

# Perioperative Events in Living and Deceased Donor Liver Transplant Recipients: A Case Control Study

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**Abstract:** Living donor liver transplantation (LD) has been implemented as an alternative to deceased donor transplantation (DD). We reviewed the perioperative course of recipients of LD and recipients of DD at our institution with specific aims to compare intraoperative events, early complication rates, resource utilization, and patient survival. **Methods:** Following Institutional Review Board (IRB) approval, the first forty LD cases were retrospectively matched by age, sex, and primary reason for transplant with controls that underwent DD between June 30, 2000 and January 25, 2005. Preoperative data, intraoperative variables, and immediate postoperative data were collected. Statistical analysis included signed rank test, McNemar's test, Wald statistics, and stratified Cox proportional hazards model. **Results:** Calculated Model for End Stage Liver Disease (MELD) scores were higher for DD (median 18 vs. 14 with  $p=0.04$ ). Anesthesia time was longer in LD (median 7.1 vs. 6.5,  $p=0.02$ ). Hospital length of stay (LOS) was higher in LD (median 12 vs. 8 days,  $P=0.002$ ). Seven of the 40 (17%) LD were deceased at the time of data collection, as were four (10%) of the DD. **Conclusions:** Comparison of DD and LD at our institution revealed few significant differences in perioperative variables. LD may have more postoperative complications and longer hospital stays but similar patient survival.

**Keywords:** Transfusion requirements, perioperative morbidity, biliary complications, wound infections, intraoperative complications.

## INTRODUCTION

Living donor liver transplantation (LD) has been implemented as an alternative to deceased donor liver transplantation (DD). With approximately 17,000 candidates awaiting DD, living donor transplantation offers an alternative for patients unlikely to receive a deceased donor liver. Over 300 living donor liver transplants were performed each year from 2002 to 2005 in the United States [1]. Anesthesiologists, surgeons, and intensivists have had much experience with DD, but much less in caring for recipients of living donor liver transplants. As living donation becomes an accepted alternative to deceased donation, the safety of this option is a concern. Several publications have reported complications and outcomes associated with LD [2-5], however direct comparisons with DD recipients may be confounded by differences in the patient characteristics of those undergoing LD versus DD [6].

Adult to adult LD was first performed at our institution in 2000; by 2005 we had carried out 40 cases. We reviewed these cases for intraoperative, early postoperative events, and outcomes. These were compared with a matched group of DD cases. We hypothesized that with case matching the

complication frequency and outcomes would be similar in both groups.

## PATIENTS AND METHODS

This study was performed with approval of the institutional review board of Mayo Clinic. Data were abstracted from prospectively maintained transplantation and anesthesia databases as well as by review of patient medical records. Each LD case was matched by age (within 12 years), gender, and etiology of liver disease leading to transplantation, to a DD primary liver transplant case. All transplants occurred during the 2000-2005 time period.

Preoperative investigations and screening for both LD and DD patients were similar. All patients, DD and LD, met UNOS minimum listing criteria. The decision to list for transplantation was made by a multidisciplinary group including transplant surgeons; transplant hepatologists; specialists in anesthesia, critical care, and infectious diseases; nurse coordinators; social workers; and other allied health members of our transplant team.

The first 40 LD procedures at the Mayo Clinic were performed by two experienced liver transplant staff surgeons (CBR and JKH). All transplants were performed with caval sparing hepatectomy without use of venous bypass. Donor liver grafts were perfused with Viaspan (UW solution) and prepared for implantation on a back table. Deceased donor iliac veins were used as interposition grafts for recipients

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with hilar cholangiocarcinoma [7] and occasionally for reconstruction of large segment V or segment VIII veins. Right liver grafts were implanted with a right hepatic vein – to recipient right hepatic vein anastomosis, and larger inferior hepatic and caudate veins were sewn directly to the recipient cava with an end-to-side anastomosis during 22 of the operations. The donor right hepatic vein was sewn to the recipient left/middle hepatic vein for a recipient with complete situs inversus. Segment V and/or segment VII veins were reconstructed in 5 patients using either deceased donor iliac veins or the recipient middle hepatic vein which had been preserved during the hepatectomy. The donor right portal vein was sewn to the recipient portal vein, and deceased donor iliac veins were used as interposition grafts for all 9 cholangiocarcinoma (CCA) patients. Following portal reperfusion, arterial reconstruction was performed between the donor right or replaced right hepatic artery and the recipient right, left, proper, or common hepatic artery. Biliary reconstruction was performed with either a duct-to-duct anastomosis or a Roux Y hepatojejunostomy over an internal biliary stent.

