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BRIEF REPORT

How Do Patients With Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria

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Objective. Systemic lupus erythematosus (SLE) presents with nonspecific signs and symptoms that are also found in other conditions. This study aimed to evaluate manifestations at disease onset and to compare early SLE manifestations to those of diseases mimicking SLE.

Methods. Academic lupus centers in Asia, Europe, North America, and South America collected baseline data on patients who were referred to them during the previous 3 years for possible SLE and who had a symptom duration of <1 year. Clinical and serologic manifestations were compared between patients diagnosed as having SLE and those diagnosed as having SLE-mimicking conditions. Diagnostic performance of the 1997 American College of Rheumatology (ACR) SLE classification criteria and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria was tested.

Results. Data were collected on 389 patients with early SLE and 227 patients with SLE-mimicking conditions. Unexplained fever was more common in early SLE than in SLE-mimicking conditions (34.5% versus 13.7%, respectively; $P < 0.001$). Features less common in early SLE included Raynaud's phenomenon (22.1% versus 48.5%; $P < 0.001$), sicca symptoms (4.4% versus 34.4%; $P < 0.001$), dysphagia (0.3% versus 6.2%; $P < 0.001$), and fatigue (28.3% versus 37.0%; $P = 0.024$). Anti–double-stranded DNA, anti–β_2-glycoprotein I antibodies, positive Coombs' test results, autoimmune hemolytic anemia, hypocomplementemia, and leukopenia were more common in early SLE than in SLE-mimicking conditions. Symptoms detailed in the ACR and SLICC classification criteria were significantly more frequent among those with early SLE. Fewer patients with early SLE were not identified as having early SLE with use of the SLICC criteria compared to the ACR criteria (16.5% versus 33.9%), but the ACR criteria demonstrated higher specificity than the SLICC criteria (91.6% versus 82.4%).

Conclusion. In this multicenter cohort, clinical manifestations that could help to distinguish early SLE from SLE-mimicking conditions were identified. These findings may aid in earlier SLE diagnosis and provide information for ongoing initiatives to revise SLE classification criteria.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multifaceted and complex condition with variable phenotypes and clinical manifestations and a relapsing–remitting course. It is acknowledged that early recognition of SLE can be beneficial for long-term outcomes, allowing early intervention and reducing damage accrual (1). New therapies for SLE offer the opportunity to prevent serious sequelae, and limiting inclusion to only those with long-standing disease may underestimate the effectiveness of a new treatment, as late-stage disease may be more difficult to treat and/or irreversible (2). Because accurate classification is a prerequisite for including SLE patients in clinical trials, the difficulty in classifying patients with early SLE may limit the conduct of clinical and translational studies on early disease.

Because SLE onset is often insidious, with clinically evident disease developing over years, the classification and diagnosis of SLE may be delayed (3). Both the American College of Rheumatology (ACR) SLE classification criteria (4,5) and the Systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria (6) demonstrate lower sensitivity in identifying early disease, compared to established disease (7). Ines et al reported a higher sensitivity of the 2012 SLICC criteria (94%) compared to the 1997 ACR criteria (86%). Importantly, while the gap between the sensitivity of the SLICC and ACR criteria was maximal for patients with SLE duration of ≤5 years (89% versus 76%, respectively) and decreased with longer duration from the time of diagnosis, both sets of criteria performed suboptimally in the initial years after diagnosis. In addition, SLE diagnosis is often challenging due to a variety of conditions that may mimic SLE, including early phases of connective tissue diseases, infectious diseases, and hematologic diseases. Therefore, the identification of clinical and serologic manifestations at disease onset that could lead the physician to a potential SLE diagnosis and an early referral is important in clinical practice.

Despite differences in the aims and means of classification and diagnosis, classification criteria enhance physicians' ability to accurately identify and recognize SLE (8). The goals of the current multicenter study were to 1) evaluate the characteristics of patients with early SLE compared to non-SLE patients, 2) identify manifestations at disease onset that may support the early diagnosis of SLE, and 3) inform the development of new classification criteria, which could potentially and accurately identify more patients in the early stages of SLE. The performance of conventional classification criteria in early SLE against the diagnosis made by rheumatologists was also evaluated.

