

Risk of Renal Failure within Ten or Twenty Years of SLE Diagnosis

Michelle Petri, Erik Barr, Laurence S. Magder

Abstract

Background: The frequency of end stage renal disease from SLE in the United States has not improved over the last few decades in large population datasets. Understanding the risk factors for renal failure in SLE could lead to earlier detection of lupus nephritis and potentially more effective treatments in those with markers of poor prognosis.

Methods: The Hopkins Lupus Cohort, comprised of 2,528 patients was used. 151 patients experienced renal failure after SLE diagnosis, defined as dialysis or renal transplant. We estimated the risk of renal failure in subgroups defined by demographics, laboratory tests and ACR/SLICC Classification criteria satisfied within one year of SLE diagnosis.

Results: The overall incidence of renal failure within 20 years of SLE diagnosis was 8.4%. The risk was much higher (20.0%) among those who experienced proteinuria within the first year of diagnosis. Demographic predictors included African American ethnicity (rate ratio 1.82, $p=0.0012$) and age less than 30 years at SLE diagnosis (rate ratio 1.96 vs. those with diagnosis over 40 years of age, $p=0.019$). Among immunologic markers, low C3 was a strong predictor of renal failure (Rate ratio 2.00, $p=0.0011$). **Conclusion:** Proteinuria within the first year of diagnosis of SLE is one of the most important predictors of end stage renal disease. Our data also confirm African American ethnicity, younger age at SLE diagnosis and low C3 as strong predictors of renal failure.

Key Indexing Terms: Lupus, Systemic Erythematosus; Lupus Nephritis; Cohort Studies; Kidney Failure; Risk Assessment

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Introduction

Models to estimate the risk of end stage renal disease after diagnosis of chronic kidney disease stages 3 to 5 have been developed for the general population (1), but comparable studies have not been performed for patients with SLE. End stage renal disease remains a major challenge in SLE management. Large population datasets have shown no improvement in SLE renal outcomes over the last few decades. (2,3). Groups particularly at risk include African-Americans and, to a lesser extent, Hispanic-Americans (4). Patient-specific factors matter as well. Our group previously showed that predictors of poor renal outcome included non-adherence with clinic visits and uncontrolled hypertension (5).

Advances in the treatment of lupus nephritis have not yet translated into improvement in long-term renal outcomes. Clinical trials have shown the equivalence (and, in non-Caucasians, the superiority) of mycophenolate mofetil over oral or intravenous cyclophosphamide (6,7) and the superiority (8) or equivalence (9) of mycophenolate mofetil over azathioprine. However, on average, only 50% of lupus nephritis patients have a complete renal response to mycophenolate mofetil at one year. The recent Phase 1 results of the NIH Foundation Amplified Medicines Partnership suggested that non-responders may have activated other renal pathways (such as interferon alpha and fibrotic pathways) that are important (10).

Several demographic and immunologic factors have been shown to predict end-stage renal disease in those already diagnosed with lupus nephritis. The most important demographic factor is ethnicity, with worse outcomes in non-Caucasians. Non-Caucasian lupus nephritis was a predictor of renal failure in lupus nephritis patients in the Netherlands (11,12). African-Americans with lupus nephritis had poorer renal outcomes in the NIH cohort (13). Both African-American and Hispanic-Americans with lupus nephritis had worse outcomes in a study in Miami (14). African-American ethnicity increases mortality after lupus nephritis (15).

The important prognostic role of immunologic markers in lupus nephritis (e.g. better prognosis with early normalization of low complement during treatment) has been identified in both cohort studies and in analyses of randomized clinical trials of lupus nephritis (16). In these studies low complement,

particularly C3, appeared to be an important marker of renal outcomes (13,17–20). However, not all lupus nephritis is associated with low complement.

Most previous studies have examined outcome only after the onset/identification of lupus nephritis. Past studies have examined predictors of renal outcome at 5 years (21) or 10 years (11) but not beyond. This is the first cohort study of predictors of end stage renal disease in a SLE population with both Caucasian and African-American ethnicity followed for almost 13 years on average in which detailed information on clinical and immunologic predictors are available since SLE diagnosis. In addition, we have developed a formula to estimate the risk of renal failure within 10 and 20 years of SLE diagnosis.

