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Lupus Nephritis in Males: Clinical Features, Course, and Prognostic Factors for End-Stage Renal Disease

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Introduction: Because of their rarity in men, systemic lupus erythematous and lupus nephritis (LN) are poorly understood in men. Our aim was to analyze the clinical presentation and course of histology-proven systemic lupus erythematous and LN in males and to determine the risk factors for progression to end-stage renal disease.

Methods: Fifty patients from 2 historical cohorts in Spain (Hospital 12 de Octubre) and Uruguay were retrospectively analyzed and compared with a female cohort matched for age and disease characteristics.

Results: The median age at the time of renal biopsy was 27 years (range, 8–79 years). The main forms of presentation were nephrotic syndrome in 26 of 50 patients (52%), and class IV LN in 34 of 50 (68%). After treatment, 21 patients (45.6%) achieved complete renal remission. During follow-up, 12 patients required renal replacement therapy, and 3 patients died of infectious causes. When patients who required renal replacement therapy were compared with those who did not require it, several parameters showed significant differences ($P < 0.05$) at the time of renal biopsy: estimated glomerular filtration rate < 60 ml/min, hypertension, hypoalbuminemia, and concomitant visceral involvement (neurologic, cardiovascular, and/or pulmonary). In the multivariate analysis, only estimated glomerular filtration rate < 60 ml/min persisted as a risk factor for progression to end-stage renal disease. When compared with a cohort of female patients with LN, there were no significant differences in remission or renal survival.

Discussion: LN in males usually presents as nephrotic syndrome, and type IV LN is the most frequent form. An estimated glomerular filtration rate < 60 ml/min at the time of renal biopsy is associated with poor renal outcomes. There were no differences in remission or progression of LN in males when compared with a cohort of female patients with LN.

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Systemic lupus erythematosus (SLE) is a systemic autoimmune condition, characterized by the production of autoantibodies, predominantly against nuclear antigens.[1] It primarily affects women of childbearing age and is rare among males. Males account for 4%–22% of all cases in various series.[2,3]

Lupus nephritis (LN) is the most frequent manifestation of lupus, being observed in 30%–75% of patients, either at the time of onset or during the course of the disease.[2] It implies severity and is considered the most important predictor of morbidity and mortality in various studies in both men and women.[4–6]

An important controversy appears when the data for males and females are compared. Historically, SLE in males has been associated with greater severity and poorer prognoses, particularly as a result of the presence of serositis and greater renal, neurologic, and hematologic impairment.[2,7,8] However, a recent study with a 30-year follow-up failed to reveal any significant sex-related differences in terms of the clinical manifestations of SLE and actually showed a greater percentage of extreme renal failure and mortality among women.[9] Part of the difficulty in understanding the clinical characteristics and severity of LN in males is related to the scanty number of such cases diagnosed annually; that is what inspired us to analyze 2 cohorts.

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Of the 4000 Spanish patients registered in the European SLE Registry, 3679 have a definitive diagnosis of SLE based on the criteria of the American College of Rheumatology. More than 90% of the patients are Caucasian, and approximately 10% are male. Involvement of the kidneys, as indicated by proteinuria and cell casts, is found in 1197 (34%). The mean age at diagnosis is 33 years.[10]

Based on the data of the Uruguayan Renal Health Program and the Program for the Prevention and Management of Glomerular Disease, in Uruguay, LN ranks second among the secondary glomerular diseases, just after systemic vasculitis. Its incidence has been stable, with 4.38 cases per million people, data obtained from an analysis of the kidney biopsies in subjects older than 14 years between 1998 and 2009.[11]

Our objectives were to conduct a retrospective analysis of 2 historical cohorts including all men diagnosed with SLE and LN in both cohorts,(50 men overall, 25 in each cohort) to evaluate the clinical and histologic presentation in patients with SLE and biopsy-documented LN and to analyze the risk factors leading to extreme chronic kidney disease that are associated with a higher mortality rate.

To determine whether there are differences in renal survival and mortality between men and women, we selected a cohort of 50 female patients with LN, 25 from the Uruguayan Registry and 25 from the Hospital 12 de Octubre.

