ORIGINAL ARTICLE

Liver Regeneration After Living Donor Transplantation: Adult-to-Adult Living Donor Liver Transplantation Cohort Study

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Adult-to-adult living donors and recipients were studied to characterize patterns of liver growth and identify associated factors in a multicenter study. Three hundred and fifty donors and 353 recipients in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) receiving transplants between March 2003 and February 2010 were included. Potential predictors of 3-month liver volume included total and standard liver volumes (TLV and SLV), Model for End-Stage Liver Disease (MELD) score (in recipients), the remnant and graft size, remnant-to-donor and graft-to-recipient weight ratios (RDWR and GRWR), remnant/TLV, and graft/SLV. Among donors, 3-month absolute growth was 676 ± 251 g (mean $\pm$ SD), and percentage reconstitution was $80\% \pm 13\%$. Among recipients, GRWR was $1.3\% \pm 0.4\%$ ($8 < 0.8\%$). Graft weight was $60\% \pm 13\%$ of SLV. Three-month absolute growth was 549 ± 267 g, and percentage reconstitution was $93\% \pm 18\%$. Predictors of greater 3-month liver volume included larger patient size (donors and recipients), larger graft volume (recipients), and larger TLV (donors). Donors with the smallest remnant/TLV ratios had larger than expected growth but also had higher postoperative bilirubin and international normalized ratio at 7 and 30 days. In a combined donor-recipient analysis, donors had smaller 3-month liver volumes than recipients adjusted for patient size, remnant or graft volume, and TLV or SLV ($P = 0.004$). Recipient graft failure in the first 90 days was predicted by poor graft function at day 7 (HR = 4.50, $P = 0.001$)

Additional Supporting Information may be found in the online version of this article.

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; BMI, body mass index; BSA, body surface area; CI, confidence interval; Co-I, co-investigator; CT, computed tomography; FLV, functional liver volume; GRWR, graft-to-recipient weight ratio; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; LDLT, living donor liver transplantation; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; OR, operating room; PI, principal investigator; RDWR, remnant-to-donor weight ratio; SFSS, small-for-size syndrome; SLV, standard liver volume; TLV, total liver volume.

Individuals who were instrumental in the planning and conduct of this study and their participating institutions are listed in the supporting information.

Potential conflict of interest: Nothing to report.

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but not by GRWR or graft fraction ($P > 0.90$ for each). Both donors and recipients had rapid yet incomplete restoration of tissue mass in the first 3 months, and this confirmed previous reports. Recipients achieved a greater percentage of expected total volume. Patient size and recipient graft volume significantly influenced 3-month volumes. Importantly, donor liver volume is a critical predictor of the rate of regeneration, and donor remnant fraction affects postresection function. ***Liver Transpl* 21:79-88, 2015.**

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Liver regeneration is critical in adult living donor liver transplantation (LDLT), and size considerations affect the selection of appropriate donor and recipient pairs.[1,2] Single-center studies have shown that recipients have rapid liver regeneration but that many donors do not regain total liver volume, even after 1 year.[3-6] Portal hemodynamics, vascular outflow, graft-to-recipient weight ratios (GRWR), humoral factors, and graft quality have all been implicated in affecting liver regeneration. Left lobe donors provide even smaller grafts, and makes the procedure potentially safer for the donor but increases the risk for the recipient.[7,8]

A principal aim of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) is to characterize liver regeneration and function and their impact on outcomes in both donors and recipients. This is the first multicenter study examining the clinical manifestations of liver regeneration in LDLT and characterizing growth patterns common to donors and recipients with a prospectively defined clinical cohort.

PATIENTS AND METHODS

Data Sources

Study Population

A2ALL enrolled potential living donors and their recipients at 9 participating transplantation centers. Transplantations occurred between March 2003 and February 2010, with follow-up through August 2010. Donors had preoperative volumetric imaging by magnetic resonance imaging (MRI) or computed tomography (CT) to determine total liver volume (TLV) and right and left lobe volumes. Grafts were weighed (or volumes measured by displacement) in the operating room (OR) after removal. Donors and recipients had imaging data at 3 months after donation/transplantation.[9] Volume (cc), as measured on imaging, and weight (g), as measured in the OR, are used interchangeably and adjusted for blood that has drained from the removed lobe. Demographic information, clinical variables, and laboratory values were collected preoperatively and at 3 months after transplantation. Preoperative imaging was available in 334 donors (310 right lobes, 24 left lobes); investigation of remnant regeneration was limited to 221 (211 right lobes, 10 left lobes) who also had graft weight (from intraoperative weight or volume or preoperative imaging) and 3-month imaged volumes. Graft weights were available for 308 recipients (291 right lobes, 17 left lobes). Investigation of graft regeneration included 150 (145 right lobes, 5 left lobes) with 3-month imaged volumes. Among the 158 recipients without 3-month imaging, 24 died or lost their graft within 3 months [6 died (5 right lobes, 1 left lobe), 16 lost their graft (all right lobes), and 2 lost their grafts and died (both right lobes)]. There were 127 (122 right lobes, 5 left lobes) donor-recipient pairs among whom both had complete volumetric data.

