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Outcomes of Living Versus Deceased Donor Liver Transplantation for Acute Liver Failure in the United States

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Abstract

Clinical outcomes for living donor liver transplantation (LDLT) for acute liver failure (ALF) in the United States remain to be determined. To address this gap in knowledge, we examined post-liver transplantation outcomes of adults with ALF undergoing LDLT and deceased donor liver transplantation (DDLT) in the United States. We analyzed Organ and Procurement and Transplantation Network data for adults with ALF who were listed for liver transplantation as status 1 or 1A and who underwent LDLT (N = 21) or DDLT (N = 2316) between October 1987 and April 2011. We found no strong evidence that the survival probabilities for adults with ALF who underwent LDLT were inferior to those who underwent DDLT ($P = .764$). In adults with ALF who underwent LDLT, 1- and 5-year survival probabilities were both 71%; for DDLT these probabilities were 79% and 71%, respectively. In adults with ALF, 1- and 5-year liver graft survival probabilities, respectively, were 62% and 57% for LDLT, and 74% and 66% for DDLT. In these series of adults with ALF who were listed as status 1 or 1A, patient and graft survival rates for LDLT were similar to those for DDLT. Our findings suggest that if deceased donor livers are unavailable, LDLT is an acceptable option in experienced centers for adults with ALF.

Acute liver failure (ALF) is a life-threatening condition characterized by rapidly deteriorating liver function [1]. At a joint review from the American Association for the Study of Liver Diseases during Digestive Diseases Week in 2001, the incidence of ALF in the United States was estimated to be more than 2000 cases each year [2].

In the pre-liver transplantation era, the survival probability for ALF ranged from only 6% to 20% [1,3-5]. Although transplant-free survival of patients with ALF depends on the etiology of liver injury (eg, higher transplant-free survival in acetaminophen-induced ALF compared to hepatitis B-induced ALF), liver transplantation significantly improved outcomes in ALF [6]. Nonetheless, due to the limited number of donated livers in the United States, the

mortality for ALF, with or without liver transplantation, remains greater than 20%, with waiting times up to 6 weeks [6].

To increase the available donor pool, living donor liver transplantation (LDLT) was initiated in the late 1980s and early 1990s [7-9]. Russo et al [10] showed that transplantation candidates who had a potential living donor had significantly reduced transplantation waiting time mortality (~10%) compared to those without a living donor. In 1997, Kato et al [11] reported successful LDLT in an adult with ALF. However, since then LDLT for ALF has been limited by ethical concerns regarding inadequate conditions for obtaining donor consent [12-14].

Initially, it was uncertain if adults with ALF receiving LDLT have increased mortality compared to those receiving deceased donor liver transplantation (DDLT) [12-14]. Whereas some centers showed poor post-LDLT survival rates in recipients with ALF [15,16], others reported excellent post-transplantation outcomes [13,17-19]. In the prospective Adult-to-Adult Living Donor Liver Transplantation Cohort (A2ALL) study, Campsen et al [13] described 13 patients in the United States who underwent liver transplantation for ALF between 1998 and April 2007. Of these 13, 10 received LDLT and 3 DDLT; post-transplantation survival was 70% and 67%, respectively [13]. In 2012, LDLTs constituted approximately 3% of all adult liver transplants performed in the United States [20].

The aim of our study was to examine the Organ and Procurement and Transplantation Network (OPTN) database to assess post-liver transplantation outcomes of adults with ALF undergoing LDLT and DDLT in the United States. Our goal was to determine if LDLT should be considered an alternative for DDLT when deceased donor livers are unavailable.

METHODS

Study Population

We performed our analysis based on OPTN data as of July 6, 2012 (data through April 30, 2012). As there is a delay in reporting recipient outcomes, we excluded transplantations performed within the last 12 months of the data creation date by the United Network for Organ Sharing (UNOS). In our analysis, we included patients 18 years or older with ALF who underwent LDLT or DDLT between October 1, 1987, and April 30, 2011 with status 1 or 1A listing.

