Severe Lupus Nephritis: Racial Differences in Presentation and Outcome

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This study assessed whether certain clinicopathologic variables could explain the impact of race on outcome in 86 patients who had severe lupus nephritis and were available for long-term follow-up after participating in a prospective, controlled, clinical trial. Fifty-four (63%) patients were white, 21 (24%) were black, and 11 (13%) were categorized as other. The proportion of patients with anti-Ro, anti-nRNP, and anti-Sm was significantly greater among black patients. Biopsies with segmental active proliferative and necrotizing lesions that involved ≥50% of glomeruli ± membranous glomerulonephritis (class III ≥50%±V) were significantly more common (white 44%, black 76%, other 36%; $P < 0.05$) and diffuse proliferative glomerulonephritis ± membranous glomerulonephritis (class IV±V) was less common (white 54%, black 24%, other 64%) among black patients. Attainment of a remission was greatest among white patients (white 52%, black 29%, other 27%; $P = 0.09$). Features that were predictive of a remission were white race, baseline serum creatinine, and class IV±V lesions. Patient survival at 10 yr (white 81%, black 59%, other 73%; $P = 0.029$) and renal survival at 10 yr (white 68%, black 38%, other 61%; $P = 0.015$) were significantly poorer in black patients. Predictors of ESRD were serum creatinine, the presence of anti-Ro antibodies, class III ≥50%±V lesions, and failure to achieve a remission. In conclusion, racial differences were observed in the serologic and histologic features at presentation, response to treatment, and outcome of patients with severe lupus nephritis. In a population of patients with severe lupus nephritis, black patients were significantly more likely to have a serologic profile and renal lesions that were associated with more aggressive renal disease and resulted in worse outcomes than white patients.

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Racial differences in the presentation and the course of systemic lupus erythematosus (SLE) are well described (1–5). SLE is much more common and is associated with a higher level of disease activity and poorer outcomes among black patients compared with white patients. Whereas the overall incidence of SLE is approximately two to five cases per 100,000 population per year, the incidence in black patients is two- to five-fold greater than in white patients (6–9). Lupus nephritis is almost twice as frequent in black patients (62%) as in white patients (32%) (1,2,10), and the prognosis in black patients with lupus nephritis is significantly worse. Progression to ESRD in black patients is almost nine times greater than in white patients (11). The poor renal survival for black patients with lupus nephritis has been attributed in part to the more severe renal lesions that they experience compared with white patients (2,12,13). However, even in studies that are restricted to diffuse proliferative glomerulonephritis (DPGN), black patients are more resistant to treatment and have a worse renal survival than white patients (14,15). The more aggressive nature of the disease and the poorer prognosis for black patients with SLE in general and with nephritis in particular have been attributed to several factors, including differences in compliance and socioeconomic status (1–3,5,16–19). However, race remains a prognostic feature in lupus nephritis even after adjustment for social features (19,20).

The 1995 World Health Organization (WHO) classification (21) of diffuse lupus nephritis (WHO class IV) included patients with focal segmental proliferative lesions that involved ≥50% of glomeruli (1982 WHO class III ≥50% [22]) in addition to patients with diffuse and global proliferative lesions. We (23,24) and others (25,26) have demonstrated that the histologic features and prognosis of these lesions are distinctly different, suggesting different pathogenic mechanisms. In our study (23,24), patients with severe segmental (1982 WHO class III ≥50%) lesions had a significantly poorer patient survival and renal survival and a lower likelihood of complete remission than did patients with diffuse proliferative glomerulonephritis (1982 WHO class IV). Previous studies that assessed racial differences in outcome in diffuse proliferative lupus nephritis did not distinguish between segmental and global class IV lesions and did not assess for racial differences in the prevalence of class IV lesions by race (12,15). To assess racial differences in the presentation and the course of patients with severe lupus nephritis, we report our experience in a well-defined group of 86 patients with long-term follow-up, taking into account the segmental and global nature of the lesions included in the categorization of class IV lupus nephritis.

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Materials and Methods

Patients

The purpose of this study was to evaluate racial differences in presentation and outcome in a well-defined group of patients with severe lupus nephritis. The 86 adult patients who participated in the prospective, controlled trial of plasmapheresis in severe lupus nephritis comprise the study group (27). Fifty-four (63%) patients were white, 21 (24%) were black, and 11 (13%) were categorized as other (six Hispanic, two Asian, one Native American, and two unspecified). At the completion of the formal trial in October 1986, 14 patients had died. In the remaining 72 patients, we attained additional follow-up, extending the overall mean follow-up to 120 mo. Because there were no significant differences between the two treatment groups during the therapeutic trial, the patient data are pooled for this follow-up study.

The entry criteria, therapeutic and medical management protocols, and results of the initial study have been reported (27,28). In brief, patients were eligible when they were ≥16 yr of age, had SLE as defined by the American Rheumatism Association (29), and had biopsy-proven severe lupus nephritis. Patients with a serum creatinine >6 mg/dl (>528 μmol/L), previous plasmapheresis, or pregnancy were excluded from the study.

Entry criteria (27) required the histologic diagnosis of severe lupus nephritis, and the histologic diagnosis was determined prospectively by the Pathology Reading Committee of the Lupus Nephritis Collaborative Study Group (see Acknowledgments), using a modification of the 1982 WHO classification of lupus nephritis (22,30,31). An adequate biopsy contained >10 nonsclerotic glomeruli, and the diagnosis of severe lupus nephritis was based on the presence of proliferation and/or necrosis in ≥50% of the nonsclerotic glomeruli with or without concomitant membranous glomerulonephritis (27,30). This pathologic rubric comprises three morphologically discrete forms of lupus glomerulonephritis: (*1*) segmental glomerulonephritis with active and/or necrotizing lesions in ≥50% of the nonsclerotic glomeruli (class III ≥50%; 24 patients; Figure 1) (22), (*2*) diffuse glomerulonephritis (class IV; 35 patients; Figure 2), and (*3*) membranous glomerulonephritis with superimposed severe segmental (≥50% glomerular involvement) or diffuse proliferative glomerulonephritis (class Vc:≥50% or Vd; 26 patients). One patient was not classifiable. The activity index (maximum score of 24 points) and chronicity index (maximum score of 12 points) were determined by the Pathology Reading Committee for each biopsy (31–33).

