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ORIGINAL ARTICLE

Variation in adult living donor liver transplantation in the United States: Identifying opportunities for increased utilization

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Abstract

In the United States, living donor liver transplantation (LDLT) is limited to transplant centers with specific experience. However, the impact of recipient characteristics on procedure selection (LDLT vs. deceased donor liver transplant [DDLT]) within these centers has not been described. Transplant registry data for centers that performed ≥1 LDLT in 2002–2019 were analyzed using hierarchal regression modeling to quantify the impact of patient and center factors on the adjusted odds ratio (aOR) of LDLT (vs DDLT). Among 73,681 adult recipients, only 4% underwent LDLT, varying from <1% to >60% of total liver transplants. After risk adjustment, the likelihood of receiving an LDLT rose by 73% in recent years (aOR 1.73 for 2014-2019 vs. 2002-2007) but remained lower for older adults, men, racial and ethnic minorities, and obese patients. LDLT was less commonly used in patients with hepatocellular carcinoma or alcoholic cirrhosis, and more frequently in those with hepatitis C and with lower severity of illness (Model for End-Stage Liver Disease (MELD) score < 15). Patients with public insurance, lower educational achievement, and residence in the Northwest and Southeast had decreased access. While some differences in access to LDLT reflect clinical factors, further exploration into disparities in LDLT utilization based on center practice and socioeconomic determinants of health is needed.

KEYWORDS
access, disparities, liver transplantation, living donation, practice variation

1 | INTRODUCTION

Living donor liver transplant (LDLT) has evolved from a novel, infrequently performed procedure to standard clinical practice, particularly in Asia where access to deceased donor organs remains limited.[1] While the technical complexity of both the donor and recipient LDLT procedures increases the risk of early bile duct and vascular complications when compared to deceased donor liver transplant (DDLT), access to

earlier liver transplant (LT) results in decreased waitlist mortality compared to waiting for DDLT. Furthermore, as experience and technical expertise has grown, recipients of LDLT have equivalent or superior outcomes to recipients of DDLT, as demonstrated in multicenter retrospective and prospective series.[2]

Although DDLT remains the dominant procedure in the United States, the profound shortage of appropriate deceased donor allografts and resulting excessive rate of death on the waiting list have recently led to expanded interest in LDLT. Following the first successful LDLT in 1989, there was rapid adoption of LDLT, which led to a peak of 524 cases in 2001. Subsequently, LDLT utilization declined to 200–300 cases per year in 2002 through 2014, following several reports of donor and recipient complications, including a widely publicized donor death.[3] However, evidence of improved outcomes in international centers (mainly from Asia and Europe), growing clinical expertise, broader sharing of deceased donor allografts leading to increased severity of illness at time of DDLT in many geographic areas have contributed to a rise in US LDLT utilization from 2014 through 2019.[4] Although the primary benefit of LDLT has historically been earlier access to LT, LDLT also expands eligiblity for LT, including for patients with nonhepatocellular malignancies (e.g., metastatic colorectal cancer[5]) who are not allocated exception points under current Organ Procurement and Transplantation Network (OPTN) policy.[6]

Donor and recipient selection for LDLT is based on structured protocols that maximize donor safety and minimize donor and recipient complications. From a medical perspective, living liver donation is restricted to healthy individuals with minimal to no comorbidities and who are at low risk of operative complications or future chronic liver disease. Surgically, inadequate donor remnant liver volume and donor arterial or biliary anatomic variations, which increase donor risk, or complexity of recipient procedure may preclude safe donation and LDLT. Recipient size and severity of illness must be considered, because recipients of partial allografts require an adequate graft-versus-recipient weight ratio (GRWR) to avoid postoperative complications such as small-for-size syndrome.[7] Center experience remains a determinant of donor and recipient outcomes.[8] Consequently, current transplant regulations limit LDLT to selected centers with sufficient volume and experience to safely perform these complex operations.[4,9] Additionally, lack of awareness of LDLT and financial barriers may affect the number of transplant candidates and potential living liver donors who are even considered.[10]

Despite the promise and growth of LDLT, this procedure continues to represent a small proportion of all LT in the United States. In October 2021, the American Society of Transplantation held a consensus conference to identify important barriers to broader expansion of LDLT in the United States, including data gaps, and to make recommendations for impactful and feasible mitigation strategies to overcome these barriers. This analysis is a product of the pre-conference workgroup that aimed to examine national transplant registry data to describe the epidemiology of US LDLT and to identify variation in utilization of LDLT among centers and patient groups to inform strategies to reduce disparities in access.

2 | METHODS

2.1 | Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN, and has been described elsewhere.[11] The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

2.2 | Cohort definition

We included all LT recipients at centers that performed ≥1 adult LDLT from 2002 through 2019. LT recipients at pediatric transplant centers were excluded, irrespective of age. All multiorgan transplants and retransplants were excluded.

2.3 | Exposures and covariates

SRTR data were queried to assess patient demographic and clinical characteristics (severity of illness, primary diagnosis, body mass index [BMI], sex) and social determinants of health (education, race and ethnicity, employment status, insurance) (Table 1). Additional analytic variables included year of transplant and total DDLT volume over the same period of analysis. Geographic areas are defined per UNOS as follows (SDC Figure 1)[12]: Northwest (WA, OR, ID, MT, AK, HI), Southwest (CA, NV, UT, AZ, NM), North Midwest (ND, MN, SD, WY, NE, IA, CO, KS, MO), South Midwest (OK, TX), Great Lakes (WI, IL, IN, MI, OH), Southeast (KY, AR, TN, NC, MS, AL, GA, SC, LA, FL, PR), Mid Atlantic (WV, VA, PA, DC, MD, DE), and Northeast (NJ, NY, CT, RI, MA, VT, NH, ME).

2.4 | Primary outcome

The primary outcome was receipt of LDLT at a center performing both LDLT and DDLT.

