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ORIGINAL ARTICLE

Outcomes of Adult Living Donor Liver Transplantation: Comparison of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study and the National Experience

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The study objectives were to determine whether the findings of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) reflect the U.S. national experience and to define risk factors for patient mortality and graft loss in living donor liver transplantation (LDLT). A2ALL previously identified risk factors for mortality after LDLT, which included early center experience, older recipient age, and longer cold ischemia time. LDLT procedures at 9 A2ALL centers ($n = 702$) and 67 non-A2ALL centers ($n = 1664$) from January 1998 through December 2007 in the Scientific Registry of Transplant Recipients database were analyzed. Potential predictors of time from transplantation to death or graft failure were tested using Cox regression. No significant difference in overall mortality between A2ALL and non-A2ALL centers was found. Higher hazard ratios (HRs) were associated with donor age (HR = 1.13 per 10 years, $P = 0.0002$), recipient age (HR = 1.20 per 10 years, $P = 0.0003$), serum creatinine levels (HR = 1.52 per loge unit increase, $P < 0.0001$), hepatocellular carcinoma (HR = 2.12, $P<0.0001$) or hepatitis C virus (HR = 1.18, $P = 0.026$), intensive care unit stay (HR = 2.52, $P< 0.0001$) or hospitalization (HR = 1.62, $P < 0.0001$) versus home, earlier center experience (LDLT case number 15: HR = 1.61, $P < 0.0001$, and a cold ischemia time >4.5 hours (HR = 1.79, $P = 0.0006$). Except for center experience, risk factor effects between A2ALL and non-A2ALL centers were not significantly different. Variables associated with graft loss were identified and showed similar trends. In conclusion, mortality and graft loss risk factors were similar in A2ALL and non-A2ALL centers. These analyses demonstrate that findings from the A2ALL consortium are relevant to other centers in the U.S. performing

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; CI, confidence interval; CIT, cold ischemia time; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; SD, standard deviation; SRTR, Scientific Registry of Transplant Recipients.

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This is publication 15 of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study.

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LDLT, and conclusions and recommendations from A2ALL may help to guide clinical decision making. ***Liver Transpl 17:789–797, 2011.*** © **2011 AASLD.**

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In response to the organ donor shortage, living donor liver transplantation (LDLT) was expanded to adult recipients, and there was rapid growth across the United States after the first reported case in 1998.[1] Limited numbers of procedures were performed at most centers, and the approaches to the recipients and donors were so diverse across centers that it was difficult to provide reliable information about outcomes that could be generalized and used for patient education. Therefore, in 2002, the National Institutes of Health, with supplemental funding from the American Society of Transplant Surgeons and the Health Resources and Services Administration (US Department of Health and Human Services), organized a consortium of 9 liver transplant centers and a data coordinating center to accrue and follow sufficient numbers of patients being considered for and undergoing LDLT to provide results from adequately powered studies. The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) was developed with the aim of providing accurate information on the risks and benefits of adult-to-adult LDLT for both donors and recipients. Retrospective and prospective studies were initiated with the primary goal of providing information on donor and recipient outcomes over the span of a decade (1998-2008). Follow-up data collection was completed in 2009, and a subsequent renewal of A2ALL with additional centers has now been funded by the National Institutes of Health.

The first report from the 9 clinical centers in the A2ALL consortium focused on the predictors of graft loss after LDLT. A learning curve was identified, with graft failure risk decreasing significantly after the first 20 adult-to-adult LDLT procedures in each center.[2] In the initial report, additional risk factors for graft failure after LDLT were also identified; these included older recipient age and the duration of cold ischemia. Variables that were not found to be significant included the Model for End-Stage Liver Disease (MELD) score, the hepatitis C virus (HCV) status, and the donor age.

Because graft failure is only one contributor to posttransplant mortality, it is also important to determine whether the significant risk factors associated with graft failure that have been identified by A2ALL also apply to recipient mortality at A2ALL and non-A2ALL centers. As A2ALL begins additional studies in its second phase, it is important to analyze the first phase of A2ALL and compare the A2ALL experience to the experience of other US centers. If the findings correlate with outcomes at other centers, then the A2ALL reports can be viewed as representative of national results. Therefore, the aim of this study was to determine whether the previously reported findings concerning the importance of center experience and other predictors of outcomes in A2ALL are reflected in the national LDLT experience.

PATIENTS AND METHODS

Data for this study were obtained from the Scientific Registry of Transplant Recipients (SRTR) under a data use agreement. SRTR data are sourced from national transplant data voluntarily submitted by all transplant centers in the United States to the Organ Procurement and Transplantation Network, and they are supplemented by data from the Social Security Death Master File to identify deaths not reported by transplant centers. The multiple-source follow-up or censoring date was calculated as the transplant anniversary (e.g., 6 months, 1 year, or 2 years) immediately before the current SRTR database snapshot date (August 1, 2008); a 3-month lag was allowed to ensure the completion of forms. *Graft failure* was defined as the date of retransplantation or death (whichever was earlier).

