Original Article

Underutilization of Living Donor Liver Transplantation in the United States: Bias against MELD 20 and Higher

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Abstract

Background and Aims: Utilization of living donor liver transplantation (LDLT) and its relationship with recipient Model for End-Stage Liver Disease (MELD) needs further evaluation in the United States (U.S.). We evaluated the association between recipient MELD score at the time of surgery and survival following LDLT. **Methods:** All U.S. adult LDLT recipients with MELD < 25 were evaluated using the 1995–2012 United Network for Organ Sharing registry. Survival following LDLT was stratified into three MELD categories (MELD < 15 vs. MELD 15–19 vs. MELD 20–24) and evaluated using Kaplan-Meier methods and multivariate Cox proportional hazards models. **Results:** Overall, 2,258 patients underwent LDLT. Compared to patients with MELD < 15, overall 5-year survival following LDLT was similar among patients with MELD 15–19 (80.9% vs. 80.3%, $p = 0.77$) and MELD 20–24 (81.2% vs. 80.3%, $p = 0.73$). When compared to patients with MELD < 15, there was no significant difference in long-term post-LDLT survival among those with MELD 15–19 (HR: 1.11, 95% CI: 0.85−1.45, $p = 0.45$) and a non-significant trend towards lower survival in patients with MELD 20–24 (HR: 1.28, 95% CI: 0.91−1.81, $p = 0.16$). Only 14% of LDLTs were performed in patients with MELD 20–24 and the remaining 86% in patients with MELD < 20. **Conclusion:** LDLT is underutilized in patients with MELD 20 and higher.

Introduction

Deceased donor liver transplantation (DDLT) has not been able to keep pace with the increasing demand for liver transplantation in the United States (U.S.). In 2013, while 10,479 candidates were added to the liver transplant waiting list, only 5,921 liver transplants were performed in adults.[1] Despite comparable outcomes between living donor liver transplantation (LDLT) and DDLT, only 211, or 3.7%, of total U.S. liver transplants were LDLT in 2013.[1,2] National trends reveal an aversion to offering LDLT to sicker patients with high Model for End-Stage Liver Disease (MELD) scores. MELD at transplant has been shown to be significantly lower among LDLT recipients compared to DDLT recipients.[2–4] However, it is unclear whether high MELD scores are even associated with lower survival following LDLT. Although the MELD score predicts liver transplantation waitlist survival,[5,6] there is uncertainty surrounding what upper limit MELD score should be used to disqualify patients as too sick for LDLT. This uncertainty stems from the paucity of large studies evaluating the effect of MELD score on survival following LDLT. Therefore, the objective of our current study was to evaluate the association of MELD score and survival following LDLT in the U.S. population.

Materials and Methods

Study population

All adult patients (age 18 years and older) who underwent LDLT in the U.S. from 1995 to 2012 were evaluated using data from the United Network for Organ Sharing/Organ Procurement Transplant Network (UNOS/OPTN) registry. MELD score at the time of LDLT was used. Recipient and donor demographics were analyzed and included age at time of LDLT, sex, and race/ethnicity. Additional clinical characteristics for recipients, including body mass index (BMI), obesity, hepatitis C virus (HCV) infection, hepatocellular carcinoma (HCC), ascites, hepatic encephalopathy, and diabetes mellitus (DM) were analyzed. Data on graft-recipient weight ratio (GRWR) and graft weight/estimated standard liver weight (GW/ESLW) were not available.

Statistical analysis

Clinical and demographic characteristics among LDLT recipients and donors were stratified into three MELD score categories: MELD < 15, MELD 15–19, and MELD 20–24. Categorical variables were presented as proportions and frequencies. Continuous variables were presented as mean ± standard deviation. Comparisons among groups used χ^2 testing for categorical variables and analysis of variance for continuous variables. Overall patient survival following LDLT was analyzed using the Kaplan-Meier method and log-rank testing for equality of survivor functions. Post-LDLT survival was stratified using the previously defined three MELD score categories. Multivariate Cox proportional hazards models were utilized to determine independent predictors of survival following LDLT. Forward stepwise regression methods included variables that were biologically important (*e.g.* age, sex), and those that demonstrated significant associations in the univariate models ($p < 0.10$). The final multivariate model was adjusted for age, sex, race/ethnicity, BMI, obesity, HCV infection, HCC, ascites, hepatic encephalopathy, and DM. Statistical significance was met with a two-tailed p value <0.05. All statistical analyses were performed using the Stata statistical package (version 10; StataCorp, TX, USA).

