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Original Article

Regional and National Trends of Adult Living Donor Liver Transplantation in the United States Over the Last Two Decades

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Abstract

Background and Aims: Liver organ shortage remains a major health burden in the US, with more patients being waitlisted than the number of liver transplants (LTs) performed. This study investigated US national and regional trends in living donor LT (LDLT) and identified factors associated with recipient survival. ***Methods:*** We retrospectively analyzed LDLT recipients and donors from the United Network Organ Sharing/Organ Procurement Transplant Network database from 1998 until 2019 for clinical characteristics, demographic differences, and survival rate. National and regional trends in LDLT, recipient outcomes, and predictors of survival were analyzed. ***Results:*** Of the 223,571 candidates listed for an LT, 57.5% received an organ, of which only 4.2% were LDLTs. Annual adult LDLTs first peaked at 412 in 2001 but experienced a significant decline to 168 by 2009. LDLTs then gradually increased to 445 in 2019. Region 2 had the highest LDLT numbers (n=919), while region 1 had the highest proportion (11.1%). Overall, post-LT mortality was 21.4% among LDLT recipients. Post-LDLT survival rates after 1-, 5-, and 10-years were 92%, 87%, and 70%, respectively. Interval analysis (2004–2019) showed that patients undergoing LDLT in recent years had lower mortality than in earlier years (hazard ratio=0.81, 95% confidence interval=0.75–0.88). ***Conclusions:*** Following a substantial decline after a peak in 2001, the number of adult LDLTs steadily increased from 2011 to 2019. However, LDLTs still constitute the minority of the transplant pool in the US. Life-saving policies to increase the use of LDLTs, particularly in regions of high organ demand, should be implemented.

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Introduction

In the US, approximately 12,000 people are on the waiting list for a liver transplant (LT), while only about 8,000 transplants are performed each year.[1] Most US liver allografts come from deceased donors, so increasing the number of living donor LTs (LDLTs) should dramatically help to reduce relative organ shortage and mortality of those on the waiting list.[2] However, in the US in 2017, adult LDLTs accounted for only 4% of the total LTs.[3]

Since 2002, the organ allocation for adult patients has been based on the Model for End-stage Liver Disease (MELD) to prioritize the sickest patients.[4] Candidates with hepatocellular carcinoma (HCC) can receive "exception points" that enable them to receive a higher priority.[5] As an adult LDLT decreases the wait time on the transplant list, it offers a life-saving opportunity for patients with low native MELD scores.[6] Advantages of LDLT over deceased donor LT (DDLT) may include optimizing LT timing, better organ quality, and lower rates of recipient mortality even among those with high MELD scores.[7–10] In January 2020, a new MELD exception policy was issued that is expected to prioritize non-HCC. Now implemented, the changes are expected to deprioritize and reduce the number of LTs for HCC.[11]

Understanding the national and regional trends in adult LDLT and studying the recipient outcomes and predictors of survival may help to improve recipient and donor outcomes and better donor-recipient matching. Two recent studies report LDLT frequency and outcomes in the US. Jalil *et al*.[12] used 2010–2017 data from the Nationwide Readmission Database (NRD) and analyzed the LDLT trends and associated outcomes, mostly related to readmissions (30- and 90-days) and other healthcare utilization factors. The research did not focus on the waitlist characteristics

Keywords: Living donor; Liver transplantation; Survival; UNOS; Organ demand.
Abbreviations: AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; CI, confidence interval; DDLT, deceased donor liver transplant; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalization ratio; LDLT, living donor liver transplant; LT, liver transplant; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; NRD, Nationwide Readmission Database; OPTN, Organ Procurement and Transplantation Network; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic shunt; UNOS, United Network for Organ Sharing ; UPMC, University of Pittsburgh Medical Center.

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or etiological background relevant to LDLT. Cotter *et al*.[13] used United Network for Organ Sharing (UNOS) data from 2010 to 2019 and compared the factors associated with the outcomes of LDLT and propensity-score matched DDLT. The authors assessed the 10-year variations in LDLT frequency, stratified by UNOS regions, age, and etiology of liver disease. However, an extensive analysis of historical data with regional variations over a more extended period may help develop policies to increase the donor pool and decrease waitlist mortality, particularly with recent changes in MELD exception policies. Therefore, the objective of this study was to evaluate the national and regional trends in adult LDLT in the US over the last two decades and examine the characteristics of LDLT donors and recipients in association with recipients' outcomes. We also attempted to identify factors associated with the survival of recipients.

Methods

Data source

The data reported here were supplied by the UNOS as the contractor for the Organ Procurement and Transplantation Network (OPTN). 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 OPTN or the US Government.[14] Because UNOS is a publicly available de-identified patient-level database, institutional review board approval was not required according to the policies of the UNOS and Beth Israel Deaconess Medical Center.

Study design and patient population

This was a retrospective cohort study using the UNOS database that follows the "Strengthening the Reporting of Observational Studies in Epidemiology" reporting guidelines. For reporting trends in LDLT in the US and regional differences, we included all adult (>18 years of age) recipients who underwent LDLT from January 1998 to December 2019. For the survival analyses, we evaluated the adult LDLT recipients from January 2004 to December 2019. We chose this timeframe for the survival analysis to analyze consistent data from the MELD era. In addition, the data on donor and recipient characteristics were more comprehensive during this period. We divided the time period into two eras to explore the differences in patient and donor characteristics. Era 1 included the years 2004 to 2011, and era 2 included those from 2012 to 2019.

Donor and recipient characteristics

Donor demographic data collected were age, gender, race or ethnicity, blood type, height, weight, and body mass index (BMI). The organ data collected were cold ischemia time, lobe donated (right or left), and microvesicular and macrovesicular fat, which were characterized as 5% cutoff on liver pathology for the subset of donors who had a liver biopsy.

Recipient demographic data included were age, gender, race or ethnicity, blood type, height, weight, and BMI. Clinical characteristics included the etiology of liver disease, HCC, diabetes, ascites, hepatic encephalopathy, prior abdominal surgery, dialysis, history of a transjugular intrahepatic shunt (TIPS) placement, portal vein thrombosis (PVT), spontaneous bacterial peritonitis (SBP), and the need for ventilator support. Laboratory data included were sodium, albumin, creatinine, total bilirubin, international normalization ratio (INR), and MELD score. Outcomes collected were days on the transplant waiting list (wait time), length of hospital stay, and survival.