2.5 | Statistical analyses

2.5.1 | Unadjusted variation in LDLT

Univariate analyses were performed to identify patient and center characteristics that were correlated with the odds of undergoing an LDLT rather than a DDLT. These univariate analyses were used to define a population of "potentially eligible" LDLT recipients. This cohort

was defined as LT recipients with a weight, age, and allocation Model for End-Stage Liver Disease (MELD) score at transplant $\leq 95^{th}$ percentile of all LDLT recipients. This limited cohort was used to further assess variation in access by center.

2.5.2 | Combined center and case-level modeling

Bi-level hierarchical models were constructed to adjust rates of LDLT among eligible candidates that were adjusted for clustering effects in LDLT utilization. Level 1 comprised recipient factors, and level 2 represented the transplant center. Empirical Bayes estimates provided the adjusted proportion (with 95% confidence intervals [CIs]) of LDLT at a center, incorporating case-mix adjustment from the hierarchical model. A 95% CI for a given center's LDLT proportion that does not include the median national rate of use indicates a practice that is statistically significantly different from expected considering clinical factors in the model.

Heterogeneity in LDLT use was quantified using median odds ratios (MORs). The MOR provides the median of the odds that recipients with identical characteristics will undergo LDLT when two centers are drawn at random (performed for all possible pairs of centers). For example, a MOR of 1.5 means that if centers are selected at random, a recipient with a given set of reference characteristics is, on average, 50% more likely to undergo LDLT at one of the randomly selected centers than at the other.[13] To account for clinical factors that may explain practice variation, the models also included age, BMI, severity of illness (i.e., MELD score), and cause of liver disease. Additional factors, such as assessments of education, insurance, and race and ethnicity, were included when they were significant in the univariate analyses.

The adjusted odds ratio ($_{95\%\,LCL}aOR_{95\%\,UCL}$ [LCL, lower confidence limit; UCL, upper confidence limit]) of receiving an LDLT was estimated for patient factors, geography, and center volume, after accounting for the effect of center differences using the hierarchical model. Data were analyzed using Stata 16, College Station, TX. Hierarchical logistic regression modeling was in Stata using the "xtmelogit" command with center as a random intercept. The MOR was calculated using the "xtmrho" (third-party suite) command.

2.6 | Approval

This analysis was approved by the institutional review board from Saint Louis University.

3 | RESULTS

From 2002 through 2019, there were 4417 adult LDLTs performed at 75 distinct US LT centers. LDLTs represented 4.5% of all 97,099 LTs performed during this period (6.0% of 73,681 LT at centers that performed at least one LDLT). Annual volume of LDLT varied significantly over time (Figure 1). Similarly, the proportion of all LTs performed with living donors has recently increased (2002-2007: 4.6%; 2008-2013: 3.6%; 2014-2019: 4.8%). The proportion of recipients who underwent LDLT varied markedly across LT centers from <1% to >60% of all LTs performed.

3.1 | Recipient characteristics associated with LDLT

Patients undergoing LDLT were significantly different than recipients of DDLT (Table 1). LDLT recipients were younger; compared with recipients aged 18-30 years, patients 31-44 (aOR, $_{.59}.70_{.83}$), 45-49 (aOR, $_{.44}.52_{.61}$), and ≥60 years (aOR, $_{.44}.51_{.61}$) were significantly less likely to receive an LDLT (Figure 2, SDC Table 1). While women (aOR, $_{1.42}1.52_{1.64}$) were more likely to undergo LDLT, patients of non-White race or ethnicity (Black: aOR, $_{.35}.42_{.51}$; Hispanic: aOR, $_{.76}.85_{.96}$; other race: aOR, $_{.41}.49_{.59}$) were less likely to undergo LDLT. LDLT use declined substantially with increases in BMI. For example, patients with a BMI > 40 (kg/m^2) were 72% less likely (aOR, $_{.21}.28_{.38}$) to receive an LDLT compared to patients with a BMI of 18.5-24.9 kg/m^2. Compared to patients without functional limitations, LDLT was less commonly performed for patients with reduced functional status (recipient requires some assistance: aOR, $_{.72}.79_{.86}$; recipient requires total assistance: aOR, $_{.52}.58_{.65}$).

There was little change in the characteristics of the living liver donor population across the study period (Table 2). Over time, donor age, gender distribution, and racial composition were similar. There was a nonsignificant increase in mean BMI. Donor-to-recipient weight ratio remained at 1.

Likelihood of receiving an LDLT was inversely correlated with severity of illness, being higher for patients with MELD score < 15 and decreasing with MELD score > 20. LDLT utilization varied markedly among patients with different causes of liver disease, even after controlling for severity of illness. Compared to patients with end-stage liver disease due to hepatitis C infection, patients with hepatocellular carcinoma (HCC), alcohol-associated liver disease, or unknown etiology of liver disease were less likely to undergo LDLT. Conversely, patients with cholestatic liver disease were nearly twice as likely to undergo LDLT (aOR, $_{1.70}1.91_{2.13}$). Finally, after controlling for BMI, those with nonalcoholic steatohepatitis (NASH) were 50% more likely (aOR, $_{1.32}1.52_{1.76}$) to have an LDLT.

Social determinants appeared to have a significant association with access to LDLT. Patients who were working at the time of transplant were 10% more likely to have an LDLT (aOR, $_{1.02}1.12_{1.23}$). When compared to LT recipients with at least a college education, patients with grade school/high school only were 22% less likely (aOR, $_{.72}.78_{.84}$) and those with unknown education level were 17% less likely (aOR, $_{.74}.83_{.94}$) to receive an LDLT. Finally, patients with public insurance as their primary source of coverage were half as likely to receive an LDLT (Medicaid: aOR, $_{.45}.51_{.59}$; Medicare: aOR, $_{.59}.65_{.71}$) than recipients with private insurance.