METHODS

The retrospective analysis of the historical cohort from the Hospital 12 de Octubre in Madrid, Spain, was performed based on the center's medical records and results of renal biopsies, and the Uruguayan cohort data were obtained from the Program for the Prevention and Management of Glomerular Disease. The Spanish cohort included patients who were treated from 1971 to 2013, and the Uruguayan cohort included patients registered between 1986 and 2013. The study included all the men diagnosed with SLE and LN in both cohorts. The protocol for the analysis in Uruguay was accepted by the ethics committee of the Hospital de Clínicas, of the University of the Republic, and meets all the criteria established by the Hospital 12 de Octubre in Madrid. Strict confidentiality of the data analyzed was preserved in all cases.

To receive a diagnosis of SLE, each patient had to meet at least 4 criteria of the American College of Rheumatology, revised in 1997.[12] The diagnosis of LN was exclusively histologic, through renal puncture biopsy. Specimens were classified according to World Health Organization definitions. The same definitions were used for re-biopsies, since most cases occurred before 2005.[13]

For the male cohort to be compared with a female cohort, each male patient was matched (1:1) with a female patient with LN selected from the same registry as the male patient, and patient's age, year of LN diagnosis, serum creatinine level, histologic form of LN, and initial treatment were taken into account.

The unavailability of renal histology test results was considered an exclusion criterion.

The endpoints were initiation of dialysis or kidney transplantation.

For statistical purposes, the results are presented as means and SDs for the continuous variables with normal distribution and medians for those without normal distribution; qualitative variables are described through percentages.

Renal survival was defined as the time elapsed between the histologic diagnosis and the initiation of renal replacement therapy (RRT) (dialysis or transplantation); deaths were considered censored.

The chi-square and Fisher exact tests were used to investigate the association between qualitative variables, as appropriate. The quantitative variables were compared by using Student t test, and binary logistic regression was conducted for the multivariate analysis.

Survival curves were developed by using the Kaplan-Meier method, and they were compared by using the log-rank test to determine whether the differences in survival were significant. Holm-Sidak's multiple comparisons test was used to detect the differences observed between groups.

A P value < 0.05 was considered statistically significant. The statistical analysis was performed with SPSS software (version 17 for Windows [SPSS Inc, Chicago, IL, USA]). Sigma Plot 12.0. (Systat Software Inc, San Jose, CA, USA) and SPSS Statistics for Windows, version 17.0 were used for graphics and survival tests.

Operational Definitions

- Hypertension (high blood pressure): blood pressure $\geq$ 140/90 mm Hg or use of hypertension-reducing agents.
- Asymptomatic urinary disorders: the presence of changes in urinary sediment (proteinuria $>$ 0.5 g/24 h, hematuria, cylindruria) with no high blood pressure and with an estimated glomerular filtration rate (eGFR) $>$ 60 ml/min per 1.73 m^2 estimated by chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
- Nephrotic syndrome was defined by the presence of edema, proteinuria $\geq$ 3.5 g/24 h, and a serum albumin level $<$ 3.5 g/dl.

- Rapidly progressive kidney failure was cataloged as a renal failure with a drop of > 50% in the eGFR from baseline levels in less than 3 months, together with active sediment, microhematuria, and proteinuria.
- Complete remission (CR) was defined as a drop of serum creatinine values to baseline values (or eGFR > 60 ml/min), associated with a reduction in proteinuria to < 0.5 g/24 h.[14]
- Partial remission (PR) was defined as the stabilization of serum creatinine levels (±25%), together with a drop of at least 50% in the baseline level of proteinuria. The patients not included in these classes are tagged as nonresponders.[14]
- Initiation of RRT was defined as the need for long-term dialysis or renal transplantation.

Involvement of any extrarenal organs, including joints, skin, and mucosa and cardiovascular, pleuropulmonary, or neurological impairment should meet the criteria suggested by the American College of Rheumatology.[12]

RESULTS

Population

The records of 50 patients were analyzed; 49 of 50 were white of European descent, and 1 was of African descent. Twenty-five male patients came from the registries of the Hospital 12 de Octubre (Madrid), and the remaining 25 patients came from the Uruguayan Program for the Prevention of Glomerular Disease. All patients had been diagnosed with SLE and renal puncture biopsy–confirmed LN. The mean age at the time of renal puncture biopsy was 27 years (range, 8–79 years). Four patients were diagnosed between the ages of 0 and 14 years, 24 between the ages of 15 and 29 years, and 18 between the ages of 30 and 44 years. Four patients were diagnosed when they were older than 45 years.

