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Outcomes in African Americans and Hispanics with lupus nephritis

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Poor outcomes have been reported in African Americans and Hispanics compared to Caucasians with lupus nephritis. The purpose of this retrospective analysis was to identify independent predictors of outcomes in African Americans and Hispanics with lupus nephritis. In total, 93 African Americans, 100 Hispanics, and 20 Caucasians with a mean age of 28±13 years and an annual household income of 32.9±17.3 (in $1000) were studied. World Health Organization (WHO) lupus nephritis classes II, III, IV, and V were seen in 9, 13, 52, and 26%, respectively. Important baseline differences were higher mean arterial pressure (MAP) in African Americans compared to Hispanics and Caucasians (107±19, 102±15, and 99±13 mmHg, $P<0.05$), and higher serum creatinine (1.66±1.3, 1.25±1.0, and 1.31±1.0 mg/dl, $P<0.025$). African Americans had lower hematocrit compared to Hispanics and Caucasians (29±5, and 31±6, and 32±7%, $P<0.05$), and lower annual household income (30.8±14.9, 33.1±15.9, and 42.2±29.3 in $1000; $P<0.05$). Lower prevalence of WHO class IV was seen in Caucasians (30%) compared to Hispanics (57%, $P=0.03$) and African Americans (51%, $P=0.09$). Development of doubling creatinine or end-stage renal disease was higher in African Americans and Hispanics than in Caucasians (31, 18, and 10%; $P<0.05$), as was the development of renal events or death (34, 20, and 10%; $P<0.025$). Our results suggest that both biological factors indicating an aggressive disease and low household income are common in African Americans and Hispanics with lupus nephritis, and outcomes in these groups are worse than in Caucasians.

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Systemic lupus erythematosus (SLE), the prototype of autoimmune diseases, commonly affects the kidney during its course. Up to 60% of adults and 80% of children in selected populations develop renal abnormalities during the disease.[1] Renal involvement adds significantly to the mortality and morbidity of SLE patients. In the 1960s and early 1970s, renal death was the most common cause of organ-specific attributable mortality[2] and 5-year patient survival was approximately 55%.[3] In the following decades, the availability of dialysis, transplantation, and the rational use of immunosuppressive therapy for patients with severe forms of lupus nephritis improved patient survival to 80% or more.[1,4] In 1997, lupus nephritis was the primary diagnosis in 2% of Medicare patients with end-stage renal disease (ESRD) supported with dialysis and in 5% of patients who received kidney transplantation.[5]

In the US, African-American and Hispanic populations with lupus nephritis have been reported to have poorer outcomes than Caucasians despite advances in immunosuppressive therapy, dialysis, and transplantation.[6–11] The precise explanations for these disparate outcomes remain unclear and controversial. Ongoing population-based prospective studies in the US have suggested that African Americans and Hispanics with SLE have higher disease activity, higher risk for relapse, death and chronic renal failure (CRF) compared to Caucasians,[6,8,12,13] while Miettunen *et al.*[14] reported that there appeared to be no difference in outcomes between a population of predominantly Asian descendants and Caucasians in Canada. In addition, a recent prospective study showed that in the US, the incidence of lupus nephritis is significantly higher in African Americans (51%) and Hispanics (43%) compared to Caucasians (14%, $P<0.0001$).[8] Similarly, Seligman *et al.*[15] reported in a retrospective study of 773 patients an increased risk to develop lupus nephritis for Asian-Americans (relative risk (RR) 1.9, 95% confidence interval (CI) 1.6–2.1), African Americans (RR 1.6, 95% CI 1.2–1.9), and Hispanics (RR 1.2, 95% CI 0.9–1.6) compared to Caucasians in the US. In other publications from Europe and Iceland, the incidence of lupus nephritis has been reported to be in the range of 20–38% in Caucasians.[16–18] Studies in other populations found the incidence of lupus

nephritis to be as high as 78% in Caribbeans,[19] 69% in Chineses,[20] and 63% in Saudi Arabians.[21] Thus, lupus nephritis may also disproportionately affect certain racial/ethnic populations.

