feel our method of assessing the association of preceding LDLT frequency and subsequent volume is robust when compared with assessing total center volume in which some outcomes are analyzed with respect to future volume. There may be unmeasured confounders such as individual surgeon experience and institutional resources that may affect the measurement of preceding LDLT frequency and subsequent outcomes. Surgical experience and skill will to some degree be transferable between institutions when 1 or more members of a surgical team from a higher volume/frequency LDLT center relocate to a lower volume/frequency LDLT center. Although the UNOS database did permit the analysis of a large number of LDLTs, it does lack some granularity of data, such as morbidity among LDLT recipients, apart from graft failure etiologies, which would be important in considering the association of LDLT on quality of life. A large proportion of graft failures were recorded as "other" or "unknown," which precluded any strong conclusions being inferred from the analysis of early graft failure among LDLT recipients. The UNOS database also contains missing data; however, these missing data were minimal.

In conclusion, our results showed an ongoing expansion of LDLT in the United States in the setting of recent donor allocation policy changes and increased transplant center competition. Consistent volume is an important predictor of outcomes close to the norm, with acceptable outcomes maintained at a preceding LDLT frequency of 3 to 20 LDLTs per year, and aspirational outcomes at a LDLT frequency of >20 LDLTs per year. LDLT will undoubtedly remain an important option as recipient indications continue to expand.[6,33,34] Future surgical innovations including the increased use of left lobes and laparoscopic or robotic approaches as well as efforts to expand the living donor candidate pool, such as nondirected living liver donors, paired exchanges, and donor champion programs, may foster the advancement of LDLT in the United States in the near future while always following the double equipoise concept in balancing the donor risk and recipient benefit.[2]

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