Research Article

Survival Advantage of African American Dialysis Patients with End-Stage Renal Disease Causes Related to APOL1

Paungpaga Lertdumrongluk^{a, b} Elani Streja^{a, d} Connie M. Rhee^{a, d}
Hamid Moradi^a Yongen Chang^a Uttam Reddy^a Ekamol Tantisattamo^a
Kamyar Kalantar-Zadeh^{a, d} Jeffrey B. Kopp^c

^aHarold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA, USA; ^bPanyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University, Nonthaburi, Thailand; ^cKidney Disease Branch, NIDDK, Bethesda, MD, USA; ^dUniversity of California Irvine School of Medicine, Orange, CA, USA

Keywords

Focal segmental glomerulosclerosis · Hypertension-attributed kidney disease · Diabetic kidney disease · Cardiovascular mortality

Abstract

Background: Observational studies show that African American (AA) dialysis patients have longer survival than European Americans. We hypothesized that apolipoprotein L1 (*APOL1*) genetic variation, associated with nephropathy in AAs, contributes to the survival advantage in AA dialysis patients. **Methods:** We examined the association between race and mortality among 37,097 adult dialysis patients, including 54% AAs and 46% European Americans from a large dialysis organization (entry period from July 2001 to June 2006, follow-up through June 2007), within each cause of end-stage renal disease (ESRD) category associated with *APOL1* renal risk variants using Cox proportional hazard models. **Results:** AA dialysis patients had numerically lower mortality than their European American counterparts for all causes of ESRD. The mortality reduction among AAs compared to European Americans was statistically significant in patients with ESRD attributed to diabetes mellitus, hypertension, and *APOL1*-enriched glomerulonephritis (GN) (HR [95% CI]: 0.69 [0.66–0.72], 0.73 [0.68–0.79], and 0.89 [0.79–0.99], respectively); these are conditions in which *APOL1* variants promote kidney

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Jeffrey B. Kopp, MD
Kidney Diseases Branch, NIDDK, NIH
10 Center Dr, 3N116
Bethesda, MD 20892–1268 (USA)
E-Mail jbkopp@nih.gov

disease. By contrast, the significant survival advantage of AA dialysis patients was not observed in patients with ESRD attributed to other kidney disease (including polycystic kidney disease, interstitial nephritis, and pyelonephritis) and other GN, which are not associated with APOL1 variants. **Conclusions:** These data suggest the hypothesis that the relative survival advantage of AA dialysis patients may be related to APOL1 variation. Further large population-based genetic studies are required to test this hypothesis. © 2019 Published by S. Karger AG, Basel

Introduction

In the general US population, African Americans (AA) have a shorter life expectancy than European Americans, whereas AA dialysis patients have longer survival than their European American counterparts [1–4]. The racial survival disparities have been described as the AA survival paradox [3]. Possible contributing factors to the survival paradox include nutritional status, inflammation, psychosocial status, and genetic variation [5–8].

Apolipoprotein L1 (APOL1) coding variants are strongly associated with increased risk for nondiabetic nephropathy in AA, most notably for HIV-associated nephropathy (HIVAN), focal segmental glomerulosclerosis (FSGS), and hypertension-attributed end-stage renal disease (HA-ESRD). Two APOL1 risk alleles are present in 12% of the AA population as controls, 72% of AA with FSGS, and 38% of AA with HA-ESRD [9]. Studies on the effect of APOL1 renal risk variants on cardiovascular disease (CVD) and death showed conflicting results [10]. Some studies reported the association between APOL1 renal risk variants and higher risk for CVD events and mortality [11, 12], whereas others observed the protective relationship between APOL1 renal risk variants and development of subclinical CVD, cerebrovascular disease, and death [13–15]. We hypothesized that AA have better survival than European Americans among dialysis patients with ESRD causes associated with APOL1. We examined whether the all-cause and cardiovascular mortality of AA compared to European Americans differs by APOL1-associated causes of ESRD in a large and contemporary cohort of maintenance dialysis patients from a large dialysis organization (LDO).

