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Patterns of Early Allograft Dysfunction (EAD) in Adult Live Donor Liver Transplantation: The A2ALL Experience

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Abstract

Background—Early allograft dysfunction (EAD) after living donor liver transplantation (LDLT) has often been attributed to inadequate graft size, and termed small-for-size syndrome (SFSS). EAD definitions include a variable constellation of findings, including hyperbilirubinemia, coagulopathy, encephalopathy, and ascites formation. Among putative causes of EAD after LDLT are excessive portal pressure and/or flow. Our objective was to evaluate patterns of EAD after LDLT.

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Authors' Contributions

This certifies that all authors listed on the manuscript's title page participated meaningfully in the study and have seen and approved the final manuscript. In accordance with ICMJE guidelines for authorship, this manuscript's authors have made substantial contributions to: the paper's conception and design; acquisition, analysis, and interpretation of data; drafting and critically revising the manuscript for important intellectual content; and giving final approval of the version to be published.

Disclosures/Conflicts of Interest

The authors of this manuscript declare no conflicts of interest.

Methods—In this study, 631 LDLT recipients were monitored for complications, EAD (defined by postoperative day 7 bilirubin >10 mg/dl or international normalized ratio >1.6), and graft failure. Approximately 200 had portal venous and arterial pressure and flow measurements before and after LDLT. Portal inflow modification (splenic artery ligation, hemi-portocaval shunt, or splenectomy) was performed at the discretion of the operating surgeon. Associations between EAD and recipient, donor, and transplant factors were examined using multivariable logistic regression.

Results—Risk of EAD was associated with left lobe grafts, lower graft weight among left lobes, higher preoperative bilirubin, higher portal reperfusion pressure, higher donor age, and higher donor body mass index (BMI). The risk of graft loss within the first 90 days was 5.2 times higher for recipients with EAD versus those without EAD ($p<0.001$).

Conclusions—EAD can be defined using postoperative day 7 labs that are highly predictive of early graft failure within 90 days. Risk factors associated with EAD after LDLT include: graft type and size, preoperative bilirubin, portal reperfusion pressure, donor age, and donor BMI.

INTRODUCTION

Early allograft dysfunction (EAD) has been characterized as functional insufficiency after orthotopic liver transplantation (LT)[1] and has been attributed to donor factors and preservation injury. EAD is characterized by a constellation of findings that may include hyperbilirubinemia, coagulopathy, encephalopathy, or ascites.[2] In living donor LT (LDLT), EAD may occur when the graft is too small to meet recipient needs, a condition termed small-for-size syndrome (SFSS). SFSS is associated with grafts smaller than 0.8% graft weight to recipient body weight (GW/RW) ratio or <40% of standard liver volume (SLV). In contrast to other forms of EAD, SFSS is complicated by signs of portal hypertension, most notably excess ascites formation. Smaller grafts, particularly those using left lobes, have been reported to have higher rates of graft failure.[3] Some studies sought to determine the minimal GW/RW ratio required to perform successful LDLT in larger recipients, noting the interaction of preoperative disease severity and graft size on the development of graft dysfunction.[4,5] Because of disappointing early results with small grafts, there was a gradual shift to more routine use of right lobe grafts in adult LDLT to optimize outcomes.[6] However, acceptable results with left lobe grafts have been reported recently, suggesting that the effects of graft size could be mitigated with technical innovation and careful patient selection.[7] In addition, factors other than size can contribute to EAD, affording opportunities to affect outcome with preemptive measures such as inflow modification.

Compared with left lobe donation, right hepatectomy may result in more donor morbidity, mortality, and “near miss” events.[8] The observation that SFSS is related to small graft size and excessive portal venous flow and/or pressure led some to investigate “inflow modification” as a mitigation strategy.[7,9,10] Improved outcome and reversal of signs and symptoms of SFSS after successful inflow modification has renewed interest in smaller left lobe grafts to reduce operative risk in donors without compromising recipient outcome.[11]

In the current study, we sought to characterize the incidence of EAD after LDLT and to develop predictive models for the development of this complication using data from the

Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL). We further tested the association between EAD and subsequent graft loss and death. The A2ALL experience includes a prospective cohort of LDLT recipients in whom hepatic hemodynamics were measured before and immediately after LDLT, with inflow modification in a substantial number of subjects. We examined predictive models of EAD to examine the association between risk factors at the time of transplant and graft function 1 week after transplant.

MATERIALS AND METHODS

A2ALL is an observational cohort study designed to investigate outcomes in donors and recipients of LDLT. It was carried out in 2 phases: A2ALL-1 spanned 2003 through 2010, and A2ALL-2 spanned 2011 through 2014. Twelve North American centers (11 US, 1 Canadian) were involved in each phase, with 6 centers spanning both phases. Patients were managed using best local practice. Each center had study protocols and consents approved by the Institutional Review Board (IRB) prior to enrolling patients.

The cohort included 631 recipients: 358 from A2ALL-1 and 273 from A2ALL-2. Data collected in A2ALL-1 included clinical and outcome variables, and spleen volume for a subset of recipients. In addition, spleen volume, intraoperative hepatic hemodynamic data, and daily laboratory values were collected in A2ALL-2.

This study used data from the Scientific Registry of Transplant Recipients (SRTR) to supplement data on graft failure and mortality for subjects transplanted at centers located in the United States. The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere. The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Pressure and Flow Data

About 70% of recipients in A2ALL-2 had simultaneous portal venous and arterial pressure and flow measurements recorded intraoperatively (Transonic Systems Inc., Ithaca NY, USA), as well as central venous pressure (CVP), cardiac output, and mean arterial pressure. At A2ALL-2 study initiation, consensus was lacking on parameters for surgical inflow modification (splenic artery ligation, splenectomy, hemi-portocaval shunt); these were performed according to surgeon judgment. Pressure and flow measurements recorded at the end of the operation, following any surgical inflow modifications, were used to assess the effects of hepatic hemodynamics on graft outcomes.

To mitigate outflow problems with right lobe grafts, the majority of centers typically reconstructed segment 5 and 8 branches draining into the middle hepatic vein that were greater than 10% of the graft volume and/or flushed briskly during backbench preservation. They were reconstructed with either autologous vein or expanded 6 mm polytetrafluoroethylene (PTFE) grafts. Similarly, large inferior or accessory right hepatic vein branches were reconstructed directly into the vena cava.

