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Original Article

Predictive factors for the development of lupus nephritis after diagnosis of systemic lupus erythematosus[☆]

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ABSTRACT

Objectives: To determine predictive factors for the development of lupus nephritis (LN) at the time of diagnosis of systemic lupus erythematosus (SLE).

Methods: A case-control study was carried out in a single center, 595 patients with a diagnosis of SLE without LN participated by clinical or laboratory parameters at diagnosis, they were followed for a mean of 6.8 (+4.5) years, conforming to the data of their files two groups: with NL (cases) and without NL (controls) at the end of the follow-up. Sociodemographic, clinical, serological, immunological variables and the albumin – globulin ratio (AGR), calculated as albumin/total protein-albumin at diagnosis, were compared between both groups. A univariate and multivariate analysis was carried out.

Results: 124 (20.8%) patients had LN during follow-up and 471 (79.2%) did not develop LN. Univariate analysis: variables significantly associated with the development of LN: smoking, oral ulcers, serositis, more than four classification criteria, abrupt onset of SLE, higher SLEDAI value, low AGR, low C3 levels, high anti-titers. –Double stranded DNA (anti-dc DNA), anti-nucleosomes and positivity of immunofluorescence in skin. Multivariate analysis: predictors of developing LN: elevated serum levels of anti-dc DNA (odds ratio (OR): 15.82; confidence interval (CI): 1.08–1.22, $P < .0001$), decrease in the C3 fraction (OR: 36.50; CI: 13.52–81.91, $P < .0001$) and the RAG < 1 (OR: 47.58; CI: 11.85–79.17, $P < .0001$).

Conclusion: The AGR below one was the greatest predictor of the appearance of LN, together with the low levels of C3 and high levels of anti-dc DNA antibodies, they may contribute to identifying patients with a higher risk of presenting LN.

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Factores predictores del desarrollo de nefritis lúpica después del diagnóstico de lupus eritematoso sistémico

RESUMEN

Objetivos: Determinar factores predictores de desarrollo de nefritis lúpica (NL) al momento del diagnóstico del lupus eritematoso sistémico (LES).

Métodos: Se realizó un estudio de casos y controles en un único centro, participaron 595 pacientes con diagnóstico de LES sin NL por parámetros clínicos o de laboratorio al diagnosticarlos, fueron seguidos durante una media de 6,8 ($\pm 4,5$) años, conformándose de los datos de sus expedientes dos grupos: con NL (casos) y sin NL (controles) al final del seguimiento. Se compararon entre ambos grupos variables sociodemográficas, clínicas, serológicas, inmunológicas y la relación albumina-globulina (RAG), calculada como la albumina/proteínas totales-albumina al diagnóstico. Se efectuó un análisis univariado y multivariado.

Palabras clave:

Lupus eritematoso sistémico

Nefritis lúpica

Relación albúmina globulina

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Resultados: En el seguimiento presentaron NL 124 (20,8%) pacientes y no desarrollaron NL 471 (79,2%). Análisis univariado: variables asociadas significativamente al desarrollo de NL: hábito de fumar, úlceras orales, serositis, más de cuatro criterios de clasificación, inicio abrupto del LES, mayor valor de SLEDAI, baja la RAG, bajos niveles de C3, títulos elevados de anti-DNA doble cadena (anti-DNA dc), anti nucleosomas y positividad de la inmunofluorescencia en piel. Análisis multivariado: factores predictores de desarrollar NL: niveles séricos elevados de anti-DNA dc (odds ratio (OR):15,82; intervalo de confianza (IC):1,08–1,22, $P < .0001$), disminución de la fracción C3 (OR: 36,50; IC: 13,52 – 81,91, $P < .0001$) y la RAG < 1 (OR: 47,58; IC: 11,85–79,17, $P < .0001$).

Conclusión: La RAG por debajo de uno fue el mayor predictor de aparición de la NL, conjuntamente con los niveles bajos de C3 y elevados de anticuerpos anti-DNA dc, pueden contribuir a identificar pacientes con mayor riesgo de presentar NL.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organs and tissues, and the development of kidney disease is the most important predictor of morbidity and mortality. Lupus nephritis (LN) is a serious complication of the disease, affecting 25%–75% of patients, its frequency is influenced by ethnicity, gender, and age at presentation, among other factors^{1–3}. Despite advances in the treatment of LN, a not insignificant group of patients will develop irreversible kidney damage^{4–6}.