Materials and Methods

Study Population

We extracted and examined data from all individuals with ESRD who underwent hemodialysis or peritoneal dialysis between July 2001 and June 2006 in any of the 580 US outpatient dialysis facilities of a LDO. The baseline quarter for each patient was the earliest calendar quarter in which the patient's dialysis duration was >90 days. APOL1-associated FSGS had a peak onset among patients aged between 15 and 45 years [16]; therefore, we limited the analysis to the patients aged between 18 and 60 years. Patients aged between 18 and 60 years, who were AA or European American, had a dialysis duration of >90 days, received dialysis during the baseline quarter, with the primary cause of ESRD, quarterly baseline data, and follow-up periods were included ($n = 41,496$). Although acquired immune deficiency syndrome (AIDS) nephropathy is strongly associated with APOL1 variants [17], the limited survival until the advent of effective combined anti-retroviral therapy was largely driven by opportunistic infections [18]. Therefore, patients with uncertain etiology of ESRD ($n = 1,372$), those with ESRD caused by AIDS nephropathy, congenital diseases, neoplasms, and miscellaneous conditions ($n = 3,027$) were excluded, resulting in 37,097 patients for this analysis (Fig. 1). The study was approved by the institutional review committee of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. The requirement for a written consent was exempted due to large sample size, patient anonymity, and the noninvasive nature of the research.

Fig. 1. Algorithm of study cohort creation. ESRD, end-stage renal disease; AIDS, acquired immunodeficiency syndrome.

Clinical and Demographic Measures

The creation of the cohort has been described previously [8]. Demographic data on age, sex, race, dialysis duration, dialysis modality, primary insurance, and presence of diabetes mellitus (DM) at baseline were obtained from the LDO database. History of preexisting comorbidities and tobacco smoking were obtained by linking the LDO database to the data from Medical Evidence Form 2728 from the US Renal Data System (USRDS). Available preexisting comorbidities were grouped into nine categories: atherosclerotic heart disease, congestive heart failure, other cardiac diseases, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), cancer, and nonambulatory state. Race was self-reported by dialysis patients and included the term Black and White. Non-Hispanic Blacks and Whites represented AA and European Americans, respectively. Dialysis duration was defined as the period of time between the first day of dialysis treatment and the day that the patient entered the cohort.

The primary cause of ESRD for each patient was obtained by linking the LDO database to the data from Medical Evidence Form 2728 from the USRDS. The primary cause of ESRD was grouped into five categories (DM, hypertension, APOL1-enriched glomerulonephritis [GN], other kidney disease, and other GN), which are known to differ in the prevalence of APOL1 renal risk alleles. The first three categories have been associated with APOL1 risk alleles. APOL1 risk variants have been associated with progression to ESRD regardless of diabetes status [19]. However, Ma et al. [15] found that APOL1 risk variants have been associated with longer hemodialysis survival only in nondiabetic AA patients. Hypertension-attributed ESRD (histologically likely to be arterionephrosclerosis) in AA is associated with APOL1 variants (OR 4.6 [20]). APOL1-enriched GN comprised FSGS (APOL1 OR 17 [17]), lupus nephritis (APOL1 OR 5 [21]), nephropathy due to heroin abuse and related drugs (recently hypothesized to be related to APOL1 variants, in light of the striking predilection among AA, although genetic data are lacking) [22], and histologically not examined GN (which we assumed to include arterionephrosclerosis). Two categories including “other kidney disease” and “other GN” have not been associated with APOL1 risk alleles or with AA predilection, and these served as comparison groups. The category “other kidney disease” included polycystic kidney disease, interstitial nephritis, and pyelonephritis. The category “other GN” consisted of membranous nephropathy, membranoproliferative GN, IgA nephropathy, IgM nephropathy, rapidly progressive GN, postinfectious GN, other proliferative GN, Henoch-Schönlein

Table 1. Baseline characteristics of 37,097 maintenance dialysis patients stratified by race