Presentation at the Time of Biopsy

Tables 1 and 2 list the clinical presentations at the time of the renal biopsy, as well as the extrarenal involvement.

Renal involvement was observed concomitantly with the onset of SLE in 29 of 50 patients (58%).

The most frequent clinical form of presentation was nephrotic syndrome in 26 of 50 patients (52%), followed by rapidly progressive kidney failure in 19 of 50 patients (38%). Five patients presented with asymptomatic urinary abnormalities.

Histology

The most common histologic finding was type IV LN in 34 of 50 patients (68%), followed by type V LN in 9 (18%), type III LN in 5 (10%), and type II in 2.

Table 1. Clinical and laboratory manifestations at the time of the renal puncture biopsy

Clinical and laboratory manifestations	[n = 50] Median ± SD
Serum creatinine levels (mg/dl)	2.18 ± 1.47
eGFR < 60 ml/min	31 (62%)
Proteinuria (g/24 h)	4.6 ± 3.5
Hematuria	49 (98%)
Hypertension	38 (76%)
SBP (mm Hg)	148.2 ± 20.2
DBP (mm Hg)	90.8 ± 16.1
Serum albumin levels (g/dl)	2.7 ± 0.6
Hemoglobin (g/dl)	11.1 ± 2.2
Low serum complement C3	42/50 (84%)
Low serum complement C4	40/50 (80%)
ANA +	48 (96%)
Anti-DNA +	37 (74%)

ANA, antinuclear antibody; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

During follow-up, 10 new biopsies were performed in 8 patients, leading to 8 re-classifications of the dominant injury pattern. The changes observed went from initial type II to IV in 1 patient, from type III to IV in 2 patients, from type IV to III in 2 patients and to V in another, and from type V to III and IV, respectively. Worsening of the histologic pathology was observed in 5 patients.

Management and Course

All patients received corticosteroids as initial therapy. Cyclophosphamide was administered to 39 patients (84.7%); 33 received i.v. boluses and 6 received it orally. Azathioprine was given to 10 patients, and mycophenolate mofetil, to 3. Twenty-three patients received azathioprine and 6 received mycophenolate mofetil as maintenance therapy.

The cohort had a median follow-up of 54 months (range, 2–360 months). At the end of follow-up, 31 patients remained in follow-up, 12 (26%) had begun receiving RRT (1 in the early kidney transplant modality), 8 of 12 after the year 2000, and 4 patients were lost to follow-up. The 3 deaths recorded were all due to

Table 2. Extrarenal manifestations at the time of the renal puncture biopsy

Extrarenal manifestations	n [50]	%
Joints	41	82
Skin – mucosa	33	66
Hematologic	30	60
Cardiovascular	18	36
Pleuropulmonary	18	36
Neurologic	14	28
N-P-C	31	62

N-P-C, concomitant neurologic, pulmonary, and/or cardiac impairment.