Corrected Graft Volumes

In donors, graft volumes estimated by preoperative imaging were higher than intraoperative graft weights, thought to be due primarily to the weight of blood in vivo.[6,8,10] Imaged volume exceeded measured weight by a mean of 146 g ± 10.6 g (18.6%, $P < 0.001$). To combine data from intraoperative and imaging measurements, an equation for in vivo graft volume based on intraoperative graft weight was developed for 253 donors who had data from both sources. The corrected graft volume was estimated as $198 + 0.939 *\cdot$ graft weight ($R^2 = 0.55$; Supporting Fig. 1). When the graft weight was not measured in the OR (n = 82), the preoperative imaged graft volume was used.

Volume Measurements

For donors, remnant volume was calculated by subtracting corrected graft volume from TLV. For recipients, "normal" liver volume was estimated by standard liver volume [SLV = 1072.8 × body surface area (BSA) − 345.7, where BSA = $[\text{weight (kg)}]^{0.425} \times [\text{height (cm)}]^{0.725} \times 0.007184$),[9] and liver size at transplant was defined as corrected graft volume. The liver fraction was defined as the percentage of the "normal" whole liver volume that the remnant or graft represented (remnant volume/TLV for donors; corrected graft weight/SLV for recipients). The GRWR was calculated from corrected graft weight in the OR and preoperative recipient weight. The remnant-to-donor weight ratio (RDWR) was calculated similarly for donors.

Outcome Measures and Regeneration Parameters

Imaged 3-month liver volume was the primary outcome measure, and 3 additional measures of regeneration were calculated. First, the absolute volume increase in cubic centimeters was defined as the difference between the 3-month imaged volume and the graft or remnant volume. Second, the percentage volume increase was the percentage increase of liver volume from time of transplant or resection to 3 months after transplantation. Third, the percentage reconstitution in cubic centimeters was defined as the percentage of the normal whole liver volume (TLV for donors; SLV for recipients) achieved by 3 months.

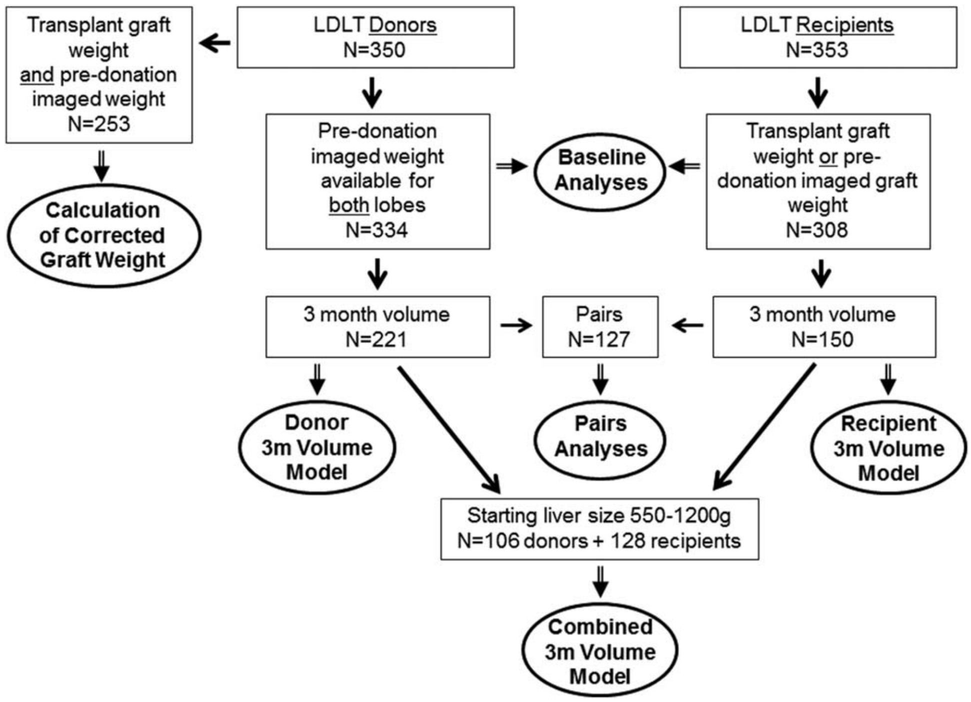

Figure 1. Study population and analysis subsets.

We chose the 3-month liver volume as the main outcome of interest because its measurement does not depend directly on remnant/graft volume. Two of the other outcomes (absolute and percentage volume increase) use remnant/graft volume in their calculation, and this prevents the latter from being a proper independent variable in statistical models of these outcomes.