Specific etiologies of liver disease that were analyzed independently were hepatitis C virus (HCV), hepatitis B virus, primary sclerosing cholangitis (PSC), nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), primary biliary cholangitis, cryptogenic cirrhosis, or autoimmune hepatitis. The "other" category included patients who did not meet the criteria for any other diagnoses.

Outcomes

The primary outcome was the post-LT mortality. To further assess the time-to-mortality, the length of follow-up was included in the survival analysis. Those who were lost to follow-up were censored from the survival analysis.

Statistical analysis

Data were extracted from the database and transferred to Statistical Analysis Software (SAS (version 9.4) and STATA software (version 16.1; StataCorp, College Station, TX, USA) for data cleaning, management, and analysis. Categorical variables were reported as numbers and percentages (%); continuous variables were reported as means and standard deviation. The association between the outcome (mortality) and the potential predictors was assessed either by the chi-square test for categorical variables or the independent *t*-test for continuous variables. Kaplan-Meier analysis was used to evaluate survival. To identify predictors of mortality, we performed a stepwise multivariate Cox proportional hazard model informed by clinical expertise. Variables included in the model were donor and recipient variables that were statistically significant at the bivariate level or those that are known to be clinically relevant. For transplant years, data were grouped into two eras, and into 24-day intervals for the length of hospital stay, and donor and recipient ages were grouped into 10-year intervals. The intervals were selected to yield clinically meaningful hazard ratios (HRs). A cutoff *p*-value of 0.05 was used to include and exclude the variables from the final model. Results were reported as HRs and 95% confidence intervals (CIs). Throughout the study, $p \leq 0.05$ was considered statistically significant.

Results

Trends in adult LDLT

Of the 223,571 candidates listed for an LT between 1998 and 2019, 57.5% (128,664) received a transplant, and only 4.2% (5,399) were LDLTs (Fig. 1A). There was an initial peak of 412 LDLTs in 2001, followed by a decline to 168 in 2009 (Fig. 1B). After 2009, LDLTs increased, reaching 445 in 2019. The proportion of LDLTs performed during that period had a similar trend, with the highest percentage in 2001 (Fig. 1C).

Trends in patients waitlisted for LT

In 2019, approximately 12,000 candidates were added to the waitlist. The number of waitlisted patients who dropped out because of death or being too sick for transplantation annually ranged from 1,612 in 1998 to 3,095 in 2014.

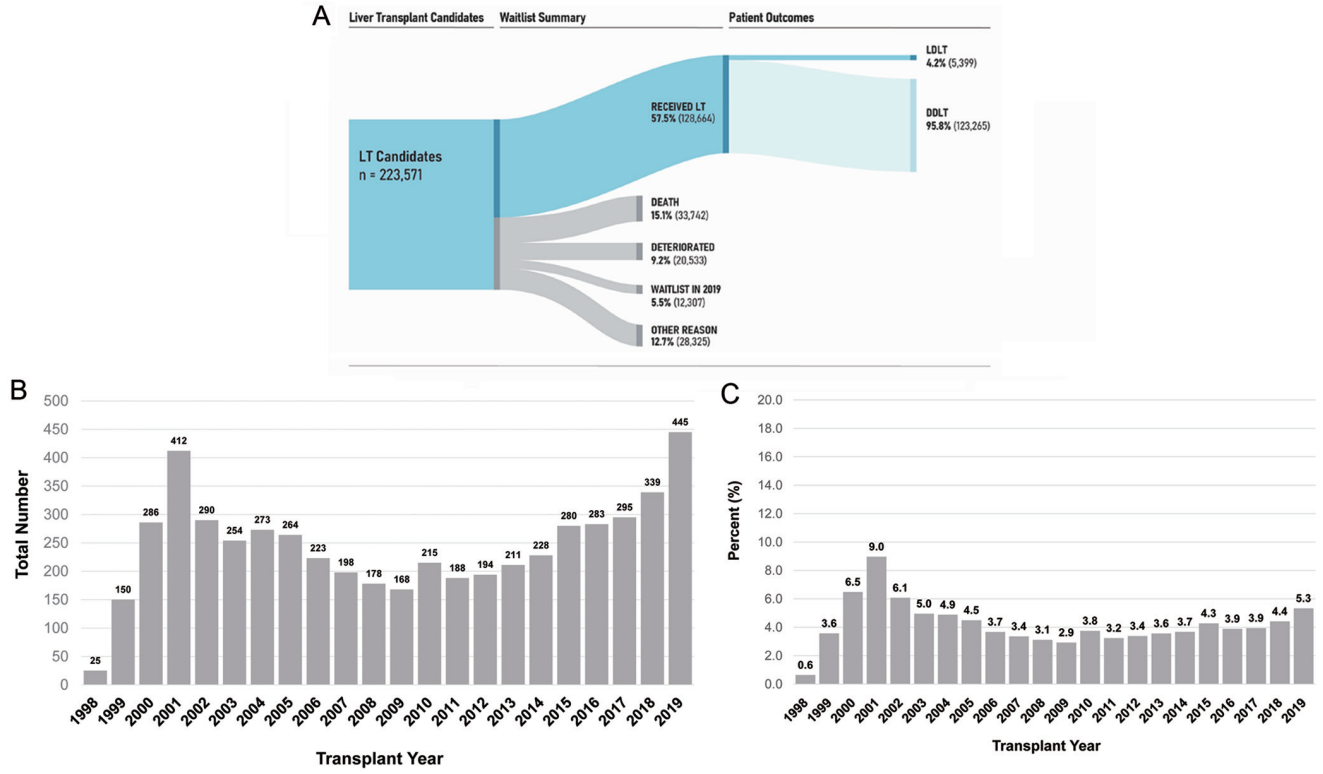

Fig. 1. (A) Sankey diagram of the distribution of adult candidates who received an LDLT from 1998 to 2019 (OPTN data as of May 16, 2021). (B) Number of adult LDLTs per year in the United States from 1998 to 2019 (*n*=5,399). C) Percentage of adult LDLTs among all LTs per year in the United States from 1998 to 2019. DDLT, deceased donor liver transplant; LT, liver transplant; LDLT, living donor liver transplant; OPTN, Organ Procurement and Transplantation Network.

Deaths of waitlisted patients ranged from 1,169 in 2018 to 1,932 in 2001 (Supplementary Fig. 1A–C).

