ORIGINAL ARTICLE

Outcomes of Living Donor Liver Transplantation for Acute Liver Failure: The Adult-to-Adult Living Donor Liver Transplantation Cohort Study

Jeffrey Campsen,[1] Andres T. Blei,[2] Jean C. Emond,[3] James E. Everhart,[4] Chris E. Freise,[5] Anna S. Lok,[6] Sammy Saab,[7,8] Karen A. Wisniewski,[9] James F. Trotter,[1] and the Adult-to-Adult Living Donor Liver Transplantation Cohort Study Group

[1]Division of Transplant Surgery, University of Colorado, Aurora, CO; [2]Department of Medicine, Northwestern University, Chicago, IL; [3]Department of Surgery, Columbia Presbyterian Medical Center, New York, NY; [4]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; [5]Department of Surgery, University of California San Francisco, San Francisco, CA; [6]Department of Internal Medicine, University of Michigan, Ann Arbor, MI; Departments of [7]Medicine and [8]Surgery, University of California Los Angeles, Los Angeles, CA; and [9]Department of Surgery, University of Michigan, Ann Arbor, MI

For acute liver failure (ALF), living donor liver transplantation (LDLT) may reduce waiting time and provide better timing compared to deceased donor liver transplantation (DDLT). However, there are concerns that a partial graft would result in reduced survival of critically ill LDLT recipients and that the rapid evolution of ALF would lead to selection of inappropriate donors. We report outcomes for ALF patients (and their donors) evaluated for LDLT between 1998 and April 2007 from the Adult-to-Adult Living Donor Liver Transplantation Cohort. Of the 1201 potential LDLT recipients, 14 had ALF, only 6 of whom had an identified cause. The median time from listing to first donor evaluation was 1.5 days, and the median time from evaluation to transplantation was 1 day. One patient recovered without liver transplant, 3 of 10 LDLT recipients died, and 1 of 3 DDLT recipients died. Five of the 10 living donors had a total of 7 posttransplant complications. In conclusion, LDLT is rarely performed for ALF, but in selected patients it may be associated with acceptable recipient mortality and donor morbidity. ***Liver Transpl 14:1273-1280, 2008.*** © **2008 AASLD.**

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There are more than 2000 cases per year of acute liver failure (ALF) in the United States.[1,2] This condition is frequently characterized by rapid evolution to coma and death, and the only effective therapy is liver transplantation. Of the 6643 liver transplants performed in the United States in 2005, 386 (5.9%) were United Network for Organ Sharing status 1, about two-thirds of which

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort; ALF, acute liver failure; DDLT, deceased donor liver transplantation; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease score; txp, transplant.

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Address reprint requests to James F. Trotter, M.D., University of Colorado Hospital, 1635 North Ursula, Campus Box 154, Aurora, CO 80262. Telephone: 720-848-2245; FAX: 720-848-2246; E-mail: james.trotter@uchsc.edu

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had ALF.[3] In ALF patients who require liver transplantation, 1-year survival after deceased donor liver transplantation (DDLT) is approximately 82%, which is slightly less than that of other indications (88%). Because of the rapid evolution of ALF and the shortage of deceased donor livers, many patients with ALF die waiting for a DDLT. Therefore, treatment strategies that could expedite transplantation in these critically ill patients might potentially improve outcomes. One such option could be living donor liver transplantation (LDLT), which may reduce waiting time and provide more optimal timing of surgery compared to DDLT. However, there may be disadvantages to LDLT in ALF patients. Many transplant centers do not perform LDLT in critically ill patients because of the high postoperative mortality rate in this setting.[4,5] In fact, the New York State Health Department guidelines consider ALF as a contraindication for LDLT.[6] In addition, there are concerns whether donor candidates can be appropriately evaluated during the rapid evolution of ALF. Unfortunately, there is very little data on outcomes in LDLT recipients with ALF since LDLT is rarely performed for this indication. The Adult-to-Adult Living Donor Liver Transplantation Cohort (A2ALL) study provides an opportunity to study LDLT in ALF because data are collected from a large cohort of LDLT candidates at 9 U.S. transplant centers. As a result, there may be sufficient patients with ALF to understand the role of LDLT in this setting. In this article, we report the outcomes of recipients with ALF and their donors from the A2ALL study.