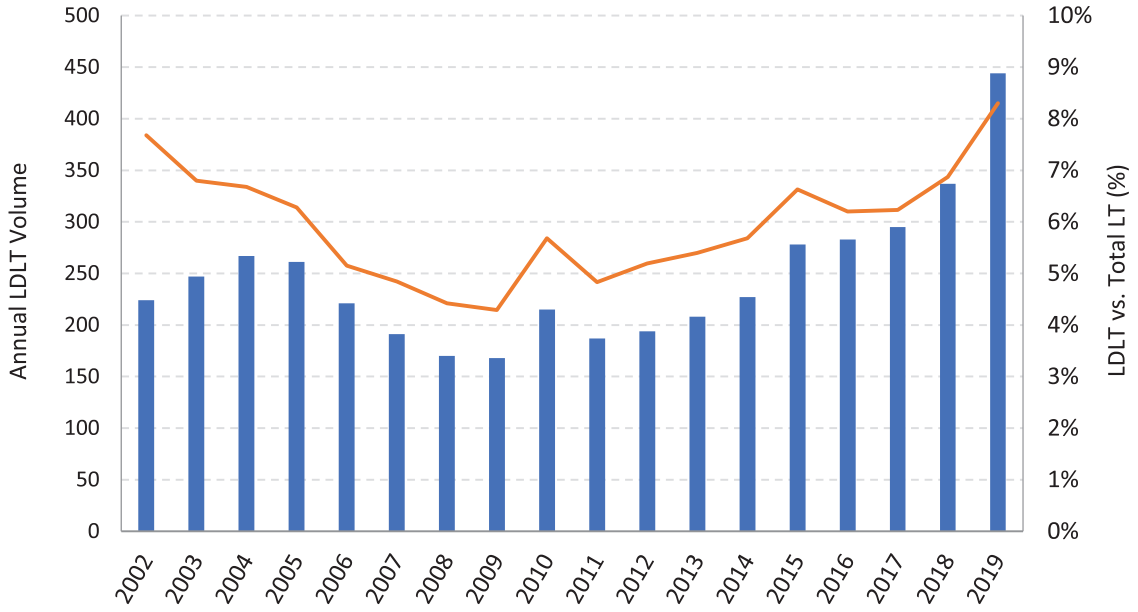

FIGURE 1 Living donor liver transplants performed annually in the United States (2002–2019). Left axis: Annual LDLT volume (bars). Right axis: LDLT as percentage of total LT in the year (orange line).

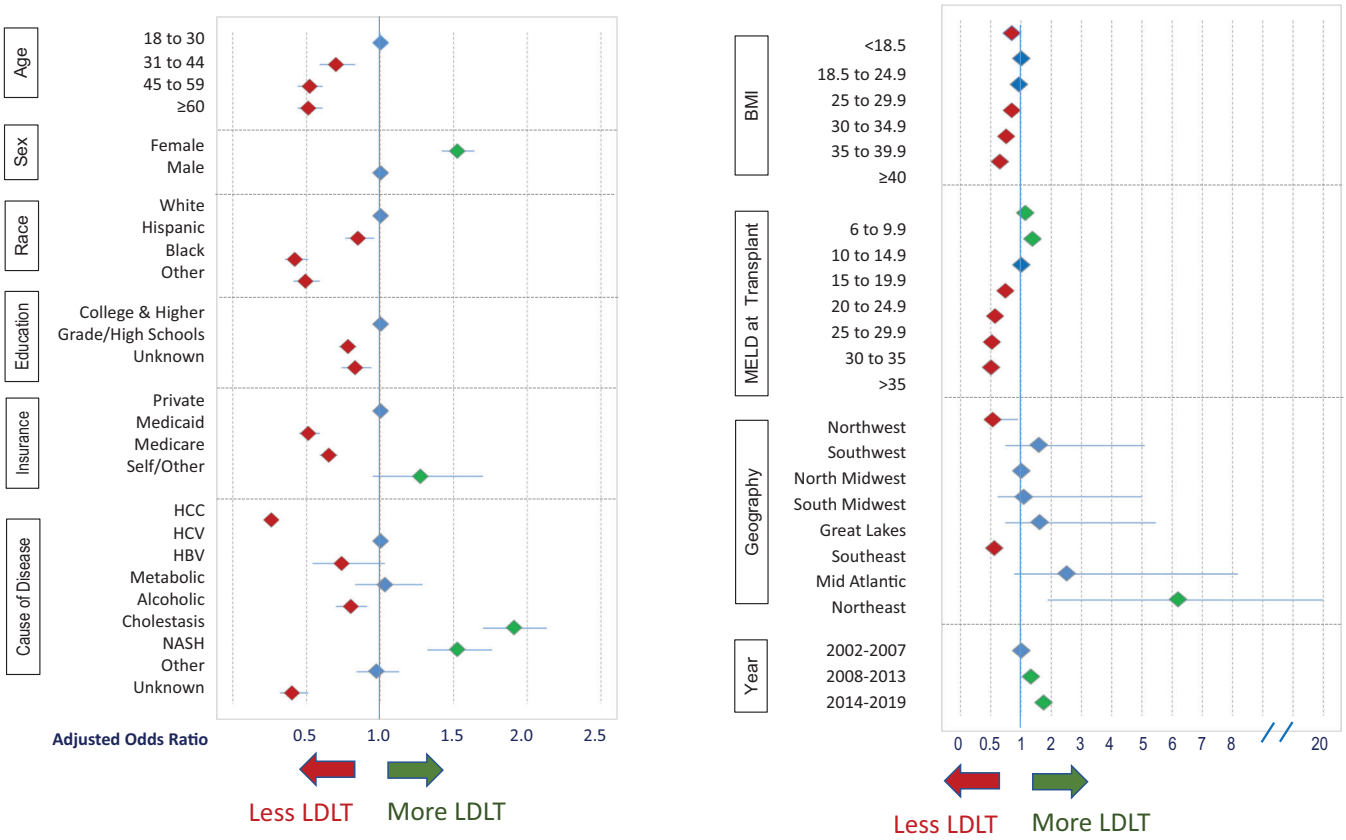

FIGURE 2 Recipient characteristics associated with receipt of a living donor versus deceased donor liver transplant in multivariable adjusted analysis. BMI, body mass index; HBV, hepatitis B, virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LDLT, living donor liver transplant; MELD, Model for End-stage Liver Disease (score); NASH, nonalcoholic steatohepatitis; Q, quartile.