Regional variation in adult LDLTs in the US

The proportion of adult LDLTs performed between 1998 and 2019 varied by OPTN region (Fig. 2A). Region 2 had the most LDLTs (*n*=919), followed by region 9 (*n*=902), region 7 (*n*=888), and region 5 (*n*=888). However, it is important to note that region 1 had the highest proportion of LDLT among total LTs between 1998 and 2019 at 11.1%, followed by region 9 (10.4%), and region 7 (7.6%). LDLTs were rare in regions 6 (*n*=3) and 3 (*n*=86). Regions 9 and 5 performed the most LDLTs in 2001 (Fig. 2B), mainly in New York and California (Fig. 3B). Region 9 abruptly declined from a peak of 136 LDLTs in 2001 to only 18 in 2009. In 2001, region 9 had the highest percentage of LDLTs (30.8%), but it decreased to 13.1% in 2019 (Fig. 2C). Although LDLTs have increased since 2009 in region 9, the region only performed 60 LDLTs in 2019 (Fig. 2B). In contrast, the number of LDLTs performed annually in region 2, including Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, and Northern Virginia, consistently increased from 2011 to 2019. With 123 LDLTs, region 2 accounted for 27.6% of the 445 adult LDLTs performed in 2019 (Fig. 2B), mainly driven by Pennsylvania, which performed 92 (75%) of the 123 LDLTs in 2019. Adult LDLTs accounted for 6.1% of all adult LTs in region 2 in 2001 and increased to 13.0% in 2019 (Fig. 2C). The number of adult LDLTs in each state between 1998 and 2019 is shown in Figure 3A. New York performed the most adult LDLTs (*n*=902), followed by California (*n*=691), Pennsylvania (*n*=683), Minnesota (*n*=488), and Massachusetts (*n*=487). Figure 3B shows the trend in the total number of adult LDLTs between 1998 and 2019 in the 10 states that performed the most adult LDLTs in the US.

Adult LDLTs in HCC patients

We evaluated annual trends in the proportion of adult HCC versus non-HCC patients receiving LDLTs. We also assessed the proportions of adult LDLT recipients with HCC and without HCC for each OPTN region between 1998 and 2019 (Supplementary Fig. 2A, B). The proportion of HCC in LDLT recipients increased after 2006, with the highest proportion in 2016 at 24% (Supplementary Fig. 2A). OPTN regions varied in the proportion of HCC patients who received LDLTs between 1998 and 2019 (Supplementary Fig. 2B). Region 9 had the highest proportion of LDLT recipients with HCC (20.5%), followed by regions 1 (17.7%), 4 (17.3%), and 5 (15.9%).

Characteristics of adult LDLT recipients

The mean recipient age at transplant was 52.4 ± 12.6 years (Table 1), 55.1% were males, and 82.6% were white. The mean BMI was 27.1±5.1 kg/m^2, and the mean MELD score was 15.5 ± 5.9. HCV (25.9%) was the most common etiology followed by PSC (18.6%), NAFLD (15.1%), and ALD (11.9%). Moreover, 17.4% had HCC, 22.0% had diabetes, 65.6% had ascites, and 51.8% had hepatic encephalopathy. The mean waiting time for LT was 320.8±552.0 days (Table 1).

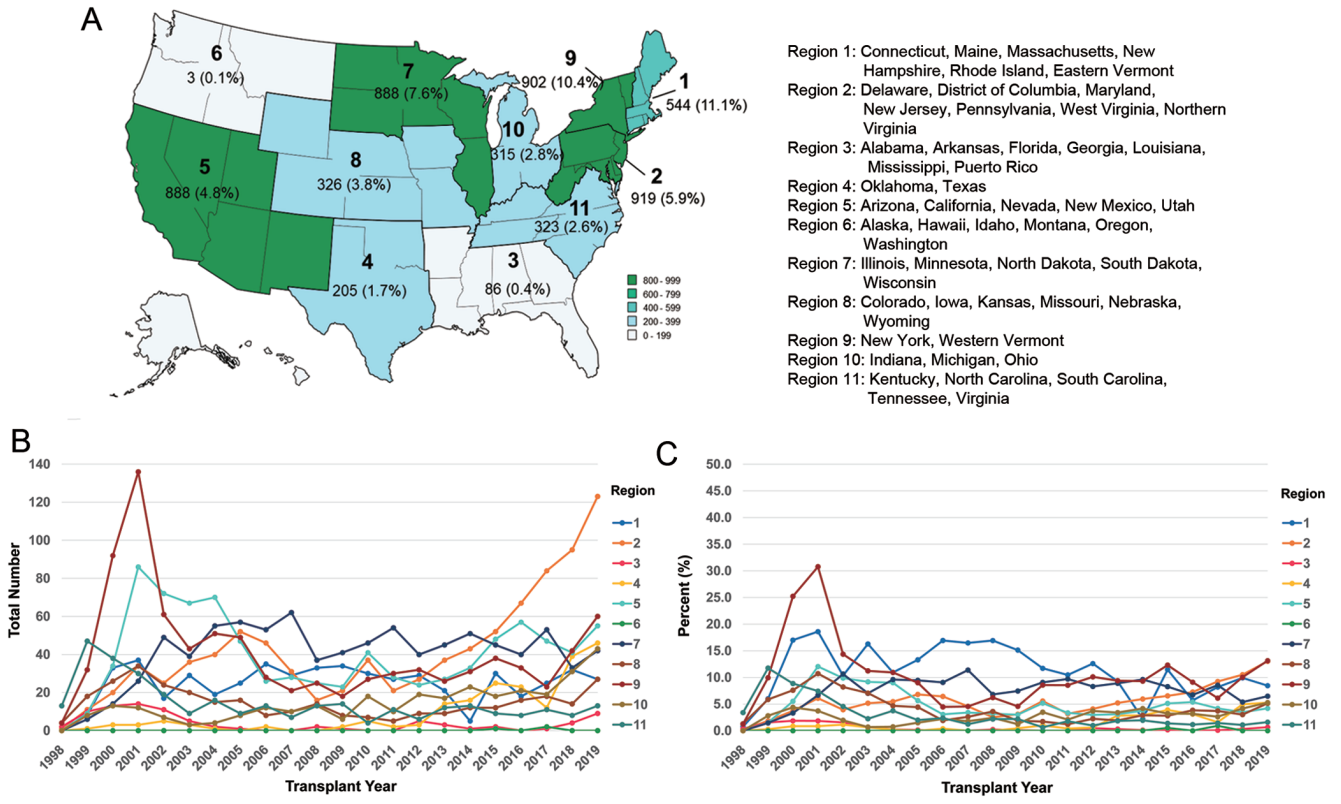

Fig. 2. (A) LDLTs as a percentage of total LTs in each United States OPTN region from 1998 to 2019. (B) Annual trend of adult LDLTs in each OPTN region from 1998 to 2019. (C) Annual trend of adult LDLTs as a percentage of all LTs by OPTN region from 1998 to 2019. LDLT, living donor liver transplant; LT, liver transplant; OPTN, Organ Procurement and Transplantation Network.

