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Research Article

Prognostic factors for chronic kidney disease and end-stage renal disease in patients with lupus nephritis: A retrospective cohort study

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Abstract

Background: Lupus Nephritis (LN) occurs in approximately half of all patients with Systemic Lupus Erythematosus (SLE) and it is the most common cause of morbidity and mortality in patients with SLE. Factors associated with poor renal outcome vary among studies, and researches coming from Brazil are scarce.

Objectives: To identify the prognostic factors associated to the development of Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD) in LN patients followed in a tertiary hospital.

Design and Settings: We conducted a retrospective cohort study set in a tertiary hospital in Fortaleza, Ceará, Brazil. Methods: We compiled a total of 214 LN patients diagnosed between 1983 and 2015. Data was collected from medical records and further analyzed using logistic regression.

Results: LN prevalence was 53.9%. The cohort had a mean follow-up of 11.2 years (SD ± 7.2 years). At the end of follow-up, 93 of 197 patients (47.2%) had CKD, and 49 of 191 (25.6%) were on regular dialysis. The main factors associated for developing CKD after logistic regression analysis were the following predictors: hypertension (HR 2.80; 95% CI 1.30-6.01; p = 0.008), time between diagnosis of SLE and diagnosis of LN (HR 0.98; 95% CI 0.97-0.99; p = 0.009) and discontinuation of medications (HR 2.41; 95% CI 1.08-5.37; p = 0.03).

Conclusion: Hypertension, discontinuation of medications, and time between diagnosis of SLE and diagnosis of LN are independent variables associated with the development of CKD and ESDR in our study.

More Information

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Introduction

Lupus nephritis (LN) occurs in approximately half of all patients with systemic lupus erythematosus (SLE), and its frequency ranges from 12% to 75%, depending on the population studied and the diagnostic criteria used [1-6]. Lupus nephritis is the most common cause of morbidity and mortality in patients with SLE [7] and the incidence and severity of this manifestation are increased in patients with African, Hispanic and Asian ancestry [1]. Multiple genetic, socioeconomic, environmental, and clinical factors may account for this phenomenon. Lupus nephritis is the most prevalent etiology of secondary glomerular disease leading to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [8]. The development of chronic kidney disease is a global public health problem, and also is associated with cardiovascular disease [9-11].

Although the renal survival rate has improved with the implementation of current immunosuppressive regimens,

nearly 10% - 20% of patients with LN still progress do ESRD [12]. Factors associated with poor renal outcomes vary among studies, and most of these studies come from Europe, the USA and Asia, with scarce reports from Brazil. The identification of epidemiologic and clinical factors associated with CKD and ESRD in different populations will improve our understanding of LN, facilitate the diagnosis and management, and improve the prognosis.

The aim of the present retrospective study was to identify the demographic, clinical, and histological factors associated with the developing of CKD and ESRD in a cohort of LN patients (with LN) of a single center in Northeastern Brazil.

Patients and methods

Patients

The initial sample consisted of 830 SLE patients previously or currently followed at the Hospital Universitário Walter Cantídio (HUWC/Universidade Federal do Ceará) in Fortaleza, Brazil, identified between 2011 and 2015 through active search of the records (including names and chart numbers) of outpatient services and wards, pharmacy and hospital databases, and research notes from earlier studies on SLE patients at HUWC. Chart numbers were arranged in increasing order (reflecting the order of hospital admission) and divided into groups of 50 patients, from which half were randomly selected for retrospective in-depth review. The decision to review approximately half the records (n = 414) was justified by logistic limitations. To be included in the sample, patients should had been diagnosed with SLE according to the criteria of the American College of Rheumatology (1982) [13], had no associated autoimmune disorder (rheumatoid arthritis, polymyositis, dermatopolymyositis, systemic sclerosis), and have been followed by the HUWC for at least one year or until their death. Records which did not meet the criteria for analysis were replaced by records drawn at random from the same group. The sample included patients from four different services at HUWC (rheumatology, nephrology, pediatrics and internal medicine). The prevalence of lupus nephritis in this sample cohort of 414 patients was 53.9% (233 patients). Nineteen patients were excluded because of incomplete data (15) or overlap with systemic sclerosis (3). We retrospectively studied all 214 patients with LN defined according to the presence, of two consecutive lab tests, of one of the following alterations: red blood cell casts or hemegranular casts, or white blood cell casts, or hematuria, or pyuria, or proteinuria (> 500mg/24 hours or ≥ 3+ on dipstick), in the absence of other causes, and/or an abnormal renal biopsy showing any classes of the World Health Organization/the International Society of Nephrology pathologic classification [14].

