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The Association between Pathologic Features from Renal Biopsies and End-Stage Renal Disease in Lupus Nephritis Patients

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The Association between Pathologic Features from Renal Biopsies and End-Stage Renal Disease in Lupus Nephritis Patients

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Abstract

The Association between Pathologic Features from Renal Biopsies and End-Stage Renal Disease in Lupus Nephritis Patients

By Deesha Patel

Background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. SLE can potentially be fatal, especially when major organs are affected. About two-thirds of SLE patients may develop inflammation of the kidneys, or lupus nephritis. Lupus nephritis can progress to end-stage renal disease (ESRD), which requires dialysis or renal transplantation. Lupus nephritis is classified through pathologic features from renal biopsies, which are categorized by the World Health Organization (WHO) morphologic classification of lupus nephritis (1995) or the International Society of Nephrology/Renal Pathology Society Classification (ISN/RPS) of Lupus Nephritis (2003). The aim of this study was to determine the association between pathologic findings from renal biopsies and ESRD in lupus nephritis patients, as well as to determine if the WHO classification of proliferative lupus nephritis was associated with ESRD.

Methods: 237 patients were selected from the Georgia Lupus Registry, a population-based registry of diagnosed SLE in metropolitan Atlanta. Inclusion criteria included validated diagnosis of SLE, a pathology report of an abnormal renal biopsy (WHO classes II-V), ESRD diagnosis after renal biopsy, and African American or White race. Final predictors, and potential confounders, were determined based on previous research, missing data, and preliminary univariate analyses; proliferative lupus nephritis was determined using WHO classification. Univariate and multivariate analyses were conducted to determine if selected pathologic features and proliferative lupus nephritis were associated with ESRD.

Results: The final predictors of interstitial damage, glomerular damage, greater than 25% of glomeruli sclerosed, arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies combined were associated with ESRD (aOR = 8.73, 95% CI: 1.19, 63.76). Glomerular damage and greater than 25% of glomeruli sclerosed were statistically significantly associated with ESRD in univariate and multivariate analyses; tubuloreticular bodies were a statistically significant protective factor for ESRD in both analyses. Proliferative lupus nephritis was not associated with ESRD in either analysis, producing almost a null effect.

Conclusion: When combined together, the selected pathologic features were greatly associated with ESRD. However, only half of those features were associated with ESRD individually. Proliferative lupus nephritis was not associated with ESRD. This study indicates the potential of pathologic features in predicting ESRD in lupus nephritis patients.

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TABLE OF CONTENTS

BACKGROUND

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a multisystem inflammatory autoimmune connective-tissue disease that consists of a vast collection of clinical presentations, including involvement of internal organs such as the kidney, arthritis, skin rashes, photosensitivity, neurologic issues, and hematologic disorders. The current consensus is that the etiology of SLE is an interaction of genetic, environmental, and hormonal factors. SLE is often characterized by unpredictable periods of relapses—or flares—and remissions. Relapses are indicated by the development or return of symptoms due to inflammation or worsening of organ involvement. SLE can potentially be fatal, especially when major organs are affected. Existing medical treatments include anti-inflammatory drugs, antimalarial drugs, corticosteroids, and immunosuppressive drugs, all of which have the potential for mild to severe side effects. The severity of SLE and the comorbidities developed from medical treatments greatly impact the quality of life of SLE patients [1, 2].

It is difficult to ascertain the true incidence and prevalence of SLE due to various factors, including a lack of access to care for high-risk populations and the complexity of diagnosis [1]. The estimated incidence of SLE in the United States is 6.9 per 100,000 per year; the estimated prevalence is 85.8 per 100,000 [3]. It seems that the incidence of lupus has been increasing over the past few decades. However, this may be due to better diagnosis practices, which captures patients with milder diseases, whereas only severe cases were identified previously.

Although it can develop in people of any age or ethnicity, SLE disproportionately affects women of childbearing age and minority groups, particularly African Americans [1, 2]. In the United States, the estimated prevalence per 100,000 for African Americans is 138 compared to 40.7 for Whites; the estimated incidence per 100,000 per year for African Americans is 10.7 compared to 3.3 for Whites [3]. African Americans have an earlier age of SLE onset and greater morbidity and mortality compared to other ethnicities. Potential factors contributing to these disparities include biological and genetic features, lack of access to healthcare, delayed or poor quality of healthcare if accessed, and limited education [4].

