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Association of Recipient *APOL1* Kidney Risk Alleles with Kidney Transplant Outcomes

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Abstract

Background—Kidney transplant survival in African-American (AA) recipients is lower compared to non-AA transplant recipients. *APOL1* risk alleles (RA) have been postulated as likely contributors. We examined the graft outcomes in kidney transplant recipients (KTR) stratified by *APOL1* RA status in a multicenter observational prospective study.

Methods—The Renal Transplant Outcome Study (RETOS) study recruited a cohort of incident kidney transplant recipients at three transplant centers in the Philadelphia area from 1999 to 2004. KTR were genotyped for *APOL1* RA. Allograft and patient survival rates were compared by presence and number of *APOL1* RA.

Results—Among 221 participants, approximately 43% carried 2 *APOL1* RA. Recipients carrying two *APOL1* RA demonstrated lower graft survival compared to recipients with only one or none of *APOL1* RA at 1-year posttransplant independently of other donor and recipient

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characteristics (Adjusted HR 3.2 [95% CI 1.0–10.4, p-value 0.05]). There was no significant difference in overall survival or graft survival after 3 years posttransplantation. There was no difference in death by *APOL1* -risk status.(P=0.11)

Conclusion—Recipients with two APOL1 high-risk alleles exhibited lower graft survival 1-year posttransplantation compared to recipients with only one or zero *APOL1* RA. Further research is required to study the combined role of the recipient and donor *APOL1* genotypes in kidney transplantation.

Introduction

There are known health disparities in kidney transplantation outcomes. African-American (AA) kidney transplant recipients (KTR) have inferior kidney transplant outcomes.[1] While there has been some improvement in allograft function for AA recipients over time, allograft survival is still inferior compared to non-AA recipients. In a recent study, using OPTN data for 65,040 donor/recipient pairs over a 20-year period, it was shown that the retrospective median graft survival in Black recipients was 12.0 years vs. 18.6 years in White recipients, 17.2 years for Hispanics and 17.1 years for Asian-Americans.[2] AA recipients who were followed for 9 years posttransplant were found to be 1.8 times more likely to experience graft failure compared to White recipients[3] and were more likely to have delayed graft function (odds ratio (OR)=1.63[95% CI 1.54–1.73]; P<0.001), which is a risk factor for poor allograft survival.[4] Likewise, having an AA kidney donor is associated with worse graft survival (adjusted hazard ratio (HR) = 1.64 [95% CI, 1.24–2.17]).[5]

Genovese et al described two independent haplotypes in the *APOL1* gene on chromosome 22, which were strongly associated with focal segmental glomerulosclerosis (FSGS) and hypertensive-attributable end-stage kidney disease (ESKD).[6] The *APOL1* gene encodes the apolipoprotein L1 protein, which is an innate resistance factor active against African trypanosomes causing African sleeping sickness.[7] The two *APOL1* risk alleles (RA), termed G1 and G2, are common in individuals with recent African descent, but absent in those without recent African descent. The G1 haplotype refers to two missense mutations that usually are inherited together: G1G (p.S342G) and G1M (p.I384M); the G nucleotide at rs73885319 (342G) is the causal allele and is sufficient to define the G1 risk allele.[8] G2 is a 6 base pair deletion (p.N388/Y389) that does not occur on the same chromosome as the G1 allele. Approximately 14% of AAs have *APOL1* high-risk genotypes (G1/G1, G1/G2, or G2/G2), while the rest have low-risk APOL1 genotypes comprising 1 (46%) or 0 (40%) RA.[8] Hispanic individuals of Caribbean descent (e.g. Puerto Rican, Cuban, or Dominican) may carry *APOL1* RA genotypes with variable prevalence due to differences in the proportion of African ancestry.[9] A recessive mode of inheritance has been found to best explain the chronic kidney disease (CKD) risk in AA.[7]

A retrospective analysis of 119 AA KTR, including 92 deceased donor allograft recipients, who had participated in a genetic study for acute rejection from 1988–2002, found no difference in allograft survival in the first 5 years posttransplant in recipients with *APOL1* high-risk genotypes compared to those with *APOL1* low-risk genotypes.[10] However, carriage of two APOL1 risk haplotypes by the kidney donor was associated with inferior

kidney transplant survival,[11] suggesting that donor but not recipient *APOL1* genotype affects allograft survival. Recently, Zhang and colleagues described in a prospective cohort that included 73 AA KTR (23 with 2 RA and 30 with 1 RA) that the presence of two APOL1 RA was associated with an increased risk of any T cell-mediated rejection.[12]

We evaluated the outcomes of 221 KTR stratified by *APOL1* RA status in a prospective cohort. We hypothesized that recipients with *APOL1* high-risk status would have worse transplant outcomes.