Study Variables

We identified adults transplanted for ALF based on the diagnosis variables of “acute hepatic necrosis” and “status 1 or status 1A” at registration in the UNOS database. Recipient and donor variables are shown in Tables 1 and 2. We defined recipient survival time as the time from the first liver transplantation until the death or last follow-up examination of the liver transplantation (for patients transplanted more than once, the last follow-up examination was defined as the last follow-up of the last liver transplantation) [21,22]. We defined liver graft survival time as the time from the first liver transplantation until the first liver graft failure or follow-up of the first liver transplantation [21,22]. We considered recipients to be “right-

censored” in the analysis if they were alive at the end of follow-up [21,22]. Liver grafts were right-censored if they had not failed by the last follow-up of the first liver graft [21,22].

Statistical Analysis

We performed statistical analysis using SAS software, version 9.2 (Cary, NC, United States) [23] and Minitab 16 statistical software (Minitab, Inc, State College, Pennsylvania, United States) [24].

For categorical variables, the chi-square and Fisher exact tests were used to assess differences between LDLT and DDLT recipients. For continuous variables, the Wilcoxon rank-sum test was used to assess differences between LDLT and DDLT recipients. We considered a P value $< .05$ to be statistically significant.

The Kaplan-Meier method [25] was used to estimate survival functions, and the log-rank test was used to compare survival functions between LDLT and DDLT recipients.

RESULTS

We identified a total of 2337 adults with ALF listed as status 1 or 1A who underwent liver transplantation between October 1, 1987, and April 30, 2011. Of these, 21 (0.9%) underwent LDLT and 2316 (99.1%) underwent DDLT.

Recipient and Donor Characteristics

The characteristics of adults with ALF listed as status 1 or 1A who underwent liver transplantation are listed in Table 1. The most common etiology of ALF was drug-induced liver injury (33.33% for LDLT vs 25.43% for DDLT, $P = .221$). The proportions of recipients on life support (76.19% vs 65.50%, $P = .363$) and with diabetes (4.76% vs 19.91%, $P = .100$) were similar for LDLT and DDLT, respectively. Whereas no one undergoing LDLT had simultaneous kidney transplantation, 1.68% of those undergoing DDLT had simultaneous kidney transplantation. The majority of recipients were women (76.19% for LDLT vs 68.61% for DDLT, $P = .637$) and white (57.14% for LDLT vs 59.84% for DDLT, $P = .221$). There was no significant difference in median age (31 vs 38 years, $P = .063$), median wait time on the liver transplant waiting list (2 vs 2 days, $P = .669$), median serum creatinine level (1.3 vs 1.3 mg/dL, $P = .768$), international normalized ratio (3.3 vs 2.9, $P = .619$), total bilirubin level (18.8 vs 19.8 mg/dL, $P = .589$) and model for end-stage liver disease score (37 vs 35, $P = .678$) between LDLT and DDLT recipients, respectively. As anticipated, the median cold ischemia time (1.0 vs 7.2 hours, $P < .0001$) and warm ischemia time (30 vs 45 minutes, $P = .0001$) were significantly shorter for LDLT recipients compared to DDLT recipients, respectively. Only 20 of 2316 DDLT patients had split grafts.

Table 2 summarizes donor characteristics. The majority of liver donors were men (66.67% for LDLT vs 57.90% for DDLT, $P = .418$) and white (57.14% vs 69.65%, $P = .418$). There were no significant differences in median age, weight, and height between those who underwent LDLT and DDLT. The majority of living donors were biologically related to recipient (67%). At 6-month follow-up, 7 of 21 living donors were able to function normally

or with minor symptoms. There was no information on functional status for the remainder (14 of 21) of the living donors.

Liver Recipient, Graft, and Donor Survival

Of 21 adults who underwent LDLT for ALF, we found no evidence that their survival probabilities were inferior to those with DDLT ($P = .764$; Fig 1). In patients with ALF who underwent LDLT, 1- and 5-year survival probabilities were 71% (95% confidence interval [CI]: 47% to 86%). Comparable probabilities for DDLT were 79% (CI: 77% to 81%) and 71% (CI: 69% to 73%), respectively (Fig 1).

We also found no evidence that liver graft survival probabilities in patients with ALF who underwent LDLT were inferior to those who underwent DDLT ($P = .569$). One- and 5-year liver graft survival probabilities were 62% (CI: 38% to 79%) and 57% (CI: 33% to 75%), respectively, for adults with ALF who underwent LDLT and 74% (CI: 72% to 76%) and 66% (CI: 64% to 68%), respectively, in those who underwent DDLT (Fig 2).