Methods

Patients: The Hopkins Lupus Cohort is an ongoing longitudinal cohort of SLE patients presenting from the community and counties surrounding Johns Hopkins University School of Medicine and which was begun in 1986. Patients who met classification criteria for SLE [either the revised ACR criteria (22,23) or SLICC Classification criteria (24)] are enrolled. All patients give written, informed consent. The study has been approved on a yearly basis by the Johns Hopkins University School of Medicine Institutional Review Board (Study Number NA_00039294).

At enrollment into the cohort, a detailed patient history of SLE is collected based on patient report and medical records. Subsequently, patients are seen quarterly (or more often if medically necessary). At each visit, disease activity indices (including the Physician Global Assessment as part of the Lupus Activity Index (25) and SELENA revision of the SLE Disease Activity Index (26)) are completed by one rheumatologist (Dr. Petri). Laboratory tests were performed at the Johns Hopkins Clinical Laboratories as well, to complete the indices (complete blood count, serum creatinine, urinalysis, urine protein/creatinine, C3, C4, anti-dsDNA by Crithidia). Renal failure was defined as the need for dialysis or renal transplant.

This analysis was based on the Hopkins Lupus Cohort database as of August 2019. At that time, there were 2577 patients in the cohort who had follow-up since SLE diagnosis. Of these, 13 were

excluded because they reported renal failure before the date of SLE diagnosis, and 30 were excluded because the date of renal failure was equivalent to the date of SLE diagnosis. Another 6 were removed due to unknown date of renal failure. The analysis was based on the remaining 2528 patients who were followed for a mean of 12.8 years. Baseline information on patients who were diagnosed with SLE before cohort entry was obtained from the review of all medical record data from onset of SLE. The patient characteristics are shown in Table 1.

Statistical Analyses: The survival analyses were based on the time from SLE diagnosis until the end of follow-up or renal failure/transplant for patients in our cohort. For patients diagnosed with SLE before entering our cohort, the date of diagnosis and clinical manifestations at the time of diagnosis were based on the comprehensive review of all medical records and patient history collected at cohort entry.

We estimated the risk of experiencing renal failure over time among all patients and within subgroups of patients using the Kaplan-Meier approach. Cox regression models were used to estimate the joint association between multiple patient characteristics and renal failure. These models were built in a stepwise fashion, including as candidates those variables found significantly associated in univariate models, and excluding those which were no longer statistically significant ($p>0.05$) after adjustment for other variables.

Results

A total of 151 patients developed renal failure after diagnosis of SLE. Figure 1 shows the estimated cumulative incidence of renal failure in our cohort. The risk of renal failure years was estimated to be 2.7% (95% CI 2.1%,-3.5%) within 5 years, 4.8% (95% CI 4.0%-5.9%) within 10 years, and 8.4% (95% CI, 7.0%-10.0%) within 20 years of SLE diagnosis.

The ten and twenty-year risk of renal failure, by patient subgroup, is shown in Table 2. In univariate subgroup analyses, we found a statistically significantly elevated risk of renal failure among those who were diagnosed with SLE at a younger age, in African Americans, and in those with lower education.

There was no statistically significant change in risk based on calendar time of diagnosis. Those with proteinuria at the time of SLE diagnosis were at the highest risk.

The ten and twenty-year risk of renal failure in patient subgroups defined by presence of immunologic markers is shown in Table 3. Patients who had low complement, anti-dsDNA, anti-Sm, or lupus anticoagulant at any time during their disease course were at higher risk of renal failure.

