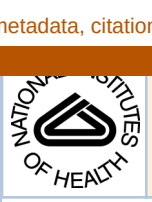

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Recipient Morbidity After Living and Deceased Donor Liver Transplantation: Findings from the A2ALL Retrospective Cohort Study†

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Abstract

Patients considering living donor liver transplantation (LDLT) need to know the risk and severity of complications compared to deceased donor liver transplantation (DDLT). One aim of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) was to examine recipient complications following these procedures. Medical records of DDLT or LDLT recipients who had a living donor evaluated at the nine A2ALL centers between 1998 and 2003 were reviewed. Among 384 LDLT and 216 DDLT, at least one complication occurred after 82.8% of LDLT and 78.2% of DDLT ($p = 0.17$). There was a median of two complications after DDLT and three after LDLT. Complications that occurred at a higher rate ($p < 0.05$) after LDLT included biliary leak (31.8% vs. 10.2%), unplanned reexploration (26.2% vs. 17.1%), hepatic artery thrombosis (6.5% vs. 2.3%) and portal vein thrombosis (2.9% vs. 0.0%). There were more complications leading to

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retransplantation or death (Clavien grade 4) after LDLT versus DDLT (15.9% vs. 9.3%, p = 0.023). Many complications occurred more commonly during early center experience; the odds of grade 4 complications were more than twofold higher when centers had performed ≤20 LDLT (vs. >40). In summary, complication rates were higher after LDLT versus DDLT, but declined with center experience to levels comparable to DDLT.

Keywords

A2ALL; complications; learning curve; liver transplant; living donor; outcomes

Introduction

The introduction of right lobe adult-to-adult living donor liver transplant (LDLT) created a new treatment option for patients in need of liver replacement. The procedure is highly technical in nature, and has not yet achieved the widespread application of deceased donor liver transplant (DDLT) (1). Given the comparatively recent introduction of LDLT, comprehensive descriptions of its associated complication rates and outcomes have been published mainly in single-center reports (2–7). The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) includes nine U.S. transplant centers with LDLT experience that have collaboratively collected retrospective and prospective LDLT data. This report details the A2ALL retrospective cohort morbidity experience among LDLT recipients and contemporaneous patients who had potential living donors, but who ultimately received a DDLT graft.

Methods

Data collection and conventions

Data for this study were derived from the retrospective component of the A2ALL study and were supplemented by data from the Scientific Registry of Transplant Recipients (SRTR) made available through a data use agreement. A2ALL data were collected based on detailed chart reviews. Entry of a recipient into the A2ALL Retrospective Cohort Study required the identification of a potential donor who completed a history and physical examination during the period January 1, 1998 to February 28, 2003 at one of nine U.S. transplant centers. A total of 819 potential adult recipients met the inclusion criteria. The current analysis included the 600 patients who proceeded to the operating room with the intention of receiving either a LDLT or DDLT for nonfulminant indications. Recipients whose procedures were aborted due to recipient reasons were included (four LDLT; three DDLT). Recipients of domino transplants (n = 2) were included in the DDLT group.

Complications were defined as unexpected events that were not inherent to the transplant procedure. Severity of complications was graded using an adaptation of the Clavien scoring system (8–10) for the classification of negative outcomes (Table 1).

Statistical methods

Descriptive statistics included means, standard deviations and proportions. Mantel–Haenszel trend tests were used to compare LDLT versus DDLT for number of complications per patient and complications by grade. Chi-square tests (and Fisher's exact tests in cases of small cell sizes) were used to compare LDLT versus DDLT for the proportion with Clavien grade 4 complications and for the proportion with complications of any Clavien grade. Since similar results were obtained by log-rank tests, most events occurred during the first 30 days and most (98% of LDLT, 96% of DDLT) follow-up times were beyond 30 days, only chi-

square test results were reported. Logistic regression analyses were used to investigate predictors of biliary leak, biliary stricture and Clavien grade 4 complications. Each of the variables in Table 2 was tested in each of the logistic regression models. Results are presented as adjusted odds ratios (AOR) and 95% confidence intervals (CI). In a previous A2ALL analysis of mortality, LDLT recipients were classified as having received their transplant when the center had less LDLT experience (had performed ≤20 LDLT) or more LDLT experience (had performed >20 LDLT) (11). To test the effect of center experience on complications using smaller increments, the sequential cases at each center were categorized as cases 1–10, 11–20, 21–40 and greater than 40 in the logistic regression models.

All analyses were carried out using SAS 9.1 statistical software (SAS/STAT 9.1 User's Guide, SAS Publishing, Cary, NC: SAS Institute Inc.).

Human subjects 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 nine participating transplant centers.

Results

The study group consisted of 384 LDLT and 216 DDLT recipients followed for a median of 2.1 years (range 0–5.9 years). The follow-up time for LDLT was longer than that for DDLT (2.2 years vs. 1.9 years, respectively; log-rank $p = 0.008$), although this difference had little impact on the analysis because most complications occurred within 30 days. At least 1 year of follow-up was available for 84% of LDLT and 69% of DDLT recipients. The characteristics of LDLT and DDLT recipients at the time of transplant are shown in Table 2. Compared to DDLT recipients, the LDLT recipients were slightly younger (mean age 49.6 vs. 51.4 years; $p = 0.037$), had less advanced liver disease (mean Model for End-stage Liver Disease [MELD] score 15 vs. 21; $p < 0.0001$) and were more medically stable (2% vs. 18% in ICU; $p < 0.0001$) at the time of transplant. The graft weight to recipient weight ratio was less than 0.8 in 30 cases (8%), with a range of 0.5–2.6.