TABLE 1 Characteristics of LDLT and DDLT recipients ($N = 73681$), among centers that performed LDLT in 2002–2019.

Characteristic	LDLT ($n = 4417$) *n* (col %)	DDLT ($n = 69264$) *n* (col %)
Recipient age, years		
18–30	360 (8.2)	2855 (4.1)
31–44	707 (16)	8912 (12.9)
45–59	2088 (47.3)	36859 (53.2)
≥60	1262 (28.6)	20638 (29.8)
Recipient sex		
Men	2456 (55.6)	46291 (66.8)
Women	1961 (44.4)	22973 (33.2)
Recipient race and ethnicity		
Black	156 (3.5)	6442 (9.3)
Hispanic	487 (11)	9679 (14)
White	3618 (81.9)	48880 (70.6)
Other	156 (3.5)	4263 (6.2)
Recipient BMI		
<18.5	97 (2.2)	1360 (2)
18.5–24.9	1645 (37.2)	19245 (27.8)
25–29.9	1542 (34.9)	23519 (34)
30–34.9	749 (17)	14773 (21.3)
35–39.9	235 (5.3)	6381 (9.2)
≥40	49 (1.1)	2737 (4)
Unknown	100 (2.3)	1249 (1.8)
Recipient cause of ESLD		
Hepatocellular carcinoma	662 (15)	19921 (28.8)
Hepatitis C virus	838 (19)	14715 (21.2)
Hepatitis B virus	49 (1.1)	1490 (2.2)
Metabolic liver disease	130 (2.9)	2018 (2.9)
Alcoholic liver disease	468 (10.6)	10120 (14.6)
Cholestatic liver disease	1408 (31.9)	8215 (11.9)
NASH	436 (9.9)	4988 (7.2)
Other	331 (7.5)	5882 (8.5)
Unknown	95 (2.2)	1915 (2.8)
Recipient lab MELD at transplant		
6–9.9	795 (18)	9280 (13.4)
10–14.9	1558 (35.3)	13180 (19)
15–19.9	1291 (29.2)	13318 (19.2)
20–24.9	571 (12.9)	10427 (15.1)
25–29.9	146 (3.3)	8416 (12.2)
30–35	43 (1)	7908 (11.4)
>35	13 (.3)	6735 (9.7)
Recipient education level		
College & Higher	2318 (52.5)	30954 (44.7)
Grade/High School	1458 (33)	29441 (42.5)
Unknown	641 (14.5)	8869 (12.8)
Recipient employment status		
Working	1091 (24.7)	10256 (14.8)
Not working	2635 (59.7)	49709 (71.8)
Unknown	691 (15.6)	9299 (13.4)
Recipient functional status		
Activities with no assistance	2474 (56)	25504 (36.8)
Activities with some assistance	1097 (24.8)	16504 (23.8)
Activities with total assistance	600 (13.6)	23237 (33.6)
Unknown	246 (5.6)	4019 (5.8)
Recipient primary source of payment		
Private	3159 (71.5)	40352 (58.3)
Medicaid	350 (7.9)	10094 (14.6)
Medicare	836 (18.9)	17961 (25.9)
Self/Other	72 (1.6)	857 (1.2)
Recipient geographic area		
Northwest	3 (.1)	1585 (2.3)
Southwest	735 (16.6)	11911 (17.2)
North Midwest	697 (15.8)	6563 (9.5)
South Midwest	197 (4.5)	4584 (6.6)
Great Lakes	639 (14.5)	10399 (15)
Southeast	80 (1.8)	14798 (21.4)
Mid Atlantic	1002 (22.7)	10260 (14.8)
Northeast	1064 (24.1)	9164 (13.2)
Cohort		
2002–2007	1411 (31.9)	21530 (31.1)
2008–2013	1142 (25.9)	21863 (31.6)
2014–2019	1864 (42.2)	25871 (37.4)
Center average annual DDLT volume		
Q1 (0–30)	241 (5.5)	4312 (6.2)
Q2 (31–50)	336 (7.6)	11297 (16.3)
Q3 (51–75)	1422 (32.2)	18905 (27.3)
Q4 (>75)	2418 (54.7)	34750 (50.2)

Note: Analysis limited to centers that performed LDLT.
Abbreviations: DDLT, deceased donor liver transplant; ESLD, end-stage liver disease; LDLT, living donor liver transplant; MELD, Model for End-stage Liver Disease (score); NASH, nonalcoholic steatohepatitis; Q, quartile.

3.2 | Transplant center characteristics associated with LDLT utilization

The use of LDLT varied significantly by location of the transplant center. Compared with LT recipients in the upper Midwest, LDLT rates were lowest among recipients in the Northwest (aOR, $_{.01}.03_{.43}$) and Southeast (aOR, $_{.04}.13_{.41}$) and highest in the Northeast (aOR, $_{1.33}3.93_{11.63}$). Patients who underwent transplant at high-volume centers (>75 DDLTs annually) were significantly more likely to receive an

TABLE 2 Demographic and clinical characteristics of US living liver donors from 2002 to 2019.

Donor characteristic	LDLT overall ($n = 4417$)	2002–2007 ($n = 1411$)	2008–2013 ($n = 1142$)	2014–2019 ($n = 1864$)
Age, years				
5th percentile	21.0	21.0	21.0	22.0
Median	37.0	38.0	36.0	36.0
95th percentile	55.0	54.0	55.0	55.0
Sex (%)				
Men	49.0	51.2	48.9	47.4
Women	51.0	48.8	51.1	52.6
Race and Ethnicity (%)				
White	82.1	83.0	84.1	80.1
Black	3.6	3.3	4.1	3.5
Hispanic	11.0	11.1	8.3	12.6
Other	3.4	2.7	3.5	3.8
BMI				
5th percentile	20.4	20.5	20.3	20.5
Median	26.0	25.9	25.7	26.4
95th percentile	32.6	32.9	32.4	32.6
Weight Rate (Donor/Recipient)				
5th percentile	.7	.7	.7	.7
Median	1.0	1.0	1.0	1.0
95th percentile	1.6	1.6	1.5	1.6

Abbreviation: BMI, body mass index.