	All	Race		<i>p</i> value*
		African-American	European American	
Number of patients	37,097 (100%)	20,154 (54%)	16,943 (46%)	NA
Age, years	47±10	46±10	48±10	<0.001
Female, %	43	45	41	<0.001
Primary cause of ESRD, %				
DM	45	40	52	<0.001
Hypertension	29	40	15	<0.001
APOL1-enriched GN ^a	13	14	12	<0.001
Other kidney disease ^b	8	3	13	<0.001
Other GN ^c	5	3	8	<0.001
Hemodialysis	89	92	85	<0.001
Dialysis duration, %				
<6 months	53	49	58	<0.001
6 to <24 months	18	18	18	0.22
2 to <5 years	20	23	17	<0.001
≥5 years	9	10	7	<0.001
Primary insurance, %				
Medicare	59	61	56	<0.001
Medicaid	7	10	4	<0.001
Other	34	29	40	<0.001
Comorbidities, %				
DM	56	53	60	<0.001
Atherosclerotic heart disease	13	9	17	<0.001
Cancer	1.8	1.3	2.4	<0.001
Congestive heart failure	21	21	21	0.04
COPD	3.8	2.6	5.2	<0.001
Cerebrovascular disease	6	5	6	0.01
Hypertension	81	84	78	<0.001
Other cardiac diseases	3.3	2.6	4.1	<0.001
Peripheral vascular disease	8	5	11	<0.001
Nonambulatory state	2.1	1.7	2.5	<0.001
Current smoking	8	7	9	<0.001

Continuous variables are expressed as mean ± SD, and categorical variables are expressed as percentages. ESRD, end-stage renal disease; DM, diabetes mellitus; GN, glomerulonephritis; COPD, chronic obstructive pulmonary disease. * *t* test for continuous variable and χ^2 test for categorical variables. ^a APOL1-enriched GN included focal segmental glomerulosclerosis, lupus nephritis, nephropathy due to heroin abuse and related drugs, and histologically not examined GN. ^b Other kidney disease included polycystic kidney disease, interstitial nephritis, and pyelonephritis. ^c For other GN, see the Methods section.

syndrome, scleroderma, hemolytic uremic syndrome, polyarteritis, granulomatosis with polyangiitis, other vasculitis, Goodpasture syndrome, and other secondary GN.

Outcome Measures

Patients were followed for outcomes including all-cause mortality and cardiovascular mortality until June 30, 2007. All-cause mortality was defined by date of death if it occurred during the cohort period. The causes of death were obtained from the USRDS, and cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, congestive heart failure, cerebrovascular accident, or other cardiac diseases. Patients who received a kidney transplant (including 2,121 AA and 3,346 European American dialysis patients) or left LDO dialysis clinics were censored at the time of event.

Table 2. All-cause mortality rates by race and primary cause of ESRD among 37,097 maintenance dialysis patients

Primary cause of ESRD	All			African American			European American		
	pa- tients, <i>n</i>	death, <i>n</i> (crude death rate, %)	crude all-cause mortality rate ^a (95% CI)	pa- tients, <i>n</i>	death, <i>n</i> (crude death rate, %)	crude all-cause mortality rate ^a (95% CI)	pa- tients, <i>n</i>	death, <i>n</i> (crude death rate, %)	crude all-cause mortality rate ^a (95% CI)
DM	16,816	7,994 (48)	184 (180–188)	8,072	3,566 (44)	155 (150–160)	8,744	4,428 (51)	216 (210–222)
Hypertension	10,607	3,653 (34)	113 (110–117)	8,087	2,652 (33)	103 (99–107)	2,520	1,001 (40)	153 (144–163)
APOL1-enriched GN ^b	4,906	1,369 (28)	93 (89–99)	2,855	777 (27)	86 (80–92)	2,051	592 (29)	106 (98–115)
Other kidney disease ^c	2,907	822 (28)	103 (96–110)	648	190 (29)	94 (81–108)	2,259	632 (28)	106 (98–115)
Other GN ^d	1,861	479 (26)	98 (90–107)	492	141 (29)	94 (80–111)	1,369	338 (25)	100 (90–111)
Total	37,097	14,317 (39)	139 (136–141)	20,154	7,326 (36)	120 (117–122)	16,943	6,991 (41)	166 (163–170)

DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis. ^a Crude all-cause mortality rate per 1,000 person-years. ^b APOL1-enriched GN included focal segmental glomerulosclerosis, lupus nephritis, nephropathy due to heroin abuse and related drugs, and histologically not examined GN. ^c Other kidney disease included polycystic kidney disease, interstitial nephritis, and pyelonephritis. ^d For other GN, see the Methods section.

