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Acute Rejection Increases Risk of Graft Failure and Death in Recent Liver Transplant Recipients

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Abstract

Background & Aims—Acute rejection is detrimental to most transplanted solid organs, but is considered to be less of a consequence for transplanted livers. We evaluated risk factors for and outcomes after biopsy-proven acute rejection (BPAR) based on an analysis of a large national sample of recipients of liver transplants from living and deceased donors.

Methods—We analyzed data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) from 2003 through 2014 as the exploratory cohort and the Scientific Registry of Transplant Recipients (SRTR) from 2005 through 2013 as the validation cohort. We examined factors associated with time to first BPAR using multivariable Cox regression or discrete-survival analysis. Competing risks methods were used to compare causes of death and graft failure between recipients of living vs deceased donors.

Results—At least 1 BPAR episode occurred in 239/890 recipients in A2ALL (26.9%) and 7066/45,423 recipients in SRTR (15.6%). In each study, risk of rejection was significantly lower when livers came from biologically related living donors (A2ALL hazard ratio [HR], 0.57; 95% CI, 0.43–0.76 and SRTR HR, 0.78; 95% CI, 0.66–0.91) (P<.001) and higher in liver transplant recipients with primary biliary cirrhosis, of younger age, or with hepatitis C. In each study, BPAR was associated with significantly higher risks of graft failure and death. The risks were highest in the 12 month post-BPAR period in patients whose first episode occurred more than 1 year after liver transplantation. The HRs for graft failure were 6.79 in A2ALL (95% CI, 2.64–17.45) and 4.41 in SRTR (95% CI, 3.71–5.23). The HRs for death were 8.81 in A2ALL (95% CI, 3.37–23.04) and 3.94 in SRTR (95% CI, 3.22–4.83). In analyses of cause-specific mortality, associations were observed for liver-related (graft failure) causes of death but not for other causes.

Conclusions—Contrary to previous data, acute rejection after liver transplant is associated with significantly increased risk of graft failure, all-cause mortality and graft failure-related death. LDLT from a biologically related donor is associated with decreased risk of rejection.

Keywords

LT; database analysis; risk factor; survival

INTRODUCTION

Management of solid organ transplant recipients has focused on preventing acute rejection, as it is a clinically significant event that compromises patient and graft survival. The exclusion to this paradigm has been liver transplantation (LT), as data prior to 2000 suggested that in most cases, acute rejection after LT is not independently associated with

graft failure or death.[1–3] Moreover, experimental models and long-term follow-up of LT recipients revealed the potential for minimization or even full withdrawal of immunosuppression in some patients, reflecting tolerogenic and regenerative aspects unique to the liver.[4] As a result, current management trends post-LT favors drug minimization to reduce complications of immunosuppression (i.e., chronic kidney disease, malignancy, cardiovascular disease), even at the expense of acute rejection, without specifically tailored immunosuppression based on donor and recipient characteristics. Furthermore, two recent publications have highlighted the superior long-term survival for select recipients of living-donor liver transplants (LDLT), although it is not clear if this improved survival is related to a lower incidence of rejection in LDLT compared to deceased donor liver transplantation (DDLT).[5, 6]

Because current knowledge of outcomes of acute rejection is based on limited historical data (including data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) of patients transplanted between 1998–2004[7]), an analysis of contemporary data is needed in order to inform initiatives to personalize (e.g. augment vs. minimize) immunosuppression and patient monitoring by more accurately quantifying the risks and impact of rejection. Thus, we used data from two large cohorts that include living and deceased donor LT recipients from the modern era to re-evaluate the predictors and impact of rejection on patient and graft survival.

METHODS

Study Design

The exploratory phase of the analysis used data from the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), an observational cohort study funded by the National Institute of Diabetes and Digestive and Kidney Diseases investigating outcomes in donors and recipients of adult-to-adult LDLT. A2ALL enrolled waitlisted patients from twelve North American centers evaluated for an LDLT between 1/1/1998 and 1/31/2014, with follow-up through 5/31/2014. Recipients who underwent LDLT or DDLT between 2003 and 2014 were included in this study. All recipients were treated per each center's standard of care management, and there were no mandated pre- or post-transplant interventions, including immunosuppressive regimens, infection prophylaxis, decision-making for liver biopsies, etc. The A2ALL centers also did not perform routine protocol liver biopsies.

