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Characterization of Patients With Lupus Nephritis Included in a Large Cohort From the Spanish Society of Rheumatology Registry of Patients With Systemic Lupus Erythematosus (RELESSER)

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Abstract: The aim of the study was to profile those patients included in the RELESSER registry with histologically proven renal involvement in order to better understand the current state of lupus nephritis (LN) in Spain.

RELESSER-TRANS is a multicenter cross-sectional registry with an analytical component. Information was collected from the medical records of patients with systemic lupus erythematosus who were followed at participating rheumatology units. A total of 359 variables including demographic data, clinical manifestations, disease activity, severity, comorbidities, LN outcome, treatments, and mortality were recorded. Only patients with a histological confirmation of LN were included. We performed a descriptive analysis, chi-square or Student's *t* tests according to the type of variable and its relationship with LN. Odds ratio and confidence intervals were calculated by using simple logistic regression.

LN was histologically confirmed in 1092/3575 patients (30.5%). Most patients were female (85.7%), Caucasian (90.2%), and the mean age at LN diagnosis was 28.4 ± 12.7 years. The risk for LN development was higher in men (M/F:47.85/30.91%, $P < 0.001$), in younger individuals ($P < 0.001$), and in Hispanics ($P = 0.03$). Complete response to treatment was achieved in 68.3% of patients; 10.35% developed ESRD, which required a kidney transplant in 45% of such cases. The older the patient, the greater was the likelihood of complete response ($P < 0.001$). Recurrences were associated with persistent lupus activity at the time of the last visit ($P < 0.001$) and with ESRD ($P < 0.001$). Thrombotic microangiopathy was a risk factor for ESRD ($P = 0.04$), as for the necessity of dialysis ($P = 0.01$) or renal transplantation ($P = 0.03$). LN itself was a poor prognostic risk factor of mortality (OR 2.4 [1.81–3.22], $P < 0.001$). Patients receiving antimalarials had a significantly lower risk of developing LN ($P < 0.001$) and ESRD ($P < 0.001$), and responded better to specific treatments for LN ($P = 0.014$).

More than two-thirds of the patients with LN from a wide European cohort achieved a complete response to treatment. The presence of positive anti-Sm antibodies was associated with a higher frequency of LN and a decreased rate of complete response to treatment. The use of antimalarials reduced both the risk of developing renal disease and its severity, and contributed to attaining a complete renal response.

Abbreviations: ACR = American College of Rheumatology, aPL = antiphospholipid antibody, APS = antiphospholipid syndrome, BILAG = British Isles Lupus Assessment Group, CI = confidence interval, eGFR = estimating glomerular filtration rate, ESRD = end-stage renal disease, GLADEL = Grupo Latinoamericano Lupus Study, HBP = high blood pressure, IGK = Severity Katz Index, ISN/RPS = International Society of Nephrology and Renal Pathology Society, LN = lupus nephritis, LUMINA = Nature versus Nurture multi-ethnic U.S. cohort, OR = odds ratio, RELESSER = Registry of Systemic Lupus Erythematosus Patients of the Spanish Society of Rheumatology (SER), SELENA-SLEDAI = Systemic Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI, SLE = Systemic Lupus Erythematosus, SLEDAI = SLE Disease Activity Index, SLICC/ACR DI = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index, WHO = World Health Organization.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem rheumatic disease affecting many organs. The involvement of the kidneys, or lupus nephritis (LN), with proteinuria and hypertension being its most prominent features, is a major cause of morbidity and mortality in SLE patients. In fact, renal injury is the most important predictor of mortality in patients with SLE.[1] Clinically evident renal disease occurs in up to half of all patients.[2] Immune complex-mediated glomerular diseases are the most common SLE-associated renal involvement.[3] Based upon clinopathologic correlations, several attempts have been made to classify LN, most notably those by the World Health Organization (WHO)[4] and by the International Society of Nephrology and Renal Pathology Society (or ISN/RPS classification).[5] Both classification systems are based exclusively on glomerular pathology and encompass 6 types. Globally, class I and II apply to minimal and proliferative mesangial glomerulonephritis, respectively. Class III and IV denote focal and segmental or diffuse glomerulonephritis with necrotizing lesions, respectively. Class V applies to membranous glomerulonephritis and, finally, class VI denotes advanced sclerosing glomerulonephritis. Most renal abnormalities emerge within 3 to 5 years after SLE diagnosis.[6] There are wide variations in the prevalence and course of SLE-associated renal disease and several clinical and demographic factors have been shown to influence the outcome.[7] The status of renal vascular lesions in LN is also important as their presence can adversely affect the course of renal disease.[8–10] However, the presence and significance of vascular lesions are often overlooked.

The heterogeneity of disease course and outcome in SLE, coupled with its low prevalence, make it difficult for physicians to acquire sufficient clinical experience in the absence of standardization and collaborative efforts. Therefore, much of the clinical research on SLE has been based primarily on registries and in their derived cohorts, which nonetheless have been an important source of new knowledge about the disease. Studies derived from registries usually have a large number of patients from nonexperimental clinical settings and allow for more extensive follow-up than can be accomplished in clinical trials.

