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ORIGINAL ARTICLE

Early Graft Failure After Living-Donor Liver Transplant

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Abstract

Background Living-donor liver transplantation (LDLT) has been increasing in the USA. While data exist on longer-term patient and graft outcomes, a contemporary analysis of short-term outcomes is needed.

Aim Evaluate short-term (30-day) graft failure rates and identify predictors associated with these outcomes.

Methods Adult (≥ 18) LDLT recipients from 01/2004 to 12/2021 were analyzed from the United States Scientific Registry of Transplant Recipients. Graft status at 30 days was assessed with graft failure defined as retransplantation or death. Comparison of continuous and categorical variables was performed and a multivariable logistic regression was used to identify risk factors of early graft failure.

Results During the study period, 4544 LDLTs were performed with a graft failure rate of 3.4% (155) at 30 days. Grafts from male donors (aOR: 0.63, CI 0.44–0.89), right lobe grafts (aOR: 0.40, CI 0.27–0.61), recipients aged > 60 years (aOR: 0.52, CI 0.32–0.86), and higher recipient albumin (aOR: 0.73, CI 0.57–0.93) were associated with superior early graft outcomes, whereas Asian recipient race (vs. White; aOR: 3.75, CI 1.98–7.10) and a history of recipient PVT (aOR: 2.7, CI 1.52–4.78) were associated with inferior outcomes. LDLTs performed during the most recent 2016–2021 period (compared to 2004–2009 and 2010–2015) resulted in significantly superior outcomes (aOR: 0.45, $p < 0.001$).

Conclusion Our study demonstrates that while short-term adult LDLT graft failure is uncommon, there are opportunities for optimizing outcomes by prioritizing right lobe donation, improving candidate nutritional status, and careful pre-transplant risk assessment of candidates with known PVT. Notably, a period effect exists whereby increased LDLT experience in the most recent era correlated with improved outcomes.

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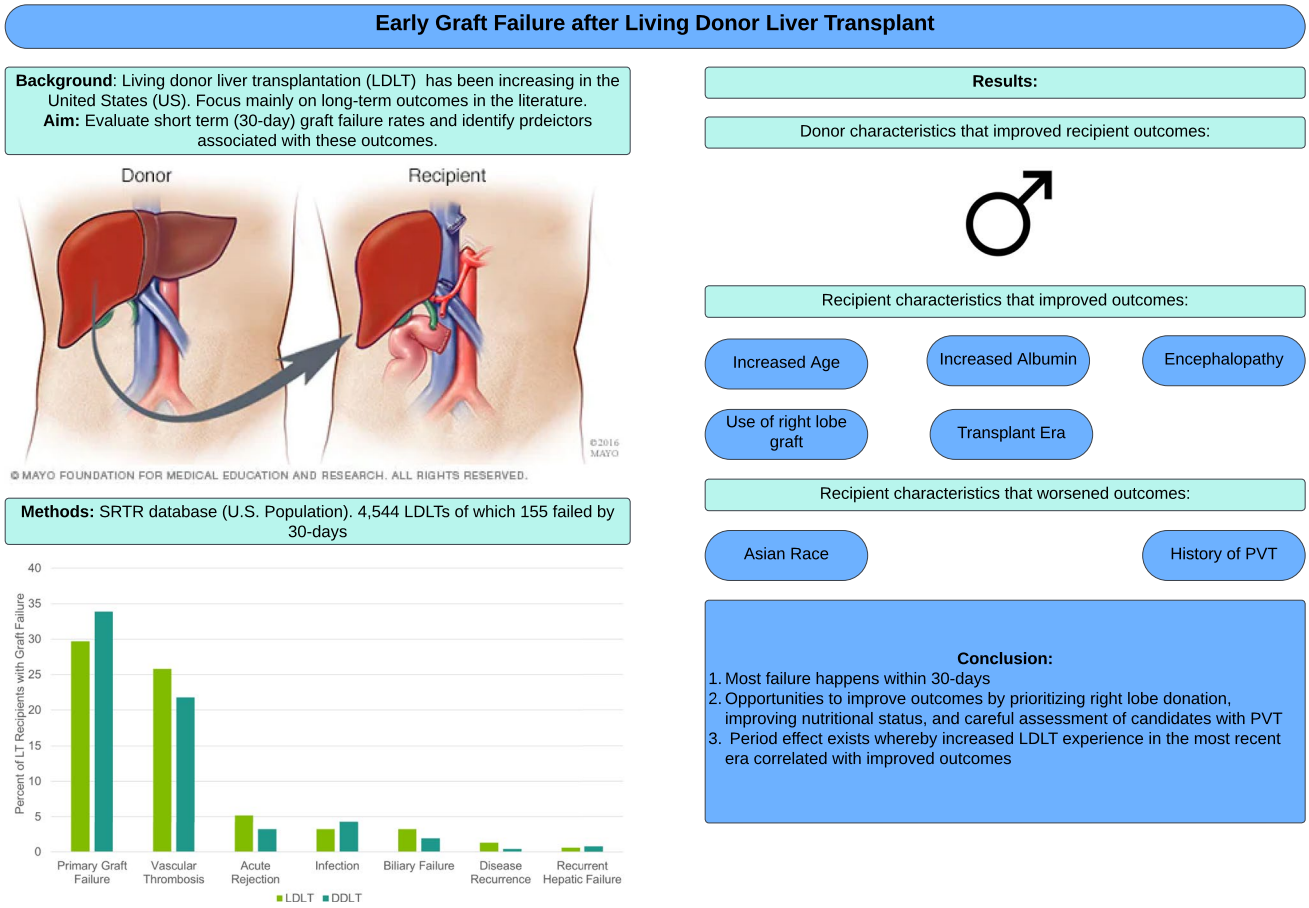
Graphical Abstract