To assess whether results from A2ALL were generalizable to the U.S. LT population in which DDLT is predominant, we conducted validation analyses of data on adult LT recipients from 1/1/2005 to 12/31/2013 from the Scientific Registry of Transplant Recipients (SRTR). The SRTR includes data on all donors, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

For both cohorts, we included first-time LT recipients ≥18 years and excluded combined organ recipients. Data elements similar to those collected by A2ALL and that were available in SRTR were included in analyses of SRTR data.

Statistical Methods

We examined factors associated with time to first biopsy-proven acute rejection (BPAR) using multivariable Cox regression for A2ALL and discrete-survival analysis for SRTR. In SRTR, the specific date of rejection was not available - only whether BPAR occurred since the last assessment. Covariates included recipient age, gender, race/ethnicity, diagnosis, transplant type, cold ischemia time, donor age, year of transplant, and immunosuppression regimens during the transplant hospitalization. Donor type was categorized as deceased-donor, biologically-related living donor (parent, child, sibling (half or full), aunt, uncle, and/or cousin), and non-biologically related living donor.

Multivariable Cox regression tested for factors associated with patient and graft survival, with timing of first BPAR episode modeled as a time-dependent covariate. For SRTR data, the time of BPAR was imputed from a uniform distribution within the reporting interval during which BPAR was recorded to have occurred; 5 datasets with imputed rejection times were created and all analyses account for variability across the 5 imputations.[8] We assessed whether excess risks of death and/or graft failure following first rejection were consistent over time by testing for proportional hazards and by explicitly testing the interaction between time from LT to first BPAR and time-varying risk after rejection in adjusted models. Time from LT to first BPAR was categorized as 0–6, >6–12, and >12 months after LT, while time since first BPAR was categorized as ≤12 and >12 months after first BPAR. In addition to the covariates tested in the time to first BPAR model, in the patient and graft survival models we also evaluated medical severity at transplant (recipient on ventilator or dialysis), body mass index, and Model for End-Stage Liver Disease (MELD) score (these covariates were not included in the BPAR models as there are neither data nor biological plausibility for their association with BPAR). MELD score was retained in all models using SRTR data to account for the different disease severity between the SRTR and A2ALL populations. The method of best subsets was used to guide model selection, and Martingale residual plots were used to guide fitting the functional form of continuous variables. Regression splines (piecewise linear) were used to fit functional forms with changing slopes. Time-dependent Cox regression was also used to explore the relationship between cause-specific mortality and BPAR in the SRTR cohort. The reference group for all time-dependent BPAR comparisons was as-yet-BPAR-free LT recipients.

Adjusted survival curves were plotted for patient and graft survival in A2ALL and SRTR, showing the time-dependent effect of each category of BPAR. The time-dependent effect of rejection was illustrated by comparing the survival curve for recipients with no BPAR to the curve representing recipients with rejection at the median time of first rejection after LT for each category of BPAR. Hazard ratios in the first 12 months post-BPAR and after 12 months post-BPAR were also plotted by category of BPAR. Competing risks methods were used to compare causes of death and graft failure between LDLT and DDLT recipients. Cumulative incidence functions were plotted for each cause using the comprisk macro

(mayoresearch.mayo.edu/mayo/research/biostat). All analyses were completed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Recipient Characteristics

In A2ALL, there were 258 DDLT recipients and 632 LDLT recipients transplanted between 2003 and 2014. In the SRTR cohort, there were 43,622 DDLT and 1801 LDLT recipients transplanted between 2005 and 2013. A2ALL recipients had a lower mean calculated MELD score and a greater proportion of recipients with immune-mediated liver diseases (Table 1).