Early allograft dysfunction and small-for-size syndrome (SFSS) were defined by the presence of jaundice (bilirubin >10 mg/dL on day 7) or coagulopathy [international normalized ratio (INR) > 1.6 on day 7], without technical complications as modified from previous definitions.[10-12]

Human Subject Protection

The study was approved by the institutional review boards and privacy boards of the University of Michigan Data Coordinating Center and each of the 9 participating transplant centers. All subjects provided written informed consent. No donor organs were obtained from executed prisoners or other institutionalized persons.

Statistical Analyses

Correlation coefficients were used to assess relationships among graft and remnant fractions, measures of regeneration, and laboratory values. Student *t*-tests were used to compare GRWR and liver fraction for recipients with and without poor function at day 7. Linear regression was used to identify predictors of 3-month liver volume separately in donors and recipients, as well as in a combined model. Potential explanatory factors were tested based on significant findings in prior studies.[11-17] For associations in donors, donor sex, age, weight, height, body mass index (BMI), BSA, TLV, remnant lobe type (left or right), remnant volume, RDWR, and remnant liver fraction were tested. For associations in recipients, donor and recipient sex, age, weight, height, BMI, and BSA; graft lobe type (left or right), graft weight, GRWR, liver fraction, and cold ischemia time; and recipient SLV, hepatitis C virus (HCV) diagnosis, and Model for End-Stage Liver Disease (MELD) score at transplant were tested.

Analysis of donor and recipient 3-month liver volumes together was restricted to subjects with a range of liver volumes at transplant common to both groups, which was 550 to 1200 g (n = 106 donors, n = 128 recipients). Variables considered for inclusion were patient type (donor or recipient), lobe type, and variables significant in the separate models (weight, TLV, graft or remnant volume, liver fraction). Statistical interactions between patient type and each of the latter factors were tested.

Logistic regression was used to test for associations between incomplete regeneration (defined as <75% reconstitution of TLV or SLV by 3 months) and 7- and 30-day postoperative albumin, bilirubin, INR, and creatinine. Logistic regression was used to examine the association between poor function at 7 days and 3-month liver volume in recipients adjusted for graft size and patient weight.

We used 3 sets of Cox regression models to investigate predictors of graft failure (including death). The first set followed patients from transplantation and tested separately whether graft weight, GRWR, or liver fraction predicted graft failure overall or in the first 90

TABLE 1. Characteristics of Donors (n = 334) and Recipients (n = 308)

	Donors			Recipients		
Characteristic	n	Mean (SD) or Percentage	Range (or IQR)	n	Mean (SD) or Percentage	Range (or IQR)
Age at donation or transplant (years)	334	38 (10)	20-63	308	52 (11)	18-72
Sex						
Male	168	50.3		165	53.6	
Female	166	49.7		143	46.4	
Ethnicity						
Hispanic/Latino	45	13.5		41	13.3	
Non-Hispanic/non-Latino	289	86.5		265	86.0	
Missing	0	0		2	1.6	
Race						
White	308	92.2		278	90.3	
African American	10	3.0		11	3.6	
Asian	5	1.5		6	1.9	
Other	11	3.3		11	3.6	
Right lobe donor or recipient	310	92.8		289	93.8	
Height at evaluation (cm)	332	172 (10)	135-196	302	171 (11)	140-203
Weight at evaluation (kg)	327	78 (15)	47-135	299	78 (17)	40-143
BMI at evaluation (kg/m^2)	326	26 (4)	16-41	297	27 (5)	16-48
TLV by Imaging at evaluation (cc) or calculated SLV at transplantation (cc)	334	1566 (298)	1353-1763*	288	1684 (263)	1501-1855*
Graft weight at donation (g)†	334	987 (204)	860-1108*	308	989 (196)	860-1108*
Calculated remnant volume at donation (g)	334	579 (240)	413-722*	—	—	—
Remnant or graft liver fraction (%)‡	334	36 (11)	30-42*	288	60 (13)	51-67*
Liver volume at month 3 (cc)	221	1241 (271)	1022-1401*	150	1542 (304)	1338-1743*
Laboratory values at day 7						
Bilirubin (IU/L)	334	1.6 (1.4)	0.4-10.6	306	5.0 (5.1)	0.3-36.7
Albumin (g/dL)	280	3.2 (0.4)	1.8-4.5	268	2.8 (0.7)	1.5-5.8
INR	289	1.2 (0.2)	0.9-1.8	232	1.3 (0.2)	0.8-2.4
Laboratory values at day 30						
Bilirubin (IU/L)	311	0.7 (0.5)	0.1-5.2	304	2.1 (4.4)	0.1-42.5
Albumin (g/dL)	295	3.8 (0.5)	2.1-5.2	277	3.2 (1.1)	1.4-18.0
INR	262	1.1 (0.1)	0.7-2.6	223	1.2 (1.1)	0.8-17.0

*IQR.
†Measured graft weight in OR corrected by blood.
‡Calculated residual lobe volume/TLV by imaging for donors; graft weight/SLV for recipients.

days. The second set followed patients from day 7 after transplantation and tested whether poor function at day 7 predicted subsequent graft failure overall or in the first 90 days. The third set followed patients from day 90 after transplantation and tested separately whether absolute growth, volume reconstitution, or percentage volume increase at day 90 predicted subsequent graft failure.