LDLT (aOR, $_{1.31}3.13_{7.50}$) than those in lower volume centers. However, there was no correlation between the median allocation MELD or calculated MELD score at transplant center and the use of LDLT (P = not significant).

3.3 | Risk-adjusted proportion of LDLTs among active centers

After bi-level adjustment to account for differences in recipient population and center characteristics, LDLT practice remained significantly different across the United States (Figure 3, SDC Table 2). Among 75 LDLT centers assessed, 22 centers (29.3%) performed significantly more LDLTs than would be expected based on recipients' characteristics. Conversely, 22 centers (29.3%) were significantly below expected rates. The MOR was 2.86, demonstrating a nearly three-fold variation in the likelihood of receiving an LDLT for a patient with similar clinical characteristics in centers performing LDLTs.

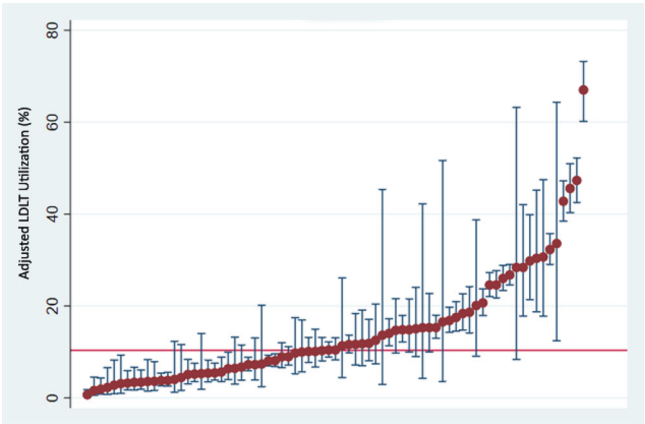

FIGURE 3 Proportion of centers' liver transplant volume performed using living donors, adjusted for recipient characteristics. LDLT, living donor liver transplant.

3.4 | Variation in use of LDLT in "potentially eligible" candidates

During the study period, 30,818 LT candidates were below the 95th percentile for age, weight, and MELD score of all LDLT liver transplants. Among these potentially eligible patients, 3089 received LDLTs (10.0%). While 40.0% of centers performed LDLT in <5% of all potentially eligible patients, 14 centers (18.7%) performed LDLT for at least 20% of potentially eligible patients (Figure 4). If all centers performed LDLT for 25% of eligible patients, an additional 4615 LDLTs could have been performed from 2002 through 2019, allowing deceased donor

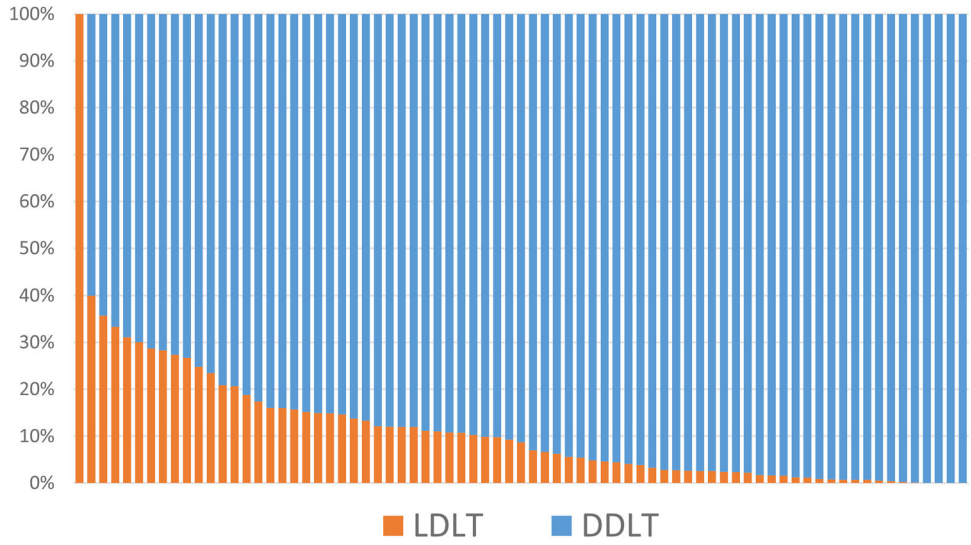

FIGURE 4 Proportion of liver transplants performed using living donors among "potentially eligible" recipients across centers. The "potentially eligible" cohort was defined as liver transplant recipients with a weight, age, and allocation Model-for End-stage Liver Disease score at transplant ≤95th percentile of all living donor liver transplants (LDLTs). DDLT, deceased donor liver transplant. Each bar represents a center.

organs to be redirected to waitlisted patients who do not meet current LDLT eligibility criteria.

4 | DISCUSSION

LDLT is underutilized in the United States. In this epidemiologic analysis, LDLTs were performed at half of 151 LT programs and LDLTs constitute only 4.4% of the total US LT volume, despite the ongoing shortage of transplantable organs and persistent death on the waiting list. Importantly, at some LT centers, the proportion of LDLTs performed is substantially higher than expected given recipient characteristics, suggesting the potential to increase utilization nationally. Access to LDLT is not uniform, with significant differences in access attributed to both biological (e.g., weight, MELD score, cause of ESLD, age, race and ethnicity) and socioeconomic (e.g., insurance, education) characteristics. Patients with conditions associated with significant morbidity but low MELD scores (e.g., cholestatic liver disease), were more often recipients of LDLT. Even after restricting the analysis to LT in patients who were comparable to potentially eligible recipients (<95th percentile for age, BMI, and MELD score for all LDLTs), only 10% of recipients underwent LDLT. If all LDLT centers increased the proportion of the potentially eligible patients undergoing transplant with LDLT to 25%, nearly 5000 additional LTs could have been performed over the study period.