A comparison of A2ALL centers and non-A2ALL centers was conducted through an analysis of LDLT recipients at 9 A2ALL centers (n = 702) and 67 non-A2ALL centers (n = 1664) from January 1, 1998 to December 31, 2007. A case number was assigned to each LDLT procedure based on the number of adult LDLT procedures previously performed at that center up to that date. *Cold ischemia time* (CIT) was defined as the time from donor cross-clamping to the removal of the graft from ice. CIT data from the A2ALL retrospective cohort study were used to augment the data available in the SRTR database because the latter was missing a substantial amount of data.

Statistical Analysis

Descriptive statistics included means, ranges, standard deviations (SDs), and proportions.

Potential predictors of the time from LDLT to death or graft failure were tested with multivariable Cox regression models that started at the time of transplantation; adjustments were made for center clustering with robust variances based on the sandwich estimator. Covariate effects are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The following covariates were evaluated: the center type (A2ALL versus non-A2ALL), the center-specific LDLT case number, the transplant year (on or before December 31, 2000 versus after December 31, 2000), the recipient age, the recipient weight, the donor age, the donor weight, diagnoses of hepatocellular carcinoma (HCC) and HCV, the presence of ascites, the pretransplant status [intensive care unit (ICU), hospital (non-ICU), or home], the CIT, the serum creatinine levels,

TABLE 1. Characteristics of the Liver Transplant Recipients in the A2ALL and Non-A2ALL Centers

	A2ALL Centers (n = 9)			Non-A2ALL Centers (n = 67)			
Characteristic	n	Range	Mean (SD) or %	n	Range	Mean (SD) or %	*P* Value*
Recipient age (years)	702	18-73	50.1 (10.9)	1664	18-78	50.6 (11.6)	0.38
Donor age (years)	702	18-65	37.1 (10)	1663	16-73	37.2 (10.8)	0.89
Recipient weight (kg)†	609	51-107	76.7 (17.3)	1582	51-107	77.6 (17.4)	0.26
Recipient MELD score	471	6-40	14.9 (5.7)	1190	6-40	14.2 (5.3)	0.02
Serum creatinine (mg/dL)	681	0.1-6.6	1.0 (0.5)	1639	0.1-11.2	1.0 (0.7)	0.26
0 to ≤0.7	181		27	532		33	0.004
>0.7 to ≤0.9	193		28	486		29	
>0.9 to ≤1.1	140		21	257		16	
>1.1	167		24	364		22	
Diagnosis of HCV	296		42	579		35	0.0007
Diagnosis of HCC	38		5	133		8	0.03
Left lobe recipient (2004-2007)	12/249		5	28/709		4	0.005
Recipient medical condition							<0.0001
Home	624		89	1363		82	
Hospitalization (no ICU)	55		8	238		14	
ICU	23		3	63		4	
CIT (hours)‡	517	0-12	1.6 (1.4)	990	0-12.8	1.9 (1.7)	<0.001
CIT > 4.5 hours	19		4	59		6	0.06
Recipient case number ≤ 15§	132		19	543		33	<0.001

NOTE: All A2ALL centers performed at least 15 LDLT procedures. Most non-A2ALL centers (42/67) performed 15 or fewer LDLT procedures.

*The *t* test was used for continuous variables; the chi-square test was used for categorical variables.

†The 5th to 95th percentiles are reported instead of the range because of outliers.

‡The CIT values are supplemented by A2ALL data; CITs ≥ 13 hours are excluded.

§A case number ≤ 15 indicates LDLT cases among the first 15 cases performed at a center (ie, during the period of less center experience).

and the biological relationship (biologically related versus unrelated). A2ALL data from SRTR were augmented with CIT data from A2ALL when they were not available from SRTR; this was not possible for the non-A2ALL data. Because of the level of missing CIT data in the SRTR database, separate CIT models were fitted with the subset of the cohort with complete CIT data. Statistical interactions between the center type and other predictors were tested. An assessment of the association of patient and graft survival with the case number was performed by the estimation of the HR by 5-case intervals (eg, cases 1-5 and cases 6-10); a case number >30 was used as the reference category. When individual center effects were added to the models with indicator variables, the variability in mortality among the centers was statistically significant ($P < 0.001$), even when it was limited to centers with more than 10 LDLT cases ($P < 0.001$); this motivated us to adjust the analysis for center clustering. *P* values ≤0.05 were considered to be statistically significant. All analyses were carried out with SAS 9.2 statistical software (SAS Institute, Inc., Cary, NC).

