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Clinical and Laboratory Predictors of Distinct Histopathogical Features of Lupus Nephritis

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Abstract: The authors aimed to explore whether distinct clinical, serological, and urinalysis findings are associated with specific histological classes of lupus nephritis. Clinical and laboratory features were recorded at the time of clinical diagnosis from 297 consecutive patients with biopsy-confirmed lupus nephritis. Univariate and logistic regression analyses were performed and a risk score was developed to estimate the risk for developing different classes of lupus nephritis. Variables independently associated with class II included absence of malar rash, negative anti-dsDNA, and ≤5 urine leucocytes/high power field (hpf); with III/IV: age at nephritis diagnosis ≤32 years old, presence of musculoskeletal features, new-onset hypertension, positive anti-dsDNA, >5 urine leucocytes/hpf, creatinine >1.2 mg/dL, cellular casts >1/hpf, and absence of nephrotic range proteinuria; with V: age at nephritis diagnosis >32 years, malar rash, absence of musculoskeletal complaints or serum C3 hypocomplementemia, nephrotic range proteinuria, and ≤9 urine erythrocytes/hpf. A risk predictive score of specific histological classes was calculated for each patient. Associations between 2, 3 or more risk factors with specific histological classes were also revealed [Odds ratios (95% confidence interval) (≥2 risk factors) was 6.7 (2.8–17.4) for class II nephritis, 15.6 (5.1–47.8), and 8.2 (3.6–19.0) for classes III/IV and for class V, respectively (≥3 risk factors)]. The identification of independent factors associated with specific classes of lupus nephritis can provide guidance in selecting specific therapeutic modalities, particularly in cases in which renal biopsy is contraindicated.

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Abbreviations: ACR = American College of Rheumatology, CI = confidence interval, hpf = high power field, MMF = mycophenolate mofetil, NRP = nephrotic range proteinuria, OR = odds ratio, ROC = receiver operating characteristic, SLE = systemic lupus erythematosus.

INTRODUCTION

Lupus nephritis affects approximately half of patients with systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality, if left untreated.[1–3] Although it may be a presenting lupus manifestation, it usually occurs within a year of diagnosis and almost always within 5 years, although it can arise any time during the disease course.[4,5] Kidney involvement in the setting of lupus is suspected by an abnormal urinalysis and/or elevation of serum creatinine and confirmed by histopathologic findings on renal biopsy. The latter has become an indispensable tool in the management of lupus nephritis as it guides further therapeutic decisions and is recommended in all patients with lupus presenting either with proteinuria >0.5 g/24 hour and/or the presence of glomerular hematuria.[6] Histological class of lupus nephritis, the degree of activity and chronicity, and the presence of complicating lesions such as interstitial nephritis and thrombotic microangiopathy have been proposed as the main histopathological features dictating further management.[6,7] Indeed, patients with evidence of class III or IV demonstrating active lesions require aggressive immunosuppressive treatment with steroids and either cyclophosphamide or mycophenolate mofetil (MMF) to prevent irreversible renal damage; in patients with class V, steroids and MMF is a recommended option, whereas patients with class II or patients with sclerotic lesions do not require any therapy.[6] On the contrary, the concomitant presence of thrombotic microangiopathy might possibly dictate the use of anticoagulants along with or instead of immunosuppression.[8]

Despite the powerful role of renal biopsy in the management of lupus nephritis, in certain clinical circumstances it poses increased risk, especially in centers with limited experience. Although several clinical and renal manifestations such as creatinine levels, the grade of proteinuria, or presence or absence of hematuria have been previously felt to predict one histological class versus the other, no systematic study so far has addressed this issue. The goal of the present study was to identify and assess the ability of clinical and simple laboratory parameters to predict distinct histological classes of lupus nephritis, which can guide therapeutic decisions in cases in which renal biopsy poses inappropriately high risk or is contraindicated.

METHODS

Medical records from our SLE cohorts, according to the revised American College of Rheumatology (ACR) criteria,[9] were reviewed for the presence of biopsy-proven lupus nephritis according to the revised classification criteria.[10] Three hundred forty-eight patients fulfilled these criteria and were included in the study. Immunofluorescence analysis of renal biopsies was available for >90% of cases. Only data from patients who had a first renal biopsy were included. Due to the retrospective nature of the study, ethical approval was not necessary.

All patients were followed at the outpatient Rheumatology Clinic, Department of Pathophysiology, School of Medicine, University of Athens and Rheumatology Clinic, Department of

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Following thorough chart review of standardized clinical notes for patients with systemic autoimmune diseases, demographic, clinical, and serological and histopathological variables were recorded in the 348 patients included in the study. Of those, patients with mixed forms of lupus nephritis (n = 32) were excluded from further analysis. As those patients display histopathological characteristics of both classes, their inclusion in the present study, could affect the ability of statistical analysis to clearly distinguish lupus nephritis classes based on distinct clinical and laboratory characteristics. Due to the small number of patients with class I and VI (12 and 7, respectively), solid conclusions could not have been drawn, and thus in the present study they were also excluded from further analysis.