In fact, among the most important data regarding LN are those extracted from multicenter registries, such as the Lupus in Minorities: Nature versus Nurture (LUMINA) multi-ethnic U.S. cohort or the Grupo Latinoamericano Lupus Study (GLADEL).[11,12]

RELESSER-TRANS (Registry of Systemic Lupus Erythematosus Patients of the Spanish Society of Rheumatology [SER], cross-sectional phase) is a hospital-based registry involving a cross-sectional stage designed to obtain a better understanding of SLE in clinical settings.

One of the main objectives of RELESSER was to describe the profile of patients with renal involvement, in order to improve guidelines on its systematic and standardized assessment. In this manuscript we present data regarding histologically proven LN, with or without thrombotic microangiopathy (TMA), and we discuss response to treatment, flares, and the risk of end-stage renal disease (ESRD).

PATIENTS AND METHODS

Research Study Network and Study Design

Members of the Systemic Autoimmune Diseases Study Group of the SER (EAS-SER) established the RELESSER Registry. The first stage, or RELESSER-TRANS, was a cross-sectional, multicenter, national study with historical data collection. A detailed description of the methodology used has been published elsewhere.[13]

The Research Unit of the SER managed all data and data processing. This unit was the coordinating center, providing expert methodological support at all stages of the project, carrying out study monitoring and identifying potential inconsistencies and solutions. The Research Unit of the SER has given expert methodological support to recognized registries of patients with different rheumatic diseases.[14–18]

The institutional research review boards at all participating centers approved this study protocol. The study was carried out in accordance with the Helsinki Declaration. Informed consent was obtained from enrolled patients, except those who died or who were lost for follow-up.

Patient Selection

Selected patients ≥ 16 years diagnosed with SLE (regardless of vital status), according to the 1997 ACR revised criteria,[19,20] considered "defined SLE," or patients with only 3 criteria but SLE diagnosed based on the clinical judgment of an expert rheumatologist, were included. For the specific study of LN, only patients who satisfied at least 4 ACR criteria for the classification of SLE were considered. In order to minimize bias in patient selection, we excluded those with ACR criteria for renal involvement but without histological confirmation.

We planned to include at least 80% of patients in follow-up (with >1 visit to a rheumatology unit) at some point in each center. We excluded those patients whose medical records lacked >50% of the data, a criteria defined as "minimum essential data" (comprising a total of 151 variables). The recruitment period was set at 10 months.

Data Collection

A specific protocol was created to collect ∼400 variables per patient and a web site for data entry was developed and implemented. The RELESSER recruitment and data collection started after a training exercise for investigators. Different procedures were followed to minimize missing data and to ensure data quality, management, and security. Ultimately, the percentage of missing data was <5% in 92% of the variables collected.

Globally, information was obtained from the following domains: (1) demographics; (2) chronological; (3) general clinical data, including vital status; (4) cumulative manifestations of SLE, defined by the glossaries of the ACR criteria for classification of SLE and 6 activity indexes (a) SLE Disease Activity Index (SLEDAI),[21] (b) the British Isles Lupus Assessment Group (BILAG) index,[22,23] (c) the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI);[24] (d) the general SLE activity index, (e) the Systemic Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI[25] Index, and (f) the severity index (Katz index) (IGK) [26]; (5) rare events (<1%); (6) comorbidities, including infections requiring hospitalization or cause of death (causal agent, location, and treatment at the time of infection) and the Charlson Comorbidity Index, as amended by Deyo;[27] (7) laboratory testing; (8) imaging or histological evidence when needed; and (9) treatments and cause of discontinuation per case. Refractory disease was defined by consensus of the Scientific Committee of RELESSER as ineffectiveness of cyclophosphamide, ineffectiveness of ≥ 2 other immunosuppressants (mofetil mycophenolate, methotrexate, azathioprine, or leflunomide), use of rituximab, or splenectomy. Ethnicity was classified as: (1) Caucasians (patients with European ancestral origins); (2) Hispanics (patients treated in hospitals included in RELESSER and residents in Spain when the study was done but from Spanish-speaking countries of Central and South America); (3) Afro-Americans; (4) Asians; and (5) Others. A detailed description of all these variables is included in Supplementary Data, http://links.lww.com/MD/A739 (Table 1).

Antiphospholipid syndrome was defined according to the Sydney criteria,[28] mixed connective tissue disease by the criteria proposed by Alarcon-Segovia and Cardiel[29] and Sjögren's syndrome as the presence of compatible sicca syndrome and a positive Schirmer test, or by biopsy/salivary gland scintigraphy.

Specific variables of renal involvement and their definitions are included in Table 1. We defined complete response after treatment of LN as the normalization of urinalysis and serum creatinine levels. Renal activity was defined as persistence of urinalysis alterations or 24 hours proteinuria > 500 mg in the last 10 days before the final evaluation. Finally, ESRD was defined according to SLICC criteria (Table 1) and/or the need of dialysis and/or renal transplantation.