Factors associated with the risk of BPAR

A2ALL Cohort—Among all 890 A2ALL LT recipients, 239 (26.9%) had ≥1 episode of BPAR at a median 49 days post-LT. The first episode of BPAR occurred 0–6 months after LT in 189 (21.2%) LT recipients, 6–12 months after LT in 21 (2.4%) recipients, and >12 months after LT in 29 (3.3%) recipients. In an adjusted multivariable Cox model, biologically-related LDLT recipients had a 43% lower risk of BPAR (HR: 0.57, 95% CI: 0.43–0.76, p<0.001) compared to non-biologically related LDLT and DDLT, while recipients with primary biliary cirrhosis (PBC) had more than twice the risk of BPAR compared to patients without PBC (HR: 2.10, 95% CI: 1.31–3.36; Table 2).

SRTR Cohort—Among 45,423 LT recipients, 7,066 (15.6%) had ≥1 episode of BPAR at a median 88.6 days post-LT (based on multiple imputation of date of BPAR). The first episode of BPAR occurred 0–6 months, 6–12 months, and >12 months after LT in 4,955 (10.9%), 1,050 (2.3%), and 1,061 (2.3%) recipients, respectively. Many demographic and clinical variables associated with higher or lower risk of BPAR were similar in A2ALL and SRTR data (Table 2). Transplant recipients with primary sclerosing cholangitis (HR: 1.32, 95% CI: 1.20–1.45) or PBC (HR: 1.37, 95% CI: 1.22–1.53) had significantly increased risks of BPAR. As in A2ALL, there was a significantly lower risk of BPAR among biologically-related LDLT in SRTR (HR: 0.78, 95% CI: 0.66–0.91, p<0.001).

Association of BPAR with graft failure and death

A2ALL Cohort—There were significant associations between BPAR and graft failure and death. Among those with BPAR in the first six months after LT, the risk of graft failure was significantly higher within the first year post-rejection but not thereafter (Table 3). Patients whose first BPAR occurred more than 12 months after LT had the highest risk of graft failure (<12 months post-rejection HR: 6.79, 95% CI: 2.64–17.45, p<0.001) but this effect also persisted beyond the first year after rejection occurred (>12 months post-rejection HR: 3.35, 95% CI: 1.16–9.73, p=0.03) (Table 3; Supplemental Figures 1a and 1b).

Results of modeling the association between BPAR and death showed a similar pattern, with recipients whose first BPAR occurring >12 months after LT at the highest risk of death within 12 months post-rejection (HR: 8.81, 95% CI: 3.37–23.04, p<0.001) and also more than 12 months post-rejection (HR: 4.38, 95% CI: 1.49–12.92, p=0.01). There was no

association between the severity of rejection (mild vs. moderate/severe) and death or graft failure.

When the cohort was stratified by HCV status, the primary results were unchanged, with significantly increased risks of graft failure and death in both HCV and non-HCV patients experiencing BPAR (Supplemental Tables 1 and 2). In A2ALL, we were able to investigate whether having >1 episode of BPAR further increased the risk of adverse outcomes. Having a second episode of rejection only further increased the risk of graft failure, but not patient death, above the already increased risk in patients with a first episode of BPAR. However, this added risk was only seen in patients with ≥2 episodes of BPAR in the first 6 months post-LT.

SRTR Cohort—Similar to A2ALL, BPAR was significantly associated with the risk of patient death and graft failure in adjusted multivariable Cox regression models (Table 3). The associations between BPAR and subsequent death and graft failure were significant for every combination of time after LT when BPAR first occurred (0–6 months, 6–12 months, >12 months after LT) and post-rejection time interval (<12 months following rejection, >12 months following rejection).

The relative increased risk of graft failure or death in transplant recipients with BPAR ranged from 24% to 341% higher than the baseline risk compared to transplant recipients without rejection (Table 3). Later onset of first BPAR was associated with higher risks of adverse outcomes, and the risks were more pronounced within the first year following rejection than thereafter (Supplemental Figures 1a and 1b).

When the cohort was stratified by HCV status, the primary results were unchanged, with significantly increased risks of graft failure and death in both HCV and non-HCV patients experiencing BPAR (Supplemental Tables 1 and 2).

