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Donor-Recipient Race Mismatch in African-American Liver Transplant Patients with Chronic Hepatitis C

Varun Saxena, MD^a, Jennifer C. Lai, MD, MBA^a, Jacqueline G. O'Leary, MD, MPH^b, Elizabeth C. Verna, MD^c, Robert S. Brown Jr., MD, MPH^c, R. Todd Stravitz, MD^d, James F. Trotter, MD^b, Kartik Krishnan, MD^a, Norah A. Terrault, MD, MPH^a, and the ConsoRtiUm to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C)

^a Department of Medicine, University of California San Francisco

^b Baylor Simmons Transplant Institute, Baylor University Medical Center, Dallas

^c Department of Medicine, New York Presbyterian Hospital-Columbia

^d Department of Medicine, Virginia Commonwealth University Medical Center

Abstract

African-American (AA) donor-recipient race mismatch has been associated with graft loss and mortality, but studies of the association between race mismatch and HCV disease severity are lacking. HCV-infected first adult liver transplant recipients from 4 U.S. centers (N=1,093, 11% AA) were followed for a median of 3.05 years to determine rates of advanced HCV disease (bridging fibrosis or cirrhosis) and graft failure. The cumulative 4-year unadjusted rate of advanced disease was 40% for Non-AAs and 56% for AAs ($p<0.01$); 59% and 54% for AA recipient-donor race matched and mismatched patients, respectively ($p=0.89$). In adjusted models, both recipient AA race (vs. nonAA) (HR=1.47, 95% CI: 1.06-2.03, $p=0.02$) and AA recipient-donor mismatch (vs. matched) (HR=1.48, 95% CI: 1.03-2.12, $p=0.03$) were significant predictors of advanced fibrosis; other independent predictors were donor age (HR=1.21; $p<0.01$) and cytomegalovirus infection (HR=1.59, $p<0.01$). The 4-year unadjusted cumulative rate of HCV-associated graft loss was 10% for Non-AAs and 17% for AAs ($p<0.01$), with 0% for matched and 21% for mismatched AA recipient-donor patients ($p<0.01$). In adjusted models, AA recipient-donor mismatched patients had a 62% higher rate of graft loss (HR=1.62, 95% CI: 1.14-2.29, $p<0.01$) and AA recipient-donor matched patients a 76% lower rate (HR=0.24, 95% CI: 0.06-0.97, $p=0.05$) of graft loss/mortality than non-AA recipients. We conclude that HCV-infected AA recipient-donor mismatched patients are at high risk for advanced HCV disease and HCV-related graft loss and are a patient group that will benefit from new therapeutic strategies to prevent graft loss.

INTRODUCTION

African-Americans (AAs) are disproportionately affected by chronic hepatitis C virus (HCV) infection, comprising 20% of the United States (U.S.) HCV-infected population [1]. Natural history studies indicate that AAs are less likely to spontaneously clear HCV after exposure [1], and are less likely to achieve successful eradication of virus with antiviral therapy [2-4], resulting in higher rates of chronic infection. However, studies also suggest that AAs with chronic infection are less likely to progress to cirrhosis than non-AAs with the

same estimated duration of disease [5-8]. The natural history of HCV disease in AA liver transplant recipients and factors influencing risk of advanced fibrosis are largely unknown.

In the U.S. approximately 10% of HCV-positive patients undergoing liver transplantation (LT) are AA [9]. Prior studies have shown patient and graft survival to be lower in AA than non-AA transplant recipients including those with HCV [10-12]. A recent study, using United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) data from 1998-2007, found HCV-positive AAs with race-mismatched donors had a 41% higher mortality than HCV-positive AA recipients with race-matched donors [9]. In another study, using UNOS/OPTN data from 2003-2005 that did not stratify by HCV status, AA donor race was not found to be an independent predictor of graft failure once adjustments were made for center effects and other potential confounders [13]. Furthermore, the reduced survival among HCV-infected AA transplant recipients has been assumed to be due to worse HCV disease outcomes but there are no prior studies evaluating HCV-specific graft outcomes in AAs versus non-AAs. The ConsoRtiUm to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C) is a multicenter cohort of 4 large U.S. transplant centers focused on defining predictors of HCV disease severity and HCV-associated graft failure and was used to evaluate the role of donor-recipient race mismatch in AA transplant recipients.