LN can be the first manifestation of SLE; its onset is usually within the first year of diagnosis, but it can develop over the course of the disease^{7,8}. Early diagnosis, use of immunosuppressive agents and response to induction therapy are important factors in achieving better results in controlling the condition^{9–12}.

When comparing the efficacy of treatments according to the time of onset of LN, whether at the beginning of the disease or during its course, the worst results have been obtained in the latter group of patients^{8,13,14}. Other studies have attempted to identify demographic, clinical, serological and immunological differences between the groups with dissimilar results^{14–16}. In addition, the association of serum globulin and albumin levels and the presence of immunoglobulin deposits at the dermoepidermal junction in the skin have been analysed in relation to the subsequent development of LN^{16–19}.

The aim of this study was to determine predictors of LN development at time of SLE diagnosis.

Patients and methods

We conducted a case-control study from the total patients diagnosed with SLE in the rheumatology department of the Hermanos Ameijeiras Hospital, Havana, Cuba, between 3 January 2005 and 31 December 2019; the patients met the American College of Rheumatology (ACR) classification criteria for SLE²⁰. Patients were excluded if they had any of the following laboratory data for clinical LN on diagnosis of the condition: proteinuria ≥ 5 g/24 h or proteinuria⁺⁺⁺, serum creatinine ≥ 123.7 μ mol/l, estimated glomerular filtration rate ≤ 60 mL/min/1.73 m², erythrocyte or leukocyte count ≥ 10 cells per high-power field, ≥ 3 granular or cellular cylinders per high-power field. Those with culture-confirmed active infection, liver dysfunction, diagnosed malignancy, pregnant women, and cases with incomplete data in their records that did not allow assessment were followed for a mean of 6.8 (± 4.5) years, the data from their records were used to create two groups: one that developed clinical LN or detected through kidney biopsy (cases) and the other without clinical LN (controls) during follow-up.

The following baseline data were collected at the time of diagnosis: age, sex, ethnicity according to skin colour and anthropometric characteristics classified by three specialists as white, black or mestizo, level of education, smoking, alcohol consumption, presence

of clinical symptoms such as arthritis, photosensitivity, facial erythema, discoid erythema, alopecia, mouth ulcers, fever, serositis, central nervous system (CNS) involvement, quantification of the number of classification criteria, form of presentation of the condition: abrupt (presentation of symptoms in less than 4 weeks) or insidious (more than 4 weeks until presentation of symptoms).

We also considered the values or presence of: haemoglobin, leukocytes, lymphocytes, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, urea, serum total protein and albumin, albumin-to-globulin ratio (AGR) obtained by the equation $AGR = \text{albumin} / (\text{total protein} - \text{albumin})$, glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), glomerular filtration rate (GFR), C3 and C4 fraction, anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-RNP, anti-nucleosome antibodies, anti-Ro/SSA and anti-La/SSB, lupus anticoagulant, presence of immunoglobulin deposits in immunofluorescence study on biopsy of healthy sun-exposed skin (lupus band). Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)²¹. To achieve the aim of the study, the existence of LN at follow-up was defined by the presence of one of the following two criteria:

- 1 By renal biopsy according to the classification of the International Society of Nephrology and Renal pathology²².
- 2 Presence of clinical LN: proteinuria ≥ 5 g/24 h or proteinuria⁺⁺⁺; and/or one of the following features attributable to SLE, present at ≥ 2 visits at least 6 months apart: proteinuria⁺⁺, serum creatinine ≥ 123.7 μ mol/l, estimated glomerular filtration rate ≤ 60 mL/min/1.73 m², erythrocyte or leukocyte count ≥ 10 cells per high-power field, ≥ 3 granular or cellular cylinders per high-power field.

The time to onset of nephritis was considered to be the interval between the diagnosis of SLE and the time of LN onset.

The research project was approved by the centre's ethics committee and scientific council, an institution of the Ministry of Public Health of the Republic of Cuba. The identity of the patients was preserved; as this was a retrospective study, informed consent was not required.

