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Original Article

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Increased risk of death in African American patients with end-stage renal disease secondary to lupus

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Abstract

Background. Systemic lupus erythematosus (SLE) is a devastating systemic disease that can lead to end-stage renal disease (ESRD). Our goal was to assess the relative mortality risk associated with race in pediatric and adult populations with ESRD secondary to SLE maintained on hemodialysis (HD).

Methods. We identified an inception cohort of patients who were started on HD in January 1990 from data collected by the United States Renal Data System (USRDS). Kaplan–Meier survival analyses were performed in these patients using the time at risk from 1 January 1990 through 31 December 2010, the last date of the USRDS data collection period in this dataset. Cox proportional hazard models were used to assess mortality, adjusted for age at dialysis initiation. Subjects were censored at transplantation or end of follow-up.

Results. There were 1580 patients with ESRD secondary to SLE, 252 pediatric patients (62% African American) and 1328 adults (56% African American). African American pediatric patients with ESRD secondary to SLE had a 2-fold increased risk of death compared with African American children with other causes of ESRD [hazard ratio (HR): 2.1, 95% confidence interval (CI): 1.4–2.9, $P < 0.01$]. Increased risk of death was also seen in African American adults with ESRD secondary to SLE compared with both Caucasians with ESRD secondary to SLE (HR: 2.3, 95% CI: 1.2–4.2, $P < 0.01$) and African American adults with ESRD secondary to other diseases (HR: 1.2, 95% CI: 1.1–1.4, $P < 0.01$).

Conclusion. Our study suggests that there is a significant increased risk for mortality in African American children and adults with ESRD secondary to SLE. This suggests that African Americans with ESRD secondary to SLE need aggressive monitoring.

Keywords: dialysis; mortality; racial disparity; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect multiple organ systems, including the kidneys. Up to 60% of adults and 80% of pediatric patients with SLE will have kidney involvement at some point in their disease course [1, 2]. Additionally, a number of patients will progress to end-stage renal disease (ESRD) requiring renal replacement therapy [3–5].

SLE has an increased prevalence in the African American population. For Caucasian women between 15 and 64 years, the prevalence of SLE is 1.43 per 1000 women. For African American women in the same age range, the prevalence is almost three times higher, with 4.08 per 1000 women affected [6, 7]. Minorities are also noted to have an increased incidence of nephritis secondary to SLE [8].

Mortality data in the United States have shown decreased survival in African American patients with SLE compared with Caucasians [8]. However, when studying patients with ESRD receiving dialysis therapy, African Americans have been shown to have significant survival advantages compared with Caucasians [9–13]. This survival advantage remains after adjustment for age, socioeconomic differences and differences in rates of kidney transplant.

In order to evaluate these disparate outcomes in survival by race in patients with SLE and those with ESRD, we utilized a large national database to define hazard ratios for mortality. Using this same database, we have previously shown that both pediatric and adult patients with ESRD secondary to SLE have increased mortality compared with patients with ESRD secondary to other causes [14]. However, we did not explore whether these differences in mortality in the SLE population vary by ethnicity or race. The goal for the current study was to explore whether there were differences in mortality in patients with ESRD secondary to SLE based on race.

Methods

United States Renal Data System

We performed a retrospective longitudinal analysis using the patient standard analytic file obtained from the United States Renal Data System (USRDS). The USRDS is a

population-based registry from all states within the US patients with ESRD receiving renal replacement therapy. At time of enrollment into the USRDS, the attending nephrologist is required to complete a Medical Evidence Report. This form establishes Medicare eligibility and provides demographic data including etiology of ESRD based on International Classification of Diseases Ninth Revision (ICD-9) codes and date of first service of renal replacement therapy. Claims forms are submitted to Medicare, which pays for renal replacement therapy in these patients. Additional mandatory data, including demographic and ethnic data, are collected by providers and reported to the Centers for Medicare and Medicaid Services (CMS). To be included in the database, patients must be receiving chronic dialysis therapy defined as >90 days or have undergone renal transplantation. Patients are excluded if they receive dialysis for acute kidney injury only, die of kidney failure before receiving dialysis or renal transplantation, or do not accept renal replacement therapy [9].