PATIENTS AND METHODS

Patient Population

This multicenter retrospective cohort study included all adult patients (18 years of age or older) receiving a first LT for HCV-related disease from March 1, 2002 through December 31, 2007 at the University of California at San Francisco, New York Presbyterian Hospital-Columbia, Virginia Commonwealth University Medical Center and Baylor University Medical Center. Anti-HCV and HCV RNA tests were used to establish the presence of HCV infection. Exclusion criteria included HCV-RNA negativity immediately after LT, graft loss 30 days after LT, and/or coinfection with human immunodeficiency virus. The institutional review boards at each of the participating study centers approved this study.

Donor characteristics including donor age, race, gender, cause of death, positive HCV-antibody, and peri-transplant factors including warm and cold ischemia times were obtained from the UNOS/OPTN database. Recipient demographic, virologic and clinical data, including immunosuppressive medications at last follow-up were collected retrospectively by individual health record review. Acute cellular rejection was defined as biopsy-proven rejection requiring treatment with high-dose bolus corticosteroids or anti-lymphocyte therapy. Cytomegalovirus infection was defined as CMV infection requiring anti-CMV therapy. HCV treatment dates were obtained as well as response status with achievement of sustained virologic response (SVR) defined by negative HCV RNA at least six months after treatment discontinuation. Each center used a standard immunosuppression regimen, however, immunosuppression regimens were not uniform among the sites.

Study Endpoints and Covariates

The primary outcome was the presence of advanced fibrosis, defined as bridging fibrosis or cirrhosis on liver biopsy. Biopsy results were based on the local pathologists' assessment. Of the 1,093 patients included, 92% had biopsies during the study period that were used for analyses of disease severity. All patients were included in the analysis of the secondary endpoints of all-cause graft loss (defined as death and/or retransplantation) and graft loss with advanced recurrent HCV disease.

For the analysis of AA recipient race, the comparator group was non-AAAs, which included Caucasians, Asians, Hispanics, and other races. For the analysis of AA recipient-donor match versus mismatch, the matched group was AA recipient with an AA donor (rAA/dAA) and the unmatched group was AA recipient with a non-AA donor (rAA/dNonAA). In these regression models, non-AA recipients (rNonAA), with or without race matched donors, were used as the reference group. An additional analysis was done in which non-AA recipients (rNonAA) were divided into those with an AA donor (rNonAA/dAA) and with a non-AA donor (rNonAA/dNonAA).

Statistical Analysis

Descriptive statistics utilized median with interquartile range (IQR) and proportions, as appropriate. For comparisons between AA and non-AA groups, the Chi-square test was used for dichotomous variables and the Wilcoxon rank sum tests used for continuous variables.

Cumulative rates of advanced fibrosis were estimated using Kaplan-Meier methods and groups compared using the log-rank test, with $p < 0.05$ defined as statistically significant. Cox proportional hazards regression was used to examine the predictors of graft survival and advanced fibrosis. The primary predictor variables were AA recipient race and AA recipient-donor race mismatch. Other recipient, donor and transplant-related factors were examined in univariable models and those covariates with $p < 0.10$ were evaluated in multivariable models. Models were built using backward elimination of covariates, using a $p < 0.05$ as the criterion for inclusion in the final model. All final models were adjusted for center effect, by including center as a covariate in the analyses. Due to the limited number of HCV-associated graft losses in AA donor-recipient matched versus mismatched patients, multivariable models were not evaluated. Sensitivity analyses limited to the Caucasian and AA recipient and donor race groups only were performed.

Statistical analyses were performed using STATA version 11 software (Stata Corporation, College Station, Texas).

RESULTS

A total of 1,093 patients were included in this study, of which 122 (11%) were AA. Among the 971 non-AAAs, 707 (65%) were Caucasian, 188 (17%) were Hispanic, 27 (2%) were Asian, and 49 (4%) were classified as Other race. A total of 21 patients (3 AA) suffered graft loss within 30 days of LT and were not included in this study. Four (0.4%) AA and 38 (3.5%) non-AA patients had incomplete donor race data and were excluded from analyses of the primary predictor of AA recipient-donor mismatch, but were included in analyses involving AA recipient race alone. Among the 122 AAs, 27 (22%) patients were in the race-matched group (rAA/dAA) and 91 (75%) were in the mismatched group (rAA/dNonAA) and 4 (3%) were missing donor race.