Patients and Methods

Study Population

The Renal Transplant Outcome Study (RETOS) study recruited a cohort of incident kidney transplant recipients at three transplant centers in the Philadelphia area from 1999 to 2004.[13] In this sub study, all AA living and deceased donor adult KTR from two transplant centers who agreed to participate and provided a DNA sample (n=221) were included. Exclusion criteria included the presence of a previous liver, heart, or lung transplant, unable to communicate in English, or unwillingness to participate. If a participant had two kidney transplants during the recruitment period, only the first transplant was included. Subjects were followed up until the development of graft failure, death and up to a total of 2000 days. Graft failure was defined as return to dialysis, retransplantation, or relisting due to eGFR < 20 mL/min. Donor data and follow-up were assessed with direct chart abstraction and/or confirmed with UNOS data. Study was approved by the participating institutions' IRBs and all subjects provided informed consent.

Genotyping

Six selected variants, including rs73885319 (S342G) and rs60910145 (I384M) defining the G1 haplotype and rs71785313 (−N388Y389) defining the G2 haplotype within *APOL1* were genotyped using Taqman PCR assays (ABI, Foster City, California) as previously described.[14] We checked completeness of all SNP genotypes, estimated allele frequencies, tested Hardy-Weinberg Equilibrium (HWE), and inspected the linkage disequilibrium (LD) structures within the *APOL1* gene.

Statistical Analysis

The distribution of demographics based on recipient *APOL1* RA status is described and comparisons between groups were made using Wilcoxon independent tests and chi-square for continuous and dichotomous variables, respectively. Medians and interquartile range (IQR) were used to summarize continuous and nonparametric variables, while proportions were used to describe categorical variables. KTR were stratified based on *APOL1* RA status. High-risk APOL1 was defined by the presence of 2 RA and low-risk APOL1 was defined by the presence of 0 or 1 RA.

The primary outcome of the study was allograft failure (interval between date of transplant and graft loss). Competing risk models were used to estimate hazard ratios (HR) for graft failure for those with high-risk status carrying two *APOL1* RA compared with the *APOL1*

low-risk group with zero or one *APOL1* RA. Analyses were performed at 1- and 3-years post transplantation. We determined the unadjusted associations of recipient and donor characteristics with the primary outcome. We then adjusted for variables with statistical significance defined by a p-value ≤0.05. A multistate survival model was also performed to assess acute rejection considering acute rejection as an intermediate state before graft failure or death. Kaplan-Meier Survival Curves and log-rank tests for survivor function were generated to compare graft survival between *APOL1* RA groups. All statistical analysis was performed using Stata 14 software (StataCorp. 2015, College Station, TX).

Results

Table 1 describes the baseline characteristics of our cohort stratified by *APOL1* RA. Approximately 43% of participants carried two *APOL1* RA. KTR with *APOL1* high-risk status were younger compared to those with low-risk status (median 42(IQR 32.5, 52) vs 51(IQR 40, 58) years old, P<0.0001). There were no differences in comorbidities between groups except for a higher prevalence of diabetes in the low-risk group. Donor and transplant characteristics were also similar between groups. The total person-time at risk was 455 318 person-days.

There were a total of 69 (32.2%) graft failures and 58 (26.2%) deaths during the follow-up period. There was no difference in allograft failure frequency by *APOL1* risk status during follow-up. Twenty-six (27%, n= 96) graft failures occurred in recipients with *APOL1* high-risk status compared to 25 (20%, n=125) graft failures in those with *APOL1* low-risk status. There was a trend of higher rates of acute rejection within the first year posttransplant in the APOL1 high-risk compared to the APOL1 low-risk (13.5% vs 4.2%, p-value 0.06) but similar rates were reflected at longer follow-up (22.4 vs 17.1, p value 0.39). There was no difference in death by *APOL1* -risk status.(P=0.11).

