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Original Article

Prognosis in proliferative lupus nephritis: the role of socio-economic status and race/ethnicity

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Abstract

Background. Studies of proliferative lupus nephritis (PLN) suggest that African-Americans have a poorer prognosis than Whites. However, no study has simultaneously examined socio-economic status. We studied rates of progression of PLN among a tri-ethnic population with respect to socio-economic status and race/ethnicity.

Methods. A retrospective cohort study was carried out using individual and census-based neighbourhood data. Consecutive patients in urban tertiary care centres with biopsy-proven PLN were studied. The main outcome was time to doubling of serum creatinine.

Results. Among 128 patients with PLN, the percentage of patients who did not double their serum creatinine at 5 years was 67.0% (±4.8%) and at 10 years was 58.9% (±5.7%). In bivariate analyses, residence in a poor neighbourhood was positively associated with progression ($P = 0.03$), as was African-American and Hispanic race/ethnicity ($P = 0.01$). Residence in a poor neighbourhood remained associated with progression of disease after adjustment for age, sex, creatinine, hypertension, cyclophosphamide treatment and race/ethnicity [relative risk (RR) 3.5, 95% confidence interval (CI) 1.2–11, $P = 0.03$]. After adjustment for poverty and insurance, the RR for African-American race/ethnicity was reduced from 3.5 to 2.7 and was not statistically associated with progression of disease in the full model ($P = 0.10$). A similar reduction in RR from 5.5 to 3.6 was seen for Hispanic race/ethnicity, but this retained statistical significance ($P = 0.03$).

Conclusions. Poverty is an important risk factor for progression of PLN, independent of race/ethnicity. Hispanics have an elevated risk similar to or greater than African-Americans. Given these findings, some of the poorer prognosis of African-American patients with PLN may result from socio-economic rather than biological or genetic factors.

Keywords: poverty; prognosis; proliferative lupus nephritis; race/ethnicity; socio-economic status; systemic lupus erythematosus

Introduction

Proliferative lupus nephritis (PLN) remains a major cause of renal failure and mortality among patients with systemic lupus erythematosus (SLE) [1–3]. Although the prognosis of PLN has improved dramatically with the advent of immunosuppressive therapy, ~25% of patients develop renal insufficiency despite aggressive therapy [4]. Several studies have tried to identify patients with PLN who will have a worse prognosis by determining clinical and histological features associated with an adverse outcome. In these studies, clinical parameters at presentation associated with a worse outcome have included serum creatinine, nephrotic-range proteinuria, hypertension and anaemia [5,6]. On renal biopsy, the presence of cellular crescents, interstitial fibrosis, and higher activity and chronicity indices are all associated with a worse prognosis [5].

In addition, African-American race/ethnicity has predicted poor long-term outcome in PLN in two studies [7,8]. Biological factors, e.g. genetic polymorphisms

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more prevalent among African-Americans, have been hypothesized to affect renal survival in PLN [9]. However, the role that socio-economic status (SES) may play in the prognosis of patients with PLN was not considered in these trials. Prior studies in PLN have used insurance status as a surrogate measure of SES [10–14]; however, insurance is a poor proxy for SES [15], particularly among these patients who are likely to have government insurance for SLE-related disability. Such lack of adjustment for SES may be an important omission. In the case of survival of patients with SLE, multiple studies suggested that African-Americans had a higher mortality rate than Whites, and various genetic factors were posited [6]. However, SES was found to account for these differences [16], suggesting that social and economic forces, not major underlying genetic differences, caused the observed disparities.

In the present study, we examined the effects of SES on prognosis of PLN, hypothesizing that patients with lower SES would have a worse renal outcome independent of race/ethnicity. In addition, we hypothesized that the poorer outcome among African-Americans was principally due to social and economic influences, rather than biological effects. To test this hypothesis, we compared renal outcomes among African-Americans and Hispanics—groups with similar economic conditions in our population—with Whites, and approximated individual SES by using census-based measures of neighbourhood poverty.