HUWC is a public university hospital and tertiary-level referral facility. Most users originated from socioeconomically underprivileged communities in Fortaleza (the state capital), the hinterland of Ceará, and other states in Northeastern Brazil.

Study parameters

Demographic data (gender, race, age at diagnosis of SLE and LN), clinical data (SLE manifestations at any stage, time between LN diagnosis and first treatment done for LN, follow-up time [from diagnosis of LN to the development of CKD, ESRD, last evaluation and/or death], induction and maintenance immunosuppressive treatment (medication administered in induction and maintenance phases), reasons of stopping medications [inefficiency, lack of adhesion, adverse events, medication unavailability], presence of arterial hypertension during the follow-up [systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or if on treatment with anti-hypertensive drugs], complete and partial renal remission after induction treatment and in the end of the follow-up, number of renal flares, time in remission), laboratory data at onset of LN, and after 3, 6 and 12 months (serum creatinine, estimated glomerular filtration rate [eGFR] CKD-Epi, and 24 h urinary protein excretion) and immunological data in any time of the disease (antinuclear antibodies, IgG/IgM anticardiolipin antibodies, lupus anticoagulant, anti-dsDNA and anti-Sm antibodies) were retrieved from the medical records using a standardized form. Complete remission (CR) was defined as proteinuria < 500 mg/24 hours, normal renal function, and inactive urine sediment. Partial remission (PR) was defined as proteinuria between 500 mg-1000 mg/24 hours, normal renal function, and inactive urine sediment. Renal flare was defined by any presence of cast, proteinuria > 500 mg/24 hours and/or hematuria after CR, and without other cause.

Regarding patients who underwent renal biopsy in any time of the follow-up, only data from the first biopsy were considered for the study, even though some patients had more than one biopsy.

Chronic kidney disease was defined according to the Kidney Disease: Improving Global Outcome definition (estimated glomerular filtration rate < 60 ml/min/1.73m^2 of body surface area for 3 months or more) [15]. CKD is classified in five stages. However, for comparison purposes, we used the cutoff point of < 60 ml/ min (correspondent to stage II CKD)

End-stage renal disease was defined as the need for permanent hemodialysis or peritoneal dialysis.

The study protocol was approved by the HUWC Research Ethics Committee and filed under number 90562917.1.3001.5045.

Statistical analysis

Statistical analysis was performed using the RedCap program. Values are expressed as means±standard deviation or median (IQR) for continuous variables and percentages for categorical variables. A p value < 0.05 was considered to indicate statistical significance. Comparisons of continuous variables were based on the t test or Mann-Whitney test.

The chi-square and Fisher exact test were used to compare categorical variables. A multivariate logistic regression analysis was applied using variables that were statistically significant in univariate analysis, and when there was less than 20% of missing data for each variable.