Statistical Analyses

Baseline characteristics within each race were analyzed as proportions, and normally or near normally distributed data summary are given as mean ± SD. Crude death rates within groups of primary cause of ESRD and race were calculated as the number of events per 1,000 person-years of follow-up. Differences in mortality were examined using time-to-event analysis. Cumulative survival curves were derived by the Kaplan-Meier method and compared using the log-rank test. We evaluated the association of race with all-cause and cardiovascular mortality within each primary cause of ESRD category. For each analysis, two models with multivariable adjustments were examined: (1) unadjusted models included race and entry calendar quarter and (2) case-mix adjusted models, which included all of the variables in the unadjusted model plus sex, age, presence of diabetes, nine pre-existing comorbidities, history of tobacco smoking, dialysis duration categories, dialysis modality, and primary insurance.

Missing covariate data were imputed by the means or medians of the existing values. Two-sided *p* values <0.05 were considered to be statistically significant. All statistical analyses were performed using Stata version 13.0 (Stata, College Station, TX, USA).

Results

The baseline demographic and clinical characteristics of the 37,097 maintenance dialysis patients (including 33,033 patients on hemodialysis and 4,064 patients on peritoneal dialysis), stratified by race, are summarized in Table 1. Cohort age at baseline was 47 ± 10 years, 43% of the patients were women, and 54% were AA. The primary cause of ESRD was DM for 16,816 (45%), hypertension for 10,607 (29%), APOL1-enriched GN for 4,906 (13%), other kidney disease for 2,907 (8%), and other GN for 1,861 (5%) patients. As expected, due to the way groups were defined, the proportion of ESRD attributed to hypertension and APOL1-enriched GN was higher among AA (40% for hypertension and 14% for APOL1-enriched GN) than among European Americans (15% for hypertension and 12% for APOL1-enriched GN). Compared to European Americans, AA were younger, more likely to be female, and included higher proportions of patients who were dialyzed for more than 2 years. AA were more likely to have hypertension, while they were less likely to have DM, atherosclerotic heart disease, cancer, COPD, cerebrovascular disease, peripheral vascular disease, and to be current smokers.

A total of 14,317 (39%) patients died during the follow-up period. The crude mortality rate was 139/1,000 person-years (95% CI 136–141) during a median (IQR) follow-up of 2.5 (1.4–4) years. CVD accounted for 6,054 (42%) deaths. The crude mortality rates were

Fig. 2. Survival curves by race and primary cause of ESRD. **a** DM. **b** Hypertension. **c** APOL1-enriched GN. **d** Other kidney disease included polycystic kidney disease, interstitial nephritis, and pyelonephritis. **e** For other GN, see the Methods section. DM, diabetes mellitus; ESRD, end-stage renal disease; GN, glomerulonephritis.

Table 3. Hazard ratios of all-cause and cardiovascular mortality in African American compared to European Americans as the reference group according to primary cause of ESRD

Primary cause of ESRD	All-cause mortality, HR (95% CI)		Cardiovascular mortality, HR (95% CI)	
	unadjusted ^a	case-mix adjusted ^b	unadjusted ^a	case-mix adjusted ^b
DM (<i>n</i> = 16,816)	0.68 (0.65–0.71)	0.69 (0.66–0.72)	0.66 (0.62–0.71)	0.68 (0.63–0.73)
Hypertension (<i>n</i> = 10,607)	0.65 (0.60–0.69)	0.73 (0.68–0.79)	0.66 (0.59–0.74)	0.76 (0.68–0.86)
APOL1-enriched GN ^c (<i>n</i> = 4,906)	0.78 (0.70–0.87)	0.89 (0.79–0.99)	0.84 (0.70–1.01)	0.94 (0.78–1.14)
Other kidney disease ^d (<i>n</i> = 2,907)	0.85 (0.72–1.00)	0.91 (0.77–1.07)	0.93 (0.71–1.21)	0.97 (0.74–1.28)
Other GN ^e (<i>n</i> = 1,861)	0.90 (0.74–1.10)	0.95 (0.77–1.17)	0.95 (0.68–1.33)	1.05 (0.73–1.49)