Table 3 compares the frequencies of complications for early and later LDLT experience groups (LDLT case number ≤20 and >20) and DDLT. In the early LDLT experience group, only 9.6% of patients had no complications, compared with 23.0% among the later LDLT experience group and 21.8% among DDLT recipients. Early LDLT experience recipients tended to have a greater number of complications per patient, a median of four, compared to a median of two in the later LDLT experience group ($p < 0.0001$) and two in the DDLT group ($p = 0.72$ compared to later LDLT experience).

The specific types of complications were aggregated into three broad categories: surgical, medical and infectious. A summary of the frequency of these complications is detailed in Table 4. Recipients transplanted during periods of later (>20 cases) versus earlier (≤20 cases) LDLT center experience experienced a lower proportion of complications in almost every category. Significant reductions (all $p < 0.04$) with increased LDLT experience were seen with biliary leak or biloma (38% vs. 27%), unplanned reexploration (36% vs. 19%), pneumothorax (3% vs. 0%), ascites (21% vs. 9%) and overall infections (48% vs. 33%), particularly blood bacterial (23% vs. 14%) and fungal (5% vs. 1%) infections. Comparing complications between the later LDLT experience group and DDLT, we still observed significantly higher (all $p < 0.04$) proportions of recipients with complications after LDLT for biliary leak or biloma (27% vs. 10%), GI bleeding (8% vs. 3%) and bile duct infections (8% vs. 3%). However, significantly lower (all $p < 0.04$) proportions of recipients with

complications were observed among the experienced LDLT group versus DDLT for pneumothorax (0% vs. 2%), pulmonary edema (10% vs. 21%), hepatic encephalopathy (4% vs. 10%), ascites (9% vs. 17%) and fungal pulmonary infections (1% vs. 7%). Table 4 reports 48 p-values, of which 12 are significant ($p < 0.05$), and 2.4 would be expected to be significant by chance if all tests were independent.

Complications graded according to the Clavien scale (Table 1) are shown in Table 5. The majority of complications were grade 1 or grade 2. As shown in Table 5, complications leading to retransplantation or death (Clavien grade 4) occurred more frequently among LDLT recipients (LDLT: n = 61 [15.9%]; DDLT: n = 20 [9.3%]; p = 0.023). Recipients with complications that led to retransplantation were more common in the LDLT group (n = 35; 9.1%) than in the DDLT group (n = 8; 3.7%; p = 0.014). Retransplantation for vascular complications occurred more frequently in LDLT recipients (n = 22; 5.7% vs. n = 2; 1.0%, respectively; p = 0.004). The number of deaths, with or without retransplantation, was not significantly different between the LDLT (n = 34; 5.6%) and DDLT (n = 14; 2.3%; p = 0.30) groups. Although the overall proportion of recipients with biliary complications was higher in the LDLT group, the subset with Clavien grade 4 biliary complications was not significantly different in the two groups (p = 0.47).

The effect of center LDLT experience on the occurrence and Clavien grade of recipient complications is shown in Table 6. The proportions of recipients who had any complications, any biliary complications, bile leak or biloma, infection and unplanned reexploration were significantly lower after 20 LDLT cases versus ≤20 LDLT cases. For vascular complications, no significant difference was found after 20 LDLT cases versus ≤20 LDLT cases (7% vs. 11%, p = 0.18). Comparing complications after 20 LDLT cases versus DDLT, the proportions with infection, unplanned reexploration and vascular complications were not significantly different, but any biliary complication and biliary leak or biloma remained significantly higher versus DDLT (p = 0.013 and $p < 0.0001$, respectively).

Center LDLT experience was associated with a significantly lower incidence of grade 4 complications overall (22% vs. 11%; p = 0.003), and a reduced but not significantly lower incidence for each tested subtype of grade 4 complication. The Mantel–Haenszel trend test across the range of Clavien grades was significant only for vascular complications (LDLT case number ≤20 vs. >20: p = 0.0291; LDLT case number >20 vs. DDLT: p = 0.0024).

Because biliary complications occurred at a higher rate in LDLT recipients and were a significant cause of morbidity, two separate logistic regression models were used to investigate risk factors for the development of a biliary leak or of a biliary stricture among LDLT recipients (Table 7A and B). Bivariate and multivariable analyses revealed three variables that were significantly associated with biliary leak. In the multivariable model, a donor with three or more bile ducts was associated with higher risk than that with one duct (AOR = 2.72, p = 0.035) and recipient HCV diagnosis was associated with lower risk than non-HCV (AOR = 0.55, p = 0.011). Center experience was grouped into cases 1–10, 11–20, 21–40 and >40, using case number >40 as the reference group. The risk of biliary leak dropped monotonically with increasing experience (Table 7A). Compared to case number >40, the risk of biliary leak was 126% higher for cases 1–10 (AOR = 2.26, p = 0.015), with a statistically significantly decreasing trend in risk from earlier to later cases by ordinal trend test (p = 0.012).