Protection of Human Subjects

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

Patient Characteristics

The characteristics of patients from A2ALL and non-A2ALL centers are shown in Table 1. The mean donor and recipient ages were similar for the A2ALL and non-A2ALL centers. The A2ALL centers reported higher mean MELD scores and a higher percentage of recipients with HCV. A2ALL centers also had a higher percentage of left lobe recipients, but this percentage was very small in both types of centers (5% versus 4%). The overall mean creatinine levels were not different, but a significantly higher percentage of non-A2ALL patients had serum creatinine levels ≤0.7 mg/dL. The non-A2ALL group also had higher percentages of HCC patients and patients in the ICU or hospital. LDLT grafts at A2ALL centers had a significantly shorter mean CIT. Because most non-A2ALL centers never exceeded 15 LDLT cases in all, the proportion of recipient case numbers ≤15 was significantly higher in this group (33% versus 19%, $P < 0.001$).

Transplant Centers and Volume

In all, 2366 LDLT procedures, including 702 (30%) at the 9 A2ALL centers and 1664 (70%) at 67 non-A2ALL centers, were performed during the study period. Approximately two-thirds (42/67) of the non-A2ALL

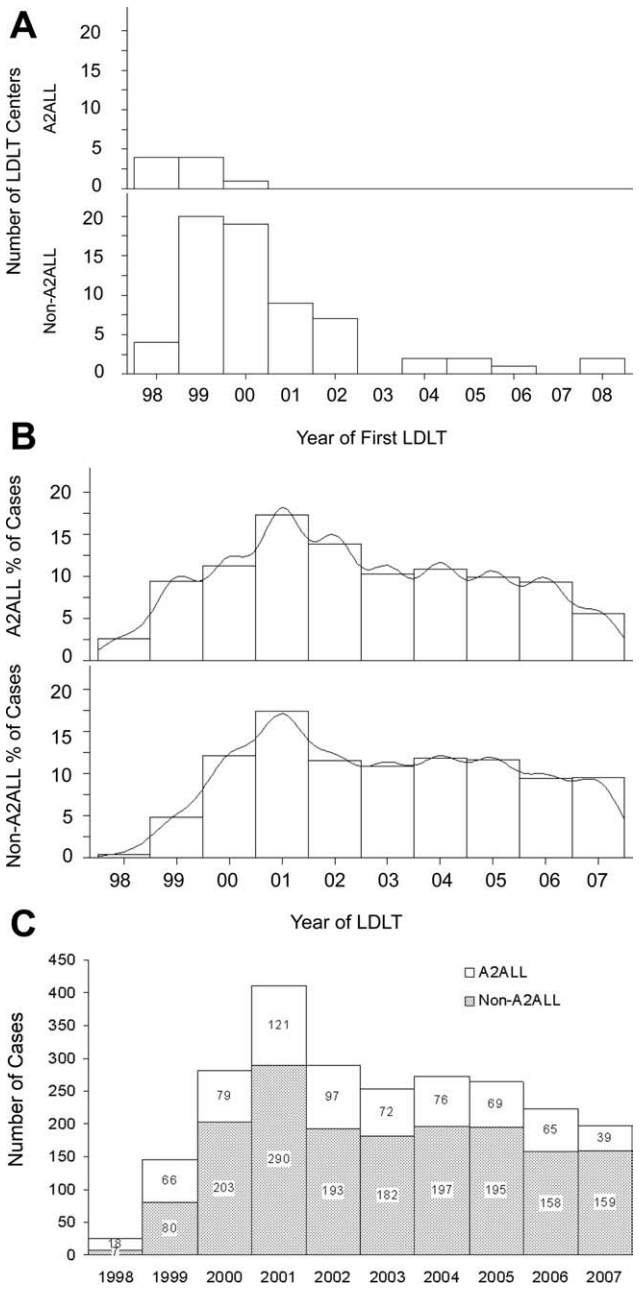

Figure 1. (A) Year of first LDLT for A2ALL (n = 9) and non-A2ALL centers (n = 67). (B) Percentage of LDLT procedures performed by year between 1998 and 2007 in A2ALL and non-A2ALL centers. (C) Number of LDLT procedures performed by year between 1998 and 2007 in A2ALL and non-A2ALL centers.

centers performed 15 or fewer LDLT procedures over the 10-year study period. Five non-A2ALL centers and 3 A2ALL centers each performed more than 100 LDLT procedures. The number of years of activity (≥1 LDLT procedure per year) between 1998 and 2007 varied widely among the non-A2ALL centers (median = 4 years, range = 1-10 years), with only 1 of 67 programs (1.5%) active for all 10 years. In contrast, 3 of 9 A2ALL centers (33%) were active during each year (median = 9 years, range = 7-10 years).