The deceased donor transplant procedures were performed by a staff surgeon and transplant surgery fellow (either as primary surgeon). All patients underwent caval-sparing hepatectomy without use of venous bypass. Implantation was accomplished with an end-to-end anastomosis between the donor suprahepatic vena cava and the recipient left/middle hepatic venous trunk; and end-to-end portal venous anastomosis; and arterial reconstruction. A deceased donor iliac artery graft to the infrarenal aorta was used for all hilar cholangiocarcinoma patients and patients with inadequate common hepatic arterial flow. Biliary reconstruction was either with a duct-to-duct anastomosis over a biliary tube inserted through the donor cystic duct stump or a Roux Y choledochojejunostomy over a biliary tube brought out through the bowel wall.

Intraoperative anesthetic management for all transplants was carried out by members of the liver transplant anesthesia group. Anesthetic management for both groups was the same, consisting of general anesthesia using isoflurane with fentanyl supplementation. Routine invasive monitoring was utilized, including direct arterial pressure and pulmonary artery catheterization. Rapid infusion and cell saver devices were used for all cases.

Postoperatively all patients were transferred to the transplant ICU where the same immediate postoperative management protocol, including the use of a ventilator weaning protocol, was followed.

**Data Collection and Analysis**

Database and patient records were reviewed for anesthesia time, surgical time, blood product transfusion, and significant pulmonary or hemodynamic events (Table 1). Postoperative information collected included blood product transfusion, cardiac and pulmonary complications, biliary complications, infections, length of intubation, acute renal dysfunction, portal vein or hepatic artery thrombosis (HAT), and hospital length of stay (LOS).

**Table 1. Data Collection**

Intraoperative cardiopulmonary events:	
Mean arterial pressure less than 50% baseline	
CPR	
Hypoxemia requiring intervention (documented on anesthetic record)	
Arrhythmia requiring intervention	
<u>Postoperative Hospitalization</u>	
Occurrence of “Postoperative event”	
Prolonged intubation (>48hrs)	
Reintubation	
At least one episode of MAP less than 50% baseline	
Institution of CPR	
Other significant alteration in cardiorespiratory status requiring emergent intervention (specify)	
Occurrence of “Postoperative diagnosis”	
Myocardial infarction- defined as diagnosis by treating physician, or Troponin >0.1	
Deep venous thrombosis- defined as diagnosis by physician, or positive LE Doppler study	
Pulmonary	
Atelectasis requiring respiratory therapy involvement	
Pneumonia defined as diagnosis by treating physician, or new infiltrate on CXR requiring antibiotic therapy	
Pulmonary embolus- defined as diagnosis by treating physician, or positive CT/angio	
Wound infection	
Ileus	
Incisional hernia	
Cholestasis	
Nerve Palsy	
Bleeding requiring transfusion (donor), or >5 units PRBCs (recipient)	
Acute renal failure (requiring dialysis)	
Cerebral vascular accident-defined as diagnosis by physician, or new area of infarction or hemorrhage on CT	
Sepsis- evidence of infection plus a systemic response as manifested by an elevated temperature, tachycardia, increased respirations, leukocytosis or an impaired peripheral leukocyte response	
Biliary tract	
Leak	
Biloma	
Stenosis	
Portal vein thrombosis	
Liver failure or persistent cholestasis, defined as total bili> 5 after postop day 10	
<b>Recipients Only</b>	
Hepatic artery thrombosis (HAT)	
Graft nonfunction	
Hepatic encephalopathy	
<u>Posthospitalization</u>	
Mortality (at time of data collection)	
Readmission for any of above complications within 3 months of transplantation	