In the UNOS database, data on the survival status of living donors were available starting from October 25, 1999. Fourteen living donors were operated after that date and all were living 6 months after donation (Table 2).

DISCUSSION

The present study reveals that among patients with ALF who were listed as status 1 or 1A, post-liver transplantation patient and liver graft survival probabilities were similar after LDLT and DDLT. The 5-year patient survival rate was greater than 70% in both groups. Among patients with ALF who underwent LDLT, 1- and 5-year liver graft survival probabilities were 62% and 57%, respectively, and among those who underwent DDLT, 74% and 66%, respectively. Although, to our knowledge, our report describes the largest study of US patients receiving LDLT, the number of patients in our study is still too small to rule out the possibility of some differences between LDLT and DDLT with respect to survival.

Although initial reports described relatively unfavorable outcomes after LDLT for ALF [15,16], more recent studies showed survival similar to those for DDLT, suggesting that outcomes of patients undergoing LDLT for ALF have improved with time. A Japanese study showed 5-year cumulative survival to be greater than 70% in patients with ALF who underwent LDLT [26]. Park et al [18] studied 44 patients with ALF who underwent liver transplantation between January 2004 and June 2007 (40 received LDLT and 4 DDLT) and found 1-year patient survival rates of 85% for LDLT and 75% for DDLT ($P > .05$). Later, a Korean study of 160 patients with ALF who underwent liver transplantation from 2000 to 2009 (36 received DDLT and 124 received LDLT) showed similar 1- and 3-year patient survival rates for DDLT (78% and 74%, respectively) and LDLT (79% and 75%, respectively; $P = .99$) [27]. The authors reported similar 1- and 3-year liver graft survival rates for DDLT (75% and 71%, respectively) and LDLT (77% and 72%, respectively; $P = .97$) [27]. Liu et al [28] examined a cohort of 50 patients with ALF who were offered evaluation for LDLT. Of 34 patients pursuing LDLT evaluation in addition to standard

DDLT listing, 16 underwent LDLT, 14 of whom survived [28]. Of 16 patients who deferred LDLT, only 1 was transplanted, whereas 15 died on the DDLT waiting list [28]. LDLT and DDLT were compared in a retrospective cohort of Turkish adults and children with ALF [29]. LDLT recipients had increased 1-year survival (79% vs 58%) and decreased mean waiting times (2 vs 5 days) compared to DDLT recipients [29].

The most common cause of ALF in our series was drug-induced liver injury, but nearly a third of the patients had ALF of unidentified etiology. This differs from reports from Asia where the most common cause of ALF is hepatitis B [18,26,30], but is in accord with other US studies where drug-induced liver injury was also the most common cause [6,31].

Wait time for liver transplantation is associated with increased mortality. Everhart et al [32] examined the effect of ABO blood type as a surrogate for liver transplantation wait time. They noted that blood group O patients had increased pretransplantation mortality compared to those with non-O blood group; this was primarily due to a 2-fold increased median wait time [32]. Because ALF progresses rapidly, treatments including liver transplantation should occur promptly. Theoretically, LDLT may decrease wait times. In a study of pediatric patients, the majority of whom developed fulminant hepatic failure, Mack et al [33] compared DDLT to LDLT. LDLT recipients had greater survival (63% vs 27% of 6-month survival) with shorter median wait times (3.5 vs 6.5 days) compared to DDLT recipients. In our analysis, there was no significant difference in median waiting time between LDLT and DDLT adult patients, which may reflect increased access to DDLT organs in the United States.

We found that cold and warm ischemia times were decreased in patients who received LDLT when compared to those who underwent DDLT. In prior studies, cold ischemia time has been associated with increased graft survival after LDLT [34]. Because of the small number of patients with ALF who underwent LDLT, we could not evaluate the role of cold and warm ischemia times on graft survival.

In the United States, the use of LDLT has been limited by several factors, including problems with acquiring donor consent and donor/recipient outcomes [16,19,35]. Regarding donor survival, Muzaale et al [36] recently analyzed both short- and long-term survival of living liver donors in the United States. Whereas short-term mortality was significantly increased in living liver donors compared to matched healthy individuals ($P = .008$), long-term mortality did not differ between living liver donors, living kidney donors, and healthy matched controls (5-year mortality was reported as 0.4% in all three groups) [36]. Our analysis showed that all living donors who had 6-month follow-up data were alive at the end of 6 months.