We used multiple Cox regression to derive a formula for risk prediction based on multiple variables. The higher risk of renal failure among African-Americans persisted after adjustment for socioeconomic status (as measured by education and income). Education was no longer statistically significantly associated with renal failure after adjustment for race and ethnicity. Although income less than \$50,000 was still a statistically significant predictor of higher risk after adjustment for other variables, we did not include it in the final risk formula because a) it was missing for 10% of the observations, and b) we chose to confine the risk model to biologic variables. The final multiple regression model is shown in Table 4. Demographic factors that remained in this final model were male gender (rate ratio 1.69, $p=0.062$), age under 30 at SLE diagnosis (rate ratio 1.96 compared to those with age of diagnosis over 40, $p=0.019$), and African-American ethnicity (rate ratio 1.92, $p=0.012$). Those with proteinuria at the time of SLE diagnosis were at significantly increased risk (rate ratio 2.75, $p<0.0001$). Low C3 was the immunologic marker with the strongest association with renal failure (rate ratio 2.00, $p=0.0011$). The other immunologic markers were not statistically significantly associated with renal failure after adjustment for low C3. The model had good discrimination ($c\text{-statistic}=0.75$) and good calibration (Figure 2).

The hazard ratios in Table 4 can be used to calculate the 20-year risk for a patient with any risk factor profile using the formula:

$$\text{Risk} = 1 - 0.971^{\text{HR}}$$

where HR is the hazard ratio for that patient relative to a female who was diagnosed with SLE before the age of 30 and who had none of the other risk factors. For example, for a male diagnosed with SLE before the age of 30 with proteinuria in the first year after diagnosis, and no other risk factors, the hazard would be increased by a factor of 1.69 (because the patient is male) and by a factor of 2.75 (because of the

proteinuria). Thus, the overall hazard ratio for such a patient would be $(1.69)(2.75)$ which equals 4.65. The 20-year risk is therefore estimated to equal to $1-.971^{4.65}$ which computes to 12.8%. The 10-year risk can be calculated in the same way after substituting 0.984 for 0.971 in the above formula. Using this approach, we estimated that for females with all other risk factors (low age at diagnosis, African-American, proteinuria, low complement, and lupus anticoagulant) the 10-year risk was equal to 21% (95% CI 13%-28%) and the 20-year risk was estimated to be 35% (95% CI 23%-45%).

Discussion

Based on our cohort, among those without renal failure at the time of SLE diagnosis, the risk of renal failure 5, 10 and 20 years after SLE diagnosis was estimated to be 2.7%, 4.8% and 8.4% respectively. Note that this did not include 1.7% of the patients who had renal failure before or at the time of SLE diagnosis, so the percentage of lupus patients with renal failure within 10 or 20 years of SLE diagnosis is somewhat higher than our estimates of incidence after diagnosis. Our five year risk estimates are consistent with those of Plantinga et al who reported 5-year risks of 2.5% and 6.4% in whites and blacks respectively in Atlanta, Georgia (27). Our findings are also consistent with the incidence rates reported in Taiwan (2.5% in 6 years) (28), and somewhat below those reported in Okinawa (9.4% in 10 years) (29). The risk of renal failure did not decline over calendar time.

There are three major findings. First, while the twenty year risk of renal failure was 8.4% for the overall cohort, for a patient with a history of proteinuria at the time of SLE diagnosis, the risk of renal failure within 20 years was 20%. This large difference in outcome, not previously appreciated, can allow consideration of more aggressive therapies in this subgroup. Examples include multi-target therapy with mycophenolate mofetil and tacrolimus (30), newer calcineurin inhibitors (31), experimental sequential regimens such as rituximab followed by belimumab (32) on a background of mycophenolate mofetil, and newer anti-CD20 biologics (ClinicalTrials.gov Identifier: NCT02550652).

Second, confirming previous studies, certain demographic factors, including male gender, African-American ethnicity and SLE diagnosis before age 40 years were statistically significant predictors of renal failure. The higher risk among African-Americans persisted after adjustment for socioeconomic status as measured by education, although it is possible that socioeconomic status may not be on par with educational attainment in certain ethnic minorities. There was no difference in risk between SLE diagnosis at less than 30 years and 30-39 years after adjustment for other predictors.

Third, consistent with the findings of other investigators (13), we found that the immunologic marker that was the strongest predictor of renal failure was low C3. Low C4 and anti-dsDNA (which are highly correlated with low C3) were not statistically significant predictors of renal failure after adjustment for low C3 (although they were significantly associated in univariate analyses).