Statistical analysis

The χ^2 or Fisher's exact test were used to compare between groups for qualitative variables, as appropriate. For quantitative variables, the Student's *t*-test for independent samples or the Mann-Whitney *U* test was used, according to the normality of the population between the groups. A multivariate binary logistic regression (BLR) was performed to identify predictors of LN. In the results of the final BLR model, odds ratios (OR) and confidence intervals (CI) were shown for each predictor variable, as well as statistical significance (*P*-value). Hypothesis tests with a $P < .05$ were considered statistically significant. ROC curves were performed for

LN predictor variables and the area under the curve (AUC) was estimated. SPSS version 20.0 was used to analyse the data.

Results

Of the 768 patients seen with a diagnosis of SLE, 148 were excluded as they had LN at disease onset (19.3%), 10 due to active infection, 8 due to liver dysfunction, 3 due to malignant disease, 2 due to pregnancy and 2 due to incomplete records, leaving 595 patients included in the study.

Of the patients 595 had no signs of LN at SLE diagnosis; 124 (20.8%) developed LN during follow-up and 471 (79.2%) remained without nephritis. The mean duration of follow-up was 6.8 (± 4.5) years and the mean time to developing LN was 14.7 (± 11.3) months. The cumulative incidence of LN was 35.4%. Of the cases included, 93.1% were female, with a female:male ratio of 13.5:1.

Nephropathy was diagnosed by biopsy in 122 cases; 67 of them (55.7%) were class IV, 21 (16.9%) class II, 19 (15.3%) class III, and 15 (12.1%) class V. It was not possible to perform biopsy in 2 patients due to coagulation disorders and it was imperative to initiate treatment; these 2 patients met the laboratory criteria indicated in the method for determining the existence of LN.

Table 1 shows that the age distribution was similar in both groups, as was the predominance of female sex, and that black ethnicity was significantly associated with the onset of LN. A set of variables presented higher values or frequencies in the group that developed LN, such as smoking, abrupt onset of the disease, SLEDAI values, anti-dsDNA, anti-nucleosomes, all with significant differences, as did low levels of C3 and AGR < 1.

Other variables compared between groups with a significance level of $P < .001$ were alopecia, oral ulcers and serositis, having more than 4 ACR classification criteria, serum creatinine, total protein, serum albumin, C3, and positive immunofluorescence of healthy skin.

All the other variables analysed were not statistically different between the two groups.

The multivariate analysis (Table 2) shows the variables that were predictors of LN, and included those that were significant in the univariate analysis; the AUC values of the ROC curves of the predictors, shown in Fig. 1 (Fig. 1A–C), were also included in the Table, highlighting an AGR below unity as the main predictor of LN. The rest of the variables that had been significant in the univariate analysis were not associated with the development of LN in the multivariate analysis.

Discussion

This study reaffirms the usefulness of the AGR value at disease onset as a predictor of risk for developing LN during the course of SLE. Patients with values lower than one have a higher prognosis of developing LN over the course of the disease; this could be explained by a higher level of globulins within the total proteins, closely linked to the elevated autoantibodies necessary for kidney involvement to be expressed²².

The AGR has been used as a prognostic indicator in other diseases such as cancer²³, but there are few reports of its use in SLE in this regard and these are from an Asian population¹⁶. Therefore we consider these results a contribution from a different population, in this case of Hispanic and African descent.

The study includes a large number of patients, and as it deals with cases from a single hospital, it may ensure greater uniformity of results in a population that is very ethnically mixed between whites, blacks, and mestizos, which inevitably entails a bias that is difficult to control when defining it, since in our setting it is not uncommon to see people of white skin colour with a close black

