GLADEL LATIN AMERICA
SCIENCE & EDUCATION

PANLAR 2025
27 CONGRESO PANAMERICANO DE REUMATOLOGÍA
PAN-AMERICAN CONGRESS OF RHEUMATOLOGY
CONGRESSO PANAMERICANO DE REUMATOLOGIA

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DELAYED DIAGNOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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on behalf of Grupo Latino Americano de Estudio del Lupus (GLADEL).

Background

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease of unknown etiology. Diagnosis is often delayed because it frequently mimics symptoms of other diseases; this also delays treatment initiation[1]. Previous studies have reported that this delay in diagnosis is associated with a worse prognosis including higher disease activity, damage accrual, decreased quality of life and increased use of healthcare resources and, therefore, higher costs[2]. In the GLADEL original cohort, a maximum time to SLE diagnosis of 24 months did not negatively influence disease outcomes (damage accrual and mortality)[3]. This study aimed to characterize delay in the diagnosis in SLE patients and its associated factors.

Methods

Study population

GLADEL 2.0 is an observational multi-ethnic, multi-national Latin-American SLE cohort. Forty-three centers from 10 Latin-American countries enrolled patients ≥18 years of age who fulfilled the 1982/1997 American College of Rheumatology (ACR) and/or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. Patients were categorized into 4 subsets according to the presence or absence of active or inactive lupus nephritis (LN)[4].

Study assessments

Baseline demographics, clinical manifestations, disease activity (SLEDAI-2K) and SLICC/ACR damage index (SDI) and treatments were examined. Based on the original GLADEL report, variables were examined according to time to diagnosis shorter versus equal or longer than 24 months, as no impact was found on outcomes before this time[3].

Statistical analysis

Continuous variables are summarized as median (Q1, Q3) and categorical variables as counts and percentages. Logistic regression models were used to identify factors independently associated with a delay in diagnosis ≥24 months. P-values <0.05 were considered significant. All analyses were done using R v4.4.0.

Results

Baseline sociodemographic and clinical characteristics

Of the 1083 patients included in this GLADEL cohort, 985 were included in these analyses. The remaining patients were excluded because of insufficient data for analysis. The median time to diagnosis was 8 months (0.27–5.67); in 97 patients (9.84%) the time to diagnosis was longer than 24 months. **Table 1** depicts the sociodemographic and clinical characteristics of SLE patients according to time to diagnosis. Patients with a time to diagnosis greater than 24 months were found to be older at diagnosis, having a higher frequency of thrombocytopenia, associated comorbidities, antiphospholipid syndrome (APS), anti-B2GPI positivity and cumulative damage with lower frequency of low complement at cohort entry.

Factors associated with delayed SLE diagnosis

After adjusting for sociodemographic, clinical and immunologic features, multivariate analysis showed that older age, middle socioeconomic status and associated APS were associated with a higher probability of diagnostic delay **(Table 2)**.

Conclusion

In the GLADEL 2.0 multiethnic cohort, we found that delay in diagnosis was more likely to occur in older SLE patients and it was associated with APS. Future analyses will allow us to identify the impact of delayed diagnosis on outcome of SLE patients.

TABLE 1: Sociodemographic and clinical characteristics of patients with SLE according to time to diagnosis

Parameter	<24 months (n = 888)	≥24 months (n = 97)	P value[a]
Time at diagnosis, months, median (Q1-Q3)	0.6 (0.1-3.3)	48.2 (31.5-72)	0.000
Age at diagnosis, years, median (Q1-Q3)	26 (20-34)	30 (23-41)	0.001
Female, n (%)	790 (89.0)	87 (89.7)	1.000
Ethnicity, n (%)			0.822
Caucasian	226 (25.5)	23 (23.7)	
African Latin American	68 (7.7)	9 (9.3)	
Mestizo[b]	583 (65.9)	64 (66.0)	
Other	8 (0.9)	1 (1.0)	
Socioeconomic status, n (%)			0.029
High	188 (21.5)	32 (34.0)	
Medium	318 (36.3)	29 (30.9)	
Medium low/low	369 (42.2)	33 (35.1)	
Medical insurance, n (%)	608 (69.2)	68 (70.8)	0.816
Cumulative clinical manifestations, n (%)			
Fever	370 (41.7)	40 (41.2)	1.000
Malar rash	556 (62.6)	53 (54.6)	0.152
Discoid lupus	69 (7.8)	11 (11.3)	0.239
Photosensitivity	564 (63.9)	57 (58.8)	0.319
Oral/nasopharyngeal ulcers	386 (43.9)	44 (45.4)	0.830
Alopecia	576 (65.0)	69 (71.1)	0.261
Arthritis	722 (81.3)	80 (82.5)	0.891
Pleuritis	228 (25.8)	25 (25.8)	1.000
Pericarditis	161 (18.3)	13 (13.4)	0.265
Persistent proteinuria	508 (57.4)	49 (50.5)	0.197
Cellular cylinders	229 (27.2)	27 (28.4)	0.809
Psychosis	29 (3.3)	2 (2.1)	0.761
Seizures	42 (4.7)	8 (8.2)	0.143
Hemolytic anemia	101 (11.5)	15 (15.6)	0.244
Leukopenia	401 (45.9)	45 (47.4)	0.829
Lymphopenia	478 (54.6)	51 (53.7)	0.914
Thrombocytopenia	193 (22.1)	33 (34.4)	**0.010**
ANA, positivity	872 (99.3)	94 (97.9)	0.182
Anti-dsDNA, positivity	676 (78.4)	73 (77.7)	0.895
Anti-Smith, positivity	269 (36.4)	25 (29.4)	0.232
Anti-lupus coagulant, positivity	114 (16.2)	18 (21.7)	0.214
Anti-cardiolipin, positivity	141 (19.0)	23 (27.1)	0.085
Anti-B2GPI, positivity	67 (11.2)	19 (26.8)	**0.001**
False-positive VDRL	26 (4.1)	7 (9.7)	0.068
C3, low	681 (78.5)	66 (68.8)	**0.038**
C4, low	682 (78.9)	66 (68.8)	**0.027**
CH50, low	68 (27.5)	4 (15.4)	0.243
Coombs, positivity	146 (23.9)	23 (33.8)	0.077
Comorbidities,[c] n (%)	428 (48.4)	60 (61.9)	**0.014**
SLEDAI-2K score at cohort entry, median (Q1-Q3)	5 (2-12)	6 (2-12)	0.634
SDI score at cohort entry ≥1, n (%)	316 (36.6)	48 (51.1)	**0.007**
Personal history of autoimmune diseases, n (%)			
Sjögren's syndrome	29 (3.3)	5 (5.2)	0.371
Rheumatoid arthritis	8 (0.9)	1 (1.0)	0.608
Antiphospholipid syndrome	51 (5.8)	13 (13.5)	**0.008**