This is the first 30 year cohort study to assess demographic, clinical, and immunologic predictors of later renal failure in SLE. It is the largest study to include a balance of Caucasian and African-American patients; and the only one to have complete data on risk factors (due to the protocolized nature of follow-up).

Our study has several limitations. As this is a single-center study of patients who agreed to participate in the research cohort, so drawing inferences about general SLE patients should be done with caution. Like most survival analyses, our estimates are based on the assumption that at any given point in time, the risk of end stage renal disease among those censored before that point in time, is similar to the risk among those observed at that specific point in time. To the extent that this assumption is violated, our estimates would be biased. Because we did not have complete information on all deaths in the cohort, we could not account for the competing risk of death in our analysis. This would result in a slight overestimation of the 10 and 20-year cumulative risk. Our multivariable model could also have been biased due to missing covariate information, or unmeasured or residual confounding. Our analyses for immunological markers were based on whether they were ever manifested during cohort follow-up rather than at SLE diagnosis, which could limit their utility for renal outcome prediction early on in disease

course. A final limitation is that, even in this large cohort, the number of events was limited to 151, limiting the power to identify subtle associations and the precision of our estimates.

We think these predictors of renal failure in SLE will be immediately useful in clinical practice to identify patients who might benefit from more aggressive treatment. In particular, those with lupus nephritis in the first year after diagnosis have a greatly increased risk of later renal failure that would justify more aggressive induction therapy. These predictors will also be important in either stratifications for randomized clinical trials or for adjustment in outcome analyses.

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Figure 1: Incidence of renal failure by time since diagnosis based on Kaplan-Meier estimation. The dotted lines constitute 95% confidence intervals for the incidence at each time point.