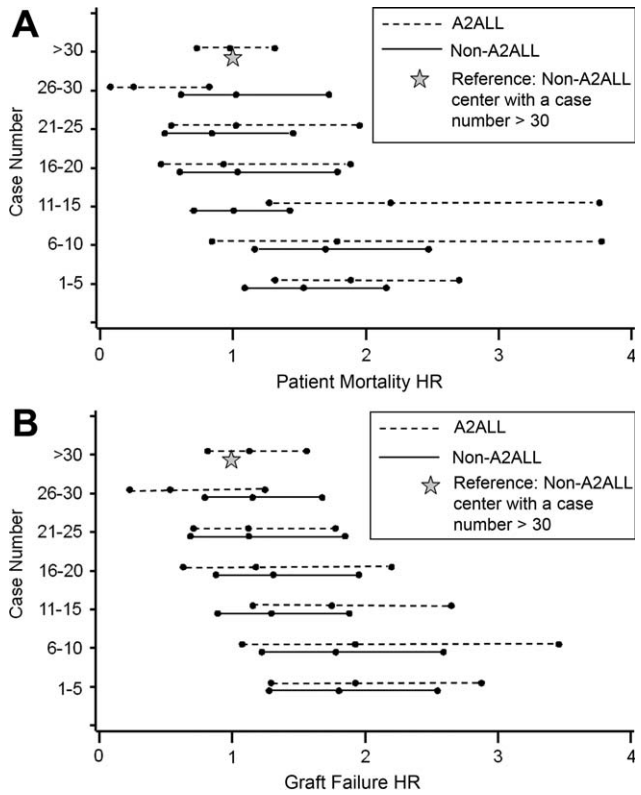

Figure 2. Relative risks of (A) patient mortality and (B) graft failure by the center LDLT case number. The reference category was a non-A2ALL center with a case number > 30. Adjustments were made for recipient and donor ages, HCC and HCV diagnoses, creatinine levels, and medical conditions at transplant; the graft failure model was also adjusted for the recipient weight.

A2ALL centers were among the first to implement LDLT programs. All 9 A2ALL centers performed their first LDLT procedures by the end of 2000, whereas approximately one-third of the 67 non-A2ALL centers performed their first LDLT procedures in 2001 or later (Fig. 1A). The distributions of LDLT procedures over time were relatively similar between the 2 groups (Fig. 1B). However, the non-A2ALL cases reflect many centers that started and stopped, whereas the A2ALL cases are from 9 centers that continued their activity throughout the study period. The national trend has been toward fewer centers performing LDLT. In 2008 and 2009, only 32 and 33 adult liver transplant programs, respectively, performed LDLT in the United States; 8 of these were A2ALL centers. A2ALL centers performed 30% and 37% of all US LDLT procedures in 2008 and 2009, respectively. The number of LDLT procedures performed in the United States peaked at 411 in 2001 and gradually declined to 198 in 2007 (Fig. 1C). Although the total number of adult LDLT procedures has continued to decline over the last 2 years in non-A2ALL centers (124 in 2008 and 106 in 2009), the A2ALL numbers slightly increased in 2008 (n = 54) and 2009 (n = 62).

TABLE 2. Cox Regression Models for Patient Survival

	A2ALL and Non-A2ALL Centers Combined				A2ALL Centers Only			Non-A2ALL Centers Only		
Predictor*	HR	*P* Value	95% CI	*P* Value for the Interaction With Center Type†	HR	*P* Value	95% CI	HR	*P* Value	95% CI
LDLT case number ≤15	1.61	<0.0001	1.28-2.02	0.04	2.24	<0.0001	1.71-2.94	1.45	0.005	1.12-1.87
Donor age per 10 years	1.13	0.0002	1.06-1.20	0.23	1.22	0.009	1.05-1.41	1.10	0.006	1.03-1.18
Recipient age per 10 years	1.20	0.0003	1.09-1.33	0.11	1.38	0.001	1.14-1.66	1.15	0.006	1.04-1.27
Serum creatinine per $\log_e$ unit increase	1.52	<0.0001	1.26-1.83	0.48	1.78	0.001	1.28-2.46	1.45	0.0007	1.17-1.79
Diagnosis of HCV	1.18	0.026	1.02-1.37	0.57	1.24	0.20	0.89-1.72	1.15	0.09	0.98-1.35
Diagnosis of HCC	2.12	<0.0001	1.68-2.69	0.52	1.86	0.013	1.15-3.02	2.30	<0.0001	1.77-2.95
Recipient medical condition				0.39						
ICU versus home	2.52	<0.0001	1.87-3.41	0.18	1.53	0.19	0.81-2.87	2.89	<0.0001	2.02-2.99
Hospitalization (no ICU) versus home	1.62	<0.0001	1.32-1.98	0.64	1.36	0.19	0.86-2.16	1.67	<0.0001	1.32-4.14
CIT > 4.5 hours‡	1.79	0.0006	1.28-2.50	0.34	2.15	0.006	1.24-3.73	1.77	0.010	1.15-2.73

NOTE: Adjustments were made for center clustering with robust variances.
*Variables that were tested but were not significant included the recipient's weight, the use of dialysis, the presence of ascites, the donor's weight, the donor's biological relationship to the recipient, and the transplant year.
†Interactions were tested one at a time in models including all the main effects listed as predictors in this table.
‡Results for CIT are based on separate models with a smaller sample size because of missing CIT values in 33% of cases.