Results

Overview

From 1995 to 2012, 2,258 patients underwent LDLT in the U.S., including 1,210 patients with MELD < 15 (53.6%), 732 with MELD 15–19 (32.4%), and 316 with MELD 20–24 (14.0%). Fig. 1 depicts the total number of LDLTs in the U.S.

stratified by MELD score categories. There has been a general decline in the number of LDLTs occurring in the U.S. over the past decade (Fig. 1). The MELD < 15 cohort represents the greatest proportion of LDLT recipients, and each higher MELD cohort, namely MELD 15–19 and MELD 20–24, represent progressively lower proportions of LDLT recipients. Fig. 2 depicts the median MELD score of patients who underwent LDLT by year. Although there has been a general decline in the total number of LDLTs, the median MELD score shows a non-significant upward trend over the past decade (Fig. 2).

Clinical and demographic characteristics

Recipient and donor age, sex, BMI, obesity, HCV, and DM were similar among the three MELD categories (Table 1). Compared to patients with MELD < 15 (63.0%), there was a significantly greater prevalence of ascites among those with MELD 15–19 (79.8%) and MELD 20–24 (82.0%) ($p < 0.001$). The same prevalence trends were seen for hepatic encephalopathy: compared with MELD < 15 (50.4%), MELD 15–19 (60.5% vs. 50.4%, $p < 0.001$) and MELD 20–24 (63.9% vs. 50.4%, $p < 0.001$). Interestingly, rates of HCC were significantly lower among the MELD 15–19 (6.4%) category compared to the MELD < 15 (12.3%) and MELD 20–24 (12.0%) categories ($p < 0.001$) (Table 1). It should be noted that the biological MELD in patients with HCC may be irrelevant as HCC patients are listed with MELD exception.

Survival following LDLT

Compared to patients with MELD < 15, overall 5-year survival following LDLT was similar among patients with MELD 15–19 (80.9% vs. 80.3%, $p = 0.77$) and MELD 20–24 (81.2% vs.
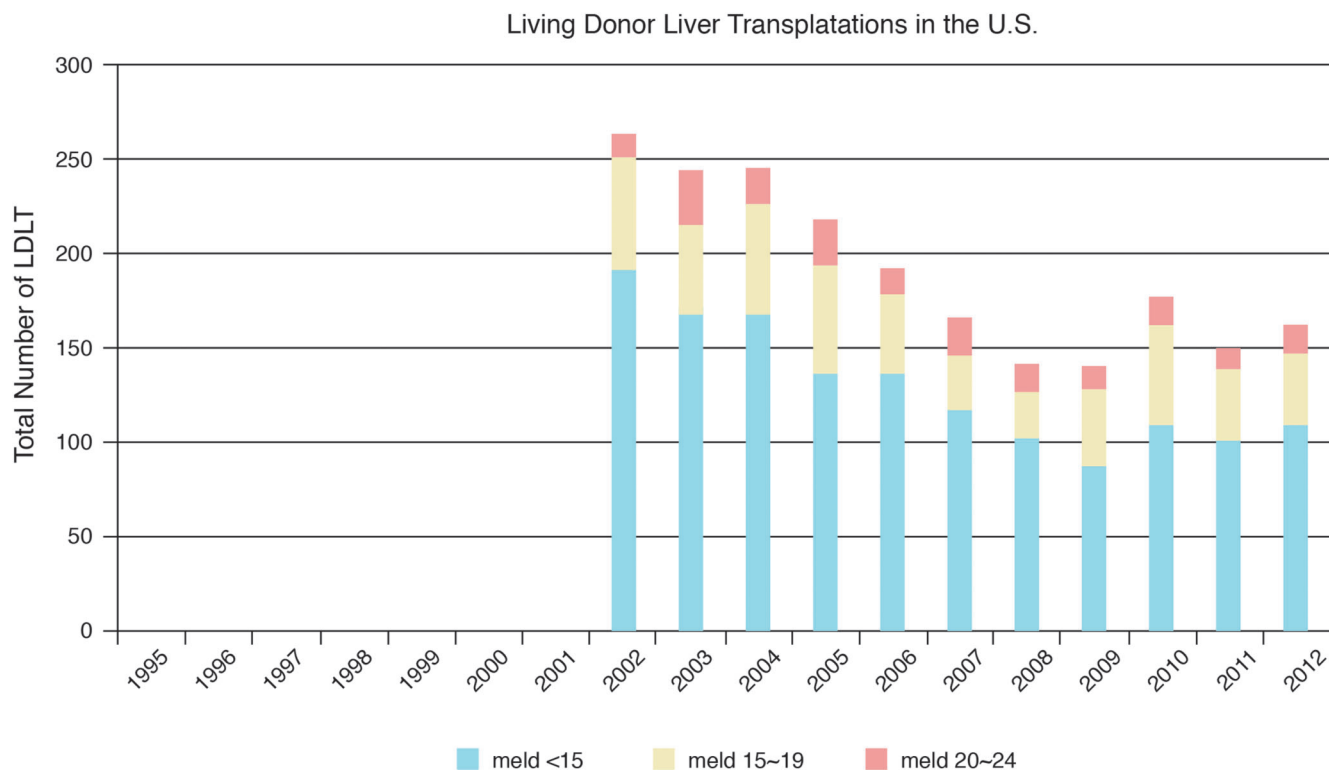