Outcome Measures

Outcome variables included mortality, morbidity, hospital length of stay, EAD, and graft failure. An A2ALL definition of EAD was based on postoperative day 7 lab values, determined as a serum bilirubin >10 mg/dl or international normalized ratio (INR) >1.6, and presented in a previous A2ALL report.[12] This definition of EAD included those that may have developed from technical complications (i.e., vascular or biliary). A sensitivity analysis was performed using criteria adapted from Dahm et al[2] as an alternate way to define EAD in LDLT. The Dahm et al definition of SFSS required the absence of a technical complication (biliary or vascular complication or biliary infection) and the presence of serum bilirubin >5 mg/dl on 3 consecutive days during the first postoperative week, and 1 or more of the following 3 conditions in the same period: coagulopathy (INR >2.0), >1 liter ascites/day, or encephalopathy.[2] The data needed to apply this alternate definition were only available for recipients in A2ALL-2; therefore, the A2ALL definition of EAD was unifying across both study periods.

Statistical Analysis

Study subjects were followed from the time of transplant to death or last available follow-up. Descriptive statistics are given as means and standard deviations for continuous variables or as proportions for categorical variables. Comparisons were made between groups using t-tests and chi-squared tests for continuous and categorical variables, respectively. Measures of graft size used in our analyses were graft weight, GW/RW ratio expressed as a percent, and liver fraction defined as graft weight/recipient SLV. SLV was calculated from a previously published formula.[13] Associations among continuous variables were examined using Pearson correlation coefficients.

Unadjusted graft and patient survival for recipients with and without EAD on day 7 were displayed using Kaplan-Meier survival curves, conditional on survival to posttransplant day 7; differences between groups were tested using log-rank tests. Graft failure was defined as the earlier of retransplant or death. Subjects in A2ALL-1 were censored at the end of A2ALL-1 follow-up; for those who later enrolled in A2ALL-2, follow-up time was left-truncated at the time of A2ALL-2 enrollment to avoid giving credit for time at risk when any graft failure or death in the time between studies would not have been observed.

To test whether patients with EAD had a stronger association with short-term than long-term graft survival, we used multivariable Cox regression models with time-dependent effects for <30 days, 30–60 days, 61–90, 91–180, 181–365 and >365 days. Based on these results, we used Cox regression to estimate the effect of graft dysfunction on 90-day graft failure, and to assess the effect of adjusting for measures of graft size.

To examine associations of demographic and clinical factors with the development of EAD, we used logistic regression models with covariate selection guided by the method of best subsets.[13] Covariates in the model selection process included graft factors (left lobe graft, graft weight, GW/RW ratio, interactions between lobe and graft size, and liver fraction <40%), recipient factors at the time of transplant (age, body mass index [BMI], Model for End-Stage Liver Disease [MELD] score, creatinine, bilirubin, INR, alanine transaminase

[ALT], aspartate aminotransferase [AST], alkaline phosphatase, albumin, sodium, hepatitis C virus [HCV], and hepatocellular carcinoma [HCC]), donor factors (age, relationship to recipient), and transplant operation factors (cold and warm ischemia times).

To examine whether spleen size was an important predictor of EAD, we added spleen volume to the set of covariates selected in the logistic regression model above for the subset of recipients with pretransplant spleen volumes available. Due to the relatively small number of subjects with intraoperative pressure and flow measurements available (n=176, events=30), these factors were tested separately for association with EAD.

Statistical analyses were carried out using SAS version 9.4 (SAS Institute; Cary, NC). Results with a 2-sided p-value ≤0.05 were considered statistically significant.

RESULTS

Characteristics of 631 LDLT recipients included in the study, along with transplant and donor information, are shown in Table 1 by A2ALL era. The majority of recipients from both eras were white males, with mean age of 51 years and BMI of 26. HCV was prevalent in about a third of all recipients, whereas HCC was present in 11% of recipients in A2ALL-1 and 23% in A2ALL-2. The mean lab MELD score was about 15 in both eras. Living donors were generally young, with mean age in the mid-30s. They provided right lobe grafts in 94% of cases in A2ALL-1 and 85% of cases in A2ALL-2 when left lobe grafts were more common. This resulted in a slightly larger mean graft size in A2ALL-1 versus A2ALL-2 (mean GW/RW 1.129 vs. 0.993 respectively, p<0.001). Two transplants performed using left lateral segment grafts were grouped with the left lobes for this analysis. In A2ALL-2, approximately 20% of recipients underwent some form of portal inflow modulation.

EAD developed in 16% of A2ALL-1 and 19% of A2ALL-2 subjects (p=0.16; Table S1). At least 1 complication after the first postoperative week was observed in 78% of A2ALL-1 and 75% of A2ALL-2 subjects (p=0.70). Overall, 30-day postoperative mortality was 1.6%.

Graft and Patient Survival by EGD

Kaplan-Meier curves for graft failure and patient mortality with and without graft dysfunction on postoperative day 7 are shown in Figure 1 panels A and B, respectively. The differences in graft failure and mortality for those with and without EAD were statistically significant (p<0.001 and p=0.001, respectively). In both graft failure and mortality, there are early losses in both groups, but the losses are much greater in recipients with EAD. Recipients meeting the definition of EAD had 24% graft failure at 90 days compared with 5% for recipients who did not meet the definition of EAD (Figure 1 panel A). The pattern of graft and patient survival was similar using the alternative definition of EAD, as shown in the Supplemental Digital Content (SDC; Figure S1).

Cox models that included time-dependent effects of EAD showed that the risk of graft failure was significantly elevated within the first 90 days for recipients with EAD compared with those without EAD (hazard ratio [HR]=5.2, p<0.001). However, beyond 90 days

posttransplant, there was no difference in the risk of graft loss between those with and without EAD on day 7 (HR=0.92, p=0.81).

We tested whether left lobe, graft weight, and GW/RW helped predict early graft loss in models with the EAD covariate. The type of graft transplanted did not confer any additional information (all p>0.29) about the risk of early graft loss after accounting for EAD. Additionally, there were no significant interactions between EAD and type of graft, indicating that likelihood of recovery from EAD did not differ by type of graft.