PATIENTS AND METHODS

Patients. Seven academic centers in Asia (Manila), Europe (Berlin and Pisa), North America (Boston, Chicago, and Toronto), and South America (São Paulo) with experience in the diagnosis and management of SLE took part in the study. Patients from a multicenter cohort collected by the Study Group on Early SLE of the Italian Society of Rheumatology (ISR) were also included. Personnel at the participating centers were asked to collect data on clinical and serologic manifestations in patients with early SLE and patients with conditions mimicking SLE, at disease onset.

Patients included in the present study had been referred to these centers for evaluation of possible SLE within the previous 3 years. Early SLE was diagnosed by experienced rheumatologists, based on clinical experience and judgment, and patients did not necessarily fulfill existing classification criteria. Non-SLE patients were those who were referred during the same period of time due to suspected SLE, but who ultimately did not receive a diagnosis of SLE by the center's experienced rheumatologists. Non-SLE conditions detected included infections, hematologic diseases (e.g., lymphoma), other defined connective tissue diseases (e.g., Sjögren's syndrome, primary antiphospholipid [aPL] syndrome, mixed connective tissue disease, systemic sclerosis), other rheumatic diseases (e.g., early rheumatoid arthritis), other autoimmune diseases (e.g., antinuclear antibody [ANA]–positive thyroiditis, autoimmune hepatitis, interstitial lung disease), and fibromyalgia. Patients with undifferentiated connective tissue disease (UCTD) who had a follow-up visit after ≥3 years were also included in the non-SLE group. This time requirement was applied due to the potential for UCTD to evolve into SLE, which occurs in the majority of cases within the first 3 years of disease (9).

Data collection. A standardized data extraction form to be used with the 1997 ACR criteria, the 2012 SLICC criteria, and an additional list of 30 items including clinical and serologic manifestations attributable to systemic autoimmune diseases was developed. Patient medical records were reviewed and investigators were asked to add to the list any other presenting manifestation that they considered relevant to the diagnosis. Standardized definitions of the clinical symptoms (e.g., pleuritis, alopecia, etc.) were not provided, since this study aimed to collect real-life data. If clinically feasible, physicians were asked to report only manifestations that were attributable to possible SLE, after excluding other explanations (e.g., fever in the presence of infection). Further analysis was carried out by attributing fever to SLE only in the setting of a normal C-reactive protein (CRP) level. Similarly, no specific requirements were made for autoantibody testing assays; negative results reported in clinical charts were also recorded.

Operating characteristics of conventional criteria in early disease. Performance characteristics of the 1997 ACR criteria and the 2012 SLICC criteria were evaluated compared to the gold standard of the diagnoses made by the lupus center rheumatologists in terms of accuracy, sensitivity, specificity,

Table 1. Demographic characteristics of the enrolled patients*

Characteristic	SLE (n = 389)	Non-SLE mimicking conditions (n = 227)	Total (n = 616)	*P*
Female	345 (88.9)	220 (96.9)	565 (91.9)	<0.001
Age at first symptom, mean ± SD years	31.4 ± 12.3	33.9 ± 13.5	32.3 ± 12.7	0.011
Ethnicity				<0.001
Caucasian	212 (54.5)	203 (89.4)	415 (67.7)	
Asian	113 (29.0)	14 (6.2)	127 (20.7)	
African descent	30 (7.7)	6 (2.6)	36 (5.9)	
American Indian	1 (0.3)	0	1 (0.2)	
Other	7 (1.8)	0	7 (1.1)	
Unknown	26 (6.7)	4 (1.8)	27 (4.4)	

* Except where indicated otherwise, values are the number (%) of patients. Non–systemic lupus erythematosus (non-SLE) mimicking conditions include undifferentiated connective tissue disease, Sjögren's syndrome, systemic sclerosis, primary Raynaud's phenomenon, fibromyalgia, antinuclear antibody–positive thyroiditis, rheumatoid arthritis, mixed connective tissue disease, hematologic diseases, infections, autoimmune hepatitis, psoriatic arthritis, miscellaneous diagnoses including rosacea, osteoarthritis, and erythema nodosum.

positive predictive value (PPV) and negative predictive value (NPV), and their 95% confidence intervals (95% CIs).