Fig. 1. Annual U.S. living donor liver transplantations by MELD score categories.
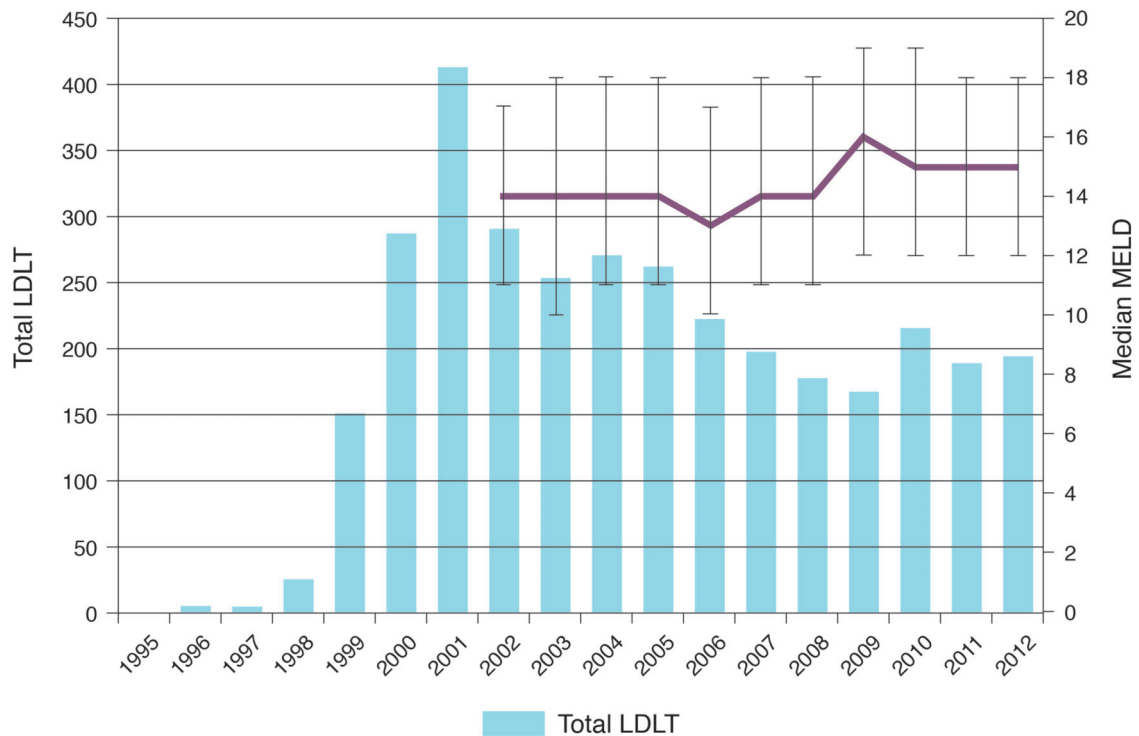
Fig. 2. Median MELD of living donor liver transplantation by year in U.S.