Association of BPAR with specific causes of death

Given our findings of a higher risk of death following BPAR in both A2ALL and SRTR, we investigated the relationship between those with or without BPAR and subsequent causes of death (Supplemental Table 3; sufficient sample size only available in SRTR). As shown in Table 4, the cumulative incidence of death due to graft failure increased the further rejection occurred post-LT, and at a faster rate within the 12 months following rejection than after 12 months following rejection. However, there were no identifiable differences in the incidence of non-liver related deaths at any time period from transplantation or following rejection. For example, compared to patients without rejection, the risk of death due to graft failure was 3.04, 5.14, and 12.02 times higher in the first 12 months post-rejection for patients with rejection <6, 6–12, and >12 months post-LT, respectively. By contrast the risk of leading non-graft failure causes of death were 1.48, 2.49, and 2.37 times higher in the first 12 months post-rejection for patients with rejection <6, 6–12, and >12 months post-LT, respectively, compared to patients without rejection.

DISCUSSION

Even though most episodes of acute rejection after solid organ transplantation are treatable, such events place recipients at increased risk of progressive graft failure and death. The classic exception to this rule has been in LT, although this concept is based on nearly 20 year old data. The current analysis directly contrasts these older data by demonstrating increased risks of graft failure and death in LT recipients who experience acute rejection, most significantly after the first year post-LT and within a year following the episode of rejection. In addition, the risk of specific graft failure-related death was high following BPAR, supporting the notion that rejection may have detrimental immunological effects contributing to liver failure and patient death, perhaps greater than its contribution to non-graft failure death causes typically related to over-immunosuppression (e.g. cardiovascular, malignancy, infection, renal failure). Furthermore, we identified several factors that influence the risk of acute rejection, such as donor-recipient biological relationships and immune diseases, which should be considered when balancing the risks of rejection during immunosuppression modifications. Taken together, acute rejection should now be considered an important event to avoid in LT, particularly in efforts to lengthen survival in this era of organ shortages.

The most important finding was the significantly increased risk of graft failure and death in LT recipients with acute rejection. These data stand in contrast to pre-2000 data which, other than recurrent or severe rejection, did not show adverse outcomes related to rejection and in some cases better outcomes.[3] The biological rationale for these findings centered on the belief that anti-donor immune responses are much lower or less impactful in liver than other organ recipients.[1, 2, 9] Our contrasting findings might be explained by several reasons. First, these previous data were based on a smaller number of LT recipients on cyclosporine-based immunosuppression followed with protocol biopsies at a few centers in the 1990s. The patients reported in our study come from two recent, large national samples with longer follow-up of the current ‘real-world’ LT population managed with tacrolimus-based immunosuppression and serial biochemical monitoring without protocol biopsies. In fact, the use of protocol biopsies in the prior data may have led to earlier diagnoses of AR that were either clinically insignificant or treated earlier, leading to the reported better outcomes.[10, 11] Second, like our cohort, LT recipients are now older, sicker at the time of LT, and have more medical comorbidities making them more susceptible to the effects of rejection on graft function or to the increased immunosuppression required to treat rejection. Third, more relaxed monitoring for rejection and less aggressive treatment of rejection, may have contributed to chronic allograft injury in the more recent era.[12–14] This hypothesis is supported by our finding that, while rejection at any time period impacted survival, late rejection was particularly associated with worse outcomes, corroborating findings from other smaller single-center studies.[15–20] In this later time period, donor-specific antibodies in combination with lower medication adherence may be contributing, akin to other organ recipients. In addition, we found an association between rejection and graft failure-related death, and while this does not prove causation, it provides support for rejection as an initiator or potentiator of sustained graft injury.

The stratified analyses evaluating the association between BPAR and graft failure or death based on HCV status have important implications as we move forward in the new era of anti-HCV therapy. Distinguishing between recurrent HCV and BPAR has been a diagnostic quandary for pathologists and treating clinicians, and separating the adverse consequences of rejection in patients with HCV was confounded by the fact that the HCV may have resulted in graft loss, rather than rejection. However our data clearly demonstrate that the increased risk of graft failure and death associated with BPAR is not limited to patients with HCV, which is an important consideration as the vast majority of LT recipients moving forward will not have HCV viremia (either no history of HCV or HCV cured with oral antiviral therapy).