Thus, the final sample consisted of 297 patients with SLE. With the exception of antibodies against extractable nuclear antigens (Ro/SSA, La/SSB, Sm, and U1RNP) that were recorded whenever noted in the chart, the remaining of clinical and laboratory data were recorded at the time of evidence of renal involvement (defined as proteinuria >250 mg in 24 hour urine or active urine sediment in urinalysis). The interval between the clinical evidence of renal involvement and the performance of the renal biopsy was ≤2 months in all cases examined. Demographic characteristics (age, sex, race), clinical manifestations including constitutional symptoms (fever, fatigue), musculoskeletal (MSK) symptoms (including arthralgias, arthritis, myalgias), photosensitivity, malar rash, mouth ulcers, alopecia, discoid rash, cutaneous vasculitis, urticaria, livedo reticularis, subacute lupus, Raynaud phenomenon, serositis (pleuritis, pericarditis), cardiac manifestations (myocarditis, endocarditis), central nervous system involvement and a history of thrombosis, hematological manifestations [anemia (hemoglobin < 13 g/dL for men and 12 g/dL for women), leucopenia (<4000/mm^3), thrombocytopenia (<100.000/mm^3), autoimmune hemolytic anemia], the presence of specific autoantibodies [(anti-dsDNA, anti-cardiolipin (aCL-immunoglobulin (Ig) G and IgM, anti-β2GPI (IgG and IgM) and lupus anticoagulant)], erythrocyte sedimentation rate levels, as well as serum levels of C3 and C4 complement components were also recorded. Furthermore, for the purpose of the present statistical analysis, different levels of proteinuria in 24-hour urine collection were recorded as following: <250 mg = 0, 250–500 mg = 1 500 mg to 3g = 2, and >3g = 3). The number of red blood cells/high power field (hpf), the number of white blood cells/hpf, cellular casts (>1/hpf), increased creatinine levels (defined as >1.2 mg/dL), newly diagnosed hypertension, hyperkalemia, and acute renal failure were also recorded. Finally, the Systemic Lupus International Collaborating Clinics/ACR damage Index at the time of renal biopsy was calculated for each patient, as previously suggested.[11]

Statistical Analysis

Two-sided Fisher exact and Mann–Whitney or Kruskal–Wallis tests were used to compare categorical and numerical characteristics, respectively, between patient groups. Both univariate and multivariate models were considered. Multivariate regression models were built with backward stepwise elimination of variables (conditional model). A total of 20 clinically meaningful variables were considered from the history, physical examination, and standard laboratory tests and included age at nephritis diagnosis >32 years old, sex, MSK manifestations, photosensitivity, malar rash, mouth ulcers, serositis, central nervous system involvement, anemia, leucopenia, presence of anti-dsDNA antibodies, presence of anti-Sm antibody, C3 and C4 hypocomplementemia (defined as complement levels <83 and 16 mg/dL, respectively), new onset hypertension, elevated creatinine levels (defined as >1.2 mg/dL), nephrotic range of proteinuria, as well as the presence of >9 erythrocytes/hpf, 5 leucocytes/hpf, and cellular casts (>1/hpf) in urinalysis. For continuous variables such as age, number of erythrocytes/hpf, and number of leucocytes/hpf, the cut-off level chosen was their median value.

Significant prognostic variables obtained in the multivariate analysis were used to calculate the risk of having a distinct class of lupus nephritis for each patient (II, III/IV, V) according to the following equation in which β0 was the constant of the model, β1 to βp were the regression coefficients of the independent variables, and xli to xpi were the values of the variable for a particular patient.[12]

$$\text{Risk} = [\exp(\beta 0 + \beta 1 \times \text{xli} + \ldots + \beta p \times \text{xpi})]/1 + [\exp(\beta 0 + \beta 1 \times \text{xli} + \ldots + \beta p \times \text{xpi})].$$

Measures of calibration (Hosmer–Lemeshow statistics) and discrimination (receiver operating characteristic statistic) were calculated to evaluate the overall performance of the predictive model. Binary logistic regression was used to explore the association between each histological class of lupus nephritis and the number of risk factors (identified in multivariate analysis) present at the time of clinical diagnosis of lupus nephritis. Additionally, odds ratios (ORs) 95% confidence intervals (CI) for detecting associations between the presence of risk factors with specific classes of lupus nephritis, as well as for the prediction of high activity and chronicity biopsy indices within proliferative lupus nephritis classes, were calculated. High activity and chronicity scores were defined as ≥5 and ≥3, respectively, as previously suggested.[13] Analyses were performed by GraphPad Prism 5.00 (GraphPad Software, Inc. La Jolla, CA 92037 USA) and SPSS software 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

RESULTS

Lupus Nephritis Classification

Among 297 patients with SLE with biopsy-proven renal involvement, 47 had nephritis class II (mesangioproliferative), 188 nephritis class III or IV (focal and diffuse proliferative glomerulonephritis), and 62 manifested lesions compatible with class V nephritis (membranous), according to the International Society of Nephrology/Renal Pathology Society 2003 classification criteria.[10] Patients with class III and IV nephritis were analyzed as 1 group, given the similarities between these groups, in terms of histopathology and implemented therapeutic approaches.