Characteristics of Subjects with EAD

EAD occurred over wide ranges of graft size and portal pressure (Figure 2). EAD was distributed across the ranges of graft weight and portal pressure (Figure 2A) but appeared to be more frequent at lower GW/RW (Figure 2B). Table 2 compares graft, donor, and recipient characteristics for recipients with and without EAD. A higher percentage of recipients of left lobe grafts met the definition for EAD compared with recipients of right lobes (34% vs. 16%). However, regardless of graft size, approximately 3/4 of recipients with EAD recovered without graft failure. Recipients with EAD also had higher mean preoperative MELD score, lower mean arterial flow, higher mean portal venous reperfusion pressure, and higher mean donor age. A higher percentage of recipients who developed EAD had a modulation performed at time of transplant than recipients who did not develop EAD (30% vs. 17%, p=0.03). The relationship between portal pressure and arterial flow is shown in Figure 3. A statistically significant correlation between higher portal pressure and lower arterial flow (arterial buffer response) is demonstrated (r=−0.14, p=0.03). Length of hospital stay for recipients with EAD was almost doubling that of those without EAD (Table 2). The incidence of technical complications (biliary and vascular) during the first posttransplant week was similar for recipients who did and did not develop EAD (16% vs. 14%, p=0.59). Results using the alternative definition of EAD, which excluded technical complications during the first posttransplant week, were similar. (See SDC Figures S2–S3 and Table S2).

Figure 4 shows the percentage of recipients with graft dysfunction by categories of graft weight (panel A) and GW/RW ratio (panel B). Among right lobe recipients, there did not appear to be a relationship between graft size and EAD. Among left lobe recipients, the percentage of recipients with EAD was higher at lower graft weight. The trend among left lobe recipients was not as striking for categories of GW/RW, but the lowest 2 categories of GW/RW had the highest percentages of EAD.

Figure 5 summarizes results by stratifying patients into those who received larger grafts (GW/RW ≥0.8%) versus those who received smaller grafts. EAD was associated with a higher risk of early graft failure (within 90 days) as shown in the models above, but this relationship was true for recipients of larger as well as smaller graft size (23% vs. 27% graft failure among those with EAD; 4% vs. 8% among those without EAD).

Predictive Models

Table 3A presents the results of a logistic model predicting EAD with baseline covariates for all subjects. This model included 552 recipients from A2ALL-1 and A2ALL-2 with outcome and baseline covariate data available. Recipients of left lobe grafts were much more likely to

meet the definition of EAD on posttransplant day 7 (odds ratio [OR]=3.5, p<0.001). Recipients of larger left lobe grafts were less likely to develop EAD than smaller left lobe grafts (OR=0.93 per 10 gram increase, p=0.02). Other factors, such as higher preoperative bilirubin (p<0.001), lower ALT (p=0.03), older donor age (p=0.02), and higher donor BMI (p=0.02), were also significantly associated with increased risk of EAD (c-statistic 0.69).

Pretransplant spleen volume, a surrogate for portal hypertension, was found to be significantly associated with EAD in the multivariable model (OR=1.07 per 100 cc increase, p=0.03) (Table 3B). This model included 371 subjects, with 60 subjects meeting EAD criteria (c-statistic 0.76). Estimates for other covariates in the model were unchanged except for donor BMI, which was no longer statistically significant.

Pressure and flow measurements were tested in univariate logistic models of EAD with the following results: hepatic artery flow OR=0.70 per 100 ml/min increase, p=0.08; portal vein flow OR=0.81 per 500 ml/min increase, p=0.08; and absolute or unclamped portal pressure OR=1.09 per 1 mm Hg increase, p=0.02. After adjusting for bilirubin, a measure of recipient condition, results were similar (hepatic artery flow OR=0.65, p=0.05; portal vein flow OR=0.83, p=0.13; unclamped portal pressure OR=1.10, p=0.01). In summary, absolute or unclamped portal pressure was the largest risk factor for developing EAD among the pressure/flow measures tested.

DISCUSSION

The current study demonstrated that EAD after LDLT was associated with left lobe grafts, lower graft weight among left lobes, higher preoperative bilirubin, higher portal reperfusion pressure, older donor age, and higher donor BMI. Patients who developed EAD after LDLT, based on postoperative day 7 bilirubin >10 mg/dl or INR >1.6, had a 24% risk of graft loss within 90 days. Among those without EAD, risk of graft loss was only 5% (p<0.001). After the first 90 days posttransplant, risk of graft loss was similar in each group. This is useful for clinicians in determining graft prognosis and may lead to changes in management during the first 90 posttransplant days.

The predictors of EAD and predictors of graft survival were distinct. EAD resolved without graft loss in approximately 75% of cases. Importantly, this was equally true for donor livers with GW/RW<0.8% and GW/RW>0.8%.

While laboratory studies of early graft injury have implicated portal overflow pathophysiology, we observed abnormal hemodynamics across a wide range of graft sizes. Furthermore, many small grafts did not have abnormal hepatic hemodynamics and did not go on to develop EAD. Because of the challenge of defining allograft dysfunction as an outcome variable, we performed a sensitivity analysis using a commonly used definition of SFSS that was adapted from published literature and included early persistent hyperbilirubinemia and the presence of coagulopathy, ascites formation, or encephalopathy.[2] The data collection format did not permit use of both definitions of SFSS or EAD across both A2ALL eras; however, results using this second definition for EAD were consistent with the primary analysis. Thus, it is unlikely that there were significant confounding

variables between the 2 A2ALL study periods. The broader A2ALL definition of EAD[1] was limited to measurements of liver function at day 7 and can be distinguished from SFSS in that it is observed across all graft sizes and does not include evidence of portal hypertension. The A2ALL definition is an easy and reliable tool for establishing EAD and requires only 2 routine postoperative day 7 laboratory values.

The mean MELD score in this study was 15 in patients without EAD, versus 17 among those with EAD ($p<0.001$). While these MELD scores are relatively low, and perhaps the difference clinically insignificant, Berg et al. demonstrated survival advantage after LDLT for non-HCC tumor patients with MELD scores less than 15, rather than remaining on the deceased donor waitlist.[14] This advantage was not seen with patients with HCC and MELD scores below 15. This observation has applicability to other regions of the world, where deceased donation is not commonplace or readily available, and LDLT can be applied earlier.

