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Outcomes Associated with Race in Males with Nondialysis-Dependent Chronic Kidney Disease

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Background and objectives: Blacks are over-represented among dialysis patients, but they have better survival rates than whites. It is unclear if the over-representation of blacks on dialysis is due to faster loss of kidney function or greater survival (or both) in predialysis stages of chronic kidney disease (CKD).

Design, setting, participants & measurements: We compared predialysis mortality, incidence of end stage renal disease (ESRD), and slopes of estimated GFR (eGFR) in 298 black *versus* 945 white male patients with moderate and advanced nondialysis-dependent CKD (NDD-CKD) from a single medical center. Mortality and ESRD incidence were compared in parametric survival models, and slopes of eGFR were assessed in mixed-effects models.

Results: Blacks had lower crude mortality and higher crude ESRD incidence. The lower mortality in blacks was explained by differences in case mix, especially a lower prevalence of cardiovascular disease, and the higher incidence of ESRD was explained by differences in case mix and baseline kidney function. The slopes of eGFR were similar in blacks and whites.

Conclusions: Lower mortality in black *versus* white patients is also observed in NDD-CKD and can be accounted for by differences in clinical characteristics. Higher mortality of black patients in earlier stages of CKD may result in the selection of a subgroup with fewer comorbidities and better survival in later stages of CKD. The higher crude ESRD rate in blacks appears to result from lower mortality in late stages of CKD, not faster progression of CKD.

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Among individuals with chronic kidney disease (CKD) receiving maintenance dialysis therapy, the proportion of black patients is significantly higher compared with their white counterparts (1,2). This can be explained by various factors (1): higher incidence of CKD in blacks (2), lower mortality rates in blacks with nondialysis-dependent CKD (NDD-CKD) (3), lower transplantation rates in blacks (4), and faster rates of CKD progression leading to higher end-stage renal disease (ESRD) incidence.

Previous studies have suggested that there was a higher population prevalence of CKD (3) or a faster rate of CKD progression in blacks (4). It is unclear, however, if differences in survival between black and white persons with moderate and advanced NDD-CKD can also have an impact on the higher ESRD incidence recorded in blacks. Because mortality and ESRD are competing end-points in NDD-CKD, lower mortality rates in blacks could inflate their ESRD rates independent of any differences in the prevalence or the progression of their kidney disease. Studies examining race-related survival have found paradoxically lower mortality in blacks compared with whites among dialysis patients (5–12), as opposed to the higher mortality seen in blacks with normal kidney function or mild to moderate CKD (13–17).

There have been no studies to examine race-related survival and progression of CKD concomitantly in patients with moderate and advanced NDD-CKD. Such studies could provide important information to guide future allocation of resources into areas that promise to best address the reasons behind the discrepant outcomes of racial minorities in the United States. To discern the relative contributions of differences in mortality and CKD progression to race-related outcomes, we examined all-cause mortality, ESRD incidence, and progression of CKD (defined as slopes of estimated GFR [eGFR]) concomitantly in an unselected group of 1243 male veterans with moderate and advanced NDD-CKD from a single medical center.

Materials and Methods

Study Population and Data Collection

We studied all 1259 outpatients referred for evaluation and treatment of NDD-CKD at Salem Veterans Affairs Medical Center (VAMC) between January 1, 1990, and June 30, 2007, and followed them until April 1, 2008. Ten female patients and six patients whose race was other than

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white or black were excluded; the final study population consisted of 1243 patients.

Patient characteristics (age, race, anthropometrics, BP, comorbidities including the Charlson index [18], medication use, and laboratory measurements) were recorded at the initial evaluation in the nephrology clinic, as detailed before(19,20). Race was ascertained from face-to-face encounters documented in the Nephrology Clinic at Salem VAMC. Values of body mass index, BP and laboratory measurements, and changes in medication utilization were recorded longitudinally during follow-up. Serum creatinine levels measured during outpatient visits were collected throughout the follow-up period until the occurrence of death, initiation of dialysis, or loss of follow-up (whichever occurred first) for the assessment of the CKD progression slopes. GFR was estimated using the abbreviated equation developed for the Modification of Diet in Renal Disease Study (MDRD) (21) and categorized according to the staging system introduced by the Kidney/Dialysis Outcome Quality Initiative (K/DOQI) Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification (22). All of the biochemical measurements were performed in a single laboratory at the Salem VAMC.