Keywords Liver transplant (LT) · Living-donor liver transplant (LDLT) · Graft failure · Portal vein thrombosis (PVT) · ReTransplantation

Introduction

Over the past six decades, liver transplantation (LT) has evolved to become a highly effective treatment for end-stage liver disease. Despite progress in prolonging recipient survival, an ongoing challenge has been the shortage of organs available [1–4]. Living-donor liver transplantation (LDLT) has become a viable alternative to help address this imbalance [5]. In 2022, 9,528 liver transplants (LT) were performed in the USA, of which 603 (6.3%) were LDLT as compared to 2004 where a total of 6171 LTs were performed, of which 323 (5.2%) were LDLT [6, 7]. Recent studies have shown that with increased utilization of LDLT, there has been an improvement in 1-year survival outcomes (88.4% survival) over time [8].

With the increased adoption, the need to benchmark outcomes of LDLT relative to deceased donor LT (DDLT) remains essential, especially in regions where both graft types are available. Prior studies have shown superior long-term outcomes (20-year follow-up) in LDLT recipients compared to DDLT [9]. Moreover, LDLT has been shown to be associated with the most life years gained and increased long-term survival (1 year) as compared to any other life-saving procedure [10]. As the main focus has been defining long-term outcomes in this patient population, limited discussion has been on early LDLT outcomes [11]. In an uncensored cohort, 30-day LDLT recipient survival was similar to DDLT (97.6% vs. 97.0%, $p = 0.13$); however, 30-day LDLT graft survival was noted to be lower than 30-day DDLT graft survival (94.4% vs. 95.8%, $p = 0.003$). Moreover, grafts from donors with brain death (DBD) LT were found to have significantly superior outcomes at 30 days compared to LDLT (aHR: 0.60, $p < 0.001$). [12]

Given the current limited data assessing short-term outcomes in LDLT recipients and the previously noted lower early graft survival rates in LDLT, we aimed to evaluate

short-term (30-day) graft failure rates and identify predictors associated with these outcomes. We felt that this data would help identify opportunities for improvement and inform patient-centered discussions regarding LDLT.

Methods

Study Design and Participants

This study used data from the Scientific Registry of Transplant Recipients (SRTR) database. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the USA, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provide oversight to the activities of OPTN and SRTR contractors. [13, 14]

Data Source and Data Management

The SRTR standard research analysis files from January 2004 through December 2021 were queried for all adult (age ≥ 18) LDLT recipients and their corresponding donors. Domino transplants were excluded. Participants who underwent DDLT during the same time period were included for comparison. The participant's data (candidates, donors, and recipients) were merged from four resource files ("DONOR_LIVE," "CAND_LIIN," "STATHIST_LIIN," "TX_LI") using the corresponding linking key indicated by the SRTR data dictionary.