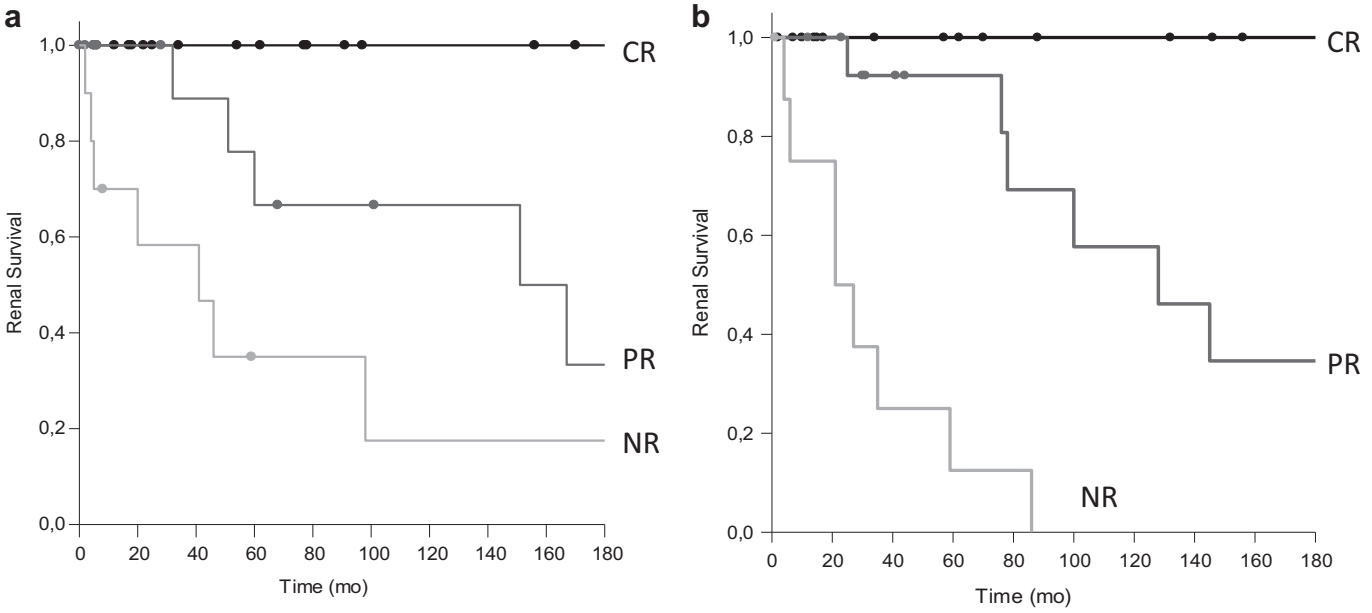

Figure 1. Remission-based Kaplan-Meier curve for renal survival in (a) males and (b) females. Graph limited to 15 years after renal biopsy. Males: CR versus PR ($P = 0.005$), CR versus NR ($P < 0.001$), PR versus NR ($P = 0.118$). Females: CR versus PR ($P < 0.001$), CR versus NR ($P < 0.001$), PR versus NR ($P < 0.001$). CR, complete remission; NR, no remission; PR, partial remission.

infections—respiratory in 2 cases (severe pneumonia, respiratory sepsis) and invasive mycosis in 1 case.

CR was achieved in 21 patients, 18 had a PR, and 7 had no remission (Figure 1a).

Therapy-related complications were found in 15 patients. Of these 15 patients, 12 had received cyclophosphamide. Some patients had more than 1 complication. Infectious complications were the most common (8 of 15), with a predominance of respiratory tract infections. Hemorrhagic complications were observed in 7 patients (5 cases of gastrointestinal bleeding, 1 complication of renal biopsy, and 1 hematoma of the abdominal wall in a patient with severe thrombocytopenia). Three of the 7 patients with hemorrhagic complications also had an associated antiphospholipid syndrome and were receiving anticoagulation therapy. There were 3 reports of steroid-associated psychosis, and 1 patient had an aseptic necrosis of the femur.

Risk Factors for Initiating RRT

Median renal survival was 229 months (range, 2–360 months). Five-year renal survival was close to 78% and more than 70% at 10 years (Figure 2).

Remission of the LN had an impact on renal survival. Significant differences were found in the renal survival of the CR group, the PR group ($P = 0.005$), and the nonremission group ($P < 0.001$). There were no significant differences in the renal survival between the PR and nonremission groups ($P = 0.118$) (Figure 1a).

When the risk factors at the time of renal biopsy of the patients who needed RRT ($n = 12$) were compared with those who did not, there were significant differences between the 2 groups in parameters such as serum albumin levels; presence of hypertension; eGFR < 60 ml/min; and concomitant neurologic, cardiac, or pulmonary impairment. However, the differences between the groups in serum creatinine levels, proteinuria, the proportion of type 3 and type 4 LN, and the number of bouts of LN were not significant (Table 3). The multivariate analysis that included the variables that were significantly associated with the initiation of RRT showed that only eGFR < 60 ml/min turned out to be significant.