Statistical Analyses

Missing baseline values for variables that were subsequently measured during follow-up (4% of serum phosphorus, 3% of serum albumin, 6% of blood cholesterol, 2% of blood hemoglobin, 5% of white blood cell count [WBC], 5% of percent lymphocytes in WBC, and 2% of 24 h urine protein) were replaced by the mean of the subsequent values in the same individual. Missing data points for comorbidity index (1% missing), serum albumin (1% missing), phosphorus (3% missing), blood cholesterol (3% missing), and 24 h urine protein (6% missing) were than imputed by linear regression using all other variables as independent predictors. Smoking (5% missing) and body mass index (BMI, 14% missing) were analyzed as categorical variables with the creation of a dummy variable corresponding to missing status.

Outcomes analysis: The starting time for survival analysis was the date of the first encounter in the Nephrology Clinic at Salem VAMC. Patients were considered lost to follow-up if no contact was documented with them for more than six months before April 1, 2008, and they were censored at the date of the last documented contact. Outcome measures were predialysis all-cause mortality ascertained from VA electronic records, ESRD (defined as initiation of maintenance dialysis therapy and ascertained from local hospital records including Medicare Form 2728), and the slopes of eGFR *versus* time.

As the hazard of mortality varied with time and thus violated the proportionality assumption, the associations between race and all-cause mortality and ESRD were evaluated by using flexible parametric survival models (23). To adjust for differences in clinical characteristics, multivariable models were built by *a priori* including the variables that showed significant differences by race groups at baseline, thus adjusting for case mix (age, cardiovascular disease including coronary artery, peripheral vascular and cerebrovascular disease, systolic and diastolic BP, and smoking), biochemistries (eGFR, serum albumin and bicarbonate, blood cholesterol, hemoglobin, WBC, percent lymphocytes, and 24 h urine protein), and medication use (calcitriol, calcium containing phosphate binders, sevelamer hydrochloride, and statins). Diabetes mellitus was forced into the models.

The association between race and the slopes of eGFR *versus* time was examined in generalized linear mixed-effects models allowing for a random intercept and slope using the XTMIXED command in STATA. The change in eGFR from baseline until death, start of dialysis, or loss of follow-up (whichever occurred first) was studied in 1205 patients who had at least three serum creatinine measurements (median: 18 measurements, range: three to 141) by using a two-stage model formulation (24). In such a model, the level 1 change describes intra-individual changes in eGFR, and the level 2 model describes how the change coefficients differ across participants. The covariates of interest (race and any other independent variables) are thus included in the level 2 models to explain interindividual differences in intra-individual change (slope). Slopes of eGFR were also examined separately in a subset of 266 patients with at least three serum creatinine measurements who reached ESRD.

Interactions were assessed by generating interaction terms, and subgroup analyses were performed if the interaction terms were significant. Sensitivity analyses were performed by using only nonimputed values of independent variables and by restricting analyses to a more contemporary cohort of patients enrolled after January 1, 2001. The association of race with mortality was also examined separately for all-cause mortality before and after the start of dialysis (without censoring for ESRD). P values of less than 0.05 were considered significant. Statistical analyses were performed using STATA statistical software version 10 (STATA Corporation, College Station, TX). The study protocol was approved by the Research and Development Committee at the Salem VAMC.

Results

The mean ($\pm$SD) age of the cohort was 68 $\pm$ 11 yr, 24% of patients were black, and the mean estimated GFR was 37 $\pm$ 17 ml/min/1.73m^2. Most patients had CKD stages 3 (57%) and 4 (30%) at baseline, with few patients categorized as CKD stage 1 (1%), 2 (8%), and 5 (5%). Seven hundred fifty-four patients (61%) were enrolled in the study after January 1, 2001. A total of 451 patients died before the initiation of dialysis therapy (mortality rate: 105/1000 patient-years, 95% confidence interval [CI]: 95 to 115), and 267 reached ESRD (ESRD rate: 62/1000 patient-years, 95%CI: 55 to 70) during a median follow-up of 2.8 yr. Thirty-five patients (2.8%) were lost to follow-up; their characteristics were not significantly different (data not shown).

Baseline characteristics in patients divided by their race are shown in Table 1. Black patients were younger, more likely to be active smokers, and less likely to have cardiovascular disease; had lower eGFR, serum albumin, bicarbonate and blood hemoglobin, and WBC levels; and had higher percent lymphocytes in WBC and 24 h urine protein. The use of phosphate-binding medications and calcitriol was more frequent, and the use of statins was less frequent in black patients; their use of ACE-inhibitors or angiotensin-receptor blockers (ACEI/ARB) was no different.