Statistical analysis. Demographic and clinical characteristics of SLE cases and non-SLE cases were tabulated. The proportion of patients with each clinical and laboratory manifestation were calculated. The distribution of variables in patients with early SLE was compared to the distribution of variables in non-SLE patients, using chi-square or Fisher's exact test. To assess the potential to improve performance of conventional criteria in correctly identifying SLE patients at early onset, 2 different multivariable logistic regression models (which added variables to the dummy variables used to indicate that ACR or SLICC criteria have been met) were developed. Covariate selection in multivariable analysis was done using clinical and statistical criteria; specifically, all variables with a *P* value of <0.10 in univariable analysis were considered for multivariable models. Backward and forward stepwise selections were used to assess model stability using *P* values less than 0.10 as a threshold to include or exclude a variable. The variance inflation factor was used to assess collinearity. The discrimination ability of the different models was assessed by calculating the area under the receiver operating characteristic curve and asymptotic 95% CI, and the C statistic was used to make comparisons. All analyses were performed using Stata 12 (StataCorp) and R version 3.2; in descriptive statistics, *P* values less than 0.05 were considered significant.

RESULTS

A total of 616 patients were evaluated (Manila: 80 patients, Berlin: 30 patients, Pisa and ISR group: 294 patients, Boston: 32 patients, Chicago: 6 patients, Toronto: 124 patients, São Paulo: 50 patients), 389 with early SLE and 227 with SLE-mimicking conditions. The SLE-mimicking conditions were identified as UCTD (n = 136 [59.9% of non-SLE patients]), Sjögren's syndrome (n = 21 [9.3%]), systemic sclerosis (n = 11 [4.8%]), primary Raynaud's phenomenon (RP) (n = 10 [4.4%]), fibromyalgia (n = 8 [3.5%]), ANA-positive thyroiditis (n = 7 [3.1%]), rheumatoid arthritis (n = 6 [2.6%]), mixed connective tissue disease (n = 4 [1.8%]), hematologic diseases (n = 2 [0.9%]), infections (n = 2 [0.9%]), autoimmune hepatitis (n = 1 [0.4%]), psoriatic arthritis (n = 1 [0.4%]), and 18 miscellaneous diagnoses including rosacea, osteoarthritis, and erythema nodosum. Demographic data on the patients are shown in Table 1. The female:male ratio was higher among patients with mimicking conditions ($P < 0.001$), while age at first diagnosis was significantly lower among subjects with early SLE ($P = 0.011$) (Table 1).

Manifestations of early SLE. ACR and SLICC criteria items were detected significantly more frequently in early SLE than in mimicking conditions (Table 2). Seizures were uncommon at disease onset, reported in 11 SLE patients (2.8%) and in 0 non-SLE patients ($P = 0.009$). No patients with early SLE presented with peripheral neuropathy. Stroke and myocardial infarction occurred in SLE patients only, but were uncommon (n = 4 [1.0%] and n = 3 [0.8%], respectively). Unexplained fever was significantly more common in SLE patients than in patients with mimicking conditions (34.5% versus 13.7%, respectively; $P < 0.001$); significance was maintained when fever in association with a normal CRP level was considered (27.5% versus 7.9%; $P < 0.001$). Additional differentiating variables between SLE patients and patients with mimicking conditions were alopecia (30.6% versus 11.9%, respectively; $P < 0.001$), weight loss (13.1% versus 4.4%; $P < 0.001$), and ascites (3.1% versus 0%; $P = 0.005$).