Characteristics of LDLT donors

From 2004 through 2019, 3,796 LDLTs were performed in the US (Table 1). The mean donor age was 37.0±10.3 years. The donors were primarily white (82.8%), 52.2% were females, and the mean BMI was 26.3±3.7 kg/m^2. Liver biopsies were performed in 28.3% of donors, with a subset having available data on microvesicular and macrovesicular fat. Evidence of microvesicular fat was present in 11.2% of donors, and 28.6% had evidence of macrovesicular fat. The mean cold ischemia time was 2.0 ± 3.3 h, and 86.2% of the surgeries were right-lobe LDLTs (Table 1).

Table 2 shows the recipient and donor characteristics in era 1 (2004–2011) and era 2 (2012–2019). Patients in era 2 were older than those in era 1 (53.3±12.9 vs. 51.0±12.1 years of age, p<0.0001). HCV was more common in era 1 (33.4%) compared with era 2 (20.4%), NAFLD and ALD were more common in era 2 (19.2% and 14.1%) than in era 1 (5.4% and 8.8%, both p<0.0001). HCC was more common in era 2 (20.4%) than in era 1 (13.4%, p<0.0001). Patients in era 2 had higher MELD scores (16.0±6.2) than those in era 1 (14.7±5.4, p<0.0001). Left lobe donation was more common in era 2 (16.0%) than in era 1 (10.6%, p<0.0001). Donor liver biopsy was less common in era 2 than in era 1 (21.7% and 37.4%, p<0.0001), and microvesicular fat was less common in era 2 (7.4%) than in era 1 (13.8%, p=0.01).

Survival of adult LDLT recipients

Of the 3,796 LDLT recipients between 2004 and 2019, 813 (21.4%) died within a median follow-up of 48 months (Q1=13 months and Q3=101 months) after transplantation (Table 1). Overall, post-LDLT survival was 92% at 1 year, 87% at 5 years, and 70% at 10-years (Fig. 4A). Overall 1-year, 3-year and 5-year post-LT in era 2 were 93.6%, 88.3%, and 84.7%, respectively, compared with 90.6%, 84.6%, and 79.9%, in era 1 (p=0.001; Fig. 4B).

Bivariate analysis identified several differences between survivors and non-survivors (Table 1). Survivors were younger (51.8±12.8 vs. 54.4±11.7 years of age), and less likely to have HCV (23.5% vs. 34.7%), diabetes (20.0% vs. 29.2%), and higher MELD scores 15.6±5.9 vs. 14.7±5.8 (all p<0.0001). A shorter hospital stay was also associated with survival (14.1±16.9 vs. 21.2±29.6 days). Factors that were significantly more common in the non-survivors were the presence of ascites (70.5% vs. 64.3%, p=0.001), hepatic encephalopathy (56.7% vs. 50.4%, p=0.002), and HCC (21.2% vs. 16.4%, p=0.002). In contrast, PSC was more common in survivors (20.2% vs. 12.4%, p<0.0001), and the BMI in both groups was comparable.

Two donor characteristics that were significantly higher in the mortality group at a significance level of p<0.0001 were older donor age (38.4±10.2 vs. 36.6±10.2 years) and previous liver biopsy (34.3% vs. 26.6%; Table 1). The percentage of donors with evidence of micro- or macrovesicular fat was comparable between groups and right vs. left lobe surgery was comparable between groups. The BMI of donors was significantly higher (26.5±3.9 vs. 26.2±3.6 kg/m^2, p=0.02) in non-survivor than in survivor recipients.

Multivariate Cox proportional hazard modeling (Table 3) found that only two variables were independently associated