Statistical Analyses

Early graft failure (death or retransplantation within 30 days) was the primary outcome and its association with donors and recipient characteristics was assessed. We used SPSS (version 25.0, IBM, Armonk, NY) and R 4.1.2 for data merging and analysis. The continuous variables are presented as mean ± standard deviation. The categorical variables are presented as frequencies and percentages. We used Chi-square or Fisher's exact test (as applicable) for the categorical variables, and Student's T test for continuous variables to compare these variables. At the multivariable level, we performed a logistic regression model to assess the association of the variables with the outcome. All clinically significant variables with p-values < 0.2 at the univariate level were assessed with multivariable analysis. Significance was interpreted at $\alpha = 0.05$. Any variables having more than 10% missing data were removed from the analysis (Supplemental Document 1).

Results

During the study period, 4544 patients underwent LDLT. LDLT recipients had a mean age 52.5 years ± 13, MELD of 15.2 ± 5.7, BMI of 27.2 ± 11.1, and 3,952 (87%) received a right lobe graft. Among all LDLT recipients, 177 (3.9%) had graft failure. Of those with graft failure, 155 (3.4%) were within the first 30 days. Of the 155 early graft failures, 131 (84.5%) received retransplant, and 24 (15.5%) died. Moreover, there were 112,121 DDLTs recipients during this time period. Among these, a total of 2,721 (2.4%) had graft failure. Of these DDLT failures, 2,093 (1.9%) developed graft failure within 30 days, 1276 (61.0%) received retransplant, and 817 (39.0%) died. In both LDLT and DDLT, most graft failure occurred within the 30 days of transplantation, with the mean being 15 days (LDLT: 15 ± 18 days and DDLT 15 ± 20 days). With increasing time from transplant, the number of graft failures in LDLT and DDLT recipients decreased**.** The etiologies of LDLT and DDLT graft failure within 30 days were similarly distributed **(**Fig. 1**).** Of note, however, 70 LDLT recipients (39.6%) had an unknown cause of graft failure.

A comparison between LDLT recipients with short-term graft failure to those without was performed (Table 1). LDLT donors of failed grafts were less likely white, male, or those with lower BMI compared to those donors without failed grafts. Regarding recipients, those with failed grafts had a lower albumin at transplant, were more likely to be female, had a higher bilirubin at transplant, higher incidence of PVT (portal vein thrombosis), and had greater incidence of hospital admission prior to transplant (Table 1). Moreover, LDLT recipients with early graft failure had a significantly higher likelihood of being transplanted in the early period (2004–2008) of the US experience and were more commonly with left lobe grafts (Table 1).

For the multivariable analysis, clinically significant variables with p-values < 0.2 on univariate analysis were accounted for and donor variables included age, gender, race, BMI, health insurance, and preoperative creatinine, AST, and ALT. Similarly, candidate characteristics included age at transplant, gender, race, BMI, previous abdominal surgery, diabetes, PVT, encephalopathy, albumin, and lab MELD score. Procedural variables included graft laterality (left vs right lobe), CIT (cold ischemia time), transplant period, and center volume. Among the donor variables, only gender was found to be significant, with male donors resulting in superior early graft outcomes compared to female donors (aOR: 0.63, CI 0.44–0.89, $p = 0.008$). For candidate characteristics, older candidates (> 60 years of age) (aOR: 0.52, CI 0.32–0.86, $p = 0.01$) and higher albumin values (aOR: 0.73, CI:

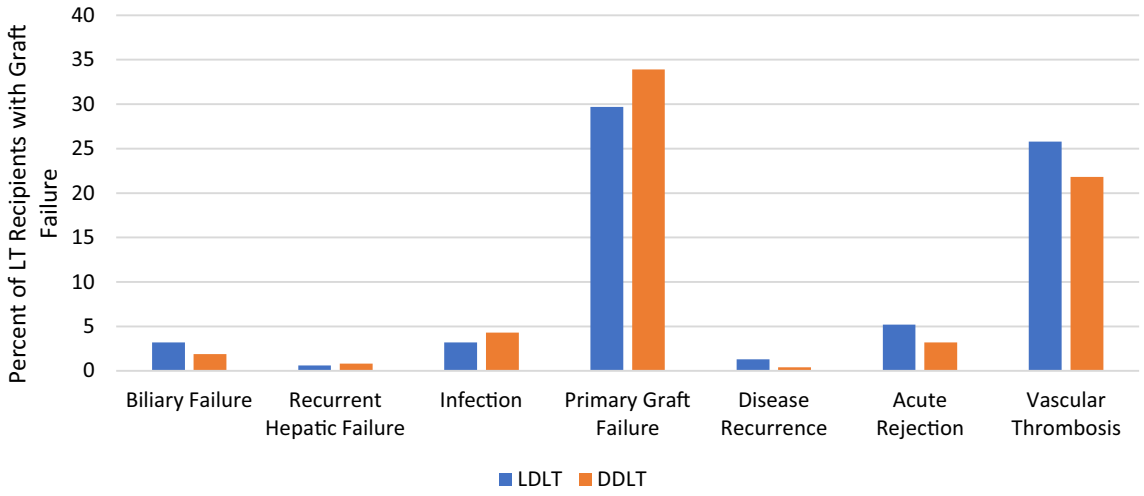


Fig. 1 Distribution of etiologies (by percentage) of 30-day graft failure within LDLT recipients and DDLT recipients. *LDLT* living-donor liver transplant, *DDLT* deceased donor liver transplant

0,57–0.93, p = 0.01) were significantly protective and resulted in lower risk of early graft failure, and Asian race (aOR: 3.75, CI 1.98–7.10, $p < 0.001$) as well as PVT (aOR: 2.7, CI 1.52–4.78, $p = 0.001$) were significantly harmful factors resulting in a higher risk of early graft failure. Right lobes were found to be protective (aOR: 0.40, CI 0.27–0.61, $p < 0.001$) as was being transplanted during the most recent time period (2016–2021) (aOR: 0.45, CI 0.29–0.70, $p < 0.001$) (Table 2).

Discussion

Early graft failure after LDLT occurs in 3.4% of patients. Our results indicate that male donors, right lobe grafts, older recipients, recipients with higher albumin, and a transplant during the most recent era (2016–2021) were associated with superior early graft outcomes, whereas Asian recipient race and a history of PVT were associated with inferior outcomes. This information is important for preoperative counseling of both donor and recipients as it helps to ensure an optimal understanding of risk, benefits, and anticipated outcomes.

Despite the majority of graft failure in both LDLT and DDLT occurring within 30 days, this study is the first of its kind assessing short-term outcomes of LDLT recipients. Interestingly, current available literature has predominantly focused on one-year survival (likely due to this being used as a publicly reported outcome metric) and thus comparisons of time to failure to prior studies are not readily possible. The most common recorded cause of graft failure in both LDLT and DDLT was primary graft failure (defined as graft loss or patient death within two weeks of transplantation), vascular thrombosis, infection, and rejection. Acute rejection has been previously shown to be significantly associated with LDLT [15], while the remainder of aforementioned etiologies have been previously shown to be significantly associated with increased morbidity in DDLT recipients. [15–18]

With regard to donor factors, grafts from male donors were shown to be protective of early survival postop. Although there is no clear data assessing early outcomes of LDLT based on gender, male donors generally yield larger grafts than females, and this may have been beneficial in ameliorating risks postoperatively. Unfortunately graft weight was not available in the dataset; however, we did note that right lobes were independently associated with better outcomes. In prior studies, it has been shown that right lobe grafts result in a lower risk of developing small for size syndrome (SFSS) and postop mortality compared to recipients receiving left lobes. [19, 20]

With regard to recipient factors, age was shown to be a protective. In prior studies of DDLT, older age (> 60 years) was shown to lead to significantly lower survival rates [21]. The increased mortality in elderly recipients was felt to be linked to non-hepatic causes of death and to increased underlying comorbidities. In the current study, the finding of older age being protective may reflect some degree of recipient selection bias. Among centers outside of the USA, patients > 70 years that underwent LDLT were not found to have significant differences when compared to younger patients and in this setting, were noted to have similar outcomes in terms of long-term survival [22, 23]. Given that LDLT is less commonly performed in the USA, when it is done for older recipients, it is more likely that these individuals may be of lower risk overall thus potentially explaining the protective findings in the current study. Asian individuals

Table 1 Univariate analysis comparing donor, recipient, and operative characteristics of living-donor liver transplants among grafts that remained viable at 30 days vs grafts that failed by 30 days