Because of the vast collection of clinical presentations and varying prognoses, diagnosing SLE is a complex process. The most commonly accepted method of diagnosis is the American College of Rheumatology (ACR) Criteria for the Classification of Systemic Lupus Erythematosus (SLE). A person is diagnosed with SLE if she has at least four of the eleven criteria, consecutively or simultaneously, during any interval of time. The criteria are malar “butterfly” rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and antinuclear antibody (ANA) [5].

Lupus Nephritis

One of the most common and serious organ involvements in SLE is the inflammation of the kidneys. Renal disease in SLE patients, otherwise known as lupus nephritis, is a strong contributor to the morbidity and mortality of this population [6-8]. Previous research suggests that within the first year of diagnosis, about 50% of SLE

patients will develop some form of renal disease [9] and two-thirds of SLE patients may develop renal disease in their lifetime [6]. Renal survival rates have increased over time due to newer medications, such as immunosuppressive and cytotoxic therapies, which prevent further deterioration of the kidneys. Similar to other manifestations of SLE, the prognosis of lupus nephritis is difficult to ascertain because it progresses differently in each patient and involves several clinical, serological, pathological, and time-dependent factors [7].

Lupus nephritis prominently affects subpopulations of SLE patients. African Americans are almost twice as more likely to develop lupus nephritis than Whites. African Americans also have more aggressive disease and poorer renal survival [10]. At least 70% of children with SLE will develop lupus nephritis during the early stages of the disease and will have more severe disease compared to adults [11]. It has also been suggested that the males may have worse cases of lupus nephritis than females [12, 13].

End-Stage Renal Disease

Despite more efficacious treatments for lupus nephritis, the incidence of End-Stage Renal Disease (ESRD) has not decreased over the past 15 years, possibly due to patients not receiving appropriate care or receiving care too late in the progression of lupus nephritis [14]. In fact, some research has indicated that the incidence has actually increased [8, 14].

Overall, 20 to 25% of patients with lupus nephritis will develop ESRD [15]. Four to 20% of patients will develop ESRD within 10 years of the onset of lupus nephritis [14,

16]; 10 to 30% patients will develop ESRD within 15 years of the onset of lupus nephritis [17]. African Americans about nine times more likely to progress to ESRD compared to Whites [10].

ESRD requires more aggressive treatments (i.e. dialysis and transplantation). ESRD also carries an increased risk of mortality because of dialysis wait times, waiting list for kidney donors, and graft failure after transplantation. Nevertheless, as with other causes of ESRD, kidney transplantation has been associated with reduced mortality and improved quality of life [8].

Several factors may influence the progression to ESRD: greater number of ACR diagnostic criteria, younger age, minority groups, Fcγ genotype, barriers to care, comorbidities such as hypertension, and greater accrued renal damage, which can be identified by renal biopsies [14, 18].

Classification of Lupus Nephritis

In order to determine if lupus nephritis is present and if so, the extent of renal damage and subsequent treatment, a renal biopsy must be completed.

Renal biopsies—assessed by light microscopy, immunofluorescence microscopy, and electron microscopy—are used to diagnose the class of disease, determine prognosis, and establish proper treatment. Renal biopsies also serve as a baseline for subsequent course of disease, allow for correlation with clinical findings, and may discover “silent lupus nephritis” or other renal lesions [9].

The results of renal biopsies are classified according to the World Health Organization (WHO) morphologic classification of lupus nephritis (1995) or the newer International Society of Nephrology/Renal Pathology Society Classification (ISN/RPS) of Lupus Nephritis (2003). Both classifications consist of six similar classes, with each class having its own pathologic criteria to account for the variability in renal lesions. Class I is defined as minimal mesangial lupus nephritis, Class II as mesangial lupus nephritis, Class III as focal lupus nephritis, Class IV as diffuse segmental or global lupus nephritis, Class V as membranous lupus nephritis, and Class VI as advanced sclerosing lupus nephritis [9, 19].

In the WHO classification system, Class I includes normal biopsies as well as those showing minimal mesangial lupus nephritis; ISN/RPS does not include normal biopsies. In both classification systems, Class II consists of mesangial hypercellularity and immune deposits. Class III indicates focal proliferative, segmental, global endocapillary or extracapillary glomerulonephritis involving less than 50% of all glomeruli. Class IV denotes diffuse proliferative, segmental, or global endocapillary or extracapillary glomerulonephritis involving at least 50% of the glomeruli. Class V consists of global or segmental subepithelial immune deposits and advanced sclerosis; it may occur in combination with Class III or Class IV. In the 1982 WHO classification system, Class V was subcategorized: a (pure membranous glomerulonephritis), b (associated with lesions of Class II), c (associated with lesions of Class III), and d (associated with lesions of Class IV). In both classification systems, Class VI indicates that at least 90% of the glomeruli are globally sclerosed without any ongoing activity [19, 20].