While there have been previous investigations of risk factors for acute rejection, these have not led to guidelines for personalized immunosuppression and monitoring.[21, 22] Earlier A2ALL data did not demonstrate differences in rejection risks based on donor type (live versus deceased).[7] However, the data focused on a smaller cohort and did not evaluate biological relatedness. By contrast, we found a 43% lower risk of BPAR in biologically-related LDLT recipients compared to non-biologically related LDLT and DDLT in A2ALL, and this result was recapitulated in national transplant registry data (23% lower risk of BPAR). These corroborative findings, which are consistent with results in other organs, may help to explain recent data demonstrating higher survival and less impact of donor specific antibodies in LDLT vs. DDLT recipients.[5, 6, 23] In regard to immune-mediated diseases, higher rejection rates in autoimmune hepatitis have led to recommendations for augmented immunosuppression.[7, 15, 22, 24] However, in A2ALL and SRTR cohorts, LT recipients with other immune-mediated liver disease (primary biliary cirrhosis, primary sclerosing cholangitis) had significantly increased risks, suggesting the need to maintain a higher level of immunosuppression in all immune-mediated diseases. These diseases affect younger individuals, and young age was also a risk factor for rejection in both cohorts. Finally, HCV infection was also a predictor of rejection in both cohorts, although it is unclear if this was due to more aggressive immunosuppression tapering in this population, viral-mediated immunity, or histological confusion between acute rejection and HCV recurrence. Fortunately, the risk of HCV recurrence and rejection in this cohort will likely be improved in the future with the advent of oral antiviral therapy leading to high HCV cure rates even in the transplant population.[25, 26]

These data must also be considered in the context of immunosuppression minimization and withdrawal protocols. In clinical trials, these interventions are conducted under close supervision, which include more frequent liver chemistry testing and protocol biopsies that, as mentioned above, are not standard clinical practice. Thus, if immunosuppression tapering continues to be promoted as an important goal in clinical practice for LT recipients, it must be done with caution until more precise monitoring tools are developed to minimize rejection, such as serial biomarkers of allo-immune activation, donor-specific antibodies, and possibly protocol biopsies.[4, 27–29] Interestingly, when we analyzed available immunosuppression data in A2ALL and SRTR, we did not find clear or consistent associations between the initial immunosuppression (type, number) and rates of rejection (Supplemental Table 4), other than CNI therapy which appeared to be protective. This

further supports the need for biomarkers that can serially assess for immune activation, regardless of the immunosuppression regimen used.

The results presented should be interpreted with limitations in mind. The A2ALL cohort was in general healthier with lower MELD scores and consisted of more LDLT than DDLT recipients. While the study focused on biopsy-proven rejection, the true incidence may not be accurate because providers may treat suspected rejection without performing a biopsy. In addition, there were no central pathology reviews for both A2ALL and SRTR, although in such real world practice situations, clinicians rely on their local pathology reads for immediate diagnosis and treatment of rejection. The SRTR data also had limitations with respect to reliance on center reporting of rejection and at intervals instead of date of biopsy. This inconsistency is reflected in the fact that data collected in the national SRTR database does not always mirror A2ALL, as evidenced by lower AR rates (15.6% vs 26.9%)[30]. We believe this is mainly due to underreporting of BPAR in SRTR, as we found that 15.2% had rejection reported in A2ALL but did not have rejection reported in SRTR, compared to 4.1% who had rejection reported in SRTR but were not reported as having rejection in A2ALL. While these issues may have not estimated the true incidence of rejection, the risk factors and outcomes seen in both cohorts were similar, suggesting the associations were likely not substantially biased. Both A2ALL and SRTR lack consistent longitudinal patient data on immunosuppression regimens, which would be important for more clearly evaluating associations between specific therapies and rejection over time. Lastly, severity of rejection was not available in SRTR, and treatment of BPAR was not fully captured in A2ALL or SRTR. We do not think this detracts from our primary findings, because in A2ALL, there was no association between BPAR severity and graft outcomes, and although the treatment of BPAR may mediate outcomes, the key finding remains that having an episode of BPAR increases a patient's risk of death or graft failure. Although the lack of an association between BPAR severity and adverse outcomes in A2ALL differs from previous analyses, this may be because we were underpowered to detect a difference, but also may reflect the random nature of liver biopsy sampling and/or the suboptimal inter-rater reliability of histological grading of rejection severity.[31]

