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Racial Survival Paradox of Dialysis Patients: Robust and Resilient

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The inception of the end-stage renal disease (ESRD) program in the United States some 40 years ago heralded the near-universal availability of life-saving kidney replacement therapy for all Americans who required this expensive treatment, irrespective of their race or ethnicity, with the intent ultimately to transplant the majority of these patients. Currently, minorities compose >50% of the approximately half-million US ESRD population, almost 35% of whom are African Americans or self-declared blacks.¹ In contrast, the African American proportion of the US general population currently is 14%.^{1,2} Dialysis patients continue to have an exceptionally high mortality rate, with ~20% of dialysis patients dying annually in the United States and a 5-year survival rate <35%. Most patients with terminal cancers live longer than dialysis patients.³

Despite poor overall survival, minority dialysis patients and black patients in particular surprisingly have better outcomes than whites. This phenomenon has been called a survival paradox because the lower mortality rate of African American dialysis patients is in sharp contradistinction to the general US population, in which whites have a longer life expectancy than blacks.¹ A recent report by Kucirka et al² in the *Journal of the American Medical Association* explored the effect of race on dialysis outcomes in more detail, finding that the commonly described African American survival advantage only holds for dialysis patients older than 50 years.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Kucirka et al² reported that for 1.3 million incident US dialysis patients over nearly 15 years (1995–2009), black dialysis patients had an overall lower death rate than white patients. However, after using a statistical model that accounts more effectively for receiving kidney transplant as a competing risk^{4,5} and stratifying the cohort by age groups, younger black patients had higher mortality than whites (93%, 46%, and 12% higher mortality at ages 18–30, 31–40, and 41–50 years, respectively), whereas older black patients paradoxically had lower mortality than whites (7%, 13%, 15%, and 13% better survival at ages 51–60, 61–70, 71–80, and >80 years, respectively). The authors concluded that the commonly cited

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survival advantage for black dialysis patients applies to only older adults, whereas blacks younger than 50 years have a higher risk of death.²

It is important to note that in the study by Kucirka et al,² despite the relatively long cohort time of up to 15 years (1995–2009), median follow-up per patient in this cohort was only 21.5 months. The major strength of long follow-up (eg, >5 years) in a dialysis patient cohort is mostly to examine or account for secular trends, such as change in practice patterns over time. Moreover, there was no distinction between Hispanic and non-Hispanic whites. The reference group combined both ethnically diverse groups into a single category for the sake of comparison to blacks.⁶ Notably, Hispanics compose nearly 20% of the US dialysis population, and the ESRD incidence rate in the Hispanic population is 1.5 times greater than for non-Hispanic whites.^{7,8} However, similar to African Americans, Hispanic dialysis patients also appear to have consistently better survival than non-Hispanic whites.^{7,8} A recent study of more than 124,000 US hemodialysis patients by Streja et al⁹ found that non-Hispanic whites had higher unadjusted and case-mix-adjusted mortality over 5 years than did Hispanics and African Americans. However, after controlling for surrogates of inflammation and nutritional status, Hispanics had mortality similar to non-Hispanic whites, whereas African Americans had higher mortality.⁹ Hence, the reported findings of higher mortality in young black patients by Kucirka et al² might be somewhat misleading because the reference group in their study is the combination of both non-Hispanic whites and the longer living Hispanics.

The effect modification by age for the lower mortality observed in African American dialysis patients that Kucirka et al² report also may have been influenced by another problem in that the overall hazard ratio of mortality for African American patients was 0.90 (and 0.84 after adjusting for differences in demographics and comorbid conditions and censoring for transplant). However, the death hazard ratios of the individual age subgroups were all higher than this, from 0.95 for the 71- to 80-year-old group to 1.94 in the 18- to 30-year-old group.¹⁰ Notwithstanding that an explanation for this finding may be related to Berkson's paradox, in which the conditional probability of an event in a subset is inflated relative to its probability in the overall sample, it is unclear whether results of the age subgroup analyses are appropriate to explain the lower mortality rate seen in black dialysis patients.¹⁰

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Recent studies have sought explanations for the better survival of blacks treated with long-term dialysis than whites. Some studies have suggested that a favorable nutritional/inflammatory profile, including larger muscle mass, may explain the survival advantages of black dialysis patients.⁹ In 2 recent studies,^{11,12} the predictive value of the proinflammatory cytokine interleukin 6 for mortality was significantly more prominent in whites than in African Americans, which implies that key inflammatory biomarkers have less impact on mortality in the black population. That African Americans appear to be less vulnerable to mortality related to dialysis-associated inflammation seems in keeping with evidence from other studies of the permissive effect that genotype has on the mortality-inflammation link.^{13,14} For example, Ricks et al¹⁵ found that of all racial/ethnic groups, the strongest and most consistent association of greater survival with higher body mass index in dialysis patients occurs in African Americans.