PATIENTS AND METHODS

Study Population and Data Sources

The A2ALL study collected data on the LDLT experience from January 1998 to April 2007 at 9 U.S. transplant centers. The study consists of both a retrospective section and a prospective (cohort) section. The primary objective of the study is to compare outcomes of patients who received an LDLT with patients who had similar prognoses and severity of liver disease. Therefore, qualification for the study required that a patient on the liver transplantation waitlist had a potential donor who underwent an initial history and physical examination, regardless of whether LDLT occurred. All donor candidates evaluated for the potential recipients were invited to participate in the study, regardless of acceptance status. Enrollment into the retrospective section of the study ended in February 2003, while recruitment into the prospective section is currently ongoing.

Recipient and donor candidate data were provided by each of the participating transplant centers on the basis of a common protocol. For the retrospective section, extensive information from chart reviews was supplemented where appropriate with data from the Scientific Registry of Transplant Recipients under a data use agreement. Data were collected prospectively for the cohort study.

ALF was defined as a status 1 listing in the Scientific Registry of Transplant Recipients combined with a primary, secondary, or tertiary diagnosis of fulminant hepatic failure (such as acute hepatic necrosis or Wilson's disease). A total of 14 ALF patients were identified, including 1 patient who was included in a previous case report.[7] The Model for End-Stage Liver Disease score was calculated both at the time of study enrollment and at transplant. Complications of donors and recipients were defined as unexpected events if they were not inherent to the transplant or donation procedure.

Statistical Analysis

Descriptive statistics included ranges, means, standard deviations, and proportions as appropriate. Comparisons of ALF characteristics by LDLT status, donor candidate characteristics by acceptance status, and posttransplant complications by graft type were performed with Fisher's exact test for categorical variables and two-sample t tests for continuous variables. All analyses were carried out with SAS 9.1 statistical software (SAS/STAT 9.1 User's Guide, SAS Publishing, Cary, NC: SAS Institute, Inc., 2004).

Human Subject Protection

The study was approved by the institutional review boards and privacy boards of the University of Michigan Data Coordinating Center and each of the 9 participating transplant centers.

RESULTS

Of the 1201 potential LDLT recipients, ALF was the indication for transplantation in only 14 (1%) patients. The age of the ALF patients ranged from 18 to 66 years with a mean of 34 years. Two patients had hepatitis A, and one each had acetaminophen toxicity, hepatitis B, autoimmune hepatitis, and Wilson's disease. No cause was identified in 8 patients.

Ten patients received LDLT, 3 underwent DDLT, and 1 clinically improved and was removed from the waitlist. All LDLT recipients received a right hepatic lobe graft. The mean length of the initial hospital stay for all 14 patients was 24 days (range: 9 to 54 days). None of the patients died while awaiting liver transplantation. For each patient, the time course from transplant listing is shown in Fig. 1, and summary information is shown in Table 1.

Of the 13 patients transplanted, the survival rates were 70% (7 of 10 patients) and 67% (2 of 3 patients) after LDLT and DDLT, respectively. Causes of death included 2 cases of graft failure and 2 cases of fungal infection. None of the patients underwent retransplantation. The 9 surviving patients had been followed for a median of 5 years (range: 1 to 8 years) after liver transplantation. Eleven of the 13 transplanted patients experienced a total of 39 complications (Table 2); this rate was similar to that experienced by patients who underwent liver transplantation in the A2ALL study.[8]