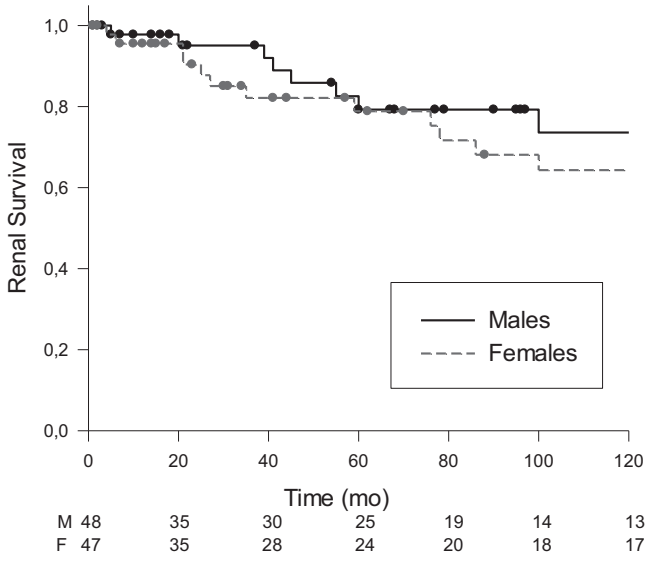

Figure 2. Renal survival in male and female patients 10 years after renal biopsy.

Table 3. Characteristics of patients receiving and not receiving renal replacement therapy

Clinical and laboratory presentation	Initiation of RRT ($n = 12$) Median ± SD	No initiation[a] ($n = 34$) Median ± SD	P value[b] Median ± SD
Creatinine level (mg/dl)	2.8 ± 1.3	2.0 ± 1.6	0.12
GFR < 60 ml/min	10	16	0.043
Proteinuria (g/24 h)	5.7 ± 3.5	4.2 ± 3.6	0.20
Types III and IV LN	11	28	0.65
Hypertension	12	24	0.044
SBP (mm Hg)	156.7 ± 14.2	146.8 ± 25.0	0.22
DBP (mm Hg)	95.8 ± 16.2	89.0 ± 17.9	0.25
Hemoglobin (g/dl)	9.7 ± 2.2	11.0 ± 1.9	0.061
N-P-C	11	16	0.013
Serum albumin level (g/dl)	2.1 ± 0.3	2.6 ± 0.6	0.008
Renal flares	5	12 (n=31)	0.87

DBP, diastolic blood pressure; GFR, glomerular filtration rate; LN, lupus nephritis; N-P-C, concomitant neurologic, pulmonary, and/or cardiac impairment; RRT, renal replacement therapy; SBP, systolic blood pressure.
[a]Excluding the patients lost to follow-up.
[b]Bilateral test.

Differences Between Sexes

Response to Treatment and Course

We compared the male cohort with a cohort of women with LN, matched for age at the time of renal biopsy, year of diagnosis, serum creatinine level, histologic LN form, and initial treatment. As shown in Table 4, there were no differences between the 2 cohorts, although female patients showed levels of proteinuria significantly lower than those of male patients ($P < 0.05$).

As shown in Figure 1, the rate of PR or CR was similar in both male and female patients. There were no differences in progression to ESRD or in mortality between male and female patients. Fourteen women and 12 men had ESRD, and 3 patients in each cohort died (P = NS). After 10 years of follow-up, there were no differences in renal or patient survival between the 2 cohorts (Figure 2).

When we analyzed differences in renal survival, women with CR had a significantly higher survival rate than patients with PR, and survival rate was also higher in patients with PR than in patients with no remission ($P < 0.05$).

DISCUSSION

We analyzed the clinical and histologic presentation and renal survival by means of long- term follow-up of a cohort exclusively made up of males with biopsy-confirmed LN. The age at diagnosis reported is higher in males than in females.[7] Although the renal form of onset was similar, male patients responded less to treatment and had a poorer course (Table 5). Very few papers in the literature reviewed focus exclusively on LN in males.[2,15,16]

Table 4. Clinical presentation and outcomes of males with lupus nephritis compared with matched females

Presentation, treatment, and outcome	Males (n = 50) Median ± SD	Females (n = 50) Median ± SD	P value
Age (yr)	27 (range, 8–79)	25 (range, 13–79)	NS
Serum creatinine (mg/dl)	2.18 ± 1.47	1.89 ± 1.31	NS
FG < 60 ml/min (CKD-EPI)	31	29	NS
Proteinuria (g/24 h)	4.6 ± 3.5	3.09 ± 3.0	0.025
WHO class III–IV	39	39	NS
Cyclophosphamide[a]	39	36	NS
Mycophenolate[a]	3	6	NS
Complete remission	21	23	NS
Partial remission	18	15	NS
No remission	7	9	NS
Lost to follow-up	4	3	NS
Renal replacement therapy	12	14	NS
Deaths	3	3	NS

CKD-EPI, chronic kidney disease epidemiology collaboration equation; GFR, glomerular filtration rate; NS, not significant; WHO, World Health Organization.
[a]Initial therapy.