ESRD, end-stage renal disease; DM, diabetes mellitus; GN, glomerulonephritis; HR, hazard ratio. ^a Unadjusted model included race and entry calendar quarter. ^b Case-mix model was adjusted for sex, age, presence of diabetes, 9 pre-existing comorbidities, history of tobacco smoking, dialysis duration categories, dialysis modality, and primary insurance. ^c APOL1-enriched GN included focal segmental glomerulosclerosis, lupus nephritis, nephropathy due to heroin abuse and related drugs, and histologically not examined GN. ^d Other kidney disease included polycystic kidney disease, interstitial nephritis, and pyelonephritis. ^e For other GN, see the Methods section.

120/1,000 person-years (95% CI 117–122) and 166/1,000 person-years (95% CI 163–170) in AA and European Americans, respectively. All-cause mortality rates within each primary cause of ESRD category stratified by race are summarized in Table 2. AA had a lower mortality rate than European Americans in all primary causes of ESRD categories. Figure 2 shows the survival curves among AA and European Americans during follow-up by cause of ESRD. AA had a higher survival rate than European Americans in ESRD attributed to DM, hypertension, APOL1-enriched GN, and other kidney disease, whereas the survival rates among AA and European Americans were not different in other GN-attributed ESRD.

In an unadjusted Cox proportional hazard model, AA had a lower risk of all-cause mortality compared to European Americans for ESRD attributed to DM, hypertension, APOL1-enriched GN, and other kidney disease. In case-mix adjusted analyses, all-cause mortality reductions among AA versus European Americans were attenuated in all causes of ESRD, but remained statistically significant in the DM (HR [95% CI]: 0.69 [0.66–0.72]), hypertension (0.73 [0.68–0.79]), and APOL1-enriched GN categories (0.89 [0.79–0.99]). In contrast, the numerically lower mortality risks of AA compared to European Americans were not statistically significant in the other kidney disease category (0.91 [0.77–1.07]) and other GN category (0.95 [0.77–1.17]) (Table 3). In case-mix adjusted analyses, cardiovascular mortality reductions among AA versus European Americans were statistically significant only for the DM category (0.68 [0.63–0.73]) and the hypertension category (0.76 [0.68–0.86]) (Table 3). In models containing interaction terms for race and cause of ESRD categories, interaction terms were statistically significant, confirming that there were differential associations between race and mortality in different cause of ESRD categories (P-interaction = 0.003 for all-cause mortality and P-interaction = 0.005 for cardiovascular mortality).

Discussion

In this cohort of 37,097 US dialysis patients, we found that AA had longer survival than European Americans among dialysis patients with ESRD attributed to DM, hypertension, and APOL1-enriched GN, whereas the magnitude of the AA survival benefit was not statistically

significant for ESRD attributed to other kidney disease and other GN. When cardiovascular mortality was considered, a significant AA survival advantage was observed among those with ESRD attributed to DM and hypertension but not for APOL1-enriched GN, other kidney disease, or other GN.