Subjects and methods

Case selection

Consecutive cases of biopsy-proven class III (focal proliferative) or class IV (diffuse proliferative) lupus nephritis at our institutions (Hospital 1 = Columbia-Presbyterian Medical Center; Hospital 2 = New York Hospital) from 1975 to 1997 were reviewed for inclusion in the cohort. By chart review, we extracted the following baseline clinical characteristics at the time of initial biopsy: serum creatinine, haematocrit, blood pressure (or use of antihypertensive medications), 24-h protein excretion and WHO Lupus class. The use of cyclophosphamide was also recorded. The following demographic parameters were also extracted: age, sex, race, insurance status and address. Race was defined as White, African-American or Hispanic, based on either the patient's or the physician's description. The primary end point was defined as a sustained doubling of serum creatinine. Age was categorized; haematocrit was dichotomized into low ($<30\%$) or normal. Proteinuria was divided into nephrotic-range (>3.0 g/day) or non-nephrotic. Serum creatinine was divided into high (>1.0 mg/dl) or normal. Patients were defined as having hypertension if they had a systolic BP >140 mmHg or a diastolic BP >90 mmHg on two or more readings at the time of biopsy, or if they required antihypertensive medications. Only cases for which there was complete baseline data and more than 2 months of follow-up were included in the cohort. Patients were excluded if there were other systemic illnesses likely to affect renal function (e.g. diabetes), if their baseline serum creatinine was >4.0 mg/dl, if they were diagnosed with biopsy-proven PLN prior to their presentation at our institutions or if their racial/ethnicity was not clearly described as White, African-American or Hispanic. The Institutional Review Board of Columbia University approved the study.

Socio-economic variables

Individual-level SES data were not available for the cases in this cohort except for insurance status. As a proxy for individual-level data, we used neighbourhood-based measures of SES from census data [15]. Each case was geo-coded to a census-defined neighbourhood, based on the subject's address at the time of initial biopsy. These census-defined neighbourhoods, termed 'block groups', consist of ~1000 residents each. Age, gender and race/ethnic-specific socio-economic data were extracted from the 1980 and 1990 US census, and variables were dichotomized. High poverty was defined as $>10\%$ of neighbourhood residents living below the Federal poverty line. Low median household income was defined as a median household income $<\$25\,000$. Low education attainment was defined as $>45\%$ of residents not completing high school, and low assets was defined as $<10\%$ of residents reporting any income from interest or dividends. This method of using neighbourhood-based SES measurements as a proxy for individual measures of SES has been validated in previous studies [15,17].

Statistical analysis

The baseline clinical, histological and demographic variables were compared across categories of race/ethnicity and tested with χ^2, Fischer's exact test and Wilcoxon rank sum test, as appropriate. The proportion of participants reaching the end point of doubling of creatinine was compared with χ^2 or, when data were sparse, Fischer's exact test. Kaplan–Meier plots were constructed, and differences by race/ethnicity and poverty were tested with the log-rank test. In addition, age-adjusted hazard ratios were calculated using a Cox proportional hazards model, stratified by centre.

Three multivariate Cox proportional hazards models were constructed. The first 'Socio-economic' model evaluated the influence of socio-economic and insurance factors on outcome from PLN without regard to race/ethnicity. A stepwise deletion approach was employed to evaluate reproducibly all covariates, except for race/ethnicity, for inclusion into the model. In addition, age and sex were forced into the model. In a second 'Race/ethnicity' model, race/ethnicity was substituted for socio-economic variables to evaluate the influence of race/ethnicity after adjustment for the same set of variables. In a third 'Combined' model, socio-economic and race/ethnicity variables were included. Results of all three models are shown. Changes in standard errors were checked to evaluate for collinearity.

Hazard ratios, or relative risks (RRs), are presented with 95% confidence intervals (CIs). All *P*-values are two-tailed, with $P < 0.05$ considered statistically significant. Analyses were performed using SAS 8 (SAS Institute, Cary, NC).