80.3%, *p* = 0.73) (Figs. 3 and 4). Using multivariate Cox proportional hazards models, the independent impact of MELD score categories on survival following LDLT was evaluated (Table 2). When compared to patients with MELD < 15, there was no significant difference in long-term post-LDLT survival among those with MELD 15–19 (HR: 1.11, 95% CI: 0.85–1.45, *p* = 0.45) and a non-significant trend towards lower survival in patients with MELD 20–24 (HR: 1.28, 95% CI: 0.91–1.81, *p* = 0.16). The presence of HCC at the time of LDLT was a significant independent predictor of lower post-LDLT survival (HR: 1.81, 95% CI: 1.25–2.63, *p* < 0.01). HCV (HR: 1.42, 95% CI: 1.10–1.83, *p* < 0.01) and DM

Table 1. Liver donor liver transplantations in the U.S., 1995–2012

	MELD < 15 (*n* = 1,210)		MELD 15–19 (*n* = 732)		MELD 20–24 (*n* = 316)		
		n		*n*		*n*	*p*-Value
Male	54.7%	662	59.8%	438	57.6%	182	0.08
Age, mean ± SD	51.9 ± 11.4		51.6 ± 11.3		51.6 ± 11.9		0.80
BMI, mean ± SD	26.5 ± 5.0		26.96 ± 4.9		26.9 ± 5.2		0.39
Obesity	24.1%	292	20.6%	151	25.6%	81	0.11
Race/ethnicity							0.02
Non-Hispanic white	85.2%	1,024	81.4%	592	81.6%	257	
Black	3.1%	37	4.0%	29	5.7%	18	
Hispanic	8.6%	103	12.2%	89	11.1%	35	
Asian	3.2%	38	2.3%	17	1.6%	5	
Hepatitis C	39.5%	351	41.2%	252	32.4%	84	0.05
Hepatocellular carcinoma	12.3%	149	6.4%	47	12.0%	3.8	< 0.001
Ascites	63.0%	762	79.8%	584	82.0%	259	< 0.001
Hepatic encephalopathy	50.4%	610	60.5%	443	63.9%	202	< 0.001
MELD, mean ± SD	10.7 ± 2.5		16.8 ± 1.4		21.7 ± 1.3		< 0.001
Diabetes	12.8%	137	13.2%	87	12.4%	37	0.95

Post Transplantation Survival
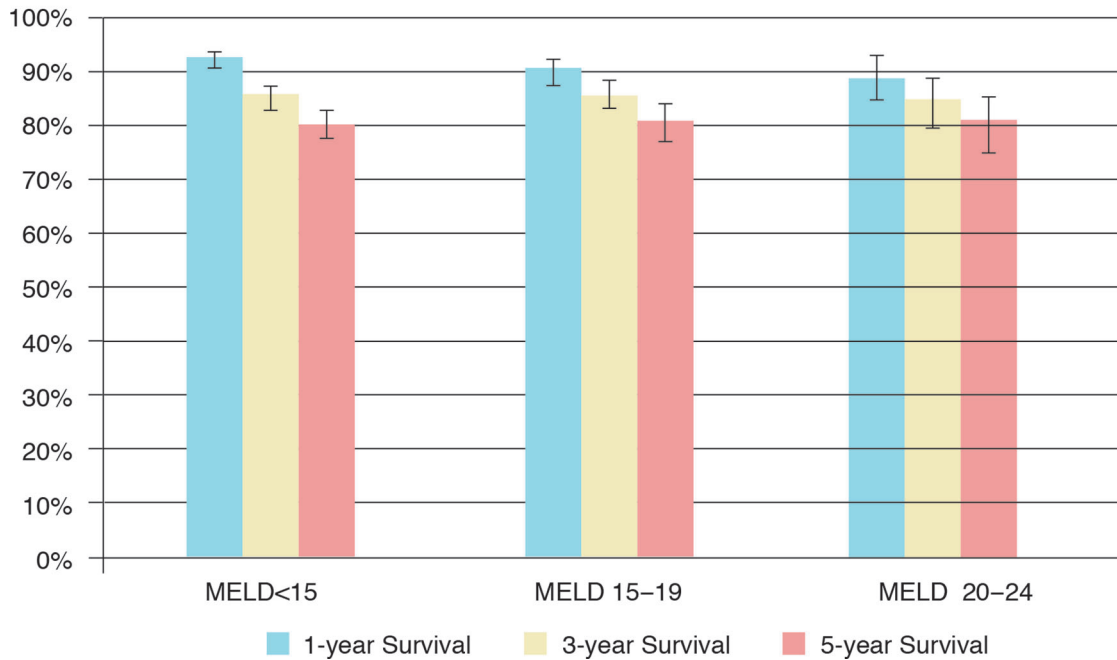## Living Donor Liver Transplantation