By its nature, the use of a partial allograft in LDLT limits the size of potential recipients given the size of the donor allograft. In general, GRWRs <0.8% are not widely used in the United States as they have been associated with higher rates of graft failure due to small-for-size syndrome.[7,14,15] The requirement for sufficient hepatic mass likely explains the observation that higher BMI, or greater recipient weight, reduces access to LDLT. Obese patients were 70% less likely to receive an LDLT, controlling for other factors.[16,17] Unfortunately, given the obesity epidemic, and the increasing prevalence of NASH as an indication for LT, the proportion of patients who are eligible for LDLT may decrease over time.[18–20] The association of weight and access to LDLT may also contribute to the improved access that women have for LDLT, which differs significantly from DDLT.[21] Women tend to have lower MELD scores (given impact of serum creatinine on MELD), which leads to lower MELD-with-sodium scores and less abdominal domain to accept large DDLT grafts, resulting in reduced access to DDLT and excess waitlist mortality compared with men with similar severity of illness.[21,22] Hence, access to LDLT is a vitally important option to improve access to LT for women, as demonstrated in a recent retrospective analysis at the University of Toronto.[23] Our analysis confirms that women are more likely to receive an LDLT in the United States, after adjustment for age, weight, and severity of liver disease. This could reflect the difficulty of finding appropriate living donors for men due to the greater graft weight required for an acceptable GRWR, as well as the decision to perform LDLT for women with cholestatic diseases who are inadequately prioritized for DDLT by the current MELD scoring formulation.

While all LT is more complex in older patients, LDLT may pose additional risk. The right hepatic artery needs to be healthy in LDLT recipients, and older age, unfortunately, leads to a greater burden of atherosclerotic disease precluding LDLT.[24] Other age-related factors include concern about physiologic reserve, coronary artery disease, and frailty.[25] This analysis confirms other multicenter data from the A2ALL group documenting limited utilization of LDLT in older patients.[16] In the A2ALL analysis, lack of acceptable donors was raised as a possible issue, given restrictions on the age of eligible donors.[26] However, recent data suggest that older patients can successfully

undergo LDLT, and increased utilization may reduce waitlist death by allowing older patients to undergo transplant with lower severity of illness and decreased risk of sarcopenia.[27]

Etiology and severity of ESLD have been clearly associated with reduced utilization of LDLT in the United States. Patients with high MELD scores appear to have less physiologic reserve, less ability to survive early allograft dysfunction from a partial graft, and a higher rate of perioperative complications.[28] Higher MELD scores also increase priority for DDLT, decreasing the need for LDLT. Accordingly, many LT centers avoid LDLT in candidates with high MELD scores, despite a recent report demonstrating successful LDLTs in patients with decompensated cirrhosis.[29–31] Our national analysis further demonstrated that rates of LDLT were correlated with etiology of ESLD. Cholestatic liver disease patients are highly represented among LDLT, presumably due to their difficulty obtaining DDLT with the current MELD-based allocation.[32] Additionally, compared to patients with end-stage liver disease due to hepatitis C virus, fewer patients with HCC, hepatitis B virus-related liver disease, and alcoholic liver disease underwent LDLT.[33,34] HCC, especially beyond conventional criteria such as Milan criteria, has become one of the leading diagnoses among recipients of LDLT in several countries outside of the United States.[35] LDLT also has the potential to expand the oncologic indications for LT for patients with nonhepatocellular malignancies ("transplant oncology"),[36] who usually have quite limited access to DDLT in the United States. Our study indicates this may be an area for LDLT to expand in the United States, as centers establish protocols and care pathways that will allow for responsible expansion in this domain of emerging indications supported by international data and initial North American experience.

While higher age, weight, and severity of illness have biologic rationales for lower utilization of LDLT, this analysis demonstrates the impact of social determinants of health, including insurance status, educational achievement, and employment, on medically risk-adjusted LDLT access. Our data suggested that the lack of employment, lower educational level, and public insurance (compared to private) appeared to reduce LDLT utilization among patients who receive LT. Prior studies in the United States[37] and other countries[38] have demonstrated adverse financial and psychosocial outcomes for some living donors, which could reduce access for recipients of lower socioeconomic status with similar potential donors. The significant observed reduction in access to LDLT for publicly-insured patients may reflect the impact of socioeconomic factors among potential donors in patients' social networks who often face similar economic barriers. Despite access to the National Living Donor Assistance Center (NLDAC) in the United States and other donor assistance programs that provide some support, many donors continue to report a significant financial burden from donation.[39] In addition, potential donors with lower socioeconomic status have higher rates of medical comorbidities that preclude donation (e.g., diabetes, obesity, coronary artery disease, NASH).[40] Our present data also demonstrate that Black patients were nearly 60% less likely to receive an LDLT, even after adjustment for age, weight, severity of illness, and diagnosis, which is consistent with prior reports.[41,42] These data are consistent with national data on LT in general, demonstrating that Black patients are less likely to be referred, complete evaluation, and undergo LT than White patients.[43]

Recent innovations have addressed several of the perceived barriers to LDLT, which may allow expanded access. Portal venous flow modulation, in combination with careful calculation of required allograft volume to avoid small-for-size syndrome while decreasing the minimal GRWR, may help to address disparity based on weight.[44] ABO-incompatible LDLT using rituximab and plasma exchange to expand the living donor pool allows transplantation from medically and surgically appropriate donors who were previously declined.[45] Paired donor exchanges have been performed to overcome ABO or human leukocyte antigen incompatibilities, similar to national kidney paired donation programs.[46] Finally, the development of minimally invasive approaches for donor hepatectomy may allow earlier return to work and responsibilities, to reduce financial barriers to LDLT.[47]

Among the most significant determinants of LDLT access in this analysis were not the patient characteristics noted above, but rather center practices and commitment to expanding LDLT access. Among centers with established programs (at least one LDLT performed), less than 5% of LTs were from living donors. Furthermore, for candidates who met the potentially eligible criteria defined in this study (age <66 years, MELD score <22, weight <101 kg), only 10% of eligible candidates received an LDLT. Because many LDLT-eligible patients received DDLTs, expanded access to LDLT would allow deceased donor allografts to be redirected to patients whose clinical characteristics are believed to preclude safe partial transplant (e.g., higher MELD patients). The observed variation in risk-adjusted use of LDLT should allow the identification of high-performing centers. Best practices from high-performing centers (above risk-adjusted proportion of LDLT) should be identified and communicated to the transplant community, which was, in part, the mission of the AST LDLT Consensus Conference effort.