Some symptoms that differed significantly between the 2 groups were detected more frequently in patients with mimicking conditions than in patients with SLE. Among these symptoms

Table 2. Clinical manifestations at disease onset in patients with early SLE and patients with SLE-mimicking conditions*

Manifestation	SLE (n = 389)	SLE-mimicking conditions (n = 227)	*P*
Fever	134 (34.5)	31 (13.7)	<0.001
Fatigue	110 (28.3)	84 (37.0)	0.02
Weight Loss	51 (13.1)	10 (4.4)	<0.001
Malar rash	193 (49.6)	14 (6.2)	<0.001
Subacute cutaneous lupus	9 (2.3)	8 (3.5)	0.37
Discoid lesions	36 (9.3)	11 (4.9)	0.04
Other rash	23 (5.9)	27 (11.9)	0.009
Photosensitivity	123 (31.6)	42 (18.5)	<0.001
Oral ulcers	84 (21.6)	12 (5.3)	<0.001
Alopecia	119 (30.6)	27 (11.9)	<0.001
Skin ulcers	8 (2.1)	3 (1.3)	0.75
Telangiectasias	4 (1.0)	5 (2.2)	0.30
Inflammatory arthritis	224 (57.6)	60 (26.4)	<0.001
Arthralgias	79 (20.3)	97 (42.7)	0.001
Pleuritis	87 (22.4)	6 (2.6)	<0.001
Pericarditis	73 (18.8)	7 (3.1)	<0.001
Ascites	12 (3.1)	0	0.005
Kidney involvement†	51 (13.1)	0	<0.001
Dry eyes	15 (3.9)	63 (27.8)	<0.001
Dry mouth	14 (3.6)	67 (29.5)	<0.001
Dysphagia	1 (0.3)	14 (6.2)	<0.001
Pneumonia	6 (1.5)	0	0.09
Alveolar hemorrhage	2 (0.5)	0	0.53
Pulmonary fibrosis	2 (0.5)	3 (1.3)	0.36
Pulmonary hypertension	5 (1.3)	5 (2.2)	0.51
Valvular disease	1 (0.3)	0	1.00
Myocardial infarction	3 (0.8)	0	0.30
Thrombosis	14 (3.6)	2 (0.9)	0.06
Swollen fingers	14 (3.6)	11 (4.9)	0.52
Raynaud's phenomenon	86 (22.1)	110 (48.5)	<0.001
Livedo reticularis	12 (3.1)	11 (4.9)	0.27
Stroke	4 (1.0)	0	0.30
Transitory ischemic attack	1 (0.3)	1 (0.4)	1.00
Cognitive impairment	6 (1.5)	1 (0.4)	0.43
Seizures	11 (2.8)	0	0.009
Psychosis	4 (1.0)	2 (0.9)	1.00
Migraine	10 (2.6)	5 (2.2)	1.00
Intestinal vasculitis	3 (0.8)	0	0.30

* Values are the number (%) of patients. SLE = systemic lupus erythematosus.
† Includes proteinuria, hematuria, pyuria, and casts.

were RP (22.1% in SLE patients versus 48.5% in non-SLE patients; $P < 0.001$), sicca symptoms (4.4% versus 34.4%, respectively; $P < 0.001$), dysphagia (0.3% versus 6.2%; $P < 0.001$), and fatigue (28.3% versus 37.0%; $P = 0.024$). Rashes outside the typical SLE symptom spectrum, such as skin vasculitis, were also slightly more frequent among patients with mimicking conditions than among those with SLE (11.9% in non-SLE patients versus 5.9% in SLE patients; $P = 0.009$).

Serologic findings. Serologic results at disease onset are reported in Table 3. Only 2 patients with early SLE (0.5%) were ANA-negative at disease onset. One patient had a completely