Among the donor-recipient pairs, correlation coefficients were used to assess relationships between paired graft/remnant absolute growth, percentage reconstitution, percentage volume increase, and 3-month volume. All analyses were performed in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Figure 1 shows the available study sample for each set of results described below.

Baseline Analyses: Donor and Recipient Characteristics

A total of 334 donors had TLV measurements (Table 1 and Supporting Table 1, by lobe). Mean age was 38 years, approximately half were men, and the majority were non-Hispanic white and biologically related to the recipient. Right lobe donors (n = 310) differed from left lobe donors (n = 24) in mean graft weight (right

TABLE 2. Predictors of 3-Month Liver Volume by Multiple Linear Regression Analysis Among Donors, Among Recipients, and Among Both Donors and Recipients

Predictor	Effect on Liver Volume (g)	95% CI	P Value
Donor model* (n = 221, R^2 = 0.57)			
Weight† (per 10 kg)	43.8	22.0, 65.5	<0.001
TLV (per 100 g)	50.9	38.8, 63.0	<0.001
Remnant liver fraction‡ (per 1%)	10.5	5.8, 15.3	<0.001
Remnant liver fraction‡ squared (per 1%)	0.40	0.25, 0.55	<0.001
Recipient model§ (n = 149,‖ R^2 = 0.38)			
Weight† (per 10 kg)	71.5	46.5, 96.4	<0.001
Graft volume (per 100 g)	60.5	39.5, 81.4	<0.001
Combined model for donors and recipients¶ (n = 232,‖ R^2 = 0.42)#			
Donor (versus recipient)	−110.4	−185.0, −35.9	0.004
Weight† (per 10 kg)	44.1	14.3, 73.8	0.004
Remnant or graft volume (per 100 g)	53.9	32.6, 75.3	<0.001
TLV or SLV (per 100 g)	24.4	3.9, 44.8	0.020

*In the donor model, donor sex, age, height, BMI, BSA (see footnote || below), remnant lobe type (left or right), remnant volume, and RDWR were tested but were not significant.
†If weight is replaced by BSA, the R^2 values are very similar for all 3 models.
‡Liver fraction is remnant/total size, centered on 50%.
§In the recipient model, donor and recipient sex, age, height, BMI, and BSA; donor weight; graft lobe type (left or right), GRWR, liver fraction, and cold ischemia time; and recipient SLV, HCV diagnosis, and MELD score at transplant were tested but were not significant.
‖One recipient missing weight was excluded from recipient and combined models. One recipient missing height (needed to calculate SLV) was also excluded from the combined model.
¶In the combined model, lobe type (left or right; remnant for donor, graft for recipient) and liver fraction were tested but were not significant, as were interactions between donor and all factors.
#Restricted to 106 donors and 128 recipients with remnant or graft liver volume (of 550-1200 g), which included 48% of remnant lobes and 85% of donated lobes.

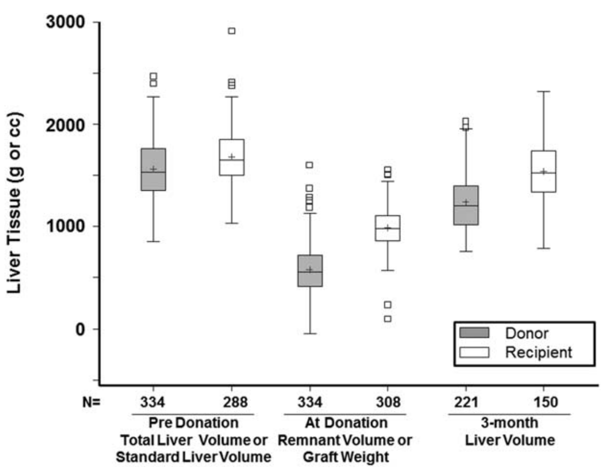

Figure 2. Box and whisker plot of liver volume before and after transplant. The bottom and top of boxes indicate the 25th and 75th percentiles, respectively; middle line indicates the median, and a plus sign indicates the mean. Whiskers extend up to 1.5 times the IQR from the bottom and top edges of the box, ending at the last actual data point within the range.

lobes, mean 1021 ± 187 g; left lobes, 672 ± 146 g; P < 0.001) and the donor remnant size both in weight (mean 548 ± 213 g after right lobe donation, 982 ± 192 g after left lobe donation, P < 0.001) and as a fraction of TLV (34% versus 59%, P < 0.001). Remnant fraction was less than 35% of TLV for 168 donors (50%); it was less than 25% of TLV for 41 (12%) right lobe donors.