	Functional ($N=4,389$)	Early graft failure ($N=155$)	p-value
Donor characteristics			
Race			
• White	4072 (93%)	142 (92%)	0.048
• Black	145 (3.3%)	2 (1.3%)	
• Asian	106 (2.4%)	9 (5.8%)	
• Other	66 (1.5%)	2 (1.3%)	
Female sex	2,326 (53%)	95 (61%)	0.042
Age (years)	37.1 ± 10.3	37.8 ± 10.4	0.454
Health insurance	3,887 (89%)	129 (83%)	0.042
BMI (kg/m^2)	26.4 ± 3.8	25.5 ± 4.7	0.01
Albumin (g/dL)	4.4 ± 0.4	4.3 ± 0.5	0.19
Alkaline phosphatase (IU/L)	66.0 ± 19.2	67.2 ± 19.6	0.44
Bilirubin (mg/dL)	0.7 ± 0.9	0.6 ± 0.4	0.9
INR	1.1 ± 1.6	1.0 ± 0.1	0.68
Creatinine (mg/dL)	0.9 ± 0.2	0.8 ± 0.2	0.13
AST (IU/L)	22.8 ± 15.7	24.7 ± 20.3	0.16
ALT (IU/L)	24.3 ± 18.3	27.2 ± 27.3	0.06
Recipient characteristics			
Race			
• White	4,086 (93%)	138 (89%)	0.005
• African American	149 (3.4%)	5 (3.2%)	
• Asian	110 (2.5%)	12 (7.7%)	
• Other	44 (1.0%)	0 (0%)	
Female sex	2,006 (46%)	74 (48%)	0.62
Age	52.6 ± 12.8	50.4 ± 12.8	0.036
BMI (kg/m^2)	27.2 ± 11.2	26.3 ± 5.0	0.32
MELD score at transplant	15.2 ± 5.7	15.8 ± 5.8	0.16
Albumin (g/dL)	3.2 ± 0.7	3.0 ± 0.7	0.025
Bilirubin (mg/dL)	4.0 ± 4.7	5.3 ± 6.6	< 0.001
INR	1.5 ± 0.7	1.5 ± 0.6	0.87
Creatinine (mg/dL)	1.0 ± 0.5	0.9 ± 0.4	0.32
Sodium (mmol/L)	136.7 ± 4.4	137.1 ± 4.6	0.25
ALT (IU/L)	84.0 ± 396.1	74.8 ± 89.1	0.82
Preop encephalopathy	2,261 (52%)	74 (48%)	0.41
Ascites	6 (50%)	0 (0%)	> 0.99
Diabetes	978 (22%)	32 (21%)	0.61
PVT	408 (9.3%)	33 (21%)	< 0.001
Previous abdominal surgery	2,045 (50%)	86 (58%)	0.054
Hospital admission 90 days prior to LT	553 (13%)	34 (22%)	< 0.001
Operative characteristics			
Center volume:			0.12
• High (> 20 LDLTs/year)	1,941 (44%)	64 (41%)	
• Medium (3–20 LDLTs / year)	2,107 (48%)	72 (46%)	
• Low (< 3 LDLTs/year)	341 (7.8%)	19 (12%)	
Transplant period:			< 0.001
• 2004–2009	1,089 (25%)	48 (31%)***	
• 2010–2015	1,196 (27%)	60 (39%)	
• 2016–2021	2,104 (48%)	47 (30%)	
Left lobe graft	554 (13%)	38 (25%)	< 0.001
CIT (hours)	2.0 + 3.3	2.0 + 2.3	0.88
WIT (minutes)	38.0 ± 20.1	41.1 ± 22.0	0.21
Extra vessel used	1,403 (32%)	46 (30%)	0.55

Table 1 (continued) Value are *n* (%) or median (interquartile range)

BMI body mass index, *INR* international normalized ratio, body metabolic index, *AST* aspartate transaminase, *ALT* alanine transaminase, *CIT* cold ischemia time, *LOS* length of stay, *MELD* model for end-stage liver disease, *PVT* portal vein thrombosis, *CIT* cold ischemia time, *WIT* warm ischemia time

Table 2 Multivariable analysis of early graft failure in LDLT recipients

Variables	aOR	CI	Multivariable *p*-value
Donor characteristics			
Male sex	0.63	0.44–0.89	0.008
Recipient characteristics			
Age (ref: 18–39 years)			
• 40–59 years	0.74	0.48–1.15	0.18
• > 60 years	0.52	0.32–0.86	0.01
Race (ref: white)			
• African American	0.74	0.27–2.06	0.55
• Asian	3.75	1.98–7.10	< 0.001
• Other	0	0	0.998
Last albumin prior to LTx	0.73	0.57–0.93	0.01
PVT	2.7	1.52–4.78	0.001
Encephalopathy	0.73	0.57–0.93	0.001
Right lobe	0.40	0.27–0.61	< 0.001
Transplant period (ref: 2004–2009)			
• 2010–2015	0.96	0.63–1.45	0.83
• 2016–2021	0.45	0.29–0.70	< 0.001