Fig. 3. Compared to patients with MELD <15, overall 1-year 3-year, and 5-year survival following LDLT were similar among patients with MELD 15–19 and MELD 20–24.

(HR: 1.52, 95% CI: 1.09−2.11, *p* < 0.02) were also associated with lower survival following LDLT (Table 2).

Discussion

In the current study of adult LDLT recipients in the U.S. from 1995 to 2012, higher MELD scores were not associated with significantly lower survival following LDLT among the adult patients with MELD < 25. Even after adjusting for potentially confounding variables in a multivariate model, including age, HCV, HCC and DM, higher MELD scores at the time of LDLT failed to demonstrate a negative impact on post-LDLT survival. However, advanced age, HCV, HCC, and DM were independently associated with lower survival following LDLT.

The paucity of data in the UNOS/OPTN database regarding LDLT recipients with MELD ≥ 25 highlights the reservations that U.S. transplant centers have regarding offering LDLT to
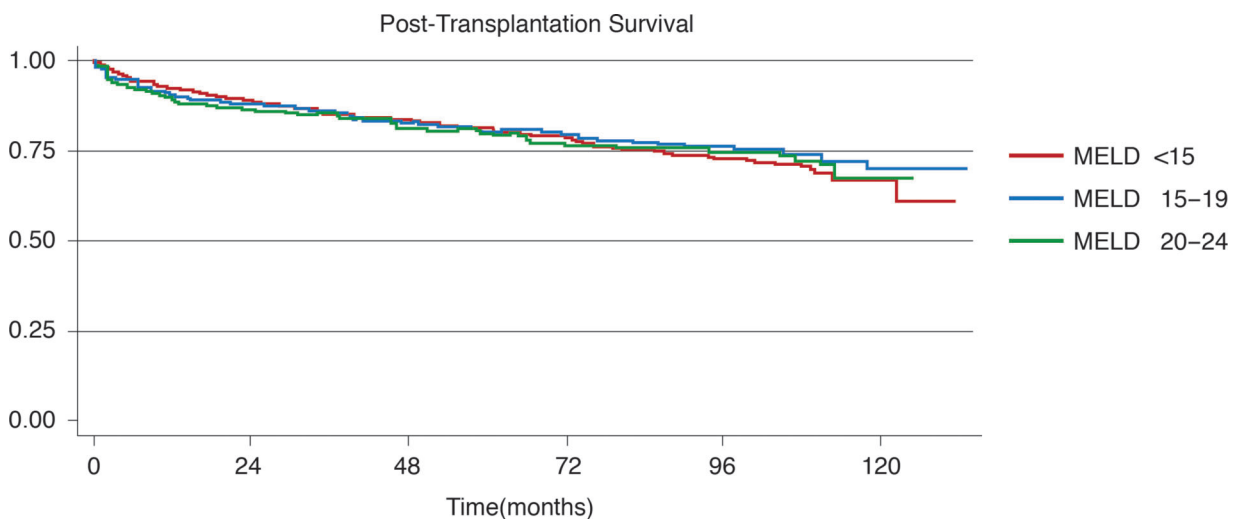

Fig. 4. Kaplan-Meier curves demonstrating that long-term survival following LDLT is similar among patients with MELD < 15, MELD 15–19, and MELD 20–24.