The median follow-up for the study cohort was 3.05 (IQR: 1.81-4.74) years with no difference in duration of follow-up between AA (2.99, IQR: 1.35-4.36) and non-AA (3.06, IQR: 1.95-4.83, $p = 0.15$). There was no difference in median duration of follow-up by racial subgroups: rAA/dAA: 3.80, IQR: 2.11-5.00; rAA/dNonAA: 2.67, IQR: 1.22-4.36; rAA/dNonAA: 3.08, IQR: 1.87-4.94; and rNonAA/dAA: 3.00, IQR: 1.64-4.47 ($p = 0.18$). The median number of biopsies per patient was 3.0 (IQR: 2.0-4.0) with no difference between AA and non-AA (3.0, IQR: 2.0-4.0 vs. 3.0, IQR: 2.0-4.0; $p = 0.51$). AA and non-AA recipients were similar except for the proportion receiving combined liver/other organ transplant, median laboratory model for end-stage liver disease (MELD) score at LT, proportion with donor AA, and median warm ischemia time (Table 1). Race-matched (rAA/

dAA) and race mismatched (rAA/dNonAA) groups were similar except for cold ischemia time (7.1 hours, IQR: 5.4-7.5 vs. 7.8 hours, IQR: 6.2-9.4; $p=0.05$).

Rates and Factors Associated with Advanced Fibrosis

A total of 113 (93%) AA and 888 (91%) non-AA patients had a biopsy during the study period and were included in this analysis of advanced fibrosis. Patients without biopsies differed from those with at least one biopsy in having shorter follow-up time, more HCC at transplant, fewer episodes of treated acute rejection and a lower rate of HCV treatment (data not shown).

A total of 47 (41%) AAs and 241 (27%) non-AAs developed advanced fibrosis during the study period ($p<0.01$). The unadjusted cumulative rate of advanced fibrosis was higher in AAs than non-AAs ($p<0.01$), but with no differences between rAA/dNonAA and rAA/dAA groups ($p=0.89$) (Figure 1). Recipient AA race was associated with a significantly higher rate of advanced fibrosis in univariable (HR=1.59, 95% CI: 1.16-2.19, $p<0.01$) and adjusted (HR=1.47, 95% CI: 1.06-2.03, $p=0.02$) models (Table 2). Compared to non-AA recipients (with any race donor), AA recipient-donor race mismatch was a significant predictor of advanced fibrosis in univariable (HR=1.61, 95% CI: 1.13-2.30, $p<0.01$) and multivariable models (HR=1.48, 95% CI: 1.03-2.12, $p=0.03$), but matched AA recipient-donor was not (Table 3). In models using rNonAA/dNonAA as the reference group, rNonAA/dAA was protective of advanced fibrosis in multivariable models (HR=0.43, 95% CI: 0.26-0.70, $p<0.01$) and the association between AA recipient-donor race mismatch (HR=1.31, 95% CI: 0.90-1.91, $p=0.15$) was attenuated.

Rates of HCV treatment were similar in AA and non-AA but response rates differed, with 66 (26%) of treated non-AAs and 5 (13%) of treated AAs achieving SVR ($p=0.05$). SVR rates for AAs with donor-recipient race match and mismatch were 11% ($n=1$) and 15% ($n=4$) respectively ($p=1.00$). Achievement of SVR was associated with lower rates of advanced fibrosis but did not significantly change the association between race and risk of advanced fibrosis in multivariable models. When treated patients were excluded from the analysis, the association between race and risk of advanced fibrosis remained in univariable (HR=1.48, 95% CI: 1.06-2.28, $p=0.05$) and multivariable (HR=1.24, 95% CI: 1.05-1.56, $p=0.04$) models.

Amongst patients with at least one biopsy during the study period and exposure to HCV treatment, 25 (64%) AAs and 180 (73%) non-AAs had a biopsy before receiving HCV treatment ($p=0.34$). When the analysis is limited to biopsies performed prior to HCV treatment, the independent association between race and risk of advanced fibrosis remained (HR=1.92, 95% CI 1.04-3.56).