The mean age of recipients was 52 years, 54% were men, and 86% were non-Hispanic white. Left lobe recipients (n = 17) were more often female than right lobe recipients (n = 291; 94% versus 44%, P < 0.001) and therefore were also shorter (P < 0.001) and lighter (P = 0.007). Mean graft volume was 989 cc, with right lobes averaging 1007 cc and left lobes averaging 685 cc (Table 1 and Supporting Table 2, by lobe). Left lobe recipient grafts as a fraction of SLV (48% versus 61%, P = 0.001) and GRWR (1.1% versus 1.3%, P = 0.005) were smaller than right lobe recipient grafts. Eight (6 right, 2 left) grafts had a GRWR <0.8%, and 11 (9 right, 2 left) had a liver fraction less than 40% (7 grafts met both criteria).

Donor and Recipient 3-Month Liver Volumes and Growth Parameters

Donor remnants had larger absolute growth at 3 months (676 cc) than recipient grafts (553 cc, P < 0.001) but lower percentage reconstitution at 3

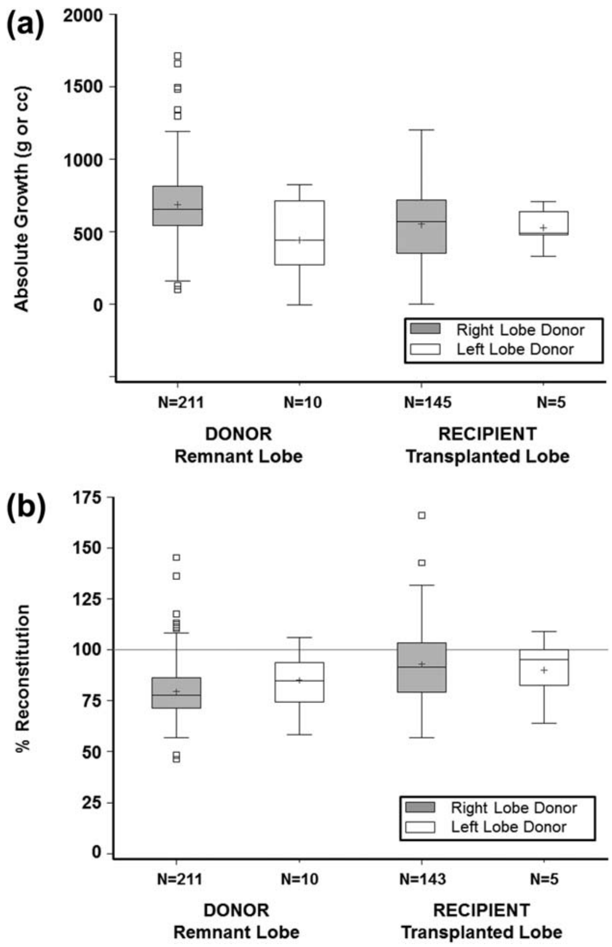

Figure 3. (A) Donor and recipient absolute growth at 3 months by lobe. (B) Donor and recipient percentage liver reconstitution at 3 months by lobe. Each regeneration measure is based on remnant lobe for donors and on transplanted lobe for recipients. The bottom and top of boxes indicate the 25th and 75th percentiles, respectively; middle line indicates the median, and a plus sign indicates the mean. Whiskers extend up to 1.5 times the IQR from the bottom and top edges of the box, ending at the last actual data point within the range.

months (80% of starting TLV versus 93% of expected SLV, $P < 0.001$; Figs. 2 and 3A,B). Only 14 donors (6.3%) achieved 100% of starting TLV by 3 months, whereas 52 (36%) recipients achieved their calculated SLV. Percentage volume increase of the remnant liver showed a wide range in both donors (median 119%, Q1 = 86%, Q3 = 176%) and recipients (median 55%, Q1 = 36%, Q3 = 79%, $P < 0.001$). At 3 months, liver volume was smaller for 211 right lobe than 10 left lobe donors (1233 ± 265 cc versus 1413 ± 361 cc, $P = 0.04$). Nevertheless, donors of right lobes (who had smaller remnants) had more absolute volume increase than donors of left lobes; recipient growth was comparable, regardless of lobe (Supporting Fig. 2A). Left lobe donors had a higher percentage reconstitution than right lobe donors. Among recipients, right lobe grafts were significantly larger than left lobe grafts at 3 months (1553 ± 302 cc versus 1225 ± 166 cc, $P = 0.02$). Recipient liver reconstitution was comparable for the 2 lobes (Supporting Fig. 2B).

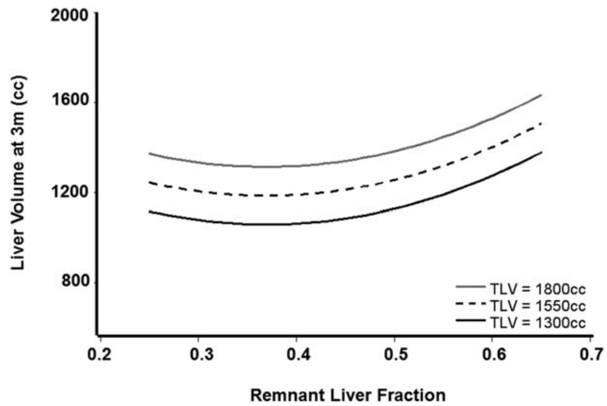

Figure 4. Predicted donor liver volume at 3 months (*y* axis) and remnant liver fraction (*x* axis) at transplantation based on donor model. Predicted values are shown for 3 hypothetical 78-kg donors with TLV of 1300, 1550, and 1800 cc.