Table 3. Serologic abnormalities and autoantibodies detected*

	SLE (n = 389)	SLE-mimicking conditions (n = 227)	*P*
ANA	387 (99.5)	216 (95.1)	<0.001
Anti-dsDNA	251 (71.7)	14 (6.9)	<0.001
Anti-Sm	90 (30.2)	5 (2.6)	<0.001
Anti-Ro	98 (33.2)	53 (25.6)	0.06
Anti-La	41 (15.1)	20 (9.9)	0.09
Anti-RNP	85 (28.5)	12 (5.9)	<0.001
IgG aCL	50 (18.1)	24 (12.1)	0.07
IgM aCL	36 (13.2)	4 (2.0)	<0.001
LAC	31 (12.7)	27 (17.6)	0.17
Anti-β_2GPI	30 (17.0)	5 (4.4)	0.001
Coombs' test positive	48 (12.3)	13 (5.7)	0.008
Low complement	243 (73.4)	104 (48.4)	<0.001
Thrombocytopenia	23 (6.6)	10 (4.8)	0.37
Leukopenia	61 (16.2)	21 (9.8)	0.02
Hemolytic anemia	18 (4.6)	1 (0.4)	0.003

* Values are the number (%) of patients. SLE = systemic lupus erythematosus; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; aCL = anticardiolipin; LAC = lupus anticoagulant; anti-β_2GPI = anti–β_2-glycoprotein.

negative autoantibody panel, and the second tested positive for anti-Sm and anti–double-stranded DNA (anti-dsDNA) antibodies, with negative ANA test results. Although positivity for ANA was the most common reason for referral of patients with mimicking conditions, 11 of the non-SLE patients (4.9%) tested negative for ANA at a cutoff titer of 1:80. Compared to patients with mimicking conditions, patients with early SLE were much more likely to have antibodies to dsDNA (71.7% of SLE patients versus 6.9% of non-SLE patients) and to Sm (30.2% versus 2.6%, respectively). Anticardiolipin IgM and anti–β_2-glycoprotein I antibodies were also more frequent in early SLE, as were positive Coombs' test results, autoimmune hemolytic anemia, hypocomplementemia, and leukopenia (Table 3). Antibodies to Ro/SSA and La/SSB did not differentiate between early SLE (33.2% anti-Ro–positive and 15.1% anti-La–positive) and mimicking conditions (25.6% and 9.9%, respectively). Thrombocytopenia was present in only 6.6% of SLE patients and 4.8% of those with mimicking conditions.

Performance characteristics of conventional criteria. Sensitivity and specificity of the 1997 ACR criteria and the 2012 SLICC criteria for early diagnosis were calculated with the physician diagnosis as the gold standard. At diagnosis, sensitivity of the ACR criteria was calculated as 66.1%, compared to 83.5% for the SLICC criteria. Of the 132 patients with early SLE who did not meet classification by ACR criteria (33.9%), 89 fulfilled 3 components of the ACR criteria, and 37 fulfilled 2 components of the ACR criteria. Six patients met only 1 ACR criteria component. Of the 64 patients with early SLE who did not meet classification by SLICC criteria (16.5%), 39 patients fulfilled 3 components of the SLICC criteria, and 19 patients fulfilled 2 components of the SLICC criteria. The 1997 ACR criteria showed a specificity of 91.6%, while the specificity of the 2012 SLICC criteria was 82.4%. Accordingly, the accuracy was 75.5% for the ACR criteria and 83.1% for the SLICC criteria. The PPV and NPV for the ACR criteria were 93.1% and 61.2%, respectively, and 89.0% and 74.5%, respectively, for the SLICC criteria.

Improvement of the 1997 ACR criteria and the 2012 SLICC criteria diagnostic performance. Based on univariable analysis (Table 4), multivariable models were used to assess improvement of current criteria with the addition of other variables. When alopecia, fever, hypocomplementemia, and anti-RNP were added to the 1997 ACR criteria, accuracy in classification of patients improved significantly ($P < 0.001$), with the area under the curve (AUC) being 0.862 (95% CI 0.830–0.895). In the multivariable logistic models, the inclusion of anti-RNP, arthralgia, dry mouth, other rash, and weight loss in the 2012 SLICC criteria resulted in an AUC of 0.899 (95% CI 0.871–0.927), with a significant improvement of the discrimination ability, compared to the SLICC criteria alone ($P < 0.001$).