We conducted a retrospective study in 213 biopsy-proven lupus nephritis patients comprising three different racial/ethnic groups followed by physicians at university and community practices in South Florida. The study was facilitated by similar distributions of racial/ethnic groups in the two settings and a close working relationship between academic and community physicians ensuring that all patients received similar therapeutic regimens. The principal objective of the study was to test the hypothesis that poorer outcomes in African Americans and Hispanics compared to Caucasians with lupus nephritis may be due to a more aggressive disease pattern at presentation rather than to different socio-economic status.

RESULTS

In all, 213 patients (89% women and 11% men) were included in the study. Patients were 28 ± 13 (range 9–63) years of age at the time of kidney biopsy. In total, 100 patients were Hispanic (47%), 93 African Americans (44%), and 20 Caucasian (9%). The annual household income was 32.9 ± 17.3 (in $1000). A total of 9% patients had WHO class II, 13% class III, 52% class IV, and 26% class V lupus nephritis. The mean activity and chronicity indices were 6 ± 5 and 2 ± 2, respectively. The latency time between SLE diagnosis and the kidney biopsy was 28 ± 42 months. At baseline, 70% of the patients had hypertension and the mean arterial pressure (MAP) was 103 ± 17 mmHg. A total of 61% of the patients had nephrotic range proteinuria (urine protein to creatinine ratio $\geqslant 3$ mg/mg). Baseline values of renal function were serum creatinine of 1.43 ± 1.1 mg/dl (126 ± 97.24 μmol/l) and urine protein to creatinine ratio of 4.6 ± 4.3 mg/mg. The baseline value of hematocrit was 31 ± 6%. Baseline SLE serology was characterized by a median anti-nuclear antibodies (ANA) titer of 1:640, anti-dsDNA titer of 860 ± 1317 UI/ml with complement component C3 of 62 ± 32 mg/dl and C4 of 13 ± 8 mg/dl. In all, 169 (79%) and 165 (78%) patients had low complement component C3 less than 79 mg/dl and C4 less than 16 mg/dl, respectively. Sixty-four (30%) patients had a reported positive test for lupus anticoagulants and/or anticardiolipin antibodies (see Table 1). Of the 193 patients with WHO class III, IV, and V lupus nephritis, 161 received immunosuppressive agents (cyclophosphamide, azathioprine, cyclosporine, methotrexate, or mycophenolate mofetil) other than corticosteroid therapy.

Forty nine patients developed CRF (doubling of serum creatinine or ESRD). Five patients died before developing a renal event. Overall, 54 (25%) patients reached the primary

Table 1 | Baseline characteristics of patients with lupus nephritis according to race/ethnicity

Characteristics	All patients (*n*=213)	Caucasians (*n*=20)	Hispanics (*n*=100)	African Americans (*n*=93)
WHO pathology, n (%)				
Class II	20 (9)	2 (10)	8 (8)	10 (11)
Class III	27 (13)	5 (25)	12 (12)	10 (11)
Class IV	110 (52)	6 (30)$^{\varnothing}$	57 (57)	47 (51)
Class V	56 (26)	7 (35)	23 (23)	26 (27)
Activity index score	6 ± 5	4 ± 4	6 ± 6	6 ± 6
Chronicity index, score	2 ± 2	2 ± 2	2 ± 3	3 ± 3
Age (years)	28 ± 13	26 ± 12	29 ± 13	27 ± 12
Male, *n* (%)	24 (11)	3 (15)	11 (11)	10 (11)
Latency time, (months)	28 ± 42	26 ± 30	33 ± 51	23 ± 33
Mean arterial pressure, (mm Hg)*	103 ± 17	99 ± 13	102 ± 15	$107 \pm 19^{\otimes}$
Hypertension, *n* (%)	155 (70)	12 (60)	72 (72)	71 (76)
Nephrotic range proteinuria, *n* (%)	129 (61)	14 (70)	58 (58)	57 (61)
Anticoagulants, *n* (%)[a]	64 (30)	4 (20)	29 (29)	31 (33)
Serum creatinine (mg/dl)**	1.43 ± 1.1	1.31 ± 1.0	$1.25 \pm 1.0^{\oplus}$	1.66 ± 1.3
Urine protein/creatinine ratio (mg/mg)	4.6 ± 4.3	4.2 ± 3.6	4.3 ± 3.6	5.1 ± 5.1
Hematocrit (%)*	31 ± 6	32 ± 7	$31 \pm 6^{\oplus}$	29 ± 5
ANA (titer)[b]	640 (40–2560)	320 (160-640)	320 (160–640)	640 (640–1280)
Anti-dsDNA (UI/ml)[c]	860 ± 1317	886 ± 1643	859 ± 1205	856 ± 1398
Complement C3 (mg/dl)[d]	62 ± 32	63 ± 25	62 ± 32	62 ± 32
Complement C4 (mg/dl)[d]	13 ± 8	14 ± 8	12 ± 7	15 ± 9
Annual Household Income (in $1000)†	32.9 ± 17.3	42.2 ± 29.3	33.1 ± 15.9	$30.8 \pm 14.9^{\theta}$