Definitions for complications are given in Table 1. Complications for a period of 3 months after transplantation were included, as was readmission to the hospital within 3

**Table 2. Patient Demographics**

Characteristic	Living Donor (n=40)	Deceased Donor (n=40)
Age, mean ± SD, y	51 ± 11	50 ± 13
Sex:		
Male	27 (67.5%)	25 (62.5%)
Female	13 (32.5%)	15 (37.5%)
Body Mass Index (kg/m <sup>2</sup> ): (p=0.02):		
< 19	1 (2.5 %)	2 (5%)
19-25	24 (60%)	10 (25%)
> 25-30	11 (27.5%)	17 (42.5%)
> 30	4 (10%)	11 (27.5%)
MELD, mean (median) (p=0.04)	14 (14)	17 (18)
Primary reason for transplant:		
Cholestatic liver disease	17 (42.5%)	
Cholangiocarcinoma cancer †	9 (22.5%)	
Alcohol-related hepatitis	3 (7.5%)	
Hepatitis C (1 with HCC also)	3 (7.5%)	
Other (includes AIH, HCC, NASH, cryptogenic, and neuroendocrine)	8 (20%)	

**Key:**  
MELD model for end stage liver disease  
PBC primary biliary cirrhosis  
PSC primary sclerosing cholangitis  
† 4 with diagnosis of PSC also  
AIH autoimmune hepatitis  
HCC hepatocellular carcinoma  
NASH non-alcoholic steatohepatitis  
Unless otherwise indicated, data are expressed as number (percentage) of patients

months. Post-operative survival was noted. Statistical comparisons were made using the signed rank test for continuous data. Categorical data were analyzed by McNemar’s test or a Wald test for marginal homogeneity. Survival data was compared using a stratified Cox proportional hazards model. P < 0.05 was considered statistically significant (Table 1).

**RESULTS**

Demographic data for both LD and DD groups are shown in Table 2. A total of 40 living donor liver transplants were carried out at our institution during the study time period. There were four gender mismatches in order to match for disease, age, and etiology. The DD group had a significantly

higher median high body mass index of 26.0 kg/m<sup>2</sup> compared to 24.0 kg/m<sup>2</sup> in the LD group (p=0.01), and also a significant difference between body mass index categories (p=0.02). Calculated MELD scores were lower in the LD group than in the DD group (median 14 vs. 18, p=0.04).

Intraoperative variables are presented in Table 3. Anesthesia time was longer in LD group with a median of 7.1 hours compared to 6.5 hours in DD (p=0.02). Longer surgical time was noted for LD with median 5.4 hours compared to 5.2 hours, but this was not statistically significant (p=0.08). Transfusion of blood, blood product or albumin did not differ between the two groups. The frequency of intraoperative events was similar in the two

**Table 3. Intraoperative Variables**

Variable	Living Donor		Deceased Donor		p-value
	Median	IQR	Median	IQR	
Surgical time, hours	5.4	4.7 - 6.8	5.2	4.2 - 6.3	0.08
Anesthesia time, hours	7.1	6.4 - 8.3	6.5	5.8 - 7.6	0.02
Autologous transfusion, units	2.0	1.0 - 5.5	2.0	1.0 - 6.5	0.49
Packed red blood cells transfusion, units	2.0	0 - 4.5	2.0	0 - 5.0	0.84
Fresh Frozen Plasma, units	0	0 - 4.0	0	0 - 6.0	0.65
Platelets transfusion, 6 pack	0	0 - 6.0	0	0 - 6.0	0.41
Any intraoperative event <sup>†</sup> , # (%) of patients	4	10%	7	18%	0.55

IQR: interquartile range, 25<sup>th</sup> percentile to 75<sup>th</sup> percentile  
<sup>†</sup> MAP < 50% of baseline (p=0.55), CPR required (p=1.00), hypoxemia requiring intervention (p=1.00), or arrhythmia requiring intervention (p=1.00)