Patient Mortality

The overall adjusted posttransplant mortality risk decreased after centers gained experience. When center experience was divided into 5-case intervals, separate models showed that case 15 was the threshold from higher mortality risk to lower mortality risk at A2ALL centers, and case 10 was the threshold at non-A2ALL centers (Fig. 2A). For subsequent analyses combining A2ALL and non-A2ALL transplants, we used case 15 as the threshold to differentiate earlier center experience (cases 1-15) from later center experience (case 16 and later cases).

In comparison with later center experience, earlier center experience was associated with significantly higher mortality risk at both A2ALL (HR = 2.24, $P < 0.0001$) and non-A2ALL centers (HR = 1.45, $P = 0.005$; Table 2 and Fig. 3A). In comparison with non-A2ALL centers that performed more than 15 LDLT procedures, mortality during the early experience was higher in both A2ALL centers (HR = 1.9, $P < 0.001$) and non-A2ALL centers that stopped by case 15 (HR = 1.44, $P < 0.001$). There was no statistical difference between A2ALL centers during the early experience and non-A2ALL centers that never performed more than 15 procedures (HR = 1.05, $P = 0.80$).

Additional significant predictors of mortality (both groups combined) were identified (Table 2). Older donor age (HR = 1.13 per 10 years, $P = 0.0002$), older recipient age (HR = 1.20 per 10 years, $P = 0.0003$), a diagnosis of HCV (HR = 1.18, $P = 0.026$), a diagnosis of HCC (HR = 2.12, $P < 0.0001$), higher serum creatinine levels (HR = 1.52 per $\log_e$ unit increase, $P < 0.0001$), the patient's medical condition (ICU versus home: HR = 2.52, $P < 0.0001$; hospitalization versus home: HR = 1.62, $P < 0.0001$), and early center experience (case number ≤ 15 versus case number > 15: HR = 1.61, $P < 0.0001$) were all significantly associated with a higher mortality risk. In a subset with available CIT data, a CIT > 4.5 hours was associated with a significantly higher mortality risk (HR = 1.79, $P = 0.0006$) but occurred in only 4% to 6% of the grafts. There was no significant difference in the patient mortality risk between the eras (on or before December 31, 2000 versus after December 31, 2000) after adjustments for center experience and other covariates.

In separate analyses of A2ALL centers and non-A2ALL centers, all associations were consistent in direction, although there were some differences in effect size and significance between A2ALL and non-A2ALL centers. The patient's medical condition was a significant predictor of patient mortality in non-A2ALL centers (ICU versus home: HR = 2.89, $P < 0.0001$; hospitalization versus home: HR = 1.67, $P < 0.0001$) but not in A2ALL centers. We tested for differences in the association of each factor by center type (ie,

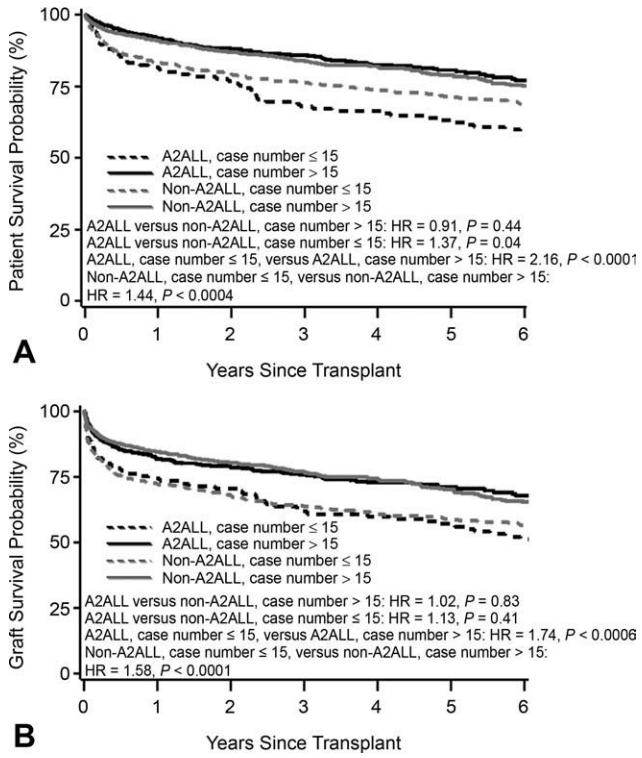

Figure 3. (A) Patient survival and (B) graft survival by the center type and the center case number from an adjusted model. Adjustments were made for the mean covariate values of the recipient (50 years) and donor ages (37 years) at transplant, diagnoses of HCC (0.07) and HCV (0.37), log creatinine levels (−0.09), and medical conditions (0.04 for ICU admission and 0.12 for hospitalization). The graft survival model was also adjusted for the recipient weight (77 kg).

statistical interaction). The only significant interaction occurred with center experience; this effect was significantly stronger at A2ALL centers versus non-A2ALL centers, as reported previously (HR = 2.24 versus HR = 1.45, interaction $P = 0.04$).