In a sensitivity analysis restricted to only Caucasian and AA donors and recipients, 102 (15%) AAs and 591 (85%) Caucasians were compared. Both AA race (HR=1.56, 95% CI: 1.07-2.26, $p=0.02$) and AA recipient-donor race mismatch (HR=1.56, 95% CI: 1.02-2.40, $p=0.04$) remained independent predictors of advanced fibrosis. In another sensitivity analysis, we restricted the outcome to stage 2 fibrosis within one year of LT to evaluate for rapid fibrosis progression. The unadjusted cumulative rate of stage 2 was not higher in AAs than non-AAs ($p=0.09$) nor was the difference between rAA/dNonAA and rAA/dAA groups ($p=0.22$). However, both AA race (HR=1.39, 95% CI: 1.02-1.88, $p=0.04$) and AA recipient-donor race mismatch (HR=1.42, 95% CI: 1.01-2.00, $p=0.04$) were independent predictors of stage 2 fibrosis within one year in multivariable models.

Rates and Factors Associated with Graft Failure

A total of 41 (34%) AAs and 266 (27%) non-AAs experienced graft failure or death during the study period. Compared to non-AAs, AAs had higher rates of cardiovascular death (4.1% vs 1.4%, $p=0.05$) and HCV-associated graft failure or death (18.9% vs. 8.5%, $p<0.01$). Unadjusted cumulative rates of all-cause graft loss did not differ between AAs and non-AAs (log-rank $p=0.09$) but rates of graft failure with advanced HCV were significantly higher in AAs than non-AAs (log-rank $p<0.01$). The highest rate of HCV-associated graft loss was seen in the AA recipient-donor mismatched group. The 4-year cumulative estimates of HCV related graft failure were 0% for rAA/dAA, 21% for rAA/dNonAA, 12% for rNonAA/dAA, and 10% for rNonAA/dNonAA (Figure 2). In multivariable models, AA race was an independent predictor of HCV-related graft failure (HR=2.41, $p<0.01$) (Table 4).

In multivariable models of all cause graft loss and mortality, glomerular filtration rate at transplant, donor age, cyclosporine use at last follow-up, HCV treatment, sustained virologic response and cytomegalovirus treatment were independent predictors of all cause graft failure but AA race was not (HR=1.35, 95% CI: 0.97-1.88, $p=0.08$). In the multivariable analyses utilizing donor-recipient race mismatch as the primary predictor, rAA/dNonAA was a strong and independent predictor of all cause graft failure (HR 1.62, $p<0.01$), whereas rAA/dAA was protective (HR 0.24, $p=0.05$) (Table 5). The median time to graft loss among those meeting the endpoint of advanced fibrosis was 0.99 years (IQR: 0.13-2.53). The unadjusted cumulative rate of graft loss after advanced fibrosis was higher in AAs than non-AAs ($p=0.01$), and highest in the rAA/dNonAA group ($p<0.01$).

A sensitivity analysis limited to Caucasian and AA races only showed that AA race remained an independent predictor of HCV-related graft failure (HR=3.06, $p<0.01$) but not of all cause graft failure (HR=1.35, $p=0.11$) in adjusted models. AA recipient/donor race mismatch was predictive of all cause graft failure (HR=1.72, $p<0.01$) in adjusted models.

DISCUSSION

This is the first study to examine the effects of AA race and AA recipient-donor race mismatch on HCV disease severity and HCV-associated graft losses in transplant recipients. We have shown that AA recipients with HCV disease have a 47% higher rate of bridging fibrosis or cirrhosis as compared to non-AA recipients, and AA recipients with a non-AA donor have a higher risk of advanced fibrosis than those with AA donors. Additionally, AA recipients have significantly higher rates of HCV-associated graft loss and AAs with race-mismatched donors appear to be at greater risk than AAs with race-matched donors.

Our study confirms and extends the findings of a prior OPTN-based study that showed that AA donor-recipient race mismatch (versus match) was associated with reduced graft survival [9]. However, our study establishes the link between advanced disease and graft loss. Our study differs from the prior study from Pang et al, in that we used a contemporary, MELD-era cohort and we did not restrict the analysis to AA and Caucasian races. However, our sensitivity analysis that compared results of AAs to Caucasians suggests that the AA recipient-donor race mismatch effect on advanced fibrosis and graft failure is not specific to Caucasian donors but is more generalizable to all non-AA donors.