Comparison groups

The USRDS contains demographic data for patients including sex, race and Hispanic ethnicity at the time of renal replacement therapy. We explored differences in mortality between the following groups: (i) Hispanic ethnicity pediatric patients with ESRD secondary to SLE versus Hispanic ethnicity pediatric patients with ESRD secondary to other causes, (ii) Hispanic ethnicity adult patients with ESRD secondary to SLE versus Hispanic ethnicity adult patients with ESRD secondary to other causes, (iii) African American pediatric patients with ESRD secondary to SLE versus Caucasian pediatric patients with ESRD secondary to SLE, (iv) African American pediatric patients with ESRD secondary to SLE versus African American pediatric patients with ESRD secondary to other causes, (v) Caucasian pediatric patients with ESRD secondary to SLE versus Caucasian pediatric patients with ESRD secondary to other causes, (vi) African American adult patients with ESRD secondary to SLE to Caucasian adults with ESRD secondary SLE, (vii) African American adults with ESRD secondary to SLE versus African American adult patients with ESRD secondary to other causes and (viii) Caucasian adults with ESRD secondary to SLE versus Caucasian adult patients with ESRD secondary to other causes.

Data analysis

According to USRDS definition, pediatric patients were defined as age $\leq$18 years at first ESRD service. Because there were no patients $\leq$5 years old with ESRD secondary to SLE, we restricted our analysis to patients between ages 6 and 18 years. Patients were divided into two categories; those with SLE (ICD9 code: 710.0) and those with other diagnoses. The most common diagnoses in the population with other causes of ESRD were structural urologic disease in pediatrics and diabetes mellitus in adults. Baseline characteristics of patients were calculated by race category and Hispanic ethnicity using *t*-test for comparison of means and chi-squared tests for comparison of groups.

We identified an inception cohort of patients who were started on hemodialysis (HD) in January 1990. Kaplan–Meier survival analyses were performed in these patients using the time at risk from 1 January 1990 through 31 December 2010, the last date of the USRDS data collection period in this dataset. Patients were censored at renal transplantation or at the end of follow-up. Deaths were recorded from the death notification forms.

Cox proportional hazard models were used to assess the risk of death in different races. In the USRDS dataset, information on race is divided into six categories: (i) Native American, (ii) Asian, (iii) African American, (iv) Caucasian, (v) unknown and (vi) other. Information on ethnicity is divided into two categories: (i) Hispanic and (ii) non-Hispanic. For this analysis, when examining differences in mortality by race, we focused on African American versus Caucasians not of Hispanic ethnicity. Other races were excluded because there were too few patients with SLE in the categories to perform statistical analysis. There were <10 patients per group of Native American pediatric SLE patients, pediatric Asian SLE patients and pediatric unknown/other SLE patients. In the adult population, there were 11 Native American adult SLE patients, 77 adult Asians, 0 adult unknown SLE patients and 18 adult other SLE patients. We controlled for potential confounding of age by adjusting for age at dialysis initiation. The proportional hazard assumption was tested prior to calculating hazard ratios and was not violated. P-values of <0.05 were considered significant. Data were analyzed using STATA, version 11 (Stata Corporation, College Station, TX, USA).

Results

We identified 121 332 patients in our inception cohort of patients who began dialysis in January 1990. There were 1720 total patients with ESRD secondary to SLE, 275 pediatric patients and 1445 adults. Of these patients, 94 were Caucasian pediatric SLE and 590 were Caucasian adults with SLE. There were 158 African American pediatric SLE patients and 738 African American adult patients with ESRD secondary to SLE. Demographic characteristics are presented in Table 1.