Demographic, Clinical, and Serological Characteristics in Distinct Histopathological Classes of Lupus Nephritis

As displayed in Tables 1 and 2, at the time of clinical diagnosis of lupus nephritis, patients with histological class III/IV manifested increased rates of MSK symptoms and anemia, compared with those with membranous class of nephritis, whereas patients with nephritis of class II manifested less frequently malar rash compared with those of proliferative or membranous nephritis. Additionally, increased rates of positive anti-dsDNA titers in combination with lower C3 levels seem to

TABLE 1. Demographic and Clinical Characteristics of Patients With Systemic Lupus Erythematosus According to the Histological Class of Lupus Nephritis (II, III/IV, and V)

Manifestations	II (n = 47)	III/IV (n = 188)	V (n = 62)	*P* Value II vs III/IV	*P* Value II vs V	*P* Value III/IV vs V
Age at lupus nephritis [mean ± SD (y)]	32.5 ± 11.9	34.2 ± 14.6	31.5 ± 10.8	NS	NS	NS
Time interval (months) between SLE diagnosis and lupus nephritis diagnosis [mean ± SD (months)]	21.5 ± 40.4	26.2 ± 48.3	28.9 ± 52.5	NS	NS	NS
Sex (female) (%)	91.5	83.0	82.3	NS	NS	NS
MSK symptoms (%)	42.6	55.4	37.7	NS	NS	0.02
Photosensitivity (%)	23.4	24.3	23.0	NS	NS	NS
Malar rash (%)	12.8	29.9	39.3	0.02	0.002	NS
Mouth ulcers (%)	6.4	9.2	8.2	NS	NS	NS
Raynaud's phenomenon (%)	14.9	25.0	18.0	NS	NS	NS
Serositis (%)	12.8	14.7	11.5	NS	NS	NS
CNS involvement (%)	8.5	8.6	4.9	NS	NS	NS
SLICC/ACR damage Index	1.3 ± 1.2	1.4 ± 1.1	1.9 ± 1.5	NS	NS	NS

CNS = central nervous system, NS = not significant, SLE = systemic lupus erythematosus, SD = standard deviation, SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

be a prominent feature of class III/IV histological class compared with both V and II. The length of the interval time (in months, mean ± standard deviation) between SLE diagnosis and lupus nephritis in each type was 21.5 ± 40.4 months for class II, 26.2 ± 48.3 for classes III/IV, and 28.9 ± 52.5 months for class V.

Finally, the mean ± standard deviation values of Systemic Lupus International Collaborating Clinics/ACR damage Index for type II, III/IV, and V nephritis were, respectively, as follows: 1.3 ± 1.2, 1.4 ± 1.1, and 1.9 ± 1.5, with a tendency—though no statistically significant—toward increased damage scores in lupus V nephritis at time of nephritis diagnosis.

Distribution of Renal Parameters in Distinct Histological Lupus Nephritis Classes

As shown in Table 3, in patients with proliferative nephritis (class III or IV), the mean number of urine red blood cells

TABLE 2. Hematological Manifestations and Autoimmune Profile in Patients With Systemic Lupus Erythematosus According to the Histological Type of Lupus Nephritis (II, III/IV, and V)

Manifestations	II (n = 47)	III/IV (n = 188)	V (n = 62)	*P* Value II vs III/IV	*P* Value II vs V	*P* Value III/IV vs V
		%				
Anemia*	57.4	64.6	42.4	NS	NS	0.004
Leucopenia†	36.2	27.6	27.1	NS	NS	NS
Autoimmune hemolytic anemia	0.0	2.2	1.6	NS	NS	NS
Anti-Ro/SSA	40.5	35.4	25.5	NS	NS	NS
Anti-La/SSB	19.0	14.0	0.0	NS	0.001	0.002
Anti-dsDNA	65.0	85.2	64.7	0.006	NS	0.002
Anti-Sm	17.6	19.4	25.0	NS	NS	NS
Anti-U1RNP	12.1	19.4	17.0	NS	NS	NS
aCL (IgG)	46.7	50.0	26.7	NS	NS	0.04
aCL (IgM)	31.0	42.3	23.3	NS	NS	NS
Anti-β2GPI (IgG)	25.0	23.5	0.0	NS	NS	NS
Anti-β2GPI (IgM)	8.3	13.3	0.0	NS	NS	NS
Lupus anticoagulant	0.0	0.5	0.0	NS	NS	NS
		Mean ± SD				
C3 (mg/dL)	60.9 ± 24.6	55.4 ± 33.8	79.8 ± 36.8		$P = 0.003$‡	
C4 (mg/dL)	12.2 ± 9.3	11.8 ± 9.3	17.7 ± 13.9		NS‡	
ESR	56.5 ± 41.8	58.0 ± 34.2	73.1 ± 34.1		NS‡	