Two variables were significantly associated with biliary stricture (duration of recipient operation and Roux-en-Y biliary reconstruction) in bivariate analyses. In the multivariable logistic regression model, five variables were significant: recipient diagnosis of cholestatic liver disease (AOR = 2.10, p = 0.040) and duration of recipient operation (AOR = 1.33 per

100 min, p = 0.014) were associated with higher risk. Two variables were associated with a lower risk of biliary stricture: use of a Roux-en-Y reconstruction (AOR = 0.49, p = 0.017) and donor hypotension (AOR = 0.45, p = 0.038). Finally, as with biliary leak, there was a significantly higher risk of biliary stricture during early center experience (Table 7B). Cold ischemia time was not a significant predictor of either biliary leak or biliary stricture.

Predictors of grade 4 complications among LDLT and DDLT recipients were investigated in a third logistic regression analysis (Table 7C). This model showed that patients who underwent LDLT during a center's earlier experience (<20 LDLT) had more than two-fold the odds of developing a grade 4 complication compared to those who underwent LDLT once the center had done >40 LDLT cases (cases 1–10: AOR = 2.33, p = 0.036). There was a statistically significantly decreasing trend in risk of grade 4 complications from earlier to later cases by ordinal trend test (p = 0.008).

In a separate model of grade 4 complications restricted to LDLT recipients, each of the donor factors in Table 2 were tested and none was found to be significant, including the graft weight to recipient weight ratio <0.8.

There was no difference in the odds of a grade 4 complication between DDLT recipients and LDLT recipients transplanted after centers had performed at least 40 cases (AOR = 0.78, p = 0.52). Although cold ischemia time could not be tested in this model because of confounding with transplant type, we tested its effect in separate models for LDLT and DDLT. In each case, longer cold ischemia time (as a continuous variable) was associated with significantly higher odds of grade 4 complications (LDLT: AOR = 1.26/h, p = 0.005; DDLT: AOR = 1.17/h, p = 0.009).

Discussion

Despite its introduction for pediatric patients nearly 20 years ago (12), the use of living donors for liver transplantation in adults has emerged more slowly. Interest in adult-to-adult LDLT increased as experience with the procedure grew in Japan and Korea, where deceased donor organs were not readily available. The increased use of split livers in the United States and Europe also contributed to the surgical skills needed to successfully perform the LDLT procedure (13). Unlike living donor kidney transplantation, where advantages of living donor over deceased donor grafts have been demonstrated in both recipient and graft survival, and where the safety of the donor operation has been documented, LDLT is still under a high level of scrutiny (14,15).

The A2ALL network was established to better assess the safety of the LDLT procedure for both donors and recipients, and to better define the situations where the procedure should be considered as an option. One primary study aim was to establish the rates of various complications for both donors and recipients in order to properly inform patients as they make decisions relating to the pursuit of living donor transplant. An important finding from the A2ALL group was the demonstration of a significant survival benefit for potential recipients when they chose to pursue living donor transplant versus remaining on the waiting list for DDLT (16). This advantage was most clear after the transplant center had done at least 20 LDLT procedures. A lingering question, however, has been the rate of complications experienced by recipients of the LDLT, and how these rates compare with DDLT. This report is the first to compare the two groups, using a cohort of recipients who all shared the common feature of having at least one donor who completed a history and physical examination for potential LDLT.

In this and other series, LDLT recipients were less ill in general than their DDLT counterparts at the time of transplantation. In the early reported experience with LDLT, it

was observed that patients who had more decompensated liver disease did less well with LDLT (17). In the period of time covered by our study, two different organ allocation schemes for DDLT were in effect, the older system utilizing hospital or ICU status and Child-Turcotte-Pugh score to determine ranking on the waiting list, and the MELD system since February 2002. Although our LDLT and DDLT recipients were comparable at study enrollment, which was the date of the potential donor's history and physical examination (16), MELD score at the time of transplant was higher in recipients of DDLT, since the latter group had a longer time until transplant. A significantly higher proportion of DDLT recipients were in the ICU and/or on dialysis at the time of transplant. This may explain the higher infection rates in DDLT recipients, since they had longer and possibly more complex pretransplant hospital stays.

The most important differences in posttransplant morbidity between recipients of LDLT and DDLT were seen in surgical complications. Biliary complications (especially biliary leak), vascular complications and unplanned reexplorations were observed at higher frequencies in LDLT recipients. Other authors have noted higher biliary and vascular complication rates among LDLT recipients compared to historic DDLT controls (18). Possible explanations include the greater technical demands of LDLT, inferior quality of the LDLT graft and the caliber of LDLT donor vessels available for anastomosis (19–25). An added dimension of this study was the systematic use of the Clavien grading system to characterize the severity of complications. In our analyses, these surgical complications led to a higher rate of retransplantation and death (Clavien grade 4) among LDLT recipients compared to DDLT recipients. The overall rate of biliary complications in LDLT recipients was 42.2% versus 24.5% in DDLT recipients, and many of these complications required repeated endoscopic or percutaneous transhepatic interventions. Such information should be helpful when counseling patients about the option of LDLT.

