A comparison of three classification criteria sets for Systemic Lupus Erythematosus – a study looking at links to outcome and mortality

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ABSTRACT

OBJECTIVES

We compared the ability of the American College of Rheumatology (ACR), Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) and European League Against Rheumatism (EULAR)/ACR Systemic Lupus Erythematosus (SLE) classification criteria sets to provide information regarding organ damage and mortality, over a 10-year follow-up period.

METHODS

Using data from 100 patients, we completed each classification set at the time of diagnosis and recorded the SLICC/ACR Damage Index (SDI), renal damage, major cardiovascular (CV) events and death, 10 years later. We reviewed the presence of other autoantibodies, linked to SLE, but not included in the classification criteria sets, and assessed whether they impacted the predictive capacity of the classification sets.

RESULTS

We found a statistically significant association between the EULAR/ACR set and renal damage and SDI, the latter, after adjustment for age and sex. In the patients negative for other autoantibodies, higher EULAR/ACR scores were associated with higher rates of organ damage.

CONCLUSION

These data suggest that the EULAR/ACR set may offer useful prognostic information, as higher scores were associated with higher rates of organ damage. These findings were clearer in patients negative for non-diagnostic-SLE autoantibodies, who may benefit more from the predictive capacity of the EULAR/ACR set.

KEYWORDS: EULAR/ACR classification criteria; outcome; SLICC Damage Index; mortality.

SIGNIFICANCE AND INNOVATIONS

- Previous studies have reported an association between several individuals features and worse outcomes in SLE patients, such as age of onset, sex, ethnicity, and disease activity.

- To our knowledge, this is the first endeavour to investigate the predictive potential of the three existing SLE classification criteria sets at the time of diagnosis and organ damage and mortality, up to 10 years.

- If further studies support our findings, by using the new EULAR/ACR set it might be possible to identify those patients who are at higher risk of developing organ damage, in order to take appropriate action to prevent it.

- Additionally, patients with more straightforward SLE patterns, namely those without overlapping clinical and immunological features with other autoimmune diseases, might constitute the ideal candidates to assess the prognostic value of this new classification set.

INTRODUCTION

In 1971, the American Rheumatism Association produced its first Systemic Lupus Erythematosus (SLE) classification criteria set (1), updated in 1982 (2) by the American College of Rheumatology (ACR), with a further final amendment in 1997 (3). Although the ACR criteria had good sensitivity and specificity, the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) felt that a further review of classification criteria was warranted, because of a failure of the ACR criteria to capture a number of patients with biopsy-proven lupus nephritis who failed to meet the criteria for the diagnosis of the disease, and the unexplained disappearance of some features, in particular, the low complement C3 level, in the latest ACR set. Thus, in 2012, the SLICC group, utilising test and re-test groups of patients with lupus and disease controls, formulated a new classification criteria set (4). This system defined clinical and serological criteria, requiring four features to be present altogether, with at least one from each of these two domains. The original ACR set similarly required the presence of four features, and, like the SLICC criteria, stipulated that they do not have to occur concurrently.

In 2017, a new classification system for SLE, based on expert opinion, was developed by the ACR in collaboration with the European League Against Rheumatism (EULAR), seeking to promote earlier diagnosis of lupus, with greater sensitivity and specificity (5). Its most innovative feature is the recognition of each criterion's importance to the disease, acknowledging the unreasonableness of giving equal value to features such as mouth ulcers and renal involvement, the latter clearly being more worrying and requiring more aggressive therapy. Thus, in the new 2019 EULAR/ACR classification criteria set, each feature has a differential weighted value (see Table 1). All patients must have antinuclear antibody levels of at least 1:80 on a HEp-2 immunofluorescence assay, or an equivalent positive test. There are 10 criteria, clinical and immunologic, each to be weighted toward the highest score attributable to the patient; a total score of at least 10 is necessary for a diagnosis of SLE. To be counted, a criterion may occur only once and isolated. Within each organ system, only the highest scoring criterion is considered.

We thought this weighting of each criteria was interesting and questioned whether it might provide useful prognostic information about outcome, in terms of death and organ damage. We thus looked carefully at a subset of patients from our cohort to ascertain a possible association between the ACR, SLICC and EULAR/ACR SLE classification criteria sets and organ damage, assessed through the SLICC SLE Damage Index (SDI) (6), and mortality, 10 years after diagnosis.