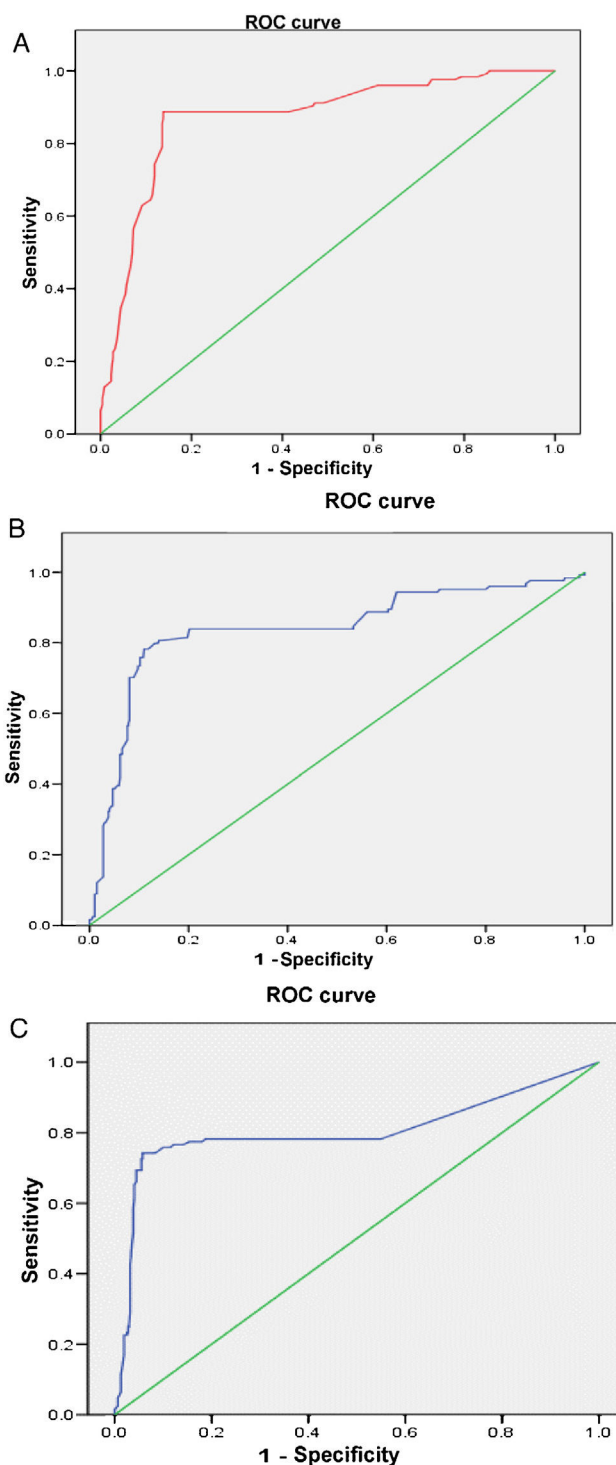


Fig. 1. ROC curves for LN predictors: A: AGR; B: C3 fraction; C: anti-dsDNA.

relative. Nevertheless, black patients were significantly associated with the development of LN, which confirms the greater severity of the disease in people of African descent, which has been repeatedly published^{24,25}.

The cumulative incidence of LN, which varies among different populations, may be due to sociodemographic, environmental and immunogenetic differences, and to the different inclusion criteria used; there are reports in Caucasian (29.1%), Hispanic (60.6%) and African American (68.9%) patients studied in the United States and a study in 391 Korean patients reported a frequency of 34.8%. A

Table 1
Characteristics at diagnosis of SLE patients who did and who did not develop lupus nephritis at follow-up (univariate analysis).

Variables	SLE with nephritis n = 124	SLE without nephritis n = 471	P
Age in years (SD)	34.1 (11.3)	33.7 (12.0)	.738
Female sex	116 (93.5%)	438 (93.0%)	.506
Ethnicity			
White	81 (65.3%)	306 (64.9%)	.177
Black	22 (17.7%)	47 (10.1%)	.021
Mestizo	21 (17%)	118 (25%)	.019
Smoking	49 (39.5%)	85 (18.0%)	<.001
Arthritis	98 (79%)	320 (67.9%)	.010
Photosensitivity	77 (62.1%)	325 (69.0%)	.089
Facial erythema	85 (68.5%)	307 (65.2%)	.277
Fever	78 (62.9%)	245 (52.0%)	.019
Alopecia	72 (58.1%)	207 (43.9%)	.003
Mouth ulcers	58 (46.8%)	146 (31.0%)	<.001
Serositis	38 (30.6%)	80 (17.0%)	<.001
Discoid erythema	15 (12.1%)	97 (20.6%)	.019
CNS manifestations	15 (12.1%)	40 (8.5%)	.145
ACR criteria, more than 4	81 (65.3%)	179 (38.0%)	<.001
Abrupt onset of disease	8 (6.5%)	0 (.0%)	<.001
SLEDAI	12.1 ± 3.5	9.3 ± 4.13	<.001
Serum creatinine (μmol/l)	76 ± 13	79 ± 12	<.001
Total protein (g/l)	74 ± 5.9	78 ± 6.8	<.001
Serum albumin (g/l)	36 ± 3.5	38 ± 3.2	<.001
AGR < 1	110 (88.7%)	66 (14.0%)	<.001
AGR	.805 ± .198	1.095 ± .289	<.001
GPT (U/l)	32.5 ± 10.7	32.3 ± 9.1	.913
GOT (U/l)	28.4 ± 10.3	30.0 ± 9.8	.072
C3 (g/l)	.7 ± .3	1.1 ± .3	<.001
C4 (g/l)	.14 ± .1	.15 ± .1	.336
Anti-nucleosome (U/l)	10.8 ± 62.6	.17 ± .38	<.001
Anti-dsDNA (U/mL)	109.6 ± 84.1	20.1 ± 42.8	<.001
Anti-Smith (U/mL)	.96 ± 9.05	.15 ± .36	.054
Anti-SSA/Ro (U/mL)	.20 ± .4	.20 ± .4	.983
Anti-SSB/La (U/mL)	.08 ± .3	.06 ± .2	.468
Anti-RNP (U/mL)	.18 ± .39	.17 ± .37	.747
Lupus anticoagulant positive	10 (8.1%)	49 (10.4%)	.428
Positive immunofluorescence of healthy skin	95 (76.6%)	144 (30.6%)	<.001