ANA, antinuclear antibody; anti-B2GPI, anti- β2 glycoprotein I; C3, complement component 3; C4, complement component 4; CH50, total complement; dsDNA, double-stranded DNA; Q, quartile; SDI, the 2012 Systemic Lupus International Collaborating Clinics/the 1982/1997 American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; VDRL, Venereal Disease Research Laboratory.
[a]Bold P values were considered statistically significant.
[b]Individuals born in Latin America who had both Amerindian and White ancestors.
[c]≥1 of the following: diabetes mellitus, arterial hypertension, or dyslipidemia.

TABLE 2: Univariable and multivariable Cox regression analyses of factors associated with delayed diagnosis in patients with SLE

Parameter	Univariate model: odds ratio (95% CI)	P value[a]	Multivariate model: odds ratio (95% CI)	P value[a]
Female	1.08 (0.54-2.15)	0.828	1.24 (0.56-2.78)	0.595
Age at diagnosis, years	1.03 (1.02-1.05)	**<0.001**	1.03 (1.01-1.05)	**0.004**
Ethnicity				
Caucasian	Ref		Ref	
African Latin American	1.30 (0.57-2.94)	0.528	1.28 (0.49-3.31)	0.616
Mestizo[b]	1.08 (0.65-1.78)	0.767	1.08 (0.62-1.89)	0.792
Other	1.23 (0.15-10.26)	0.849	1.35 (0.15-12.14)	0.791
Socioeconomic status				
High	Ref		Ref	
Medium	0.54 (0.31-0.91)	**0.022**	0.48 (0.25-0.89)	**0.021**
Medium low/low	0.53 (0.31-0.88)	**0.015**	0.55 (0.29-1.06)	0.072
Educational level, years				
0-7	Ref		Ref	
8-12	1.57 (0.60-4.12)	0.359	1.68 (0.6-4.65)	0.321
≥13	1.47 (0.57-3.83)	0.427	1.4 (0.48-4.05)	0.537
SDI score at cohort entry ≥1	1.81 (1.18-2.77)	**0.007**	1.24 (0.74-2.08)	0.412
SLEDAI-2K score at cohort entry	1.01 (0.98-1.03)	0.604	1.02 (0.99-1.06)	0.161
Comorbidities[c]	1.73 (1.13-2.66)	**0.012**	1.31 (0.79-2.16)	0.296
Personal history of autoimmune disease				
Sjögren's syndrome	1.61 (0.61-4.27)	0.336	1.17 (0.4-3.47)	0.771
Rheumatoid arthritis	1.15 (0.14-9.27)	0.897	1.05 (0.11-9.97)	0.963
Antiphospholipid syndrome	2.54 (1.33-4.87)	**0.005**	2.6 (1.21-5.59)	**0.014**
Clinical domains				
Constitutional	0.98 (0.64-1.50)	0.928	1.22 (0.74-2.00)	0.434
Mucocutaneous	0.76 (0.41-1.42)	0.399	0.76 (0.38-1.51)	0.429
Musculoskeletal	1.08 (0.62-1.88)	0.779	1.06 (0.56-1.99)	0.859
Serosal	1.02 (0.65-1.60)	0.924	1.18 (0.71-1.96)	0.528
Renal	0.69 (0.45-1.05)	0.084	0.71 (0.41-1.23)	0.220
Neuropsychiatric	1.16 (0.63-2.16)	0.637	0.93 (0.45-1.93)	0.842
Hematologic	1.12 (0.70-1.79)	0.649	0.97 (0.57-1.65)	0.917
Immunology domains				
Anti-dsDNA, positivity	0.96 (0.57-1.60)	0.865	1.28 (0.7-2.33)	0.422
C3, low	0.60 (0.38-0.95)	**0.030**	0.86 (0.43-1.69)	0.654
C4, low	0.59 (0.37-0.93)	**0.024**	0.66 (0.34-1.30)	0.227

C3, complement component 3; C4, complement component 4; CI, confidence interval; dsDNA, double-stranded DNA; Ref, reference; SDI, the 2012 Systemic Lupus International Collaborating Clinics/the 1982/1997 American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
[a]Bold P values were considered statistically significant.
[b]Individuals born in Latin America who had both Amerindian and White ancestors.
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Acknowledgments

This study was sponsored by Janssen Research & Development, LLC. Editorial support was provided by Panita M. Trenor, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

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