Predictors of 3-Month Volume: Donors and Recipients

Among donors, greater body weight, TLV, and liver fraction were significantly and positively associated with greater 3-month liver volume (Table 2). When adjusted for these 3 measures, neither remnant volume nor lobe donated had a statistically significant effect on 3-month volume. On average, liver volume at 3 months was 43.8 cc higher for every 10 kg of donor body weight ($P < 0.001$) and 51 cc higher for every 100 cc of original TLV ($P < 0.001$); the latter is demonstrated in Fig. 4, which shows the predicted 3-month liver volume for donors with 3 different TLVs for remnant liver fractions between 0.2 and 0.7, accounting for 87.3% of donors. The relationship with liver fraction was not linear; 3-month liver volumes were similar for remnant liver fractions between 0.2 and 0.5, with increasing 3-month volumes for liver fractions >0.5.

Recipient body weight and graft size were positively and significantly associated with 3-month liver volume (Table 2). Liver volume at 3 months was on average 71 cc higher for every 10 kg of recipient weight ($P < 0.001$) and 60 cc higher for every 100 cc of transplanted graft weight ($P < 0.001$). Unlike the donors, the relationship between starting liver fraction and 3-month liver volume was linear, without the parabolic tail seen for the smaller remnants ($P = 0.42$).

We tested weight, continuous BMI, and BMI categories (normal, overweight, and obese) in donors and recipients for all measures of regeneration. In both donor and recipient models, we found weight to be the stronger predictor of regeneration as measured by 3-month volume in donors and recipients and absolute volume increase in the donors. After adjusting for weight, BMI provided no additional predictive information. We assessed the influence of HCV, hepatocellular carcinoma, and diabetes on liver growth. None of these variables were significantly associated with parameters of liver regeneration.

TABLE 3. Clinical Correlates of Donor Remnant Fraction and Recipient Graft Fraction

	Donor Remnant Fraction		Recipient Graft Fraction	
Laboratory value	*r*	*P* Value	*r*	*P* Value
Day 7 after donation				
Bilirubin	−0.13	0.02	0.03	0.61
INR	−0.13	0.03	−0.27	<0.001
Albumin	0.09	0.13	0.004	0.95
Creatinine	0.05	0.37	0.03	0.63
Day 30 after donation				
Bilirubin	−0.12	0.03	0.005	0.93
INR	−0.13	0.03	0.01	0.88
Albumin	0.18	0.002	0.13	0.04
Creatinine	0.22	0.0001	0.007	0.91
1 year after donation				
Platelet drop since evaluation	−0.13	0.08	—	—

Previous reports have used 3 additional measures of liver growth to assess liver regeneration: absolute growth, percentage volume increase, and percentage reconstitution. The significant predictors for these outcomes were liver fraction (all outcomes), remnant/graft size (percentage reconstitution), and donor/recipient weight (percentage reconstitution and absolute volume increase). In addition, the following donor/recipient variables were tested and found to not be significant. For donors: sex, age, BMI, and graft type (left/right lobe). For recipients: graft type (left/right lobe), SLV, sex, age, BMI, HCV, hepatocellular carcinoma, diabetes, MELD score, cold ischemia time, and donor age, sex, and BMI. Thus, the main predictors of liver regeneration, no matter how they are measured, are remnant/graft size, liver fraction, and weight.

Predictors of 3-Month Volume: Combined Donors and Recipients

Predictors of 3-month liver volume in 106 donors and 128 recipients were examined over the range of common lobe weights (550-1200 g; Table 2). Positive associations with 3-month donor and recipient volumes were seen for donor or recipient weight, remnant or graft volume, and donor TLV. The effects of these 3 features were similar for donors and recipients, with no significant interaction between patient type and any of these factors. Most importantly, we found that after adjustments for these factors, 3-month volumes were greater for recipient than for donor livers by 110 g on average ($P = 0.004$).

Paired Comparisons Between Lobes

Donor and recipient data were complete for 127 pairs. There was no correlation between the liver lobes for absolute growth ($r = -0.1$, $P = 0.28$), percentage reconstitution ($r = -0.14$, $P = 0.11$), or percentage volume increase ($r = -0.07$, $P = 0.46$). There was a significant correlation between 3-month volumes for these pairs ($r = 0.26$, $P = 0.003$) that was lost when adjusted for donor TLV ($r = -0.03$, $P = 0.73$).