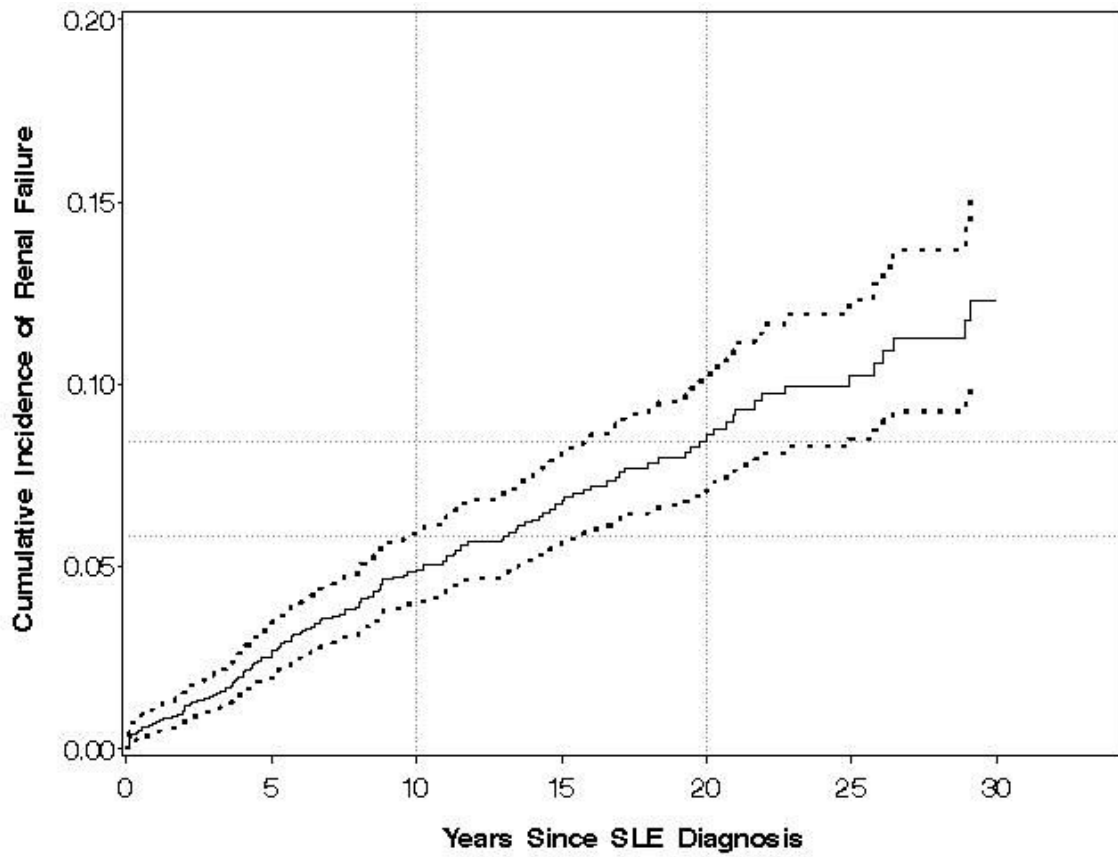


Figure 2: Calibration Plots for the estimation of 20-year risk of ESRD with the Cox models: Dark bars indicate the average 10-year risk in each group based on the model. Gray bars indicate the Kaplan-Meier estimates of the 10-year risk in each group.

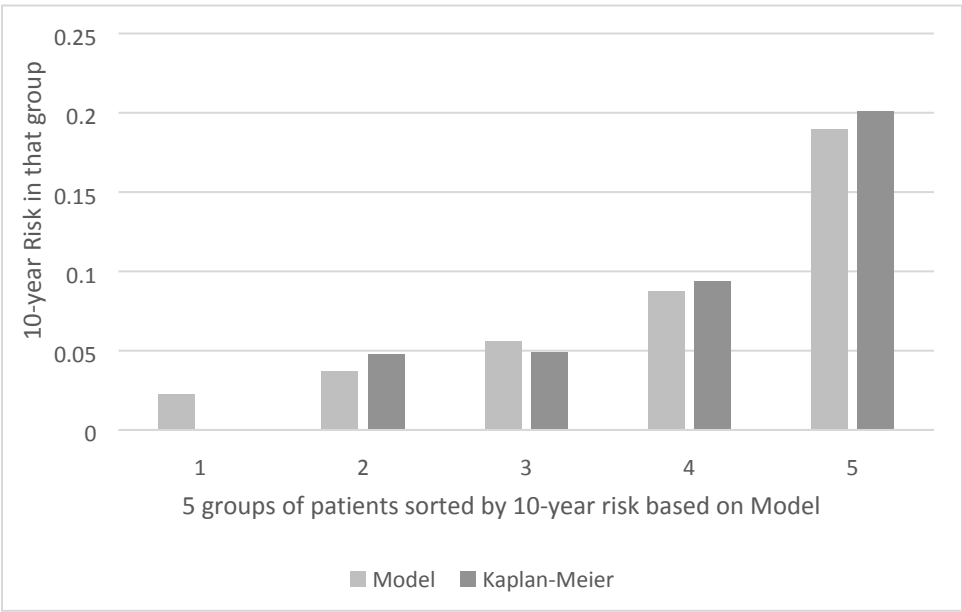


Table 1. Characteristics of Patients Included in the Analysis

Characteristic	Number (%)
Gender	
Female	2334 (92%)
Male	194 (8%)
Ethnicity	
Caucasian	1335 (53%)
African-American	992 (39%)
Other	201 (8%)
Age at Diagnosis (years)	
18-29	1285 (51%)
30-39	613 (24%)
40-49	378 (15%)
50-59	180 (7%)
60+	72 (3%)
Year of Diagnosis	
<1985	294 (12%)
1985-1994	640 (25%)
1995-2004	964 (38%)
2005+	630 (25%)
Follow-up time (since Diagnosis)	
0-5 years	638 (25%)
5-10 years	536 (21%)
10-15 years	445 (18%)
15-20 years	349 (14%)

>20 years	560 (22%)
Years of Education	
<High school	216 (9%)
High school	583 (24%)
Some college	670 (28%)
College graduate	949 (39%)
Family annual income (in 2019 dollars)	
<\$50,000	852 (38%)
\$50,000-\$99,000	686 (30%)
>=\$100,000	726 (32%)
SLE manifestations at the time of SLE diagnosis ¹	
Malar Rash	867 (35%)
Discoid Rash	310 (12%)
Photosensitivity	931 (37%)
Oral ulcers	759 (30%)
Musculoskeletal	1259 (51%)
Neurologic	113 (4%)
Serositis	573 (23%)
Hematologic	911 (36%)
Proteinuria	468 (19%)
Immunologic	1098 (43%)
Alopecia	717 (29%)
Immunologic Markers Ever Positive	
Anti-ds DNA	1563 (62%)
Low C3	1380 (55%)