Table 2. Predictors of post-transplantation survival among living donor liver transplantations in U.S.

	Univariate			Multivariate		
	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
MELD Score						
< 15	1.00	Reference	-	1.00	Reference	-
15–19	0.96	0.77 − 1.19	0.68	1.11	0.85 − 1.45	0.45
20–24	1.01	0.76 − 1.36	0.93	1.28	0.91 − 1.81	0.16
Male (vs. female)	1.15	1.00 − 1.33	0.05	0.94	0.73 − 1.21	0.63
Age	1.03	1.02 − 1.04	< 0.001	1.03	1.02 − 1.04	< 0.001
Obesity	1.21	1.03 − 1.43	< 0.01	1.08	0.82 − 1.43	0.57
Race/ethnicity						
Non-Hispanic white	1.00	Reference	-	1.00	Reference	-
Black	1.40	1.01 − 1.94	< 0.05	0.87	0.47 − 1.60	0.64
Hispanic	0.87	0.69 − 1.10	0.24	0.84	0.56 − 1.25	0.39
Asian	0.98	0.65 − 1.48	0.93	0.61	0.27 − 1.39	0.24
Hepatitis C	1.38	1.18 − 1.63	< 0.001	1.42	1.10 − 1.83	< 0.01
Hepatocellular carcinoma	1.69	1.35 − 2.12	< 0.001	1.81	1.25 − 2.63	< 0.01
Ascites	1.17	0.95 − 1.43	0.15	-	-	-
Hepatic encephalopathy	1.31	1.08 − 1.58	< 0.01	1.27	0.97 − 1.65	0.08
Diabetes	1.48	1.12 − 1.96	< 0.01	1.52	1.09 − 2.11	< 0.02

the sickest patients with end-stage liver disease. Moreover, the MELD < 15 cohort represented the greatest proportion of LDLT recipients and each higher MELD cohort, namely MELD 15–19 and MELD 20–24, represented progressively lower proportions of LDLT recipients; this suggests that higher MELD scores are deterring hepatologists and liver transplant surgeons from offering this therapeutic option to sicker patients. This notion is corroborated by Samstein *et al.*[2] who demonstrated a significant difference in MELD at transplant between DDLT and LDLT (mean, 20.3 vs. 15.2) among 1,036 liver transplant recipients.[3] Analysis of U.S. registry data by Hoehn *et al.*[4] demonstrated a median MELD score of 15 among LDLTs compared to 19 among DDLTs. Between 2007 and 2012, only 14 LDLTs were performed among patients with MELD 28–34 and 3 among patients with MELD 35–40.[4]

The number of LDLTs in the U.S. peaked in 2001, when 506 were performed.[7] Subsequently, media attention surrounding the donor death of a New York man who donated the right lobe of his liver to his brother spurred a decline in LDLTs performed, down to 353 in 2002.[7] The decline persisted over the decade to follow. However, a recent study by Muzaale *et al.*[8] reveals that the risk of early death, defined as within 3 months of LDLT, from live liver donation in the U.S. is only 1.7 per 1000 donors. Moreover, these investigators found that overall survival among live liver donors did not differ from that of healthy, matched individuals from the National Health and Nutrition Examination Survey (NHANES) over a mean follow-up of 7.6 years.[8] This finding is akin to previous data demonstrating that long-term overall survival among live kidney donors did not differ from a comparably matched cohort from NHANES, which is significant because live kidney donation is generally regarded as safe and has become widespread in the U.S.[9] Furthermore, long-term prospective follow-up of 372 live liver donors reveals that most maintain

above average health-related quality of life up to 11 years following LDLT.[10] Given growing evidence of donor safety after live donation, LDLT may be ready for more widespread availability for patients with end-stage liver disease in the U.S.

