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Donor Risk Index for African American Liver Transplant Recipients with Hepatitis C Virus

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Abstract

African-American (AA) liver transplant (LT) recipients with hepatitis C virus (HCV) have higher rates of graft loss than other racial/ethnic groups. The Donor Risk Index (DRI) predicts graft loss but is neither race nor disease-specific and may not be optimal for assessing donor risk for AA HCV-positive LT recipients. We developed a DRI for AA with HCV with the goal of enhancing graft loss predictions. All U.S. HCV-positive adult AA first deceased donor LTs surviving ≥30 days from 3/2002 to 12/2009 were included. A total of 1766 AA LT recipients were followed for median 2.8 (IQR 1.3–4.9) years. Independent predictors of graft loss were donor age (40–49 yrs: HR 1.54; 50–59 yrs: HR 1.80; 60+ yrs: HR 2.34, p<0.001), non-AA donor (HR 1.66, p<0.001) and cold ischemia time (CIT) (HR 1.03 per hour >8 hours, p=0.03). Importantly, the negative effect of increasing donor age on graft and patient survival among AAs was attenuated by receipt of an AA donor. A new donor risk model for AA (AADRI-C) consisting of donor age, race and CIT yielded 1, 3 and 5-year predicted graft survival rates of 91, 77 and 68% for AADRI <1.60; 86, 67 and 55% for AADRI 1.60–2.44; and 78, 53 and 39% for AADRI >2.44. In the validation dataset, AADRI-C correctly reclassified 27% of patients (net reclassification improvement p=0.04) compared to the original DRI. We conclude that AADRI-C identifies grafts at higher risk of failure and this information is useful for risk-benefit discussions with recipients. Use of AA donors allows consideration of older donors.

Keywords

HCV; African Americans; donor race; liver transplant; disparity

Background

Hepatitis C virus (HCV) is the leading indication for liver transplantation (LT) in the United States (1). Compared to Caucasians, African-Americans (AA) have relatively superior outcomes with chronic HCV disease prior to transplantation (2, 3), but experience more aggressive recurrence of HCV disease after liver replacement (4, 5). The 2- and 5-year graft survival for HCV-positive AA LT recipients has been reported to be as much as 10% lower than in non-AA recipients (6, 7). The reason for this disparity in outcome is poorly

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understood. A lower likelihood of responding to antiviral therapy post-LT may be one factor (8, 9). Donor factors are likely to be of importance also.

The Donor Risk Index (DRI)--derived from 20,023 predominantly pre-MELD era United States liver transplants--was originally proposed in 2006 to predict LT recipient outcome based on available donor factors. Containing 7 donor variables, DRI predicts post LT graft failure using a continuous, numerical scoring system (10). The DRI was a milestone in highlighting the importance of donor quality on LT outcomes, and while the inclusion of a large, heterogeneous recipient pool maximized its generalizability, the DRI may have more limited prediction among specific subgroups, such as those transplanted for HCV. Prior retrospective studies have shown a strong and consistent association between donor age and severity of HCV recurrence (11, 12). Interestingly, in the original DRI, allografts from African American donors, compared to Caucasian donors, were associated with an increased risk (HR 1.19, 95%CI 1.10–1.29, $p<0.001$) of post-transplant graft failure (death or re-LT); but, several recent studies of HCV-infected transplant recipients have independently demonstrated a trend of improved graft outcomes when AA donor livers were paired with HCV-positive AA recipients.(4, 13, 14) With these observations in mind, we sought to define the donor factors of importance in AA recipients with HCV and to develop a donor risk model that accurately estimates risk of graft loss for this patient subgroup.

Methods

With IRB approval, we examined adult AA recipients of deceased donor liver transplants from March 1, 2002 to December 31, 2009 (MELD-era) with primary, secondary or other diagnosis of HCV recorded in the UNOS Standard Transplant Analysis and Research (STAR) file created on June 30, 2011. We excluded liver re-transplants and recipients with Status 1, HIV-coinfection, or less than 30 days of follow-up. The primary outcome was post-LT graft loss (recipient death or re-transplant).