The reason for the increased advanced fibrosis associated with AA recipient-donor race mismatch in HCV infected AAs is unknown. We speculate that it may be related to “protective” genetic factors associated with the donor liver. The importance of donor and recipient *IL28B* polymorphisms has been highlighted by recent studies. Recipients with favorable alleles have been shown to have less inflammatory activity on biopsies post-LT [14] and higher rates of response to antiviral therapy [14-17]. Interestingly, *IL28* SNPs in

both the donor *and* recipient were predictive of post-transplant outcomes [15, 16]. While IL28B polymorphisms are critical in understanding HCV-associated outcomes post-LT, especially response to HCV treatment, they are unlikely to explain the race-match and mismatch effects seen in AAs. Population studies have shown that AAs have a substantially lower frequency of the favorable IL28B alleles compared to Caucasians [18]. If HCV disease outcomes are influenced by IL28B genotype, one could hypothesize that AAs with AA donors are more likely overall to have unfavorable IL28B genotypes than AA with non-AA donors, and yet this group had the best outcomes. Thus, other recipient and donor genetic factors, including but not limited to Killer cell immunoglobulin-like receptor (KIR) receptors and ligands [19], and/or viral factors [15] are likely of importance.

Natural killer (NK) cells and KIRs modulate the immunological response to HCV with KIRs specifically recognizing human leukocyte antigen (HLA) class I antigens present on target cells. The effector function of NK cells are influenced by inhibitory KIR interaction with self-HLA class I ligands, with HLA-C being the most predominant. Previous studies have found that a decrease in the number of HLA-C allele mismatches correlated with a decrease in the number of rejection episodes [20, 21]. Furthermore, mismatched KIR-HLA-C ligands between donor-recipient pairs favored progression to advanced fibrosis in recurrent HCV disease, but only in the presence of KIR2DL3 [19]. One could hypothesize that mismatching KIR-HLA-C ligands could underscore the race mismatch effect we have shown. However, further studies examining KIR-HLA-C and race mismatch are needed to further examine this hypothesis.

While evaluation of donor-recipient mismatch in non-AA recipients was not the focus of our study, an apparent protective effect of AA donor (vs non-AA) race on risk of advanced fibrosis was seen non-AA recipients. Differences in donor quality (e.g. donor cause of death, donor age) were explored post-hoc and found to not explain this association (data not shown). Thus, other unmeasured donor, recipient and transplant-related factors are likely at play.

In our study, achievement of a sustained virologic response was protective of HCV-associated graft failure and all-cause graft failure, as has been shown in other studies [22, 23]. Treatment rates were similar between AAs versus non-AAs but rates of sustained virologic response were higher in non-AAs than AAs [2-4]. This differential rate of response to therapy, is partially explained by the IL28B polymorphisms [24] and interestingly, in liver transplant recipients, the IL28B polymorphisms may be an even stronger predictor of response than in non-transplant recipients [14], suggesting an interaction between IL28B actions and immunosuppression. Given the recognized importance of treatment responses in achieving long-term graft survival, new treatment options with efficacy in patients groups with unfavorable IL28B genotypes, such as AAs, are essential.

In most epidemiologic studies, the gold standard for race classification has been use of “self-identified” race [25, 26]. In this study, recipient and donor race data was obtained from the UNOS/OPTN database, which does not require self-designation of race and thus some misclassification bias may exist. However, this limitation is not unique to this study but rather a limitation of all studies of race that utilize UNOS/OPTN data [2, 4-10, 27]. Moreover, among members of a self-identified race, genetic heterogeneity is recognized due to variable admixtures with other racial groups. [28, 29]

There were some limitations of our study. First, due to its retrospective nature and lack of systematic data collection, some factors of potential importance in disease progression, such as donor steatosis or diabetes, IL-28B polymorphisms in recipient/donor and detailed immunosuppression information, are lacking. Second, given our relatively small sample

size, interactions could not be statistically examined. Third, despite inclusion of four large U.S. transplant programs, the total number of AAs in the study, particularly those matched to AA donors, is modest and limits our ability to perform extensive multivariable analysis between matched and mismatched recipient-donor subgroups. However, the proportion of AAs in our cohort is very consistent with the proportion of AAs undergoing LT in the U.S. and thus we believe our results are generalizable. Fourth, there is a possibility of misclassification bias within a race group. Despite these limitations, this is the largest cohort of patients with biopsy data evaluating disease severity post-transplantation and includes detailed information on other cofactors known to influence disease progression such as donor age, acute rejection and receipt of HCV treatment.