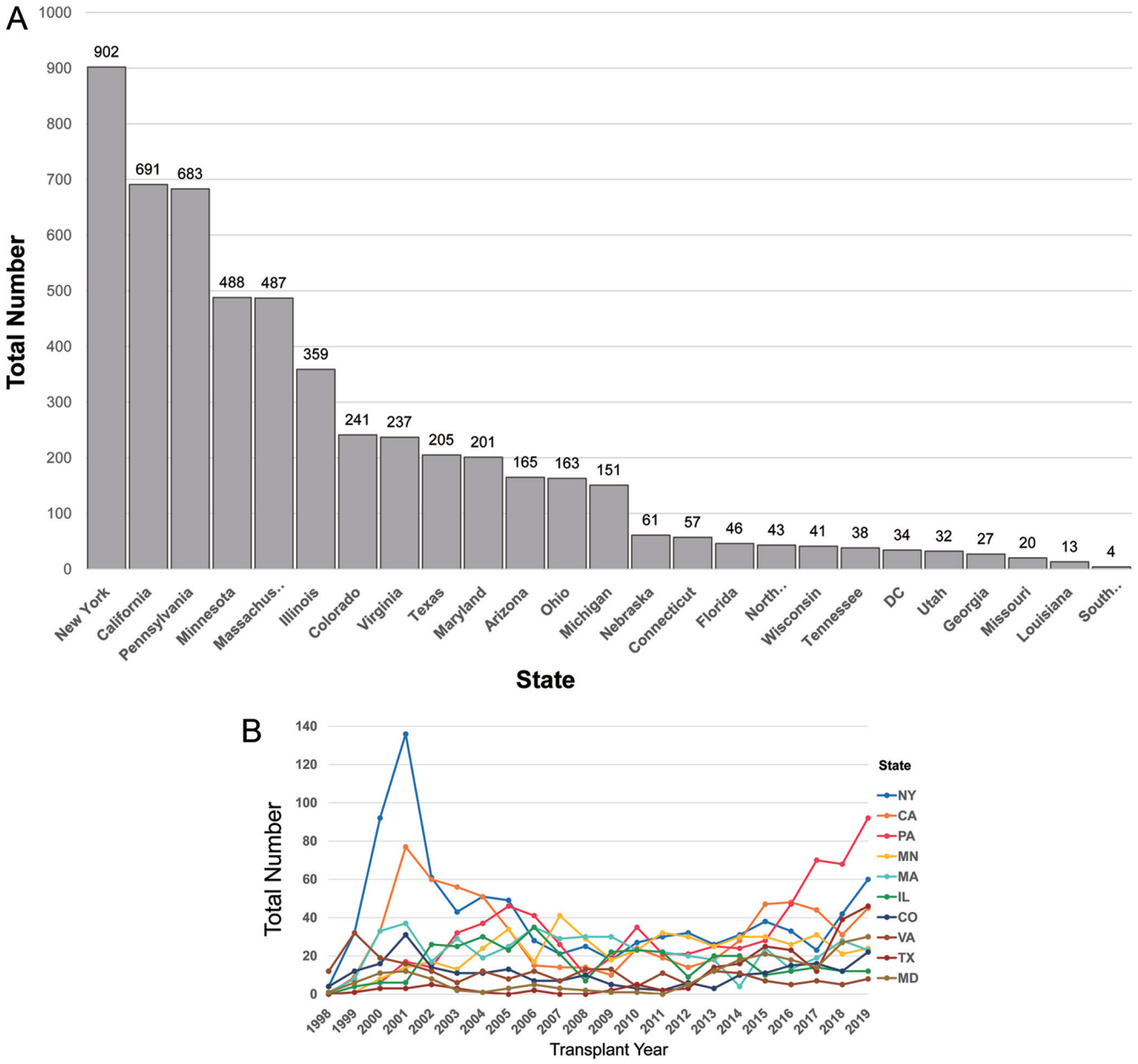

Fig. 3. (A) Adult LDLTs performed between 1998 and 2019 in the 25 with the most volume of transplants. (B) Annual trend in the total number of LDLTs per year in the 10 States with the most volume of transplants. LDLT, living donor liver transplant.

with reduced risk of mortality, PSC [HR=0.75 (95% CI: 0.60–0.93)] and era 2 LDLT [HR=0.67 (95% CI: 0.57–0.80)]. Six variables were independently associated with increased risk of mortality–recipient-related: older age [HR=1.17 (95% CI: 1.09–1.25)], diabetes [HR=1.53 (95% CI: 1.31–1.79)], HCC [HR=1.46 (95% CI 1.23–1.74)], high creatinine [HR=1.13 (95% CI: 1.03–1.23)], and length of hospital stay following LDLT [HR=1.25 (95% CI: 1.20–1.30)]; and donor-related: older age [HR=1.18 (95% CI: 1.10–1.26)].

Discussion

Using a retrospective analysis of the UNOS database over 22 years, we found that the total number of adult LDLTs performed in the US grew rapidly from 1998 to a peak in 2001, after which there was a sharp decline until 2009, when the numbers began to increase again. By 2019, the number of LDLTs performed exceeded those of 2001 at the national level. It has been postulated that the decline observed in 2002 was related to at least three factors: (1) the implementation of the MELD system in 2002, which prioritized waitlist patients with HCC for DDLT, (2) the results of a National Institute of Health Conference on LDLT that highlighted complications associated with the procedure, and (3) a widely publicized donor death following LDLT that occurred in 2002.[15,16] After 2009, the number of adult LDLTs started to increase.

Table 1. Characteristics of LDLT recipients and donors in the US between 2004 and 2019 and their association with mortality

		Total (*n*=3,796)	Mortality		*p*-value
			No (*n*=2,983)	Yes (*n*=813)	
Recipient characteristics					
Age, years		52.4±12.6	51.8±12.8	54.4±11.7	<0.0001
Gender	Female	1,706 (44.9)	1,361 (45.6)	345 (42.4)	0.10
	Male	2,090 (55.1)	1,622 (54.4)	468 (57.6)	
Race	White	3,134 (82.6)	2,447 (82.0)	687 (84.5)	0.11
	Black/African American	122 (3.2)	91 (3.0)	31 (3.8)	
	Hispanic	405 (10.7)	332 (11.1)	73 (9.0)	
	Asian	99 (2.6)	85 (2.8)	14 (1.7)	
	Other	36 (0.9)	28 (0.9)	8 (1.0)	
Blood type	A	1,601 (42.2)	1,259 (42.2)	342 (42.1)	0.90
	AB	62 (1.6)	51 (1.7)	11 (1.3)	
	B	374 (9.9)	292 (9.8)	82 (10.1)	
	O	1,759 (46.3)	1,381 (46.3)	378 (46.5)	
Height, cm		170.2±10.2	170.1±10.2	170.2±10.4	0.95
Weight, kg		78.9±17.5	78.7±17.2	79.2±18.6	0.48
BMI, kg/m^2		27.1±5.1	27.1±5.0	27.2±5.3	0.46
Etiology	HCV	982 (25.9)	700 (23.5)	282 (34.7)	<0.0001
	PSC	704 (18.6)	603 (20.2)	101 (12.4)	
	NAFLD	573 (15.1)	422 (14.1)	86 (10.6)	
	ALD	450 (11.9)	370 (12.4)	80 (9.8)	
	PBC	323 (8.5)	264 (8.8)	59 (7.3)	
	Cryptogenic	178 (4.7)	123 (4.1)	55 (6.8)	
	AIH	150 (4.0)	128 (4.3)	22 (2.7)	
	HBV	89 (2.3)	72 (2.4)	17 (2.1)	
	Other	334 (8.8)	241 (8.1)	93 (11.4)	
	Unknown	78 (2.1)	60 (2.0)	18 (2.2)	
HCC		662 (17.4)	490 (16.4)	172 (21.2)	0.002
Diabetes		834 (22.0)	597 (20.0)	237 (29.2)	<0.0001
Ascites		2,492 (65.6)	1,919 (64.3)	573 (70.5)	0.001
Hepatic encephalopathy		1,966 (51.8)	1,505 (50.4)	461 (56.7)	0.002
Dialysis		28 (0.7)	20 (0.7)	8 (1.0)	0.35
TIPS		314 (8.3)	248 (8.3)	66 (8.1)	0.86
PVT		160 (4.2)	131 (4.4)	29 (3.6)	0.30
SBP		196 (5.2)	146 (4.9)	50 (6.1)	0.15
Life support		10 (0.3)	7 (0.2)	3 (0.4)	0.51
Ventilator support		7 (0.2)	5 (0.2)	2 (0.3)	0.65
Prior abdominal surgery		1,769 (46.6)	1,389 (46.6)	380 (46.7)	0.93
Sodium, mEq/L		136.6±4.3	136.6±4.3	136.3±4.2	0.08
Albumin, g/dL		3.1±0.7	3.1±0.7	3.0±0.7	0.0008
Creatinine, mg/dL		1.1±0.5	1.1±0.4	1.2±0.6	<0.0001
Total bilirubin, mg/dL		4.1±4.8	4.2±4.9	3.6±4.5	0.0002
INR		1.5±0.6	1.5±0.6	1.4±0.7	0.005