ESR = erythrocyte sedimentation rate, Ig = immunoglobulin; NS = not significant, SD = standard deviation.
* Hemoglobin <12 g/dL in women and <13 g/dL in men.
† Persistently low leukocytes (<4000/μL).
‡ By Kruskal–Wallis test.

TABLE 3. Renal Variables in Patients With Systemic Lupus Erythematosus According to the Histological Type of Lupus Nephritis

Manifestations	II (n = 47)	III + IV (n = 188)	V (n = 62)	*P* Value II vs III/IV	*P* Value II vs V	*P* Value III/IV vs V
		%				
Absence of proteinuria[a]	15.9	7.3	3.3	NS	0.03	NS
Mild proteinuria[b]	22.7	16.8	15.0	NS	NS	NS
Moderate proteinuria[c]	45.5	54.2	43.3	NS	NS	NS
Severe proteinuria[d]	15.9	21.8	38.3	NS	0.02	0.02
Hematuria (>5 erythrocytes/hpf)	45.7	75.1	38.9	0.0002	NS	0.0001
Pyuria (>5 leucocytes/hpf)	23.9	60.2	40.7	0.0001	NS	0.02
Increased Creatinine[e]	23.3	33.3	11.1	NS	NS	0.002
New onset hypertension[f]	8.5	8.2	12.1	NS	NS	NS
		Mean ± SD				
No. of RBCs	7.5 ± 9.3	18.1 ± 21.1	5.7 ± 6.4		$P < .0001$[g]	
No. of WBCs	4.1 ± 7.7	11.8 ± 14.8	6.8 ± 10.4		$P < .0001$[g]	

hpf = high power field, NS = not significant, RBCs = red blood cells, SD = standard deviation, WBCs = white blood cells.
[a] 24 h urine < 250 mg.
[b] 24 h urine: 250–500 mg.
[c] 24 h urine: 500 mg to 3 g.
[d] 24 h urine > 3 g.
[e] >1.2 mg/dL.
[f] Consistently high blood pressure (> 140 mmHg systolic blood pressure) of less than one month duration.

was higher compared with those with class V and class II. Class II nephritis patients were characterized by a significantly decreased mean number of urine white blood cells compared with both proliferative and membranous nephritis as well as by increased rates of normal protein levels in the 24-hour urine collection compared with those with nephritis of class V. In the latter, increased rates of nephrotic syndrome were observed versus those with proliferative or class II nephritis, whereas increased rates of elevated creatinine levels were recorded in patients with proliferative class of SLE nephritis compared with those with class V nephritis.

Identification of Independent Predictors of Histological Class of Lupus Nephritis

To identify independent predictors of 1 histological class versus the other, a multivariate model was constructed, as

TABLE 4. Identification of Independent Predictors of Distinct Histological Classes of Lupus Nephritis by Multivariate Logistic Regression Analysis

Groups compared	Parameter	β-coefficient*	*P* Value
II vs all other types	Malar rash	−1.574	0.05
	Anti-dsDNA	−1.619	0.01
	Number of leucocytes in urinalysis >5	−1.240	0.04
III-IV vs all other types	Age at diagnosis of nephritis >32 years old	−1.294	0.02
	Musculoskeletal symptoms	1.816	0.001
	New onset hypertension	2.119	0.04
	Anti-dsDNA	2.251	0.001
	Serum creatinine levels>1.2 mg/dL	1.400	0.03
	Number of leucocytes in urinalysis >5	1.625	0.005
	NRP	−2.140	0.001
	Presence of cellular casts >1/hpf	1.732	0.04
V vs all other types	Age at diagnosis of nephritis >32 years old	2.374	0.009
	MSK symptoms	−2.719	0.003
	Malar rash	2.728	0.003
	C3 hypocomplementemia	−1.924	0.02
	Number of erythrocytes in urinalysis>9	−1.858	0.01
	NRP	3.291	<0.001

hpf = high power field.
* Models include age >32 years old, sex, musculoskeletal manifestations, photosensitivity, malar rash, mouth ulcers, serositis, central nervous system involvement, anemia, leucopenia, presence of anti-dsDNA antibodies, presence of anti-Sm antibody, C3 and C4 hypocomplementemia (defined as complement levels <83 and 16 mg/dL, respectively), new-onset hypertension, elevated creatinine levels (defined as >1.2 mg/dL), nephrotic range of proteinuria, the presence of >9 erythrocytes/hpf >5 leucocytes/hpf and cellular casts (>1/hpf) in urinalysis.