At first year posttransplant APOL1 high RA in the recipient was associated with a higher risk of graft failure (SHR 3.3 [1.05–10.55] p-value 0.04) and remained significant in our multivariate model. Additional characteristics included in the kidney donor profile index were not associated with graft failure at first-year posttransplant (Table 2). At 3 years of follow-up there was a higher risk of graft failure in recipients with APOL1 high RA (SHR 2.1 [1.01–4.29] p-value 0.05) but the effect was diminished after adjusting by additional donor and recipient characteristics including age, history of diabetes, cardiovascular disease, cause of death and history of rejection within first-year posttransplant (Table 3). No significance was found between APOL1 RA groups and graft failure at 3 years follow-up. Figure 1 shows the Kaplan-Meier Survival graph stratified according to *APOL1* high-risk and low-risk status. Log-rank tests for survivor function were significant at 1 year and 3 years (p-value=0.03 and p-value=0.05, respectively).

Discussion

We report that *APOL1* high-risk status in KTR was associated with earlier graft failure following transplantation. Individuals with both *APOL1* high RA genotype showed lower graft survival time compared to recipients with only one or neither of the two RA within the

first-year posttransplant. We also found that KTR with two *APOL1* RA were transplanted at a significantly younger age as previously described.[10,15]

APOL1 high-risk status increases the risk of CKD and progression from CKD to ESKD among AA in the general population.[16] In the Atherosclerosis Risk in Communities (ARIC) Study, participants without CKD at baseline but with 2 *APOL1* RA had a 1.49-fold increased risk of CKD and a 1.88-fold increased risk of ESKD compared with low-risk APOL1. *APOL1* high-risk status has been associated with more rapid progression of CKD in the AA with established CKD, and increased albuminuria.[17] In a population-based cohort of young black and white adults with initially preserved kidney function, Peralta et al demonstrated that young black adults with *APOL1* high-risk status had the highest rate of incident albuminuria and more rapid decline in GFR.[18] Our work has shown that *APOL1* high-risk status confers a similar risk for CKD in Hispanics with African ancestry.[9]

Histologically, the presence of APOL1 high-risk status has been associated with an increased frequency of segmental and global glomerulosclerosis with collapsing features, tubular injury, and interstitial fibrosis.[19] A proposed hypothesis is that APOL1 is expressed in podocytes and the expression of the G1 and G2 variant proteins leads to podocyte injury by enhanced lysosomal membrane permeability or mitochondrial dysfunction, often magnified in the presence of other adverse host factors.[20] Others have found that 2 risk alleles lead to an enhanced APOL1 channel function that directly damages podocytes and ultimately lower podocyte density compared.[21,22] A recent 13-week study of 13 individuals who had two APOL1 variants, biopsy-proven focal segmental glomerulosclerosis, and proteinuria showed that daily inaxaplin reduced proteinuria by 48%.[23]

Lee et al in a retrospective study of KTR from both living donors (n=27) and deceased donors (n=92) initially recruited to an acute rejection trial with a follow-up period up to 5 years found no differences in graft survival by number of *APOL1* RA (P=0.85).[10] Their prevalence of *APOL1* high-risk status was similar to ours at 48.7% in the recipients. In a cohort of 106 Black donors with 15% having high-risk *APOL1* status, the investigators reported higher graft loss and rapid eGFR decline in recipients of kidneys from donors carrying two *APOL1* RA. This cohort failed to assess the effect of recipient genotype on graft outcome giving missing data on recipient genotype.[24] Recently, using two large prospective cohorts, Zhang et al showed that recipient *APOL1* high-risk status was associated with death-censored kidney allograft survival and rejection episodes. Even though the number of recipients with two APOL1 RA was low, there was an association between the number of recipients *APOL1* G1/G2 alleles and an increased risk of death-censored allograft loss within the subgroup of African American and Hispanic recipients (HR = 2.36; P = 0.003). They also found that recipients with two *APOL1* RA had an increased risk of any form of T cell–mediated rejection up to 2 years after transplantation.[12] In our cohort, we found a trend toward higher rates of acute rejection within the first year. Unfortunately, given the era of our cohort no clinical information regarding the differentiation between antibody-mediated or cellular-mediated rejection is available.

Our data supports that APOL1 risk status in recipients has an impact on graft survival outcomes within the first-year posttransplant. Impact diminishes after the first-year

posttransplant likely when other donor and recipient characteristics such as acute rejection have increased importance (Figure 2).

Our study has several strengths, such as the prospective nature as well as being the largest cohort of kidney recipients with two *APOL1* RA up to this date. However, we acknowledge it is still a small cohort unable to fully assess the associated risk of graft failure with known predictors of poor outcomes in kidney transplant recipients. We also acknowledge the limitations encountered by the recruitment era of this cohort. BK virus surveillance, improved identification of antibody-mediated rejection or monitoring of donor specific antibodies were not available when our cohort was recruited and we are not able to determine how they could have impacted our outcomes. Although donor APOL1 RA status has been associated with inferior graft outcomes in other studies,[11,24] we could not address this issue since APOL1 genotypes were not available for the donors in this cohort.