In conclusion, we demonstrate that acute rejection in LT recipients should be viewed as an important clinical event associated with an increased risk of graft failure and death. These data represent a paradigm shift in the importance of rejection following LT that needs consideration in guiding the implementation of more optimal donor/recipient selection, immunosuppression protocols, and immune monitoring strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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Abbreviations

A2ALL	Adult-to-Adult Living Donor Liver Transplantation Cohort Study
BPAR	biopsy-proven acute rejection
DDLT	deceased donor liver transplantation
LDLT	living donor liver transplantation
HCV	hepatitis C virus
HIV	human immunodeficiency virus

MELD	Model for End-Stage Liver Disease
OPTN	Organ Procurement and Transplantation Network
PBC	primary biliary cirrhosis
SRTR	Scientific Registry of Transplant Recipients
U.S.	United States

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Table 1

Recipient characteristics in A2ALL and SRTR

	A2ALL (n=890) N (%) or Mean (SD)	SRTR (n=45,423) N (%) or Mean (SD)
Recipient age at transplant (years)	52.1 (11.1)	54.2 (10.1)
Female	367 (41%)	14903 (33%)
Hispanic/Latino	117 (13%)†	5942 (13%)
Race		
White	779 (88%)†	38644 (85%)
Black	41 (5%)†	4166 (9%)
Asian	29 (3%)†	2092 (5%)
Other race	37 (4%)†	521 (1%)
Recipient diagnosis (multiple possible)		
Acute liver failure	27 (3%)	3325 (7%)
Alcohol-related cirrhosis	126 (14%)	11720 (26%)
Autoimmune hepatitis	52 (6%)	1629 (4%)
Cryptogenic cirrhosis	78 (9%)	3593 (8%)
HBV	22 (2%)	1618 (4%)
HCV	330 (37%)	19427 (43%)
Metabolic liver disease	35 (4%)	1642 (4%)
PBC	79 (9%)	1717 (4%)
PSC	161 (18%)	2445 (5%)
Other diagnosis	69 (8%)	10774 (24%)
MELD at transplant	16.7 (6.8)δ	20.9 (9.7)†
Recipient on ventilator at transplant	16 (2%)†	2187 (5%)
Recipient on dialysis at transplant	12 (1%)¥	3160 (7%)†
Donor age at transplant (years)	37.9 (12.9)¥	41.9 (16.8)
Transplant type		
Biologically related LDLT	397 (45%)	1172 (3%)
Non-biologically related LDLT	235 (26%)	629 (1%)
DDLT	258 (29%)	43622 (96%)
Cold ischemia time (min) (LDLT/DDLT)	66.4 (77.6)/430.3 (187.1)δ	142.8 (280.4)/414.8 (194.4)δ

†Missing <1%

¥Missing <3%

δMissing <10%.

All other variables had no missing data.

Table 2

Predictors of first biopsy-proven acute rejection based on multivariable Cox regression (A2ALL) and multivariable discrete survival analysis (SRTR)*