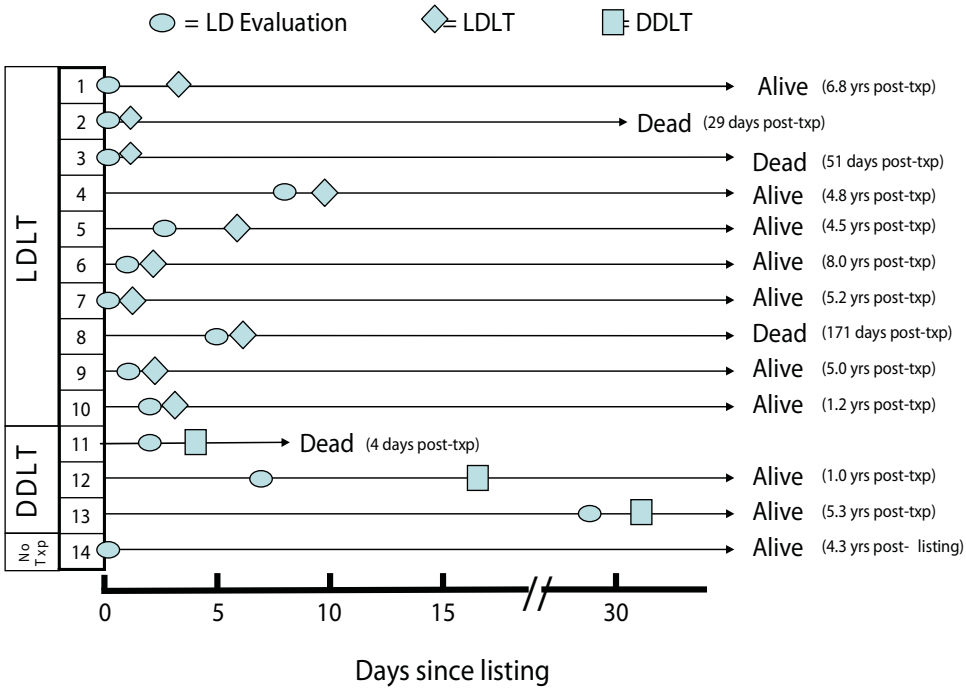

Figure 1. Outcome of 14 patients with acute liver failure evaluated for LDLT. Abbreviations: DDLT, deceased donor liver transplantation; LD, living donor; LDLT, living donor liver transplantation; txp, transplant.

Of the 20 donor candidates evaluated for the 14 recipient candidates, 19 were enrolled in the A2ALL study. Ten recipient candidates had only 1 donor candidate evaluated, 3 had 2 donor candidates, and 1 had 4 donor candidates. The 1 patient who had 4 potential donors evaluated underwent LDLT.[9] Table 3 depicts the donor demographics. LDLT donors were predominantly (80%) male with a mean age of 36 years (range: 20 to 50 years). Five of the 10 living donors who proceeded with the donor surgery were siblings or spouses. The mean duration of the post-donation hospitalization was 6 days (range: 3 to 10 days). Of the 10 who donated, 5 (50%) donors experienced a total of 7 complications (Table 2); this is comparable to the rate of complications experienced by all donors in the A2ALL study of 37.7%.[10] The donor perioperative survival was 10/10 or 100%.

DISCUSSION

This study demonstrates that LDLT may be performed safely in patients with ALF. The survival rate of LDLT recipients (70%) in this study was comparable to that of those who underwent DDLT (82%) for ALF in the United States.[3] Both donor and recipient complication rates were comparable to those for LDLT for other indications in the A2ALL study.[8,10] In addition, none of the patients evaluated for LDLT died while awaiting liver transplantation. This may represent one of the most important benefits of LDLT. However, our data represent a relatively limited experience, and continued analysis is required to affirm these conclusions.