Some research has suggested that the WHO classification system has prognostic value, especially in regards to proliferative lupus nephritis. Proliferative lupus nephritis is indicated by WHO Class III, Class IV, Class Vc, or Class Vd. A case-control study by Contreras et al. found that patients who reached the outcome of doubling serum creatinine, ESRD, or death primarily had proliferative lupus nephritis (Class IV: 32%, Class III: 30%, Class V: 18%, Class II: 5%) [21]. Class IV, in particular, has been shown to have the worst prognosis, with 11 to 48% of these patients progressing to ESRD within five years [22]. Overall, proliferative lupus nephritis is associated with a more aggressive disease course and decline in renal function; it is a significant contributor to morbidity due to its severity and consequentially longer times to remission and high relapse rates [7, 21, 23].

Although these classification systems have accounted for various pathologic features, they do not include all of the pathologic findings in renal biopsies, such as interstitial fibrosis, tubular information, atrophy, and arteriolopathy [21]. Information about these pathologic findings used to be found in the activity and chronicity indices, which were recorded by pathologists along with the classification. Pathologists obtained the activity and chronicity scores by grading and adding the injured components of the biopsy [19]. The activity index contained scoring of active lupus nephritis (glomerular proliferation, leucocyte exudation, hyaline deposits, interstitial inflammation, as well as karyorrhexis/fibrinoid necrosis and cellular crescents, each of which were multiplied by 2) with a maximum score of 24; the chronicity index contained scoring of irreversible lupus nephritis (glomerular sclerosis, tubular atrophy, fibrous crescents, and interstitial fibrosis) with a maximum score of 12 [24].

Activity index and chronicity index scoring are rarely used in pathology today, and using only the WHO or ISN/RPS classification systems may leave out a substantial amount of information from the biopsy, which could be used to help further classify the degree of damage, provide a better prognosis, and choose the most efficacious treatments. Austin et al. discovered that patients with activity index scores of 12 or greater had a significantly increased risk of ESRD; at the end of 4-year observation, the estimated probability of ESRD was 40% for the high risk group versus 7% for the low risk group. They also found that the rate of ESRD was significantly increased among patients with mid- or high-range chronicity index scores. Individually, cellular crescents, severe fibrinoid necrosis, tubulointerstitial disease, glomerular sclerosis, fibrous crescents, tubular atrophy, and interstitial fibrosis were associated with an increased risk of ESRD [24]. Another study found cellular crescents to be the most predictive active pathologic feature and interstitial fibrosis to be the most predictive chronic pathologic feature for ESRD [7].

Because prognoses of lupus nephritis differs among patients [7], it would be ideal to examine and consider all pathologic findings of the renal biopsy in order to make an accurate diagnosis of lupus nephritis and therefore choose the most beneficial treatments to prevent progression to ESRD. Not only will this relieve suffering of the patients, but it will help to ease societal burden since a substantial proportion of these patients receive public health insurance or have no health insurance [17].

The primary aim of this study was to determine the association between pathologic findings from renal biopsies and ESRD in patients with lupus nephritis. The

secondary aim of this study was to determine if the WHO classification of proliferative lupus nephritis was associated with ESRD.

METHODS

Hypotheses

This study hypothesized that glomerular damage, interstitial damage, greater than 25% of glomeruli sclerosed, arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies would be associated—individually and combined—with ESRD among lupus nephritis patients. This study also hypothesized that the WHO classification of proliferative lupus nephritis would be associated with ESRD among lupus nephritis patients.

Study Design

Patients for this study were selected from the Georgia Lupus Registry (GLR), a population-based registry of SLE that primarily aims to determine the prevalence in 2002 and incidence in 2002 - 2004 of diagnosed SLE in Fulton and DeKalb Counties (metropolitan Atlanta). In order to maximize case ascertainment, GLR used multiple sources: health care providers, hospitals, community organizations, population data, lupus research databases, and commercial laboratories. Potential cases must have had International Classification Diseases, Ninth Revision (ICD-9), Clinical Modification billing codes of 710.0 (SLE), 695.4 (discoid lupus), 710.8 (other specified connective tissue disease), or 710.9 (unspecified connective tissue disease). Confirmation of residency in Fulton County or DeKalb County during the period of interest (2002 – 2004) was required. SLE cases were validated if they met at least 4 of the 11 revised 1982 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by a rheumatologist [25].

