

Original Paper

Risk Factors for Renal Failure in Patients with Lupus Nephritis: Data from the Spanish Registry of Glomerulonephritis

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Key Words

Lupus nephritis • Renal failure • Demographics • Risk factors • National registry data

Abstract

Background: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus. Data from national registries based on renal biopsies are scarce. The aim of our study was to analyze the demographic characteristics, clinicopathological correlations, and risk factors associated with renal failure in patients with LN at the time of renal biopsy. **Methods:** We performed a cross-sectional observational study based on data from the Spanish Registry of Glomerulonephritis for the years 1994–2009. The outcome measure was the presence of renal failure (eGFR <60 ml/min/1.73 m²). We also recorded age, gender, proteinuria levels, hypertension, and histological class. **Results:** We collected 17,525 native renal biopsies, of which 1,648 biopsies showed LN lesions. In total, 609 patients (37%) showed renal failure at the time of renal biopsy. The univariate analysis showed that these patients were older, had higher levels of proteinuria, and a higher prevalence of hypertension than the group with eGFR ≥60 ml/min/1.73 m². The histological class of LN was recorded for 566 patients, and multivariate logistic regression analysis showed that the independent risk factors for renal failure at the time of renal biopsy were age (OR 1.03; 95% CI 1.01–1.04), male gender (OR 1.94; 95% CI 1.12–3.10), hypertension (OR 3.18; 95% CI 2.16–4.67), proteinuria (OR 1.15; 95% CI 1.08–1.24), and histological classes III and IV (OR 1.82; 95% CI 1.16–2.87). **Conclusions:** Data from the Spanish Registry of Glomerulonephritis provide valuable information about risk factors for renal failure in patients with LN at the time of renal biopsy.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune, connective-tissue disorder with a broad range of clinical presentations. Lupus nephritis (LN) is common in SLE patients and manifests mainly with proteinuria, hematuria, and, less commonly, severe renal failure [1].

LN occurs in approximately half of all patients with SLE, and its frequency ranges from 25 to 75%, depending on the population studied and the diagnostic criteria used [2–3]. Despite improvements in the management of LN, 10–15% of patients remain at risk of developing end-stage renal disease (ESRD) [4]. Previous reports have documented powerful risk factors for ESRD in patients with LN such as demographic characteristics (age, race, gender, and socioeconomic status), clinical and laboratory data [blood pressure, levels of serum creatinine (SCr), proteinuria, anti-dsDNA titer, and hypocomplementemia], histopathological findings [International Society of Nephrology/Renal Pathology Society (ISN/RPS) class and activity and chronicity indexes], and treatment schedules [5]. However, assessments of data from large national registries based on renal biopsies are scarce.

Renal biopsy remains the mainstay of LN diagnosis and is usually indicated as a result of abnormal urinary sediment, proteinuria, or elevated SCr. Biopsy is an essential tool for establishing prognosis and scheduling treatment [6].

Our study was based on individual patient data from the Spanish Registry of Glomerulonephritis (1994–2009) [7, 8]. Thus, our objective was to analyze demographic characteristics, clinicopathological correlations, and risk factors associated with renal failure in a large cohort of patients with LN at the time of renal biopsy.

Patients and Methods

Study Design

We performed a cross-sectional observational study to identify risk factors associated with renal failure in a large cohort of patients with LN.

Patients

Between 1994 and 2009, we collected 17,525 native renal biopsies from the Spanish Registry of Glomerulonephritis. Data from 112 renal units in Spain were recorded to analyze the demographic characteristics, clinicopathological correlations, and risk factors for renal failure in Caucasian patients with biopsy-proven LN. LN histological class was based on the World Health Organization (WHO) and ISN/RPS classifications [9]. In particular, we used the WHO classification during the period 1994–2004, whereas we used the ISN/RPS classification from 2004 to the end of the study. We completed one questionnaire per patient to collect the following variables: age, gender, blood pressure, SCr (mg/dl), proteinuria (g/day), urinary sediment (normal, hematuria, leukocyturia, casts, and telescoped sediment), and the main clinical syndromes (nephrotic, nephritic, asymptomatic urinary abnormalities, arterial hypertension, acute renal failure, chronic renal failure, and macroscopic hematuria). Nephrotic syndrome was defined as proteinuria >3.5 g/day. Nephritic syndrome was defined as hematuria, hypertension, oliguria, edema, and reduced glomerular filtration rate (GFR). Urinary abnormalities included persistent non-nephrotic proteinuria, microscopic hematuria, or both. Hypertension was defined as blood pressure >140/90 mm Hg or the use of antihypertensive medication. Estimated GFR (eGFR) was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [10]. Acute renal failure was defined as a rapid decrease in renal function over days to weeks, while

chronic renal failure was defined as a persistent eGFR of <60 ml/min/1.73 m² for at least 3 months.