described in the statistics section. As illustrated in Table 4, absence of malar rash together with negative anti-dsDNA serum titers and number of leucocytes in urinalysis ≤5/hpf appear to be independent predictors for class II nephritis. On the contrary, age at nephritis diagnosis ≤32 years old, the presence of MSK symptoms and new-onset hypertension, positive anti-dsDNA titers, elevated creatinine levels, presence of >5/hpf of white blood cells and >1 cellular cast/hpf in urinalysis, and absence of nephrotic range proteinuria (NRP) are highly predictive of proliferative forms of nephritis (III/IV). Age at nephritis diagnosis >32 years old, malar rash, NRP, urine hematuria ≤9 red blood cells/hpf, absence of MSK symptoms, and serum C3 hypocomplementemia were found to independently predict the occurrence of lupus nephritis class V.

To handle patients with missing data, we performed 2 data analyses: first we excluded patients with missing data and second we created multiple imputed datasets, applied the statistical model on each of them leading to a combined set of results.[14] As both analyses yielded qualitatively similar findings (data not shown), we present only the results of the multivariate analyses in which patients with missing data were excluded. For all values recorded, missing data did not exceed 10%.

Based on the results of the logistic regression analysis, predictive modeling was attempted. In this model, the risk of having biopsy confirmed class II (risk II), III/IV (risk III/IV) and V nephritis (risk V) was calculated for each patient according to the following equations, as previously suggested[12,15,16]:

(1) Risk II = exponential [0.389 + presence of malar rash × (−1.574) + presence of anti-dsDNA × (−1.619) + number of leucocytes/hpf >5 × (−1.240)]/1 + EXP [0.389 + presence of malar rash × (−1.574) + presence of anti-dsDNA × (−1.619) + number of leucocytes/hpf>5].

(2) Risk III/IV = exponential [−2.430 + age >32 × (−1.294) + presence of MSK manifestations × 1.816 + presence of anti-dsDNA × 2.251 + new onset hypertension × 2.119 + number of leucocytes/hpf >5 × 1.625 + increased creatinine levels × 1.400 + NRP × (−2.140) + presence of cellular casts >1/hpf × 1.732]/1 + EXP [−2.430 + age >32 × (−1.294) + presence of MSK manifestations × 1.816 + presence of anti-dsDNA × 2.251 + new onset hypertension × 2.119 + number of leucocytes/hpf >5 × 1.625 + increased creatinine levels × 1.400 + NRP × (−2.140) + presence of cellular casts >1/hpf × 1.732].

(3) Risk V = exponential [−1.987 + age >32 × 2.374 + presence of MSK manifestations × (−2.719) + presence of malar rash × 2.728 + C3 hypocomplementemia × (−1.924) + number of red blood cells/hpf >9 × (−1.858) + NRP × 3.291]/1 + EXP [−1.987 + age >32 × 2.374 + presence of MSK manifestations × (−2.719) + presence of malar rash × 2.728 + C3 hypocomplementemia × (−1.924) + number of red blood cells/hpf >9 × (−1.858) + NRP × 3.291].

In these formulas, binary variables were coded as follows: age >32 = 1, age ≤32 = 0; MSK manifestations: presence = 1, absence = 0; malar rash: presence = 1, absence = 0; positive serum anti-dsDNA antibodies: presence = 1, absence = 0; new-onset hypertension: presence = 1, absence = 0; increased creatinine levels: presence = 1, absence = 0; NRP: presence = 1, absence = 0; number of red blood cells/hpf >9: presence = 1, absence = 0; number of leucocytes/hpf >5: presence = 1, absence = 0; C3 hypocomplementemia (C3 complement levels <83 mg/dL): presence = 1, absence = 0; cellular casts >1/hpf: presence = 1, absence = 0.

When receiver operating characteristic curves for the predictive models were fitted, area under the curve were 0.72, CI (95%): 0.64–0.80, $P < .001$ for class II nephritis; 0.83, CI (95%): 0.77–0.89, $P < .001$ for class III/IV nephritis; and 0.76, CI (95%): 0.68–0.85, $P < .0001$ for class V (Figure 1A to C). Hosmer–Lemeshow goodness-of-fit statistics were 3.34, $P = .50$ for class II, 5.68, $P = .68$ for class III/IV, and 1.88, $P = .99$ for class V.

Binary logistic regression was used to determine associations between number of risk factors and specific histological classes of lupus nephritis. 84.2% of patients with histological class II nephritis present with ≥2 risk factors. Additionally, 96.3% and 80%, respectively of patients with class III/IV and V, had ≥3 risk factors. The ORs along with the corresponding CIs and P values for class II nephritis were 6.7 (2.8–17.4). The corresponding values for class III/IV and V nephritis were 15.6 (5.1–47.8) and 8.2 (3.6–19.0), respectively (Figure 2A to C).