**Table 4. Postoperative Complications, Number of Events (%)**

Event	Living Donor	Deceased Donor	p-value
Wound infection	4 (10%)	3 (8%)	1.00
Acute Renal Dysfunction	2 (5%)	4 (10%)	0.69
Hepatic Artery Thrombosis	6 (16%)	1 (3%)	0.13
Portal Vein Thrombosis	0 (0%)	2 (5%)	0.50
Biliary leak	5 (13%)	1 (3%)	0.22
Biliary stenosis	1 (3%)	0 (0%)	1.00
Cholestasis	2 (5%)	0 (0%)	0.50
Graft nonfunction	1 (3%)	0 (0%)	1.00
Sepsis	1 (3%)	1 (3%)	1.00
Returned to Operating Room (OR)	9 (24%)	5 (13%)	0.39
Rehospitalization	19 (49%)	21 (54%)	0.80
Other*	11 (28%)	11 (28%)	1.00

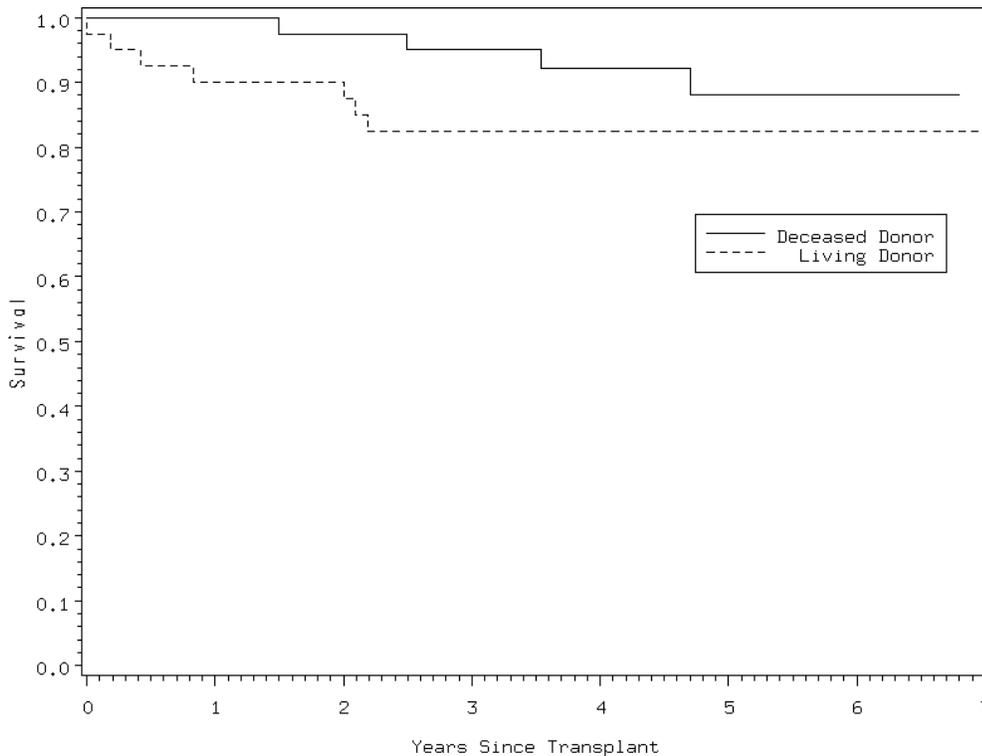
\* Immunosuppressant toxicity, supraventricular arrhythmia, line infections, acute cellular rejection that resolved, and traumatic urinary catheter removal  
 Note: N=39 pairs used in comparisons, except for Hepatic artery thrombosis (HAT) (N=38) due to missing outcomes

groups. There was one intraoperative death in the LD group and none in the DD group.

Postoperative transfusion of fresh frozen plasma, cryoprecipitate, platelets, and albumin showed no significant differences, however, the DD group had a significantly higher postoperative packed red blood cells transfusion (p=0.04). Intensive care unit LOS did not significantly differ between the groups with LD median of 0.95 days compared to 0.96 days in DD. Hospital LOS was significantly longer for LD (median of 12 days ) *versus* DD (8 days , p=0.002).

Postoperative complications are compared in Table 4. There were no significant differences in the variables.