Recipient and donor factors were described with frequency distributions and medians (interquartile ranges). Covariates evaluated included recipient age, gender, height, body mass index (BMI), blood type, diabetes, life support at transplant, region of transplant center, previous abdominal surgery, dialysis week prior to transplant, HBV surface antigen, hepatocellular carcinoma (HCC), simultaneous kidney transplant, laboratory values at transplant (MELD, creatinine, bilirubin, albumin) and donor age, gender, gender match, ethnicity, height, weight, BMI, blood type, blood type match, cytomegalovirus status match with recipient, anti-hypertensives pre-cross clamp, HCV antibody, hepatitis B core antibody, vasodilators, diabetes, history of hypertension, blood urea nitrogen, creatinine, SGOT, SGPT, bilirubin, donation after cardiac death, cause of death, share type, partial/split liver, cold ischemic time (CIT), and transplant year. Missing CIT (7%) and CIT less than 2 hours or greater than 20 hours (1.5%) were imputed with the median CIT for the region by share type.

The Kaplan-Meier method was used to estimate observed post-transplant graft survival. The log-rank test compared survival estimates across strata and Bonferroni corrected p values adjusted for multiple comparisons.

We used the Cox proportional hazards model to evaluate recipient and donor factors associated with graft loss. Time to graft loss was defined as days from liver transplant to the first of retransplant or death. Patients alive or lost to follow-up were censored at the date of last follow-up. When valid Social Security death dates were available for patients coded as alive or lost to follow-up, post-transplant follow-up status and date were updated with data from the Social Security death certificate master file. Donor factors with a pre-specified statistical significance of p value < 0.1 were analyzed by multivariate Cox regression models. Backwards elimination with $p<0.05$ was used to select the multivariate donor model. The final model was adjusted for recipient age, gender, HCC, blood type match, laboratory MELD and albumin at transplant and region. A novel donor risk model specific for AA recipients with HCV (AADRI-C) was developed. We investigated the interaction between donor age and donor race. The adjusted donor model was stratified by donor race (AA versus non-AA) to quantify and demonstrate differences in the risk of graft failure for the donor age by donor race interaction. Predicted survival estimates for tertiles of AADRI-C (tertile 1, AADRI-C <1.6; tertile 2, AADRI-C 1.6–2.44; and tertile 3, AADRI-C >2.44) and DRI (tertile 1, DRI <1.18; tertile 2, DRI 1.18–1.55; and tertile 3, DRI >1.55) were derived from the Cox proportional hazards model.

To compare the AADRI-C to the DRI, we identified a separate cohort of 294 HCV-positive AA patients receiving liver transplants between January 1, 2010 and January, 31, 2011 in the UNOS STAR file (created April 30, 2012) meeting our study selection criteria. These patients were not included in the original development dataset. In this validation dataset, we measured model discrimination (the ability of a model to correctly classify subjects into events and non-events) with the overall C-index (15). We assessed improvement in model performance by quantifying the proportion of correct risk reclassification by AADRI-C at 1 year post-LT using the net reclassification improvement (NRI) (16). NRI utilized apriori 1-year graft loss risk groups stratified as <7.5%, 7.5% to <10%, 10% to <12.5% and 12.5% to <15% and ≥15% to compare the AADRI-C model to DRI. Statistical analyses were conducted using SAS v9.2 (Cary, NC) and figures were created using Stata version 11.1 (College Station, TX).

Results

Recipient and Donor Characteristics

A total of 1,766 MELD-era AA LT recipients followed for a median of 2.8 (IQR 1.3–4.9) years were included (Table 1). Recipients were 70% male, had median age of 54 years and 38% were transplanted with HCC. The corresponding donors (Table 2) were 60% male with a median age of 42 years (IQR: 26–53), 22% were African American race and 7.3% were anti-HCV positive. The median CIT was 7 (IQR: 5.3–8.3) hours.