In conclusion, this study shows that AAs have higher rates of advanced fibrosis and graft loss associated with HCV than non-AAs, and that AAs with recipient-donor race mismatch represent the highest risk group. The importance of donor selection is highlighted by our results, and use of high quality donors, i.e. younger donors, race matched or those with low donor risk index, may be one strategy to minimize the risk of disease progression, especially among high risk groups such as AAs. We do not advocate for routine matching of recipients and donors based upon race, but it may be a factor to be weighed favorably when assessing a graft, particularly if from an extended criteria donor, for an AA recipient. Our results also argue for closer monitoring of disease progression in AA LT recipients, possibly with more frequent use of liver biopsies, and earlier consideration of antiviral therapy. Clearly, there is also a need for antiviral therapies with improved efficacy in all transplant recipients, but among AA, this is particularly critical given their truncated timeline to the development of recurrent cirrhosis.

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Figure 1.

Unadjusted Kaplan-Meier Cumulative Estimates of Advanced Fibrosis in the Recipient-Donor Race Groups. Two- and 4-year cumulative estimates of advanced fibrosis were 33% (95% CI: 23%-46%) and 56% (95% CI: 43%-71%) for rAA/dNonAA, 36% (95% CI: 19%-61%) and 59% (95% CI: 36%-83%) for rAA/dAA, 21% (95% CI: 18%-25%) and 41% (95% CI: 37%-47%) for rNonAA/rNonAA, and 10% (95% CI: 6%-18%) and 27% (95% CI: 17%-41%) for rNonAA/rAA ($p<0.01$). Numbers below x-axis represent number of patients at risk at each two-year time point.

Figure 2.

Kaplan-Meier Cumulative Estimates of HCV Related Graft Failure in the Recipient-Donor Race Groups. Two- and 4-year cumulative estimates of HCV related graft failure were 18% (95% CI: 11%-28%) and 21% (95% CI: 14%-32%) for rAA/dNonAA, 0% and 0% for rAA/dAA (95% upper CI: 13%), 6% (95% CI: 4%-8%) and 10% (95% CI: 8%-13%) for rNonAA/rNonAA and 7% (95% CI: 3%-13%) and 12% (95% CI: 7%-20%) for rNonAA/rAA ($p<0.01$). Numbers below x-axis represent number of patients at risk at each two year time point.

Table 1

Characteristics of AA and non-AA Liver Transplant Recipients

Characteristics	AAs (n=122)	Non-AAs (n=971)	p-value
Recipient age yrs, median (IQR)	53.8 (50.0-57.0)	53.0 (49.0-57.4)	0.56
Recipient male (%)	70	76	0.12
Other organ transplant* (%)	8.2	3.7	0.03
Lab MELD at transplant, median (IQR)	20 (15-24)	17 (13-22)	<0.01
GFR at transplant, median (IQR) ml/min/1.73m ²	73.6 (48.6-102.7)	75.1 (51.6-106.3)	0.73
HCC at transplant (%)	42	40	0.70
Donor AA (%)	22	15	0.03
Donor age, yrs, median (IQR)	41.5 (29.00-51.0)	42.0 (27.0-53.0)	0.80
Donor male (%)	58	60	0.70
Non-anoxia donor cause of death (%)	47	46	0.84
Cold ischemia time, hrs, median (IQR)	7.5 (6.0-9.2)	8.0 (6.0-10.0)	0.09
Warm ischemia time, mins, median (IQR)	41 (35-46)	45 (38-52)	<0.01
Donor anti-HCV positive (%)	7	9	0.60
Cyclosporine use at last follow-up (%)	31	30	0.75
Treated acute rejection (%)	28	20	0.06
At least one episode of acute rejection before advanced fibrosis (%)	27	20	0.07
HCV treatment (%)	32	26	0.19
HCV treatment before advanced fibrosis (%)	25	22	0.49
Sustained virologic response (%)	5	7	0.26
Cytomegalovirus treatment (%)	11	14	0.49
All cause graft failure (%)	34	27	0.17
HCV related graft failure (%)	19	9	<0.01
Advanced fibrosis (%)	41	27	<0.01

* one patient had a combined liver-heart transplant, while all others had a combined liver-kidney transplant.