DISCUSSION

In the present study, we investigated clinical symptoms and serologic findings (at disease onset) from a large multicenter, multiethnic cohort of 389 SLE patients who received initial diagnoses at lupus referral centers and compared them to the findings in 227 patients referred for possible SLE, who were ulti-

Table 4. Univariable logistic regression models for the association with SLE*

	OR	95% CI	*P*
Clinical manifestation			
Malar rash	14.981	8.42–26.65	<0.001
Discoid rash	2.003	1–4.02	0.051
Photosensitivity	2.037	1.37–3.03	<0.001
Oral ulcer	4.934	2.63–9.26	<0.001
Inflammatory arthritis	3.779	2.64–5.4	<0.001
Kidney involvement†	16.975	4.09–70.43	<0.001
Pericarditis	7.260	3.28–16.07	<0.001
Peripheral edema	30.309	4.15–221.34	0.001
Alopecia	3.265	2.07–5.15	<0.001
Fever	3.322	2.16–5.12	<0.001
Fatigue	0.671	0.47–0.95	0.025
Weight loss	3.274	1.63–6.59	0.001
Other rash	0.465	0.26–0.83	0.010
Dry eyes	0.104	0.06–0.19	<0.001
Dry mouth	0.089	0.05–0.16	<0.001
Arthralgia	0.613	0.44–0.86	0.005
Dysphagia	0.039	0.01–0.3	0.002
Hypertension	15.522	2.09–115.34	0.007
Raynaud's phenomenon	0.302	0.21–0.43	<0.001
Neurologic involvement‡	4.512	1.02–19.91	0.047
CNS symptom (≥1)	2.721	1.18–6.29	0.019
Serositis	6.624	3.55–12.35	<0.001
Serologic manifestation			
ANA	9.854	2.16–44.87	0.003
Anti-dsDNA	34.046	18.86–61.46	<0.001
Anti-Sm	16.269	6.47–40.9	<0.001
IgG aCL	1.597	0.94–2.7	0.081
IgM aCL	7.329	2.56–20.95	<0.001
LAC	0.679	0.39–1.19	0.177
Anti-β_2GPI	4.438	1.67–11.81	0.003
Anti-Ro	1.445	0.97–2.15	0.068
Anti-La	1.624	0.92–2.87	0.095
Anti-RNP	6.352	3.37–11.99	<0.001
Leukopenia	1.789	1.06–3.03	0.031
Piastrinopenia	1.411	0.66–3.03	0.376
Coombs' test	2.317	1.23–4.38	0.010
Hypocomplementemia	3.016	2.15–4.23	<0.001

* OR = odds ratio; 95% CI = 95% confidence interval; CNS = central nervous system; ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; aCL = anticardiolipin; LAC = lupus anticoagulant; anti-β_2GPI = anti–β_2-glycoprotein.
† Includes proteinuria, hematuria, pyuria, and casts.
‡ As defined in the American College of Rheumatology systemic lupus erythematosus (SLE) classification criteria.

mately given another diagnosis after clinical and serologic evaluation at the same centers. We identified parameters that could help in identifying patients with early SLE and could guide the physician in a differential diagnosis with mimicking conditions. In addition, we identified items relevant for the development of new classification criteria for SLE, with specific interest in improving sensitivity and specificity for the classification of early disease.

Descriptive statistical analyses revealed that some symptoms were more prevalent in SLE than in SLE-mimicking conditions. As expected, among clinical manifestations, standard items in existing classification criteria were more prevalent in SLE than in SLE-mimicking conditions; some signs and symptoms that are not part of current classification criteria were also associated with early SLE, including fever and weight loss. Noninfectious fever was more prevalent in early SLE than in SLE-mimicking conditions (34.5% versus 13.7%). Of the serologic variables, ANAs, anti-dsDNA antibodies, anti-RNP antibodies, and aPL antibodies were also more prevalent in the SLE subgroups, in addition to a positive Coombs' test result and hemolytic anemia. However, no differences between the groups were observed with respect to leukopenia, thrombocytopenia, or anti-Ro/La antibodies.