Presentation As Nephrotic Syndrome and Rapidly Progressive Kidney Failure

As reported by other authors who analyzed series including both men and women, nephrotic syndrome was the most frequent renal presentation, with type IV LN as the predominant histologic form.[3,4,17] It is noteworthy that 19 of 50 (38%) of all the patients in our series presented with rapidly progressive kidney failure. Despite the lack of symptoms, the histology of 3 of the 4 patients who presented with asymptomatic urinary abnormalities had proliferative forms (1 with type III and 2 with type IV LN), emphasizing the need to perform a renal biopsy when there is persistent asymptomatic urinary abnormalities, given the lack of clinical and histologic correlation. This is also consistent with the results obtained by Christopher-Stine *et al.*, who found that types III and IV LN were the most common histologic patterns found in the biopsies of patients with SLE and proteinuria < 1 g/24 h.[18]

Table 5. Studies with lupus nephritis confirmed through renal biopsy

Author	Men (M) /women (W)	CR	PR	NR	RRT
Chen *et al.*[19]	14/72	43%	24%	32%	17.4%
Moroni *et al.*[22]	8/85	63.4%	19.3%	10.9%	6.4%
Wang *et al.*[20,a]	45/270	M 17.8% W 35.2%	M 35.6% W 56%	M 46.7% W 8.9%	M 11% W 10.7%
Chan *et al.*[23]	6/60	82.4%	11.8%	5.8%	0%
Kono *et al.*[24]	36/150	83.3%	11.6%	5.1%	4.8%
Urrestarazú	46/47	M 45.6% W 48.9%	M 39.1% W 31.9%	M 15.2% W 19.1%	M 26% W 29.7%

CR, complete remission; NR, no remission; PR, partial remission; RRT, renal replacement therapy.
[a]Percentages for men and women are shown separately.

Low CR Rate in Males

CR was reached in 21 of 46 patients (45.6%) and PR in 18 of 46 (39.1%); 7 of 46 patients (15.2%) did not respond, which had a deleterious effect on renal survival (Figure 1). Our cohort shows remission levels similar to those reported by Chen *et al.*[19] and higher than those reported by Wang *et al.*[20] Both series mostly consist of women with proliferative LN. In the series reported by Wang *et al.*, men had significantly lower remission rates and higher therapeutic failure and mortality rates compared with women.[20] Another study that enrolled 93 patients with LN in Brazil, which compared subjects with similar clinical and histologic characteristics, revealed poorer renal outcomes in males versus females during follow-up.[21] In other studies that describe groups consisting predominantly of women with proliferative LN (Moroni *et al.*[22] and Chan *et al.*[23]), CR was reached by more than 60% of patients; however, in both studies, the presence of renal failure at onset was rare, and the patients with severe renal failure had been excluded. Another recent Asian study addressing patients with LN (most of them women with a follow-up of more than 10 years) showed high CR levels (83.3%), with dialysis-free renal survival exceeding 90% during follow-up. In this study, the baseline mean serum creatinine level was 0.75 mg/dl, 36% of the patients had type I or II LN, and chronicity scores were low. Being male and level of proteinuria were the factors associated with a poor renal prognosis[24] (see Table 5).

Although our analysis corresponds to a historical cohort starting in 1971 in Spain and in 1986 in Uruguay, with only 3 patients treated with mycophenolate mofetil and 39 treated with cyclophosphamide as baseline therapy, this prognostic discrepancy poses the question of whether we are facing more severe cases of SLE or whether the diagnosis was late because the patients were men. That issue cannot be elucidated solely on the basis of our data, since it is a retrospective study, and the time spans between the onset of symptoms and diagnosis are not available.

The comparison with a matched (1:1) female cohort showed no differences in initial treatment rate response or in renal and patient survival. Because the cohort selection criteria included serum creatinine level, histologic form, and initial treatment, our analysis included female and male patients with similar characteristics at the time of diagnosis.

The discrepancy between our findings and those of previous studies that demonstrated a better prognosis for female patients with LN should be addressed.[21–23] These reports included all LN cases in both sexes during a specific period. Our analysis is different because we compared the male cohort with a matched female cohort with similar LN characteristics at diagnosis, probably representing more severe female cases.