GLR also had access to Center for Medicare and Medicaid Services (CMS) data and therefore information about dialysis treatment and renal transplantation, both of which are indicative of ESRD. When a patient begins treatment for ESRD, medical providers complete the ESRD Medical Evidence Form (2728), which establishes Medicare eligibility for new beneficiaries or reclassifies current beneficiaries as ESRD patients and collects demographic and diagnostic information on new patients. Information from these forms is stored in the U.S. Renal Data System (USRDS) [26]. The USRDS database and the GLR database were merged for patients who had an ICD-9, Clinical Modification billing code indicating SLE as their primary diagnosis.

GLR was funded by a grant from the Centers for Disease Control and Prevention (CDC). IRB approvals were obtained from Emory University, CDC, and Georgia Department of Community Health [25].

Study Population

GLR patients with a validated diagnosis of SLE were considered for this study if GLR had a pathology report of at least one renal biopsy dated before or during the period of interest. If patients had more than one renal biopsy, the earliest renal biopsy pathology report was used. All renal biopsy pathology reports were classified using the WHO morphologic classification system [19]. Patients were excluded if their renal biopsy was graded Class I (normal or minimal damage) or Class VI (indicative of irreversible renal damage that causes severe insufficiency of renal function or ESRD). Seven patients who were not African American or White were also excluded. Another four patients were

excluded because they had begun ESRD treatments before the date of the earliest renal biopsy and therefore were not applicable to this study [Figure 1].

All renal biopsy pathology reports were abstracted through GLR protocol and were scanned as Portable Document Format (PDF) files into the registry. OmniPage 17 (Nuance) was used to convert the PDF files into Microsoft Word documents in order to easily search for variable names.

Variables

For the first model, initial predictor variables were determined based on previous research and common pathologic findings from renal biopsies. Each variable was searched in each pathology report using the "Find" function in Microsoft Word. Most variables were coded as present and not present, some variables were defined in categories (undocumented, mild, mild-to-moderate, moderate, moderate-to-severe, severe), and continuous variables were recorded as is.

Final predictor variables were determined by previous research, missing data, and preliminary univariate analysis [Table 1]. The final predictor variables for Model 1 consisted of interstitial damage (at least one of the following: interstitial fibrosis, interstitial inflammation, acute tubular necrosis, tubular atrophy), glomerular damage (at least one of the following: fibrous crescents, cellular crescents, necrosis, karyorrhexis, endocapillary proliferation), percentage of sclerosed glomeruli (greater than 25% versus 0-25%), arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies. The reference

group for percentage of sclerosed glomeruli was 0-25%, and the reference group for the rest of the predictors was absence of said predictor.

The second model only had one predictor variable, which was the dichotomized version of the WHO classification in proliferative (predictor) and no proliferative (reference) lupus nephritis. Classes III, IV, Vc, and Vd are indicative of proliferative lupus nephritis, whereas Classes II, Va, and Vb typically do not have proliferative elements in the glomeruli (such as endocapillary or extracapillary proliferation) [21].

Potential confounding variables were the same for both models. Race (White as the reference group versus African Americans) and sex (male as the reference group versus females) were included. Age at time of first renal biopsy (years) and time between date of SLE diagnosis and date of earliest renal biopsy (years) were kept continuous. Mucocutaneous ACR criterion (at least one of the following: malar rash, discoid rash, photosensitivity, oral ulcers), arthritis ACR criterion, serositis ACR criterion, neurologic disorder ACR criterion, hematologic disorder ACR criterion, and immunologic disorder ACR criterion were also included as confounders. Renal ACR criterion was excluded due to likely collinearity, and ANA ACR criterion was excluded because it is a screening test with low specificity [27] and poor measure of disease activity [28]. The data for all of the confounders were collected from the GLR database (not renal biopsy pathology reports).

Because such a huge disparity exists between African Americans and Whites in terms of SLE and specifically lupus nephritis [3, 10], both initial models contained interaction terms involving the products of the predictor variables and race.

Statistical Analysis

Descriptive and univariate analyses were conducted for all of the initial and final predictor variables, as well as potential confounders.