There were 103 Hispanic children with ESRD secondary to other causes and 23 Hispanic children with ESRD secondary to SLE. These Hispanic children with ESRD secondary to SLE were older than children with other causes of ESRD with a mean age of 18.2 ± 1.8 versus 16.8 ± 2.8 years ($P < 0.01$). There was no significant difference in female gender between groups (82% SLE versus 80% other, $P = 0.7$). There was no significant difference in mortality between these groups with a hazard ratio (HR) of 0.7 with a 95% confidence interval (CI) between 0.2 and 2 ($P = 0.5$).

The 117 adults with Hispanic ethnicity and ESRD secondary to SLE were younger than the 838 Hispanic adults with other causes of ESRD (33.9 ± 10.3 versus 36.5 ± 10.8 years, $P < 0.01$). There was no difference in gender between groups ($P = 0.7$). There was no significant difference in mortality between these groups with an HR of 0.8, 95% CI: 0.5–1.1, $P = 0.2$. As numbers were small, patients of Hispanic ethnicity were not included in subsequent comparisons.

In the pediatric population, African Americans had an increased risk of death compared with Caucasians with an HR for mortality of 1.3 with a 95% CI between 1.1 and 1.5, after controlling for age at HD initiation ($P < 0.01$). Among African American children with SLE, there was an increased risk of death compared with Caucasian children with SLE (HR 2.8, 95% CI 1.2–6.6, $P = 0.01$) (Figure 1). There was no difference in age at death between African American and Caucasian children with SLE (22.6 versus 22.7

Table 1. Demographic characteristics

	Pediatric patients				Adult patients			
	SLE		Other		SLE		Other	
	Caucasian (*n* = 94)	African American (*n* = 158)	Caucasian (*n* = 3375)	African American (*n* = 1685)	Caucasian (*n* = 590)	African American (*n* = 738)	Caucasian (*n* = 66 683)	African American (*n* = 39 185)
Mean Age at Initiation of HD [years (SD)]	15 (2.4)	15.1 (2.5)	10.8 (5.8)	12.2 (5.2)	41.6 (14.8)	38.2 (11.9)	61.4 (14.9)	54.8 (14.7)
% female	76	78	45	40	79	84	44	49
Years on HD	5.2	5.1	5.2	5.3	8.8	8.6	8.2	8.2

Pediatric patients with ESRD secondary to SLE were older with an increased female and African American predominance compared with other pediatric patients (P-value <0.01). Adults with ESRD secondary to SLE were younger with an increased female and African American percentage compared with other adults (P-value <0.01). There were also significantly more African American patients in the pediatric SLE population (62%) compared with the adult SLE population (55%) (P-value <0.01). There was no significant difference in the years maintained on HD between SLE groups (pediatric, P = 0.9, adult, P = 0.09).

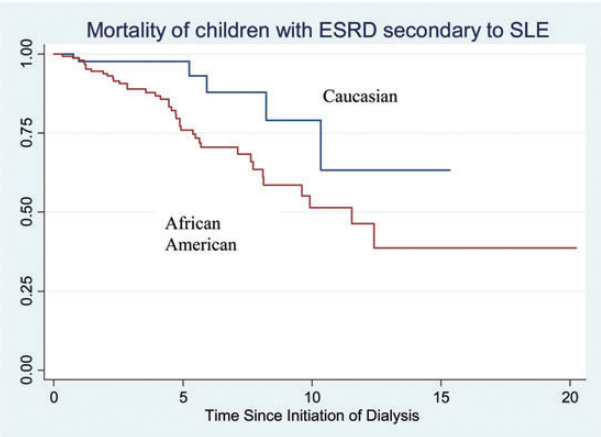

Fig. 1. African American pediatric patients with SLE had a higher risk of death (hazard ratio: 2.8, 95% CI: 1.2–6.6, P = 0.01) compared with Caucasian children with ESRD secondary to SLE.