Statistical Analysis

Means and standard deviations or medians and interquartile ranges for numeric variables based on normal distribution, and absolute and relative frequencies for qualitative variables were calculated. Normality was analyzed with descriptive and graphical methods. Subsequently, we used Skewness, Kurtosis, and Shapiro-Wink tests for normality. The relation of each independent variable with the dependent variable (LN) was assessed by application of different statistical tests: Student's t-test for numerical variables and chi-square when comparing categorical variables among groups. In order to assess associated factors with the presence of nephritis, an assessment calculating crude odds ratios (OR) and adjusted odds ratio with confounding factors through logistic regression was carried out.

Model multivariate analysis included as independent variables possible confounders such as sociodemographic variables and those that deemed clinically relevant.

If 2 variables showed a correlation, our approach was to select the explanatory variable (Covariate) that was more strongly related to the response variable, unless a clinical judgment based on our research weighed in favor of the other.

The number of patients with ESRD and deaths in the cohort were calculated on the basis of age, sex, and ethnicity.

Statistical significance was assumed as $P < 0.05$. All analyses were performed using SPSS 21.0 for Windows (SPSS Inc, Chicago, IL) and Stata 13.1 (StataCorp 4905 Lakeway Drive College Station, TX).

RESULTS

Cohort Characteristics

Among the 4024 patients originally included, 3679 (91%) fulfilled SLE criteria. Ultimately, we were able to complete at least 50% of SLE-related required information in 3575 (89%) patients. Investigators from the 45 participating Rheumatology Departments between 2011 and 2012 enrolled these patients. The median follow-up time was 105(50–173) months. Renal involvement, based on ACR criteria, was established in 1296 patients, although LN was histologically confirmed in 1092 (30.5%) patients with ≥ 4 SLE criteria (ACR-1997), based on WHO classification.[4] The latter individuals were those finally classified as LN-positive patients. Figure 1 shows the flowchart diagram of the patient selection process.

TABLE 1. Specific Variables of Renal Involvement and Definitions of Each

Variables	Definition
Lupus nephritis (LN)	Clinical or laboratory signs of LN not requiring a biopsy
Date of LN diagnosis	
WHO histological subtype of LN:	WHO classification of LN
	Type I: minimal mesangial
	Type II: mesangial proliferative
	Type III: focal
	Type IV: diffuse
	Type V: membranous
	Type VI: advanced sclerosis
	Other subtypes
Highest level of serum creatinine at the beginning of LN	
Estimating glomerular filtration rate (eGFR)	Calculated according to the CKD-EPI* Equation for estimating GFR expressed for specified race, sex, and serum creatinine in mg/dL
Highest level of 24 h proteinuria at the beginning of LN	
High blood pressure (HBP) at LN onset	Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90, or treatment for HBP at the beginning of LN
Activity:	
Urinary casts in the last patient assessment and at the beginning of LN.	Heme-granular or red blood cell casts (SLEDAI definition).
Hematuria in the last patient assessment and at the beginning of LN.	> 5 red blood cells/high power field. Exclude stone, infection, or other cause (SLEDAI definition).
Proteinuria in the last patient assessment and at the beginning of LN.	> 0.5 g/24 hours. New onset or recent increase of more than 0.5 g/24 h (SLEDAI definition).
Highest level of 24 h proteinuria during follow-up	
Pyuria in the last patient assessment and at the beginning of LN.	> 5 white blood cells/high power field. Exclude infection (SLEDAI definition).
Relapses:	
LN relapse	Worsening of renal function, increase in proteinuria levels or urine sediment impairment that required an increase in the dose of steroids and/or the use of a new immunosuppressant.
Number of LN relapses and the date of first and last ones.	
New LN biopsy and the date when performing it.	New renal biopsy performed because of LN relapses
Change in the histological subtype.	
Damage accrual:	
Estimated or measured GFR < 50%, for ≥ 6 mo, and the date of onset.	According to SLICC/ACR DI definition
24 h proteinuria ≥ 3.5 g, for ≥ 6 months, and the date of onset.	According to SLICC/ACR DI definition
End-stage renal disease, regardless of dialysis or transplantation, and the date of onset.	According to SLICC/ACR DI definition
Treatment with dialysis.	
Renal transplantation.	

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, eGFR = estimating glomerular filtration rate, HBP = high blood pressure, LN = lupus nephritis, SLEDAI = Systemic Lupus Erythematosus Disease Activity index, SLICC/ACR DI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

* $GFR = 141 \times \min (S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.159$ (if black) where: S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

Comparative demographic characteristics of patients with and without histological LN:

Most LN patients were female (85.7%) with a median age at disease onset of 28.4 (12.7) years. Median duration of disease was 148.7(79.7–236.8) months and most patients were Caucasian (90.2%). However, when reviewing the data by decade, we found that the frequency of Hispanic ethnicity increased significantly from 1996 to the present (22.51%), compared to the percentages recorded during 1975 to 1985 (0.93%) and 1986 to 1995 (1.85%) ($P < 0.001$). The risk of LN development was significantly higher among men (OR 2.57 [CI95% 2.02–3.29], $P < 0.001$), and also significantly higher when the age of disease onset was lower. Compared to patients 50 years and older, the OR for developing LN was 6.06 (CI95% 4.29–8.56), $P < 0.001$, and 2.52 (CI95% 1.91–3.32), $P < 0.001$, in patients < 16 years old and 16 to 50 years old, respectively.
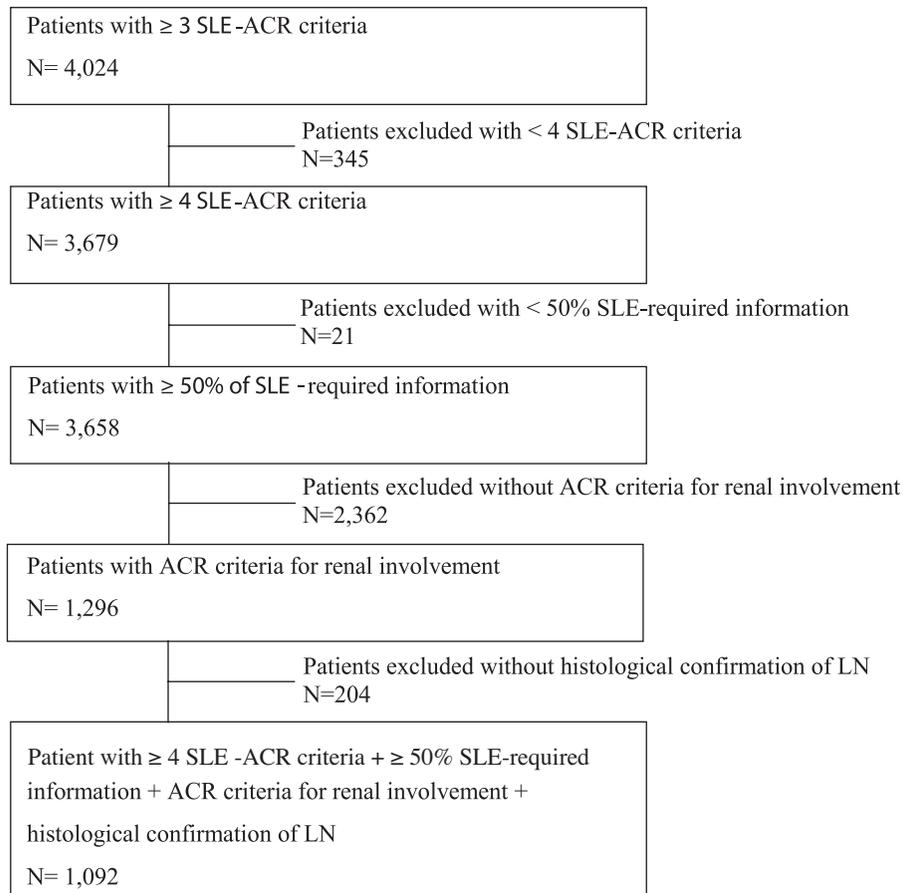
FIGURE 1. Flowchart diagram of the patient selection process.

Hispanic ethnicity was independently associated with a higher risk of renal disease (OR 1.85 [CI95% 1.37–2.51], $P < 0.001$), even in the multivariate analysis after adjusting by gender and/or age of patients. Multivariate analysis also confirmed that male gender and younger patients more frequently developed LN, after adjusting by ethnicity and age or gender, respectively. Comparative demographic characteristics of patients with and without histological LN are detailed in Table 2.

Clinical Characteristics of Patients With Histological LN

In 22.44% (245) of those patients who ever developed LN, it was already present at disease onset, which held true even when we considered their gender or age. Most patients with LN developed it in the first 12 months after SLE diagnosis: 550/977 (56.3%) and 807/977 (82.6%) in the first year and at 5 years, respectively.

TABLE 2. Comparative Demographic Characteristics of Patients With and Without Histological Lupus Nephritis

	Total n = 3350	LN-Negative n = 2258	LN-Positive n = 1092	P Value
Female (%)	3018 (90.3)	2085 (92.5)	933 (85.7)	<0.001
Age at disease onset (y)[*]	35.0 (14.6)	37.6 (14.7)	28.4 (12.7)	<0.001
Duration of the disease (mo)[*]	124.4 (64.0–206.3)	115.2 (58.1–187.1)	148.7 (79.7–236.8)	<0.001
Ethnicity (%)				
Caucasian	3027 (93.1)	2073 (94.5)	954 (90.2)	
Hispanic	171 (5.3)	92 (4.2)	79 (7.5)	<0.001
Other	54 (1.7)	29 (1.3)	25 (2.4)	

LN negative = patients without lupus nephritis (LN), LN positive = patients with histological LN.
[*] Mean (standard deviation) or median (interquartile range).

Most patients (70.2%) suffered a WHO proliferative subtype of LN (III or IV with or without V subtypes). Clinical characteristics of patients with histological LN are detailed in Table 3.