In conclusion, *APOL1* high-risk status in KTR was associated with early kidney graft failure. Further research is needed to investigate the role of the combination of the recipient and donor APOL1 genotypes on kidney transplant outcomes. The *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO) funded by NIH was established in 2017. Studies designed and conducted by the APOLLO Network should help to determine the impact of *APOL1* RA on outcomes in KTR who received kidneys from *APOL1* high-risk donors, as well as follow the course of AA kidney donors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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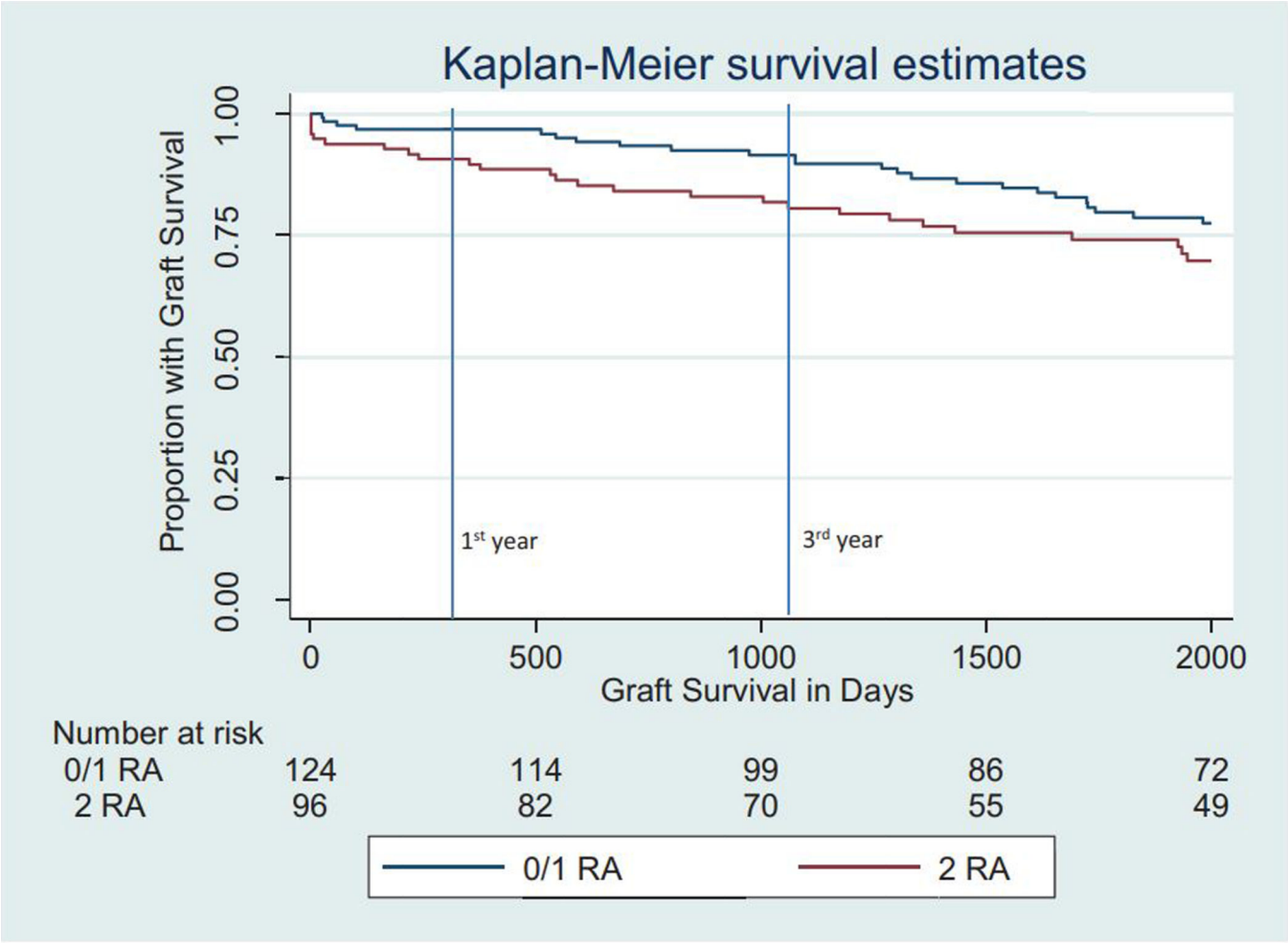

Figure 1.