Table 2

Predictors of Advanced Fibrosis for AA vs. Non-AA Recipients

Covariate	All Patients (n=1001) HR (95% CI) p-value	
	Univariable	Multivariable *
Recipient AA	1.59 (1.16-2.19) <0.01	1.47 (1.06-2.03) 0.02
Recipient age, yrs	0.98 (0.96-1.00) 0.03	--
HCC at transplant	0.78 (0.61-1.00) 0.05	--
Donor age, yrs	1.22 (1.13-1.31) <0.01	1.21 (1.12-1.30) <0.01
Non-anoxia donor cause of death	1.52 (1.20-1.93) <0.01	--
Donor HCV	1.80 (1.20-2.68) <0.01	--
Cyclosporine use at last follow-up	1.45 (1.13-1.86) <0.01	--
At least one episode of acute rejection before fibrosis	1.25 (0.96-1.63) 0.10	--
Sustained virologic response	0.50 (0.30-0.83) <0.01	--
Cytomegalovirus treatment	1.75 (1.31-2.36) <0.01	1.59 (1.18-2.15) <0.01

* Adjusted for center effects

Table 3

Predictors of Advanced Fibrosis in Recipient-Donor Race All

Covariate	All Patients (n=959) HR (95% CI) p-value	
	Univariable	Multivariable *
rAA/dAA [‡]	1.55 (0.82-2.92) 0.18	1.31 (0.68-2.53) 0.42
rAA/dNonAA [‡]	1.61 (1.13-2.30) <0.01	1.48 (1.03-2.12) 0.03
Recipient age, yrs	0.98 (0.96-1.00) 0.04	--
HCC at transplant	0.77 (0.60-1.00) 0.05	--
Donor Age, yrs, per decade	1.22 (1.13-1.31) <0.01	1.21 (1.13-1.30) <0.01
Non-anoxia donor cause of death	1.55 (1.22-1.98) <0.01	--
Donor HCV	1.81 (1.21-2.71) <0.01	--
Cyclosporine use at last follow-up	1.46 (1.13-1.88) <0.01	--
Sustained virologic response	0.51 (0.31-0.84) <0.01	--
Cytomegalovirus treatment	1.71 (1.26-2.31) <0.01	1.55 (1.14-2.11) <0.01

* Adjusted for center effects

[‡]rNonAA was designated as the reference group

Table 4

Predictors of HCV Related Graft Failure for AAs vs. Non-AAs

Covariate	All Patients (n=1093) HR (95% CI) p-value	
	Univariable	Multivariable
Recipient AA	2.41 (1.52-3.83) <0.01	2.41 (1.50-3.89) <0.01
Recipient male	0.64 (0.42-0.95) 0.03	--
HCC at transplant	0.63 (0.42-0.96) 0.03	0.61 (0.40-0.93) 0.02
Donor age, yrs, per decade	1.44 (1.27-1.63) <0.01	1.38 (1.21-1.56) <0.01
Non-anoxia donor cause of death	1.76 (1.18-2.63) <0.01	--
Donor HCV	1.74 (0.95-3.19) 0.07	--
Treated acute rejection	1.91 (1.28-2.85) <0.01	1.83 (1.21-2.78) <0.01
HCV Treatment	1.65 (1.13-2.43) 0.01	1.73 (1.15-2.61) 0.02
Sustained virologic response	0.18 (0.05-0.57) <0.01	0.27 (0.08-0.88) 0.03
Cytomegalovirus treatment	1.89 (1.19-2.98) <0.01	--

*Adjusted for center effects

Table 5

Predictors of All Cause Graft Failure in Recipient-Donor Race Mismatched All

Covariate	All Patients (n=1054) HR (95% CI) p-value	
	Univariable	Multivariable *
rAA/dAA [‡]	1.67 (1.18-2.37) <0.01	1.62 (1.14-2.29) <0.01
rAA/dNonAA [‡]	0.26 (0.06-1.03) 0.06	0.24 (0.06-0.97) 0.05
Recipient Male	0.78 (0.60-1.01) 0.06	--
GFR at transplant ml/min/1.73m ²	1.00 (0.99-1.00) 0.06	1.00 (0.99-1.00) <0.01
HCC at transplant	0.81 (0.64-1.04) 0.09	--
Donor Age, yrs, per decade	1.22 (1.14-1.31) <0.01	1.19 (1.11-1.28) <0.01
Non-anoxia donor cause of death	1.33 (1.05-1.69) 0.02	--
Cyclosporine use at last follow-up	0.79 (0.60-1.03) 0.09	0.69 (0.52-0.93) 0.01
HCV treatment	0.60 (0.45-0.80) <0.01	--
Sustained virologic response	0.22 (0.09-0.55) <0.01	0.22 (0.09-0.53) <0.01
Cytomegalovirus treatment	1.70 (1.28-2.25) <0.01	1.50 (1.12-2.00) <0.01

* Adjusted for center effects

[‡]rAA/dAA was designated as the reference group