Our results are similar to the reported worldwide experience of LDLT in ALF, most of which is from Asia (Table 4). Conclusions from 2 reports from Hong Kong were that right lobe LDLT improved the overall survival rate of patients with ALF and should be offered as a treatment option.[11,12] Japanese investigators published several series of LDLT for ALF. Uemoto et al.[13] reported outcomes in 15 adult ALF patients who received either a left lobe (8 patients) or right lobe (7 patients) LDLT, including 3 auxiliary partial orthotopic liver transplants. The mean time between transfer to the transplant center and transplantation was 2.0 days with a range of 0 to 7 days, with overall survival (including pediatric recipients) of 59% at 3 years. No significant donor problems were reported. These investigators observed that LDLT with a left hepatic lobe was insufficient for critically ill ALF patients and was more likely to lead to "small-for-size syndrome" and primary nonfunction compared to LDLT with the right hepatic lobe. Two other centers in Japan reported greater than 80% survival in adult LDLT recipients after a follow-up period from 1 to 43 months.[14,15] There were limited donor outcome data other than a statement that all donors survived. Thus, the Asian experience of LDLT in ALF is similar to the experience of our cohort, in that ALF was an uncommon indication for LDLT and recipient outcomes were favorable. Some of the reports from Asia suggested that the outcome in ALF patients is dependent on a critical liver mass. There was no evidence of a prohibitively high rate of donor problems in the Asian studies, although data were sparse.

There have been case reports only from the United States describing LDLT for ALF. There have been reports of successful left lobe LDLT from the University of

TABLE 1. Characteristics of Patients at Time of Donor Evaluation

Characteristic	Overall (n = 14)	LDLT (n = 10)	Non-LDLT* (n = 4)	*P* Value
Age	34 (14.6)	39 (15.0)	23 (4.1)	0.07
Sex				0.60
Male	5	4	1	
Female	9	6	3	
Race				0.10
White	13	10	3	
African American	1	0	1	
Specific primary diagnosis				0.25
Acetaminophen toxicity	1	0	1	
Hepatitis A	2	2	0	
Hepatitis B	1	1	0	
Autoimmune hepatitis	1	1	0	
Wilson's disease	1	0	1	
Etiology unknown	8	6	2	
MELD at enrollment				0.28
6-10	0	0	0	
11-20	1	0	1	
21-30	5	4	1	
31-40	7	5	2	
Missing	1	1	0	
MELD at transplant*				1.00
6-10	0	0	0	
11-20	0	0	0	
21-30	4	3	1	
31-40	8	6	2	
Missing	2	1	1	
Recipient medical condition				—
ICU	14	10	4	
Respiratory failure requiring mechanical ventilation	7	5	2	1.00
Renal failure requiring dialysis	4	3	1	0.85
Year of evaluation				0.02
1998-2001	10	9	1	
2002-2006	4	1	3	
Time from listing to donor evaluation (days)	4 (7.6)	2 (2.7)	10 (13.3)	0.10
Time from donor evaluation to transplant (days)*	2 (2.5)	2 (1.1)	5 (4.6)	0.06
Transplant hospitalization (from admission)				
Length of hospital stay	24 (14.4)	24 (12.8)	24 (20.3)	0.98
Length of ICU stay	13 (15.3)	14 (18.2)	9 (4.5)	0.56
Patient survival				0.85
Alive	10	7	3	
Dead†	4	3	1	
Graft survival*				0.91
Functioning	9	7	2	
Failed‡	4	3	1	
Number of potential donors§				0.33
4	1	1	0	
3	0	0	0	
2	3	3	0	
1	10	6	4	

NOTE: Data are presented as N or mean (standard deviation).

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort; DDLT, deceased donor liver transplantation; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease score.

*Non-LDLT includes DDLT recipients (n = 3) and one fulminant that was not transplanted because of an improvement in his medical condition and removal from the waitlist.

†Time to death (days): LDLT = 29, 51, and 171; DDLT = 4.

‡Time to graft failure (days): LDLT = 9, 29, and 171; DDLT = 4.

§One donor evaluated for a DDLT recipient did not enroll in the A2ALL study; data are not shown for this patient in Table 2.