In our cohort of 616 patients, the 1997 ACR criteria demonstrated a sensitivity of 66.1% and a specificity of 91.6%, and the 2012 SLICC criteria demonstrated a sensitivity of 83.5% and a specificity of 82.4% for early diagnosis (8,10,11). As a result, 132 patients with a clinical diagnosis of SLE (33.9%) were not classified as having SLE according to the ACR criteria, and 64 with a clinical diagnosis of SLE (16.5%) did not fulfill the SLICC classification criteria. These patients were more likely to present milder cases, which included conditions such as arthritis, hematologic manifestations, malar rash, lymphadenopathy, noninfectious fever, alopecia, ANA-positive thyroiditis, and the presence of anti-dsDNA or aPL antibodies. In contrast, some patients were inaccurately classified as having SLE by the ACR criteria (n = 19) and SLICC criteria (n =40). The accuracy of the 1997 ACR criteria and the 2012 SLICC criteria was 75.5% and 83.1%, respectively.

SLE is a disease characterized by a large variety of autoantibodies, and their production has been shown to increase shortly before disease onset (10). A fundamental decision made in the development of the SLICC criteria was that patients were required to have serologic evidence of antibodies or immune complex deposition (6). Within the current SLE classification criteria approach, a meta-analysis of published data showed that ANA positivity by HEp-2 testing, at a titer of ≥1:80, was 98% sensitive for SLE (11). Our cohort results support the idea that ANA positivity might be an important discriminant variable in the assessment of patients in whom SLE is clinically suspected. In fact, at disease onset, only 2 patients diagnosed as having SLE were recorded to be ANA-negative, and in 1 of the 2 this was apparently a false-negative result.

In addition to negativity for ANA, manifestations such as fatigue, dysphagia, RP, and some skin lesions (i.e., purpura and skin vasculitis), especially in serologically negative patients, are either not useful to distinguish from SLE-mimicking conditions or may steer toward alternative diagnoses. These data also emphasize that the differential diagnosis process for SLE is long and requires comprehensive experience with other autoimmune and related diseases. In recent years, several studies have characterized SLE patients in the early phases of the disease, highlighting the importance of non–classification criteria symptoms (12–16).

Recently, Rees et al examined the clinical manifestations in SLE patients at onset, in order to develop a risk prediction model for SLE that can be used at the time of referral to a general practitioner, rather than at a later referral to a rheumatologist or lupus expert (12). This study showed that SLE patients consult their physicians frequently in the 5 years preceding their diagnosis, for manifestations such as arthralgias, rash, and alopecia. While the median time from clinical presentation of SLE to SLE diagnosis was >1 year, manifestations like thrombocytopenia and nephrotic syndrome were more likely to be associated with acute care management (i.e., hospital admission or urgent referral) and an earlier diagnosis of SLE. Since 1990, different studies have examined clinical manifestations and serologic features at SLE onset; among non-criteria symptoms, arthralgias, fever, alopecia, RP, non-hemolytic anemia, and lymphadenopathy were the most frequently reported (13–16).

There are some inconsistencies between the results of these studies and ours; presumably, differences in inclusion criteria and disease duration limit the comparability of the results. We enrolled patients independent of whether they fulfilled ACR classification criteria or SLICC classification criteria. In contrast to other cohort studies that enrolled patients upon fulfillment of classification criteria (mainly the 1997 ACR criteria), our study design allowed for the inclusion of patients at very early disease onset, even before the accrual of standard classification criteria. This methodology was crucial for identifying variables that could distinguish patients with very early SLE, particularly in the absence of disease-specific markers such as lupus nephritis, disease-specific skin manifestations, or autoantibodies that might develop later in the course of disease.

Some limitations of our study need to be acknowledged. Due to its observational nature, some of the variables included in the analysis were collected in different ways among the diverse centers, according to local clinical practice. For instance, the SLE group and the SLE-mimicking condition group were compared in order to explore factors that may help identify SLE patients, and no sample size calculation was performed a priori, because patients in the 2 groups were selected on the basis of availability. Thus, group sample sizes were different (i.e., the non-SLE group was smaller than the SLE group), which can potentially affect the results and power of the analysis. Other methodologic limitations to be acknowledged when interpreting results include the limited sample size for some manifestations and the bivariate nature of almost all of the analyses, such that instead of taking into account the overall spectrum of variables, they are limited to pairwise comparisons.