Results

A total of 214 LN patients were studied. Most of the patients were female (90.6%), and non-white (80%), with a mean age at diagnosis of SLE of 25.8 ± 8.9 years and a mean age at diagnosis of LN of 27.3 ± 9.2 years (Table 1). Clinical manifestations were mostly musculoskeletal (82.2%), dermatological (73.8%), serosites (46.7%), and leucolymphopenia (41.5%). The ANA test was positive in 95%, with autoantibodies in the following order of frequency: anti-dsDNA (58%), anti-Sm (38.9%), lupus anticoagulant (26.4%) and anticardiolipin (15.5%). The mean serum creatinine on LN diagnosis was 1.45 ± 1.28 mg/dL, urinary protein were 2903.9 ± 3051.3 mg/24 hours, the mean serum albumin was 2.51 ± 0.78 g/dL, and the eGFR-CKD-EPI was 77.5 ± 40.9 ml/min/1.73m^2. Among the 214 patients, 102 patients (47.6%) underwent renal biopsy and the most prevalent histological lupus nephritis classes were class IV (53.9%) and class III (21.6%). Only 14 patients (13.7%) showed class V. The renal activity index was 7.6 ± 4.4 and the renal chronicity index was 1.1 ± 1.9. Thrombotic microangiopathy was described in only one patient who presented antiphospholipid antibody syndrome. Of the 214 patients, one hundred and ninety-four had information recorded on charts about the first immunosuppressive drug to induce remission of LN. The most used was IV cyclophosphamide (55.6%), azathioprine (AZA) (33.5%) and mycophenolate mofetil (MMF) (10.8%). After 6 months using the first induction treatment for remission, only 39 (18.2%) and 7 (3.3%) patients reached CR and PR, respectively. The median time to reach remission was 12 months (IQR 6-28 months). The total number of patients who had renal flares during follow-up was 81 (38.9%). The cohort had a mean follow-up of 11.2 years (SD ± 7.2 years). At the end of follow-up, 93 of 197 patients (47.2%) had CKD, and 49 of 191 (25.6%) were on regular dialysis (Table 1). During the follow-up, methylprednisolone pulse (0.5-1g/day for 3 days) was used for induction of remission 125 times in 214 patients (58.9%), IV cyclophosphamide was used 152 times (55.6%), AZA was used 133 times for induction of remission (33.5%) and MMF in 51.9% of the time. The reasons for discontinuing the medications in any time of the treatment are presented in the table 2.

Table 1: Demographics and disease related features in 214 patients with lupus nephritis.

Variable	
Female; *n* (%)	194 (90.6)
Level of schooling; *n* (%) Basic literacy Elementary school High school College or higher Unknown information	 23 (10.7) 33 (15.4) 58 (27.1) 12 (5.6) 88 (41.2)
Racial distribution; *n* (%) White Non-white Unknown information	 31 (14.5) 115 (53.7) 57 (26.7)
Age at diagnosis of SLE; mean ± SD	25.8 ± 8.9
Age at diagnosis of LN; mean ± SD	27.3 ± 9.2
Time between SLE and LN diagnosis; median (IQR), months	0 (0-19.5)
Serum creatinine at diagnosis of LN; mean ± SD, mg/dL	1.45 ± 1.28
Proteinuria 24 hours at diagnosis of LN; mean ± SD, mg	2903.9 ± 3051.3
Serum albumin at diagnosis of LN; mean ± SD, g/dL	2.51 ± 0.78
eGFR; mean ± SD (ml/min/1.73m^2)	77.5 ± 40.9
Low levels of C3 and/or C4; % (*n* /total)	78.2 (100/128)
Anti dsDNA; % (*n* /total)	58 (47/81)
Dialysis at diagnosis of LN; % (*n* /total)	6.2 (12/192)
Histological classification of LN (122 patients): III; % (*n* /total) IV; % (*n* /total) V; % (*n* /total) Activity index; mean ± SD Chronicity index; mean ± SD	 21.6 (22/102) 53.9 (55/102 13.7 (14/102) 7.6 ± 4.4 1.1 ± 1.9
First treatment to induction of remission; % (n/total) Intravenous cyclophosphamide Azathioprine Mycophenolate mofetil	 55.6 (108/194) 33.5 (65/194) 10.8 (21/194)
Time between NL diagnosis and treatment; median (IQR), months	0 (0-1)
Complete remission after first induction of remission treatment; % (n/total) Partial remission after first induction of remission treatment; % (n/total)	18.2 (39/214) 3.3 (7/214)
Time to achieve CR or PR; median (IQR), months	12 (6-28)
Renal flare; % (*n* /total)	38.9 (81/208)
Follow-up duration; mean ± SD, years/ median (IQR), years	11.2 ± 7.2/ 10 (0-32)
Chronic kidney disease; % (*n* /total)	47.2 (93/197)
Time to develop CKD; median (IQR), months	60 (12-141)
End-stage renal disease: % (n/total)	25.6 (49/191)
Time to develop ESRD; median (IQR), months	72 (20-150)

SLE: Systemic Lupus Erythematosus; LN: Lupus Nephritis; eGFR: estimated Glomerular Filtration Rate; CR: Complete Renal Remission; PR: Partial Renal Remission; IQR: Interquartile Range; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease.