The reasons for the infrequent use of mycophenolate mofetil as initial therapy may be that most of the cases occurred before 2005 and that a significant number of patients (19 of 50) presented with rapidly progressive kidney failure.

Initiation of RRT

Twelve of 46 patients (26%) required initiation of RRT. The initiation rate was higher than the rate reported in the studies analyzed earlier that enrolled mostly female patients (Table 5).

The univariate analysis at the time of renal puncture biopsy indicated that an eGFR $<$60 ml/min; hypertension; a low serum albumin level; and the presence of concomitant neurologic, cardiac, or pulmonary involvement were associated with the need for RRT. The multivariate analysis only showed eGFR$<$ 60 ml/min as an independent predictor of the need for RRT. These data suggest that patients who needed RRT had a more severe presentation, with hypertension; hypoalbuminemia; and neurologic, pulmonary, or myocardial involvement. A recent Spanish multicenter study revealed a significant association between the need to initiate RRT and concomitant neurologic, pulmonary, and myocardial involvement secondary to SLE.[25]

Eleven of the 12 patients who began receiving RRT had proliferative histologic forms of LN (type III in 2 and type IV in 9).

None of the patients who began receiving RRT experienced CR during follow-up, and significant differences were found in renal survival when comparing CR versus PR ($P = 0.005$), and also when comparing CR versus the nonremission group ($P < 0.001$). Achieving a CR—or even a PR—is of great value in terms of long-term renal survival, a finding previously reported by Chen *et al.*[19] The risk of end-stage renal disease increases when severe organ involvement, hypertension, hypoalbuminemia, and/or low eGFR are present at the moment of diagnosis of lupus nephritis, highlighting the importance of early diagnosis.[25–28]

When we analyzed renal survival related to response to treatment, we found that patients with a partial response had significantly poorer outcomes than patients who attained a CR. This is important because in clinical studies, CR and PR are often combined as an outcome measure, and it is commonly thought that partial responders have a much better long-term outcome than nonresponders. We need to address the following issues: the number of patients in our study was small, and differences in renal survival were significant after more than 10 years of follow-up. Studies with larger cohorts and longer follow-up are needed to confirm our findings. The

difference in outcome between PR and no remission was not observed in the female cohort.

As reported by other authors, infections (primarily respiratory tract infections) ranked first among the complications observed during follow-up and are one of the leading causes of morbidity and mortality in these patients.[5–7] The 3 deaths reported were related to severe infections.

When both the Spanish and the Uruguayan male cohorts were compared separately, there were no statistical differences in the clinical and histologic forms of onset or in their treatment or course of the disease (Supplementary Table S1).

The limitations of our study are related to its retrospective nature. The retrospective design and large amount of time elapsed between the first and last cases make it very difficult to reach conclusions. Types of treatments, especially renoprotective drugs, have changed over the past 30 years, and these changes could have influenced the final outcome. No additional data are available on renin- angiotensin axis blockers, lipid-lowering drugs, hydroxychloroquine, and other pharmacologic agents. Mycophenolate mofetil was added in the 1990s to the treatment armamentarium of LN. In our study, only 3 men and 6 women received this treatment.

There are no data available concerning the socioeconomic status and histology with chronicity and activity scores based on the renal biopsy. Four of 50 patients were lost to follow-up.

Finally, these findings apply to patients with European ancestry and may not be applicable to members of other ethnicities or races.

CONCLUSIONS

In men, lupus nephritis is typically manifested in the context of extrarenal involvement. Nephrotic syndrome was the most common renal syndrome, and type IV LN was the predominant histologic form.

The low level of glomerular filtration; high blood pressure; low serum albumin levels; and neurologic, cardiac, or pulmonary involvement at diagnosis, together with the proliferative forms (LN types III and IV) and the failure to achieve CR during follow-up, suggest adverse renal outcomes.