Because we previously showed that the prognosis of these lesions is defined by the distribution of the proliferative component (segmental *versus* global inflammation), we combined them into class III ≥50%±V (44 patients) and class IV±V (41 patients) (24). These histologic classes are similar to class IV-S (segmental) ± V and IV-G (global) ± V in the classification recently proposed by the International Society of Nephrology and Renal Pathology Society (ISN/RPS) (34,35), but there are important differences. In the classification used by the Lupus Nephritis Collaborative Study Group (22,30,31), a segmental lesion (class III) could involve only one glomerulus or essentially all glomeruli in a biopsy, and there was no upper limit to the extent of involvement within the glomerulus. This was a consensus diagnosis of four experienced renal pathologists who were able to identify the segmental nature of this lesion even when most of the tuft was involved. In contrast, the ISN/RPS classification relegates biopsies with segmental lesions that involve >50% of the glomerular tuft or >80% of glomeruli to class IV-G. The inclusion of the most widely distributed segmental lesions to ISN/RPS class IV-G easily could conceal differences in outcomes between patients with class IV-S and IV-G lesions. Because this article addresses critical differences in outcomes between white and black patients with segmental and diffuse glomerular lesions, we continue to use the original classification.

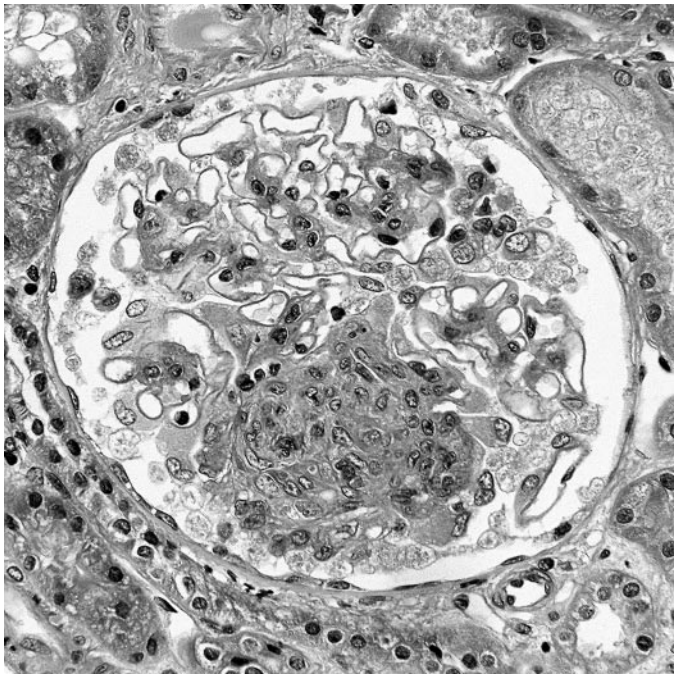


Figure 1. Segmental necrosis with obliteration of capillaries, proliferation of podocytes, and karyorrhectic debris. The uninvolved portion of the glomerulus has patent capillaries with mesangial proliferation. This segmental lesion was defined in the former World Health Organization (WHO) classification (1982) as III. When the percentage of glomeruli involved was ≥50% the term "severe segmental glomerulonephritis" often was used. It is important to note that the relatively small sample size of glomeruli in a biopsy obliged a large coefficient of variation with respect to absolute percentage of glomeruli involved (49). The report of an absolute percentage of glomeruli therefore could be inaccurate. The current International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification calls this lesion diffuse proliferative glomerulonephritis-segmental (IV-S) (34,35). Magnification, ×250 (hematoxylin and eosin).

Clinical, biochemical, and serologic information was obtained at baseline and at specified follow-up times during the initial study. The study was terminated in March 1986, but patients were followed formally through December 1988 (27). Clinical follow-up now has been extended to June 1998, and the patients' current clinical status with respect to death, ESRD, and biochemical results for serum creatinine and urine protein were recorded.

Laboratory Analysis

Baseline serum creatinine, C3 and C4 complement components, anti–double-stranded DNA antibodies (anti-dsDNA), C1q binding activity, and cryoprecipitable immune complex (cryoglobulin) (36) concentrations were determined in a central laboratory as described previously (37). Serum creatinine was measured by a Creatinine Analyzer II (Beckman Instruments, Fullerton, CA) with the use of a modified alkaline picrate method. Serum C3 and C4 were measured by radial immunodiffusion (Calbiochem-Behring, La Jolla, CA), and anti-dsDNA was measured by RIA (Amersham, Arlington Heights, IL). Antibodies to Ro, La, nRNP, and Sm were determined by Dr. Morris Reichlin, MD (Oklahoma City, OK) using an ELISA with affinity-purified antibodies as described previously (38,39).