(continued)

Table 1. *(continued)*

		Total (*n*=3,796)	Mortality		*p*-value
			No (*n*=2,983)	Yes (*n*=813)	
Laboratory MELD		15.5±5.9	15.6±5.9	14.7±5.8	0.0001
Wait time, days		320.8±552.0	320.8±550.2	320.8±558.7	1.00
Length of hospital stay, days		15.7±20.6	14.1±16.9	21.2±29.6	<0.0001
Duration		5.2±4.4	5.5±4.5	3.8±3.9	<0.0001
Donor characteristics					
Age, years		37.0±10.3	36.6±10.2	38.4±10.2	<0.0001
Gender	Female	1,982 (52.2)	1,560 (52.3)	422 (51.9)	0.84
	Male	1,814 (47.8)	1,423 (47.7)	391 (48.1)	
Race	White	3,143 (82.8)	2,453 (82.2)	690 (84.9)	0.050
	Black/African American	116 (3.1)	85 (2.8)	31 (3.8)	
	Hispanic	389 (10.3)	318 (10.7)	71 (8.7)	
	Asian	90 (2.4)	78 (2.6)	12 (1.5)	
	Other	58 (1.5)	49 (1.6)	9 (1.1)	
Blood type	A	1,048 (27.6)	809 (27.1)	239 (29.4)	0.58
	AB	19 (0.5)	15 (0.5)	4 (0.5)	
	B	211 (5.6)	170 (5.7)	41 (5.0)	
	O	2,518 (66.3)	1,989 (66.7)	529 (65.1)	
Height, cm		171.3±9.9	171.4±9.9	171.2±9.8	0.66
Weight, kg		77.3±14.5	77.2±14.4	77.9±14.9	0.22
BMI, kg/m^2		26.3±3.7	26.2±3.6	26.5±3.9	0.02
BMI ratio		1.0±0.2	1.05±0.22	1.04±0.24	0.42
Cold ischemia time, h		2.0±3.3	2.0±3.2	2.1±3.5	0.39
Lobe[a]	Right	3,184 (86.2)	2,521 (86.1)	663 (86.8)	0.61
	Left	509 (13.8)	408 (13.9)	101 (13.2)	
Liver biopsy		1,074 (28.3)	795 (26.6)	279 (34.3)	<0.0001
Microvesicular fat[b]	≥5	69 (11.2)	50 (10.9)	19 (12.1)	0.67
Macrovesicular fat[c]	≥5	209 (28.6)	155 (28.5)	54 (28.9)	0.92

Data are means ± standard deviation or number (%) as indicated. [a]2.7% were missing, [b]618 patients with a liver biopsy had available data for review, [c]731 patients with a liver biopsy had available data for review. AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalization ratio; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

Analysis by OPTN region showed that regions 2, 5, 7, and 9 performed the most LDLTs. In addition to the changes in MELD that prioritized HCC patients for DDLT in 2002, the total number and percentage of HCC in DDLT recipients significantly increased from 5.3% in 2001 to 21.8% in 2002.[17] The downward trend in adult LDLT in region 9 was temporally linked to the highly publicized case of the death of a living liver donor in New York,[18] which prompted requirements related to donor health insurance and a moratorium on LDLT in the region.[18] Although it is possible that the incident contributed to decreased LDLT rates across the country, the same did not occur after two subsequent donor deaths in the US. Thus, it is likely that the implementation of MELD exception points simultaneously played a role in the initial LDLT decline. Before then, patients having HCC as a primary indication for LT were not given priority on the waiting list, so adult LDLT was occasionally an option for candidates with HCC.

In contrast, region 2 had the highest increase in LDLT. The gap between deceased donors and the number of patients on the waiting list, which reached a new high in 2019, may be driving this trend. Disproportionate expansion of individual LDLT programs has also contributed to this increase. In 2018, the University of Pittsburgh Medical Center (UPMC) led the country as the only center that performed more LDLTs than DDLTs, with 30% of the total number of LT.[7] By adopting the philosophy that LDLT is the "first and best option for most patients with liver disease," the UPMC has significantly reduced mortality on the waitlist and overall waiting time.[7] Of two recent publications on LT trends in the US, Cotter *et al*.[13] reported a 13-fold difference in LDLT numbers between high- and low-performing UNOS regions from 2010 to 2019. The other study did not categorize LT centers by UNOS regions, but identified 85.3% of LDLTs (*n*=1,316; NRD; 2010–2017) were performed in large bed-size centers.[12] For survival analysis, we selected data from the post-MELD era. We found that the 10-year survival of adult LDLT recipients was 70%, indicating a high success rate for the procedure. Risk factors associated with recipient mortality included greater recipient age, diabetes, HCC, higher creatinine levels, prolonged hospitalization, and older donor age.