Donor Factors Associated with Graft Survival

Overall, 1-, 3- and 5-year graft survival rates for HCV-positive AA LT recipients were 85%, 65%, and 54%, respectively. Donor characteristics associated with graft loss in univariate analysis (Table 2), including age, female donor/female recipient match, non-AA/AA mismatch, cause of death, HBV core antibody, diabetes, history of hypertension, cold

ischemia time, BMI and blood urea nitrogen met the criteria for evaluation in multivariate analysis. After adjusting for recipient age, gender, HCC, blood type match, region, and laboratory values at transplant (MELD and albumin),the only donor characteristics independently predicting graft loss were older donor age (40–49 yrs: HR 1.54; 50–59 yrs: HR 1.80; 60–69 yrs: HR 2.03; ≥70 yrs: HR 2.83; p<0.001), donor non-AA (HR 1.66, p<0.001) and CIT per hour increase over 8 hours (HR 1.03 per hour increment, p=0.03) (Table 3).

We detected a significant interaction between donor age and donor race (p=0.047). Stratifying the model by donor race (AA n=395, non-AA n=1371) revealed an attenuation of the increased risk of graft loss with increasing age among AA donors (Table 4, Supplemental Figure 1). Risk of graft loss increased with increasing donor age among recipients of non-AA donor grafts across all donor age categories (p<0.001) compared to donors age 10–39. In contrast, risk of graft loss was not significantly increased in recipients of AA donors ages 40–49 (HR 1.09, P=NS) or 50–59 (HR 1.17, p=NS) compared to donors age 10–39. Risk of graft loss did not increase until AA donors were ≥60 years of age (HR 1.93, p=0.02). Overall, the 5-yr post-LT graft survival in AAs receiving an AA donor 40 years of age or older was significantly higher compared to AA receiving a non-AA donor of similar age (p=0.02 to p<0.001) (Supplemental Figure 1).

AADRI-C Development and Evaluation

Donor age, AA donor status and CIT were included in a new risk model for HCV-positive African American liver transplant recipients (AADRI-C). Observed 5-year graft survival estimates by tertiles of AADRI-C (tertile 1, AADRI-C <1.6; tertile 2, AADRI-C 1.6–2.44; and tertile 3, AADRI-C >2.44) were 69%, 54% and 39%, respectively (p<=0.001) (Figure 1). The 1-, 3- and 5-yr predicted graft survival for AADRI-C tertile 1 were 91%, 77% and 68%; for AADRI-C tertile 2 were 86%, 67% and 55%; and for AADRI-C tertile 3 were 79%, 53% and 39%, respectively. Predicted graft survival for tertiles of AADRI-C and DRI are shown (Supplemental Figure 2).

Examples of combinations of donor age, donor race and CIT and the corresponding predicted AADRI-C survival rates are shown in Table 5. These examples reflect the strong favorable influence of AA donor race on HCV-positive AA recipient graft outcomes. For example, an HCV-positive African American receiving a 59 year old graft from an AA with 8 hours CIT would be predicted to have approximately 15% higher graft survival than receiving a similar graft donated by a non-AA or comparable graft survival to receiving a<40 year old graft from a non-AA donor with 8 hours of CIT.

Compared to the original DRI, AADRI-C better predicted risk of graft failure in AA HCV positive recipients in both the development (C-index 0.56 and 0.60, respectively) and validation (C-index 0.51 and 0.55, respectively) datasets. Furthermore, estimated 1-year risk of graft loss calculated by AADRI-C correctly reclassified 19% of patients (NRI p<0.001) in the development dataset and 27% of patients (NRI p=0.04) in the validation dataset.

Discussion

In our disease- and race-specific assessment of donor quality and its association with graft failure in HCV-infected AA transplant recipients, the only donor factors of importance were age, race and CIT. The AADRI-C classifies risk of graft loss among AA recipients more accurately than the original DRI. Donor age—as in the original DRI--remains the dominant predictor of graft outcome in HCV-positive recipients in the AADRI-C model. However, for the first time, we identify a potential age effect modifier – namely donor AA race. We found that receipt of an AA donor liver attenuated the negative effect of increasing donor age on graft survival. Specifically, compared to AA recipients with donors under the age of 40 years, AA recipients of livers from AA donors had no statistically significant decline in graft survival until the donor age was 60 years or greater. This is a particularly important finding given that the original DRI found that, among all transplant recipients, graft outcomes were inferior with use of livers from AA donors (10).