Results

There were records of 200 consecutive patients with biopsy-proven PLN at our institutions. Of these, demographic and follow-up data were available for

155 patients, and 147 cases could be matched to a census-defined neighbourhood. Census data were available for 142 of these patients. Thirteen patients were neither White, African-American nor Hispanic, and one had a baseline creatinine >4.0 mg/dl.

The final cohort consisted of 128 patients, of whom 22 (17%) were African-American, 51 (40%) were Hispanic and 55 (43%) were White. Eighty-two percent of patients were female and 34% came from neighbourhoods defined as high poverty. Table 1 describes the baseline clinical and demographic characteristics of this cohort stratified by race/ethnicity. Clinical variables were generally similar across categories of race/ethnicity, but SES measures and insurance differed markedly by race/ethnicity. Neighbourhood poverty was highest and median income lowest among Hispanics. Educational attainment, measured by lack of a high school degree, was lowest among Hispanics; measures of educational attainment, however, are often unreliable among immigrant groups. Assets were lowest among African-Americans, reflecting national trends in the USA.

Bivariate analysis

Over a mean follow-up time of 63 months, 38 (30%) patients reached the primary end point of doubling of serum creatinine. By analysis of Kaplan–Meier survival curves, the percentage of patients who did not double their serum creatinine at 5 years was 67.0% (±4.8%) and at 10 years was 58.9% (±5.7%). The proportions of patients who doubled their creatinine, stratified by demographic, clinical and SES predictors are shown in Table 2, as are age-adjusted hazard ratios for each predictor. The proportion reaching the end point differed by race/ethnicity ($P = 0.01$): compared with Whites, the RR for doubling of creatinine for African-Americans was 3.1 (95% CI 1.2–7.8) and for Hispanics, 3.7 (95% CI 1.7–8.3). Figure 1 shows the Kaplan–Meier curves by race/ethnicity of time to doubling of creatinine. African-Americans and Hispanics had a worse prognosis than Whites ($P < 0.001$). Hispanics qualitatively had a worse outcome than African-Americans, but this difference did not reach statistical significance.

All clinical variables, except for low haematocrit, were associated with an adverse outcome (Table 2). The use of cyclophosphamide was marginally associated with a worse outcome in these bivariate analyses (RR = 2.4, 95% CI 0.9–5.6). In addition, outcomes did not differ between institutions.

Among the socio-economic variables derived from census-based neighbourhood values, high poverty was predictive of progression of PLN (RR 2.9, 95% CI 1.5–5.8, and Figure 2). Other socio-economic variables showed a trend towards poorer outcomes; however, none were statistically significant (Table 2).

Insurance status also had a significant effect on outcome. Patients with Medicare insurance (Government insurance that is available to US residents over the age of 65 years) had a significantly worse outcome than privately insured patients (RR 3.2, 95% CI 1.4–7.7). Medicaid (Government insurance that is available to

Table 1. Patient characteristics at baseline

	African-American	Hispanic	White	*P*-value
Number	22	51	55	
Demographic				
Mean age ± SD	30 ± 12	28 ± 9	29 ± 13	
Female gender (%)	86	84	78	0.60
Clinical				
Hypertension (%)	59	46	34	0.13
WHO class IV (%)	59	67	55	0.44
Elevated serum creatinine (%)	50	33	35	0.36
Nephrotic-range proteinuria (%)	41	51	45	0.70
Low haematocrit (%)	47	43	44	0.98
Received intravenous cyclophosphamide (%)	64	78	67	0.31
Source: hospital 1 (%)	77	71	73	0.84
Socio-economic				
Living in neighbourhood with:				
High poverty (%)	36	67	2	<0.001
Median household income (US$, IQR)	26 021 (19 589–33 029)	22 634 (18 847–31 837)	51 030 (42 131–71 126)	<0.001 <0.001
No high school degree (%)	5	75	0	<0.001
Low assets (%)	77	49	7	<0.001
Insurance (%)				
Medicare	50	57	4	<0.001
Medicaid	14	14	11	
Private	36	29	85	

IQR, interquartile range.
Thresholds were defined as: elevated serum creatinine, >1.0 mg/dl; proteinuria, >3.0 g/day; low haematocrit, <30%; high poverty, >10% of neighbourhood residents living below the Federal poverty line; low education attainment, >45% of residents not completing high school; low assets, <10% of residents reporting any income from interest or dividends.