Univariate analyses were performed to identify the predictors for the development of CKD and ESRD, as show in table 3. With regard to CKD, thrombocytopenia and hypertension were more frequent in patients who developed CKD. Closer time between LN and SLE diagnosis (11.5 ± 27.6 *vs.* 27.3 ± 49.1 months; p = 0.01), longer time to initiate treatment after LN diagnosis (2.6 ± 5.6 *vs.* 1.0 ± 4.2 months; p = 0.004), and dialysis onset at LN diagnosis (10% *vs.* 2.9%; p = 0.04) were more associated with CKD. Sustained remission for more than 5 years was more frequent in non-CKD patients (74.4% *vs.* 25.6%; p = 0.05). In terms of nephritis laboratory findings, patients with CKD at the time of onset of LN had higher creatinine levels (1.63 ± 1.26 *vs.* 1.21 ± 0.90 mg/dL; p = 0.005), lower eGFR (70.4 ± 40.0 *vs.* 84.8 ± 39.2; p = 0.016), and higher 24 hours proteinuria (3507.4 ± 3606.6 *vs.* 2595.5 ± 2605.9 mg; p = 0.048). Creatinine, eGFR and 24 hours proteinuria at 6 and 12 months were also associated with CKD.

With regard to ESRD, various factors appeared to be risk factors, including younger age at diagnosis of LN (24.8 ± 8.2 *vs.* 28.4 ± 9.6 years; p = 0.03), shorter interval between

Table 2: Reasons for discontinuing the immunosuppressive drugs in lupus nephritis.

Reasons to stop; *n* (%)	EV Cyclophosphamide (*n* = 145*)	Mycophenolate mofetil (*n* = 105*)	Azathioprine (*n* = 127*)	Rituximab (*n* = 7*)
Inefficiency	36 (24.8)	22 (20.9)	59 (46.4)	2 (28.6)
Nonadherence	28 (19.3)	15 (14.3)	16 (12.6)	0
Adverse event	26 (17.9)	22 (20.9)	23 (18.1)	3 (42.8)
Lack of the drug	0 (0)	14 (13.3)	4 (3.1)	0

*: number of times the patient discontinued the medication for a known reason.

Table 3: Clinical predictors of poor renal outcome in patients with lupus nephritis.

Variable	With CKD (*n* = 93)	Without CKD (*n* = 104)	*p*	With ESRD (*n* = 49)	Without ESRD (*n* = 142)	*p*
Sex; % Female Male	 46.4 55.6	 53.6 44.4	 0.45	 26.0 22.2	 74.0 77.8	 0.99
Age at diagnosis of LN; mean ± SD, year	26.6 ± 9.4	28.0 ± 9.1	0.22	24.8 ± 8.2	28.4 ± 9.6	0.03
Thrombocytopenia; %	58.5	41.5	0.05	33.3	66.7	0.14
Hypertension; % Yes No	 55.6 32.4	 44.4 67.6	 0.002	 26.8 23.5	 73.2 76.5	 0.61
Time between diagnosis of SLE and diagnosis of LN; mean ± SD/ median (IQR), months	11.5 ± 27.6 0 (0-6)	27.3 ± 49.1 1 (0-36)	0.01	6.6 ± 20.3 0 (0-2)	24.5 ± 45.6 0 (0-34.5)	0.02
Time between diagnosis of LN and initiation of treatment; mean ± SD/ median (IQR), months	2.6 ± 5.6 0 (0-2)	1.0 ± 4.2 0 (0-0.6)	0.004	2.4 ± 5.4 0 (0-1)	1.6 ± 4.9 0 (0-1)	0.49
Chronicity index; mean ± SD/ median (IQR)	1.7 ± 2.3 1 (0-2)	0.6 ± 1.1 0 (0-1)	0.20	2.2 ± 2.8 2 (0-3)	0.7 ± 1.1 0 (0-2)	0.05
Dialysis at LN diagnosis; % Yes No	 75.0 45.2	 25.0 54.8	 0.04	 66.6 22.4	 33.3 77.6	 0.001
Partial or complete remission; *n* (%)	14 (32.5)	29 (67.5)	0.06	5 (11.6)	38 (88.4)	0.04
Number of relapses; mean ± SD	1.6 ± 1.3	1.4 ± 0.7	0.61	2.0 ± 1.7	1.3 ± 0.6	0.05
Sustained remission > 5 years; %	25.6	74.4	0.05	5.2	94.8	0.03
Nonadherence (EV cyclophosphamide); %						
Serum creatinine; mean ± SD, mg/dl Baseline At 6 months At 12 months	 1.63 ± 1.26 1.24 ± 1.00 1.44 ± 1.56	 1.21 ± 0.90 0.79 ± 0.23 0.73 ± 0.18	 0.005 0.0001 0.0001	 1.89 ± 1.55 1.14 ± 0.78 1.85 ± 2.08	 1.23 ± 1.04 0.93 ± 0.68 0.81 ± 0.26	 0.012 0.26 0.07
Proteinuria 24 hours; mean ± SD, mg Baseline At 6 months At 12 months	 3507.4 ± 3606.6 1792.2 ± 1736.1 1915.3 ± 2424.5	 2595.5 ± 2605.9 902.0 ± 920.2 927.8 ± 1182.9	 0.048 0.012 0.001	 3318.4 ± 3407.6 2076.3 ± 1912.7 2077.9 ± 1858.9	 2958.6 ± 3100.2 1093.6 ± 1193.4 1226.4 ± 1938.3	 0.33 0.06 0.001
eGFR; mean ± SD, ml/min/1.73m^2 Baseline At 6 months At 12 months	 70.4 ± 40.0 84.2 ± 36.8 85.3 ± 39.9	 84.8 ± 39.2 105.2 ± 26.2 110.1 ± 22.7	 0.016 0.002 0.001	 67.3 ± 42.7 91.2 ± 35.5 84.8 ± 46.9	 82.1 ± 38.4 98.2 ± 31.8 103.2 ± 27.6	 0.03 0.46 0.18