The DRI remains a landmark innovation for discussing donor risk in LT. However, limitations in the DRI noted since its original presentation may hamper its current utility. For instance, DRI includes a great deal of pre-MELD era data that may not reflect post MELD trends in donor quality. Also, over time, donors have become older and more obese, while recipients have become more ill on average (17, 18). Most important in terms of our analysis, the DRI evaluated donor factors in a heterogeneous cohort of adult deceased-donor liver recipients, including all varieties of transplant indications and recipient races/ethnicities. Therefore, it may perform differently in patient and disease and subsets. For example, Maluf et al found that the same DRI score predicts significantly worse outcomes for HCV-positive patients than in HCV-negative recipients (19). For these reasons, we developed a donor risk model specific to HCV-positive recipients in the MELD era of LT, and focused on AA recipients because of their previously described poor long-term graft survival.

There is currently a donor shortage in Western countries. In 2009, the United States alone had 26% of patients listed for liver transplant die or become too ill to transplant (17). Most patients removed from the list without transplant receive at least one offer before they dropped off the list and most of those offers are refused for perceived issues of donor quality (20). The ability to utilize older donors in specific patient subsets without compromising outcomes provides a modest means of expanding the donor pool and potentially reducing wait-list mortality.

The matching of AA donors with HCV-positive AA’s has previously been criticized as too impractical to apply to day to day donor selection (21). However, given the significant risk of graft loss within 5 years for AA with non-AA donors, especially older non-AA donors, plausible clinical scenarios that may allow matching of AA donors to AA recipients should be considered. The AADRI-C may also be useful is in identifying AA recipients at highest risk for graft loss who may benefit from more intensive monitoring and/or early HCV treatment post-LT. An HCV-positive AA recipient transplanted with a high AADRI-C graft (>2.44) has a predicted 3-year graft survival of only 53% compared to 3-year survival with a

low AADRI-C (<1.6) donor of 77%. A clinician might target this high AADRI-C recipient for timely antiviral therapy.

The underlying pathogenesis linking AA derived allografts with improved post liver transplant outcomes in AAs is unclear. In a pre-transplant setting, AAs carry a disproportionate burden of HCV infection in the US population and there is epidemiological evidence suggesting AAs spontaneously clear acute HCV infection less often than non-AAs (22–24). However, chronically infected AAs may actually progress to cirrhosis more slowly than Caucasians (25). Investigators have looked for racial differences in immune response to HCV that explain the apparent dichotomy in AA outcomes with HCV infection acutely and chronically. It has been theorized that ethnic trends in HLA typing and KIR type predicts spontaneous viral clearance and sustained virological response to interferon-based therapy (26). For example, HLA-A*02 and HLA-DRB1*12 genotypes were associated with treatment-induced viral clearance in non-Caucasians but not in Caucasians, and natural killer cell immunoglobulin receptor KIR2DL3 was associated with both treatment and spontaneous clearance in HLA-C patients (26, 27). Also, differences in CD4 T cell responses and programmed cell death differ significantly among Caucasians and AAs and independently associate with odds of viral response to treatment prior to liver transplant (28, 29). It is likely that complex, ethnically-based differences in immune response to HCV underlie the benefit of matching grafts from AA donors to AA liver recipients.

Most famously, IL28-B CC (versus non-CC) genotype has a well-described linkage to viral clearance pre-transplant; and the disparity of CC prevalence in AAs versus non-AAs partially explains poorer response to interferon-based treatments (23, 30). Charlton et al have recently confirmed that IL28B CC recipient status and CC donor status are positively associated with post-liver transplant SVR (31). Interestingly, however, genotype CC donors were associated with greater post-transplant fibrosis, graft failure, and liver related death. Biggins et al recently confirmed these latter findings with more severe HCV disease seen with IL28B CC grafts, especially when transplanted into non-CC recipients (32). It may be that the lower likelihood of IL28B-CC genotype among AA donors underlies the superior outcomes in HCV-positive AA recipients receiving AA donor grafts.

Our study has limitations inherent to the retrospective collection of donor characteristics and recipient outcomes in a large database. However, the size of the database and the relatively standardized, prospective collection of pre-transplant recipient and donor data add statistical power and generalizability to our results. It represents the largest possible cohort of HCV-positive AAs recipients and is consistent with prior results from multicenter and center-specific studies of HCV disease outcomes in AA recipients (5, 14).