METHODS

We assessed 100 patients (from a cohort size of N = 715, seen at the Centre for Rheumatology, University College Hospital, UCL). The only stipulations were that there were adequate data at the time of diagnosis to complete all 3 sets of classification criteria sets, with up to 10 years of follow-up. For ease of recall, we focused on those patients fully captured in our hospital's electronic data system, established in 2003. These 100 patients were representative of the cohort as a whole. For example, the prevalence of biopsy-proven lupus nephritis in our sample was 29%, and in the UCL cohort 30% of the patients has nephritis. We completed the classification criteria at the time of diagnosis for the 1997 ACR (3), 2012 SLICC (4) and 2019 EULAR/ACR (5) sets and recorded the SDI score, 10 years after diagnosis, as well as other major outcomes, namely death, renal damage (defined as positive renal SDI score) and major CV events (stroke or myocardial infarction).

In our laboratories, the C3 levels were measured by laser nephelometry and the antibodies to dsDNA and the extractable nuclear antigens by enzyme immunoassay (ELISA).

Analysis was performed using IBM SPSS Statistics version 25 for Windows. Discrete variables were summarised with number (percentage) and continuous variables with median [interquartile range, IQR]. Linear regression was used to assess associations between the classification sets and SDI scores. Logistic regression analysis was used for categorical variables, namely, renal damage, major CV events, and death. A model adjustment analysis was performed for age, sex and ethnicity.

To determine the effects of other autoantibodies not included in the classification criteria sets (usually performed in our SLE patients), we divided the patients into antibody positive and negative groups and performed the previously stated linear and logistic regression.

For all statistical analyses, p-value ≤ 0.05 were considered significant and confidence intervals (CI) were calculated at the 95% level.

RESULTS

Baseline characteristics of the patients are described in table 2.

Significant results are summarized in Table 3.

We found a statistically significant association between the EULAR/ACR set and renal damage, which persisted after adjustment for age and sex, but not with CV events or death. In addition, this association persisted after the renal domain (all 3 criterion) was removed from the final score (p-value 0.018, β 0.211). We found no differences in terms of organ damage between patients with proliferative (grade III and IV) and membranous (grade II and V) nephritis. Although without statistical significance, our results might hint at a higher frequency of overall organ damage (SDI) in patients with higher EULAR/ACR scores (p-value 0.051). Adjustment for age and sex showed that higher EULAR/ACR scores were associated with higher SDI. No associations were found between the ACR and SLICC sets and outcomes. We could not identify an association between ethnicity and outcome based on the EULAR/ACR criteria [data now shown].

We reviewed the presence (at diagnosis) of other autoantibodies not included in the classification criteria sets, namely the Rheumatoid Factor (RF) and antibodies to RNP, Ro and La, dividing the patients into antibody positive/negative groups. The antibody-positive group did not show any association between the classification

sets and outcome. However, the antibody-negative group demonstrated that higher EULAR/ACR scores were significantly associated with higher SDI, when testing for each antibody separately and when all the ENA antibodies were negative. RF negativity did not show an association between the new set and SDI. No association was established between the ACR and SLICC scores and SDI. In addition, antibody negativity reiterated the previously stated association between the EULAR/ACR score and renal damage (in all groups) and showed an association between the ACR score and renal damage (patients negative for antibodies to Ro, RNP and all ENA) and the SLICC score and renal damage (patients negative for antibodies to La and RNP).

DISCUSSION

This is the first description that we are aware of that directly compares the ACR, SLICC, and new EULAR/ACR SLE classification criteria sets, seeking to determine a link between criteria scores at onset and outcome over the ensuing decade. Previously, several individual features have been shown to be associated with worse outcomes, notably renal involvement, disease activity, sex, ethnicity, age of onset, presence of antiphospholipid antibodies (and antiphospholipid antibody syndrome) (7).

Our study showed that in patients with higher EULAR/ACR scores at the time of diagnosis there was a trend towards an increased incidence of organ damage. In addition, these patients had higher rates of renal damage (which persisted after removal of the renal domain from the final classification score) and, after adjustment for age and sex, higher rates of organ damage, i.e. higher SDI scores. We did not find an association between this classification criteria score and major cardiovascular events or death. Neither did we find a link to outcome based on EULAR/ACR criteria with ethnicity, but a rather larger study is needed to confirm this.

Interestingly, when assessing the effects of other autoantibodies outside the scope of the classification criteria sets (to RNP, Ro and La), we found a statistically significant association between the EULAR/ACR score and SDI and renal damage, in the antibody-negative group; thus, in this subset of patients, higher scores at

diagnosis were associated with higher rates of organ damage. This group also showed that higher ACR and SLICC scores were associated with higher rates of renal damage.