Additionally, the fact that patients were enrolled after visiting expert rheumatologic centers might constitute a bias, as patients may present differently to different specialists. However, since the disease diagnosis was considered the gold standard in this study, we also believe this selection has the advantage of additional information (e.g., patient sex, race, and age at onset) being integrated into the diagnostic decision. Relying on expert diagnosis also has the advantage of a clear-cut, binary response, which allows for analysis of every submitted case, instead of an adjudication process that would have led to the exclusion of certain patients. A final limitation of the study might be the relatively small number of patients identified as Hispanic or of African descent; these patients might have a different disease expression or severity, and our results need further confirmation in these ethnic groups.

In conclusion, the present study has identified clinical and serologic characteristics of patients with early SLE that may help physicians differentiate between SLE and SLE-mimicking conditions. Additionally, we identified features at symptom onset that may help in the identification of early SLE. Limitations of the 1997 ACR criteria and the 2012 SLICC criteria in the accurate classification of early SLE were also identified in this cohort. This study is an element in the item-generation phase of an ongoing international effort to devise new SLE classification criteria with a focus on early disease, consecutively informing both the nominal group technique exercise for item reduction and the multivariable decision analysis for item weighting.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mosca had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Oglesby A, Korves C, Laliberte F, Dennis G, Rao S, Suthoff ED, et al. Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. Appl Health Econ Health Policy 2014;12:179–90.
2. Touma Z, Gladman DD. Current and future therapies for systemic lupus erythematosus: obstacles and recommendations for the development of novel treatments. Lupus Sci Med 2017;4: e000239.
3. Urowitz MB, Gladman DD, Ibanez D, Sanchez-Guerrero J, Romero-Diaz J, Gordon C, et al. American College of Rheumatology criteria at inception, and accrual over 5 years in the SLICC inception cohort. J Rheumatol 2014;41:875–80.
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
6. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64:2677–86.
7. Ines L, Silva C, Galindo M, Lopez-Longo FJ, Terroso G, Romao VC, et al. Classification of systemic lupus erythematosus: Systemic Lupus International Collaborating Clinics versus American College of Rheumatology Criteria. A comparative study of 2,055 patients from a real-life, international systemic lupus erythematosus cohort. Arthritis Care Res (Hoboken) 2015;67:1180–5.
8. Aringer M, Dorner T, Leuchten N, Johnson SR. Toward new criteria for systemic lupus erythematosus—a standpoint. Lupus 2016;25:805–11.
9. Mosca M, Tani C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a new frontier for rheumatology. Best Pract Res Clin Rheumatol 2007;21:1011–23.
10. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33.
11. Leuchten N, Hoyer A, Brinks R, Schoels M, Schneider M, Smolen J, et al. Performance of antinuclear antibodies for classifying systemic lupus erythematosus: a systematic literature review and meta-regression of diagnostic data. Arthritis Care Res (Hoboken) 2018;70:428–38.
12. Rees F, Doherty M, Lanyon P, Davenport G, Riley RD, Zhang W, et al. Early clinical features in systemic lupus erythematosus: can they be used to achieve earlier diagnosis? A risk prediction model. Arthritis Care Res (Hoboken) 2017;69:833–41.
13. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al, and the European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. Medicine (Baltimore) 1993;72:113–24.
14. Pons-Estel BA, Catoggio LJ, Cardiel MH, Soriano ER, Gentiletti S, Villa AR, et al. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". Medicine (Baltimore) 2004;83:1–17.
15. Sebastiani GD, Prevete I, Piga M, Iuliano A, Bettio S, Bortoluzzi A, et al. Early Lupus Project—a multicentre Italian study on systemic lupus erythematosus of recent onset. Lupus 2015;24:1276–82.
16. Canora J, García M, Mitjavila F, Espinosa G, Suárez S, González-León R, et al. Clinical characteristics during diagnosis of a prospective cohort of patients with systemic lupus erythematosus treated in Spanish departments of internal medicine: the RELES study. Rev Clin Esp 2017;217:7–14.