Possible explanations for the higher rate of biliary complications after LDLT (and proposed solutions) have been described (26,27). One study characterized preoperative and intraoperative findings that were associated with a higher rate of biliary complications (28). In the current study, certain technical details of the biliary reconstruction were captured. Having three or more bile ducts in the liver graft was associated with higher risk of biliary leak. Preoperative imaging and determination of the planned line of transection through the liver may permit predictions about the number of ducts that may require anastomosis. If the proposed graft is expected to yield three or more ducts, consideration could be given to selecting a different donor, or at least counseling the recipient about the higher risk of leak. In terms of biliary stricture, the use of a Roux-en-Y anastomosis was associated with a lower odds of stricture formation, as was donor hypotension. We are unable to ascribe a causative relationship between the anastomotic technique and the occurrence of biliary stricture, since the choice of technique is often dictated by operative findings. The best technique for reconstruction continues to be a topic of debate (29–32), and given limited details in our retrospective data collection, it may be premature to suggest that a Roux-en-Y should be done in every case. The basis for the association between biliary stricture and donor hypotension is unclear. Data currently being collected in the A2ALL Prospective Cohort Study may illuminate both of these issues in the future.

The level of experience with a procedure, especially one as complicated as LDLT, should be considered in analyses of outcomes. Thus, in the current study, the adjusted odds of a biliary leak or stricture were higher when centers had not yet performed 40 LDLT. The rate of biliary stricture after DDLT, for which techniques of biliary reconstruction are well established, has been reported in 10–30% of recipients. This suggests that the rate of this complication after LDLT may be difficult to reduce further (33). The inability to accurately

assess the viability of biliary tissue at the time of anastomosis may contribute to this problem.

Another important finding related to center experience was the lack of difference in the odds of Clavien grade 4 complications (defined as leading to retransplantation or death) between DDLT and LDLT recipients once the center had performed more than 20 LDLT cases. This finding is consistent with the improved survival seen with LDLT in experienced centers versus remaining on the waitlist for a DDLT (16). In both LDLT and DDLT, we found a significant relationship between cold ischemia time and the likelihood of grade 4 complications. This is consistent with our previous identification of cold ischemia time as a significant predictor of the overall risk of LDLT graft failure, and further emphasizes the unique importance of even the comparatively short cold ischemia times associated with LDLT transplantation (11). When patients are evaluated and treatment options are reviewed, these aspects should be considered by the patient and caregivers in the decision whether to proceed with LDLT.

We have previously shown that graft size in the A2ALL retrospective cohort was not associated with a significantly higher risk of graft failure (11), and in the current study, the low graft weight to recipient weight ratio (<0.8) was not a significant predictor of bile leak, biliary stricture or grade 4 complications.

Many advances in LDLT have occurred over the last decade, but its exact place in the treatment armamentarium for patients with end-stage liver disease and liver cancer is still being defined. This study not only provided details on complications of liver transplantation but also defined complications that are more frequent in LDLT. Despite a higher rate of complications among LDLT recipients, complications requiring retransplantation or leading to death were not significantly higher in LDLT once centers were experienced with the procedure. This finding, in concert with our previous conclusion that choosing LDLT over continuing on the waitlist leads to a survival advantage in experienced centers, underscores the impact of the learning curve on this highly technical procedure. Potential LDLT recipients need to hear about the rates of complications, and this study will help to define those rates. The decision to proceed, however, must be balanced against the possibility of deteriorating or dying while on the waitlist. We acknowledge that in this study the LDLT recipients had relatively low MELD score at transplant and our results may not be applicable to patients who are more ill. As the practice of LDLT matures, it will be important to continually reevaluate the morbidity associated with the operation and identify opportunities to improve its outcomes.

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Appendix

The following individuals were instrumental in the planning, conduct and/or care of patients enrolled in this study at each of the participating institutions as follows:

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Table 1

Clavien system for the classification of negative outcomes in general surgery and solid organ transplantation (adapted from references 8–10)

Grade 1	Any alteration from the ideal postoperative course, with complete recovery or which can be easily controlled and which fulfills the following general characteristics:
	(a) Not life threatening
	(b) Not requiring use of drugs other than immunosuppressants, analgesics, antipyretics, antiinflammatory agents, antiemetics, drugs required for urinary retention or lower urinary tract infection, arterial hypertension, hyperlipidemia or transient hyperglycemia
	(c) Requiring only therapeutic procedures that can be performed at the bedside
	(d) Postoperative bleeding requiring ≤3 units of blood transfusion
	(e) Never associated with a prolongation of ICU stay or total hospital stay to more than twice the median stay for the procedure in the population of the study
Grade 2	Any complication that is potentially life threatening or results in ICU stay >5 days, hospital stay >4 weeks for the recipient, but which does not result in residual disability or persistent disease
Grade 3	Any complication with residual or lasting functional disability or development of malignant disease
Grade 4	Complications that lead to retransplantation (grade 4a) or death (grade 4b)

Table 2

Characteristics of living donor (LDLT) and deceased donor liver transplant (DDLT) recipients and LDLT living donors