Low C4	1201 (48%)
Anti-SM	531 (22%)
Anticardiolipin	1158(47%)
Lupus Anticoagulant	639 (26%)
Coombs in the absence of hemolytic anemia	300 (14%)

¹ Denominators used to calculate percentages for some manifestations was not exactly equal to 2,528 due to missing values.

Table 2. Ten year and Twenty year Risk of Renal Failure in Patient Subgroups

Subgroup	Estimated percent risk of developing renal failure within 10 years (95% CI)	Estimated percent risk of developing renal failure within 20 years (95% CI)	P-value (log-rank test) ¹
All	4.8 (4.0, 5.9)	8.4 (7.0, 10.0)	
Gender			0.075
Female	4.4 (3.6, 5.5)	8.3 (6.9, 10.0)	
Male	9.9 (5.9, 16.4)	9.9 (5.9, 16.4)	
Age of SLE diagnosis			0.0007
<30	6.6 (5.2, 8.3)	11.0 (8.9, 13.5)	
30-39	3.4 (2.1, 5.5)	6.4 (4.2, 9.5)	
40+	2.0 (1.1, 3.7)	4.1 (2.3, 7.2)	
Ethnicity			0.0006
White	3.4 (2.5, 4.7)	6.1 (4.6, 8.2)	
Black	6.8 (5.3, 8.9)	11.6 (9.2, 14.6)	
Other	4.0 (1.8, 8.7)	7.4 (3.3, 16.0)	
Year of Diagnosis			0.29
<1985	4.2 (2.4, 7.2)	10.3 (7.2, 14.7)	
1985-1994	5.4 (3.8, 7.7)	8.3 (6.1, 11.2)	
1995-2004	4.7 (3.4, 6.5)	6.7 (4.8, 9.3)	
2004-2015	4.3 (2.5, 7.3)	14.3 (6.5, 30.2)	
Years of Education			0.031

<High school	5.2 (2.7, 9.9)	10.9 (6.4, 18.4)	
High school	5.9 (4.1, 8.5)	10.4 (7.5, 14.2)	
Some college	4.6 (3.1, 6.9)	8.3 (5.9, 11.6)	
College graduate	3.4 (2.3, 5.0)	6.2 (4.3, 8.9)	
Family annual income (in 2019 dollars)			<0.0001
<\$50,000	6.1 (4.6, 8.2)	11.7 (9.1, 15.0)	
\$50,000-\$99,000	3.4 (2.1, 5.4)	5.3 (3.5, 8.0)	
>=\$100,000	3.0 (1.9, 4.8)	5.6 (3.7, 8.6)	
SLE manifestations at the time of SLE diagnosis			
Malar Rash			0.84
No	4.7 (3.6, 6.0)	8.2 (6.1, 11.0)	
Yes	4.9 (3.5, 6.8)	8.5 (6.8, 10.7)	
Discoid Rash			0.37
No	4.9 (4.0, 6.0)	9.1 (7.5, 11.0)	
Yes	4.1 (2.2, 7.5)	4.1 (2.2, 7.5)	
Photo Sensitivity			0.0042
No	5.9 (4.7, 7.4)	10.3 (8.4, 12.7)	
Yes	3.0 (2.0, 4.6)	5.6 (3.9, 8.0)	
Oral Ulcers			0.062
No	5.3 (4.2, 5.7)	9.0 (7.3, 11.0)	
Yes	3.8 (2.5, 5.8)	6.8 (4.6, 10.0)	
Musculoskeletal			0.15
No	5.6 (4.3, 7.3)	9.4 (7.4, 12.0)	
Yes	4.3 (3.1, 5.7)	7.3 (5.6, 9.5)	
Neurologic			0.13