Mortality

As shown in Table 2, black patients experienced significantly lower crude predialysis all-cause mortality rates compared with white patients (unadjusted mortality hazard ratio, 95% confidence interval [CI]: 0.75 [0.59 to 0.95], $P = 0.02$). Sequential adjustment for differences in baseline variables (especially case-mix characteristics), however, negated this difference (Table 2). Significant interaction was only present between race and cardiovascular disease ($P = 0.03$ for the interaction term). In four subgroups of patients divided according to categories of mutually exclusive race and cardiovascular disease, and using

Table 1. Baseline characteristics of individuals stratified by their race[a]

	White	Black	*P*
	(n = 945)	(n = 298)	
Age (years)	69.4 ± 10.1	64.9 ± 12.3	<0.0001
DM	515 (55)	167 (56)	0.6
ASCVD	576 (61)	132 (44)	<0.001
CAD	458 (50)	89 (31)	<0.001
PVD	232 (25)	59 (21)	0.1
CVA	166 (18)	31 (11)	0.01
Smoking	212 (23)	91 (32)	0.01
Comorbidity index	2.5 ± 1.7	2.5 ± 1.8	0.9
Calcitriol use	269 (28)	114 (38)	0.001
Calcium containing medication use	233 (25)	104 (35)	0.001
Sevelamer HCl use	92 (10)	42 (14)	0.03
ACEI/ARB use	712 (75)	230 (77)	0.5
Statin use	638 (68)	172 (58)	0.01
BMI (kg/m^2)	29.3 ± 5.8	29.2 ± 6.1	0.7
SBP (mmHg)	148 ± 26	155 ± 26	0.0001
DBP (mmHg)	72 ± 15	81 ± 16	<0.0001
eGFR ($ml/min/1.73m^2$)	38.2 ± 17.3	34.9 ± 16.0	0.01
K/DOQI stage of CKD 1/2/3/4/5	18 (2)/74 (8)/544 (58)/279 (29)/30 (3)	1 (1)/20 (7)/159 (53)/92 (31)/26 (9)	<0.001
Serum Albumin (g/dl)	3.64 ± 0.49	3.57 ± 0.54	0.03
Serum Cholesterol (mg/dl)	189 ± 55	195 ± 59	0.12
Serum Calcium (mg/dl)	9.1 ± 0.5	9.2 ± 0.6	0.5
Serum Phosphorus (mg/dl)	3.8 ± 0.8	3.8 ± 0.8	0.8
Serum Bicarbonate (mEq/l)	25.8 ± 3.4	25.1 ± 3.3	0.01
Blood Hgb (g/dl)	12.8 ± 1.9	12.2 ± 1.9	<0.0001
Blood WBC ($1000/mm^3$)	7.5 (7.3-7.7)	6.8 (6.6-7.0)	<0.0001
Blood lymphocytes (%WBC)	22.3 ± 7.9	26.3 ± 9.7	<0.0001
Proteinuria (g/24 h)	701 (633-776)	891 (760-1,045)	0.02

[a]Data is presented as means ± SD, number (% of total) or geometric means (95% confidence interval). DM, diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; WBC, white blood cell count. Comparisons are made by t-test or chi^2 test.

Table 2. Outcomes associated with black race, compared to white race[a]

	Unadjusted	Case-mix adjusted	Case-mix + laboratory + medications adjusted
Predialysis all-cause mortality Hazard Ratio (95% CI)	0.75 (0.59,0.95)	1.02 (0.80,1.31)	1.03 (0.80,1.34)
ESRD Hazard Ratio (95% CI)	1.64 (1.28,2.12)	1.42 (1.08,1.86)	1.06 (0.78,1.43)
eGFR slope $ml/min/1.73m^2/yr$ (95% CI)	−0.3 (−0.7,0.1)	−0.2 (−0.6,0.3)	−0.1 (−0.6,0.3)

[a]Fixed end points (mortality and ESRD) were examined in parametric survival models, and slopes were examined in multilevel mixed-effects models for change. Models we adjusted as indicated for case mix (age, diabetes mellitus, cardiovascular disease, smoking status, and blood pressure), baseline laboratory values (estimated glomerular filtration rate [except for slope analyses], serum albumin, bicarbonate, white blood cell count, percentage of lymphocytes in the white blood cell count, blood hemoglobin, 24 h urine protein) and medication use (calcitriol, phosphate binders and statins).

ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate.

white patients with cardiovascular disease as reference, black patients with cardiovascular disease had the highest mortality rate, with lower mortality seen in white patients without cardiovascular disease, and the lowest mortality in black patients without cardiovascular disease (Figure 1). The association of black race with all-cause pre- and postdialysis mortality (without censoring for ESRD) was similar to the associations found in the censored (competing risk) model (data not shown).