Recipient characteristic	LDLT (n = 384); mean (SD) or n (%)	DDLT (n = 216); mean (SD) or n (%)	p-Value*
Age	49.6 ± 10.7	51.4 ± 9.7	0.037
Sex			0.649
Female	162 (42)	88 (41)	
Male	222 (58)	128 (59)	
Ethnicity			0.822
Hispanic	74 (19)	40 (19)	
Non-Hispanic	310 (81)	176 (81)	
Race			0.368
White	348 (91)	190 (88)	
African American	12 (3)	13 (6)	
Asian	15 (4)	7 (3)	
Other	9 (2)	6 (3)	
Body mass index[1] (kg/m^2)	27 ± 5	27 ± 5	0.780
Diagnosis (multiple diagnoses possible)			
Hepatitis C diagnosis (HCV)	184 (48)	102 (47)	0.870
Hepatocellular carcinoma diagnosis (HCC)	63 (16)	39 (18)	0.606
Alcohol	52 (14)	32 (15)	0.666
Cholestatic liver disease	71 (18)	39 (18)	0.895
Noncholestatic cirrhosis other than HCV/alcohol	80 (21)	48 (22)	0.690
Acute hepatic necrosis	6 (2)	9 (4)	0.050
Metabolic disease	11 (3)	7 (3)	0.795
Biliary atresia	3 (1)	0 (0)	0.557
Malignancy other than HCC	11 (3)	5 (2)	0.688
Other	9 (2)	3 (1)	0.551
MELD score at transplant[1,2]			
Categorical			<0.0001
6–10	80 (21)	22 (10)	
11–20	229 (60)	104 (48)	
21–30	48 (13)	45 (21)	
31–40	10 (3)	41 (19)	
Missing	16 (4)	4 (2)	
Continuous	15 ± 6	21 ± 9	<0.0001
Medical condition at transplant			<0.0001
Not hospitalized	335 (87)	130 (60)	
Hospitalized (not ICU)	42 (11)	48 (22)	
ICU	7 (2)	38 (18)	
Severity			
Ventilator	5 (1)	15 (7)	0.0002

Recipient characteristic	LDLT (n = 384); mean (SD) or n (%)	DDLT (n = 216); mean (SD) or n (%)	p-Value*
Ascites	222 (58)	160 (74)	<0.0001
Dialysis	5 (1)	14 (6)	0.001
Intraoperative			
Cold ischemia time (minutes)[3]	87 ± 94	441 ± 215	<0.0001
Duration of recipient operation (minutes)[1]	511 ± 129	371 ± 96	<0.0001
LDLT living donor characteristics			
Age	37 ± 9.7		
Intraoperative hypotension (<100 mmHg)[1]	88 (23)		
Number of donor bile ducts			
1	205 (53)		
2	135 (35)		
≥3	21 (5)		
Missing	23 (6)		
Type of anastomosis			
Roux-en-Y	199 (52)		
Other	218 (47)		
Missing	5 (2)		
Graft weight to recipient weight ratio <0.8[4]	30 (8)		

*p-values comparing LDLT versus DDLT for continuous variables are based on t-tests, and for categorical variables are based on the chi-square or Fisher's exact tests.

[1]Values are missing in less than 5% for these variables.

[2]MELD = model for end-stage liver disease.

[3]Values are missing in 17%.

[4]N = 378; graft weight was obtained from intraoperative measurement (47%), imaging (29%), or 0.6 × donor SLV (23%) and was missing in 1%. Imaging volume was multiplied by 0.8, which was an empirical correction based on a regression analysis of actual versus imaging values.

Table 3

Number of complications per transplanted recipient[1]

	(A) number LDLT case ≤ 20 (n = 167)		(B) LDLT number > 20 case (n = 217)		(C) DDLT (n = 216)	
Number of complications	**Number of recipients**	**%**	**Number of recipients**	**%**	**Number of recipients**	**%**
0	16	9.6	50	23.0	47	21.8
1	21	12.6	38	17.5	40	18.5
2	27	16.2	32	14.7	36	16.7
3	18	10.8	24	11.1	19	8.8
4	14	8.4	15	6.9	24	11.1
5	14	8.4	17	7.8	10	4.6
6	11	6.6	11	5.1	4	1.9
7	15	9.0	5	2.3	8	3.7
8	7	4.2	7	3.2	7	3.2
9	9	5.4	7	3.2	5	2.3
≥10	15	9.0	11	5.1	16	7.4

[1] Mantel-Haenszel trend test comparing columns (A) versus (B): $p < 0.0001$ and (B) versus (C): $p = 0.7216$.

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Table 4

Specific complications of recipients of living donor liver transplants (LDLT) transplanted during periods of less or more center experience (case number ≤20 and case number >20) and deceased donor liver transplants (DDLT)

	(A) LDLT case number ≤ 20 (n = 167)		(B) LDLT case number > 20 (n = 217)		(C) DDLT (n = 216)			
Complication[1]	**n**	**%**[3]	**n**	**%**[3]	**n**	**%**[3]	**p-Value**[2] **A vs. B**	**p-Value**[2] **B vs. C**
Surgical complications								
Biliary complications[4]	84	50.3	77	35.5	53	24.5	**0.0032**	**0.0128**
Biliary leak or biloma	63	37.7	59	27.2	22	10.2	**0.0243**[5]	**<0.0001**
Biliary stricture	36	21.6	39	18.0	35	16.2	0.3963	0.6090
Unplanned reexploration	60	35.9	42	19.4	37	17.1	**0.0005**	0.3757
Hepatic artery thrombosis	14	8.4	11	5.1	5	2.3	0.1934	0.1287
Portal vein thrombosis	7	4.2	4	1.8	0	0.0	0.2178	0.1233
Intraabdominal bleeding	13	7.8	14	6.5	17	7.9	0.5956	0.5393
Intraabdominal abscesses	17	10.2	17	7.8	11	5.1	0.4094	0.2565
Ileus	5	3.0	11	5.1	10	4.6	0.3169	0.8315
Bowel obstruction	9	5.4	4	1.8	4	1.9	0.0593	1.0000
Pneumothorax	5	3.0	0	0.0	5	2.3	**0.0140**	**0.0302**[5]
Wound dehiscence	5	3.0	5	2.3	7	3.2	0.7512	0.5472
Incisional hernia	22	13.2	18	8.3	18	8.3	0.1099	0.9767
Inferior vena cava thrombosis	0	0.0	3	1.4	4	1.9	0.2606	1.0000
Neuropraxia	2	1.2	3	1.4	5	2.3	1.0000	0.5011
Medical complications								
GI bleeding	16	9.6	17	7.8	6	2.8	0.4999	**0.0195**
Pulmonary edema	24	14.4	22	10.1	45	20.8	0.2074	**0.0021**
Respiratory arrest	4	2.4	7	3.2	15	6.9	0.7615	0.0838
Hepatic encephalopathy	9	5.4	9	4.1	22	10.2	0.5550	**0.0148**[5]
Myocardial infarction	1	0.6	2	0.9	1	0.5	1.0000	1.0000
Congestive heart failure	2	1.2	0	0.0	2	0.9	0.1869	0.2448
Pleural effusion	37	22.2	41	18.9	45	20.8	0.3922	0.5958
Cardiopulmonary arrest	5	3.0	3	1.4	9	4.2	0.3012	0.0789