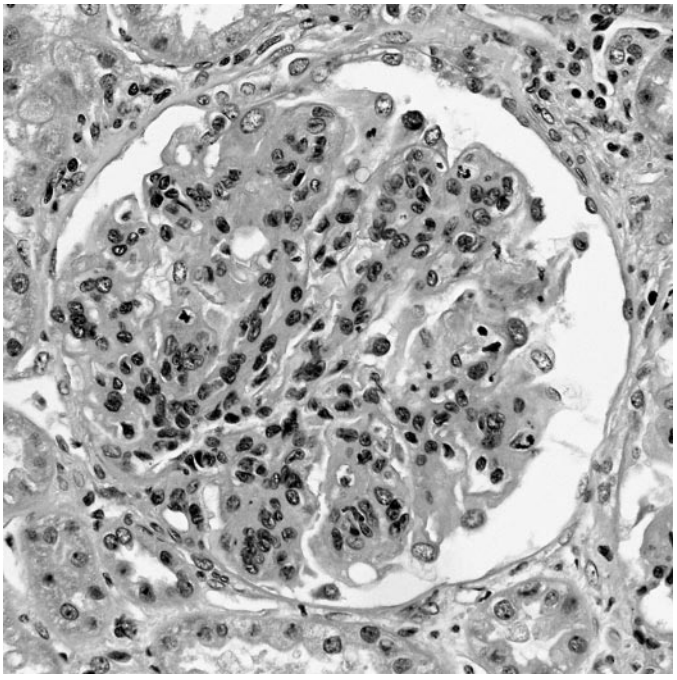


Figure 2. Diffuse endocapillary proliferation with occlusion of the capillaries, marginated neutrophils and monocytes, and wire loops. Previous WHO classifications of renal disease called this lesion class IV, diffuse proliferative glomerulonephritis (21,22). The current ISN/RPS recommendations classify this lesion as diffuse proliferative glomerulonephritis-global (IV-G) (34,35). Magnification, ×250 (hematoxylin and eosin).

Treatment Protocol

The details of the treatment protocols for this study have been published (27,28). All patients initially received 60 mg/d prednisone orally and 2 mg/kg per d cyclophosphamide orally. Forty patients were randomly assigned to receive standard therapy plus plasmapheresis three times weekly for 4 wk in addition to this treatment. After the initial 4 wk of treatment, patients who improved clinically received cyclophosphamide at 1 mg/kg per d for an additional month, after which it was discontinued. The dosage of prednisone was tapered gradually over a 22-wk period to 20 mg on alternate days. Patients whose renal symptoms had worsened at 4 wk (see below) were continued on the initial high-dosage prednisone and cyclophosphamide for an additional 4 wk, and patients in the plasmapheresis arm of the study also received an additional 12 treatments. Thereafter, renal and extrarenal flares were treated on the basis of other standardized protocols of intensive drug therapy as described previously (28). In brief, minor extrarenal flare was treated with a return to daily prednisone at 30 mg/d for 2 wk. Major extrarenal flare was treated with a return to cyclophosphamide 2 mg/kg per d for 5 wk followed by 1 mg/kg per d for 3 wk along with daily prednisone at 60 mg/d for 3 wk. Mild renal flare was treated with a return to daily prednisone at 30 mg/d for 2 wk. Moderate renal flare was treated with a return to daily prednisone at 60 mg/d for 4 wk. Severe renal flare was treated with another course of treatment with the initial randomized therapy. After the formal study ended, the course of treatment was determined by the individual investigator; however, many patients remained in therapeutic programs that reflected the protocols that were used during the study.

Outcome Variables

The following outcomes were evaluated from the time of entry into the study: (*1*) Time to remission (serum creatinine of ≤1.4 mg/dl [≤123 μmol/L] and proteinuria of ≤0.33 g/d) within 5 yr of entering study, (*2*) time to ESRD (defined by a serum creatinine of ≥6 mg/dl [≥528 μmol/L] or the initiation of renal replacement therapy), and (*3*) time to death.

An assessment of renal function was made at 4 wk. Worsening of renal function was defined by an increase in serum creatinine of ≥0.3 mg/dl (≥27 μmol/L) or doubling of urinary protein to twice baseline. Patients who did not meet these criteria were otherwise considered as stable.

Lupus flares were defined as follows: Minor extrarenal flare involved skin rash, mild hemolytic anemia, mild thrombocytopenia, mild serositis, mild myalgias or arthralgias, or fever without infection. Major extrarenal flare involved failure of mild extrarenal exacerbation to improve after 2 wk of increased prednisone dosage, severe hemolytic anemia (hemoglobin <5 g/dl), severe thrombocytopenia (<50,000/mm^3), severe pulmonary hemorrhage, central nervous system involvement, vasculitis, uveitis or retinitis, severe serositis, or severe myositis. Mild renal flare involved reappearance of active urine sediment (red blood cell casts). Moderate renal flare involved a sudden increase in serum creatinine of >0.3 mg/dl (>27 μmol/L) or an increase in proteinuria of >1.0 g/d. Severe renal flare involved a sudden increase in serum creatinine of >1 mg/dl (>88 μmol/L) (27,28).

Statistical Analyses

Comparison of the clinical and laboratory characteristics among the groups of patients used the Fisher exact test for categorical data (40) and the Wilcoxon rank-sum test for continuous data (41). For the analysis of length of time from entry to remission, ESRD (renal survival), death (patient survival), or ESRD or death (survival without ESRD), product-limit life-table distributions were compared with the log-rank test statistic (42). A proportional hazards regression model was used to evaluate potential clinical, laboratory, serologic, histologic, and therapeutic predictors of remission, progression to ESRD, and progression to ESRD or death (42). Results are reported as mean ± SD, and $P < 0.05$ was considered significant.

Results

Baseline Clinical and Serologic Characteristics

Clinical characteristics at baseline, duration of lupus nephritis, time from biopsy until entry into the study, and treatment randomization were similar among white, black, and other patients (Table 1). There also were no significant differences in serologic parameters with regard to anti-dsDNA, C3, C4, or cryoprecipitable immune complex (cryoglobulin) levels at baseline among the groups (Table 2). However, the proportion of patients who were positive for anti-Ro, anti-nRNP, or anti-Sm antibodies was significantly greater in black patients and others compared with white patients. The presence of combined positivity for anti-Ro, anti-nRNP, and anti-Sm was significantly greater in black patients (four [20%] of 20) and other patients (three [30%] of 10) than in white patients (two [4%] of 50; $P = 0.012$).