No	4.8 (3.9, 5.8)	8.3 (6.9, 9.9)	
Yes	6.2 (2.8, 13.3)	12.3 (6.2, 2.3)	
Serositis			0.25
No	4.8 (3.8, 6.0)	8.7 (7.2, 10.6)	
Yes	5.0 (3.3, 7.6)	7.3 (4.8, 11.1)	
Hematologic			0.90
No	4.8 (3.8, 6.1)	8.3 (6.7, 10.3)	
Yes	4.9 (3.4, 6.9)	8.8 (6.4, 12.0)	
Proteinuria			<0.0001
No	3.3 (2.5, 4.3)	5.6 (4.4, 7.2)	
Yes	10.8 (8.0, 14.6)	20.0 (15.4, 25.9)	
Immunologic			0.12
No	5.4 (4.2, 6.8)	9.2 (7.4, 11.4)	
Yes	4.1 (2.9, 5.7)	7.2 (5.2, 9.9)	
Alopecia			0.83
No	5.2 (4.2, 6.6)	8.4 (6.8, 10.3)	
Yes	3.8 (0.2, 5.9)r	8.4 (5.9, 12.0)	

¹ The log-rank test assesses the evidence against the hypothesis that the survival curves are equivalent across the entire range of time.

Table 3. Ten and Twenty Year Risk of Renal Failure in Patient Subgroups defined by immunologic markers¹

Immunologic marker ever present during study follow-up	Estimated percent risk of renal failure within 10 years of SLE diagnosis (95% CI)	Estimated percent risk of renal failure within 20 years of SLE diagnosis (95% CI)	P-value (log-rank test)²
Anti-dsDNA			0.0002
No	2.7 (1.7, 4.2)	5.2 (3.3, 7.9)	
Yes	6.0 (4.8, 7.4)	10.0 (8.3, 12.2)	
Low C3			<0.0001
No	1.9 (1.1, 3.1)	4.7 (9.2, 13.4)	
Yes	7.0 (5.7, 8.7)	11.1 (9.2, 13.4)	
Low C4			0.0015
No	2.9 (2.1, 4.2)	6.0 (4.3, 8.3)	
Yes	6.7 (5.3, 8.4)	10.8 (8.7, 13.2)	
Anti-SM			0.037
No	4.4 (3.4, 5.6)	8.0 (6.5, 9.9)	
Yes	6.6 (4.6, 9.4)	10.1 (7.2, 14.2)	
Anticardiolipins			0.29
No	5.2 (3.9, 6.8)	8.6 (6.6, 11.1)	
Yes	4.5 (3.3, 6.0)	8.2 (6.3, 10.5)	
Positive dRVVT test			0.0089

No	4.5 (3.5, 5.7)	6.6 (5.2, 8.3)	
Yes	5.5 (3.9, 7.9)	12.7 (9.5, 16..7)	
Coombs in absence of hemolytic anemia			0.32
No	4.7 (3.8, 6.0)	8.0 (6.5, 9.8)	
Yes	6.0 (3.6, 10.0)	10.5 (6.5, 16.8)	

¹Subgroups defined based on whether a patient ever tested positive for the markers.

² The log-rank test assesses the evidence against the hypothesis that the survival curves are equivalent across the entire range of time

Table 4. Predictors of Renal Failure Based on a Multivariable Cox Proportional-Hazards Model¹

Variable	Rate Ratio (95% CI)	P-value
Male (vs. female)	1.69 (0.97, 2.93)	0.062
History of Proteinuria at SLE diagnosis	2.75 (1.94, 3.89)	<0.0001
Age of SLE diagnosis (in years)		
30-39 (vs. < 30)	0.82 (0.53, 1.27)	0.37
40+ (vs. <30)	0.51 (0.29, 0.90)	0.019
Ethnicity		
Black (vs. White)	1.82 (1.27, 2.60)	0.0012
Other (vs. White)	1.07 (0.52, 2.18)	0.86
Low C3 ever (vs. never)	2.00 (1.32, 3.03)	0.0011
Lupus anticoagulant ever (vs. never)	1.44 (1.01, 2.04)	0.043

¹ The multivariable model was based on only 2351 patients due to missing values for some included variables