Kaplan-Meier survival estimates of graft survival stratified by *APOL1* RA status throughout follow-up RA risk allele.

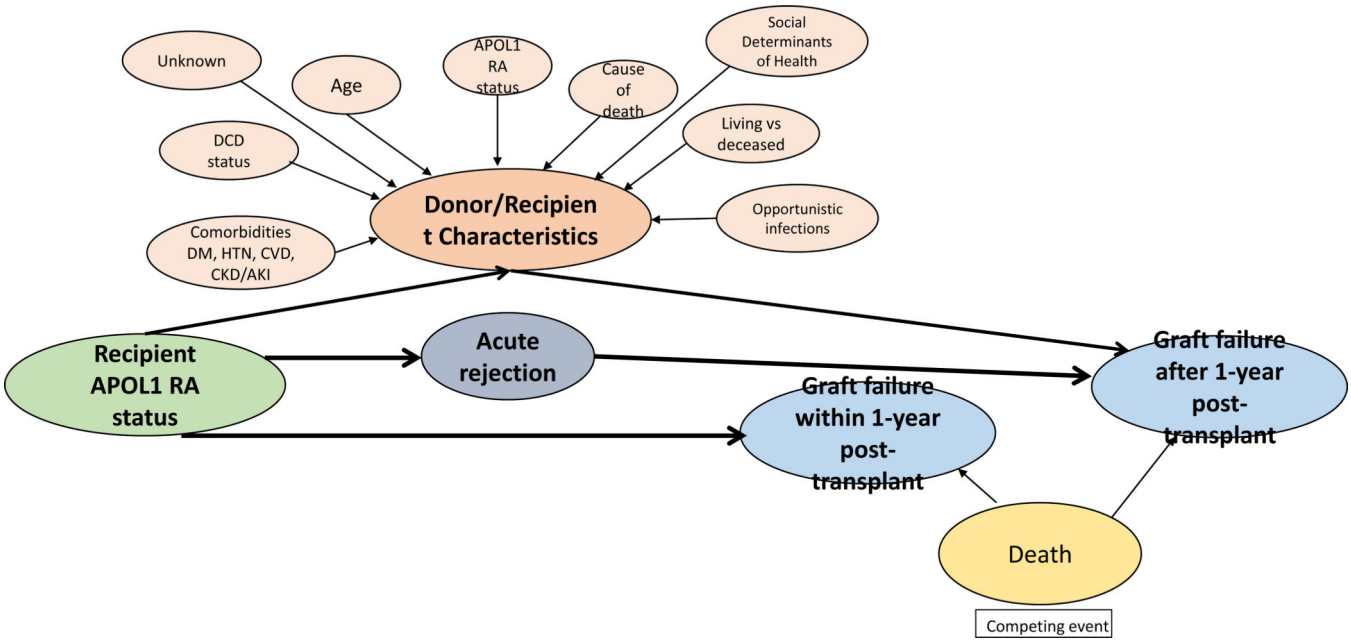

Figure 2.

Directed acyclic graph of the association of recipient *APOL1* RA status and graft failure. AKI, acute kidney injury; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; RA, risk allele.

Table 1.

Demographic and clinical characteristics of participants.

	Number of *APOL1* RAs in kidney recipient		
	High-risk 2 RAs (n=96)	**Low-risk 0 or 1 RA (n=125)**	***P***
Recipient characteristics			
Male sex, n (%)	56 (58.33)	67 (53.6)	0.48
Age at transplant, median (IQR), y	42 (32.5–52)	51 (40–58)	<0.001
Diabetes, n (%)	22 (22.92)	60 (48)	<0.001
Hypertension, n (%)	94 (97.92)	121 (96.80)	0.61
Hypercholesterolemia, n (%)	40 (41.67)	60 (48)	0.35
Cardiovascular diseases, n (%)	30 (31.35)	42 (34)	0.59
Donor characteristics			
Living donor, n (%)	26 (27.08)	30 (24.59)	0.68
Age at transplant, median (IQR), y	42 (26–50)	42.5 (27–53)	0.33
Body mass index, median (IQR), kg/m^2	25.11 (22.39–29.98)	25.29 (22.09–29.86)	0.90
Ethnicity, n (%)			0.29
White	55 (57.39)	66 (54.1)	
Black/African American	30 (31.25)	47 (38.52	
Asian	9 (9.38)	5 (4.1)	
Other	2 (2.08)	4 (5.28)	
DCD status, n (%)	7 (7.29)	15 (12)	0.25
Cause of death (CVA), n (%)	36 (37.5)	42 (37.5)	0.55
Diabetes, n (%)	7 (9.86)	6 (6.06)	0.61
Hypertension, n (%)	20 (28.17)	21 (21.21)	0.54
Last creatinine, median (IQR)	1.0 (0.7–1.5)	1.0 (0.8–1.3)	0.89
Transplant characteristics, n (%)			
Induction therapy			0.95
ATG	35 (36.46)	43 (34.40)	
Basiliximab	6 (6.25)	8 (6.40)	
No induction	55 (57.29)	74 (59.2)	
Acute rejection within first year	7(13.46)	3(4.17)	0.06
Acute rejection throughout follow up	17 (17.7)	28 (22.4)	0.39