Biliary complications (leak or stenosis) were more frequent in the LD group (5 *vs.* 1) and the frequency of hepatic artery thrombosis (HAT) was also greater in the LD group (6 *versus* 1). Neither difference reached statistical significance. One LD required relisting on postoperative day 19, with HAT/stenosis requiring intervention. Two LD patients underwent early retransplantation (within 90 days of transplant) for HAT, and none of the DD patients required early



**Fig. (1).** Kaplan-Meier survival curves of DD and LD. p=0.118 by stratified Cox proportional hazards model.

retransplantation. None of the DD group were relisted in the 90 days after transplantation.

The Clavien scale was utilized to compare complications.[8,9] Chi-Square analysis comparing Clavien Grades 0-1 with Grades 2-4 was not significant ( $p = 0.254$ ). Please see Table 5.

There were 7 total deaths in the LD group (6 in the postoperative period), and 4 in the DD group at the time of data collection (July 31, 2007). Fig. (1) displays the Kaplan-Meier survival curves. At 7 years post-transplant the estimated death rates were 18% and 12% for LD and DD, respectively. The hazard ratio comparing LD to DD was 3.50 (95% CI 0.73-16.85,  $p = 0.118$ ).

## DISCUSSION

We found that LD recipients had a longer anesthesia time and longer hospital stay than matched DD recipients. There were more biliary complications and HAT in the LD group but these differences did not reach statistical significance. Otherwise postoperative morbidity was similar between LD and DD groups. This implies that the greater number of complications in LD patients resulted in longer hospital stays, however whether other intergroup differences contributed should be discussed.

The mean calculated MELD scores are low for patients undergoing liver transplantation. This is probably related to the index group being the LD recipients. More than 25% of this group underwent transplantation for tumors (cholangiocarcinoma, hepatocellular carcinoma, neuroendocrine tumor), such patients typically have low calculated MELD scores. Matching by primary etiology for transplantation will hence introduce an equal group of such patients into the DD

group. The mean MELD in the DD group was significantly higher than in the LD group. This would imply longer hospital stay in this group likely due to postoperative complications [10,11] rather than the shorter time observed.

The DD group had a significantly higher BMI which may also increase the complication rate, although previous reports of the influence of obesity on post-transplant complications are not uniform [12-15]. Again, this would tend to result in a longer hospital stay in the DD group, contrary to our findings.

It is also possible that the longer hospital stay in the LD group was a result of a more conservative approach to hospital discharge in these patients than in the DD group. We have no way of assessing this possibility with the data available. A recent study from the Adult-to-Adult Living Donor Liver Consortium (A2ALL) reported a median LOS of 13 days in LD recipients, similar to our LD group [4].

There was a longer total operating room time in the LD group (median 7.1 hours compared to 6.5 hours), despite little difference in the surgical times. Both patient groups received the same invasive monitors and line placement, although some DD came to the operating room from the ICU, and may have some lines in place prior to anesthetic induction. In addition one anesthesiologist supervised both the donor and recipient cases, which may have contributed to the longer operating room time. Another factor may be our attempts to appropriately coordinate the donor and recipient procedures, which may have resulted in longer time between induction of anesthesia and incision in the LD group. Our median surgical time for LD was 5.4 hours, which compares favorably with recently reported operative times with a mean of 8.5 hours and median of 11.9 hours [3,4].

## ADDENDUM 1

**Table 5. Graded Complications of Living Donor and Deceased Donor Recipients**

Clavien Grade	Clavien Definition	LD	DD
1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.	10	18
2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	16	13
3	Requiring surgical, endoscopic or radiological intervention a. Intervention not under general anesthesia b. Intervention under general anesthesia	6 11	8 6
4	Life-threatening complication (including central nervous system complications)* requiring intermediate care/intensive care unit management a. Single organ dysfunction (including dialysis) b. Multi-organ dysfunction	1 0	1 0
5	Death of a patient	0	0

Comparison of Grades 0-1 vs. Grades 2-4 ( $p=0.254$ )

LD living donor liver transplant

DD deceased donor liver transplant

\* Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks.