In summary, we have identified the key donor factors associated with graft survival among AA LT recipients with HCV: donor age, donor race and CIT. The AADRI-C will be helpful to clinicians making decisions about specific donor offers for HCV-positive AAs, in guiding the intensity of post-LT monitoring and timing of post-LT antiviral therapy, and in framing discussions with AA recipients regarding graft selection. Ultimately, with the use of AADRI-C, as well as improved therapeutic interventions, it is anticipated that AA LT

recipients with HCV will enjoy the same post-LT outcomes as other non-AA liver recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AA	African Americans
AADRI-C	African American HCV DRI
HCV	Hepatitis C
DRI	donor risk index
CIT	cold ischemia time
CI	confidence interval
LT	liver transplant
HR	hazard ratio
HIV	human immunodeficiency virus

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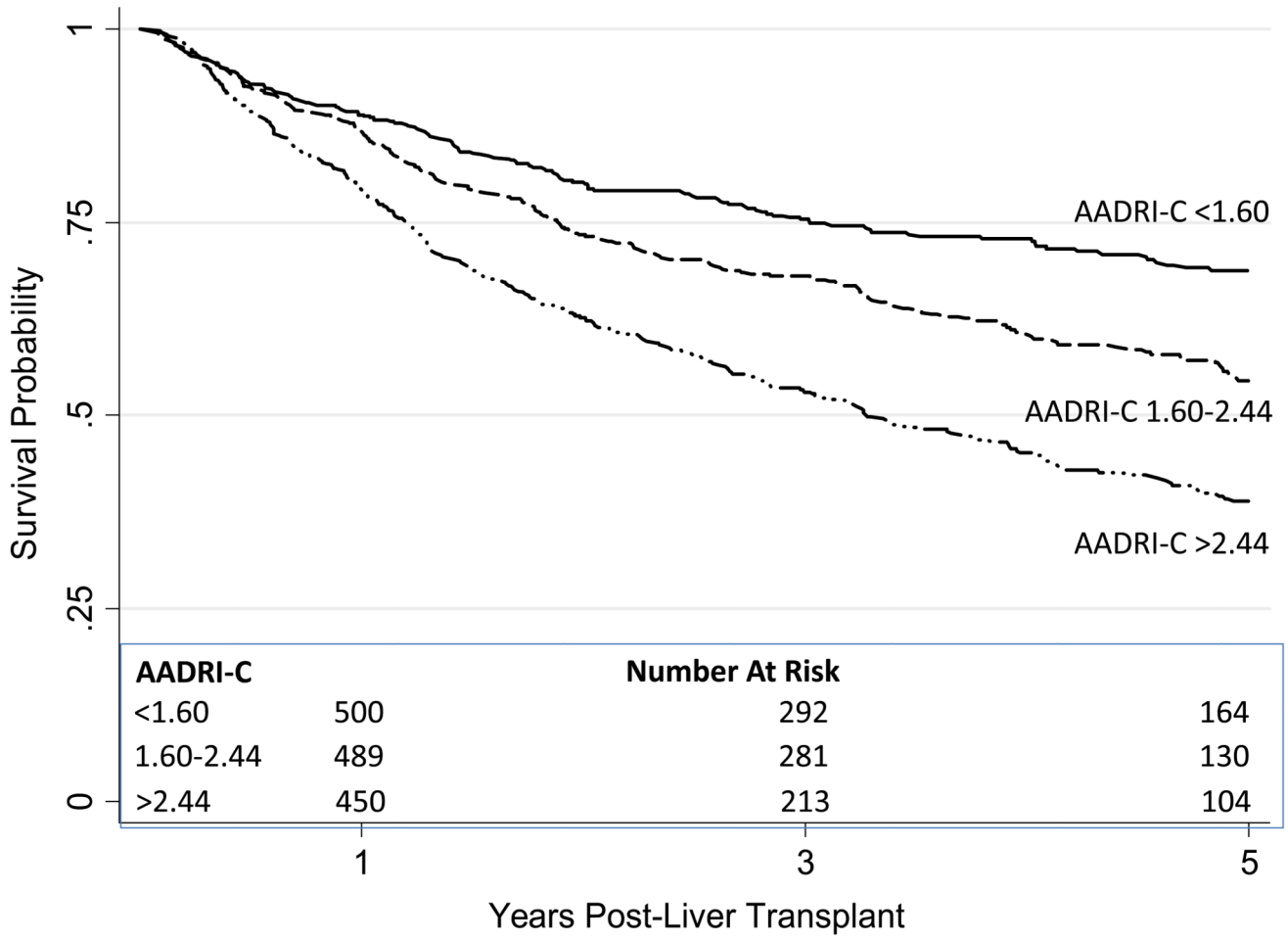