TABLE 2. Complications of Recipients [LDLT (n = 10) and DDLT (n = 3)] and Actual Donors (n = 10)

	Number of Patients with Complications		
	Recipients		Donors
Complication	LDLT	DDLT	
Any complication	8	3	5
Bile leak/biloma	1	0	2
Biliary stricture	2	1	0
Other surgical complications*	4	2	1
Cardiopulmonary complications†	4	3	2
Encephalopathy	1	0	0
Other medical complications‡	3	1	1
Overall infection	3	2	1
Other complications	0	1	0

NOTE: Complications were not collected on those who did not undergo surgery.
Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.
*Other surgical complications include intra-abdominal bleeding, prolonged ileus, localized intra-abdominal abscess, and re-exploration.
†Cardiopulmonary complications include pleural effusion, pulmonary edema, and respiratory arrest.
‡Other medical complications include upper/lower gastrointestinal bleeding, histological evidence of chronic rejection, neuropraxia, and recurrence of liver disease.

Miami in 1997[16] and successful right lobe LDLT from Virginia Commonwealth University in 2000.[7] The latter patient was included in this report. Outside the United States, there are 4 case reports from the University of Western Australia[17] (1 patient) and the Tel Aviv Medical Center[18] (3 patients) using right and left lobes. Not only is LDLT for ALF a rare event in the United States, but its use may be declining. In the current study, 10 of the 14 LDLT evaluations occurred during the first half of the observation period. The reason(s) for this are not entirely clear but may be related to guidelines from the New York Department of Health on LDLT after a well-publicized donor death. These guidelines proscribe ALF as a recommended indication for LDLT because the committee promulgating these guidelines had concerns about (1) the donor's capacity to make an informed decision in the setting of ALF and (2) outcomes in critically ill recipients receiving LDLT.

An important concern is whether donor candidates can be appropriately evaluated during the rapid evolution of ALF. In most studies, the donor evaluation period is measured in hours or a few days, which is much shorter than the period for LDLT for other indications. Based on our experience, broad guidelines for approaching LDLT in the setting of ALF can be made. The physicians and surgeons at each transplant center must first decide whether they would choose to offer LDLT in the setting of ALF. If the decision is affirmative, then the recipient and donor evaluation proceeds in a fashion similar to that for candidates with chronic disease. The rapid evolution of ALF presents special concerns in the evaluation of living liver donor candidates. Given the rapid evolution of ALF, the most expeditious means of proceeding would be to evaluate ideal donor candidates with a high likelihood of acceptance. Marginal donor candidates, who may require a complex evaluation and a high non-acceptance rate, are not well suited to donate to patients with ALF. The compressed time frame of the donor evaluation also presents special concerns regarding donor coercion. Some donor candidates suitable for recipients with chronic disease may be unsuitable for recipients with ALF. The proper evaluation of a donor candidate in the setting of ALF requires a donor evaluation team with experience and judgment. In this study, there were insufficient patients to determine if the expedited donor evaluation was associated with worse donor outcomes. The potential consequences of an expedited donor evaluation could be increased donor postoperative complications and worse psychological problems. The rate of complications in our donors (50%) was comparable to the rate of donor complications for all indications in the A2ALL study (37.7%).[10] There were no severe psychological complications noted in these 10 donors versus 4% in the A2ALL study.[19] We acknowledge that quality of life and emotional well being were not prospectively studied and follow-up of donors was limited. These information are prospectively collected in the A2ALL study.

Finally, the evaluation of a donor candidate should not preclude or delay a DDLT should a suitable deceased donor liver become available during the liver donor evaluation.

Another concern is the outcome of critically ill recipients receiving a partial graft. The survival rate of our recipients who underwent LDLT was comparable to published data on DDLT for ALF. The complication rate of the recipients who underwent LDLT was similar to that of other recipients who underwent LDLT in the A2ALL study. Specifically, none of the patients had "small-for-size syndrome," and none required retransplantation.