Given that our renal biopsy registry includes information over a long study period (16 years), we arbitrarily divided our analysis into three time periods (1994–1998 vs. 1999–2004 vs. 2005–2009) in order to detect tendencies in clinical and histological presentations.

Main Outcome and Outcome Measures

The main study outcome was the identification of the risk factors associated with renal impairment in patients with LN at the time of renal biopsy. The outcome measure was the presence of renal dysfunction, defined as an eGFR <60 ml/min/1.73 m², in patients with LN at the time of renal biopsy. Independent variables were age, gender, presence of hypertension, and LN histological class.

Statistical Analysis

Data were initially stored in a national database (MS Access 2000) and tested for normality of distribution using the Kolmogorov-Smirnov test. The results are expressed as mean \pm SD or median and interquartile range (IQR) when the parameters did not follow a normal (Gaussian) distribution. Comparisons of quantitative data were based on the t test or Mann-Whitney test. The χ^2 test and Fisher exact test were used to compare qualitative variables. An analysis of variance or the Kruskal-Wallis test was used to compare continuous measures in different groups depending on the type of LN. Multivariate logistic regression analysis was performed to determine independent predictors of renal dysfunction. We collected the following variables: age, gender, arterial hypertension, proteinuria, and class of glomerulonephritis. LN classes III and IV were grouped to perform the logistic regression analysis. The Hosmer-Lemeshow goodness of fit was the principal criterion for the selection of the final model. A p value <0.05 (two-tailed) was considered to indicate statistical significance. The statistical analysis was performed using SPSS 15.0 (SPSS Systat Inc., Chicago, Ill., USA).

Missing Values

Data on renal function were accurate and complete. However, some clinical data were not available for all of the 1,648 patients. In general, there were relatively few missing values. As an example, data on gender were available for 99%, data on hypertension for 95%, and data on proteinuria for 93%. Missing data were treated by means of random effects simple imputation. For quantitative data, mean values and standard deviations were estimated from the available data, and the values were randomly generated under the assumption of normality. For categorical variables, missing data were also randomly imputed, taking into account the relative frequency of each category. This allowed us to avoid possible bias from exclusion of patients with one or more missing values. We also performed a separate analysis for the subset of patients with no missing data in covariates included in the final multivariate logistic regression to confirm that missing values did not have major effects on the results. In any case, missing data were not found to have major effects on the final results.

Results

LN was reported in 1,648 biopsies (9.4% of all biopsies). Patients were aged 34 ± 13 years at the time of renal biopsy. As expected, 81% were women and 19% were men. Diagnosis of SLE was made according to the criteria of the American College of Rheumatology [11]. The most common clinical presentation was nephrotic syndrome, and the most frequent pathological finding in sediment was microhematuria. At baseline, 39% of patients

Table 1. Baseline clinical and demographic characteristics (n = 1,648 biopsies)

Mean age ± SD, years	34 ± 13
Gender, %	
Male	19
Female	81
Clinical syndrome, %	
Nephrotic	39.4
Urinary abnormalities	36.4
Nephritic	7.9
Acute renal failure	5.9
Chronic renal failure	4.2
Urinary sediment, %	
Microhematuria	53.8
Telescoped	19.3
Normal	9.3
Median SCr (IQR), mg/dl	1 (0.8–1.6)
Median eGFR (IQR), ml/min/1.73 m ²	75.8 (42.9–102)
eGFR <60 ml/min/1.73 m ² , %	37
Median proteinuria (IQR), g/day	3 (1.5–4.6)
Proteinuria >0.5 g/day, %	94
Hypertension, %	38.9
First biopsy, %	80

Table 2. Clinical characteristics according to the histological type

	Type I and II	Type III	Type IV	Type V	p value
Patients, n (%)	71 (12.5)	92 (16.3)	315 (55.7)	88 (15.5)	
Age, years	37.4 ± 13.6	37.2 ± 12.7	35.1 ± 12.7	33.4 ± 12.8	0.112
Gender					
Male	29.6	26.1	16.2	17	0.022
Female	70.4	73.9	83.8	83	
SCr, mg/dl	1.2 ± 0.7	1.4 ± 1.3	1.5 ± 1.3	1.2 ± 1.4	0.08
eGFR, ml/min/1.73 m ²	79.8 ± 37.3	79.2 ± 35.2	69.1 ± 35.8	92.2 ± 35.1	<0.001
Proteinuria, g/day	2.5 ± 2.4	2.6 ± 2.6	3.9 ± 3	3.9 ± 2.8	<0.001
Hypertension	12.8	15	62.8	9.4	0.003

Data are presented as mean ± SD for continuous variables and percentages for categorical variables.

had hypertension and 63% of patients had an eGFR ≥60 ml/min/1.73 m². These patients were categorized according to different stages of CKD. In particular, the proportions of stage 3A, stage 3B, stage 4, and stage 5 were 27.1, 23.8, 30.1, and 19%, respectively. In 80% of patients, the biopsy was the first biopsy, whereas in 20% of patients, the biopsy was a second biopsy (table 1).