	(A) LDLT case number ≤ 20 (n = 167)		(B) LDLT case number > 20 (n = 217)		(C) DDLT (n = 216)			
Complication[1]	**n**	**%**[3]	**n**	**%**[3]	**n**	**%**[3]	**p-Value**[2] **A vs. B**	**p-Value**[2] **B vs. C**
Aspiration	5	3.0	3	1.4	4	1.9	0.3027	1.0000
Pulmonary embolism	1	0.6	1	0.5	0	0.0	1.0000	1.0000
Ascites	35	21.0	19	8.8	36	16.7	**0.0006**	**0.0127**[5]
Chronic rejection	8	4.8	11	5.1	12	5.6	0.9055	0.8213
Recurrence of disease, excluding HCV and HCC	9	5.4	10	4.6	4	1.9	0.7272	0.1030
Deep vein thrombosis	2	1.2	2	0.9	5	2.3	1.0000	0.2844
Infections								
Overall infections	80	47.9	72	33.2	73	33.8	**0.0031**	0.8914
All bacterial infections:	69	41.3	71	32.7	68	31.5	0.0827	0.7827
Bile duct	19	11.4	17	7.8	7	3.2	0.2377	**0.0367**
Wound	21	12.6	21	9.7	23	10.6	0.3671	0.7382
Blood	38	22.8	31	14.3	31	14.4	**0.0321**	0.9843
Liver abscess, separate from cholangitis	7	4.2	4	1.8	2	0.9	0.2209	0.6853
Pulmonary	17	10.2	15	6.9	19	8.8	0.2508	0.4662
Central nervous system	1	0.6	1	0.5	0	0.0	1.0000	1.0000
Urinary tract	22	13.2	16	7.4	24	11.1	0.0592	0.1793
All viral infections	7	4.2	6	2.8	12	5.6	0.4435	0.1458
All fungal infections:	21	12.6	13	6.0	24	11.1	**0.0244**	0.0567
Pulmonary	5	3.0	1	0.5	14	6.5	0.0897	**0.0006**
Urinary tract	2	1.2	5	2.3	12	5.6	0.7037	0.0815
Wound	6	3.6	2	0.9	3	1.4	0.0828	0.6853
Bile duct	0	0.0	2	0.9	0	0.0	0.5072	0.4988
Blood	8	4.8	2	0.9	7	3.2	**0.0235**	0.1053
Liver	4	2.4	1	0.5	0	0.0	0.1716	1.0000
Central nervous system	3	1.8	1	0.5	0	0.0	0.3213	1.0000
Other complications	48	28.7	60	27.6	51	23.6	0.7641	0.3493

[1] Values are missing in less than 3% for each variable.

[2] Fisher's exact test was used when any cell had an expected count less than 5.

[3] Percent of LDLT case number ≤ 20, LDLT case number >20, or DDLT.

[4] Biliary complications include biliary leak/biloma and biliary stricture.

[5] Nonsignificant when adjusted for MELD at transplant. In the case of complete separation (pneumothorax), the likelihood ratio test was used.

Table 5

Graded complications of living donor (LDLT) and deceased donor (DDLT) recipients: LDLT (n = 384) versus DDLT (n = 216)