There are important comparisons that can be drawn between our cohort and other patients with ALF. In the most comprehensive report of ALF in the United States,

TABLE 3. Characteristics of Potential Donors at Time of Donor Evaluation

Characteristic	Overall (n = 19)	Accepted Donors (n = 10)	Non-Accepted Donors (n = 9)	*P* Value
Age	35 (8.1)	36 (9.2)	34 (7.0)	0.51
Sex				0.51
Male	14	8	6	
Female	5	2	3	
Ethnicity				0.41
Hispanic/Latino	6	4	2	
Non-Hispanic/non-Latino	13	6	7	
Race				0.28
White	18	10	8	
African American	1	0	1	
Height (cm)	170 (12.1)	173 (12.1)	167 (12.4)	0.40
Weight (kg)	73 (19.0)	71 (14.7)	75 (27.7)	0.74
Body mass index (kg/m^2)	25 (4.4)	24 (3.0)	26 (6.1)	0.28
Reason for non-acceptance				—
Medical contraindications	—	—	3	
Anatomical contraindications	—	—	4	
Recipient received DDLT[‡]	—	—	1	
Recipient improved	—	—	1	
Relatedness to recipient				0.32
Biologically related				
Parent	0	0	0	
Child	4	1	3	
Sibling	6	4	2	
Other biological	1	1	0	
Not biologically related				
Spouse	1	1	0	
Other nonbiological	5	3	2	
Unknown/Missing	2	0	2	
Year of evaluation				0.21
1998-2001	15	9	6	
2002-2006	4	1	3	
Donation hospitalization*				
Length of hospital stay	—	6 (1.8)	—	—
Length of ICU stay	—	0 (0.5)	—	—
Survival				0.33
Alive	18	9	9	
Dead[†]	1	1	0	

NOTE: Data are presented as N or mean (standard deviation).
Abbreviations: DDLT, deceased donor liver transplantation; ICU, intensive care unit.
*Hospitalization information was not collected on those who did not donate.
[†]The cause of death for the living donor occurred 16 months after donation and was unrelated to donation.
[‡]Although there were 3 DDLTs, only one was the reason for donor non-acceptance.

TABLE 4. Worldwide Performance of Living Donor Liver Transplantation for Acute Liver Failure

Center	Year	Right Lobe	Left Lobe	Reference
University of Hong Kong	2002	11	0	12
Kyoto University	2000	7	8	13
Shinshu University	1999	0	2	14
Kyushu University	1999	0	15	15
University of Miami	1997	0	1	16
Medical College of Virginia	2000	1	0	7
University of West Australia	2001	1	0	17
Tel Aviv Medical Center	2004	2	1	18

the most common etiology of ALF was acetaminophen toxicity (39%), whereas only 1 of the 14 patients in the A2ALL study had this etiology of ALF.[20] One potential explanation for the small proportion of acetaminophen patients in our study may be the high spontaneous recovery associated with acetaminophen toxicity (approximately 90%). An alternative explanation may be the high incidence of psychosocial and drug abuse problems, which are common in acetaminophen overdose patients.[21] Consequently, patients with acetaminophen poisoning may have been excluded from the complex donor and recipient evaluation required for LDLT. There is some evidence to suggest that patients with ALF who are considered for LDLT are predicted to have more favorable outcomes than the typical ALF patients. The median age of LDLT recipient candidates in our cohort (28 years) was younger than the median age of the patients in the study cited above (38 years). In addition, 13 of our 14 patients (93%) were white versus 74% in the Ostapowicz study.[20] Finally, a higher percentage of patients in our cohort underwent transplantation. Ostapowicz et al. reported that of the 135 patients with ALF who were listed for liver transplant, 89 (66%) were transplanted, 30 (22%) died on the list waiting for liver transplant, and 16 (12%) spontaneously recovered. In our study, 13 of 14 patients (93%) underwent transplantation, and none died waiting for transplant. The higher transplant rate in our study may reflect the identification of ideal LDLT candidates early in disease progression. Alternatively, an expeditious transplant with a living donor may reduce waiting list mortality.

In summary, these preliminary findings suggest that LDLT is a safe treatment option in selected patients with ALF. We also found that the risk to the donor is comparable to the risk of LDLT for other indications. Finally, these results provide a rational basis for the continued, careful application of LDLT in patients with ALF.

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