Table 2. Characteristics of LDLT recipients and their donors in the United States according to time era between 2004 and 2019

		Era		*p*-value
		1 (*n*=1,603)	2 (*n*=2,193)	
Recipient characteristics				
Age, years		51.0±12.1	53.3±12.9	<0.0001
Gender	Female	699 (43.6)	1,007 (45.9)	0.16
	Male	904 (56.4)	1,186 (54.8)	
Race	White	1,346 (84.0)	1,788 (81.5)	0.24
	Black/African American	53 (3.3)	69 (3.2)	
	Hispanic	151 (9.4)	254 (11.6)	
	Asian	40 (2.5)	59 (2.7)	
	Other	13 (0.8)	23 (1.1)	
Height, cm		170.5±10.4	169.9±10.1	0.12
Weight, kg		78.3±17.5	79.2±17.6	0.17
BMI, kg/m^2		26.9±5.0	27.3±5.2	0.007
Etiology	HCV	535 (33.4)	447 (20.4)	<0.0001
	PSC	301 (18.8)	403 (18.4)	
	NAFLD	86 (5.4)	422 (19.2)	
	ALD	141 (8.8)	309 (14.1)	
	PBC	142 (8.9)	181 (8.3)	
	Cryptogenic	94 (5.9)	84 (3.8)	
	AIH	63 (3.9)	87 (4.0)	
	HBV	39 (2.4)	50 (2.3)	
	Other	41 (2.6)	37 (1.7)	
	Unknown	161 (10.0)	173 (7.9)	
HCC		214 (13.4)	448 (20.4)	<0.0001
Diabetes		315 (19.7)	519 (23.7)	0.003
Ascites		1,133 (70.7)	1,359 (62.0)	<0.0001
Hepatic encephalopathy		890 (55.5)	1,076 (49.1)	<0.0001
Dialysis		15 (0.9)	13 (0.6)	0.22
TIPS		116 (7.2)	198 (9.0)	0.05
PVT		37 (2.3)	123 (5.6)	<0.0001
Sodium, mEq/L		136.4±4.2	136.7±4.4	0.03
Albumin, g/dL		3.0±0.7	3.2±0.7	<0.0001
Creatinine, mg/dL		1.2±0.5	1.1±0.4	0.04
Total bilirubin, mg/dL		4.0±5.1	4.2±4.6	0.26
INR		1.4±0.4	1.5±0.7	<0.0001
Laboratory MELD		14.7±5.4	16.0±6.2	<0.0001
Wait time, days		341.0±525.0	306.0±570.5	0.05
Length of hospital stay, days		15.1±17.2	16.0±22.7	<0.20
Donor characteristics				
Age, years		37.3±10.3	36.8±10.2	0.1
Gender	Female	834 (52.0)	1,148 (52.3)	0.85

(continued)

Table 2. *(continued)*

		Era		*p*-value
		1 (*n*=1,603)	**2 (*n*=2,193)**	
	Male	769 (48.0)	1,045 (47.7)	
Race	White	1,362 (85.0)	1,781 (81.2)	0.005
	Black/African American	47 (2.9)	69 (3.2)	
	Hispanic	146 (9.1)	243 (11.1)	
	Asian	35 (2.2)	55 (2.5)	
	Other	13 (0.8)	45 (2.1)	
Height, cm		171.5±9.8	171.2±10.0	0.35
Weight, kg		77.3±14.9	77.3±14.3	0.94
BMI, kg/m^2		26.2±3.8	26.3±3.6	0.38
Cold ischemia time, h		2.3±4.3	1.8±2.3	<0.0001
Lobe[a]	Right	1,341 (89.4)	1,843 (84.0)	<0.0001
	Left	159 (10.6)	350 (16.0)	
Liver biopsy		599 (37.4)	475 (21.7)	<0.0001
Microvesicular fat[b]	≥5	50 (13.8)	19 (7.4)	0.01
Macrovesicular fat[c]	≥5	125 (29.6)	84 (27.2)	0.47

Data are means ± standard deviation or number (%). [a]2.7% were missing, b618 patients with a liver biopsy had available data for review, c731 patients with a liver biopsy had available data for review. Era 1, 2004–2011; Era 2, 2012–2019; AIH, autoimmune hepatitis; ALD, alcoholic liver disease; BMI, body mass index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalization ratio; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.

Cotter *et al*.[13] reported that increased donor and recipient age, diabetes, or need for life support were associated with graft failure. Factors conferring a better prognosis in our study were PSC as the underlying liver disease and a later year receiving the LDLT. The data are consistent with other studies showing that LDLT has good long-term outcomes in patients with PSC.[19] The association of a later year of transplant with improved survival is consistent with studies showing that advancements in surgical techniques and experience with LDLT have improved recipient outcomes and minimized donor risk.[20] Another study found superior survival following LDLT compared to DDLT,[7] even in HCC patients with extended criteria.[8] Some suggest that the benefit of LDLT extends even to patients with high MELD.[9] A study by Yadav *et al*.[10] analyzing the outcome of 1,000 LDLT recipients concluded that pretransplant high MELD scores did not negatively affect the post-transplant outcome. Those data and ours support the call for revisiting LDLT guidelines with the objective to implement policies to expand adult LDLT in the US.[7]

White patients are the predominant recipients of LDLTs (82.6%), followed by Hispanics (10.7%), African American/Blacks (3.2%), and Asians (2.6%). That is an important observation in our study. However, it is not entirely clear why such a significant difference is seen in utilizing a life-saving option, such as LDLT among various races. Others have shown that African Americans/Blacks had a lower odds of becoming a candidate for LT, a longer time for the recommendation to be made, and less likelihood of receiving the

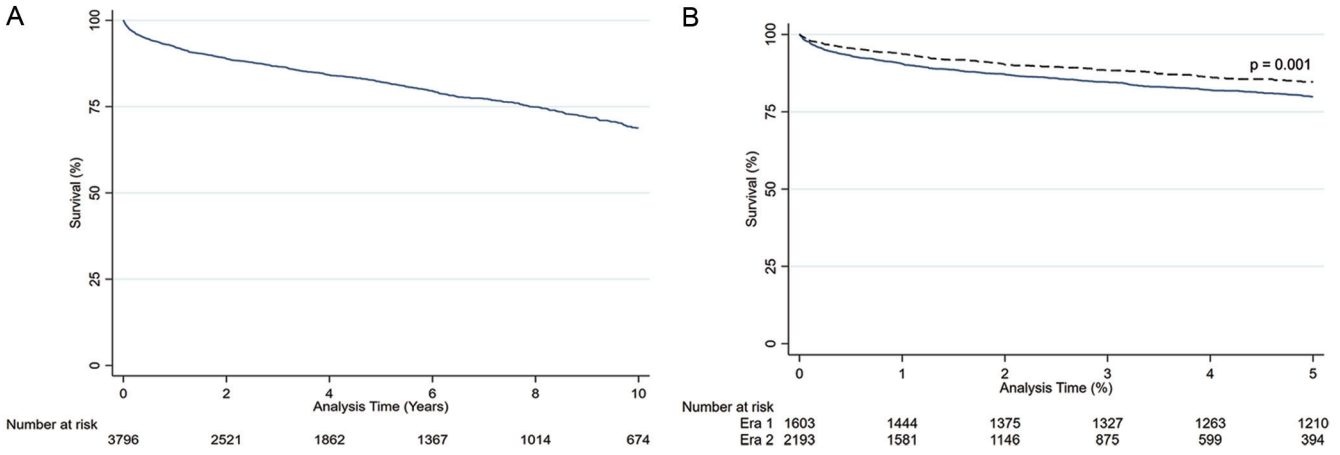

Fig. 4. Survival of LDLT recipients. (A) From 2004 to 2019. (B) In era 1 (2004 to 2011) and era 2 (2012 to 2019). LDLT, living donor liver transplant.