Graft Failure

When the center experience was divided into 5-case intervals, the threshold from higher graft failure risk to lower graft failure risk was identified as case 15 at A2ALL centers and as case 10 at non-A2ALL centers (Fig. 2B). As we did with the mortality analyses, we used case 15 as a threshold to differentiate earlier center experience from later center experience in models that included A2ALL and non-A2ALL centers.

A2ALL and non-A2ALL centers had similarly higher risks of graft failure during the early experience period (combined HR = 1.61, $P < 0.0001$) versus the later experience period (ie, after the completion of at least 15 cases; Table 3 and Fig. 3B). During their early experience, non-A2ALL centers that never performed more than 15 procedures had significantly higher graft failure rates than the non-A2ALL centers that performed more than 15 procedures (HR = 1.30, $P = 0.002$). This significant difference in the early experience was not seen when non-A2ALL centers that performed ≤15 LDLT procedures were compared with A2ALL centers during their early experience (HR = 1.23, $P = 0.25$).

Significant predictors of graft failure (both groups combined) were identified (Table 3). Older donor age (HR = 1.13 per 10 years, $P = 0.0002$), a diagnosis of HCC (HR = 1.87, $P < 0.0001$), higher serum creatinine levels (HR = 1.26 per $\log_e$ unit increase, $P = 0.05$), the patient's medical condition (ICU versus home: HR = 2.67, $P < 0.0003$; hospitalization versus home: HR = 1.49, $P < 0.0001$), and early center experience (case number ≤ 15 versus case number > 15: HR = 1.61, $P < 0.0001$) were associated with an increased risk of graft failure. Older recipient age ($P = 0.26$), heavier recipient weight ($P = 0.06$), and a diagnosis of HCV ($P = 0.23$) were also associated with increased graft failure and were retained in the model for face validity, even though they were not statistically significant. In the subset with CIT data, a CIT > 4.5 hours (HR = 1.49, $P = 0.05$) was associated with a higher graft failure risk.

In separate analyses of A2ALL and non-A2ALL centers that considered factors associated with graft failure, all associations except recipient age, recipient weight, and hospitalization versus home were consistent in direction. Older recipient age (HR = 1.26 per 10 years, $P = 0.01$), serum creatinine levels (HR = 1.43, $P = 0.02$), and a diagnosis of HCV (HR = 1.41, $P = 0.02$) were more significant predictors of graft failure at A2ALL centers versus non-A2ALL centers. The effect of CIT on the graft failure risk was significantly stronger at A2ALL centers (HR = 3.25, $P < 0.0001$) versus non-A2ALL centers (HR = 1.29, $P = 0.34$). The recipient's weight (HR = 1.09 per 10 kg, $P = 0.011$) and medical condition (ICU versus home: HR = 3.12, $P < 0.0001$; hospitalization versus home: HR = 1.58, $P = 0.0002$) were significant predictors of graft failure in non-A2ALL centers but not in A2ALL centers. We tested for differences by the center type (ie, statistical interactions) and found that the center type had a significant statistical interaction only with recipient age ($P = 0.03$) and CIT ($P = 0.03$).

DISCUSSION

As the transplant community continues to make efforts to define the most appropriate role for LDLT, it is important to identify the significant clinical risk factors associated with graft failure and recipient mortality. Within the A2ALL consortium, one of the first observations about adult-to-adult LDLT was the significant learning curve: improved graft survival was found after the first 20 cases at each center.[2] We have also recently described a decrease in the incidence of recipient and donor complications after a period of experience.[3,4] Similar findings have been reported in large single-center reports: patient and graft survival has improved significantly after the initial center experience.[5–7] Significant clinical characteristics associated with graft loss, including older recipient age and