This analysis has several important limitations. First, these data are limited to recipients of an LT and do not consider potential LT candidates who were not offered LT. Some of these patients may have "dropped out" while waitlisted due to disease progression. Similarly, occasional patients may have had a living donor approved but received a DDLT prior to moving forward to LDLT. Second, the analysis preceded recent changes in the liver allocation system, including the reduction of priority for patients with HCC. This policy change may affect the observed geographic disparities in LDLT, as areas with high MELD scores are now able to draw more organs, decreasing the need for LDLT; However, MELD score at transplant is not well correlated to LDLT utilization, diminishing the impact of this change. While historically patients with HCC were less likely to receive LDLTs, it is possible that reduction in DDLT allocation priority may lead to changes in this practice pattern. Additional outcomes data are needed, although outcomes for LDLT in patients with HCC appear to often be quite good.[48] Third, anatomic concerns affecting the candidacy of LDLT (e.g., poor transjugular intrahepatic portocaval shunt placement, portal vein thrombosis, etc) were not assessed in the analysis of LDLT versus DDLT utilization in transplant candidates. Fourth, the recent increase in the proportion of candidates with NASH and the marked

reduction in patients with hepatitis C virus–related liver disease may affect LDLT utilization rates in the future.[18–20] However, in the analysis of potentially eligible candidates, we addressed patients whose weight and severity of disease would be expected to allow LDLT using current approaches, and demonstrated persistent and significant differences between centers. While we define characteristics of actual donors, it is not possible to determine what portion of the potential donors this represents. Efforts such as the SRTR Living Donor Collective may bring much needed information on US donor candidates,[49] as well as data on other factors such as anatomic complexity. We also do not study donor outcomes, which have been reported in large US and international studies.[50]

In conclusion, LDLT utilization is increasing nationally in the United States. We note with concern that patients with low socioeconomic status continue to have significantly reduced access to LDLT. Additionally, even after accounting for recipient characteristics, LDLT center practice was still immensely variable, with some centers performing almost no LDLTs and others having performing LDLT in up to 60% of LT recipients. Despite improving LDLT outcomes and increasing waitlist mortality risk, only a small minority of apparently eligible recipients seem to receive this option to undergo transplant sooner with a high-quality organ. Further outreach is needed to identify and support donors, particularly for members of at-risk populations, which may help to reduce disparity in access to LDLT for racial and ethnic minority populations and those with low socioeconomic status.

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CONFLICTS OF INTEREST

Krista L. Lentine and David A. Axelrod are senior scientists for the SRTR. Dr. Lentine is Scientific Director of the SRTR Living Donor Collective, chair of the AST Living Donor Community of Practice, member of the American Society of Nephrology Policy and Advocacy Committee, member of the National Living Donor Assistance Center Advisory Group, and member of the National Kidney Foundation Transplant Advisory Committee.

DATA AVAILABILITY STATEMENT

SRTR data are publicly available.

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REFERENCES

1. Rela M, Reddy MS. Living donor liver transplant (LDLT) is the way forward in Asia. *Hepatol Int*. 2017;11:148-151.
2. Abu-Gazala S, Olthoff KM. Status of adult living donor liver transplantation in the United States: results from the adult-to-adult living donor liver transplantation cohort study. *Gastroenterol Clin North Am*. 2018;47:297-311.
3. Miller C, Florman S, Kim-Schluger L, et al. Fulminant and fatal gas gangrene of the stomach in a healthy live liver donor. *Liver Transpl*. 2004;10:1315-1319.
4. Cotter TG, Minhem M, Wang J, et al. Living donor liver transplantation in the United States: evolution of frequency, outcomes, center volumes, and factors associated with outcomes. *Liver Transpl*. 2021;27:1019-1031.
5. Simoneau E, D'Angelica M, Halazun KJ. Liver transplantation for colorectal liver metastasis. *Curr Opin Organ Transplant*. 2019;24:175-181.
6. Lunsford KE, Javle M, Heyne K, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol*. 2018;3:337-348.
7. Kiuchi T, Kasahara M, Uryuhara K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation*. 1999;67:321-327.
8. Olthoff KM, Abecassis MM, Emond JC, et al. Outcomes of adult living donor liver transplantation: comparison of the adult-to-adult living donor liver transplantation cohort study and the national experience. *Liver Transpl*. 2011;17:789-797.
9. Li C, Mi K, Wen T, et al. A learning curve for living donor liver transplantation. *Dig Liver Dis*. 2012;44:597-602.
10. Nephew LD, Serper M. Racial, gender, and socioeconomic disparities in liver transplantation. *Liver Transpl*. 2021;27:900-912.
11. Leppke S, Leighton T, Zaun D, et al. Scientific registry of transplant recipients: collecting, analyzing, and reporting data on transplantation in the United States. *Transplant Rev (Orlando)*. 2013;27:50-56.