In this retrospective series, CR was reached in a smaller number of male patients than in the female-predominant series. This could be due to either poorer outcomes in males or later diagnoses. When we compared our male cohort with a similar female cohort, rates of remission were similar. The RRT initiation rate was higher than the rates observed in female-predominant series. When our male cohort was compared with a selected female cohort, there were no differences in renal and patient survival.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Characteristics of both cohorts at the time of renal biopsy.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Borchers AT, Leibushor N, Naguwa SM, et al. Lupus nephritis: a critical review. *Autoimmun Rev*. 2012;12:174–194.
2. Lu L-J, Wallace D, Ishimori M, et al. Male systemic lupus erythematosus: a review of sex disparities in this disease. *Lupus*. 2010;19:119–129.
3. Cervera R, Khamashta MA, Hughes GRV. The Euro-lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus*. 2009;18:869–874.
4. Danila MI, Pons-Estel GJ, Zhang J, et al. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. *Rheumatology*. 2008;48:542–545.
5. Yap DY, Tang CS, Ma MK, et al. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transpl*. 2012;27:3248–3254.
6. Bernatsky S, Boivin J-F, Joseph L, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum*. 2006;54:2550–2557.
7. Tan TC, Fang H, Magder LS, et al. Differences between male and female systemic lupus erythematosus in a in a multiethnic population. *J Rheumatol*. 2012;39:759–769.
8. Ding Y, He J, Go JP, et al. Gender differences are associated with the clinical features of systemic lupus erythematosus. *Chin Med J (Engl)*. 2012;125:2477–2481.
9. Renau AI, Isenberg DA. Male versus female lupus: a comparison of ethnicity, clinical features, serology and outcome over a 30 year period. *Lupus*. 2012;21:1041–1048.
10. López-longo FJ, Calvo-Alén J, Galindo-Izquierdo M, et al. Registro nacional de pacientes con lupus eritematoso sistémico de la Sociedad de Reumatología: objetivos y metodología Espa nola. *Reumatol Clin*. 2014;10:17–24.
11. Mazzuchi N, Acosta N, Caorsi H, et al. [Frequency of diagnosis and clinic presentation of glomerulopathies in Uruguay]. *Nefrologia*. 2005;25:113–120.
12. Smith EL, Shmerling RH. The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: strengths, weaknesses, and opportunities for improvement. *Lupus*. 1999;8:586–595.
13. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int*. 2004;65:521–530.
14. Kidney Disease Improving Global Outcomes. KDIGO Clinical practice guideline for glomerulonephritis. *Kidney Int Suppl*. 2012;2:1–274.

15. Kaufman LD, Gomez-Reino JJ, Heinicke MH, et al. Male lupus: retrospective analysis of the clinical and laboratory features of 52 patients, with a review of the literature. *Semin Arthritis Rheum*. 1989;18:189–197.
16. Sthoeger ZM, Geltner D, Rider A, et al. Systemic lupus erythematosus in 49 Israeli males: a retrospective study. *Clin Exp Rheumatol*. 1987;5:233–240.
17. Pons-Estel BA, Catoggio LJ, Cardiel MH, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine (Baltimore)*. 2004;83:1–17.
18. Christopher-Stine L, Siedner M, Lin J, et al. Renal biopsy in lupus patients with low levels of proteinuria. *J Rheumatol*. 2007;34:332–335.
19. Chen YE, Korbet SM, Katz RS, et al. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol*. 2008;3:46–53.
20. Wang Y-F, Xu Y-X, Tan Y, et al. Clinicopathological characteristics and outcomes of male lupus nephritis in China. *Lupus*. 2012;21:1472–1481.
21. Resende AL, Titan SM, Barros RT, et al. Worse renal outcome of lupus nephritis in male patients: a case-control study. *Lupus*. 2011;20:561–567.
22. Moroni G, Quaglini S, Gallelli B, et al. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant*. 2007;22:2531–2539.
23. Chan TM, Tse KC, Tang CSO, et al. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone and oral cyclophosphamide followed by azathioprine. *Lupus*. 2005;14:265–272.
24. Kono M, Yasuda S, Kato M, et al. Long-term outcome in Japanese patients with lupus nephritis. *Lupus*. 2014;23:1124–1132.
25. Galindo-Izquierdo M, Rodriguez-Almaraz E, Pego-Reigosa JM, et al. 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). *Medicine (Baltimore)*. 2016;95:e2891.
26. Contreras G, Pardo V, Cely C, et al. Factors associated with poor outcomes in patients with lupus nephritis. *Lupus*. 2005;14:890–895.
27. Ayodele OE, Okpechi IG, Swanepoel CR. Predictors of poor renal outcome in patients with biopsy-proven lupus nephritis. *Nephrology (Carlton)*. 2010;15:482–490.
28. Austin HA, Boumpas DT, Vaughan EM, et al. Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. *Kidney Int*. 1994;45:544–550.