TABLE 3. Cox Regression Models for Graft Survival

	A2ALL and Non-A2ALL Centers Combined				A2ALL Centers Only			Non-A2ALL Centers Only		
Predictor*	HR	*P* Value	95% CI	*P* Value for the Interaction With the Center Type†	HR	*P* Value	95% CI	HR	*P* Value	95% CI
LDLT case number ≤15	1.61	<0.0001	1.31-1.99	0.54	1.81	<0.0001	1.48-2.00	1.58	0.0008	1.21-2.06
Donor age per 10 years	1.13	0.0002	1.06-1.21	0.15	1.22	0.005	1.06-1.40	1.10	0.005	1.03-1.18
Recipient age per 10 years	1.05	0.26	0.96-1.16	0.03	1.26	0.01	1.05-1.52	0.99	0.81	0.92-1.07
Recipient weight per 10 kg	1.05	0.06	1.0-1.11	0.16	0.96	0.45	0.87-1.07	1.09	0.011	1.02-1.17
Serum creatinine per $\log_e$ unit increase	1.26	0.05	1.00-1.58	0.66	1.43	0.02	1.06-1.93	1.22	0.17	0.92-1.62
Diagnosis of HCV	1.11	0.23	0.94-1.31	0.09	1.41	0.02	1.05-1.88	1.01	0.93	0.84-1.21
Diagnosis of HCC	1.87	<0.0001	1.50-2.33	0.46	1.64	0.02	1.09-2.45	1.99	<0.0001	1.57-2.54
Recipient medical condition				0.17						
ICU versus home	2.67	<0.0001	2.10-3.39	0.07	1.67	0.12	0.87-3.20	3.12	<0.0001	2.37-4.11
Hospitalization (no ICU) versus home	1.49	0.0003	1.20-1.85	0.12	0.99	0.94	0.77-1.27	1.58	0.0002	1.24-2.02
CIT > 4.5 hours‡	1.49	0.05	0.99-2.25	0.03	3.25	<0.0001	1.79-5.90	1.29	0.34	0.77-2.14

NOTE: Adjustments were made for center clustering with robust variances.
*Variables that were tested but were not significant included the use of dialysis, the presence of ascites, the donor's weight, the donor's biological relationship to the recipient, and the transplant year.
†Interactions were tested one at a time in models including all main effects listed as predictors in this table.
‡Results for CIT are based on separate models with a smaller sample size because of missing CIT values in 33% of cases.

CIT, were also identified. With the first phase of A2ALL completed and the second phase beginning, it was important to determine whether the findings of the A2ALL consortium are representative of centers throughout the United States with respect to experience and posttransplant outcomes (specifically graft failure and patient mortality). Equally important were the goals of (1) identifying any significant similarities and differences between A2ALL and non-A2ALL centers with respect to other factors affecting outcomes that might alter the applicability of A2ALL findings to the general pool of patients undergoing LDLT and (2) providing evidence regarding the most appropriate recipients of LDLT.

In this report, we have again shown an association between center experience and both patient and graft outcomes after LDLT in the United States. Non-A2ALL centers that never performed more than 15 procedures had significantly higher rates of graft failure than centers that performed more procedures. After the first 15 cases, both A2ALL and non-A2ALL centers demonstrated significant decreases in posttransplant mortality. Although the A2ALL centers had significantly higher mortality rates for their first 15 cases, the results for non-A2ALL centers improved after only 10 LDLT cases, perhaps because many non-A2ALL centers started in later years, with experienced teams moving from centers that had already performed LDLT. In comparison, the compositions of surgery and hepatology teams remained stable in most A2ALL centers over the years.

Learning curves are often described after the introduction of a new procedure, but no new complex procedures have been introduced into the field of liver transplantation in the last 10 years except for right lobe LDLT. Relationships between experience and outcomes for kidney, liver, and heart transplantation have been reported,[8,9] with outcomes being better at high-volume centers, and a strong relationship has been reported between higher surgeon volume and decreased morbidity and mortality with other complex surgical procedures.[10,11] Therefore, the learning curve noted here was not unexpected because the introduction of adult-to-adult LDLT was a major technical development from deceased donor liver transplantation.

It was equally important to determine what other clinical factors contribute to mortality after LDLT and whether these factors are comparable between A2ALL and non-A2ALL centers. These findings can help centers to select the most appropriate donors and recipients for LDLT to achieve the best outcomes. For all centers, we found that older recipient age, donor age, a

diagnosis of HCC, higher creatinine levels (a major component of the MELD score), and hospitalization or ICU admission contributed to recipient mortality. When we explored the clinical risk factors for mortality in A2ALL and non-A2ALL centers that were available, we found that these risk factor effects were not significantly different between A2ALL and non-A2ALL centers. The separate A2ALL and non-A2ALL models gave results of consistent direction and fairly similar magnitudes.