12. United Network for Organ Sharing (UNOS). COVID-19 and solid organ transplant. Accessed: 5/30/2021. https://unos.org/covid/
13. Merlo J, Chaix B, Ohlsson H, et al. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health*. 2006;60:290-297.
14. Tuttle-Newhall JE, Collins BH, Desai DM, Kuo PC, Heneghan MA. The current status of living donor liver transplantation. *Curr Probl Surg*. 2005;42:144-183.
15. Feng Y, Han Z, Wang X, Chen H, Li Y. Association of graft-to-recipient weight ratio with the prognosis following liver transplantation: a meta-analysis. *J Gastrointest Surg*. 2020;24:1869-1879.
16. Trotter JF, Wisniewski KA, Terrault NA, et al. Outcomes of donor evaluation in adult-to-adult living donor liver transplantation. *Hepatology*. 2007;46:1476-1484.
17. Yamashiki N, Sugawara Y, Tamura S, et al. Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. *Liver Transpl*. 2006;12:1077-1083.
18. Noureddin M, Vipani A, Bresee C, et al. Leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol*. 2018;113:1649-1659.
19. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547-555.
20. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology*. 2017;152:1090-1099 e1.
21. Kim WR, Mannalithara A, Heimbach JK, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. *Gastroenterology*. 2021;161(6):1887-1895 e4.
22. Wahid NA, Rosenblatt R, Brown RS. A review of the current state of liver transplantation disparities. *Liver Transpl*. 2021;27:434-443.
23. Karnam RS, Chen S, Xu W, et al. Sex disparity in liver transplant and access to living donation. *JAMA Surg*. 2021;156:1010-1017.
24. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*. 2012;111:245-259.
25. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. *J Hepatol*. 2019;70:745-758.
26. Ryu S, Yoon SC, Hong KE, Kim JM. Psychosocial issues related to donor's decision-making in living donor liver transplantation. *Ann Transplant*. 2019;24:576-583.
27. Hakeem AR, Fathima R, Padmanaban H, et al. Propensity score-matched analysis of posttransplant outcomes in living donor liver transplantation for older adult recipients. *Liver Transpl*. 2021;27:1273-1282.
28. Ikegami T, Imai D, Wang H, et al. D-MELD as a predictor of early graft mortality in adult-to-adult living-donor liver transplantation. *Transplantation*. 2014;97:457-462.
29. Humar A, Ganesh S, Jorgensen D, et al. Adult living donor versus deceased donor liver transplant (LDLT versus DDLT) at a single center: time to change our paradigm for liver transplant. *Ann Surg*. 2019;270:444-451.
30. Yadav SK, Saraf N, Saigal S, et al. High MELD score does not adversely affect outcome of living donor liver transplantation: experience in 1000 recipients. *Clin Transplant*. 2017:31.
31. Selzner M, Kashfi A, Cattral MS, et al. Live donor liver transplantation in high MELD score recipients. *Ann Surg*. 2010;251:153-157.
32. Khungar V, Goldberg DS. Liver transplantation for cholestatic liver diseases in adults. *Clin Liver Dis*. 2016;20:191-203.
33. Lucey MR. Liver transplantation for alcoholic liver disease. *Nat Rev Gastroenterol Hepatol*. 2014;11:300-307.
34. Singhvi A, Welch AN, Levitsky J, Singhvi D, Gordon EJ. Ethical considerations of transplantation and living donation for patients with alcoholic liver diseases. *AMA J Ethics*. 2016;18:163-173.
35. Goldaracena N, Gorgen A, Doyle A, et al. Live donor liver transplantation for patients with hepatocellular carcinoma offers increased survival vs. deceased donation. *J Hepatol*. 2019;70:666-6673.
36. Sapisochin G, Hibi T, Toso C, et al. Transplant oncology in primary and metastatic liver tumors: principles, evidence, and opportunities. *Ann Surg*. 2021;273:483-493.
37. DiMartini A, Dew MA, Liu Q, et al. Social and financial outcomes of living liver donation: a prospective investigation within the adult-to-adult living donor liver transplantation cohort study 2 (A2ALL-2). *Am J Transplant*. 2017;17:1081-1096.
38. Levy GA, Selzner N, Grant DR. Fostering liver living donor liver transplantation. *Curr Opin Organ Transplant*. 2016;21:224-230.
39. Thuluvath AJ, Peipert J, Berkowitz R, et al. Donor quality of life after living donor liver transplantation: a review of the literature. *Dig Med Res*. 2021;4.
40. Volaco A, Cavalcanti AM, Filho RP, Precoma DB. Socioeconomic status: the missing link between obesity and diabetes mellitus? *Curr Diabetes Rev*. 2018;14:321-326.
41. Nobel YR, Forde KA, Wood L, et al. Racial and ethnic disparities in access to and utilization of living donor liver transplants. *Liver Transpl*. 2015;21:904-913.
42. Norman SP, Lu Y. Structural barriers to African American living donor kidney transplant. *JAMA Surg*. 2021;156:1130.
43. Mazumder NR, Simpson D, Atiemo K, et al. Black patients with cirrhosis have higher mortality and lower transplant rates: results from a metropolitan cohort study. *Hepatology*. 2021;74:926-936.
44. Masuda Y, Yoshizawa K, Ohno Y, Mita A, Shimizu A, Soejima Y. Small-for-size syndrome in liver transplantation: definition, pathophysiology and management. *Hepatobiliary Pancreat Dis Int*. 2020;19:334-341.
45. Lee SD, Kim SH, Kong SY, Kim YK, Lee SA, Park SJ. ABO-incompatible living donor liver transplantation without graft local infusion and splenectomy. *HPB (Oxford)*. 2014;16:807-813.
46. Delmonico FL, Morrissey PE, Lipkowitz GS, et al. Donor kidney exchanges. *Am J Transplant*. 2004;4:1628-1634.
47. Broering D, Sturdevant ML, Zidan A. Robotic donor hepatectomy: a major breakthrough in living donor liver transplantation. *Am J Transplant*. 2022;22:14-23.
48. Limkemann AJP, Abreu P, Sapisochin G. How far can we go with hepatocellular carcinoma in living donor liver transplantation? *Curr Opin Organ Transplant*. 2019;24:644-650.
49. Kasiske BL, Lentine KL, Ahn Y, et al. OPTN/SRTR 2020 Annual Data Report: Living Donor Collective. *Am J Transplant*. 2022;22(Suppl. 2):553-586.
50. Ladner DP, Dew MA, Forney S, et al. Long-term quality of life after liver donation in the adult to adult living donor liver transplantation cohort study (A2ALL). *J Hepatol*. 2015;62:346-353.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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