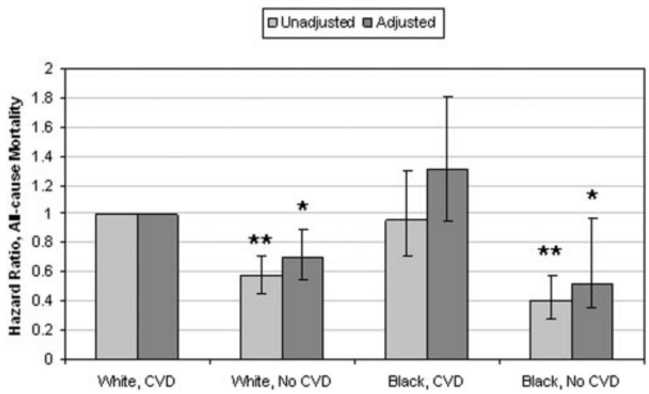

Figure 1. Multivariable adjusted hazard ratios of all-cause mortality in patients categorized by mutually exclusive race and cardiovascular disease status in parametric survival models, unadjusted and adjusted for age; diabetes mellitus; cardiovascular disease; systolic and diastolic BP; smoking status; estimated GFR; serum albumin; bicarbonate; blood hemoglobin; white blood cell count; % lymphocytes in white blood cell count; and 24 h urine protein and use of calcitriol, phosphate binders, and statin medications. The group of white patients with cardiovascular disease served as referent. $^{*}P < 0.01$, $^{**}P < 0.001$

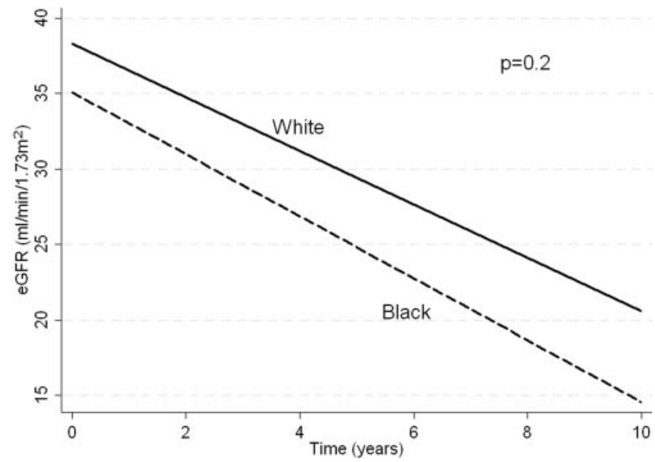

Figure 2. Predicted slopes of estimated GFR in groups of patients divided by race in an unadjusted multilevel mixed-effect model.

ESRD and Progression of CKD

Black patients had significantly higher crude ESRD rates compared with white patients (unadjusted ESRD hazard ratio, 95%CI: 1.64 [1.28 to 2.12], $P < 0.001$). This difference diminished and subsequently became nonsignificant after sequential adjustments for differences in case mix, laboratory values, and medication use between black and white patients (Table 2). There were no significant interactions.

In a multilevel mixed-effects model of change in eGFR, the overall slope of eGFR *versus* time was -2.2 ml/min/1.73m^2/yr (95% CI: -2.5 to -1.9). Figure 2 depicts the estimated slopes of eGFR in white and black patients based on a two-stage model of eGFR change including only race as a stage 2 variable, showing that blacks had a -0.3 ml/min/1.73m^2/yr steeper slope that was not significantly different from whites (95% CI: -0.7 to 0.1, $P = 0.2$, Table 2). Adjustment for case mix and laboratory characteristics further weakened this association (Table 2). In the subgroup of patients who reached ESRD, slopes tended to be steeper in black patients, albeit the difference still did not reach statistical significance (adjusted difference in slope associated with African American race: -0.9 ml/min/1.73m^2/yr, 95% CI: -2.1 to 0.2, $P = 0.11$).

The above associations were not significantly different when including only nonimputed independent variables in multivariable models and when restricting analyses to the more contemporary cohort of patients enrolled after January 1, 2001 (data not shown).

Discussion

We examined clinical outcomes as a function of race in a moderately large group of male patients with NDD-CKD. We found that, similar to patients on maintenance dialysis (5–11), black patients with moderate and advanced NDD-CKD experience significantly lower all-cause mortality compared with white patients. Unlike in dialysis patients, the difference in our study was explained by differences in the case mix of the study population, especially differences in the baseline prevalence of cardiovascular disease between blacks and whites. Black patients also experienced a significantly higher incidence of ESRD, which was also explained by differences in baseline characteristics. The lower all-cause mortality seen in black patients appeared to be mostly responsible for their higher incidence of ESRD, since the overall slopes of eGFR in blacks were only slightly steeper compared with whites, and the difference was not statistically significant.