There may be other conditions that can lead to greater survival of black dialysis patients. Miller et al¹⁶ reported that survival had different associations with dose or time of hemodialysis treatment when examined in different combinations of race or sex. Feroze et al¹⁷ found that dialysis patients with increased body fat, worse nutritional status

(hypoalbuminemia), or smaller muscle mass (estimated by lower serum creatinine concentration) perceived a poorer health-related quality of life, and that worse physical health in African American patients correlated less strongly with mortality than in whites. Finally, in another recent study, the survival advantage of African American dialysis patients, who often have higher parathyroid hormone levels, was most notable in those receiving the highest doses of a vitamin D mimetic (paricalcitol >10 µg/wk), whereas no survival difference was found for those who received no vitamin D analogue.¹⁸ Other potential factors predisposing to better survival for blacks include more favorable coping mechanisms and social-mental support in black communities upon dealing with conditions that would be considered much more devastating by other subcultures.¹⁹ Interestingly, a similar survival paradox has been reported for dialysis patients in Israel, as Arab Israelis have greater survival than Jewish Israelis, even though transplant rates are somewhat similar between the 2 groups.¹ Another similar paradox outside the ESRD population is the greater survival of black premature infants compared with their white counterparts, whereas for full-term infants, the opposite is the case, suggesting a biologic advantage in distressed circumstances, possibly in utero epigenetic changes.²⁰

What do prior data tell us about why younger African Americans may not have the survival advantage of older African Americans? Several factors may have a role (Table 1). First, there may be differences in insurance mix; younger African Americans have lesser insurance, whereas in older patients, there is more parity in insurance coverage, which may provide more inclusive health and medication coverage in addition to dialysis treatment. A large number of young urban African Americans have challenging social situations²¹ and may have an even greater distrust of institutions, including medical establishments, leading to delayed/reduced visits and/or lesser adherence even if access to care is available. In the general (nondialysis) population, younger otherwise healthy African Americans have higher mortality than other people, probably driven by factors other than chronic disease. For instance, in 1999, the injury death rate for black male Americans aged 15–24 years was 180% of the value for whites.²² Furthermore, there is a large subset of young black dialysis patients with hypertension-induced kidney failure, many of whom may have associated substance abuse and a lifestyle issue that would predispose to worse quality of life and mental health and early mortality.^{21,23} At the same time, older African Americans could be steered away from transplants because of the perception that their mortality risk is lower on dialysis therapy.²⁴ This could create a bias against mortality rates similar to the greater survival of Japanese dialysis patients, for whom the transplant rate is exceptionally low. Also, there has been a decrease in the death rate in dialysis patients, specifically with a noted decrease in the cardiovascular death rate since 2004.²⁵ This is attributed in large part to the increased use of cardioprotective agents, such as β-blockers (60%) and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ARBs) (50%) being administered fairly evenly across all age groups and racial/ethnic groups.²⁵ If this is a major contributor to improved survival, the reduction in cardiovascular deaths in younger dialysis patients would disproportionately enhance the relative impact of noncardiovascular deaths. This would preferentially favor overall survival improvements in young white dialysis patients because young minorities (aged 22–45 years) are more likely to die of homicide, motor vehicle accident, suicide, and drug overdose than their white counterparts.²³

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Because the effect-modifying impact of age on race was not previously noted, the initial response by the nephrology community was that this must be an aberration of some sort.²⁴ The observed racial disparity and the “paradox within paradox” appear interesting and consistent with the racial disparities in most other health care arenas. However, it is important to note that the median age of incident dialysis patients in most countries,

including the United States, is older than 60 years.² Hence, only a small proportion of US and global dialysis patients, including African Americans, are younger than 50 years, making the applicability of these findings somewhat limited. Given the younger mean age of African American dialysis patients, these findings still have important implications for the care of this at-risk cohort, notwithstanding that according to the authors' own data, black dialysis patients older than 50 years, composing the majority of African Americans, maintained the known survival advantage, and this effect could not be explained by any factors in this study.²

In conclusion, we believe that the survival advantage of African American dialysis patients compared with non-Hispanic whites is rather robust and resilient, and the reduced survival in younger African American dialysis patients, if true, represents more of a societal effect on survival independent of chronic disease. Effective interventions to improve poor conditions and health of younger African Americans in urban areas should target hypertension and other risk factors for chronic kidney disease in this age group. Although we do not dismiss the possibility of a paradox within paradox and the likelihood of less survival benefit of race for younger African American dialysis patients, we suggest that rather than dismissing these survival paradoxes as wrong, unimportant, or residual confounders, better understanding of the roots of the racial/ethnic survival differences may advance our understanding of the pathobiology of chronic disease and its expression in different settings, helping to improve outcomes. Discovering the factors responsible for the survival advantages of African American and Hispanic dialysis patients may have major clinical and public health implications, not only for dialysis patients, but also for other populations with chronic disease states and poor survival.

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Table 1**Potential Contributory Factors for the African American Survival Differential Between Younger Versus Older Dialysis Patients**

Potential Mechanism	Description	Suggested Solution
Lower transplant rate in African Americans	African Americans could be steered away from transplants because of the general perception of lower mortality on dialysis therapy. This could inflate artificially the survival advantage (similar to Japanese dialysis patient survival).	Use survival models that adjust for competing censorship.
Inclusion of Hispanics in the reference group	Pooling “white” or “nonblack” patients into a single reference leads to the inclusion of Hispanic whites (and in some cases Asians), who traditionally have better survival, analogous to blacks.	Exclude minorities from the reference groups.
Higher background mortality of young African Americans	In persons 15–44 years of age, minorities have higher death rates from homicide, motor vehicle accident, suicide, and drug overdose.	Adjust for background mortality disparities of the non-ESRD population.
Differences in insurance mix	Younger African Americans have less insurance, whereas in older patients, there is more parity in insurance coverage.	Adjust for insurance mix in multivariate models.
Differences in trust of institutions	Younger African Americans may have an even greater distrust of institutions, including medical establishments, leading to delayed/reduced visits and/or lesser adherence even if access to care is available.	Adjust for adherence surrogates in multivariate models.
Age permissibility of genetic factors	Age may exert a permissive or effect-modifying role on the genetic factors that impact on survival.	Conduct gene expression studies.

Abbreviation: ESRD, end-stage renal disease.