There is vast international experience with LDLT, particularly in East Asian nations, and specifically in Japan and South Korea, where cultural factors significantly limit adoption of deceased organ donation. In the U.S., the multi-institutional Adult-to-Adult Living Donor Liver Transplantation Study (A2ALL) prospectively involved 9 major transplant centers and demonstrated overall 1-year and 3-year patient survivals of 94% and 78%, respectively.[11] Goldberg *et al.*[12] demonstrated that overall patient survival following LDLT is equivalent, if not superior, to DDLT when performed at experienced centers based on UNOS/OPTN registry data.

Data assessing the impact of MELD score on survival following LDLT are lacking. Existing literature is from foreign centers, limited in sample size, or dated. Single center data for 335 patients who underwent LDLT in Japan suggested that MELD ≥ 20 was an independent predictor of lower graft survival (HR: 2.9, 95% CI: 1.6−5.2, *p* < 0.01), but these investigators did not evaluate the association of MELD with overall patient survival.[13] Further analysis from the same center revealed no difference in graft survival following LDLT between 46 patients with MELD ≥ 25 and 311 patients with MELD < 25.[14] Data from a large Korean university hospital analyzing 167 LDLTs performed between 1999 and 2005 demonstrated that MELD > 25 did not predict 1-year patient survival. Similarly, single center data from a Canadian center analyzed 271 patients who underwent LDLT between 2002 to 2008 and reported comparable 1-year, 3-year and 5-year graft and patient survival in MELD < 25 and MELD ≥ 25 groups.[15] In a single center U.S. study, Hayashi *et al.*[16] evaluated the association of MELD scores at time of transplant

with 1-year post-LDLT graft and patient survival; they noted that MELD predicts neither overall graft nor patient survival following LDLT.

Overall, the existing literature fails to provide a consensus on the U.S. experience in LDLT. Asian data regarding the adoption and success of LDLT may not be extrapolated to the U.S. population due to higher prevalence of chronic hepatitis B and HCC in Asia. In addition, a larger volume of LDLT in Asia may be associated with differences in surgical experience and outcomes versus the U.S. population. In light of this, the findings of our study provide valuable insight into outcomes following LDLT in the U.S. and suggest that LDLT can be offered to sicker patients with higher MELD scores without compromising survival outcomes.

The current study uses population-based data that includes all adult LDLTs performed in the U.S. from 1995 to 2012. The comprehensive nature of the cohort improves consistency of comparisons among geographic areas and minimizes the potential for selection bias, improving overall generalizability. However, our study is limited by factors inherent in registry-based research and lack of granular data, which may be significant; this would need to be studied in future analysis. Our retrospective study design limited the ability to evaluate the accuracy of the information captured. Furthermore, our study reveals that LDLTs are rarely performed on patients with MELD $\geq$ 25, which precluded us from including this cohort in our analysis due to the limited sample size. Despite these limitations, the utilization of large population-based data stratified by MELD categories adds considerable strength and generalizability to our findings.

In conclusion, our large population-based study of U.S. adult LDLT recipients demonstrates that survival following LDLT is not affected by MELD scores up to 25. LDLT is under-utilized in patients with MELD score 20 and higher. Our study findings suggest that LDLT can be offered as a therapeutic option to patients with chronic liver disease and MELD score between 20–24. Indeed, we are not suggesting a MELD cutoff of 25 as an exclusion criterion for LDLT. Rather, we want to highlight the current lack of LDLT being performed in our sickest patients and would recommend that a patient-specific approach be taken to assess candidacy in this patient population. Large prospective studies are warranted to investigate outcomes of LDLT in patients with MELD $\geq$ 25.

Conflict of interest

None

Author contributions

Study concept and design (RBP, ERY, GC, LH, MD, WCC, CAB, ZMY, RJW, AA), acquisition of data (RBP), analysis and interpretation of data (RBP, ERY, GC, LH, MD, WCC, CAB, ZMY, RJW, AA), drafting of the initial and final manuscript (RBP, ERY, GC, LH, MD, WCC, CAB, ZMY, RJW, AA), critical revision of the manuscript (ERY, GC, LH, MD, WCC, CAB, ZMY, RJW, AA), and study supervision (AA).

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