Histologic Features

The baseline histologic features are shown in Table 3. A significantly larger proportion of black patients had class III ≥50%±V lesions than white patients or others. A similar proportion of patients had coexisting membranous lesions (class V; white 15 [27%] patients, black nine [43%] patients, and other two [18%] patients; NS). There were no differences among the groups in activity or chronicity indices, but black patients and

Table 1. Baseline clinical characteristics[a]

Characteristic	White	Black	Other	*P*
n	54 (63)	21 (24)	11 (13)	
Age (yr)	32 ± 13	29 ± 11	34 ± 10	NS
Female	46 (85)	17 (81)	9 (82)	NS
BP (mmHg)				
systolic	144 ± 19	138 ± 17	141 ± 19	NS
diastolic	89 ± 13	86 ± 12	87 ± 11	NS
Serum creatinine (mg/dl)	1.8 ± 1.1	1.9 ± 1.3	1.8 ± 1.4	NS
median (mg/dl)	1.5	1.6	1.4	
Proteinuria (g/d)	6.2 ± 3.9	5.4 ± 3.5	5.3 ± 5.2	NS
median (g/d)	6.3	5.3	3.5	
Presentation of clinical nephritis to entry (mo)	19 ± 38	12 ± 24	6 ± 12	NS
median	1.6	0.9	0.8	
Biopsy to entry (mo)	0.5 ± 0.7	0.3 ± 0.3	0.4 ± 0.4	NS
median	0.2	0.2	0.2	
Treatment				
standard	30 (56)	12 (57)	4 (36)	NS
plasmapheresis	24	9	7	

[a]Data are *n* (%) or means ± SD. To convert serum creatinine from mg/dl to μ mol/L, multiply by 88.

Table 2. Baseline serology[a]

Parameter	White	Black	Other	*P*
n	54	21	11	
Anti-dsDNA (mU/L)	205 ± 359	421 ± 642	448 ± 934	NS
>20 mU/L	52 (96)	21 (100)	10 (91)	NS
C3 (mg/dl)	42 ± 19	39 ± 15	31 ± 12	NS
<80 mg/dl	52 (96)	21 (100)	11 (100)	NS
C4 (mg/dl)	16 ± 12	15 ± 11	10 ± 9	NS
<15 mg/dl	35 (65)	12 (57)	7 (94)	NS
Cryo-level (μg/ml)	160 ± 308	204 ± 183	138 ± 111	0.07
>21 μg/ml	49 (91)	21 (100)	9 (82)	NS
n	50	20	10	
Anti-Ro	12 (24)	9 (45)	6 (60)[b]	0.04
Anti-La	3 (15)	1 (5)	2 (20)	NS
Anti-nRNP	17 (34)	13 (65)[c]	5 (50)	0.05
Anti-Sm	13 (26)	12 (60)[c]	4 (40)	0.02

[a]Data are *n* (%) or means ± SD. Cryo, cryoprecipitable immune complex; dsDNA, double-stranded DNA.
[b]$P = 0.05$ other *versus* white.
[c]$P < 0.05$ black *versus* white.

other patients had a higher proportion of biopsies whose combined indices were ≥16.

Follow-Up

The follow-up information is in Table 4. At 4 wk, the proportion of patients with stable renal function was similar between black and white patients but significantly less in the other patients. The proportion of white patients who entered remission was almost twice that of black ($P = 0.07$) or other ($P = 0.19$) patients, but this did not reach statistical significance (Table 4, Figure 3). There were no significant differences in the number of patients who had renal flares among the groups. There were no significant differences among the groups with regard to overall status at last follow-up even though the proportion of white patients with stable renal function was ≥1.5 times greater than black or other patients (white patients 54%, black patients 33%, and other patients 36%). However, the proportion of patients who reached ESRD overall (ESRD + renal death) was significantly greater in black patients than white patients (62 *versus* 35%; $P < 0.05$). Although the overall proportion of deaths (renal death + nonrenal death) were greater in black patients (43%) and other patients (36%) compared with white patients (20%; NS), the differences were not

Table 3. Baseline histologic features[a]

Parameter	White	Black	Other	*P*
n	54	21	11	
Biopsy (class)				
III≥50%±V	24 (44)	16 (76)[b]	4 (36)	0.03
III>50%	15	7	2	
III>50%+V	9	9	2	
IV±V	29 (54)	5 (24)	7 (64)	
IV	23	5	7	
IV+V	6	0	0	
Unclassified	1 (2)			
AI	11.3 ± 4.4	12.9 ± 4.6	13.3 ± 5.4	NS
≥12	26 (48)	12 (57)	4 (36)	NS
CI	3.3 ± 2.4	3.4 ± 2.2	3.7 ± 3.2	NS
≥4	24 (44)	12 (57)	5 (45)	NS
AI + CI	14.6 ± 4.5	16.4 ± 5.6	17.0 ± 6.9	NS
≥16	21 (39)	13 (62)	6 (55)	NS

[a]Data are *n* (%) or means ± SD. AI, activity index; CI, chronicity index.
[b]$P = 0.02$ black *versus* white and $P = 0.05$ black *versus* other.

Table 4. Follow-up[a]

Parameter	White	Black	Other	*P*
n	54	21	11	
Follow-up (mo)	134 ± 62	94 ± 58[b]	101 ± 73	0.01
median	155	94	110	
Renal status at week 4				
stable	47 (87)	20 (95)	7 (64)[c]	0.04
worsening	7	1	4	
Remission	28 (52)	6 (29)	3 (27)	0.09
no remission	26	15	8	
Renal flares (*n*)				
total	28 (52)	14 (67)	5 (45)	NS
moderate/severe	25 (46)	14 (67)	4 (36)	NS
Status at last follow-up				
ESRD	14 (26)	5 (24)	3 (27)	NS
renal death	5 (9)	8 (38)	2 (18)	
nonrenal death	6 (11)	1 (5)	2 (18)	
stable renal function	29 (54)	7 (33)	4 (36)	

[a]Data are *n* (%) means ± SD.
[b]$P < 0.05$ black *versus* white.
[c]$P < 0.05$ black *versus* other.

statistically significant. In black patients, essentially all deaths could be attributed to renal deaths because there was only one nonrenal death (Table 4).