Table 2. Predictors of progression of proliferative lupus nephritis

Baseline characteristic	Percent reaching end point	*P*-value	Age-adjusted hazard ratio (95% CI)
Demographic			
Age at onset:		0.06	
≤18 years	12		0.2 (0.05–1.0)
18–24 years	31		0.8 (0.4–1.6)
25–29 years	33		0.9 (0.4–2.1)
>30 years	33		1
Gender:		0.93	
Female	30		0.7 (0.3–1.6)
Male	30		1
Race/ethnicity:		0.01	
Caucasian	16		1
African-American	41		3.1 (1.2–7.8)
Hispanic	39		3.7 (1.7–8.3)
Clinical			
Hypertension:		0.002	
Yes	42		3.2 (1.5–6.9)
No	16		1
WHO class:		0.02	
IV	38		3.3 (1.5–7.3)
III	18		1
Elevated serum creatinine:		<0.001	
Yes	51		4.3 (2.1–8.7)
No	17		1
Proteinuria:		<0.001	
Yes	47		3.8 (1.8–8.0)
No	15		1
Low haematocrit:		0.51	
Yes	32		1.6 (0.7–4.0)
No	26		1
Received i.v. cyclophosphamide:		0.09	
Yes	34		2.4 (0.9–5.6)
No	19		1
Source hospital:		0.48	
1	28		0.5 (0.3–1.1)
2	34		
Socio-economic			
Living in neighbourhood with:			
High poverty		0.03	
Yes	42		2.9 (1.5–5.8)
No	24		1
Low median household income		0.028	
Yes	35		1.8 (0.9–3.6)
No	26		1
Low educational attainment		0.06	
Yes	41		2.4 (1.2–4.6)
No	25		1
Low assets		0.34	
Yes	35		1.6 (0.8–3.1)
No	27		1
Insurance:		0.009	
Medicaid	26		1.3 (0.6–2.9)
Medicare	62		3.2 (1.4–7.7)
Private	24		1

Thresholds were defined as: elevated serum creatinine, >1.0 mg/dl; proteinuria, >3.0 g/day; low haematocrit, <30%; high poverty, >10% of neighbourhood residents living below the Federal poverty line; low median household income, <$25 000; low education attainment, >45% of residents not completing high school; low assets, <10% of residents reporting any income from interest or dividends.

indigent patients) patients had a slightly worse prognosis than private patients, but this difference did not reach statistical significance.

Multivariate analysis

Results of the 'Socio-economic' model are shown in Table 3, first column. After adjustment for age, sex, hypertension and baseline creatinine, but without regard for race/ethnicity, living in a poor neighbourhood was associated with a 6-fold increased risk of progression of PLN ($P < 0.001$). Insurance status also predicted renal outcome.

When race/ethnicity was evaluated in a 'Race/ethnicity' model without regard to socio-economic variables (Table 3, second column), risk among