Clinical Correlates

Correlation of Recipient Regeneration With Graft Function and Failure

Twenty-four recipients died or lost their graft in the first 90 days. Forty-nine recipients (44 right lobes, 5 left lobes) had early allograft dysfunction and symptoms of SFSS (16% overall; 15% of right lobe, 29% of left lobe recipients). Among them, 38 (34 right lobes, 4 left lobes) survived for at least 90 days with a functioning graft. Poor graft function at day 7 predicted progression to graft failure both overall (HR = 2.5, $P = 0.004$) and in the first 90 days following transplantation (HR = 4.5, $P = 0.001$).

Ten of 12 recipients with GRWR <0.8% or graft fraction <40% survived for at least 90 days with a functioning graft. Neither GRWR nor graft fraction was associated with graft failure overall or in the first 90 days or with poor function at day 7. Adjusted for graft size and patient weight, grafts with dysfunction at 1 week (with 3-month imaging) were a mean of 140 cc larger at 3 months ($P = 0.02$) than those without early dysfunction.

There were only 15 graft failures beyond 3 months, and none of the measurements of liver regeneration (3-month volume, absolute or percentage volume increase, or percentage reconstitution) were significantly associated with subsequent graft failure. However, this result must be considered in light of the low statistical power.

Correlation With Laboratory Values in Donors and Recipients

For donors (Table 3), remnant fractions correlated with 7- and 30-day bilirubin and INR and 30-day albumin and creatinine. Bilirubin at 7 days after donation correlated with liver volume at 3 months ($r = 0.19$, $P = 0.004$). Platelet counts decreased from evaluation to year 1 after donation more for donors with smaller remnants (Table 3). Compared with left lobe donors, right lobe donors had significantly higher bilirubin at days 7 and 30 and lower albumin at 30 days (3.8 versus 4.1, $P = 0.006$; Supporting Table 1).

Among recipients, significant correlations with graft liver fractions were seen for 7-day INR and 30-day albumin (Table 3). Liver volume at 3 months was also correlated ($P < 0.05$) with bilirubin and creatinine at 7 days after transplantation, and albumin and creatinine at 30 days after transplantation.

We also correlated laboratory values (bilirubin, albumin, and INR) with the 3 measures of liver regeneration (absolute and percentage volume increase, and percentage reconstitution) for donors and recipients. For donors, the only significant correlation was between day 7 bilirubin and absolute volume increase. For recipients, day 7 bilirubin was consistently correlated with liver regeneration, and INR was correlated with 2 of the regeneration measures (Supporting Table 4).

DISCUSSION

In living donor transplantation, donor and recipient livers need to regenerate while maintaining adequate metabolic function. This process is central to donor safety and to avoiding liver dysfunction in the recipient.[7,18,19] The current study confirms previous observations that regeneration was brisk in donors and recipients, with substantial, though not always complete, mass restoration by 3 months.[14,20] A unique aspect of this study is that this is the first multicenter study of the clinical manifestations of liver regeneration in LDLT in the West. Using a prospectively defined clinical cohort, we were able to characterize growth patterns common to donors and recipients, despite the vagaries of local surgical practice.

An important finding is the apparent relationship between donor regeneration and both TLV and remnant liver fraction. Uncertainty remains within the living donor community regarding the minimum remnant liver size in the donor, with proposed lower limits between 25% and 35% of total volume. Though right lobes and left lobes differed markedly with respect to both graft size and remnant liver volume, they appear to regenerate in a similar pattern. Importantly, donor remnant size is a critical predictor of the rate of regeneration. Regeneration in donors was related to body weight, predonation total liver volume, and fraction of total liver remaining after donation, regardless of lobe used, which aligns with recent findings by others. Klink et al.[21] recently reported on regeneration in 47 donors followed up to 84 months. Regeneration at 1 year was 87.3% for right lobes and 80% for left lobes. No serious complications were observed in long-term follow-up. Early regeneration was assessed by Gruttadauria et al.[5] in a series of 70 right lobe donors. Their modeling identified greater BMI, a smaller functional liver volume (FLV), and a higher ratio of SLV/FLV as positive predictors of regeneration. In a series of 101 cases of LDLT, Tanemura et al.[22] identified donor age as a significant predictor of regeneration, an observation not made in our study.

Interestingly, analyses of regeneration in donor-recipient pairs did not show any correlation in the regeneration parameters between the 2 parts of the same liver, and this indicates that the host plays a significant role in driving the process. In A2ALL, significant numbers of the donors had less than 35% calculated residual volume, all after right lobe resection. We demonstrated a parabolic relationship in donors between 3-month volume and remnant fraction, with the smallest remnants regenerating faster. Despite very rapid regeneration, early postoperative hepatic function, as measured by bilirubin, INR, and albumin, was compromised with very small remnant liver size, demonstrating an association between liver mass and function.[23-25] Avoidance of very small remnants in donors is one element supporting the trend toward greater use of the left lobe in LDLT to minimize the extent of hepatectomy.