	Clavien grade 1		Clavien grade 2		Clavien grade 3		Clavien grade 4								Any Clavien grade	
Complications	**LDLT (%)**	**DDLT (%)**	**LDLT (%)**	**DDLT (%)**	**LDLT (%)**	**DDLT (%)**	**LDLT (%)**	**Retxp and alive**	**Died w/o retxp**	**Retxp and died**	**DDLT (%)**	**Retxp and alive**	**Died w/o retxp**	**Retxp and died**	**LDLT (%)**	**DDLT (%)**
Any complication	22 (5.7)	19 (8.8)	163 (42.5)	79 (36.6)	33 (8.6)	19 (8.8)	61 (15.9)	27	26	8	20 (9.3)	6	12	2	279 (72.7)	137 (63.4)
Any biliary complication	14 (3.6)	2 (0.9)	113 (29.4)	38 (17.6)	19 (4.9)	7 (3.2)	15 (3.9)	5	6	4	6 (2.8)	2	3	1	161 (41.9)[3]	53 (24.5)[3]
Biliary leak or biloma	14 (3.6)	2 (0.9)	83 (21.6)	15 (6.9)	12 (3.0)	2 (0.9)	13 (3.4)	5	5	3	3 (1.4)	0	2	1	123 (32.0)[3]	22 (10.2)[3]
Biliary stricture	3 (0.8)	0 (0)	59 (15.0)	26 (12.0)	10 (2.6)	6 (2.8)	3 (0.8)	0	1	2	3 (1.4)	2	1	0	75 (19.5)	35 (16.2)
Intraabdominal bleeding	0 (0)	0 (0)	21 (5.5)	14 (6.5)	1 (0.3)	0 (0)	5 (1.3)	3	2	0	3 (1.4)	0	3	0	27 (7.0)	17 (7.9)
GI bleeding	3 (0.8)	1 (0.5)	23 (6.0)	3 (1.4)	2 (0.5)	0 (0)	5 (1.3)	2	2	1	2 (0.9)	0	2	0	33 (8.6)[3]	6 (2.8)[3]
Intraabdominal abscesses	1 (0.3)	0 (0)	20 (5.2)	7 (3.2)	5 (1.3)	3 (1.4)	8 (2.1)	1	5	2	1 (0.5)	0	1	0	34 (8.8)	11 (5.1)
Ileus	10 (2.6)	6 (2.8)	2 (0.5)	2 (0.9)	2 (0.5)	0 (0)	2 (0.5)	1	0	1	2 (0.9)	0	2	0	16 (4.2)	10 (4.6)
Bowel obstruction	4 (1.0)	3 (1.4)	8 (2.1)	1 (0.5)	1 (0.3)	0 (0)	0 (0)	0	0	0	0 (0)	0	0	0	13 (3.4)	4 (1.9)
Unplanned reexploration	7 (1.8)	2 (0.9)	67 (17.4)	27 (12.5)	5 (1.3)	1 (0.5)	16(4.2)[2]	6	6	4	2 (0.9)[2]	0	2	0	95 (24.7)[3]	32 (14.8)[3]
Hepatic encephalopathy	6 (1.6)	4 (1.9)	6 (1.6)	10 (4.6)	1 (0.3)	4 (1.9)	5 (1.3)	2	2	1	4 (1.9)	0	3	1	18 (4.7)[3]	22 (10.2)[3]
Ascites	18 (4.7)	21 (9.7)	21 (5.2)	6 (2.8)	5 (1.3)	6 (2.8)	10 (2.6)	1	8	1	3 (1.4)	1	1	1	54 (14.0)	36 (16.7)
Vascular complications[1]	0 (0)	0 (0)	11 (2.9)	6 (2.8)	0 (0)	1 (0.5)	24 (6.3)[2]	18	2	4	2 (0.9)[2]	2	0	0	35 (9.1)[3]	9 (4.2)[3]
Chronic rejection	12 (3.1)	8 (3.7)	3 (0.8)	2 (0.9)	1 (0.3)	1 (0.5)	3 (0.8)	2	1	0	1 (0.5)	0	1	0	19 (4.9)	12 (5.6)
Recurrent disease-not HCV or HCC	7 (1.8)	1 (0.5)	2 (0.5)	0 (0)	5 (1.3)	1 (0.5)	5 (1.3)	1	2	2	2 (0.9)	1	1	0	19 (5.0)	4 (1.9)
Deep vein thrombosis	0 (0)	1 (0.5)	3 (0.8)	3 (1.4)	0 (0)	0 (0)	1 (0.3)	1	0	0	1 (0.5)	0	1	0	4 (1.0)	5 (2.3)
Neuropraxia	2 (0.5)	1 (0.5)	1 (0.3)	0 (0)	2 (0.5)	4 (1.9)	0 (0)	0	0	0	0 (0)	0	0	0	5 (1.3)	5 (2.3)
Infection	17 (4.4)	4 (1.9)	100 (26.0)	58 (26.9)	10 (2.6)	3 (1.4)	25 (6.5)	2	19	4	8 (3.7)	1	7	0	152 (39.6)	77 (33.8)

[1] Vascular complications include hepatic artery thrombosis, portal vein thrombosis and inferior vena cava thrombosis.

[2] The chi-square test comparing % Clavien grade 4 in LDLT versus DDLT: unplanned reexploration ($p = 0.026$), vascular complications ($p = 0.002$).

[3] The chi-square test comparing % any Clavien grade in LDLT versus DDLT: any biliary complication ($p < 0.001$), biliary leak/biloma ($p < 0.001$), upper/lower GI bleeding ($p = 0.006$), unplanned reexploration ($p = 0.004$), hepatic encephalopathy ($p = 0.01$) and vascular complications ($p = 0.03$).