We finally sought to explore which of the independent predictors for class III and IV nephritis could identify high activity and chronicity indices in renal biopsies of patients with proliferative forms of lupus nephritis. As shown in Table 5, the presence of > 5 white blood cells/hpf in urinalysis together with creatinine levels >1.2 mg/dL were associated with increased risk for higher activity scores [OR 95% CI: 2.4 (1.1–5.6) and 2.6 (1.1–6.7), respectively]. On the contrary, age at nephritis onset >32 years old was predictive of higher chronicity scores in these patients [OR 95% CI: 2.3 (1.1–4.8)]. However, larger number of patients would have been required to draw definite conclusions.

DISCUSSION

To our knowledge, no previous study to date has aimed at validating a risk score and a predictive model to estimate the risk of distinct histological classes of lupus nephritis based on clinical and routine laboratory parameters at the time of clinical diagnosis of renal involvement. This approach provides a novel tool to establish an early diagnosis of distinct classes of lupus nephritis and initiate individualized treatment without delay. Toward this direction, we retrospectively analyzed the charts of 297 consecutive patients with lupus nephritis derived from 2 large University Rheumatology Departments in an attempt to associate specific clinical and laboratory features occurring at the time of renal biopsy (within 2 months) with the histological class of lupus nephritis identified. Given that renal biopsy is often associated with adverse events or can be contraindicated due to substantial comorbidities, clues from the clinical picture and simple laboratory measures would provide valuable guidance to our therapeutic approach. Thus, the presence of ≥2 of predictors that include absence of malar rash together with negative anti-dsDNA serum titers and number of leucocytes in urinalysis ≤5/hpf is associated with class II nephritis, in which immunosuppression is not mandated. On the contrary, ≥3 of any of the following risk factors that include age at nephritis diagnosis <32 years old, the presence of MSK manifestations, new-onset hypertension, positive serum titers of anti-dsDNA antibodies, increased number of leucocytes (>5/hpf) in urinalysis, elevated serum creatinine levels, presence of cellular casts >1/hpf, and absence of NRP are highly associated of proliferative forms of nephritis, in which aggressive immunosuppression with steroids and either intravenous cyclophosphamide or MMF is highly warranted. Of note, whereas the presence of

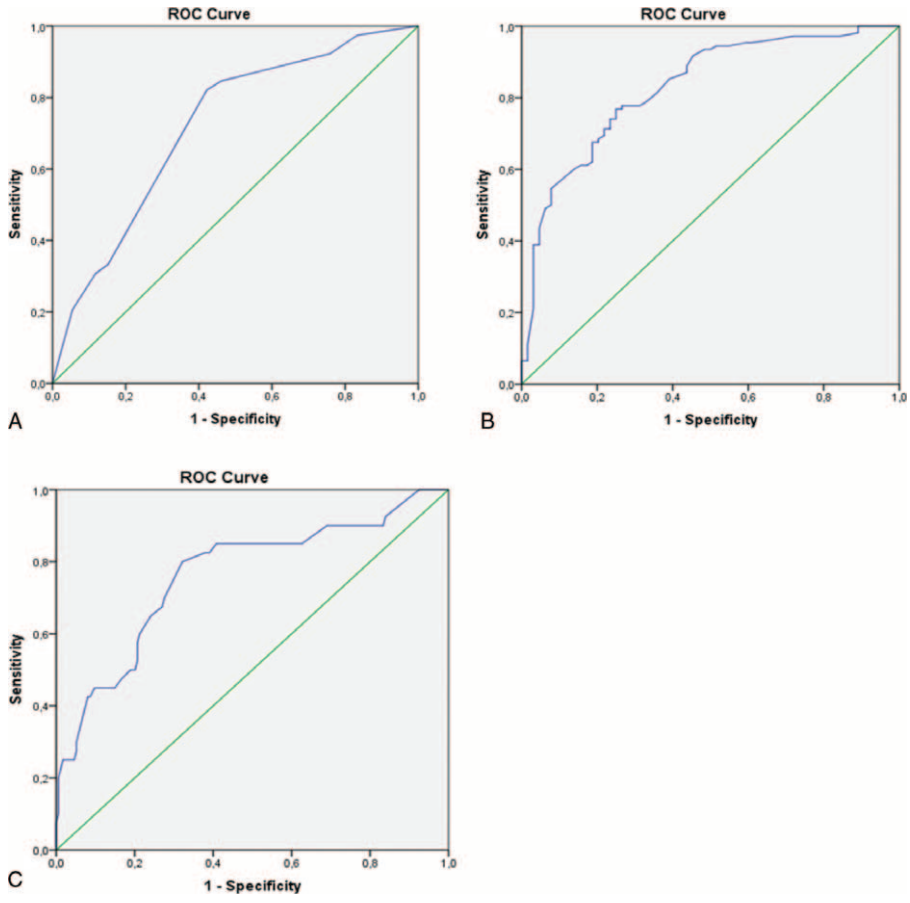

FIGURE 1. Receiver operating characteristic (ROC) curve for the histological diagnosis of class II (A), class III/IV (B), and class V (C) nephritis based on risk scores II, III/IV, and V, respectively. Area under the curve (AUC) were 0.72 ($P < 0.001$) for class II nephritis, 0.83 ($P < 0.0001$) for class III/IV nephritis, and 0.76 ($P < 0.0001$) for class V.