Multivariate logistic regression using modeling strategy was conducted for this study in order to obtain odds ratios (ORs) while controlling for potential confounding and effect modification. Model 1 examined the predictive potential of interstitial damage, glomerular damage, greater than 25% of glomeruli sclerosed, arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies on ESRD. Model 2 examined the predictive potential of proliferative lupus nephritis, as defined by WHO classification, on ESRD.

Collinearity was assessed using a SAS MACRO developed at the CDC and Emory University. Collinearity is indicated when there is a high condition index and when two variance decomposition proportions (VDP) excluding the intercept are high. There are no established cut-points; however, Kleinbaum and Klein suggest using the cut-points of 30 for condition index and 0.5 for VDP. Following the hierarchically well-formulated principle, the interaction term with the highest VDP corresponding to the highest condition index was dropped from the model [29]. This process was repeated until the lowest condition index was approximately 33 for Model 1 and 36 for Model 2, respectively, and all VDPs were below 0.5. For both models, all of the interaction terms were highly collinear and therefore had to be dropped from the models.

Because of the large number of potential confounding variables, confounding was assessed for both models using the backward elimination approach provided that the final

OR remained within 10% of the gold standard (full) model's OR. After confounding assessment for Model 1, the following confounders remained: race, sex, time between date of SLE diagnosis and date of earliest renal biopsy, arthritis ACR criterion, serositis ACR criterion, neurologic disorder ACR criterion, and hematologic disorder ACR criterion. After confounding assessment for Model 2, only neurologic disorder ACR criterion and hematologic disorder ACR criterion remained.

All statistical analyses were conducted in SAS 9.3 (Cary, NC) with a significance value of $p < 0.05$.

RESULTS

Descriptive Statistics

The analyses consisted of 237 patients. 213 (89.87%) patients were African American. 201 (84.81%) patients were female. The average age at the earliest renal biopsy was 33.69 ± 12.37 years. The average time between date of SLE diagnosis and date of earliest renal biopsy was 4.33 ± 5.78 years. Neurologic disorder ACR criterion was present in the least number of patients, whereas hematologic disorder ACR criterion was present in the most number of patients [Table 2]. 65 patients had developed ESRD (27.4%) as of 2005.

Only 47 (19.83%) pathology reports indicated arteriosclerosis or arteriolosclerosis. 61 (36.97%) indicated greater than 25% of glomeruli sclerosed, and 67 (28.27%) indicated tubuloreticular bodies. More than half of the patients had glomerular damage (62.45%); over half of the patients also had proliferative lupus nephritis (66.24%). A majority of the patients (81.43%) had interstitial damage [Table 3].

Univariate Analysis

Univariate analyses were completed for each initial predictor and potential cofounders, as well as each final predictor, on ESRD. Among the initial predictors, serum creatinine, percentage of sclerosed glomeruli (continuous), category of interstitial inflammation (dichotomized), cellular crescents, fibrotic crescents, and category of tubular atrophy (dichotomized) produced statistically significant ORs for developing

ESRD. Tubuloreticular bodies were found to be negatively associated with ESRD (OR = 0.48, 95% Confidence Interval (CI): 0.24, 0.97) [Table 1].

Among potential confounders, only race, neurologic disorder ACR criterion, and hematologic disorder ACR criterion were statistically significantly association with ESRD [Table 2].

Among the final predictor variables, tubuloreticular bodies, glomerular damage, and greater than 25% of glomeruli sclerosed were statistically significantly associated with ESRD. Arteriosclerosis or arteriolosclerosis and interstitial damage, as well as proliferative lupus nephritis, were not statistically significantly associated with ESRD [Table 3].

Multivariate Analysis

All interaction terms were highly collinear in both models and therefore not included in the models. Using the backward elimination approach and accounting for an OR within 10% of the GS model, seven confounders remained in Model 1 and two confounders remained in Model 2.

For Model 1, all of the predictor variables together were statistically significantly associated with ESRD when controlling for race, sex, time between date of SLE diagnosis and date of earliest renal biopsy, arthritis ACR criterion, serositis ACR criterion, neurologic disorder ACR criterion, and hematologic disorder ACR criterion. Controlling for the aforementioned confounders, the odds of developing ESRD is 8.73 (95% CI: 1.19, 63.76) times higher among patients with interstitial damage, glomerular

damage, greater than 25% of glomeruli sclerosed, arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies compared to patients without any of these predictors.