We found statistically significant, although clinically subtle, differences in relationships between preoperative disease severity (MELD), lower GW/RW, and arterial flow in the setting of higher portal pressure and the occurrence of EAD. Interestingly, portal flow was not found to be statistically significant, although the effect may have been mitigated to some extent in recipients who received inflow modification at the time of surgery.

The major limitation of this study is that clinical practice is biased to avoid circumstances that might favor EAD in terms of patient selection and intraoperative manipulations. Clinical experience has led to a sense that smaller grafts are best used in recipients with lower MELD scores, obtained from younger, thinner donors. In addition, the frequent use of portal flow modulation may have obscured the impact of portal overflow.

When this study was initiated, clear indications for inflow modification were not well-established. Therefore, surgeons performed inflow modification based on *gestalt* rather than definitive data. The incidence of EAD was paradoxically higher in those who received inflow modification compared with those who did not (31% vs. 18%), likely reflecting treatment by indication bias. In the majority of cases, however, inflow modification produced the intended result of lower portal pressure and flow and/or higher hepatic artery flow. We speculate that even more recipients would have developed EAD if inflow had not been performed. A detailed examination of the impact of inflow modulation will be reported in a separate A2ALL manuscript. However, informal survey among the principal recipient surgeons in this series suggested that inflow modulation was performed based on several parameters including early reperfusion absolute portal pressure >20 mm Hg,[15] portal gradient pressure (absolute portal pressure minus CVP or portal pressure distal to a clamped portal vein) that exceeded 12–15 mm Hg,[7] or graft portal venous hyperperfusion >2.5 cc/gm/min.[16] Absolute hepatic arterial flow <100 cc/min was also used as a threshold by some surgeons, especially in the setting of high portal venous flow or pressure. Large spleen size was used along with other parameters by 1 surgeon. The variable indications for performing inflow modifications by the surgeons in this report indicate the need for further study to determine meaningful threshold values.

Our findings confirm published observations of a complex interplay of preoperative disease severity, graft and recipient weight, portal venous and arterial pressure and flow, and the development of allograft dysfunction. Because of the multifactorial nature of EAD, we propose that EAD may be a more appropriate term to describe functional insufficiency after LDLT. It may be appropriate to consider SFSS a subset of EAD that occurs in small grafts in which excess portal flow is a primary contributor to graft injury.[2,17–20] Further study is also needed to determine the levels of tolerance for each inflow parameter to provide accurate risk assessment to aid surgical decision-making regarding the type of graft used and whether inflow modulation is needed. As suggested in the literature and the surgeon preferences in this study, only rough estimates for each parameter exist and probably vary for each individual patient and graft. Troisi et al demonstrated the negative influence of high portal flow on significantly reducing arterial flow to the graft.[21] This phenomenon was reversible with inflow modification (splenic artery ligation), resulting in increased hepatic arterial flow.[21] It can be reproduced with several forms of inflow modification in addition to splenic artery ligation and can include splenectomy, hemi-portocaval shunt, and medical modulation.[7,22–25] Luca et al demonstrated that reduction of portal pressure gradient after splenic artery occlusion strongly correlated with liver/spleen volume ratio.[26] For patients with liver-spleen volume ratio above 0.5, there was a significantly larger reduction in portal pressure gradient after inflow modulation by splenic artery occlusion. This observation, along with other parameters previously discussed, may help surgeons tailor inflow modification decisions.

It is hoped that further study will allow us to develop a specific “EAD risk index” that incorporates many of these preoperative and intraoperative factors and could aid the surgeon with decisions about performing inflow modification, type of graft used, or suitability of the recipient for living donor transplantation. Modeling in this study suggests that left lobe grafts, elevated recipient preoperative bilirubin, and grafts obtained from older donors with elevated BMI significantly increase the risk for EAD. Hopefully, mitigation of risk can be achieved with surgical innovation and perhaps pharmacologic assistance. At any risk level, successful outcome after LDLT will continue to require meticulous preoperative and intraoperative planning, technical acumen, and attention to detail.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

A2ALL	Adult to Adult Living Donor Liver Transplantation
AHN	Acute Hepatic Necrosis

ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ASTS	American Society of Transplant Surgeons
BMI	Body Mass Index
CVP	Central Venous Pressure
EAD	Early Allograft Dysfunction
GW/RW	Graft Weight/Recipient Weight
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HR	Hazard Ratio
HRSA	Health Resources and Services Administration
INR	International Normalized Ratio
IRB	Institutional Review Board
LDLT	Living Donor Liver Transplantation
LL	Left Lobe
LT	Liver Transplantation
MELD	Model for End-Stage Liver Disease
MMRF	Minneapolis Medical Research Foundation
OPTN	Organ Procurement and Transplantation Network
PTFE	Polytetrafluoroethylene
RL	Right Lobe
SD	Standard Deviation
SDC	Supplemental Digital Content
SFSS	Small-for-Size Syndrome
SGD	Segmental Graft Dysfunction
SLV	Standard Liver Volume
SRTR	Scientific Registry of Transplant Recipients

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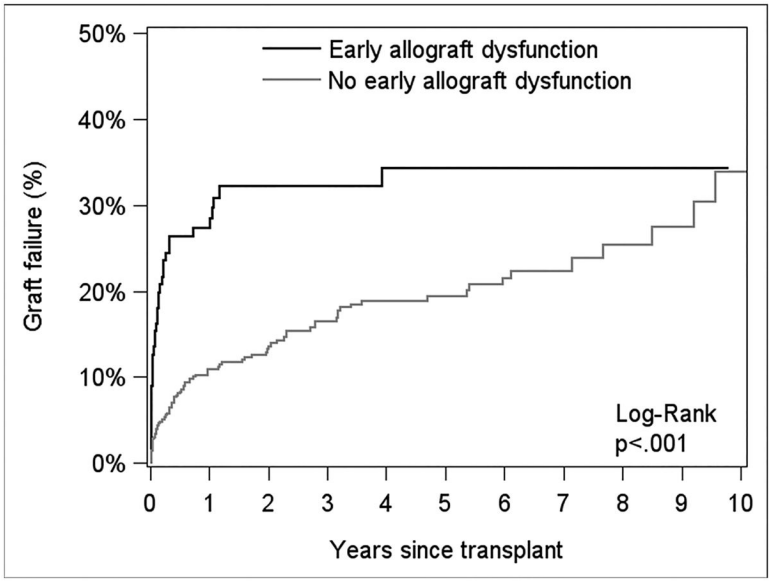