	A2ALL (n=890)			SRTR (n=45,423)		
Variable	**Hazard Ratio**	**95% Confidence Interval**	**P-value**	**Hazard Ratio**	**95% Confidence Interval**	**P-value**
Biologically related LDLT vs. non-biologically related LDLT and DDLT**	0.57	(0.43, 0.76)	<0.001	0.78	(0.66, 0.91)	0.002
Recipient age, per 10 years, for age < 55	0.71	(0.59, 0.84)	<0.001	0.76	(0.74, 0.79)	<0.001
Recipient age, per 10 years, for age > 55	1.12	(0.77, 1.64)	0.54	0.86	(0.81, 0.92)	<0.001
Female vs. Male	1.14	(0.85, 1.52)	0.40	1.19	(1.13, 1.25)	<0.001
Race (ref = White)			0.20			<0.001
Black	1.15	(0.62, 2.15)	0.65	1.26	(1.16, 1.35)	<0.001
Asian	1.91	(1.05, 3.47)	0.03	0.87	(0.77, 0.98)	0.03
Other races	1.03	(0.57, 1.86)	0.93	0.95	(0.76, 1.19)	0.67
Recipient diagnosis: HCV	2.22	(1.57, 3.16)	<0.001	1.11	(1.05, 1.18)	<0.001
Recipient diagnosis: Autoimmune hepatitis	1.16	(0.66, 2.06)	0.60	0.99	(0.88, 1.12)	0.87
Recipient diagnosis: PSC	1.08	(0.71, 1.65)	0.72	1.32	(1.20, 1.45)	<0.001
Recipient diagnosis: PBC	2.10	(1.31, 3.36)	0.002	1.37	(1.22, 1.53)	<0.001
MELD at transplant (per 5 points)	-	-	-	0.99	(0.98, 1.00)	0.17

*Model included adjustments for induction immunosuppression and immunosuppression at discharge from transplant hospitalization, presented in Supplemental Table 4

**No significant difference between non-biologically related LDLT and DDLT (p=0.71 in A2ALL, p=0.57 in SRTR).

LDLT = living donor liver transplant, DDLT = deceased donor liver transplant, HCV = hepatitis C virus, PSC = primary sclerosing cholangitis, PBC = primary biliary cirrhosis,, MELD = model for end stage liver disease.

Table 3

Predictors of patient death and graft failure based on multivariable Cox regression in A2ALL and SRTR*

	Patient Death						Graft Failure					
	A2ALL (n=890)			SRTR (n=45,423)			A2ALL (n=890)			SRTR (n=45,423)		
Variable	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**	**Hazard Ratio**	**95% Confidence Interval**	**p-value**
Biopsy-proven rejection within 6 months post-LT												
< 12 months following rejection	1.86	(1.00, 3.47)	0.05	1.66	(1.52, 1.83)	<0.001	1.91	(1.21, 3.01)	0.01	1.77	(1.63, 1.92)	<0.001
> 12 months following rejection	1.23	(0.63, 2.41)	0.54	1.24	(1.13, 1.36)	<0.001	1.11	(0.60, 2.05)	0.74	1.32	(1.21, 1.43)	<0.001
Biopsy-proven rejection 6–12 months post-LT												
< 12 months following rejection	2.02	(0.27, 15.24)	0.49	2.99	(2.14, 4.18)	<0.001	1.57	(0.21, 11.63)	0.66	3.35	(2.54, 4.40)	<0.001
> 12 months following rejection	1.29	(0.17, 9.66)	0.80	1.53	(1.28, 1.83)	<0.001	0.96	(0.13, 7.04)	0.96	1.62	(1.37, 1.91)	<0.001
Biopsy-proven rejection > 12 months post-LT												
< 12 months following rejection	8.81	(3.37, 23.04)	<0.001	3.94	(3.22, 4.83)	<0.001	6.79	(2.64, 17.45)	<0.001	4.41	(3.71, 5.23)	<0.001
> 12 months following rejection	4.38	(1.49, 12.92)	0.01	1.64	(1.31, 2.04)	<0.001	3.35	(1.16, 9.73)	0.03	1.70	(1.39, 2.08)	<0.001
Medical severity at transplant (recipient on ventilator or dialysis)	3.32	(1.51, 7.28)	0.003	1.69	(1.58, 1.82)	<0.001	2.95	(1.54, 5.64)	0.001	1.60	(1.50, 1.71)	<0.001
Recipient age, per 10 years, < 55	1.18	(0.83, 1.67)	0.35	1.13	(1.09, 1.17)	<0.001	0.97	(0.77, 1.22)	0.78	1.02	(0.99, 1.05)	0.31
Recipient age, per 10 years, > 55	2.52	(1.66, 3.83)	<0.001	1.45	(1.38, 1.52)	<0.001	1.83	(1.29, 2.60)	0.001	1.31	(1.25, 1.37)	<0.001
Donor age, per 10 years	1.20	(1.04, 1.38)	0.01	1.11	(1.10, 1.13)	<0.001	1.23	(1.10, 1.38)	<0.001	1.13	(1.12, 1.14)	<0.001
Recipient diagnosis: HCV	1.13	(0.73, 1.76)	0.57	1.45	(1.38, 1.51)	<0.001	1.17	(0.83, 1.66)	0.37	1.40	(1.34, 1.46)	<0.001
Recipient diagnosis: Autoimmune hepatitis	0.28	(0.07, 1.18)	0.08	0.99	(0.88, 1.12)	0.91	0.28	(0.09, 0.88)	0.03	1.01	(0.91, 1.12)	0.85
Recipient diagnosis: PSC	0.60	(0.30, 1.18)	0.14	0.69	(0.62, 0.78)	<0.001	0.74	(0.46, 1.19)	0.21	0.84	(0.76, 0.92)	<0.001
Recipient diagnosis: PBC	1.04	(0.52, 2.10)	0.90	0.76	(0.67, 0.86)	<0.001	0.76	(0.41, 1.42)	0.39	0.83	(0.75, 0.93)	0.001
MELD at transplant, per 5 points	.			1.04	(1.03, 1.05)	<0.001	.			1.02	(1.01, 1.04)	<0.001