Data reported as mean and s.d.
*$P<0.05$ for difference among different race-ethnic groups. **$P<0.025$ for difference among different race-ethnic groups.
$^{\oplus}P<0.025$ Hispanic vs African American. $^{\otimes}P<0.05$ African Americansvs Hispanic or Caucasian. $^{\theta}P<0.05$ African American vs Caucasian. $^{\varnothing}P<0.05$ Caucasian vs Hispanic.
$^{\dagger}P<0.05$ for difference among different race-ethnic groups by Friedman analysis of variance.
[a]Lupus anticoagulants and/or anticardiolipin antibodies.
[b]ANA values were only available for 201 patients and the data were reported as median and 95% CL.
[c]Anti-dsDNA values were only available for 162 patients.
[d]Complement component C3 and C4 values were only available for 196 patients.
Note: To convert serum creatinine in mg/dl to μmol/l, multiple by 88.4.
ANA, anti-nuclear antibodies.

Table 2 | Development of hard outcomes as a function of race/ethnicity

Events	Caucasians	Hispanics	African Americans
Renal events, *n* (%)**	2 (10)	18 (18)	29 (31)
Renal events per 100 patient-year	2.9	5.9	10.2
Renal or death events, *n* (%)*	2 (10)	20 (20)	32 (34)
Renal or death events per 100 patient-year	2.9	6.5	11.3

Renal events=doubling serum creatinine or end-stage renal disease.
*$P<0.025$, **$P<0.05$ for difference among different race/ethnic groups.

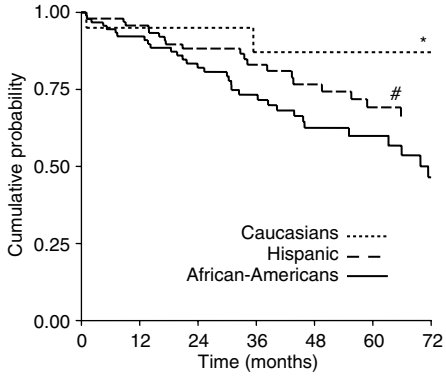

Figure 1 | Free of doubling creatinine, ESRD, or death as a function of race/ethnicity. The cumulative probability to remain free of a composite end point of doubling serum creatinine, ESRD, or death for Caucasians, Hispanics, and African-Americans during 72-months of follow-up is shown. *$P=0.04$ for African Americans vs Caucasians and #$P=0.05$ African Americans vs Hispanics.

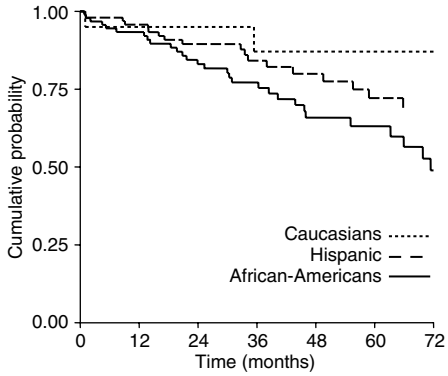

Figure 2 | Free of doubling creatinine or ESRD as a function of race/ethnicity. The cumulative probability to remain free of a composite end point of doubling serum creatinine or ESRD for Caucasians, Hispanics, and African-Americans during 72-months of follow-up. $P=0.06$ for African Americans vs Caucasians or Hispanics.