Association of each predictor variable, when controlling for all other predictors and confounders, with ESRD was also examined. Glomerular damage (adjusted OR = 3.07, 95% CI: 1.19, 7.93) and percentage of sclerosed glomeruli (aOR = 3.62, 95% CI: 1.52, 8.61) were statistically significant risk factors of ESRD. Tubuloreticular bodies remained a protective factor in the multivariate model (aOR = 0.26, 95% CI: 0.10, 0.71) [Table 4].

For Model 2, the association between proliferative lupus nephritis, as dichotomized by WHO classification, and ESRD was a nearly null effect (aOR = 0.99, 95% CI: 0.52, 1.90) when controlling for neurologic disorder ACR criterion and hematologic disorder ACR criterion [Table 5].

DISCUSSION

The primary aim of this study was to determine if particular pathologic findings from renal biopsies—individually and combined—were associated with ESRD. Having interstitial damage, glomerular damage, greater than 25% of glomeruli sclerosed, arteriosclerosis or arteriolosclerosis, and tubuloreticular bodies were statistically significantly associated with ESRD. Individually, glomerular damage, greater than 25% of glomeruli sclerosed, and tubuloreticular bodies were statistically significantly associated with ESRD. The secondary aim was to determine if proliferative lupus nephritis was associated with ESRD. Proliferative lupus nephritis was not statistically significantly associated with ESRD.

The results of this study reflect the importance of glomerular damage and sclerosed glomeruli in predicting progression of lupus nephritis to ESRD, as suggested by previous research [7, 21, 24, 30]. However, proliferative lupus nephritis, as dichotomized by WHO classification, was not associated with ESRD, as found by previous research [7, 21-23]. It is unclear why proliferative lupus nephritis had nearly a null effect on ESRD in this study. One explanation could be that patients with advanced proliferative lupus nephritis, who were excluded in the analysis for having Class VI disease, did not get renal biopsies early enough, and therefore shifted the OR towards the null. Another explanation could be survival bias. Proliferative lupus nephritis is a marker of ESRD, which is of a marker of mortality [7]. Thus, those with advanced lupus nephritis may not have even made this study cohort. A third explanation could be an under-ascertainment of the earliest renal biopsy pathology reports for SLE cases with long-standing ESRD.

Currently, it is believed that tubuloreticular bodies are associated with minimally treated and clinically active disease [9]. However, this study found that tubuloreticular bodies, both in univariate and multivariate analyses, were statistically significant protective factor against ESRD. It is difficult to ascertain why this is the case. It seems that the role of tubuloreticular bodies in predicting prognosis of lupus nephritis is not yet defined. For instance, Austin et al.'s study that found that absence of tubuloreticular bodies had a higher rate of renal failure, albeit insignificant, compared to the presence of tubuloreticular bodies [24].

It is also important to note that the neurologic disorder and hematologic disorder ACR criteria were statistically significantly associated with ESRD. Neurologic and hematologic SLE manifestations have been found to be associated with worse outcomes such as mortality [31]. One could speculate that some patients with severe lupus nephritis may be more likely to have other serious systemic manifestations, such as neurologic or hematologic disorders, due to severe immune imbalance affecting multiple systems.

In summary, this study provides a group of pathologic features as well as individual pathologic features that are associated with ESRD. This study also raises the question of whether the WHO classification is the ideal classification system in terms of defining proliferative lupus nephritis.

Strengths and Weaknesses

One of the strengths of this study included the population-based registry from which the study population was chosen. Another was the ability to merge the USRDS and

GLR databases, which allowed GLR to determine which lupus nephritis cases had progressed to ESRD. Because a population-based registry reflects the actual population of the disease and provides a large number of patients [25], and because GLR specifically has a thorough amount of data, the results of this study may be generalizable to SLE patients of similar demographics. Previous studies examining the relationship between pathologic features and SLE outcomes like ESRD have been based on selected samples from specialized centers [6, 10, 24, 30].

Weaknesses included the lack of standardization among renal biopsy pathology reports (variation in hospitals, pathology labs, time periods, etc.), absence of renal biopsy pathology reports using ISN/RPS classification, and failure of controlling for comorbidities, such as hypertension, and socioeconomic factors, such as lack of access to care, which may affect prognosis of lupus nephritis [17].

Future Directions

All pathologic findings from renal biopsies should be examined in order to provide patients with the most accurate diagnosis and prognosis, and subsequently, most efficacious treatment. More research is needed in identifying which pathologic features, including those in the classification systems and those that are not, are indicative of poor lupus nephritis prognosis and ESRD. Prospective cohort studies are needed to more accurately identify predictors of ESRD.