ATG, antithymocyte globulin; CVA, cerebrovascular accident; DCD, donation after circulatory death; IQR, interquartile range; RA, risk allele.

Table 2.

Adjusted and unadjusted SHRs for graft failure 1 year after transplant.

	UNADJUSTED SHR (95% CI)	*P*	Multivariable model, SHR (95% CI)	*P*
APOL1 risk, high risk	3.3 (1.1–10.6)	0.04	3.2 (1.0–10.4)	0.05
Recipient age at time of transplant, y	0.9 (0.9–1.0)	0.14		
Acute rejection within first year	3.7 (0.9–15.7)	0.08		
Diabetes in recipient, yes	0.1 (0.02–0.9)	0.05	2.5 (0.5–12.1)	0.25
Cardiovascular disease recipient, yes	0.2 (0.02–1.1)	0.06		
Donor age at time of transplant, y	1.03 (0.9–1.1)	0.16		
Diabetes in donor, yes	2.8 (0.6–12.6)	0.18		
Hypertension in donor, yes	0.3 (0.04–2.5)	0.28		
Donor race, AA	0.7 (0.2–2.3)	0.59		
BMI donor	0.9 (0.9–1.04)	0.23		
HCV donor, yes	0.9 (0.2–3.9)	0.91		
Living donor, yes	1.2 (0.4–3.7)	0.79		
Deceased donor cause of death (cerebrovascular disease)	2.5 (0.9–7.1)	0.09		
DCD status, yes	2.5 (0.7–8.9)	0.15		
Last creatinine donor	0.6 (0.1–3.7)	0.61		

AA, African American; BMI, body mass index; CI, confidence interval; DCD, donation after circulatory death; HCV, hepatitis C virus; SHR, subdistribution hazard ratio.

Table 3.

Adjusted and unadjusted SHRs for graft failure 3 years after transplant.

	Unadjusted SHR (95% CI)	*P*	Multivariable model, SHR (95% CI)	*P*
APOL1 risk (high risk)	2.1 (1.01–4.29)	0.05	1.45 (0.7–3.02)	0.32
Recipient age at time of transplant, y	0.9 (0.9–0.99)	0.03	0.9 (0.9–1.1)	0.31
Acute rejection within first year	6.7 (2.9–14.7)	<0.001	5.9 (2.3–14.9)	<0.001
Diabetes in recipient	0.2 (0.5–0.6)	0.03	0.3 (0.1–0.8)	0.02
Cardiovascular disease recipient, yes	0.3 (0.1–0.78)	0.02	0.3 (0.1–0.8)	0.01
Donor age at time of transplant, y	1.03 (1.01–1.1)	0.02	1.3 (0.9–1.1)	0.09
Diabetes in donor, yes	2.02 (0.6–6.9)	0.18		
Hypertension in donor, yes	1.3 (0.6–2.9)	0.53		
Donor race, AA	0.8 (0.4–1.7)	0.51		
BMI donor	0.9 (0.9–1.03)	0.29		
HCV donor, yes	0.8 (0.3–2.4)	0.73		
Living donor, yes	0.9 (0.4–2.1)	0.79		
Deceased donor cause of death (cerebrovascular disease)	2.6 (1.3–5.3)	0.01	1.6 (0.6–4.12)	0.35
DCD status, yes	1.02 (0.3–3.5)	0.97		
Last creatinine donor	0.8(0.4–1.7)	0.61		

AA, African American; BMI, body mass index; CI, confidence interval; CVC, ; DCD, donation after circulatory death; HCV, hepatitis C virus; SHR, subdistribution hazard ratio.