composite end point (CRF or death) during a mean follow-up of 37 ± 24 months. Renal events or deaths were significantly higher in African Americans and Hispanics compared to Caucasians (34, 20, and 10%, respectively; $P<0.025$), as were renal events alone (31, 18, and 10%, respectively; $P<0.05$) (see Table 2 and Figures 1 and 2). Important baseline differences were a higher MAP in African Americans compared to Hispanics and Caucasians (107 ± 19, 102 ± 15, and 99 ± 13 mmHg, respectively; $P<0.05$), and a higher serum creatinine (1.66 ± 1.3, 1.25 ± 1.0, and 1.31 ± 1.0 mg/dl, respectively; $P<0.025$). African Americans had a lower hematocrit compared to Hispanics and Caucasians (29 ± 5, 31 ± 6, and 32 ± 7%, respectively; $P<0.05$). Lower prevalence of WHO class IV was seen in Caucasians (30%) compared to Hispanics (57%, $P=0.03$) and African Americans (51%, $P=0.09$). Estimates of annual household income were lower in African Americans compared to Hispanics and Caucasians (30.8 ± 14.9, 33.1 ± 15.9, and 42.2 ± 29.3 in $1000; $P<0.05$) (see Table 1). Other baseline characteristics and the immunosuppressive agents received at the time and subsequently to the renal biopsy were similar among the three groups (see Tables 1 and 3).

DISCUSSION

In high-risk SLE patients with lupus nephritis, CRF and death are two clinical events of critical importance. Over the last 30 years, many epidemiologic studies have identified patients with lupus nephritis who have demographic, clinical, and histologic features associated with a worse prognosis. SLE has been reported to follow a less favorable outcome among African Americans and Hispanics in the past 10 years.[6–9,12,13] In the current study, African Americans with lupus nephritis had the worst outcome when compared to Hispanics and Caucasians. Consistent with recent findings,[6,8,13,22] we observed that the development of renal events or death was three times higher in African Americans and two times higher in Hispanics when compared to Caucasians. Barr *et al.* made similar observations in a study of SLE patients with proliferative lupus nephritis. Both African Americans (RR 3.1, 95% CI 1.2–7.8) and Hispanics (RR 3.7, 95% CI 1.7–8.3) had a similarly unadjusted increased risk of doubling serum creatinine compared to Caucasians.[22] Likewise, Austin *et al.*[7] reported that African Americans were more likely to double their serum creatinine than Caucasians. Dooley *et al.*[9] reported a significantly poorer renal survival (free of ESRD) in African Americans compared to Caucasians treated with cyclophosphamide for lupus nephritis. The precise explanations for these disparate outcomes remain unclear and controversial.

In the US, population-based prospective studies in SLE patients emphasized that African Americans and Hispanics have high disease activity, frequent renal involvement, and a high risk for CRF.[6,8,13,23] The PROFILE study[6] showed that CRF was more frequent among Hispanics followed by

Table 3 | Immunosuppressive agents received at the time or subsequently to the renal biopsy[a]

Drug	Caucasians *N* (%)	Hispanics *N* (%)	African Americans *N* (%)
Cyclophosphamide	15 (75)	65 (65)	72 (77)
Azathioprine	8 (40)	30 (30)	34 (37)
Methotrexate	1 (5)	5 (5)	4 (4)
Cyclosporine	1 (5)	3 (3)	5 (5)
Mycophenolate mofetil	3 (15)	12 (12)	13 (14)

[a]Some patients received more than one agent during follow-up.

African Americans, and it was the least common among Caucasians (18, 10.6, and 4.6%, respectively). In the LUMINA (Lupus in Minorities; nature vs nurture) study,[13] there were 15% deaths among African Americans, 12.2% deaths among Hispanics, and 7% among Caucasians. The LUMINA study also showed that African Americans were more likely to have renal and neurological involvement and they share more frequently HLA-DRB1*1503 (DR2) alleles. Hispanics were more likely to have renal and cardiac involvement with a high frequency of HLA-DRB1*08 (DR8) alleles. African Americans had a higher systemic lupus activity measure score than Caucasians (14.7 ± 8 vs 10.3 ± 6; $P < 0.05$) and African Americans and Hispanics combined together had higher physician's global assessment of disease activity than Caucasians (4.4 ± 2 vs 3.3 ± 2; $P < 0.05$).[23]

Our population appears to be different from prior studies in that Hispanics were predominantly of Cuban and South American rather than Mexican, Central American, Dominican, and Puerto-Rican descent.[11,12,22,23] In our study, the three clinical features of MAP, creatinine, and hematocrit at baseline were worse in African Americans. In addition, aggressive forms of lupus nephritis such as WHO class IV lupus nephritis were more frequent in Hispanics and African Americans than Caucasians. High MAP and serum creatinine, low hematocrit, and high frequency of WHO class IV nephritis at baseline all pointed towards an aggressive disease pattern. This observation corroborates the notion that lupus nephritis exhibits a more aggressive disease pattern in African Americans and Hispanics in the US.