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TABLES

Table 1. Descriptive and Univariate Analyses of Initial Predictors on ESRD

Variable	N	Mean (SD)	Frequency (%)	Odds Ratio	95% Confidence Interval	p-value[1]
Serum Creatinine (mg/dL)	119	1.97 (1.80)		1.39	1.10, 1.74	0.0051
Creatinine Clearance (mL/min)	42	72.04 (41.19)		0.98	0.96, 1.00	0.0625
24 Hour Urine Protein (g/24 hours)	80	4.51(3.74)		0.95	0.80, 1.13	0.5607
Total Glomeruli	143	22.22 (13.57)		0.98	0.95, 1.01	0.1730
Percentage of Glomeruil Sclerosed	165	24.23 (24.71)		1.02	1.01, 1.04	0.0015
Interstitial Fibrosis	237		128 (54.01)	0.91	0.51, 1.61	0.7468
Categorized[2]	128		46 (35.94)	1.90	0.85, 4.23	0.1173
Glomerular Fibrosis	237		19 (8.02)	1.61	0.60, 4.29	0.3409
Interstitial Inflammation	237		135 (57.00)	1.09	0.61, 1.94	0.7744
Categorized[2]	135		31 (22.96)	2.75	1.18, 6.37	0.0187
Glomerular Inflammation	237		22 (9.28)	0.39	0.11, 1.36	0.1404
Cellular Crescents	237		92 (38.82)	2.16	1.21, 3.85	0.0095
Fibrous Crescents	237		30 (12.66)	2.28	1.04, 5.01	0.0403
Thickened Basement Membrane	237		135 (56.96)	0.92	0.52, 1.63	0.7631
Acute Tubular Necrosis	237		4 (1.69)	8.27	0.85, 81.01	0.0695
Arteriosclerosis or Arteriolosclerosis	237		47 (19.83)	1.31	0.66, 2.63	0.4419
Karyorrhexis	237		61 (25.74)	0.57	0.28, 1.15	0.1181
Endocapillary Proliferation	237		87 (36.71)	0.84	0.46, 1.53	0.5743
Necrosis	237		43 (18.14)	1.35	0.66, 2.76	0.4055
Wire Loops	237		35 (14.77)	1.07	0.48, 2.37	0.8694
Hyaline Thrombi	237		15 (6.33)	1.35	0.43, 4.11	0.5973
Hypercellularity	237		87 (36.71)	0.57	0.31, 1.07	0.0787
Tubuloreticular Bodies	237		67 (28.27)	0.48	0.24, 0.97	0.0419
Tubular Trophy	237		145 (61.18)	0.86	0.48, 1.53	0.5975
Categorized[2]	145		28 (19.58)	2.84	1.19, 6.81	0.0190

[1]p-values for the association between potential confounders and ESRD at alpha=0.05

[2]Mild to moderate, moderate, moderate to severe, and severe vs. mild and undocumented (reference)

Table 2. Descriptive and Univariate Analyses of Potential Confounders on ESRD

Variable N = 237	**Mean (SD)**	**Frequency (%)**	**Odds Ratio**	**95% Confidence Interval**	**p-value**[1]
Race			9.87	1.31, 74.62	0.0265
African American		213 (89.87)			
White[2]		24 (10.13)			
Sex			0.53	0.25, 1.12	0.0974
Female		201 (84.81)			
Male[2]		36 (15.19)			
Age at earliest biopsy (years)	33.69 (12.37)		0.99	0.96, 1.01	0.2646
Time between SLE diagnosis and earliest renal biopsy (years)	4.33 (5.78)		1.00	0.96, 1.05	0.9083
Mucocutaneous ACR Criterion		127 (53.59)	1.01	0.57, 1.80	0.9607
Arthritis ACR Criterion		152 (64.14)	1.24	0.68, 2.27	0.4831
Serositis ACR Criterion		128 (54.01)	1.40	0.78, 2.50	0.2562
Neurologic Disorder ACR Criterion		54 (22.78)	3.82	2.01, 7.25	<.0001
Hematologic Disorder ACR Criterion		212 (89.45)	10.37	1.37, 78.22	0.0233
Immunologic Disorder ACR Criterion		196 (82.70)	1.21	0.56, 2.63	0.5999

[1]p-values for the association between potential confounders and ESRD at alpha=0.05
[2]Reference group