The histological class of LN was only recorded for 566 patients. The most frequent was class IV followed by class III, class V, class II, and class I. Patients with histological class IV LN had a significantly lower eGFR (p < 0.001) and a higher prevalence of hypertension (p = 0.003) than the other classes. Proteinuria levels were significantly higher in patients with histological classes IV and V (p < 0.001) than in the other groups, but no differences were detected among these two groups of patients (p = 0.99). The proportion of women was significantly higher in patients with histological classes IV and V (p = 0.02) than in the other groups, but was similar in both groups. The most common clinical presentation in this group

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Table 3. Clinical features according to the study period

	1994–1998	1999–2004	2005–2009	p value
Patients, n (%)	524 (31.8)	544 (33)	580 (35.2)	
Age, years	32.8 ± 14.1	34.1 ± 13.4	34.3 ± 13.6	0.01
Gender				
Male	18.3	19.3	19.1	n.s.
Female	81.7	80.7	80.9	
SCr, mg/dl	1.6 ± 1.6	1.6 ± 1.7	1.3 ± 1.4	0.03
eGFR, ml/min/1.73 m ²	69.9 ± 36.4	70.7 ± 36.9	79.4 ± 36.4	<0.001
Proteinuria, g/day	3.7 ± 2.9	3.7 ± 2.7	3.5 ± 2.7	n.s.
Hypertension	38.4	37.9	40.3	n.s.
Clinical syndrome				
Nephrotic	30.2	35.4	34.5	0.019
Urinary abnormalities	34.7	30.5	34.8	
Nephritic	27.7	25.4	46.9	
Acute renal failure	24.5	35.7	39.8	
Chronic renal failure	20.3	39.1	40.6	

Data are presented as mean ± SD for continuous variables and percentages for categorical variables. n.s. = Nonsignificant.

Table 4. Comparison of two groups of patients based on eGFR levels

	eGFR <60 ml/min/1.73 m ² (n = 609 patients; 37%)	eGFR ≥60 ml/min/1.73 m ² (n = 1,039 patients; 63%)	p value
Age, years	38.7 ± 15	31.7 ± 11.8	<0.001
Gender			
Male	40.4	59.6	0.172
Female	36.2	63.8	
SCr, mg/dl	2.6 ± 2.2	0.8 ± 0.2	<0.001
eGFR, ml/min/1.73 m ²	33.3 ± 15.7	97.1 ± 22.4	<0.001
Proteinuria, g/day	4.9 ± 3.1	3.2 ± 2.7	<0.001
Hypertension	57.6	42.4	<0.001

Data are presented as mean ± SD for continuous variables and percentages for categorical variables. The χ^2 , t test, or Mann-Whitney test was used as appropriate.

was nephritic syndrome followed by acute renal failure. All patients were of similar age and had similar SCr values (table 2).

We arbitrarily divided our analysis into three time periods and only found that patients in the third period had significantly higher eGFR, although the most frequent clinical presentation was nephritic syndrome (table 3).

Patients were grouped according to the presence of renal dysfunction at the time of renal biopsy. Thus, patients with an eGFR <60 ml/min/1.73 m² (n = 609; 37%) and patients with an eGFR ≥60 ml/min/1.73 m² (n = 1,039; 63%) were compared. Univariate analysis showed that the group of patients with an eGFR <60 ml/min/1.73 m² was older (38.7 ± 15 vs. 31.7 ± 11.8 years; p < 0.001) and had higher levels of proteinuria (4.3 ± 3.1 vs. 3.2 ± 2.7 g/day; p < 0.001) and a higher prevalence of hypertension (57.6 vs. 42.4%; p < 0.001) than patients with an eGFR ≥60 ml/min/1.73 m². No differences in gender were observed (table 4).

Multivariate logistic regression analysis was applied in the subgroup of patients for whom a histological class was available (566 patients) in order to determine the independent

Table 5. Risk factors associated with eGFR <60 ml/min/1.73 m² at the time of renal biopsy

	Adjusted OR	95% CI	p value
Age (years)	1.031	1.016–1.047	<0.001
Male gender	1.946	1.218–3.107	0.005
Proteinuria (g/day)	1.158	1.081–1.240	<0.001
Hypertension	3.180	2.162–4.675	<0.001
Histological classes III and IV	1.829	1.163–2.877	0.009

Multivariate logistic regression. Hosmer-Lemeshow $\chi^2 = 5.095$ and $p = 0.74$. Area under the ROC curve 0.75 (95% CI 0.71–0.79).

variables associated with an eGFR <60 ml/min/1.73 m² at the time of renal biopsy. Age, male gender, intensity of proteinuria, presence of hypertension, and LN classes III and IV were independently associated with renal failure (table 5).