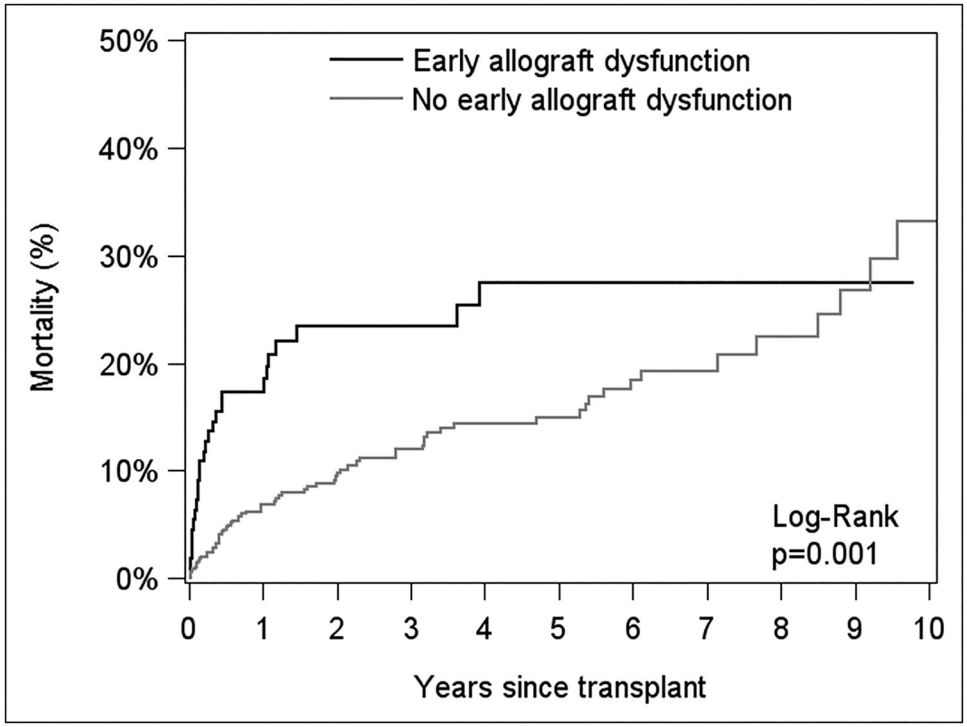
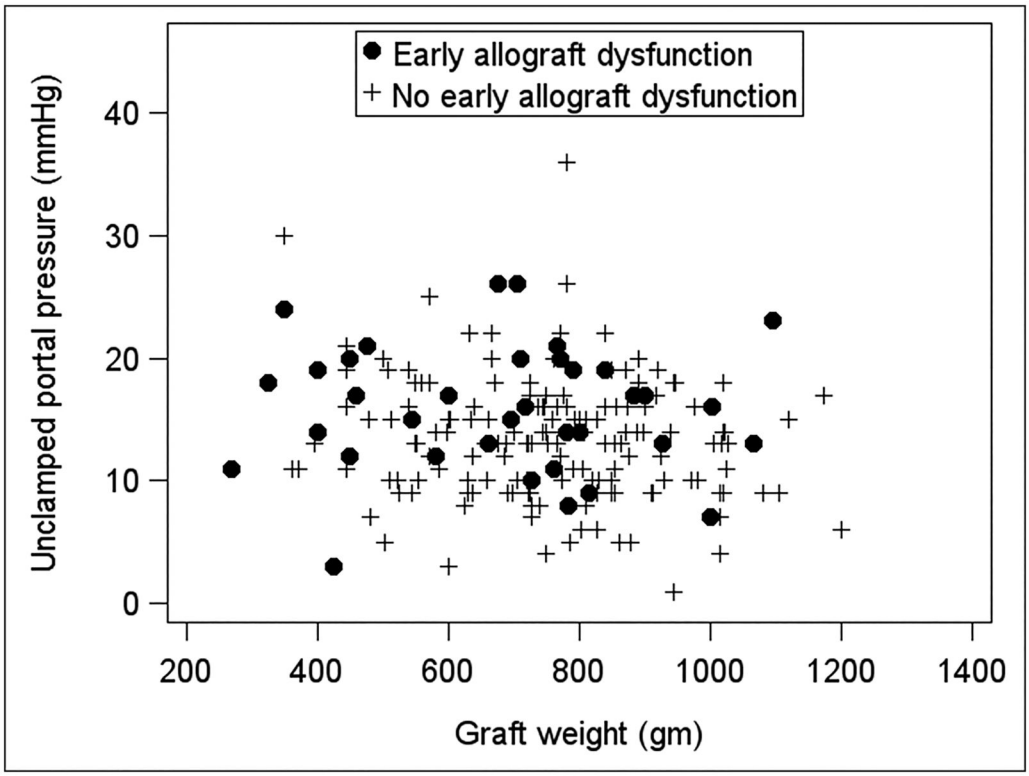


Figure 1.

Figure 1A. Graft failure by early allograft dysfunction (EAD)

Figure 1B. Patient mortality by early allograft dysfunction (EAD)