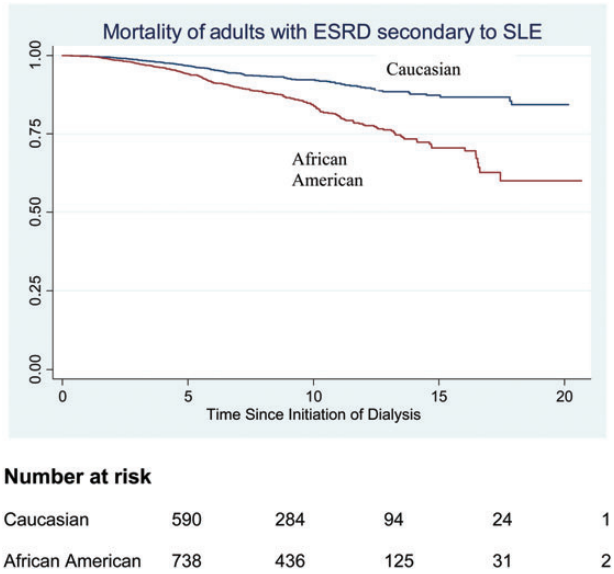

Fig. 2. African American adult patients with SLE had a significantly higher risk of death compared with Caucasian adult patients with ESRD secondary to SLE (hazard ratio: 2.3, 95% CI: 1.2–4.2, P < 0.01).

years, P = 0.9). When comparing African American children with SLE to African American children with other causes of ESRD, there was a significant increased risk of death (HR 2.1, 95% CI: 1.4–2.9, P < 0.01). There was no difference in risk of death among Caucasian children with SLE compared with Caucasian children with ESRD due to other causes (HR: 0.8, 95% CI: 0.4–1.9, P = 0.6).

In the overall cohort, after adjusting for age at initiation of HD, African American adults with ESRD had a lower risk of death compared with Caucasians (HR: 0.7, 95% CI: 0.6–0.9, P < 0.01). There was a significant difference in death between African American and Caucasian adults with ESRD secondary to SLE (HR: 2.3, 95% CI: 1.2–4.2, P < 0.01) (Figure 2). African American adult patients with SLE were significantly younger at death than Caucasian adults with SLE (47.8 versus 51.9 years, P < 0.001). African American adults with SLE were at an increased risk of death compared with African American race patients with other causes of ESRD (HR: 1.2, 95% CI: 1.1–1.4, P < 0.01). There was a lower risk of death in Caucasian adults with SLE compared with Caucasian adults with ESRD from other causes (HR: 0.4, 95% CI: 0.3–0.7, P = 0.01).

The causes of death were noted in the death notification forms and we report the three most prevalent reasons in each subset of patients. African American pediatric patients with ESRD secondary to SLE died of cardiovascular disease and cardiac arrest, followed by ischemic brain damage, and septicemia/infections. African American pediatric patients with other causes of ESRD died from cardiovascular disease infections, and diabetes. In African American adult patients with ESRD secondary to SLE the three leading causes of death were cardiovascular disease and cardiac arrest, followed by septicemia/infections, and unknown etiology. In African American adults with other causes of ESRD, the main causes of death were cardiovascular disease, infections and malignancy. Caucasian pediatric patients with ESRD secondary to SLE died of cardiac arrest, unknown etiology and septicemia; Caucasian pediatric patients with ESRD from other causes died from

cardiovascular disease, infections and coagulation disorders. Caucasian adult patients with and without SLE died of cardiovascular disease, malignancy and diabetes.

Discussion

In this study, we found that both African American children and African American adults with ESRD secondary to SLE have an increased risk of death compared with two distinct groups: (i) Caucasian subjects with ESRD secondary to SLE and (ii) African Americans with ESRD secondary to other causes. This is in contrast to previously published reports in the ESRD population in which African American patients have lower mortality compared with Caucasians [9, 15]. To our knowledge, this study is one of the first to focus on patients with ESRD secondary to SLE and differences in mortality risk between races in this population.

In the ESRD literature, the reason for lower mortality in African American patients is not known. The higher residual renal function seen in African American patients with ESRD may be associated with lower mortality [15]. Additionally, higher body mass index noted in African American patients is associated with a lower mortality risk [16]. These variables were not studied in our population secondary to lack of data.