With respect to graft failure, we also found similar risk factor estimates for the A2ALL and non-A2ALL groups. When the cohorts were combined, older donor age, a diagnosis of HCC, higher serum creatinine levels, and ICU admission were all associated with a higher risk of graft loss. There were some differences in the effects of individual predictors between the 2 groups; recipient age and CIT were the only 2 variables for which statistically significant differences in their effects were demonstrated between the A2ALL and non-A2ALL cohorts. The CIT discrepancy may be explained by the fact that we were able to supplement missing SRTR data with A2ALL data for this field, and although the missing CIT data in the SRTR database may have affected the coefficient estimates, we have previously reported that CIT is significantly associated with various outcomes in A2ALL.[2,3,12,13] It is more difficult to explain the difference in the significance of recipient age in the A2ALL group versus the non-A2ALL group. Nonetheless, each of these factors may be clinically important, either alone or in combination, and should be considered when decisions regarding donor and recipient selection for LDLT are being made.

The A2ALL multicenter consortium was formed to address outcomes for both donors and recipients with detailed prospective data collection; its goal is to generalize these results to the national experience because detailed data collection and reporting are not feasible on a national scale. This report demonstrates that the A2ALL study results are generally representative of national outcomes. Although incomplete data collection and a lack of granularity in the SRTR data may have contributed to some of the differences noted in this study, we have shown comparability between the groups with respect to the magnitude and direction of risk factor effects.

Limitations of this study may include missing data and misclassification in the SRTR database for the covariates and outcomes investigated[14] and potential secular trends not captured in the statistical modeling, although era effects (on or before December 31, 2000 versus after December 31, 2000) were tested. Also, because of the limitation of variables available in the SRTR database, we were not able to demonstrate the comparability of A2ALL and non-A2ALL centers for other published A2ALL results, such as donor and recipient complications and graft size.

From the results of all US centers performing LDLT, we have shown that gaining initial experience is important for improving survival after LDLT, regardless of when a center starts an adult LDLT program. The data also demonstrate a continuing decline in the number of adult LDLT procedures performed outside the A2ALL consortium, and this may demonstrate the natural tendency of these procedures to gravitate to experienced centers.

The analyses presented here support the application of findings from the A2ALL consortium to other centers in the United States performing LDLT. As we embark on further studies in the second phase of A2ALL, the goals of the A2ALL consortium are that (1) analyses of detailed data and lessons learned will contribute to future advances on a national scale, and (2) A2ALL findings will be used to provide guidance for center performance and clinical decision making in the field of adult-to-adult LDLT.

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REFERENCES

1. Wachs ME, Bak TE, Karrer FM, Everson GT, Shrestha R, Trouillot TE, et al. Adult living donor liver transplantation using a right hepatic lobe. Transplantation 1998;66: 1313-1316.
2. Olthoff KM, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL consortium. Ann Surg 2005;242:314-323.
3. Freise CE, Gillespie BW, Koffron AJ, Lok AS, Pruett TL, Emond JC, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL retrospective cohort study. Am J Transplant 2008; 8:2569-2579.
4. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, et al. Donor morbidity after living donation for liver transplantation. Gastroenterology 2008;135: 468-476.
5. Lo CM, Fan ST, Liu CL, Yong BH, Wong Y, Lau GK, et al. Lessons learned from one hundred right lobe living donor liver transplants. Ann Surg 2004;240: 151-158.
6. Pomposelli JJ, Verbesey J, Simpson MA, Lewis WD, Gordon FD, Khettry U, et al. Improved survival after live donor adult liver transplantation (LDALT) using right lobe grafts: program experience and lessons learned. Am J Transplant 2006;6:589-598.
7. Shah SA, Levy GA, Greig PD, Smith R, McGilvray ID, Lilly LB, et al. Reduced mortality with right-lobe living donor compared to deceased-donor liver transplantation when analyzed from the time of listing. Am J Transplant 2007;7:998-1002.
8. Axelrod DA, Guidinger MK, McCullough KP, Leichtman AB, Punch JD, Merion RM.Association of center volume with outcome after liver and kidney transplantation. Am J Transplant 2004;4:920-927.
9. Weiss ES, Meguid RA, Patel ND, Russell SD, Shah AS, Baumgartner WA, Conte JV. Increased mortality at low-volume orthotopic heart transplantation centers: should current standards change? Ann Thorac Surg 2008;86: 1250-1260.
10. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137: 511-520.
11. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349: 2117-2127.
12. Berg CL, Gillespie BW, Merion RM, Brown RS Jr, Abecassis MM, Trotter JF, et al. Improvement in survival associated with adult-to-adult living donor liver transplantation. Gastroenterology 2007;133:1806-1813.
13. Shaked A, Ghobrial RM, Merion RM, Shearon TH, Emond JC, Fair JH, et al. Incidence and severity of acute cellular rejection in recipients undergoing adult living donor or deceased donor liver transplantation. Am J Transplant 2009;9:301-308.
14. Gillespie BW, Merion RM, Ortiz-Rios E, Tong L, Shaked A, Brown RS, et al. Database comparison of the Adult-To-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) and the SRTR U.S. Transplant Registry. Am J Transplant 2010;10:1621-1633.