*In SRTR, time of rejection was randomly assigned in the interval in which rejection was reported to occur.

Table 4

Risk of Death due to Graft Failure and Non-Graft Failure Causes (SRTR Only)

	Death due to graft failure			Death due to leading non-graft failure causes*		
	HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Biopsy-proven rejection (time-dependent) in the first 6 months post-transplant						
< 12 months post-rejection	3.04	(2.45, 3.77)	<0.001	1.48	(1.28, 1.72)	<0.001
> 12 months post-rejection	2.06	(1.66, 2.56)	<0.001	1.08	(0.93, 1.24)	0.31
Biopsy-proven rejection (time-dependent) 6–12 months post-transplant						
< 12 months post-rejection	5.14	(3.25, 8.12)	<0.001	2.49	(1.67, 3.73)	<0.001
> 12 months post-rejection	2.41	(1.44, 4.03)	0.001	1.57	(1.17, 2.11)	0.003
Biopsy-proven rejection (time-dependent) > 12 months post-transplant						
< 12 months post-rejection	12.02	(8.54, 16.93)	<0.001	2.37	(1.62, 3.47)	<0.001
> 12 months post-rejection	2.84	(1.37, 5.89)	0.01	1.53	(1.10, 2.12)	0.01
Medical severity at transplant (recipient on ventilator or dialysis)	1.14	(0.93, 1.40)	0.21	1.99	(1.79, 2.22)	<0.001
Recipient age, per 10 years, < 55	0.88	(0.80, 0.96)	0.005	1.28	(1.21, 1.36)	<0.001
Recipient age, per 10 years, > 55	1.00	(0.85, 1.16)	0.97	1.56	(1.46, 1.68)	<0.001
Donor age, per 10 years	1.24	(1.20, 1.28)	<0.001	1.09	(1.07, 1.11)	<0.001
MELD at transplant, per 5 points	1.09	(1.05, 1.12)	<0.001	1.01	(0.99, 1.03)	0.31
Recipient diagnosis: Autoimmune hepatitis	0.92	(0.63, 1.35)	0.67	1.03	(0.87, 1.23)	0.71
Recipient diagnosis: PSC	0.54	(0.36, 0.80)	0.002	0.79	(0.67, 0.94)	0.01
Recipient diagnosis: PBC	0.82	(0.55, 1.23)	0.35	0.71	(0.59, 0.85)	<0.001
Recipient diagnosis: HCV	3.14	(2.75, 3.59)	<0.001	1.20	(1.12, 1.28)	<0.001

*Cardiovascular, renal, infection, malignancy