We further investigated the demographic, clinical, and histological features associated with poor outcomes within each of those groups. In our study, African Americans who developed CRF or died had significantly shorter latency time between SLE diagnosis and kidney biopsy (11 ± 15 vs 30 ± 38 months, $P < 0.006$), and higher chronicity index (4 ± 3 vs 2 ± 2, $P < 0.002$) compared to African Americans without any of these important clinical events. Short latency time indicates aggressive disease, and high chronicity index is a sign of damaging disease. Similarly, Arbuckle *et al.*[24] showed in a retrospective analysis of 130 military medical records of patients with SLE that African-American men had a more rapid clinical progression than other groups, and lupus nephritis commonly was among the presenting symptoms. Austin *et al.*[7] found that African Americans were more likely to have high-risk histological features particularly interstitial fibrosis than other participants in their clinical trials. In our study, Hispanics who developed CRF or died had significantly higher baseline serum creatinine concentrations (1.85 ± 1.51 vs 1.08 ± 0.67 mg/dl, $P = 0.02$) and had a higher proportion of males (46 vs 19%, $P = 0.04$) compared to Hispanics without any of these clinical events. A high baseline serum creatinine indicates aggressive disease. Likewise, males have a more aggressive disease. It seems that early recognition of this disease and prompt referral to adequate medical care are important in African Americans and Hispanics who have an aggressive disease.

Barr *et al.*[22] reported that worse outcomes in African Americans and Hispanics with diffuse proliferative lupus nephritis might result from socio-economic rather than biological factors. In their study, the baseline blood pressure, serum creatinine, and hematocrit were generally similar among African Americans, Hispanics, and Caucasians. However, African Americans and particularly Hispanics had significantly lower annual household income, education level, assets, and frequency of private insurance compared to Caucasians. Whereas both African Americans (RR 2.7, 95% CI 0.8–8.7) and Hispanics (RR 3.6, 95% CI 1.1–11) had an increased risk of doubling serum creatinine when adjusting for socio-economic status, however, the increased risk only retained statistical significant in Hispanics. In the LUMINA study, socio-economic and behavioral factors did not predict the increased morbidity among African Americans and Hispanics. However, poverty as well as disease activity and disease damage appeared to be important determinants of mortality in this multiethnic US cohort of SLE patients.[13] In our study, the socio-economic status assessed by the distribution of annual household income was significantly different among the three studied groups. African Americans had the lowest annual household incomes with a skewed distribution in opposite direction to Caucasians' income distribution. Low socio-economic status has been associated with inferior outcomes in other chronic diseases, such as diabetes.[25] However, given that in the US African Americans and Hispanics are more likely to have a low socio-economic status,[26] there may be an interaction between race/ethnicity and socio-economic status, and membership in a certain racial/ethnic group *per se* may predict outcomes.

Our study has several limitations that are worth mentioning. Firstly, being a retrospective analysis, we describe associations but cannot be sure about causalities. Secondly, poorer outcomes in African Americans and Hispanics compared to Caucasians were attributed to

differences in biological factors and the annual household income. Associations between poor outcomes and baseline biological factors clearly indicate an aggressive disease. However, a causal association between poor outcome and low annual household income is difficult to understand and complex. It is possible that African Americans and Hispanics with more aggressive disease would not able to maintain a good job resulting in a low income. It is necessary to point out that the socio-economic status among different racial/ethnic groups encompasses also socio-demographic, behavioral, psychological, and cultural variables, which we did not account for and may also influence the course of the disease.[11,13,22,23] Racial/ethnic groups differ in behavioral, psycho-social, and cultural variables that may influence access to healthcare, patient-provider interactions, and adherence to medical therapy, which in turn influence outcomes.[27] Including only annual household income and excluding these variables precludes establishing definitive conclusions about the relative influence of the disease itself independent of socio-economic status in the outcome of our SLE patients. Thirdly, another limitation of our study includes the relative small numbers of Caucasians followed for a relative short time, which could have potentially underestimated the risk for poor outcomes in this group. In a larger cohort study of Caucasians with higher prevalence of Class IV lupus nephritis (53%) followed for a longer time (mean for patients with nephritis: 87.7 months), a higher incidence of CRF or death (combined: 36%) compared to our Caucasian group (10%) was reported by Nossent *et al.*[16] Finally, there was a lack of inclusion of other US populations such as Asian and Indian Americans in our study. However, we were able to include a substantial number of patients of a diverse population mix, all with histological classification and assessment of activity and chronicity of the biopsy.