aOR adjusted odds ratio; *PVT* portal vein thrombosis, *LTx* liver transplant

were shown to be at a disadvantage in early graft failure outcomes. This finding warrants further investigation as we were unable to elucidate any further factors that may be driving this association in the current study. Another recipient factor noted to impact outcomes was pre-transplant albumin levels. In patients with advanced cirrhosis, serum albumin is reduced and undergoes functional and structural variations resulting in a substantial decrease in native and effective albumin [24–29]. Candidates with lower albumin preop have thus been found to have more advanced cirrhosis and poorer survival [30, 31]. Importantly, treatment of hypoalbuminemia with nutritional supplementation in patients with advanced cirrhosis has been found to be beneficial in improving overall patient survival and outcomes. [32]

Technical factors remain an important cause of morbidity and mortality after LDLT and with PVT have been previously noted to have poorer outcomes postop [33–35]. This can also be seen in DDLT in which morbidity, graft failure, and mortality was increased in candidates perioperative PVT [36–38]. In the current study, the presence of recipient PVT at the time of LDLT was found to be an independent risk factor for early graft failure. Kadry et al. demonstrated that more than 60% of 47 transplant centers from all over the world surveyed considered PVT as either an absolute or relative contraindication to LDLT [39]. The degree of PVT and the presence/absence of collateral vessels or other options for portal inflow are important in making this decision and assessing risk. These factors were unavailable in the current database but should be considered in future studies in order to further delineate the extent or grade at which PVT substantially increases recipient risk in LDLT and inform management strategies to deal with this.

Recent policy changes and advancements have resulted in increased interest and utilization of LDLT use in the USA [8, 40]. As LDLT prevalence and center experience evolves, LDLT outcomes have improved [41–44]. Specifically, there has been an increase in 1-year survival in LDLT recipients during the past decade with a decreased rate of retransplantation between the years 2015 and 2019 [8]. In the current report, these findings are corroborated as being transplanted during the latest period (2016–2021) resulted in significantly decreased risk of early LDLT graft failure compared to transplant during an earlier time period. Other factors that are important to consider include institutional volume and experience, especially when starting new programs or considering expansion of LDLT to higher risk recipients. [8]

There are inherent limitations to our study, most of which are due to the nature of the SRTR database. First, primary causes of graft failure within the 30-day post-LT were limited, and while we do have some data as described, only had 60% of LDLT and 66% of DDLT recipients had a reported causes. Second, there was an inability to properly control for socioeconomic status in recipients of different backgrounds. Finally, lack of graft size and operative technical details (i.e., outflow reconstructive technique, portal hemodynamics, and modulation) limited the ability to properly assess the impact of these known variables on early LDLT outcomes.

In conclusion, although graft failure after LDLT is uncommon, when it does occur, it most often happens within 30 days of transplant with the majority of cases resulting in retransplantation. Importantly, specific donor, recipient, and graft factors have been shown to portend lower risk. These data allow for patient-centered counseling of donors as well as recipients and have potential to inform strategies that lead to better short-term and eventual long-term outcomes post-LDLT. Multi-institutional efforts should aim to further assess the findings of our study with the addition of granular LDLT-specific variables that may further influence early outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-024-08280-5.

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Data availability The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the USA, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provide oversight to the activities of OPTN and SRTR contractors.

Declarations

Conflict of interest AA, MAH, and CH have no relevant disclosures. Dr. Patel is supported as the Dedman Scholar of Clinical Care at UT Southwestern Medical center. The funder had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript. Dr. Cotter is supported by the American Association for the Study of Liver Diseases (AASLD) Clinical, Translational and Outcomes Research Award (CTORA) and National Institute for Alcohol Abuse and Alcoholism (NIAAA) K23AA031310 grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Lee is supported by U01 DK58369 and by research support from Intercept, Aurora, Gilead, Novo Nordisk, Alexion, Eiger, Camurus and Lipocine and consults for Forma, SeaGen, GSK, Karuna, and Cortexyme. Dr. VanWagner is supported by NIH grant R56 HL155093 and by research support from W.L. Gore & Associates and the American Society for Transplantation, consults for Gerson Lehrman Group and Numares, and serves as an expert witness.

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