Acute TMA was described in only 16 patients. Although TMA with antiphospholipid syndrome (APS) occurred in 31.3% of these patients, we did not find any significant relationship between TMA and the presence of arterial thrombosis or any of the laboratory criteria for APS, even when considering patients with double or triple positivity for lupus anticoagulant, anticardiolipin, and ant-β2GP1 antibodies, respectively. Serum creatinine levels at the time of renal biopsy were higher among patients with TMA (1.3 mg/dL [0.89–1.8] vs 93 mg/dL [0.72–1.31], $P = 0.02$), as well as lower were the estimating glomerular filtration rates (eGFR) (73.75 mL/min/1.73 m^2 [42.55–86.44] vs 87.30 mL/min/1.73m^2 [57.73–107.81], $P = 0.04$), whereas no difference was found in the degree of proteinuria or abnormalities in urinalysis tests.

Clinical bivariate associations between LN and other lupus manifestations, as well as multivariate analysis after adjusting by age at disease onset and disease duration are presented in Supplementary Data, http://links.lww.com/MD/A739.

We found that cardiovascular and cerebrovascular events were significantly more frequent in patients with LN (OR 2.69 [CI95% 1.49–3.44], $P = 0.001$). This effect of LN was demonstrated even after multivariable analysis including high blood pressure (HBP) and/or ESRD and/or age of patients (OR 1.63 [CI95% 1.25–2.12], $P < 0.001$).

The risk of mortality increased in the LN patient group (OR 3.57, [CI95% 2.58–4.95], $P < 0.001$). Hispanic patients had an increased risk of mortality, but here the difference did not reach statistical significance. In the multivariate analysis, these results were adjusted for age as a continuous variable and sex, although only age proved relevant.

Renal Outcome

Overall, 68.3% of patients with LN achieved a complete response after treatment. Conversely, 17.9% still presented renal activity when the cross-sectional analysis was completed. We did not find any difference in the response or persistence of activity among all the histological subtypes, either in terms of age at disease onset or sex.

Achieving a complete response did not depend on baseline serum creatinine and eGFR levels or on the degree of proteinuria. However, a higher risk for persistent renal activity was found in those with higher levels of baseline serum creatinine (1 ± 0.6 mg/dL vs 0.91 ± 1.0 mg/dL, $P = 0.004$) and proteinuria (2.76 ± 3.9 g/day vs 2.4 ± 4 g/day, $P = 0.006$), whereas no difference was found on baseline eGFR levels. The percentage of patients with a complete response was lower in the case of proliferative forms (69.1% vs 73.9%, $P = 0.27$), but this difference was not statistically significant.

ESRD was found in 113 patients (113/1092, 10.35%). We found a higher risk for ESRD development as the baseline serum creatinine increased (OR 1.67 [CI95% 1.40–1.99], $P < 0.001$) or eGFR decreased (OR.98 [CI95%0.97–0.99], $P > 0.001$) and among patients with hematuria (3.59 [CI95% 1.54–8.35], $P = 0.003$), pyuria (3.25 [CI95% 1.93–5.8], $P < 0.001$) or cellular casts (2.11 [CI95% 1.21–3.56], $P = 0.008$). This was similarly true if patients suffered HBP since the onset of LN. The presence of TMA was a risk factor for ESRD (OR 3.82 [CI95% 1.2–12.12], $P = 0.04$), as well as for the necessity of dialysis (OR 4.81 [CI95% 1.61–14.38], $P = 0.01$) or renal transplantation (OR 5.11 [CI95% 1.38–18.88], $P = 0.03$). Among patients with ESRD, 55 received a kidney transplant (45%). The rate of patients with LN who received a renal allograft decreased significantly over time (OR 0.42 [CI95%0.31–0.58], $P < 0.001$). Comparative demographic and clinical characteristics of patients with LN with and without ESRD are detailed in Table 4.

ESRD was clinically associated with other SLE manifestations such as positive a-dsDNA (OR 3.97 [CI95% 1.92–8.23], $P < 0.001$), low complement levels (OR 3.14 [CI95% 1.52–6.5], $P = 0.002$), pleuritis (OR 3.27 [CI95% 2.17–4.91], $P < 0.001$), pericarditis (OR 4.39 [CI95% 2.92–6.64], $P < 0.001$), seizures (OR 4.23 [CI95% 2.55–7.001], $P < 0.001$), and/or hemolytic anemia (OR 2.02 [CI95% 1.15–3.56], $P = 0.015$).

ESRD was an independent mortality risk factor (OR 9.28 [CI95% 5.81–14.83], $P < 0.001$). After multivariate analysis, adjusted for age of LN onset, sex, and ethnicity, ESRD still proved to be an independent risk factor for mortality (OR 3.88 [CI95% 2.09–7.22], $P < 0.001$).