Figure 1.

Observed MELD era 5 year liver allograft survival in HCV+ recipients stratified by African American HCV Donor Risk Index (AADRI-C) tertiles 1, 2, and 3 were 69% (95%CI 64–73), 55% (95%CI 50–60), and 39% (95%CI 34–44), respectively.

Table 1

Recipient Characteristics and Univariate Association with Graft Loss

Recipient characteristic	Median	IQR	HR (95% CI)	P Value
Age	54	51–58	1.11 (0.99–1.24)*	0.07
Height	175	168–180	0.99 (0.92–1.07)**	0.84
BMI (kg/m^2)	27.8	24.5–31.4	1.00 (0.99–1.01)	0.79
Bilirubin at transplant (ln)	3.0	1.5–6.0	0.93 (0.87–0.99)	0.03
Albumin at transplant (g/dL)	2.7	2.2–3.2	0.92 (0.83–1.01)	0.09
	N	**%**		
Female	524	29.7	1.07 (0.92–1.26)	0.37
Diabetes	487	27.6	1.01 (0.86–1.19)	0.89
Life support at LT	36	2.0	1.26 (0.79–2.02)	0.33
HBsAg positive	56	3.2	0.90 (0.58–1.39)	0.64
HCC	667	37.8	1.15 (0.99–1.33)	0.07
SLK transplant	220	12.5	1.03 (0.82–1.28)	0.82
Creatinine at transplant				
<=1.00	625	35.4	1.00	
1.01–2.5	755	42.8	0.98 (0.83–1.16)	0.81
>2.5	386	21.9	1.10 (0.90–1.33)	0.35
Lab MELD at transplant				
6–14	457	25.9	1.00	
15–20	418	23.7	0.97 (0.79–1.18)	0.74
21–26	446	25.3	1.05 (0.86–1.28)	0.61
>26	441	25.0	0.96 (0.78–1.18)	0.69

* per 10 year increase

** per 10 cm increase

Table 2

Donor and Transplant Characteristics and Univariate Association with Graft Loss

Donor characteristic	Median	IQR	HR (95% CI)	P Value
Cold ischemic time (per hr >8 hrs)	7.0	5.3–8.3	1.04 (1.01–1.07)	0.006
Height (cm)	173	165–180	0.99 (0.98–1.00)	0.007
Weight (kg)	77.1	65.8–89.8	1.00 (0.997–1.004)	0.776
BMI (kg/m^2)	25.6	22.6–29.4	1.01 (1.00–1.02)	0.078
BUN mg/dL (ln)	14	9–22	1.14 (1.03–1.27)	0.014
Creatinine mg/dL (ln)	1.1	0.8–1.5	1.00 0.88–1.12	0.931
SGOT U/L: (ln, centered at 10)	45	28–81	0.95 (0.89–1.02)	0.131
SGPT U/L (ln)	33	21–59	0.96 (0.88–1.05)	0.358
Total bilirubin g/dL (ln)	0.8	0.5–1.2	1.00 (0.90–1.10)	0.926
	N	**%**		
Age				
10–39	804	45.53	1.00	
40–49	388	21.97	1.45 (1.19–1.7)	<0.001
50–59	344	19.48	1.72 (1.42–2.10)	<0.001
60–69	166	9.4	2.03 (1.60–2.58)	<0.001
70+	64	3.62	2.83 (2.06–3.90)	<0.001
Female	694	39.3	1.26 (1.09–1.45)	0.002
Gender match (recip/donor)				
M/M	798	45.2	1.00	
F/F	250	14.2	1.38 (1.12–1.70)	0.003
F/M	274	15.5	0.94 (0.75–1.17)	0.583
M/F	444	25.1	1.16 (0.97–1.39)	0.102
Ethnicity				
African American	395	22.4	1.00	
Non-African American	1371	77.6	1.54 (1.27–1.87)	<0.001
Share type				
Local	1355	76.73	1.00	
Regional	314	17.78	1.10 (0.91–1.33)	0.322
National	97	5.49	0.94 (0.68–1.30)	0.694
CMV− R+/D−	183	10.4	1.11 (0.88–1.39)	0.379
Partial Split Liver	19	1.1	0.65 (0.29–1.44)	0.287
DCD	81	4.59	1.11 (0.78–1.58)	0.582
Blood type				
O	898	50.85	1.00	
A	445	25.2	0.94 (0.79–1.12)	0.464
AB	45	2.55	0.79 (0.48–1.30)	0.355
B	378	21.4	0.94 (0.78–1.13)	0.505