SLE: Systemic Lupus Erythematosus; LN: Lupus Nephritis; eGFR: estimated Glomerular Filtration Rate; IQR: Interquartile Range; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease

Table 4: Multivariable regression analysis of the predictors of chronic kidney disease in patients with lupus nephritis.

Variables	HR (95% CI)	*p* value
Time between diagnosis of SLE and diagnosis of LN	0.98 (0.97 – 0.99)	0.009
Hypertension	2.80 (1.30 – 6.01)	0.008
Discontinuation of medications	2.41 (1.08 – 5.37)	0.03

HR: Hazard Ratio; CI: Confidence Interval.

diagnosis of SLE and diagnosis of LN (6.6 ± 20.3 *vs.* 24.5 ± 45.6 months; $p = 0.02$), higher chronicity index (2.2 ± 2.8 *vs.* 0.7 ± 1.1; $p = 0.05$), lower remission rate after induction treatment (11.6% *vs.* 88.4%; $p = 0.04$), more flares (2.0 ± 1.7 *vs.* 1.3±0.6; $p = 0.05$), and lower sustained remission (5.2% *vs.* 94.8%; $p = 0.03$). In terms of nephritis laboratory findings, patients with ESRD had higher creatinine levels (1.89 ± 1.55 *vs.* 1.23 ± 1.04 mg/dL; $p = 0.012$) and lower eGFR (67.3 ± 42.7 *vs.* 82.1 ± 38.4; $p = 0.03$) at baseline, and higher levels of 24 hours proteinuria at 12 months (2077.9 ± 1858.9 *vs.* 1226.4 ± 1938.3 mg; $p = 0.001$).

After the logistic regression analysis for developing CKD, only the following variables were predictors for CKD: hypertension (HR 2.80; 95% CI: 1.30-6.01; $p = 0.008$), time between diagnosis of SLE and diagnosis of LN (HR 0.98; 95% CI: 0.97-0.99; $p = 0.009$) and discontinuation of medications caused by adverse event, inefficiency or non-adherence (HR 2.41; 95% CI: 1.08-5.37; $p = 0.03$).

Discussion

The prognosis of LN depends on many demographic,

clinical, histological, laboratory, and therapeutic variables. A number of studies have looked for these predictors with most studies coming from Europe, the USA and Asia. Our study is the first cohort study that evaluated prognostic factors in a single-center from Northeast of Brazil.