Survival Outcomes

The patient survival, renal survival, and patient survival without ESRD data are shown in Table 5 and Figures 4 through 6. In all cases, the patient survival (Figure 4), renal survival (Figure 5), or patient survival without ESRD (Figure 6) was poorer for black patients and other patients compared with white patients, but the difference was significant for only black patients. The median patient survival without ESRD was 182 mo for white patients, 40 mo for black patients, and 133 mo for other patients.

Renal survival and survival without ESRD were determined for white and black patients on the basis of the histologic lesion at presentation (Tables 6 and 7). The overall renal survival for white and black patients (Table 6) was significantly worse for patients with class III ≥50%±V lesions compared with patients with class IV±V lesions ($P = 0.008$), and the difference remained significant for white patients ($P = 0.01$). The renal survival was similar for white and black patients with the combined class III ≥50%±V lesion. When evaluated separately, the renal survival was not

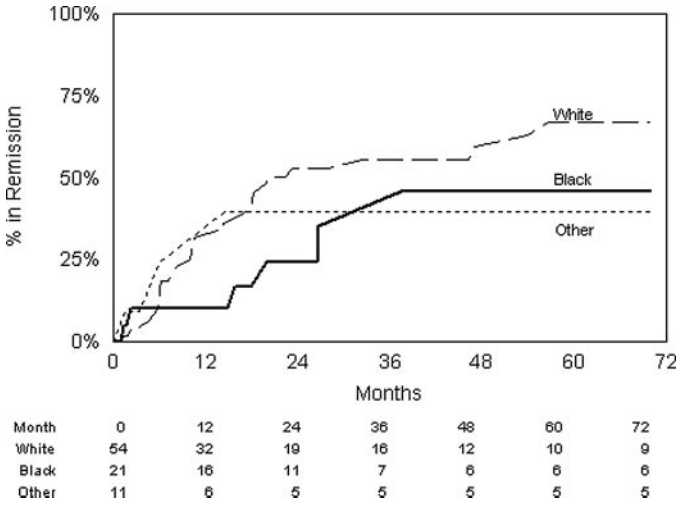


Figure 3. Renal remission. The number of patients at risk in each group is shown below the survival curve (NS).

Table 5. Patient and renal survival

Parameter	White (%)	Black (%)	Other (%)
Patient survival[a]			
1 yr	94	95	82
5 yr	85	71	73
10 yr	81	59	73
Renal survival[b]			
1 yr	91	85	71
5 yr	74	50	71
10 yr	68	38	61
Patient survival without ESRD[c]			
1 yr	85	81	64
5 yr	66	48	64
10 yr	60	36	55

[a] $P = 0.029$ black *versus* white.
[b] $P = 0.015$ black *versus* white.
[c] $P = 0.045$ black *versus* white.

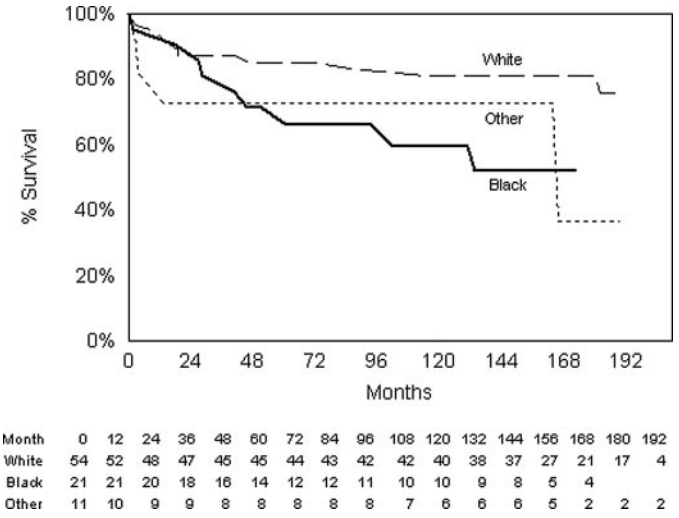


Figure 4. Patient survival in patients with severe lupus nephritis on the basis of race. The number of patients at risk in each group is shown below the survival curve ($P = 0.029$, black *versus* white; NS for black *versus* other and for other *versus* white).

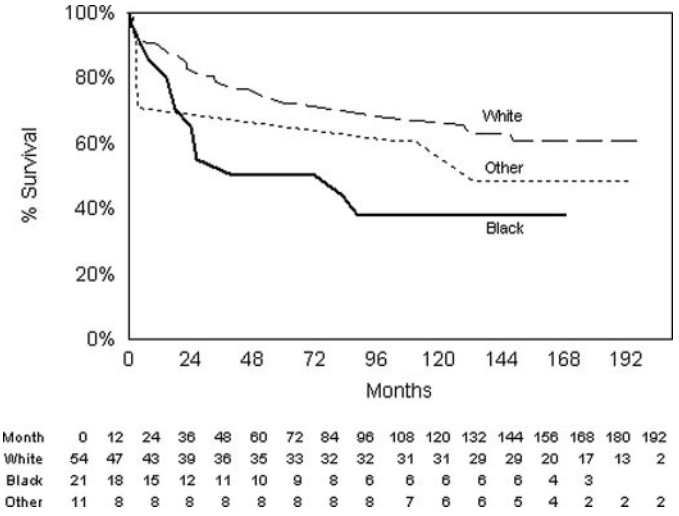
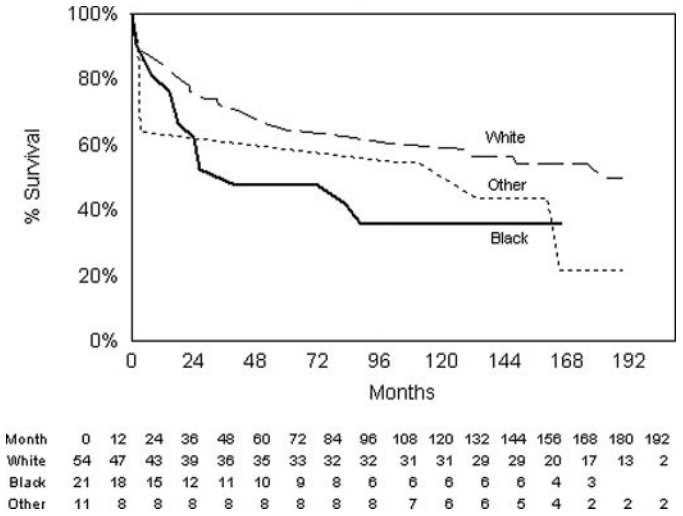