Our study provides a US population-based estimate of recipient outcomes and characteristics after LDLT for ALF; this is the largest reported series to date of ALF patients listed as status 1 or 1A undergoing LDLT in the United States. However, there are limitations to the current work. The number of patients with ALF who underwent LDLT was very small making it difficult to estimate survival probabilities with precision in that group. Furthermore, because of the small number of ALF patients undergoing LDLT, it was not

possible to assess factors influencing recipient mortality or graft failure. As this is a retrospective analysis of prospectively collected data by different medical centers, bias may be present. Furthermore, the dataset includes missing data and misclassification for some covariates and outcomes investigated. These limitations have been reported by other groups using the OPTN (UNOS) dataset [37,38]. However, all eligible patients are included with few data missing, and we report all missing information. Most importantly, this study provides limited data on complications of LDLT and living donor survival. This is significant, as justification of LDLT for ALF is dependent on both recipient and donor outcomes.

In summary, we found no strong evidence of a difference in survival probabilities between adults with ALF who underwent LDLT and those who underwent DDLT. Additional studies are necessary to assess risk factors associated with recipient mortality and graft failure in LDLT for ALF. In experienced centers, following proper assessment and open discussions of risks and benefits with both recipients and potential donors, LDLT may be considered an option for adults with ALF when deceased donor livers are unavailable.

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Fig 1.
Post-liver transplantation patient survival for adults with ALF listed as Status 1 or 1A who underwent LDLT or DDLT.

Fig 2.
Post-liver transplantation graft survival in patients with ALF listed as Status 1 or 1A who underwent LDLT or DDLT.

Table 1
Demographic and Clinical Characteristics of Adult Patients With ALF Who Were Listed as Status 1, 1A and Underwent LDLT or DDLT Between 10/01/1987 and 4/30/2011

Recipient Characteristics	LDLT N = 21		DDLT N = 2316		P Value
	N	%	N	%	
Sex					.637
Men	5	23.81	727	31.39	
Women	16	76.19	1589	68.61	
Race					.221
White	12	57.14	1386	59.84	
Black	3	14.29	471	20.34	
Hispanic	6	28.57	267	11.53	
Asian	0	0	140	6.04	
Unknown	0	0	52	2.25	
Etiology of ALF					.221
Drug-induced	7	33.33	589	25.43	
Hepatitis A	1	4.76	89	3.84	
Hepatitis B-HBsAg +	0	0	288	12.44	
Others	3	14.29	547	23.62	
Unknown	10	47.62	803	34.67	
Life support at transplantation					.363
Yes	16	76.19	1517	65.50	
No	5	23.81	799	34.50	
Dialysis at transplantation					.093
Yes	7	33.33	386	16.67	
No	13	61.90	1535	66.31	
Unknown	1	4.76	394	17.02	
Missing			1		
Simultaneous kidney transplantation					1.000
Yes	0	0	39	1.68	
No	21	100.00	2277	98.32	

Recipient Characteristics	LDLT N = 21		DDLT N = 2316		P Value
	N	%	N	%	
Education level					.232
Grade 0–8	2	9.52	41	2.09	
High school (9–12) or GED	5	23.81	563	28.72	
College/technical school	3	14.29	262	13.37	
Associate/bachelor degree	4	19.05	203	10.36	
Post-college graduate Degree	0	0	69	3.52	
Not applicable	0	0	2	0.10	
Unknown	7	33.33	817	41.68	
None	0	0.00	3	0.15	
Missing			356		
ABO blood type					.298
A	5	23.81	869	37.52	
B	2	9.52	319	13.77	
AB	0	0	99	4.27	
O	14	66.67	1029	44.43	
Number of transplants					.082
1	16	76.19	2066	89.21	
2	4	19.05	218	9.41	
3	1	4.76	30	1.30	
4	0	0	1	0.04	
5	0	0	1	0.04	
Post-transplantation survival status					.654
Alive	15	71.43	1547	66.80	
Dead	6	28.57	769	33.20	
Graft failed					.705
Yes	9	42.86	899	38.82	
No	12	57.14	1417	61.18	
Diabetes					.100
Yes	1	4.76	461	19.91	
No	20	95.24	1855	80.09	