Our findings suggest the hypothesis that *APOL1* genetic variants could contribute to the noncardiovascular survival advantage among AA versus European American dialysis patients. These results extend the work of Ma et al. [15] who made a similar observation, namely that *APOL1* high risk genotypes are associated with longer hemodialysis survival in nondiabetic subjects ($n = 275$, HR 0.57) but not in diabetic subjects ($n = 450$, HR 1.29). In our study, which lacks *APOL1* genotype data but has larger sample sizes, the AA survival advantage was observed in the *APOL1*-associated nephropathy group including ESRD attributed to DM, hypertension, and APOL1-enriched GN. Parsa et al. [19] observed that *APOL1* risk variants have been associated with higher rates of ESRD and progression of chronic kidney disease among diabetic AA subjects, and the prevalence of two *APOL1* risk alleles was 19% among AA with DM who progressed to ESRD [19]. *APOL1* risk variants are associated with hypertension-attributed nephropathy and its progression in AA [20, 23]. The presence of two *APOL1* risk alleles was 23% in AA with hypertension-attributed nephropathy, and it was 49% among those who progressed to ESRD [20]. In our study, APOL1-enriched GN category consisted of FSGS, lupus nephritis, and histologically not examined GN. The previous studies found that 72% of AA subjects with FSGS had two *APOL1* risk alleles [17], and 25% of AA patients with ESRD attributed to lupus nephritis had two *APOL1* risk alleles [24]. Patients characterized as having histologically not examined GN likely had a primary kidney disease, and it is also likely that many, if not most, had either FSGS or arterionephrosclerosis; therefore, in the present study, they were categorized as APOL1-enriched GN.

Thus, we found the AA survival advantage among dialysis patients with APOL1-associated nephropathies, with the most potent survival benefit observed in DM-attributed ESRD. We detected that the magnitudes of mortality risk reduction in AA dialysis patients with ESRD attributed to hypertension and APOL1-enriched GN were lower than observed in those with DM-attributed ESRD. We speculate that APOL1-G0, compared to the risk variants, affects cardiovascular molecular pathways to mortality in DM-attributed ESRD and possibly hypertension-attributed ESRD that are distinct or particularly activated, compared to those driving mortality in GN. In our study, we restricted the analyses to subjects between 18 and 60 years of age because *APOL1*-associated FSGS had a peak onset among patients aged between 15 and 45 years [16]. Kucirka et al. [25] found the survival advantage of AA dialysis patients only in subjects older than 50 years, while AA younger than 50 years had a higher risk of death compared to their White counterparts. One difference between the two studies was that Kucirka et al. adjusted for age-stratified differences in renal transplantation rates between AA and European Americans. From these studies, it appears that multiple factors may contribute to survival differences between AA and European American populations, and these interactions among APOL1 genotype, cause of kidney disease, age and comorbidities, with regard to dialysis survival, are likely to be complex.

The associations of *APOL1* renal risk variants with CVD and death have been inconsistent in patients without ESRD. Freedman et al. [14] found an association between *APOL1* nephropathy risk variants and lower levels of subclinical atherosclerosis and reduced risk of all-cause mortality in AA with DM type 2. However, some studies suggested that the *APOL1* risk alleles are associated with increased risk of CVD in AA [11, 12], while another study failed to detect the association between *APOL1* risk variants and CVD [26]. Study design and outcome ascertainment differences may explain such differences [11, 26, 27].

Several limitations of this study should be mentioned. First, our analyses were based on observational data, and hence a causal relationship could not be established from the study

results. We evaluated the association of *APOL1* genetic variation and survival among AA compared to European American dialysis patients by comparing survival in ESRD groups categorized by potential associations with *APOL1* risk alleles, but we lacked genotype data for subjects. *APOL1*-associated nephropathy in our study was categorized based on primary cause of ESRD obtained by the data from the USRDS; therefore, not all patients had biopsy-proven renal disease categorized in one of the five defined groups in our study. Since some patients may not truly have renal disease associated with *APOL1* risk alleles, this potential misclassification would tend to reduce the observed association and favor the null hypothesis. In addition, we lacked data on patient compliance with dialysis treatments, and information on comorbidities was not updated during follow-up, which may result in residual confounding. Last, our analysis of prevalent, rather than incident, dialysis patients introduced the potential for survivor bias.

In conclusion, we observed that the survival advantage of AA was restricted to dialysis patients with ESRD due to nephropathy associated with *APOL1* genetic variation. Our findings suggest that *APOL1* variation may contribute to the survival advantage of AA dialysis patients. Further population-based genetic studies in dialysis patients that include populations of African descent and others are warranted to confirm these findings.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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