RELESSER was not designed to analyze the effects of specific treatments for LN. However, we found that among patients taking antimalarials (77.8%), the frequency of LN was significantly lower (OR.58 [CI95%0.48–0.70], $P < 0.001$) and the risk for ESRD was even lower in these patients (OR.23 [CI95%0.14–0.36], $P < 0.001$). This group showed an increased rate of achieving a complete response to a specific treatment for LN (OR 1.61 [CI95% 1.10–2.36], $P = 0.014$). The severity of disease, calculated using the Katz index, did not alter the effects of the antimalarials (OR.65, [CI95%0.52–0.81], OR.23, [CI95%0.15–0.37], and OR 1.65 [CI95% 1.18–2.32], respectively).

TABLE 3. Clinical Characteristics of Patients With Histological LN

	LN-Positive n = 1092
WHO LN subtypes (%)	
Type I	22 (2.5)
Type II	121 (13.6)
Type III	165 (18.6)
Type IV	433 (48.7)
Type V	92 (10.3)
Type VI	8 (0.9)
Type II + V	10 (1.1)
Type III + V	9 (1.0)
Type IV + V	17 (1.9)
Other	12 (1.3)
Serum creatinine at LN onset (mg/dL)*	0.9 (0.7–1.3)
Estimating glomerular filtration rate (mL/min/1.73 m^2)	87.05 (56.99–107.54)
24 h proteinuria > 500 mg (%)	1014 (94.7)
24 h proteinuria at LN onset (g)*	2.5 (1.2–4.4)
Cellular casts (%)	667 (66.6)
Hematuria (%)	819 (79.4)
Pyuria (%)	578 (58.5)
High blood pressure at LN onset	396 (38.6)

LN = lupus nephritis
*Mean (standard deviation) or median (interquartile range).

TABLE 4. Comparative Clinical Characteristics of Patients With LN With and Without ESRD

	LN-Positive/ ESRD-Positive	LN-Positive/ ESRD- Negative	P Value	OR (CI95%)	P Value	Adjusted OR[**]	P Value
Age at LN onset	28 (19−37)	30 (23−41)	0.043				
Gender							
Male/female (%)	16 (17.58)/75 (82.42)	137 (14.15)/831 (85.8)	0.374	0.77 (CI95%0.44−1.36)	0.375	0.7 (CI95%0.39−1.24)	0.221
Ethnicity			0.807				
Caucasian (%)	80 (88.9)	851 (90.63)					
Hispanic (%)	8 (8.9)	66 (7.03)		1.29 (CI95%0.60−2.78)	0.517	1.32 (CI95%0.61−2.87)	0.482
Other (%)	2 (2.2)	22 (2.34)		0.97 (CI95%.22−4.19)	0.964	0.96 (CI95%0.22−4.21)	0.962
Baseline serum creatinine (mg/dL) at LN[*] onset	1.5 (1.2−2.3)	0.9 (0.72−1.26)	<0.001	1.67 (CI95%1.40−1.99)	<0.001	1.75 (CI95%1.44−1.99)	<0.001
Baseline eGFR (mL/min/1.73 m²)	56.5 (30.6−101.5)	87.3 (59.2−107.7)	<0.001	0.98 (CI95%0.97−0.99)	<0.001	0.98 (CI95%0.97−0.99)	<0.001
24 h proteinuria (g) at LN onset[*]	3.7 (2.68−5)	2.4 (1.2−4.3)	0.058				
Cellular casts (%)	68 (80.00)	588 (65.5)	0.008	2.11 (CI95% 1.21−3.56)	0.008	2.11 (CI95% 1.19−3.73)	0.01
Hematuria (%)	78 (92.86)	725 (78.48)	0.005	3.59 (CI95% 1.54−8.35)	0.003	3.43 (CI95% 1.47−8.04)	0.004
Pyuria (%)	64 (81.01)	485 (56.74)	<0.001	3.25 (CI95% 1.93−5.8)	<0.001	3.11 (CI95% 1.73−5.6)	<0.001
High blood pressure at LN onset (%)	56 (65.88)	337 (36.71)	<0.001	3.32 (CI95% 2.08−5.32)	<0.001	3.53 (CI95% 2.20−2.67)	<0.001
Thrombotic microangiopathy (%)	4 (4.76)	12 (1.29)	0.02	3.82 (CI95% 1.20−12.12)	0.02	3.74 (CI95% 1.17−12.00)	0.03

eGFR = estimating glomerular filtration rate, ESRD = end-stage renal disease, LN = lupus nephritis, OR = odds ratio.
[*] Mean (Standard deviation) or median (interquartile range).
[**] Adjusted by the age, sex, and ethnicity.

Lupus Nephritis Recurrence

Globally, there were 326 recurrences, with a median number per patient of 1 (0–7). Most patients suffered only 1 recurrence (70%), whereas 20% experienced 2 relapses. Mean time to first relapse was 47 (0–280) months. A new renal biopsy was performed in 139 patients (120 patients with only 1 repeated biopsy, 19 with >1). Histopathological changes were found in 54% of new biopsies (56% in the first re-biopsy and 67% in consecutive tests). Patients with WHO type II at the first biopsy had the highest rate of worsening in consecutive biopsies although this difference did not reach statistical significance.