Survival in black patients on dialysis is superior to that seen in white patients (5–11), which is in stark contrast with the significantly higher mortality observed in blacks in the general population (13–15) and in patients with mild-to-moderate degrees of CKD (16–17). This phenomenon could be explained by the survival selection of a group of black patients with less cardiovascular disease who would than progress to more advanced CKD and ultimately ESRD. Indeed, black patients without cardiovascular disease experienced the lowest mortality in our study; the reason for the survival advantage in this subgroup is unclear and requires further exploration.

A higher incidence of ESRD in blacks has been consistently observed (1,25–29). Potential explanations for this observation are a higher prevalence of CKD in the studied population(s) *versus* faster progression of CKD *versus* selection bias secondary to lower mortality in blacks, or a combination of the above. Several studies using serum creatinine level as a marker of CKD contended that there is a higher population prevalence of CKD in blacks (3,30), potentially related to lower GFR as a result of their greater incidence of low birth weight resulting in lower numbers of nephrons (31), an increased prevalence of hypertension and diabetes (32), or a combination of these. These studies, however, did not account for racial differences in muscle mass and tubular handling of creatinine (33–35). A study using the MDRD equation to estimate GFR in the Third National Health and Nutrition Examination Survey (NHANES III) found that the prevalence of CKD in the US population was not higher in non-Hispanic blacks, but their incidence of ESRD was fivefold higher compared with non-Hispanic whites, suggesting that faster progression of CKD could explain the higher incidence of ESRD in blacks (4). However, this study did not assess individual-level changes in kidney function and, as such, could not discern the effects of faster loss of kidney function from selection bias related to lower mortality in blacks in explaining their results (4). As death and ESRD are competing end points in NDD-CKD, any group with lower mortality can experience higher rates of ESRD even if its rate of CKD progression is identical (34). Ours is, to our knowledge, the first study to examine not only fixed end points, but also individual-level slopes of eGFR to describe race-associated outcomes in an unselected group of patients with moderate and advanced NDD-CKD. We found a significantly higher incidence of ESRD in black patients, but we could not substantiate the hypothesis that a faster progression of CKD is the reason for the higher incidence of ESRD in blacks. It is possible that blacks may experience faster progression of CKD in subgroups of patients with better survival, as the difference between the slopes of eGFR of blacks and whites approached significance in the subgroup of patients who reached ESRD in our study. The latter finding may resolve the apparent discrepancy between our findings and those from the MDRD study that described a steeper decline in kidney function in black patients (36). Another explanation for this would be that participants in the MDRD study had different demographic and comorbidity characteristics, and they experienced very low mortality rates and, thus, may not have been representative of the general population with NDD-CKD.

Several limitations of our study need to be mentioned. The retrospective nature of our study allows for the detection of associative, but not causative, relationships. Since we examined exclusively male patients from a single medical center, our results may not be representative of the overall population with NDD-CKD. Furthermore, our study examined a referral population with a relatively high rate of ESRD incidence, which may not be representative of the general population, where the incidence of ESRD in patients with CKD is much lower relative to the risk of dying (37). As patients with advanced NDD-CKD referred for nephrology care represent a population that is more likely to proceed to ESRD, we believe that examining such populations can be more conducive to success when trying to explain the mechanism responsible for the higher incidence of ESRD and the lower mortality seen in black patients on dialysis. We examined patients enrolled over an extended period of time, thus temporal changes in clinical practice and laboratory measurements (such as serum creatinine) could have biased our results. To address this shortcoming, we separately examined patients enrolled more recently and found similar results.

Conclusions

We describe significantly lower mortality and a higher incidence of ESRD in black patients with moderate and advanced NDD-CKD. The lower all-cause mortality was explained by differences in case-mix characteristics, especially by the lower incidence of baseline cardiovascular disease seen in black patients, suggesting that the higher cardiovascular mortality observed in blacks with earlier stages of CKD may result in those black patients with lower CKD burden surviving to reach later stages of CKD and ESRD. The overall lower mortality rates seen in blacks in these more advanced stages of CKD appeared to be mostly responsible for their higher ESRD incidence, as the slopes of eGFR were not significantly different between blacks and whites. Interventions meant to address discrepant outcomes of blacks in the United States should primarily focus on preventing the higher mortality in patients with normal or mildly decreased kidney function. More research is needed to determine the reasons behind the lower mortality seen in black patients without cardiovascular disease in our study.

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Disclosures

None.

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