Recipients also demonstrated rapid regeneration, achieving 93% of calculated SLV by 3 months. Larger recipients and those who received a larger graft had greater volume at 3 months. Unlike the donors, a smaller fraction of SLV was not associated with 3-month liver volume, possibly because of SLV being only a rough approximation of original liver size. With regard to function, smaller grafts had higher INR at 1 week and 1 month.

A unique contribution of our study is the comparative analysis of liver growth between the donor and the recipient. In a combined model of donors and recipients, patient weight, larger starting liver volume (remnant or graft), larger TLV or SLV, and patient type (donor versus recipient) each significantly predicted 3-month liver volume. We demonstrated that recipient liver grafts grew more rapidly in the first 3 months than the donor remnants. This recipient-donor divergence did not appear to be due to the variations in the starting lobe size; we demonstrated that, in recipients and donors with similar graft or remnant sizes, the recipient liver growth was greater. Fewer donors achieved their baseline liver volume than recipients who achieved their predicted liver volumes by 3 months. Only 6.3% of donors achieved 100% of starting TLV, whereas 35% of recipients achieved 100% of SLV. Others have noted related observations,[4] which likely reflect the very distinct physiology between donors and recipients. We speculate that the ischemic stress and metabolic demands in recipients provide a growth stimulus to activate priming cytokines for initiation of liver regeneration, whereas the donor has less metabolic demand and no immune pressure or other obvious outward regenerative enhancing stimuli. The relative illness of the recipient may be an impetus for more rapid growth resulting from higher metabolic demand.[26] Both mechanisms are clinically plausible, shifting the energy balance of the recipient toward faster and greater growth than that in the donor. Finally, it is possible that the larger size of the recipient livers may not reflect "normal" hepatocyte mass but perhaps increased water content or other metabolic alterations of the recipient parenchyma compared with the regenerating donor tissue. Our ongoing mechanistic studies in liver regeneration may provide supporting molecular evidence for these findings. Recognizing these differences in magnitude of regeneration, we also demonstrated some commonalities between donor and recipient in that donor and/or recipient weight, TLV, and/or SLV, as well as remnant liver and/or graft volume were all predictors of 3-month volume.

Several large studies, including A2ALL, have shown that older recipients, greater donor age, cold ischemia time, MELD score, and graft size affect outcome.[2,13,27] There is evidence that small liver grafts transplanted into a metabolically stressed recipient, eg, those in the ICU, those with fulminant failure, renal failure, and high MELD scores, have less favorable outcomes than those transplanted into the more advantageous environment of a healthier recipient.[26,28] However, several recent studies have shown that smaller grafts can be used effectively if other parameters are carefully managed or limited, such as donor and recipient age or the presence of significant portal hypertension.[16,17] Others have shown that it is possible to transplant successfully patients with higher MELD scores with living donors if carefully selected.[29,30] In this current study, we did not observe an effect of MELD on regeneration, but there were very few subjects with high MELD scores, and this warrants further investigation.

We were also unable to demonstrate a relationship between any of the regeneration parameters and graft loss in this cohort. Early graft dysfunction, as evidenced by persistent jaundice or coagulopathy at day 7, was seen in 16% of recipients, with more left lobe recipients displaying these features (29% versus 15%). In addition, poorly functioning grafts were 2.5 times more likely to have subsequent graft failure. However, we did not observe a correlation between postoperative graft failure and graft size, and this suggests that early graft dysfunction is dependent on a combination of factors. Identifying these other factors will be important for extending the limits of donation in the future and is a continued focus of A2ALL.

We recognize the limitations of this study, which resulted primarily from missing volumetric data in a significant percentage of patients. In addition, clinical variables that we did not collect, such as variables that better define poor graft function or intraoperative physiologic measurements such as portal pressures and flows, may affect regeneration. The study of regeneration in vivo depends on the reliability of image-based volumetry of the liver and presents numerous challenges, including prediction of the projected graft based on an imaged transection line, the normal variation of the ratio of liver size to body weight or surface area, and the shape and relative lobar volumes. We also noted significant center variation in measurement discrepancies. Although others have used differing approaches,[10,31-34] we estimated the volume of blood in the liver as a linear relationship between the in vivo volume and the weight of the resected lobe, not forced to pass through the origin.

In conclusion, current practice in adult-to-adult LDLT is well within the limits of safe regeneration for both donors and recipients. Thus, it should be possible to move farther by understanding how the quality of the parenchyma, the size of the remnant lobe and the graft, and the status of the recipient affects early regeneration and function. Certainly, the error and variability in measuring liver volume in vivo must be considered when we are evaluating a potential donor-recipient pair to determine the residual remnant fraction and graft volume. Better definitions of these parameters and limits will lead to expanded use of adult LDLT. To this end, mechanistic studies of biomarkers associated with regeneration are ongoing with specimens collected from these A2ALL subjects. Because LDLT provides a laboratory to observe liver growth in the human setting, it is important for the research community to use this unique opportunity to study biological interventions that may enhance liver growth and improve liver function.

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