TABLE 5. Predictors of High Activity and Chronicity Scores Among Proliferative (III and IV) Classes of Lupus Nephritis

	High Activity Index*				High Chronicity Index†			
	Presence (%)	Absence (%)	*P* Value	OR 95% (CI)	Presence (%)	Absence (%)	*P* Value	OR 95% (CI)
NRP‡	22.7	8.3	0.08	3.2 (.9–11.7)	20.0	17.9	0.82	1.2 (0.9–2.9)
Age >32 y§	48.9	47.2	1	1.1 (.9–2.3)	60.0	39.1	0.03	2.3 (1.1–4.8)
MSK	59.3	58.3	1	1.1 (.5–2.3)	61.1	57.4	0.71	1.2 (0.6–2.4)
Hypertension‖	10.3	8.3	1	1.3 (.3–4.9)	13.0	7.2	0.36	1.9 (0.6–6.4)
Anti-dsDNA	89.3	90.6	0.55	0.6 (.2–2.1)	88.2	84.4	0.6	1.39 (0.4–4.1)
Creatinine >1.2 mg/dL	41.4	21.2	0.05	2.6 (1.1–6.7)	40.7	31.8	0.34	1.5 (0.7–3.1)
Pyuria¶	66.7	45.2	0.05	2.4 (1.1–5.6)	65.4	57.1	0.40	1.4 (0.7–3.1)
Casts#	23.9	7.7	0.09	3.8 (.8–17.7)	23.5	16.9	0.58	(0.5–4.2)

CI = confidence interval, hpf = high power field, MSK = musculoskeletal manifestations, NRP = nephrotic range proteinuria, OR = odds ratio.
* Activity of SLE nephritis in renal biopsy ≥5.
† Chronicity of SLE nephritis in renal biopsy ≥3.
‡ >3 g protein in 24 h urine.
§ Age at nephritis diagnosis.
‖ New onset.
¶ White blood cells >5/hpf in urinalysis.
# Presence of ≥1 cellular casts/hpf in urine sediment.

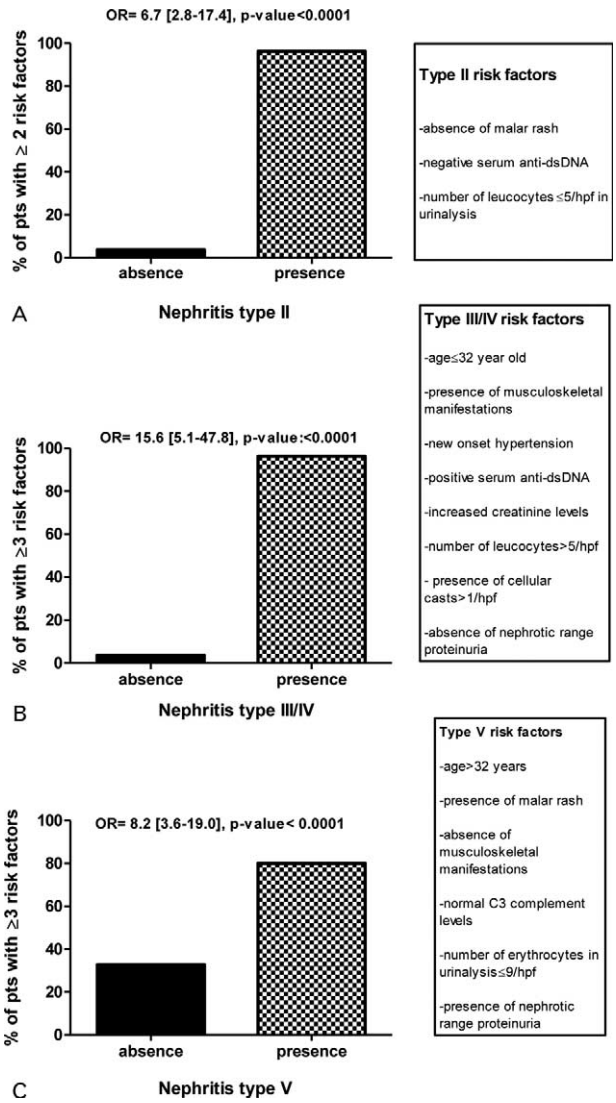

FIGURE 2. Prognostic probability of histological diagnosis of class III/IV according to clinical and laboratory measures at the time of clinical renal involvement. Percentages indicate the proportion of patients with 2, 3 or more risk factors in the presence or absence of class II (A), class III/V (B) and class V (C) lupus nephritis.

pyuria and higher creatinine levels was found to be associated with higher activity scores in these patients, age at nephritis diagnosis >32 years old was predictive of higher chronicity scores. Finally, the presence of >3 predictive factors including older age at nephritis diagnosis (>32 years), malar rash, absence of MSK symptoms, NRP, normal C3 complement levels, and urine red blood cells ≤9 /hpf are highly associated with membranous class V lupus nephritis, in which steroids and MMF is recommended as first-line immunosuppressive agent.