Discussion

This cross-sectional study demonstrates that male gender, older age, level of proteinuria, hypertension, and histological classes III and IV at the time of kidney biopsy are independent risk factors associated with renal failure in patients with LN.

Previous studies have shown that epidemiological and clinical data as well as more severe histological lesions present at the diagnosis of LN are associated with a high risk for developing ESRD during follow-up [12–16]. Our study was based on data from a large national database, the Spanish Registry of Glomerulonephritis, which may better elucidate important risk factors associated with this entity. In addition, it may represent a useful screening tool to identify patients at high risk for progressive renal failure in whom early targeted treatment interventions may be indicated to minimize this complication.

SLE can occur at any age, and previous reports have demonstrated that age at onset was associated with clinical presentations and outcome [17, 18]. Although pediatric series of SLE have documented that renal disease was more frequent and severe in children than in adults [19, 20], other studies did not show such findings [18, 21]. In fact, we found that older patients had an increased risk of impaired renal function at the time of renal biopsy. In other words, the risk was increased 1.39-fold with every 10 years of age. Whether ageing-related histological renal lesions may contribute to poorer renal outcome in patients with LN is undetermined.

LN mainly affects young women, although several studies have demonstrated that disease course and severity is different in men, who have a worse prognosis and present more severe renal impairment. Accordingly, our results showed that men had a 1.9-fold higher risk than women to have an eGFR <60 ml/min/1.73 m² at the time of renal biopsy. Genetic factors may in part account for these differences [22, 23]. The fact that estrogen receptor gene polymorphisms have been associated with higher susceptibility for developing LN in men supports this view [24]. Further analyses in large cohort studies are required to confirm these genetic pathways.

Proteinuria is a characteristic feature of renal disease, appearing in nearly 100% of patients. Its pathogenesis involves immunological factors; glomerular injury is caused by immune complex deposition and non-immune mechanisms associated with other disorders

such as hypertension, dyslipidemia, and diabetes [25]. In addition, the presence of proteinuria is a factor that relates to the development of progressive renal failure [26]. Thus, regression or remission of proteinuria has resulted in improved renal survival in these patients [16]. Consistent with the findings of other studies [27], proteinuria >0.5 g/day was present in 94% of our patients, of whom 48% had nephrotic-range proteinuria. Consequently, our analysis showed that an increase in proteinuria of 1 g/day increases the likelihood of worse renal function by 15% at the time of renal biopsy.

Several studies have established a correlation between the clinical features of SLE and development of hypertension. Although more common in patients with advanced renal disease, hypertension has also been associated with medication (corticosteroids and cyclosporine), age, and obesity [28] in these patients. We found arterial hypertension to be associated with an increased risk of renal dysfunction. This is consistent with earlier reports, in which hypertension was a poor prognostic factor for renal outcome [13, 14, 21]. Our data confirm that baseline hypertension is the clinical parameter indicating the highest risk of impaired renal function. Therefore, control of blood pressure should be considered an important clinical goal in the treatment of SLE patients with renal disease.

The most frequent histopathology finding in our study was diffuse proliferative glomerulonephritis (WHO LN class IV: 56%, followed by class III: 16%), which is consistent with most studies [29, 30]. Histopathological results can provide invaluable prognostic information about LN patients. In retrospective studies, patients with LN WHO classes III and IV are at risk of poorer renal outcomes [21, 31]. Accordingly, we found that patients with LN class IV had a significantly lower eGFR at the time of renal biopsy than patients with LN classes II, III, and V. Thus, it is plausible to think that aggressive therapeutic measurements could slow the decline of renal function in this population. Future longitudinal studies are needed to elucidate this concern.

We arbitrarily divided our analysis into three time periods and found that patients in the third period had better GFR, which can be assumed to indicate renal biopsy at an earlier time.

This study has some limitations. First, we were able to analyze risk factors associated with impaired renal function only at the time of renal biopsy, and no clinical data were collected during follow-up. In addition, as our renal biopsy registry includes information from many centers over a long study period, histological diagnostic criteria could have varied between pathologists. Despite these limitations, our study is based on a large cohort and provides representative data about the main clinical syndromes of LN in Spain, as well as about the main variables associated with renal failure at the time of renal biopsy. Our findings may help to target prophylactic interventions in this high-risk population for progressive renal failure in order to improve outcome in the long term.

In summary, this large study of LN patients from the Spanish Registry of Glomerulonephritis shows that the most important clinical features associated with renal failure are age, male gender, presence of proteinuria, baseline hypertension, and histological classes III and IV at the time of renal biopsy.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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