The two hundred and fourteen patients were followed for a mean time of 11 years. Almost half of patients (47.2%) developed CKD, and 25.6% progressed to dialysis. These are one of the highest rates among studies worldwide. It has been reported that approximately 5% - 30% of adults patients with LN will progress to ESRD within 10 years after diagnosis [2,12,16-21], and the incidence of LN-associated ESRD has increased from 1.16 cases per million in 1982 to 4.9 cases per million in 2004 in the United States [22,23]. This increase in the incidence of ESRD attributable to LN is a cause for concern, and the identification of risk factors related with the progression of LN to ESRD is very important to change this scenario. Some of these factors are not modifiable, such as ethnicity, age, gender, immunological profile, histological class of nephritis, response to immunosuppressive therapy. There is a greater likelihood of progression to ESRD among African American and Hispanic patients with LN than among Whites [24]. Pediatric patients with LN show progression to ESRD in 18% - 50% [25]. Although our study included only adult patients, lower age was associated with ESRD. Male gender was found to be a poor prognostic factor in some studies [26,27], but not in more recent reports [28,29]. High serum creatinine levels, diffuse proliferative nephritis, tubular atrophy, poor response to immunosuppressive therapy have also been reported to be independent risk factors for ESRD progression [12,18,2,29,30]. Otherwise, some other documented risk factors may be modified, such as delay in treatment of LN [31], hypertension [16-19,32], diabetes mellitus [32], lack of access to medical care [33], no use of standardized protocols for treating LN [34], among others.

In our study, some factors may explain the high rate of CKD and ESRD. First, our patients came from a low socioeconomic background of a tertiary care university hospital. In general, these patients have more severe disease, and with a longer disease duration without diagnosis. At the time of LN diagnosis, our patients had a mean creatinine level of 1.45 mg/dL, a mean 24 hours proteinuria of 2903 mg; they had low mean serum albumin (2.5 mg/dL), and mean eGFR of 77.5 ml/min/1.73m^2; and most of them had anti dsDNA positive (58%), and hypocomplementenemia (78.2%). Furthermore, 6.2% of the patients required hemodialysis at the time of LN diagnosis. Of the 122 patients who underwent renal biopsy, seventy seven (75.5%) presented with class III and IV. All these factors are associated with more severe disease and poor long-term renal outcome.

Delay in diagnosis and treatment of LN is an important risk factor associated with poor renal outcomes [31]. In our univariate analysis, longer time between diagnosis of LN and initiation of treatment was associated with CKD. Delay of two months on average to begin LN treatment had an impact on outcome. Dialysis, higher serum creatinine, higher 24 h proteinuria, and lower eGFR at LN diagnosis were also risk factors for CKD in our study. All of these factors are well established as risk factors for poor renal outcomes [16-20, 35-40].

The long-term follow-up of our study (>10 years) has also to be considered to explain the high rates of CKD and ESRD. The longest follow-up study looking for the risk factors for long-term renal outcomes was a cohort of Chinese patients with a mean follow-up period of 93.3 ± 60.4 months (~7.8 years) [18]. Of the 1814 patients with LN, ESRD developed in 201 (11.1%) patients.

The immunosuppressive medications for LN in our hospital are supplied by the Secretary of Health of the State of Ceara. However, sometimes the drugs are lacking at the hospital pharmacy, and patients have to stop or switch medications (conversion to other imunossupressive drug), contributing to poorer renal outcomes. Nonadherence is also another reason that may had led patients to progress to CKD and ESRD, and it has proven to be a challenging issue in the treatment of SLE. Rates of nonadherence in patients with SLE vary between 10% - 50%, depending in the evaluation methods used [41]. Sometimes severe relapses of LN observed especially in young patients may actually be due to nonadherence rather than to refractory disease [42]. Other reasons for stopping treatment are inefficiency and adverse effect. In our study, the most prevalent reason to stop medication was no therapeutic response which occurred in 46.4%, 24.8%, and 20.9% with AZA, cyclophosphamide, and MMF, respectively. Nonadherence ranged from 12.6% to 19.3% among the three main drugs. It is very important consider that in 16.4% of the time, the reason for discontinuing the immunosuppressive drugs was unavailability in hospital pharmacy, where the MMF is the most lacked drug. The reason for that is the high costs of the drug and the increasing number of patients who needs MMF. As MMF is an effective drug to induce and maintain remission of LN, the discontinuation of treatment may contribute to poorer renal outcomes in our studied population. After multivariable regression analysis of the predictors of CKD, on our patients with LN, the discontinuation of medication for any reason was significantly associated with the development of CKD.