Table 3. Multivariate Cox proportional hazards models for risk of mortality after LDLT. Only the variables significantly affecting mortality are shown

Variable	Hazard ratio (95% CI)	*p*-value
Recipient		
Age (10-year intervals)	1.17 (1.09–1.25)	<0.0001
Diabetes	1.53 (1.31–1.79)	<0.0001
PSC	0.75 (0.60–0.93)	0.01
HCC	1.46 (1.23–1.74)	<0.0001
High creatinine	1.13 (1.03–1.23)	0.007
Era 2	0.67 (0.57–0.80)	<0.0001
Length of hospital stay (25-day interval)	1.25 (1.20–1.30)	<0.0001
Donor		
Age (10-year interval)	1.18 (1.10–1.26)	<0.0001

Variables in the model: Recipient: gender, age, BMI, HCC, HCV, NAFLD, PSC, diabetes, SBP, PVT, TIPS, ascites, hepatic encephalopathy, dialysis, transplant year, cold ischemia time, wait time, creatinine, INR, bilirubin, albumin, serum sodium, MELD, and length of stay; Donor: gender, age, BMI, liver biopsy. Era 1, 2004–2011; Era 2, 2012–2019. Hospital stays of 25-day intervals, and donor and recipient age in 10-year intervals were selected to yield clinically meaningful hazard ratios. A cutoff *p*-value of 0.05 was used to include and exclude variables from the final model. BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus, INR, international normalization ratio; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic shunt.

transplant than White Americans.[21] Further studies need to assess racial disparity and analyze whether minorities have the same access to adult LDLT.

Since 2012 in the US, there has been a decrease in mortality among waitlisted patients, but it still remains unacceptably high.[3] There are only 51.4 DDLTs per 100 waitlist-years in North America.[2] Waitlist dropouts among HCC patients have significantly increased to a cumulative probability of 24% in OPTN regions with long wait times (e.g., regions 1, 5, and 9).[22] Therefore, other valid and life-saving strategies, such as the use of HCV-infected livers and LDLT, among other approaches, must be considered to avoid death on the waiting list.

Other countries have widely adopted the use of LDLT. In many Asian countries, LDLT is the primary form of LT.[23–28] In Japan in 2017, LDLTs accounted for 95% of LTs.[25] However, adult LDLTs in the US accounted for only 5% of the total LTs in 2013.[3] In North America, Canada has the largest and most active LDLT program, accounting for 30% of total LTs.[26] Increases in LDLTs in Canada, Japan, South Korea, Saudi Arabia, and Turkey mean that some transplant programs perform over 200 LDLTs per year.[2,10,23–28] In contrast, in the US in 2016, only 11 centers performed more than 12 LDLTs per year, and only two centers did more than 24 LDLTs per year.[2] In the setting of an ethical risk/benefit profile and financial neutrality for living donors (i.e. no out-of-pocket costs) and donor team preparedness, adult LDLTs in the US may reach levels comparable to other countries which are leading the world in LDLT.[29]

Accordingly, in 2019, the American Society of Transplantation Liver Donor Community of Practice developed Living Donor Crisis Management Plan Talking Points as a step to help living donor programs proactively contemplate donor safety and advocacy and team preparedness at every stage of the donation process.[29] Increasing adult LDLT numbers will be a complex task for the US for multiple reasons, including the healthcare system and the litigiousness of society.[29] The Living Donor Protection Act introduced in March 2021 addresses crucial financial barriers relevant to LDLT in the US, with the potential to increase the donor pool and reduce waiting time to LT.[30]

Despite various challenges, increasing LDLT is a worthy goal. Based on OPTN data, the total number of candidates on the LT waitlist has been growing, with 12,307 candidates in 2019. In addition, in 2019, there were a significant number of deaths (n=1,176) and dropouts because of death/too ill for transplant (n=2,347) on the waitlist (Supplementary Fig. 1A–C). Finally, with the current updated policies, patients listed for transplant with "exception points," particularly HCC, will wait longer on the transplant list. We should consider the importance of LDLT as a life-saving option in these cases.

The strengths of this study are the long timeframe of the analysis, spanning two decades, and the analysis of comprehensive national data. Limitations are those common to any retrospective data analysis, including the inability to distinguish between transplant-related mortality and all-cause mortality and limited granularity of the data, such as the absence of detailed donor information, donor liver weight relevant to recipient body size and details of post-operative outcomes. In addition, because of the dramatic inequity of LDLT distribution across centers, national or regional analysis may obscure some trends.

In summary, LDLT is a safe procedure for recipients and has a 70% probability of 10-year survival. Although regional variability is observed, the number of adult LDLTs in the US has been steadily rising from a low in 2009. However, LDLT still comprises less than 5% of adult LT in the US, with significant regional variability. Life-saving policies to increase the use of LDLT, particularly in regions of high organ demand, need to be implemented.

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Conflict of interest

AB declares activities with Scientific Advisory Boards, Intercept, Primary Investigator for trials for Gilead and CARA. BS has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2016. All other authors have no conflict of interests related to this publication.

Author contributions

Guarantor of the article (BS), concept and design (SAA, AG,

HT, TDS, AB, ZF, MK, DEE, MPC, BS), acquisition of data (BS), statistical analysis and interpretation of data (SAA, HT, BS), and drafting and revision of manuscript (SAA, AG, HT, TDS, AB, ZF, MK, DEE, MPC, BS). All authors approved the final version of the article.

Data sharing statement

As stated in section 2.1, the data reported in this work were supplied by the United Network for Organ Sharing (UNOS) as the contractor for the Organ Procurement and Transplantation Network (OPTN).

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