ACR: American College of Rheumatology; AGR: Albumin-to-globulin ratio; CNS: Central Nervous System; ds: double stranded; SD: Standard Deviation; SLEDAI: Systemic lupus erythematosus disease activity index; GOT: Glutamic Oxaloacetic Transaminase; GPT: Glutamic Pyruvic Transaminase.

Table 2
Predictors of the development of lupus nephritis (multivariate analysis).

Variables	OR	95% CI	P	AUC
anti-dsDNA	15.82	1.08–1.22	<.0001	.80
Low C3	36.50	13.52–81.91	<.0001	.83
ARG <1	47.58	11.85–79.17	<.0001	.87

AGR: Albumin-to-globulin ratio; AUC: Area under the curve; CI: Confidence Interval; ds: double stranded; OR: odds ratio.

multinational research study involving countries in the Americas, Europe, and Asia, with a total of 1827 patients, reported a frequency of LN at follow-up of 38.3%^{16,24–26}. The cumulative incidence established in our study (35.4%) is among the reported values, but lower than the published value in African American and Hispanic patients studied in the United States and that of the Latin American GLADEL cohort. We consider that this can be attributed to the different genetic characteristics of the Cuban population^{24,27}.

Smoking was associated with the subsequent development of nephritis, which could be related to a greater presence of anti-dsDNA antibodies that have a pathogenic relationship with the development of LN²⁸. This is a modifiable variable, which should be considered from the onset of the disease and should be addressed by educating patients and family members. The association of pleurisy, higher disease activity values, as well as a higher number of criteria at diagnosis and abrupt onset, were variables that were associated with the subsequent presence of LN and are results reported in the literature²⁴.

Low C3 levels were another variable of high prognostic value for the subsequent development of LN. This finding suggests the activation of the alternative complement pathway for damage to occur

in LN. Previous studies have shown the association between this variable and the presence of anti-dsDNA antibodies with LN^{29,30}.

The study has its limitations. It is a retrospective research study in which only variables present at diagnosis were considered, and therefore there were no evaluation points at follow-up that could have added other variables, such as treatments and responses to treatments, which may influence the development of LN. In relation to antimalarials, studies in a Latin American population with various ethnic groups conducted by Pons-Estel et al. in the framework of the GLADEL multinational cohort found that the use of these drugs was associated with less kidney disease^{24,27}.

In conclusion, we show in the Cuban population that a low AGR present at diagnosis of SLE is associated with the risk of developing LN during the course of the disease; moreover, it is a relatively low-cost test that, together with other indicators, such as low C3 levels and elevated anti-dsDNA antibodies, can help identify patients at increased risk of developing LN from the time of diagnosis. It is true that C3, anti-dsDNA, albumin levels and/or AGR may be affected by subclinical nephropathy and may already be marking the presence of kidney disease rather than predicting its development. This is a plausible hypothesis, like that established when autoantibodies

are detected in serum before the disease is clinically expressed²⁹, but we also consider that determining their presence means we can design preventive strategies to avoid the clinical expression of nephritis on the one hand and of disease on the other. We can also, within these actions, programme patient monitoring to detect clinical or laboratory signs of nephritis promptly and initiate early treatment which will benefit the long-term prognosis of the disease.

Conflict of interests

The authors have no conflict of interests to declare.

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