Donor characteristic	Median	IQR	HR (95% CI)	P Value
ABO Match				
Identical	1623	91.9	1.00	
Compatible	132	7.47	0.92 (0.70–1.21)	0.545
Incompatible	11	0.62	0.00 (0–2.23e140)	0.944
Cause of death				
Head trauma	653	36.98	1.00	
Anoxia	290	16.42	1.15 (0.92–1.46)	0.224
Other	61	3.45	1.58 (1.07–2.32)	0.021
Stroke	762	43.15	1.47 (1.25–1.73)	<0.001
Anti-hypertensives pre-cross clamp	352	19.9	0.92 (0.76–1.10)	0.358
Hep C antibody positive	129	7.3	0.86 (0.64–1.16)	0.333
HBV Core antibody positive	141	7.98	1.29 (1.00–1.66)	0.048
Vasodilators	224	12.68	1.10 (0.89–1.37)	0.386
Diabetes	188	10.6	1.34 (1.07–1.67)	0.010
History of hypertension	590	33.4	1.34 (1.16–1.56)	<0.001

Table 3

Adjusted Independent Variables Included in AADRI-C Model Predicting Risk of Graft Loss

	HR	95% CI	P-value
Donor age 10–39	1.00		
40–49	1.54	1.27–1.88	<0.001
50–59	1.80	1.48–2.20	<0.001
60+	2.34	1.89–2.90	<0.001
Donor AA	1.00		
Non–AA	1.66	1.36–2.01	<0.001
CIT (per hr >8 hrs)	1.03	1.00–1.06	0.03

* Adjusted for recipient age, gender, HCC, blood type match, laboratory MELD and albumin at transplant and region.

Table 4

Risk of Graft Loss Stratified by Donor Age and Race

	AA Donor (n=395)			Non-AA Donors (n=1371)		
Donor age	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
10–39	1.00	--	--	1.00	--	--
40–49	1.09	0.68–1.71	0.72	1.64	1.30–1.99	<0.001
50–59	1.17	0.70–1.82	0.54	1.97	1.59–2.44	<0.001
60+	1.93	1.16–3.21	0.02	2.39	1.84–2.90	<0.001

* Adjusted for recipient age, gender, HCC, blood type match, laboratory MELD and albumin at transplant and region.

Table 5

Example Combinations of Donor Risk Factors and the Corresponding AADRI-C Predicted Survival

	Ref donor	Example 1	Example 2	Example 3
Donor Age	<40	<40	50–59	50–59
Donor Race	AA	non–AA	AA	non-AA
CIT	8	8	8	8
AADRI-C*	1.00	1.66	1.80	2.98
AADRI-C Tertile	1	2	2	3
Median 5 yr Survival	68.7%	54.5%	54.5%	38.8%

* Calculation: AADRI-C = exp[(0.433 if 40<=age<50)+(0.588 if 50<=age<60)+(0.850 if age>=60)+(0.504 if non-AA race)+((CIT-8)*0.033)].