Comparison of overall intraoperative event rates was not significantly different between the LD and DD groups. We observed no difference in transfusions of blood or blood products. Our transfusion amounts for packed red blood cells in the LD group was slightly lower than those reported in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) for LD [4]. We had 75% of LD receive 0-4 units packed red blood cells, compared to 47% in the A2ALL study [4]. In the A2ALL results, 14% of LD received 13-56 units, 15% received 9-12 units, and 24% received 5-8 units of packed red blood cells. The one intraoperative death in the LD group was due to uncontrollable hemorrhage in a patient with diffuse intrahepatic neurovascular cancer and multiple extensive prior upper abdominal operations.

There were no significant differences in any of the postoperative complications we assessed; however biliary complications and HAT were more frequent in the LD group. Biliary complications have recently been reported in 12.9% of LD at 1 year post-transplant, which is similar to our 15% in our initial LD experience [16]. In other recent publications, incidence of 30-33% biliary leaks and 8-24% biliary stricture are noted in LD [3,4]. Our data did show a trend towards more biliary complications in LD, and was significantly increased in the A2ALL Cohort Study [6].

Wound infections were noted in 10% of LD and 7.7% of DD. Wound infections were previously reported in 37% of LD performed in 2001 and 2002 by Iinuma *et al.*, and 32% in the A2ALL study [4,17].

Acute renal dysfunction developed in 5% of LD compared to 10% of DD, which was not a significant difference. We defined acute renal dysfunction as change from baseline creatinine of greater than 50%. Recently, Akamatsu *et al.* reported a 29% incidence of renal impairment, with a definition of this as serum creatinine of greater than 1.5 in patients with normal baseline creatinine [18]. The difference between our findings and those from Akamatsu may be due to variation in definition.

Complications by Clavien classification did not reveal significant differences between the groups, with comparison of Grades 0-1 with Grades 2-5. Our assessment of complications in Table 4 included rehospitalization, which was counted in addition to reason for rehospitalization in the first three months after transplant. This was not done in the Clavien grading. There appeared to be more grade 3a and 3b complications in the LD group, but this did not reach statistical significance. Friese *et al.* found higher early complications (with first 20 LD) performed at a center, but this decreased with more experience [6]. Our finding of no difference between LD and DD with our first 40 cases may be attributable to single center *vs.* multiple center experience.

There were 4 deaths in our LD within 1 year of transplant, which corresponds to a 90% one-year survival from a Kaplan-Meier survival curve (Fig. 1). This is comparable to published data - recently Morioka reported a 73% 1 year, Ghobrial *et al.* report an 88% 1 year, and the A2ALL study reported a 89% 1 year survival [3,4,19]. Causes of death in the LD group included metastatic disease (cholangiocarcinoma) and multi-system organ failure. These were also seen in the DD group, in addition to newly diagnosed cancer. Comparison of death rates at the time of last follow-up was

not statistically significant. The hazard ratio for LD was 3.50 but the wide 95% confidence interval (0.73-16.85) warns against reading any significance into this value.

Our study has limitations. It is retrospective. The statistical power is limited both by the number of patients (40 cases, 40 controls) and the small number of events in the study groups. Because of this we cannot determine if our finding of a non-statistically significant difference in complication between LD and DD groups reflects a true difference as in previous studies [3,4,19], or whether in our series the rates do not differ significantly. Altering the case:control matching, for example to 1:2 rather than 1:1 could potentially increase the power; however, we were obliged to extend our age range for matching (from 10 to 12 years) and accept 4 gender mismatches to conclude a 1:1 ratio so this was not feasible. To resolve this issue a reanalysis of our data after more LD have been performed will be necessary.

## CONCLUSION

This case controlled study comparing LD to DD recipients demonstrated longer OR time and longer hospital stays for LD recipients. There was tendency toward more biliary and vascular complications in the LD recipients which may account for the longer hospital stays. Patient survival was similar. In order to optimize our understanding of perioperative outcomes in LD recipients versus DD recipients, a larger, prospective, multi-center, study would be necessary. For now practitioners should be aware of the potential for postoperative differences between the two groups based on both retrospective single-center and multi-center studies.

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