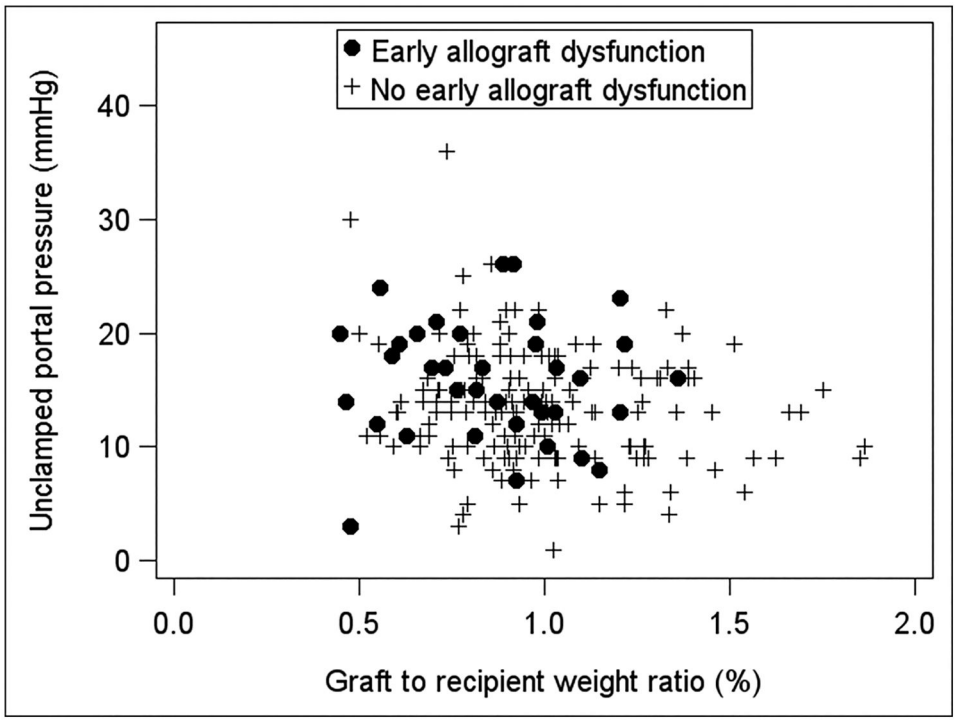


Figure 2.

Figure 2A. Scatter plot of portal pressure and graft weight by early allograft dysfunction (EAD)

Figure 2B. Scatter plot of portal pressure and graft weight to recipient body weight (GW/RW) ratio by early allograft dysfunction (EAD)

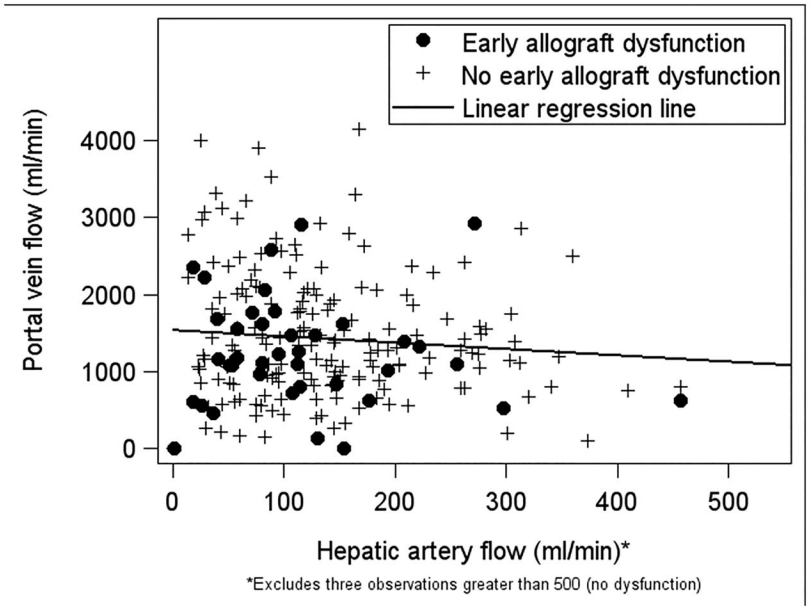
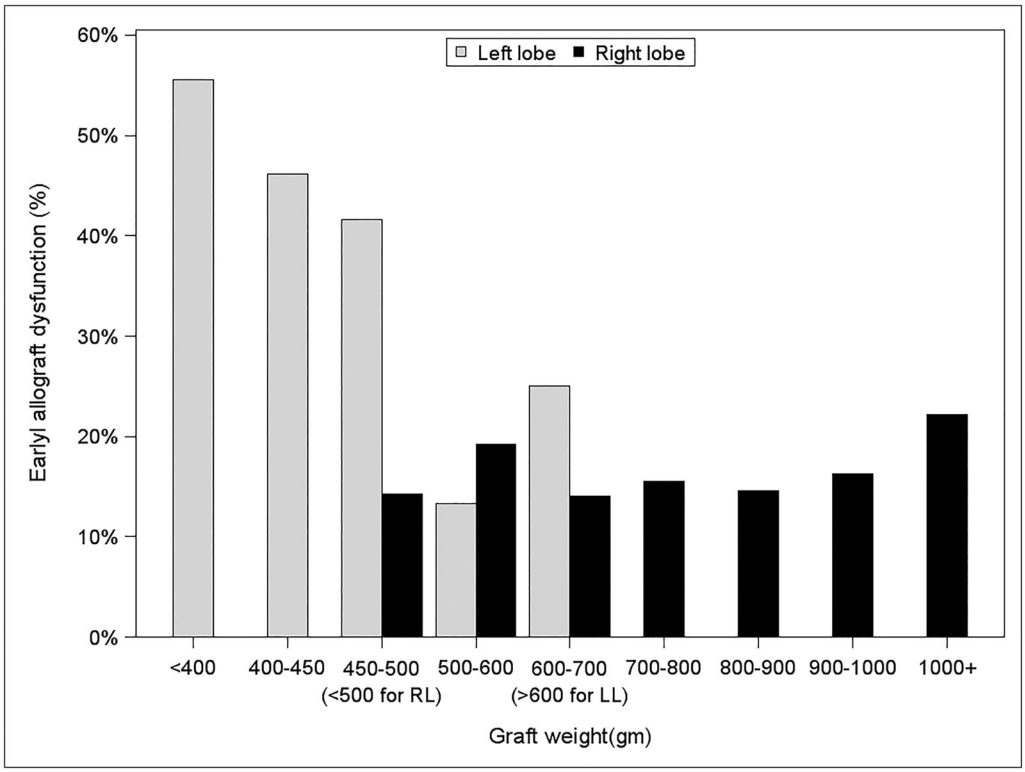


Figure 3.
Scatter plot of portal vein flow and hepatic artery flow by early allograft dysfunction (EAD)