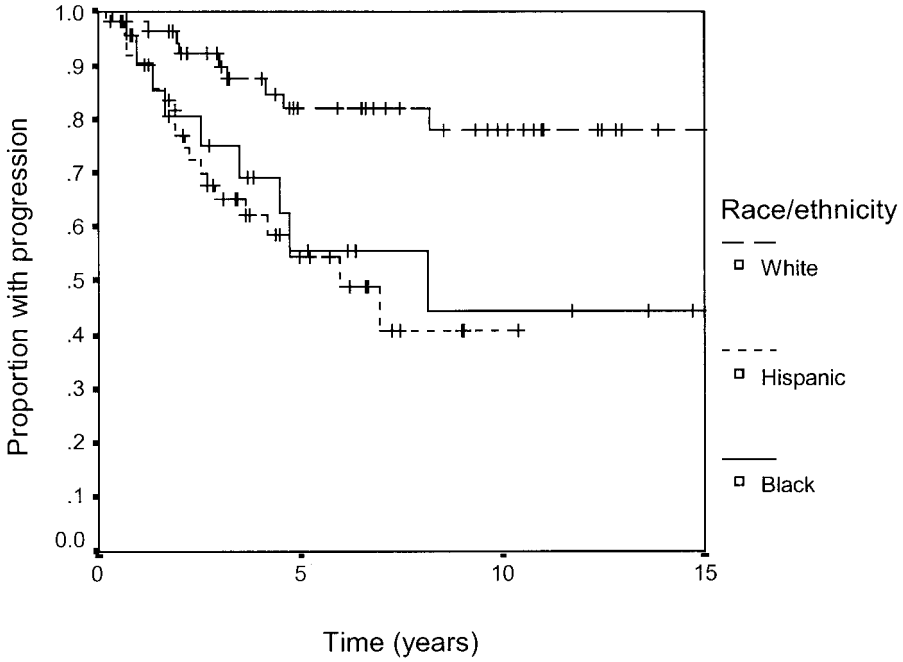

Fig. 1. Progression of proliferative lupus nephritis over time, stratified by race/ethnicity.

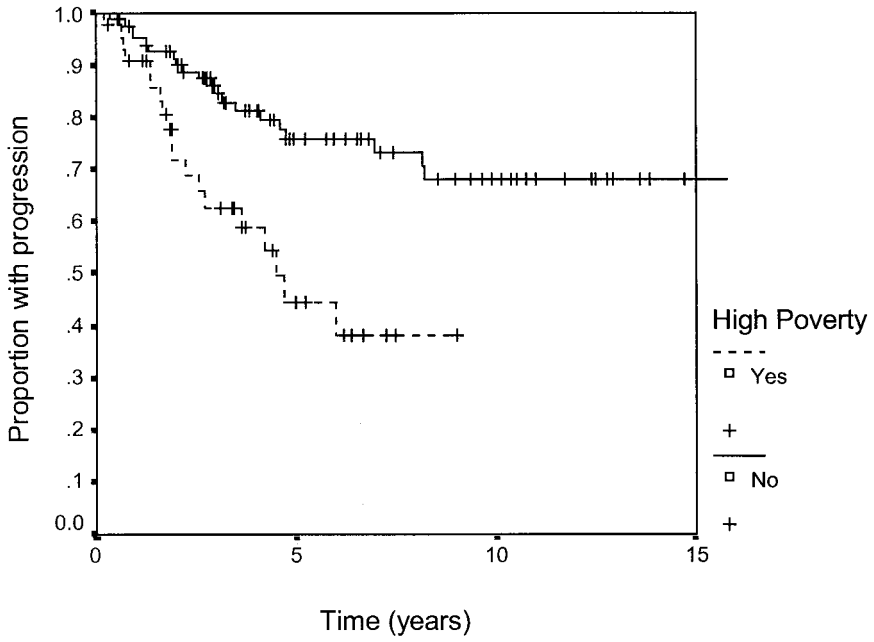

Fig. 2. Progression of proliferative lupus nephritis over time, stratified by proportion in poverty.

African-Americans was elevated compared with Whites (RR 3.5, 95% CI 1.2–10). Relative risk for the Hispanic race/ethnicity model was even higher (RR 5.5, 95% CI 2.0–15).

In the 'Combined' model (Table 3, third column), living in poverty was associated with increased risk of progression of PLN, independent of race/ethnicity. However, the magnitude of the association was considerably reduced by adjustment for race/ethnicity. Insurance status was similarly associated with poor outcome, and was not affected by adjustment for race/ethnicity. In contrast, after adjustment for socio-economic factors, the magnitude of the association of African-American race/ethnicity was reduced and was no longer statistically significant (RR 2.7, 95% CI 0.9–8.7, $P = 0.10$). A similar pattern was seen for Hispanic race/ethnicity, except that it remained statistically associated with progression of PLN (RR 3.6, 95% CI 1.1–11, $P = 0.03$). Alternative models to the Combined model—including intravenous