Figure 5. Renal survival (censuring for nonrenal death) in patients with severe lupus nephritis on the basis of race. The number of patients at risk in each group is shown below the survival curve ($P = 0.015$, black *versus* white; NS for black *versus* other and for other *versus* white).

significantly different among white and black patients with the class III ≥50%+V lesion and although NS, the renal survival was worse for black patients with class III ≥50% compared with white patients ($P = 0.056$). When comparing patients with class III ≥50% *versus* class III ≥50%±V lesions, the renal survival was significantly different for white patients with class III ≥50%+V lesions ($P = 0.02$). However, there was no significant difference in outcome for black patients with class III ≥50% *versus* class III ≥50%+V lesions. Among patients with combined class IV±V lesions and in patients with only class IV lesions, black patients had significantly poorer renal survival compared with white patients. There was no significant difference in outcome for white patients with class IV *versus* class IV+V lesions.

When the overall survival without ESRD for white and black patients (Table 7) was evaluated, patients with class III ≥50%±V lesions continued to have a significantly worse outcome compared with patients with class IV±V lesions ($P = 0.02$), and the difference remained significant for white patients ($P = 0.04$). However, the survival without ESRD was not significantly different between white and black patients among the various lesions. When patients with class III ≥50% *versus* class III ≥50%+V lesions were compared, the outcome was significantly worse for white patients with class III ≥50%+V lesions ($P = 0.04$). However, there was no significant difference in survival without ESRD for black patients with class III ≥50% *versus* class III ≥50%+V lesions. There also was no significant difference in outcome for white patients with class IV *versus* class IV+V lesions. Thus, the overall renal survival and survival without ESRD is poorer in white and black patients with class III ≥50%±V lesions compared with class IV±V lesions. In



Month	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192
White	54	47	43	39	36	35	33	32	32	31	31	29	29	20	17	13	2
Black	21	18	15	12	11	10	9	8	6	6	6	6	6	4	3		
Other	11	8	8	8	8	8	8	8	8	7	6	6	5	4	2	2	2

Figure 6. Patient survival without ESRD in patients with severe lupus nephritis on the basis of race. The number of patients at risk in each group is shown below the survival curve (P = 0.045, black *versus* white; NS for black *versus* other and for other *versus* white).

Table 6. Renal survival based on lesion for white and black patients

Parameter	*n*	1 yr (%)	5 yr (%)	10 yr (%)	*P*
Class III≥50%±V	40	85	61	46	0.008[a]
white	24	83	66	52	NS[b]
black	16	87	54	38	
class III≥50%[c]					
white	15	93	79	65	0.056
black	7	100	43	21	
class III≥50%+V					
white	9	67	40	27	NS
black	9	76	63	51	
Class IV±V	34	94	77	77	
white	29	96	84	84	0.04
black	5	80	40	40	
class IV[d]					
white	23	96	86	86	0.04
black	5	80	40	40	
class IV+V					
white	6	100	75	75	
black	0				

[a]Class III≥50%±V *versus* class IV±V; P = 0.008 overall, P = 0.01 for white patients, NS for black patients.
[b]White *versus* black in each category.
[c]Class III≥50% *versus* class III≥50%+V; P = 0.02 for white patients, NS for black patients.
[d]Class IV *versus* class IV+V; NS for white patients.

black patients, the poor outcome that was associated with the class III ≥50% lupus nephritis was independent of the coexistence of a membranous lesion.

Table 7. Survival without ESRD on the basis of lesion for white and black patients

Parameter	*n*	1 yr (%)	5 yr (%)	10 yr (%)	*P*
Class III≥50%±V	40	83	54	43	0.02[a]
white	24	83	62	48	NS[b]
black	16	81	50	36	
class III≥50%[c]					
white	15	93	67	53	NS
black	7	100	43	21	
class III≥50%+V					
white	9	67	40	22	NS
black	9	67	56	44	
Class IV±V	34	85	68	68	
white	29	86	72	72	NS
black	5	80	40	40	
class IV[d]					
white	23	91	78	78	NS
black	5	80	40	40	
class IV+V					
white	6	67	50	50	
black	0				

[a]Class III≥50%±V *versus* class IV±V; P = 0.02 overall, P = 0.04 for white patients, NS for black patients.
[b]White *versus* black in each category.
[c]Class III≥50% *versus* class III≥50%+V; P = 0.04 for white patients, NS for black patients.
[d]Class IV *versus* class IV+V; NS for white patients.

In assessing the impact of the initial treatment, we found that the survival without ESRD at 5 and 10 yr was similar for patients in the plasmapheresis group (60 and 53%) compared with patients who received standard therapy (63 and 55%; NS). There was no significant difference in the outcome for these therapies among white, black, or other patients.