The earlier the onset of the disease, the greater was the risk of recurrence. The recurrence rate was 41.3% when the onset was < 16 years, 29.3% between 16 and 50 years, and 18% if > 50 years. The risk was significantly higher in the first group compared to the others ($P < 0.001$).

Patients who suffered LN relapses had significantly higher baseline levels of serum creatinine (1 [0.72–1.31 vs 1 [0.79–1.4] mg/dL, $P = 0.004$) and proteinuria (2.6 [1.22–4.32] vs 2.46 [1.2–4.4] g, $P = 0.006$), but no difference was observed in baseline eGFR levels.

Patients without LN recurrences also had a greater likelihood of achieving complete response (OR.70 [CI95%0.53–0.93], $P = 0.016$). Conversely, patients with LN recurrences suffered an increased risk for maintaining current renal activity, OR 2.25 (CI95% 1.62–3.12), $P < 0.001$.

DISCUSSION

Our results show the most relevant characteristics of histologically proven LN in patients included in RELESSER, the largest European registry of patients with SLE compiled to date.

Lupus nephritis can be regarded as a very prevalent manifestation that often leads to worse prognosis in terms of patient survival. We found that 30% of patients from our series had histological LN, consistent with the frequency reported in the literature, which ranges between 25 and 60%.[2] We should point out that we used WHO criteria versus ISN/RPS classification for LN because in many patients renal biopsy was performed long before the latter guidelines were published.

LN initially developed at SLE onset in 22% of patients. The time from the onset of disease and LN development was longer in older patients and shorter in women ($P < 0.001$). However, the onset time of LN during the course of SLE did not affect the outcome of renal function in our series. These results contrast with those previously reported, suggesting that delayed LN development tends to progress in tandem with renal damage compared to the good therapeutic response that LN typically manifests at SLE onset.[30] Nevertheless, more than two-thirds of patients with LN developed it within 5 years of SLE diagnosis, as has been repeatedly described.[31] The risk for developing LN was higher in males, in younger patients, and in Hispanics. Data from several cohorts have confirmed that the risk for LN is higher in males, leading to poorer survival rates.[32,33] In contrast, we did not find an increased risk for ESRD or a worse prognosis. One possible explanation is that our registry was not specifically designed to examine renal outcome and many confounding and not-included factors may be involved.

Over time Hispanics were diagnosed with LN increasingly rates, which might reflect a parallel increasing migration pattern. We could not demonstrate any effect of ethnicity on the outcome of renal function. Other large cohorts and registries[34–36] have reported disappointing results. However, whether genetic or environmental factors or a combination of the two are responsible has yet to be determined. From a cultural viewpoint, Hispanic ethnicity includes a homogeneous population group, though from a genetic standpoint, the ad mixture is quite varied.[36] Our registry does not permit us to classify Hispanics according to their potential Amerindian ancestry, much less to quantify their degree of ad mixture, and a possible Caucasian genetic background similar to Spaniards could be found in this group. Mean time of follow-up in these patients was shorter than for Caucasians, although we did not observe any association between the lengths of follow-up at our hospitals and renal function outcome or mortality. The lack of differences in renal outcomes suggests not only that genetic factors may be important at disease onset, but also that socioeconomic factors, including access to healthcare services, may take precedence as time goes on. In our series, Hispanic patients had full access to health services, thus reducing the potential impact of these variables, although confirmation of this hypothesis will require larger and more prospective type studies.

Lupus nephritis was associated to a significant degree with an increased frequency of systemic manifestations such as cutaneous lesions, pleuritis and/or pericarditis, as well as severe central nervous system, lung or hematological symptoms, even after adjusting by age, sex, or duration of disease. The frequency of APS was also higher among LN patients, in particular the presence of thrombosis, although we cannot exclude the effect of renal function and nephrotic syndrome on vascular involvement. From a serologic viewpoint, 1 limitation of our study is that it did not include any data related to LN activity at time of diagnosis such as a-dsDNA antibodies or C3 and C4 levels. However, the association between LN and the presence of positive anti-Sm antibodies is worth noting; this proved true even in a multivariate analysis after adjusting by ethnicity, gender, and age (OR 1.69 [CI95% 1.4–2.04], $P < 0.001$). Moreover, the presence of positive anti-Sm antibodies was associated with a decreased rate of achieving complete response to treatment (OR.78 [CI95%0.65–0.93], $P < 0.001$) and an increased risk for persistent renal activity (OR 1.41 [CI95% 1.19–1.68], $P < 0.001$). The pathogenic involvement of these antibodies in LN development is not well known and the literature contains conflicting results about their presence and renal involvement.[37–39] Although we were not able to establish a causal relationship, there were more cases of avascular bone necrosis, cardiovascular and cerebrovascular events, and premature gonadal failure in those patients with LN. For vascular events, such risks were apparent in patients with LN and consequent HBP or in those who developed ESRD. Avascular bone necrosis and premature gonadal failure could be related to treatment with high doses of steroids or cyclophosphamide, as well as to secondary vascular risk factors such as diabetes or HBP.