Table 3. Multivariate predictors of progression of proliferative lupus nephritis

	Socio-economic model		Race/ethnicity model		Combined model	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Living in neighbourhood with high poverty	6.1 (2.1–17)	< 0.001	–	–	3.5 (1.2–11)	0.03
Insurance:			–	–		
Medicare	3.3 (1.2–8.8)	0.02			3.0 (1.1–8.1)	0.03
Medicaid	0.7 (0.2–2.1)	0.48			0.6 (0.2–1.9)	0.38
Private	1				1	
Race/ethnicity:						
Caucasian	–	–	1		1	
African-American			3.5 (1.2–10)	0.02	2.7 (0.8–8.7)	0.10
Hispanic			5.5 (2.0–15)	0.001	3.6 (1.1–11)	0.03
Hypertension	2.3 (1.0–5.2)	0.047	2.1 (0.9–4.9)	0.07	2.2 (0.9–5.1)	0.07
Elevated serum creatinine	4.0 (1.7–9.2)	0.001	4.5 (1.9–11)	0.001	4.1 (1.6–10)	0.004

The 'Socio-economic' model shows relative risk of progression of PLN associated with living in a poor neighbourhood, adjusted for age, sex, intravenous cyclophosphamide treatment, hypertension, serum creatinine and insurance status, but not race/ethnicity. The 'Race/ethnicity' model shows relative risks for African-American and Hispanic race/ethnicity, adjusted for age, sex, intravenous cyclophosphamide treatment, hypertension and serum creatinine, but not socio-economic measures. The 'Combined' model shows relative risks adjusted for all variables in the table, plus age, sex and intravenous cyclophosphamide treatment.
Thresholds were defined as: elevated serum creatinine, > 1.0 mg/dl; high poverty, > 10% of neighbourhood residents living below the Federal poverty line.

cyclophosphamide, including proteinuria and removing baseline creatinine—produced quantitatively similar results for socio-economic and race/ethnic variables (data not shown). Variables in the study were not severely collinear.

Discussion

In this tri-ethnic cohort of patients with PLN, poverty predicted progression of renal function independently of clinical and race/ethnic factors. In addition, we found that Hispanics had an elevated risk of progression of PLN similar to or greater than African-Americans, compared with Whites, and that differences between African-Americans and Whites were not independent of the effects of poverty.

A strong, independent association ties low SES to morbidity and mortality from multiple diseases [18] and, in general, SES is a stronger predictor of mortality than race [19]. Among patients with SLE, several studies have found SES to be an independent predictor of morbidity and mortality, after adjustment for the effects of race/ethnicity [10–14]. Therefore, the observation that poverty is associated with greater progression of PLN is consistent with a large prior literature on socio-economic influences of other diseases. Possible mechanisms may relate to differences in nutritional habits, greater stress and resultant hyper-adrenergic state [20], subsequent development of co-morbid disease and differential access to care. For example, poor patients may have greater difficulty affording all the necessary medications for treatment of SLE, and the resultant non-compliance is associated with a higher incidence of clinical nephritis in a cohort of SLE patients [21].

Despite studies suggesting that African-American race/ethnicity is associated with a poor prognosis in PLN [6,7,22], only one of these studies adjusted for any measure of SES. That study used insurance status as a marker of SES [23]. However, insurance status is not a reliable marker for SES, particularly among patients likely to have disabilities, and may change frequently over the course of time. In contrast, in the present study, we used neighbourhood-based measurements of SES derived from census data, which have been demonstrated in earlier studies to approximate individual measures of SES [15] and are predictive of multiple other diseases [17]. After adjustment for these neighbourhood measures, this study found that neither insurance status nor African-American race/ethnicity was independently associated with an adverse outcome in multivariate models.

Prior studies have hypothesized heritable genetic and biological factors related to selective pressures in Africa or between Africa and America that are more prevalent among African-Americans than Whites. For instance, Salmon *et al.* demonstrated that specific low binding alleles of receptors for immunoglobulin are more common in African-Americans with PLN [9], suggesting that these patients may have genetically determined deficiencies in clearing antigen–antibody complexes. Other studies have demonstrated specific association between complement component deficiencies, major histocompatibility complex (MHC) class molecule alleles and SLE among various ethnic groups [24,25].