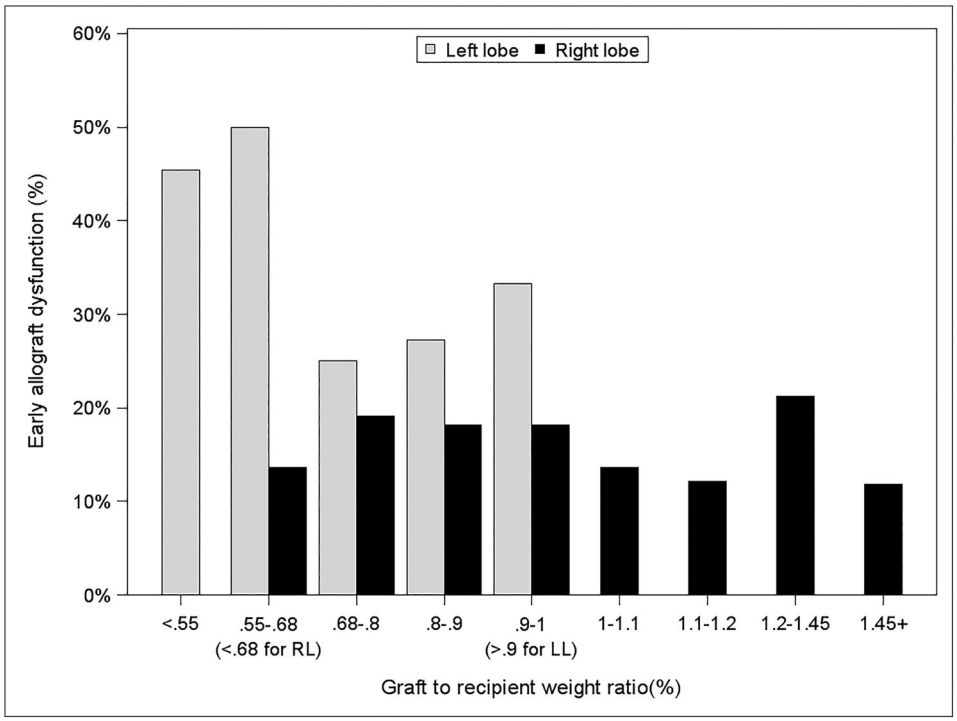


Figure 4.

Figure 4A. Percentage of recipients with early allograft dysfunction (EAD) by graft weight and lobe. The label of <500 for RL indicates that all right lobes weighing less than 500 gm

were included in this category. Any left lobes weighing more than 600gm were included in the bar labeled >600 for left lobe (LL).

Figure 4B. Percentage of recipients with early allograft dysfunction (EAD) by graft weight to recipient body weight (GW/RW) ratio and lobe. The label of <.68 for RL indicates that all right lobes with GW/RW less than .68% were included in this category. Any left lobes with GW/RW more than .9% were included in the bar labeled >.9 for LL.

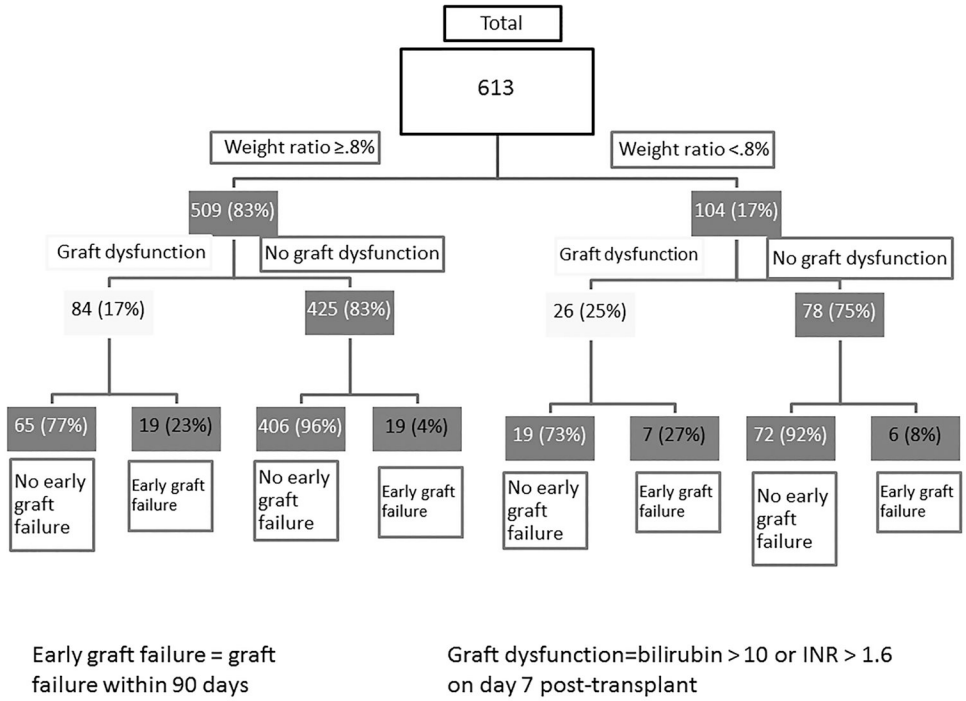


Figure 5.

Flow diagram of patients stratified by GW/RW ≥0.8%, with outcomes of early allograft dysfunction (EAD), and subsequent graft failure.

Table 1

Recipient, donor, and transplant characteristics of the study cohort of live donor transplant recipients (n=631) by A2ALL era (A2ALL-1, 2003–2010; A2ALL-2, 2011–2014)

		A2ALL-1	A2ALL-2	p-value*
		n=358	n=273	
Recipient Information				
Sex	Male	192 (53.6%)	172 (63.0%)	0.02
	Female	166 (46.3%)	101 (36.9%)	
Age	n	358	273	0.59
	Mean (SD)	51.4 (10.8)	51.8 (12.0)	
Race	White	326 (91.0%)	250 (91.5%)	0.82
	Non-white	32 (8.9%)	23 (8.4%)	
Height (m)	n	353	273	0.74
	Mean (SD)	1.71 (0.11)	1.71 (0.10)	
Weight (kg)	n	323	273	0.24
	Mean (SD)	76.8 (16.8)	78.1 (18.5)	
BMI	n	319	273	0.16
	Mean (SD)	26.2 (4.8)	26.8 (5.5)	
Diagnosis of HCC	No	317 (88.5%)	211 (77.2%)	<0.001
	Yes	41 (11.4%)	62 (22.7%)	
Diagnosis of HCV	No	227 (63.4%)	190 (69.5%)	0.10
	Yes	131 (36.5%)	83 (30.4%)	
Diagnosis of AHN	No	346 (96.6%)	270 (98.9%)	0.07
	Yes	12 (3.3%)	3 (1.0%)	
Lab MELD score	n	347	263	0.25
	Mean (SD)	15.2 (5.4)	15.8 (6.0)	
SLV	n	321	273	0.40
	Mean (SD)	1674 (251)	1688 (251)	
Donor and Transplant Information				
Donor age	n	358	260	0.29
	Mean (SD)	37.2 (10.1)	36.3 (10.5)	
Donor BMI	n	325	273	0.54
	Mean (SD)	26.3 (4.0)	26.5 (3.9)	
Graft weight (gm)	n	321	273	<0.001