Table 6

Graded complications by transplant type and case number*

Complications		Clavien grade 1	Clavien grade 2	Clavien grade 3	Clavien grade 4	Any Clavien grade
Any complication	(A) LDLT ≤ 20[1]	8 (5%)	82 (49%)	9 (5%)	37 (22%)	136 (81%)
	(B) LDLT > 20[1]	14 (6%)	81 (37%)	24 (11%)	24 (11%)	143 (66%)
	(C) DDLT[1]	19 (9%)	79 (37%)	19 (9%)	20 (9%)	137 (63%)
	p-value A vs. B	0.4874	**0.0207**	**0.0494**	**0.0032**	**0.0007**
	p-value B vs. C	0.3579	0.871	0.431	0.5352	0.5904
Any biliary complication	(A) LDLT ≤ 20	5 (3%)	64 (38%)	7 (4%)	8 (5%)	84 (50%)
	(B) LDLT > 20	9 (4%)	49 (23%)	12 (6%)	7 (3%)	77 (35%)
	(C) DDLT	2 (1%)	38 (18%)	7 (3%)	6 (3%)	53 (25%)
	p-value A vs. B	0.5499	**0.0008**	0.5488	0.4327	**0.0035**
	p-value B vs. C	**0.0332**	0.1953	0.2449	0.7847	**0.013**
Biliary leak or biloma	(A) LDLT ≤ 20	6 (4%)	46 (28%)	3 (2%)	8 (5%)	63 (38%)
	(B) LDLT > 20	8 (4%)	37 (17%)	9 (4%)	5 (2%)	59 (27%)
	(C) DDLT	2 (1%)	15 (7%)	2 (1%)	3 (1%)	22 (10%)
	p-value A vs. B	0.9612	**0.0133**	0.1893	0.1817	**0.0279**
	p-value B vs. C	0.1053	**0.0012**	**0.0332**	0.724	**<0.0001**
Infection	(A) LDLT ≤ 20	6 (4%)	52 (31%)	7 (4%)	15 (9%)	80 (48%)
	(B) LDLT > 20	11 (5%)	48 (22%)	3 (1%)	10 (5%)	72 (33%)
	(C) DDLT	4 (2%)	58 (27%)	3 (1%)	8 (4%)	73 (34%)
	p-value A vs. B	0.4857	**0.0459**	0.11	0.085	**0.0034**
	p-value B vs. C	0.0672	0.2522	1.000	0.6373	0.8919
Unplanned reexploration	(A) LDLT ≤ 20	5 (3%)	38 (23%)	5 (3%)	8 (5%)	56 (34%)
	(B) LDLT > 20	2 (1%)	29 (13%)	0 (0%)	8 (4%)	39 (18%)
	(C) DDLT	2 (1%)	27 (13%)	1 (0%)	2 (1%)	32 (15%)
	p-value A vs. B	0.2472	**0.0162**	**0.015**	0.5915	**0.0005**
	p-value B vs. C	1.000	0.7888	0.4988	0.1053	0.3749
Vascular complications	(A) LDLT ≤ 20	0 (0%)	9 (5%)	0 (0%)	10 (6%)	19 (11%)
	(B) LDLT > 20	0 (0%)	2 (1%)	0 (0%)	14 (6%)	16 (7%)
	(C) DDLT	0 (0%)	6 (3%)	1 (0%)	2 (1%)	9 (4%)

Complications		Clavien grade 1	Clavien grade 2	Clavien grade 3	Clavien grade 4	Any Clavien grade
	p-value A vs. B	-	**0.0121**	-	0.8524	0.1766
	p-value B vs. C	-	0.1751	0.4988	**0.0023**	0.1526

*p-values from the chi-square test or Fisher's exact test (when any cell had an expected count less than 5).

[1]LDLT case number ≤ 20 (n = 167), LDLT case number > 20 (n = 217) and DDLT (n = 216).

Table 7

Logistic regression models fitted to identify significant predictors of biliary leak (A), biliary stricture (B) and Clavien grade 4 complications (C)

	Adjusted odds ratio	95% confidence limits		p-Value
A. Predictors of biliary leak[1] (among LDLT only)				
LDLT case number:				
1–10 vs. >40	2.26	1.18	4.34	**0.015**
11–20 vs. >40	1.77	0.94	3.34	0.079
21–40 vs. >40	1.50	0.81	2.78	0.198
HCV diagnosis	0.55	0.35	0.87	**0.011**
No. of donor bile ducts from right lobe[2]:				
2 vs. 1	1.54	0.99	2.49	0.074
≥ 3 vs. 1	2.72	1.08	6.88	**0.035**
Type of anastomosis: Roux-en-Y vs. other	0.71	0.45	1.13	0.150
B. Predictors of biliary stricture[1] (among LDLT only)				
LDLT case number:				
1–10 vs. >40	3.32	1.45	7.57	**0.004**
11–20 vs. >40	1.84	0.76	4.47	0.178
21–40 vs. >40	2.37	1.06	5.31	**0.036**
Cholestatic liver disease	2.10	1.03	4.27	**0.040**
Duration of recipient operative procedure (per 100 min)	1.33	1.06	1.68	**0.014**
Donor hypotension (<100 mmHg)	0.45	0.21	0.96	**0.038**
No. of donor bile ducts from right lobe[2]:				
2 vs. 1	0.77	0.42	1.43	0.408
≥3 vs. 1	1.57	0.46	5.37	0.470
Type of anastomosis: Roux-en-Y vs. other	0.49	0.27	0.88	**0.017**
C. Predictors of any grade 4 complication[1] (LDLT and DDLT)				
DDLT vs. LDLT case number >40	0.78	0.38	1.64	0.517
LDLT case number:				
1–10 vs. >40	2.33	1.06	5.11	**0.036**
11–20 vs. >40	2.06	0.96	4.42	0.065
21–40 vs. >40	0.96	0.42	2.22	0.921

[1] All variables listed in Table 2 were tested for inclusion in each of the three models above. Among LDLT recipients, n = 78, 89, 109 and 108 transplants were performed for case numbers 1–10, 11–20, 21–40 and >40, respectively.

[2] Missing values (n = 22) were assumed to be one bile duct.