The recommendations for LN management published by Joint European League against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) propose that a complete renal response or at least a partial response should be achieved preferably within 6 months and no later than 12 months after the induction treatment [43]. Many studies

have demonstrated that complete or partial remission at 12 months is correlated with better renal outcome [22,39,44]. Korbert, et al. reported that the risk for progression to ESRD was 8.2 times greater for patients in whom remission did not occur compared with patients with remission [45]. In our study, lower remission rate was significantly associated with ESRD. In studies of LN, the criteria for response have varied. We used a more rigorous criteria, both for complete and partial remission. Therefore, after 6 months of induction therapy, only 16.4% of the patients achieved remission, and the median to achieve CR or PR was 12 months in our study. In previous reports, the average duration to remission has ranged from 10 to 16 months after induction therapy [46,47]. The durability of remission might be a predictor of renal outcome and survival, as reported by Pakchotanon, et al. [21]. Sustained remission more than 5 years was also associated with better outcome in our study. Renal flares, however, may occur after remission, and they are disadvantageous to the renal function and contribute to morbidity in patients with SLE [44]. In our study, the rate of renal flare was 38.9%, and it was associated with ESRD. It has been reported that 27% - 66% of LN patients experienced at least one renal flare during their follow-up period [48].

In recent years, some studies have brought proteinuria as an important marker for the long-term renal outcome in lupus nephritis [18,49-51]. Interestingly, we found an association of 24-hour proteinuria at baseline, at 6 months, and 12 months with CKD, and a proteinuria at 12 months with ESRD. We also found that serum creatinine and eGFR at baseline, at 6 months, and 12 months were associated with CKD, and both values at LN diagnosis were correlated with ESRD on univariate analysis. Mackay, et al. [51]. published a very recent study proposing risk models to predict future kidney outcomes based on 24-hour proteinuria and serum creatinine at 12 months for use in clinicals trials.

In our study, three factors remained significantly associated with the development of CKD: the time between diagnosis of SLE and diagnosis of LN, hypertension and discontinuation of medications.

Moon, et al. [35] reported that patients with delayed-onset LN (defined as newly developed LN after the onset of SLE) progressed more to CKD, than patients with initial-onset LN (defined as LN diagnosed at the time of SLE onset) (28% *vs.* 16%; p = 0,004), while Ahn, et al. [52]. reported no difference in renal and overall survival rates between delayed-onset and initial-onset. We demonstrated the opposite: LN diagnosis closer to SLE diagnosis was more associated with the development of CKD. This is worthy of further investigation, but may reflect the severity of nephritis when it is already installed early.

For hypertension, many studies have shown it as a risk factor for CKD [16,17,21,35-39,53]. Presence of hypertension has also been found to be a predictor in Brazilian patients of African extraction [54]. A study using person-year analysis indicated that blood pressure at any time in the clinical course of SLE is a risk factor for deterioration of renal function within 12 or 24 months after the blood pressure measurement [55]. This study proposes that the mean arterial pressure during all follow-up should not exceed 96.5 mm Hg.

As expected, discontinue treatment for any reason is an important risk factor for CKD, and this should be a warning for patients, doctors and managers, to stimulate the adherence to treatment, to minimize adverse effects, and to create public policies to make the medications ever available.

This study had several limitations. First, all of the data were collected from charts, and detailed information was not available for all variables. Second, the expertise of the various clinicians involved in the management of these patients differed and this would have impacted on the outcome. Third, some critical variables that might impact renal outcomes were not included in our study. In addition, renal biopsies were not performed in all patients and were done at different times of LN. For this reason, we could not analyze the relationship between renal histology and prognosis of nephritis. However, the majority of previous studies have already shown poor renal outcomes in patients with proliferative LN and favorable renal outcomes in patients with class II and V. Despite these limitations, our study is based on a large cohort of a single-center of Northeast of Brazil, and therefore provides representative data about low-income LN patients in Brazilian public tertiary hospital. Additionally, we followed up for a long period of time. Our mean follow-up was 11.2 years, which provided sufficient strength to determine the predictive factors for bad renal outcomes.

Conclusion

In conclusion, this study showed that CKD and ESRD occurred in 47.2% and 25.6% of Brazilian patients with LN, respectively, within 11 years after the diagnosis of LN. Multivariate analysis identified hypertension, discontinuation of medications, and time between diagnosis of SLE and diagnosis of LN as independent variables for the development of CKD.

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