Multivariate Analysis

Features at baseline that were predictive of progression to ESRD and patient survival without ESRD are shown in Tables 8 and 9. Clinical features that were predictive of ESRD (Table 8) were serum creatinine, anti-Ro antibodies, and class III ≥50%±V lesions. When remission status was added to the model, the relative risk for progression to ESRD was 6.8 times greater (95% confidence interval 2.1 to 22.1; P = 0.0014) in patients who failed to enter a remission. Baseline characteristics

Table 8. Multivariate analysis for predictors of ESRD[a]

Variable	RR	95% CI	*P*
Serum creatinine[b]	2.86	2.0 to 4.1	0.0001
Anti-Ro present	2.35	1.1 to 4.8	0.02
Class III≥50%±V	2.77	1.3 to 5.9	0.007

[a]Model excludes remission status. CI, confidence interval; RR, relative risk.
[b]RR per increase of 1 mg/dl.

Table 9. Multivariate analysis for predictors of death or ESRD[a]

Variable	RR	95% CI	*P*
Age >50	3.3	1.6 to 7.0	0.002
Serum creatinine[b]	2.32	1.7 to 3.1	0.0001
Nonwhite race	2.28	1.22 to 4.27	<0.01

[a]Model excludes remission status.
[b]RR per increase of 1 mg/dl.

that were predictive of death or ESRD were age, serum creatinine, and race (Table 9). The baseline features that were predictive of a remission are shown in Table 10. White patients were 2.6 times as likely to enter a remission compared with black patients and other patients, and those with class IV±V lesions were 2.6 times as likely to enter a remission compared with patients with class III ≥50%±V lesions.

Discussion

We find that there are significant racial differences in the presentation and outcome of patients with severe lupus nephritis. Although the presenting clinical and serologic features were similar among black and white patients, black patients were more likely to have antibodies to Ro, nRNP, and Sm than white patients. The patient survival, renal survival, and patient survival without ESRD all were significantly poorer in black patients compared with white patients. Although not statistically significant, white patients were almost twice as likely to attain a remission as black patients. The predominant glomerular lesion in black patients was severe segmental proliferative glomerulonephritis (1982 WHO class III ≥50%±V), and white patients were twice as likely to have diffuse proliferative glomerulonephritis (WHO class IV±V) as black patients. By multivariate analysis, predictors of ESRD were level of serum creatinine, the presence of anti-Ro antibodies, and class III ≥50%±V lesions, and predictors of death or ESRD were age >50 yr, serum creatinine, and nonwhite race. In addition, failure to attain a remission was a strong predictor of progression to ESRD, and predictors for attaining a remission were white race, serum creatinine level, and class IV±V lesions. These findings reflect our previously published observations that patients with severe segmental proliferative glomerulonephritis (class III >50%) have a poorer prognosis than do patients with global inflammatory diffuse proliferative glomerulonephritis (class IV). The higher likelihood that black patients have WHO class III ≥50% is in keeping with the poorer outcomes on the basis of racial origin. In addition, the poorer outcomes for black patients with class III ≥50% lesions was independent of the presence of membranous lesions. Thus, we find that the serology at presentation is different, the glomerular pathology is different, and the prognosis is significantly poorer for black compared with white patients with severe lupus nephritis.

Table 10. Multivariate analysis for predictors of remission

Variable	RR	95% CI	*P*
White race	2.63	1.2 to 5.8	0.017
Serum creatinine[a]	0.21	0.1 to 0.41	0.0001
Class IV±V	2.65	1.3 to 5.5	0.008
Cryo-level[b]	1.002	1.01 to 1.02	0.008

[a]RR per increase of 1 mg/dl.
[b]RR per increase of 1 μg/ml.

Black patients with SLE long have been reported to have a worse patient and renal survival compared with white patients. Ward *et al.* (18) found that the 5-, 10-, and 15-yr survivals were significantly worse for 197 black patients (76, 65, and 55%) compared with 211 white patients (87, 76, and 70%; $P = 0.005$) with SLE. Similarly, Neuman *et al.* (43) found that black patients had a poorer 5-yr patient survival than nonblack patients (87 *versus* 98%; $P = 0.02$). These differences have been attributed to socioeconomic status, more severe lupus, and genetic differences. We find that although patient survival is significantly worse for our black patients, the majority of deaths were renal deaths (*i.e.*, patients died with ESRD), with black patients having four times as many renal deaths as white patients (38 *versus* 9%). The proportion of nonrenal deaths, although comparatively less, were twice as common among white patients (11 *versus* 5%). The poorer patient survival in black patients in our study seems to be linked to the poorer renal survival and to the larger proportion of renal-related deaths.

Progression to renal failure in patients with lupus nephritis is significantly greater in black patients. Neuman *et al.* (43) found the 5-yr renal survival was 72% for black patients with lupus nephritis compared with 91% for white patients ($P = 0.001$). The authors found that the poorer renal survival in black patients was associated with their having more severe forms of lupus nephritis compared with white patients. Contreras *et al.* (13) found that black patients were almost twice as likely to have WHO class IV lesions as white patients (51 *versus* 30%). In addition, black patients were three times more likely to double their serum creatinine or reach ESRD (31 *versus* 10%; $P < 0.05$) than white patients. The 5-yr renal survival (free of doubling serum creatinine or ESRD) was 63% in black patients and 88% in white patients ($P < 0.05$), and the 5-yr renal survival without death was 56% for black patients and 88% for white patients ($P = 0.06$). On the basis of their poor renal prognosis and tendency to develop progressive renal disease, the poor prognosis in black patients may relate to their having more severe lupus nephritis.

Even among patients with the most severe form of lupus nephritis (WHO class IV, diffuse proliferative lupus nephritis), black patients have a worse outcome. In 1995, Austin *et al.* (12) reported their experience in 166 patients (103 white patients, 49 black patients, and 14 other patients), 77% of whom had severe lupus nephritis with DPGN. They found that black race, serum creatinine, and the presence of cellular crescents and interstitial fibrosis were independent predictors of doubling of serum creatinine. At 5 yr, 41% of black patients had doubled their serum creatinine compared with 18% of white patients ($P = 0.0006$). Dooley *et al.* (15) in a study of 89 patients (51 black and 38 white) with severe lupus nephritis (DPGN) also demonstrated that, despite similar

baseline clinical, laboratory, and pathologic features and the use of aggressive treatment, black patients had a poorer renal outcome. Progression to ESRD occurred in 16% of black patients compared with 5% of white patients, and the renal survival at 5 yr was 58% for black patients and 95% for white patients ($P = 0.007$). By multivariate analysis, black patients had a relative risk for progressing to ESRD that was 11 times that of white patients ($P = 0.03$). The experience reported in these studies is similar to ours. The reason for the poorer outcome in black patients despite similar clinical, laboratory, and histologic classification remains unclear. However, on the basis of our findings, there are a number of possibilities.