Surprisingly, the frequency of patients with LN who attained a complete response was 68.3%, which is particularly noteworthy given the fact that we defined complete response as normalization of renal function and resolution of urine sediment abnormalities, including the absence of proteinuria at the last evaluation, albeit without factoring in treatment status. Previous reports have indicated that sustained response is associated with female gender, older age, Caucasian ethnicity, higher nonrenal SLEDAI scores, lower serum creatinine at baseline, and stable renal function following 4 weeks of therapy.[40] However, we did not find any significant association. We defined complete response only when cross-sectional analysis was completed.

The activity index of LN is an important issue for the prognosis and treatment strategy of LN. However, this data was not included in our registry. We can hypothesize that LN was managed according to current clinical guidelines and therefore almost two-thirds of patients have received long-term immunosuppressive drugs and antimalarials and that most of the included patients have been treated and followed-up at experienced clinical centers. Therefore, this kind of study often presents a higher frequency of measurement error, as well as limited information on potential confounding factors.

Consistent with previous reports,[8,41] the presence of TMA itself was a poor prognostic factor for developing ESRD, whereas it was not associated with an increased risk of mortality. The presence of renal TMA in our cohort was lower than in previous studies.[42,43] We should point out that information about TMA was obtained from 1042 biopsies and, therefore, some data were lost. Moreover, diagnosis of TMA in SLE may be overlooked because these 2 disorders share similar clinical features, and the pathological criteria are considered the ''gold standard'' in patients with SLE.[42] However, acute thrombosis in LN detected with routine histology is rarely observed possibly because of its relatively sparse presence and the small size of tissue samples obtained with renal biopsy. One-third of our patients with TMA had also been diagnosed with APS, although this association did not reach statistical significance. The precise role of antiphospholipid antibodies (aPL) in the development of lupus-related TMA has not been elucidated, and immunomediated platelet activation could be involved leading to renal microthrombosis, both in positive or negative aPL patients.[44,45]

During this long-term follow-up ($120.2 + 87.6$ months) ~30% of patients developed at least 1 flare that required further treatment. We should point out that a weakness in our findings here is that less than half of recurrences were documented by histology. On the other hand, most patients who completely recovered after treatment did not develop chronic renal insufficiency. Consistent with previous studies, favorable factors for good long-term outcome include complete renal remission and the absence of nephritic flares and their complete reversibility after therapy.[46]

The number of patients that developed ESRD was surprisingly low: only 10.35% of patients with LN. Our results only revealed a significant association with serum creatinine at LN onset, which remains the most frequently reported clinical predictor of progression towards ESRD.[47] Certainly, we cannot draw conclusions concerning any effects of specific therapies, although the elevated antimalarials (77.8%) and cyclophosphamide (60.7%) prescriptions among our patients with LN could explain these results. On the other hand, 60.18% of patients with LN remained on immunosuppressive treatment at their last evaluation, as well as on antimalarials (65.33%) or glucocorticoids (70.5%). Finally, all patients included in RELESSER have been followed-up in rheumatology services with expertise in SLE management.

On the other hand, ESRD was significantly associated with an increased mortality risk, most often stemming from SLE, severe infections, malignancy or vascular events. We did not find differences when we considered the sex or age of the patients.

Our results confirm that the use of antimalarials in SLE patients is associated with a reduced risk of developing renal disease, and with a lower severity of LN. We have also shown that, statistically, the concomitant use of antimalarials contributes to attaining a complete renal response. Although with our data, we cannot conclude if LN was less frequent in patients taking antimalarials because they were less severely affected, similar findings were confirmed after adjusting by the degree of severity of disease (Katz index), thus strengthening the significance of the association. These results are consistent with those previously reported in LUMINA, GLADEL, and the Hopkins Lupus cohorts.[48–50] Finally, we could not infer the exact temporal relationship between renal damage and antimalarial use from the data collected.

Our study has the obvious disadvantages inherent to retrospective data collection. We cannot exclude random associations due to the large number of variables analyzed. However, we have tried to minimize this risk by using multivariate analysis. On the other hand, we have considered only patients with histologically proven LN in order to minimize the internal validity, although this limits the generalizability of our results. The main objectives of this registry did not include analysis of the specific effects of therapies on individual manifestations. However, our study also possesses numerous strengths that help overcome this limitation: different strategies to both minimize the absence of certain data and to increase the quality of the remaining data, as well as a really large sample size.

CONCLUSIONS

Histopathologic LN affects one-third of SLE patients included in RELESSER, being more severe among males, young people and Hispanics. Frequently, LN develops in association with numerous manifestations of systemic involvement. The presence of positive anti-Sm antibodies is associated with a higher frequency of LN and a decreased rate of complete response to treatment. However, in our registry the rate of complete response and the frequency of ESRD development were better and lower, respectively, than has been previously described. Interestingly, our results suggest that the use of antimalarials reduces the risk of developing renal disease, as well as its severity, and contributes to attaining a complete renal response.

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