In conclusion, our results indicate that both biological factors indicating an aggressive disease and low household income are common in African Americans and Hispanics with lupus nephritis, and outcomes in these groups are worse than in Caucasians. Future research aimed at elucidating the interplay between genetic disposition, biological factors, and socio-economic variables are needed to reduce morbidity and mortality in African Americans and Hispanics with SLE.

MATERIALS AND METHODS

Patients

The study population consisted of patients with an SLE diagnosis and biopsy-proven lupus nephritis whose first biopsies were performed between June 1983 and December 2003 and whose histologic specimens were available at the Department of Pathology, Jackson Memorial Hospital and Veterans Affairs Medical Center, University of Miami, Florida, USA. The 213 patients included in the study fulfilled the American Rheumatologic Association criteria of SLE[28] at the time of their kidney biopsy and had complete records that allowed assessment of outcomes for purposes of analysis. The local institutional review board on human research approved the study waiving the need for written informed consent. All study procedures were carried out in accordance with the Declaration of Helsinki Principles regarding research involving human subjects.

Data collection

Date of biopsy with full report (light, immunofluorescent, and electron microscopy), age, gender, referring physician name and address, racial/ethnic category, baseline (peak value -3 to $+3$ months of the biopsy) serum creatinine, urinalysis, urine protein to creatinine ratio, hematocrit, ANA titer, antibodies titer against double-stranded deoxyribonucleic acid (anti-dsDNA), complement components C3 and C4, blood pressure, the type of immunosuppressive therapy administered after the kidney biopsy, data regarding follow-up renal function, and patient vital status were extracted from the patients' medical record. Individual annual household income was obtained from estimates reported by the 'Florida Census' based on Zip-code of residency.

Definitions

Lupus nephritis was defined as the histological diagnosis of glomerulonephritis based on the WHO classification.[29] *Activity and chronicity indices* were estimated based on Pollak *et al.*[2] scoring system modified by Austin *et al.*[30] A renal pathologist blinded to the patient outcome reviewed all biopsies. *CRF* was defined as doubling of serum creatinine over the baseline value or development of ESRD (need for chronic dialysis or kidney transplantation). *Hypertension* was defined as a systolic blood pressure of $\geqslant 140$ mmHg, a diastolic blood pressure of $\geqslant 90$ mmHg, or the use of any antihypertensive medications. *Socio-economic status* was estimated using the mean annual household income (in \$1000) reported based on Zip-code of residency. Three different *racial/ethnic* groups were distinguished in this study: Hispanics, African Americans, and Caucasians reflecting South Florida's predominant groups. The patient group was defined based on either the patient's or the physician's description. Patients from other racial/ethnic groups were excluded from this study because there were less than five patients from any other group.

Statistical analysis

The outcomes of the study were the following important clinical events: patient death, doubling of serum creatinine, and ESRD. The primary outcome was a composite end point of death or any renal event. In addition, a composite renal event outcome (doubling of creatinine or ESRD) was analyzed separately. Analyses were performed using mostly χ^2, analysis of variance, and survival statistics. In the survival analysis of the primary composite outcome, lost to follow-up was censored. In the survival analysis of the composite renal outcome, lost to follow-up and death were censored. The cumulative survival curves were derived by the Kaplan–Meier method and differences between survival curves were compared by the log-rank test. Comparisons of categorical variables among the three groups were performed using χ^2 tests. Comparisons of continuous variables among the three groups were performed using analysis of variance. Comparisons of continuous variables between two groups were performed using the *t*-test when distributions were approximately normal and variances approximately equal, the Aspin–Welch test when distributions were approximately normal but variances unequal, and the Wilcoxon Rank-Sum test when distributions were not normal. Data were presented as mean and standard deviation. Statistical significance was considered with a P-value <0.05. All statistical analyses were carried out using the NCSS 2000 software package (NCSS, Kaysville, UT, USA).

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