Hispanic patients with SLE have been reported to have a worse prognosis than Caucasians [16]. However, the finding that Hispanics have a similar or greater risk of progression of PLN than African-Americans has not been reported previously, to our knowledge, and requires modification of the above hypotheses. An alternative hypothesis is that African-Americans and Hispanics share the same 'harmful' genetic and biological factors, with respect to PLN, that Whites do not harbour. Recently, Zuniga *et al.* found an

increased frequency of low binding alleles for immunoglobulin receptors in Hispanic patients developing PLN [26]. However, Hispanics were not subject to the same environmental pressures that African slaves were, and no similar founder effect or genetic drift should be present among Hispanics in America. A second, alternative explanation is that race/ethnicity was misclassified in this study and that many persons labelled as Hispanic in this study were actually African-American. This explanation would suggest that Hispanics would have a risk intermediate between Whites and African-Americans; however, our results show that Hispanics had the highest risk of progression of PLN in bivariate and multivariate analyses. A third alternative is that African-Americans and Hispanics in this population shared social and economic conditions that predisposed to progression in PLN. Measures of SES were generally similar between African-Americans and Hispanics in this study and were much higher among Whites, consistent with this hypothesis.

Also consistent with the socio-economic hypothesis is the observation of the reductions in risks associated with both African-American and Hispanic race/ethnicities in multivariate analyses. The reductions suggest that associations of race/ethnicity with progression of PLN were confounded by poverty. Although not statistically significant, relative risks for African-Americans in the combined model still remained above the null. Because we relied on neighbourhood-level rather than individual-level data for poverty, poverty was less well measured than other variables in the analysis. Multivariate adjustment for poverty may therefore be incomplete, and it is possible that the observed multivariate risks for African-Americans and Hispanics resulted from this incomplete adjustment for poverty rather than a true association with race/ethnicity. That said, caution should be exercized when interpreting these models as causal due to the observational nature of the data, the relatively small number of subjects and the complex relationships mediating SES and race/ethnicity [27]. Cycles of poverty and their relationship to race/ethnicity suggest that treating poverty as a confounder of the relationship between race/ethnicity and disease—or treating race/ethnicity as a confounder of the relationship between poverty and disease—may be an oversimplification.

As a retrospective cohort analysis, the study may be biased by differential follow-up. However, less frequent follow-up among minorities or patients living in poor neighbourhoods would tend to bias estimates for these groups toward the null due to delays in or missed diagnoses of creatinine elevations. Although we selected consecutively biopsied patients at our institutions, many patients are not biopsied and not all patients in the New York area receive care at our institutions. The study was therefore not population based. This attribute may affect the generalizability of our results if biological and social factors affect progression differently among studied and non-studied patients, but should not, *per se*, affect the validity of the study. Changes in patterns of care over the study period may also introduce bias, although use of intravenous cyclophosphamide was included in multivariate models. Definitions of race/ethnicity are complex, and we relied on self-report or physician's report. As discussed above, misclassification, particularly of Hispanics, should bias results in the opposite direction, as observed in this study. The effect of poverty influencing disease outcome via impaired access to health care may not be valid in other industrialized countries with universal health care. The findings of this study with respect to other multiracial countries is particulary important where inhomogeneties in access to health care and poverty may influence outcome of chronic diseases such as lupus.

As with many other diseases, SES is an important risk factor for progression of PLN, independent of race/ethnicity. Given that Hispanics have an elevated risk of progression similar to African-Americans and given the results of multivariate analyses, much of the poorer prognosis of African-American patients with PLN may be due to socio-economic rather than biological or genetic factors. Indeed, the relative importance of genetic factors may be amplified by environmental factors that are associated with poverty. We believe that social and economic causes of inequity across income and race/ethnicity should be aggressively investigated and that studies that aim to find putative major genes or haplotypes to explain race/ethnic disparities should consider SES.

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Conflict of interest statement. None declared.

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