Recipient Characteristics	LDLT N = 21			DDLT N = 2316			P Value
	Median	Quartile Range	%	Median	Quartile Range	%	
Age (y)	31.0		15.0	38.0		21.0	.063
Days on the waiting list	2.0		1.0	2.0		2.0	.669
MELD score at transplantation	37.0		14.0	35.0		11.0	.678
Total bilirubin at transplantation (mg/dL)	18.8		14.3	19.8		19.0	.589
INR at transplantation	3.3		2.7	2.9		2.3	.619
Serum creatinine level at transplantation (mg/dL)	1.3		2.4	1.3		1.9	.768
Cold ischemia time (h)	1.0		1.9	7.2		3.9	<.0001
Warm ischemia time (min)	30.0		7.0	45.0		23.0	.0001
Recipient weight (kg)	64.4		23.1	73.1		23.5	.052
Recipient height (cm)	163.0		10.0	167.6		12.4	.146
Patient post-liver transplantation follow-up time (y)	5.3		9.0	4.1		8.5	.949
First liver graft follow-up time (y)	1.1		9.3	3.5		7.9	.447

Abbreviations: ALF, acute liver failure; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; GED, general educational development (test for high school equivalency diploma); MELD, Model for End-stage Liver Disease; INR, international normalized ratio.

Demographic and Clinical Characteristics of Donors for Adult Patients With ALF Who Underwent LDLT or DDLT Between 10/1/1987 and 4/30/2011

Table 2

Donor Characteristics	LDLT N = 21		DDLTL N = 2316		P Value
	N	%	N	%	
Donor sex					.418
Men	14	66.67	1341	57.90	
Women	7	33.33	975	42.10	
Donor race					.418
White	12	57.14	1613	69.65	
Black	3	14.29	302	13.04	
Hispanic	6	28.57	333	14.38	
Asian	0	0	39	1.68	
Unknown	0	0	29	1.25	
Donor ABO blood type					.794
A	4	19.05	615	26.55	
B	1	4.76	116	5.01	
AB	0	0	28	1.21	
O	16	76.19	1556	67.18	
Unknown	0	0	1	0.04	
Donor education level					N/A
High school (9–12) or GED	4	21.05	N/A	N/A	
College/technical school	2	10.53	N/A	N/A	
Associate/bachelor degree	3	15.79	N/A	N/A	
Post-college graduate degree	2	10.53	N/A	N/A	
Unknown	8	42.11	N/A	N/A	
Missing		2318			
Non-heart-beating donor					N/A
Yes	N/A	N/A	38	1.95	
No	N/A	N/A	1912	98.05	
Donor survival status (at 6 month follow-up)					
Alive	14	78.57	N/A	N/A	

Donor Characteristics	LDLT N = 21			DDLT N = 2316			P Value
	N	%		N	%		
Missing	7			N/A			N/A
Donor relationship to recipient							N/A
Biological, blood-related parent	4	19.05		N/A			N/A
Biological, blood-related child	1	4.76		N/A			N/A
Biological, blood-related identical twin	1	4.76		N/A			N/A
Biological, blood-related full sibling	7	33.33		N/A			N/A
Biological, blood related other relative	1	4.76		N/A			N/A
Non-Biological, Spouse	2	9.52		N/A			N/A
Non-biological, other unrelated Donation (boyfriend, fiancé, brother-in-law, friend)	5	23.81		N/A			N/A
Donor liver reoperation (first 6 weeks)							N/A
Yes	1	12.50		N/A			N/A
No	7	87.50		N/A			N/A
Missing	13			N/A			N/A
Functional status (at 6-month follow-up)							
Normal, no complaints, no evidence of disease	4	50.00		N/A			N/A
Performs activities of daily living with no assistance	1	12.50		N/A			N/A
Able to carry on normal activity: minor symptoms of disease	2	25.00		N/A			N/A
Unknown	1	12.50		N/A			N/A
Missing	13			N/A			N/A
Donor age (y)	Median	Quartile Range	Median	Quartile Range			P Value
	36.0	15.0	35.0	29.0			.650
Donor weight (kg)	75.6	22.9	72.6	19.4			.910
Donor height (cm)	170.2	15.2	170.2	13.0			.875

Abbreviations: ALF, acute liver failure; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; GED, general educational development (test for high school equivalency diploma).