Overall, in patients with SLE, it has been shown that African Americans have a worse prognosis compared with Caucasians. In the Hopkins Lupus Cohort with over 1500 adult patients (~60% Caucasian, ~40% African American), the risk of African Americans with SLE developing nephritis is 75% compared with 30–40% of Caucasians [8, 17]. In a population-based study, 31% of recently diagnosed African American patients with SLE had some form of renal disease in the first 6 months of diagnosis compared with 13% of Caucasians [18]. In other population studies, overall mortality for African American adults with SLE is worse compared with Caucasians [19–21]. In a study by Contreras *et al.* [22], doubling of serum creatinine and death were more common in African Americans (11.3 events per 100 patient years) compared with Caucasians (2.9 events per 100 patient years).

Similar to the adult literature, African American pediatric patients with SLE are also thought to have more aggressive disease than Caucasians with SLE. In a study of the Toronto pediatric SLE population, African American patients presented at a younger age than Caucasians (12.6 versus 14.6 years). Renal disease was also more common in African American than Caucasian patients (62 versus 45%) [23]. In African American children with lupus nephritis, severe diffuse proliferative glomerulonephritis and comorbid neuropsychiatric lupus have been associated with worse prognosis and increased rate of ESRD and mortality [24, 25]. African American children with lupus nephritis are also noted to have more treatment resistance compared with other populations [26]. This trend of worse survival in African American pediatric patients with SLE was also noted in our study, confirming that the increased mortality in this patient population does not change, even after kidney failure.

In this analysis, we censored patients at the time of kidney transplant as the populations before and after transplant may not be comparable. Reports have shown that there are differences in the rate of kidney transplant between African American and Caucasian patients with ESRD secondary to SLE. Hiraki *et al.* [27] noted that there were fewer kidney transplants in African American pediatric patients with ESRD compared with Caucasian pediatric SLE patients. Another study from the United Network for Organ Sharing showed that mortality was almost 2-fold higher in patients with SLE following transplantation compared with other causes of ESRD [28].

The most common reason for death in the SLE population was cardiovascular disease. The leading cause of death in the patients with ESRD from other causes was also cardiovascular disease; however, the patients with SLE died at a significantly younger age compared with the others. One hypothesis for the increased cardiovascular disease in patients with SLE is ongoing, chronic inflammation. This may lead to an increase in serum markers of C-reactive protein and tumor necrosis factor alpha. Increased levels of these proteins have been associated with an increased risk of cardiovascular disease and accelerated atherosclerosis in patients with SLE [29–31].

Socioeconomic status may influence observed racial differences in mortality in SLE. The Lupus in Minorities: Nature versus Nurture (LUMINA) investigators noted a higher cumulative incidence of lupus nephritis among non-whites, in whom lower education levels and poverty were important predictors of lupus activity [32]. However, in a study of the Hopkins Lupus Cohort, Petri *et al.* noted that socioeconomic status did not confound the relationship between race and SLE morbidity. One limitation of our study is that we did not adjust for region of residence or potential socioeconomic factors that may influence mortality differences. Other limitations of our study include the possibility of misclassification bias for disease diagnosis, race or ethnicity secondary to either missing data or incorrect coding. The misclassification of patients could result in skewing of the hazard ratio towards the null. Additionally, specific data on SLE diagnosis such as kidney biopsy results, SLE onset and other organ system involvement are not recorded in the USRDS.

Although we have the noted limitations, our study still has significant strengths. The USRDS is one of the largest databases of patients with ESRD. Our study includes the considerable sample size of the largest populations of pediatric and adult patients with ESRD secondary to SLE.

Our study demonstrates that there is a significant increase in the risk of death among African American pediatric and adult patients with ESRD secondary to SLE. This is the opposite of what has traditionally been reported in the ESRD population, where African Americans are thought to have a survival advantage. This suggests that African American patients with SLE may have different risk factors for death and should be monitored closely by providers, including careful control of ongoing disease activity and inflammation which may exaggerate the risk of cardiovascular disease in these patients.

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

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Conflict of interest statement. None declared

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