Table 3. Descriptive and Univariate Analyses of Final Predictors on ESRD

Variable	N	Frequency (%)	Odds Ratio	95% Confidence Interval	p-value[1]
Interstitial Damage[2]	237	193 (81.43)	1.59	0.72, 3.52	0.2539
Glomerular Damage[3]	237	148 (62.45)	2.26	1.19, 4.28	0.0126
Greater than 25% of Glomeruli Sclerosed	165	61 (36.97)	3.14	1.57, 6.30	0.0013
Arteriosclerosis or Arteriolosclerosis	237	47 (19.83)	1.31	0.66, 2.63	0.4419
Tubuloreticular Bodies	237	67 (28.27)	0.48	0.24, 0.97	0.0419
Proliferative Lupus Nephritis (WHO)[4]	237	157 (66.24)	1.21	0.65, 2.23	0.5504

[1]p-values for the association between final predictors and ESRD at alpha=0.05
[2]At least one of the following: interstitial fibrosis, interstitial inflammation, acute tubular necrosis, tubular atrophy
[3]At least one of the following: fibrous crescents, cellular crescents, necrosis, karyorrhexis, endocapillary proliferation
[4]WHO Classes III, IV, Vc, Vd vs. WHO Classes II, Va, Vb (reference)

Table 4. Final Model 1 (Logistic Regression)

Variable	Parameter Estimate	Standard Error	p-value[1]	Adjusted Odds Ratio	95% Confidence Interval
Interstitial Damage[2]	0.90	0.67	0.1822	2.45	0.66, 9.14
Glomerular Damage[3]	1.12	0.48	0.0207	3.07	1.19, 7.93
Greater than 25% of Glomeruli Sclerosed	1.29	0.44	0.0037	3.62	1.52, 8.61
Arterio[lo]sclerosis	0.21	0.51	0.6831	1.23	0.45, 3.33
Tubuloreticular Bodies	-1.34	0.51	0.0084	0.26	0.10, 0.71
Race	1.82	1.13	0.1061	6.20	0.68, 56.69
Sex	-0.83	0.61	0.1708	0.44	0.13, 1.43
Time between SLE diagnosis and earliest renal biopsy (years)	-0.04	0.04	0.2888	0.96	0.90, 1.03
Arthritis ACR Criterion	-0.54	0.49	0.2656	0.58	0.22, 1.51
Serositis ACR Criterion	0.51	0.46	0.2622	1.67	0.68, 4.07
Neurologic Disorder ACR Criterion	1.32	0.48	0.0057	3.73	1.47, 9.48
Hematologic Disorder ACR Criterion	2.09	1.10	0.0574	8.06	0.94, 69.34

[1]p-values for the association between final predictors/confounders and ESRD at alpha=0.05
[2]At least one of the following: interstitial fibrosis, interstitial inflammation, acute tubular necrosis, tubular atrophy
[3]At least one of the following: fibrous crescents, cellular crescents, necrosis, karyorrhexis, endocapillary proliferation

Logit P(ESRD) = -5.78 + 0.90(Interstitial Damage) + 1.12(Glomerular Damage) + 1.29(Greater than 25% of Glomeruli Sclerosed) + 0.21(Arterio[lo]sclerosis) – 1.34(Tubuloreticular Bodies) + 1.82(Race) - 0.83(Sex) – 0.04(Time between date of SLE diagnosis and date of earliest renal biopsy) – 0.54(Arthritis ACR Criterion) + 0.51(Serositis ACR Criterion) + 1.32(Neurologic Disorder ACR Criterion) + 2.09(Hematologic Disorder ACR Criterion)

Table 5. Final Model 2 (Logistic Regression)

Variable	Parameter Estimate	Standard Error	p-value[1]	Adjusted Odds Ratio	95% Confidence Interval
Proliferative Lupus Nephritis[2]	-0.01	0.33	0.9751	0.99	0.52, 1.90
Neurologic Disorder ACR Criterion	1.29	0.34	0.0001	3.64	1.89, 7.03
Hematologic Disorder ACR Criterion	2.24	1.04	0.0313	9.39	1.22, 72.15

[1]p-values for the association between predictor/confounders and ESRD at alpha=0.05
[2]WHO Classes III, IV, Vc, Vd vs. WHO Classes II, Va, Vb (reference)

Logit P(ESRD) = -3.43 – 0.01(Proliferative Lupus Nephritis) + 1.29(Neurologic ACR Criterion) + 2.24(Hematologic ACR Criterion)

FIGURES

Figure 1. Selection of patients for this study.