		A2ALL-1	A2ALL-2	p-value*
		n=358	n=273	
Graft weight to recipient body weight (GW/RW) ratio (%)	Mean (SD)	842 (187)	755 (200)	
	n	291	273	<0.001
	Mean (SD)	1.129 (0.300)	0.993 (0.296)	
Liver fraction (graft weight/recipient SLV)	n	289	273	<0.001
	Mean (SD)	0.509 (0.116)	0.451 (0.121)	
Graft type	Right lobe	338 (94.4%)	232 (84.9%)	<0.001
	Left lobe	19 (5.2%)	40 (14.6%)	
	Left lateral segment	1 (0.2%)	1 (0.3%)	

*Chi-squared tests for categorical variables and t-tests for continuous variables.

Abbreviations: A2ALL, Adult to Adult Living Donor Liver Transplantation Cohort Study; AHN, acute hepatic necrosis; BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; SD, standard deviation; SLV, standard liver volume.

Table 2

Graft, donor, and recipient characteristics and recipient outcomes by early allograft dysfunction (EAD)

Characteristic	Group or Statistic	No Graft Dysfunction	Graft Dysfunction	p-value*
Total		503	110	
Left lobe or segment	No	464 (92.2%)	90 (81.8%)	<0.001
	Yes	39 (7.7%)	20 (18.1%)	
Graft weight (gm)	n	470	106	0.22
	Mean (SD)	808 (185)	777 (238)	
Graft weight to recipient body weight (GW/RW) ratio (%)	n	445	101	0.04
	Mean (SD)	1.077 (0.304)	1.006 (0.311)	
Donor age	n	494	107	0.003
	Mean (SD)	36.3 (10.2)	39.6 (10.5)	
Lab MELD score	n	489	104	<0.001
	Mean (SD)	15.1 (5.5)	17.3 (6.2)	
Length of transplant hospital stay (days)	n	497	110	<0.001**
	Mean (SD)	13.6 (20.7)	22.5 (25.3)	
Technical complication*** during week 1	No	435 (86.5%)	93 (84.5%)	0.59
	Yes	68 (13.5%)	17 (15.5%)	
Number of complications (>1 week posttransplant)	0	120 (23.8%)	19 (17.2%)	0.16
	1	97 (19.2%)	20 (18.1%)	
	2	79 (15.7%)	13 (11.8%)	
	3	54 (10.7%)	18 (16.3%)	
	4	46 (9.1%)	8 (7.2%)	
	5+	107 (21.2%)	32 (29.0%)	
Portal flow modulation	No	171 (83.0%)	37 (69.8%)	0.03
	Yes	35 (17.0%)	16 (30.2%)	
Spleen volume (cc)	n	326	65	<0.001
	Mean (SD)	773 (485)	1055 (477)	
Hepatic artery flow (ml/min)	n	182	42	0.03
	Mean (SD)	154.1 (147.4)	115.4 (88.5)	
Portal vein flow (ml/min)	n	184	42	0.08
	Mean (SD)	1460.0 (817.2)	1216.8 (701.0)	
Portal pressure – absolute	n	157	36	0.01
	Mean (SD)	13.5 (5.1)	15.8 (5.3)	
Portal pressure – gradient	n	99	21	0.78

Characteristic	Group or Statistic	No Graft Dysfunction	Graft Dysfunction	p-value*
	Mean (SD)	11.4 (9.0)	10.9 (6.2)	
Mean arterial pressure	n	193	48	0.30
	Mean (SD)	71.8 (14.7)	69.3 (16.5)	
Central venous pressure	n	195	48	0.71
	Mean (SD)	8.8 (3.8)	9.0 (4.0)	
Cardiac output (L/min)	n	149	29	0.34
	Mean (SD)	9.89 (3.31)	9.27 (2.45)	

*Chi-square tests for categorical variables and t-tests for continuous variables.

Abbreviations: MELD, model for end-stage liver disease; SD, standard deviation.

**t-test was performed on $\log_e$-transformed values due to skewed distribution of hospital days

***Technical complications were biliary or vascular complications.

Table 3

Predictors of early allograft dysfunction (EAD) based on logistic regression with (A) all subjects and (B) subjects with spleen volume available

(A) All subjects (n=552*, events=97)			
Covariate**	**Odds Ratio**	**p-value**	**95% CI**
Left lobe or segment	3.5	<0.001	1.8 – 7.0
Graft weight for left lobes (per 10 grams)	0.93	0.02	0.87 – 0.99
ln(bilirubin)	2.1	<0.001	1.5 – 2.9
ALT (per 10 units)	0.95	0.03	0.92 – 0.99
Donor age (per 10 years)	1.3	0.02	1.05 – 1.6
Donor BMI	1.07	0.02	1.01 – 1.14
(B) Subjects with spleen volume data (n=371, events=60): Model A covariates plus spleen volume			
Covariate	**Odds Ratio**	**p-value**	**95% CI**
Left lobe or segment	4.6	<0.001	2.1 – 10.2
Graft weight for left lobes (per 10 grams)	0.94	0.04	0.88 – 1.00
ln(bilirubin)	2.5	<0.001	1.6 – 3.9
ALT (per 10 units)	0.92	0.03	0.85 – 0.99
Donor age (per 10 years)	1.4	0.03	1.03 – 1.9
Donor BMI	1.05	0.18	0.98 – 1.13
Spleen volume (per 100 cc)	1.07	0.03	1.01 – 1.13

*Nineteen subjects were excluded from the model because the information needed to determine EAD was not available. There were 61 recipients excluded for missing covariate values (37 missing graft weight, 12 missing donor age, and 12 missing ALT).

**The following variables were tested but not significant in the multivariable model: liver fraction <40%, MELD, creatinine, INR, AST, ALP, albumin, sodium, recipient age, BMI, HCV, HCC, donor relationship to recipient, cold ischemia time, and warm ischemia time.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MELD, model for end-stage liver disease.