Although several studies so far attempted to identify predictors of outcome particularly in proliferative form of lupus nephritis, to our surprise, there were scarce data in regard to histological class prediction. Nevertheless, several clinical or laboratory predictors such as mild or no hematuria, urine protein/creatinine of <1.0, and normal serum creatinine have been previously felt to predict class II nephritis.[17] This assumption was challenged by a subsequent study with limited number of patients, in which proteinuria levels <1 g in the presence or absence of hematuria was also associated with proliferative lupus nephritis forms.[18] On the contrary, in an earlier study by Gladman et al,[19] the presence of active clinical disease—initially thought to be associated with proliferative forms of lupus nephritis—was also identified in some patients with class II. Finally, the presence of positive anti-dsDNA titers and hematuria have been found to be associated with proliferative forms of the disease,[20–23] whereas hypertension and tubulointerstitial changes were recently shown to correlate with hypertension and elevated creatinine levels.[23]

Despite a longstanding debate in regard to the role of renal biopsies in the diagnosis of lupus nephritis,[24] recent recommendations from both sides of the Atlantic[6,7] have advocated the role of renal biopsy in aiding the therapeutic approach. Although at no means our present findings would substitute the need for renal biopsy in cases of renal involvement in patients with lupus, it offers, however, a practical guide in cases in which renal biopsy is contraindicated or poses high patient risk due to comorbidities.

According to a position paper by the American College of Physicians several years ago,[25] uncontrolled severe hypertension, uncorrectable bleeding diathesis, uncooperative patients, and a solitary kidney are considered absolute contraindications for renal biopsy. Additionally, relative contraindications such as small hyperechoic kidneys, cysts, or other anatomical abnormalities, as well as perirenal and over the biopsy site skin infections consist relative contraindications and should be taken into account into individual patients.[25] On the other hand, SLE-related issues, such as chronic anticoagulation within the setting of secondary antiphospholipid syndrome,[26] anemia, thrombocytopenia, and impaired kidney function[27] have been all shown to confer increased risk for renal hemorrhage following renal biopsy, and therefore should be carefully considered.[28] Thus, in a clinical setting, decisions taking into account both the risk for recurrent thrombosis by the temporary discontinuation of the anticoagulation therapy and the increased bleeding risk related to concomitant comorbidities can be difficult, posing life-threatening patient risks. In this context, we suggest that implementation of simple laboratory measures in predicting the histological class is of major importance. As delay of biopsy and treatment from the time of clinical onset of nephritis has been previously shown to be an independent risk factor for poor outcome,[29] information derived from clinical examination and simple laboratory measures such as urinalysis, would allow the early establishment of appropriate therapies preventing chronic renal damage.

However, the present findings should be interpreted in the context of potential limitations. The retrospective nature of the study did not allow a more comprehensive evaluation of each case, and therefore information about antiphospholipid syndrome related or chronic sclerotic changes were not obtained.[8] Additionally, our analysis was mainly focused in predicting distinct histopathological classes, without taking into account prior immunosuppressive treatments and histopathological features such as tubulointerstitial involvement or vascular changes included in the International Society of Nephrology/2003 classification criteria.[10] Validation of the present results in an independent cohort is highly warranted.

Although beyond the scope of the present study—principally aimed to provide an easy clinical/laboratory algorithm for the practicing physicians—it would be highly interesting to clarify the underlying pathophysiological mechanisms of

distinct clinical pictures and histopathological patterns of lupus nephritis. Unfortunately, due to the retrospective nature of the present work, no stored sera or whole blood specimens were available from these patients that precluded the possibility to identify biological markers in association with specific lupus nephritis classes. Future prospective well designed studies are highly desired to allow the identification of specific biological pathways and potentially therapeutic targets for each lupus nephritis type.

In conclusion, in the present study, we present a predictive score of distinct histological classes of lupus nephritis based on clinical and simple laboratory measures, which ultimately guides the subsequent treatment and therapeutic outcome. Thus, these predictors might provide a useful tool for the practicing physician in identifying patients in which early treatment is warranted or the type of immunosuppressive treatment needed, particularly in cases in which renal biopsy is contraindicated or poses unacceptably high patient morbidity and eventually mortality.

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