The different outcomes may be related to differences in the severity of the DPGN lesion among the races. Austin *et al.* (12) suggested that the poorer renal prognosis in black patients with severe lupus nephritis resulted from the fact that they were more than twice as likely to have "high risk" histology, that is the presence of cellular crescents and interstitial fibrosis, as white patients (29 *versus* 13%; $P < 0.05$). Furthermore, the lesions that are categorized as DPGN in lupus nephritis have a more heterogeneous histology, pathogenesis, and prognosis than previously thought. The 1995 WHO classification of DPGN (WHO class IV) included patients with focal segmental lupus nephritis (WHO class III) when lesions involved ≥50% of glomeruli (21). It has been shown that patients who have severe lupus nephritis with segmental lesions are more likely to have fibrinoid necrosis and less likely to have immune aggregate deposits when compared with patients with global lesions of DPGN. The necrotizing nature of the segmental lesions and the paucity of immune reactants suggest a vasculitic pathogenic mechanism rather than immune complex disease (22,24,25).

Severe segmental lupus glomerulonephritis (class III ≥50%±V) has prognostic significance because patients with this lesion are less likely to enter a remission and are more likely to progress to ESRD than patients who have diffuse lupus nephritis with global lesions. We previously reported that patients with the global inflammatory lesion of WHO class IV were more than eight times more likely to enter remission compared with patients with the severe segmental lesion of WHO class III ≥50% ($P = 0.0001$) and that patients with WHO class III ≥50% lesions were almost three times as likely to progress to ESRD compared with patients with WHO class IV lesions (24). Similarly, Yokoyama *et al.* (26) found that only 33% of patients with severe segmental lupus nephritis (ISN/RPS class IV-S) entered remission compared with 65% of patients with diffuse and global disease (ISN/RPS class IV-G). Progression to ESRD also was greater in patients with IV-S compared with patients with IV-G (65 *versus* 29%). Thus, the racial difference in response to therapy and outcome may be related to a more severe form of glomerular disease in black patients identified by the presence of segmental lesions in ≥50% of the glomeruli (*i.e.*, WHO class III ≥50% or ISN/RPS IV-S), and this finding is independent of the coexistence of membranous lesions.

Genetic factors may lead to racial differences in disease activity or severity because serologic and immunologic profiles among black and white patients with SLE are different (20). Patients with HLA-DRB1*15, uniquely found in black patients, have a greater likelihood of renal disease (19). In addition, the presence of FcγRIIA-R131, an allelic variant of the IgG receptor FcγRIIA that results in decreased ability to clear immune complexes, is significantly more frequent among black patients with lupus nephritis (44). Although we were unable to demonstrate racial differences in our study population with respect to serum complement component levels, the level of cryoprecipitable immune complexes was highest in our black patients, but this did not reach statistical significance. It also has been shown that serologic profiles that are associated with the development and the severity of lupus nephritis are more common in black patients. The likelihood of lupus nephritis is high in patients with anti-Ro antibodies, and it has been suggested that antibodies to Ro are pathogenic in lupus nephritis, because high titers have been found in the eluates from kidneys of patients with progressive renal disease (45). Lupus nephritis occurs in >50% of patients with various antibody profiles involving anti-Ro, anti-nRNP, and anti-Sm, and patients with the profile of anti-Ro, anti-Sm, and anti-nRNP, commonly seen in black patients and uncommon in white patients, are significantly more likely to have severe lupus nephritis (46). Arnett *et al.* (47), found that the presence of anti-Sm was more frequent in black patients compared with white patients (25 *versus* 10%; $P = 0.02$) as was the presence of anti-nRNP (40 *versus* 23%; $P = 0.03$) and anti-Sm and/or anti-nRNP (52 *versus* 26%; $P = 0.003$). In a study by Alba *et al.* (48), in 127 patients with biopsy-proven nephritis and 206 patients with SLE without nephritis, black race and the presence of anti-Sm were risk factors for lupus nephritis. Thus, the presence of antibodies to Ro, nRNP, and Sm seen in a significant proportion of black patients in our study supports a genetically determined immunologic predisposition for racial differences in outcome even among patients with severe lupus nephritis.

A number of studies have attributed the poorer outcome for black patients with lupus nephritis to socioeconomic factors. Black patients have greater poverty and lower annual incomes and are less compliant than white patients, all of which have been associated independently with worse outcomes in patients with lupus nephritis (2,5,13,17). Availability of medical care may differ among racial groups, but we were unable to show that there was a racial difference in either the duration of disease process to diagnosis or time from diagnosis to diagnostic renal biopsy. In a study of 459 patients with lupus nephritis (among whom 37% were black patients), Alcorn *et al.* (16) recently found that genetic factors were more important than socioeconomic status in explaining the racial differences in renal outcomes. Socioeconomic factors were not evaluated in our study, and racial differences in socioeconomic status conceivably could have been a contributing factor. However, this may have been less of an issue in our study because the patients were part of a prospective trial in which the therapeutic approach was defined clearly and the patients were closely monitored.

Conclusion

We find significant racial differences in the outcome of patients with severe lupus nephritis. Black patients are less likely to respond to treatment and are more likely to progress to ESRD and/or death. The poorer prognosis in black patients

may be linked to genetically different immunologic factors that result in a greater likelihood of having class III ≥50% lesions, the most aggressive form of lupus nephritis.

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Disclosures

None.

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