Although these findings need to be independently confirmed, our results allow us to hypothesize that the new EULAR/ACR set might provide some insight into the long-term prognosis of SLE patients, especially regarding renal damage, helping us to classify those patients who have higher EULAR/ACR scores at the time of diagnosis as being at greater risk of developing organ damage. In addition, we hypothesize that patients who are negative for non-diagnostic-SLE-autoantibodies may benefit more from the (potential) predictive capacity of this new set, as they showed a clearer statistical association between the EULAR/ACR set and SDI. This finding could be explained by the fact that patients who show overlapping features with other rheumatic diseases, for example, Rheumatoid Arthritis (RA), may develop non-SLE related damage, perhaps explaining why the EULAR score predicted damage better in the autoantibody-negative group. However, seropositivity for antibodies is not synonymous with the presence of another disease (thus rheumatoid factor is not confined to patients with rheumatoid arthritis) and their (clinical) significance in SLE patients remains to be determined. It is possible that non-diagnostic SLE autoantibodies could be markers of increased subclinical autoimmune activity contributing to long-term damage. The damage in those patients who are negative for other autoantibodies, could, to a greater extent (if not exclusively), be attributable to SLE, thus explaining why the EULAR/ACR classification score performed better in this group.

One of the strengths of our study derives from the fact that it was a single-centre endeavour, allowing a more homogeneous sampling of our population, as all the data were uniformly registered in our digital system in the same fashion. However, we acknowledge our lack of model adjustment for disease activity or treatment (previous or current), though that will form part of another study.

REFERENCES

1. Cohen A, Canoso J. Criteria for the Classification of Systemic Lupus Erythematosus-Status 1972. *Arthritis Rheum*. 1972;15:540–3.

2. Tan E, Cohen A, Fries J, Masi A, McShane D, Rothfield N, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271–7.

3. Hochberg M. Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus. *Arthritis Rheum*. 1997;40:1725.

4. Petri M, Orbai A-M, Alarcón G, Gordon C, Merrill J, Fortin P, et al. Derivation and Validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheum.* 2012;64:2677–86.

5. Aringer M, Costenbader K, Brinks R, Boumpas D, Daikh D, Jayne D, et al. Validation of New Systemic Lupus Erythematosus Classification Criteria [abstract]. Arthritis Rheumatol 2018;70 (suppl 10).

6. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus. *Arthritis Rheum*. 1996;39:363–9.

7. Kasitanon N, Magder L, Petri M. Predictors of Survival in Systemic Lupus Erythematosus. *Med*. 2006;85:147–56.

Table 1. 2019 EULAR/ACR SLE classification criteria

Clinical domains	Points	Immunologic domains	Points
Constitutional		Antiphospholipid antibody	
Fever	2	Anticardiolipin IgG > 40 GPL or	
Mucocutaneous		anti-β2GP1 IgG > 40 units or	2
Non-scarring alopecia	2	lupus anticoagulant	
Oral ulcers	2		
Subacute cutaneous or discoid lupus	4	Complement	
Acute cutaneous lupus	6	Low C3 or low C4	3
Arthritis		Low C3 and low C4	4
Synovitis in at least two joints or			
tenderness in at least two joints, and	6	Highly specific antibodies	
at least 30 minutes of morning stiffness		Anti-dsDNA antibody	
Neurologic		Anti-Smith antibody	6
Delirium	2		
Psychosis	3		
Seizure	5		
Serositis			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Hematologic			
Leukopenia	3		
Thrombocytopenia	4		
Autoimmune hemolysis	4		
Renal			
Proteinuria > 0.5 g/24 hours	4		
Class II or V lupus nephritis	8		
Class III or IV lupus nephritis	10		

Table 2. Baseline characteristics of the 100 patients

Female patients, N (%)	90 (90)
Age at diagnosis, median [IQR] (range) years	31 [23-39] (12-63)
Female	31 [24-39] (12-59)
Male	35 [22-50] (18-63)
Ethnicity, N (%)	
Caucasian	54 (54)
African/Caribbean	24 (24)
South Asian	7 (7)
East Asian	6 (6)
Other	9 (9)
Classification score at diagnosis, median [IQR]	
ACR	5 [5-6]
SLICC	7 [6-8]
EULAR/ACR*	24 [19-27]
Renal involvement at diagnosis, N (%) **	21 (21)
SDI score 10 years after diagnosis, median [IQR]	1 [0-2]
Patients with renal damage, N (%)	7 (7)
Patients with major CV events, N (%) ***	8 (8)
Deceased patients, N (%) ****	7 (7)

* Only 2 patients had a score below 10 (the stipulated cut-off for diagnosis), having scored 6 and 8.

** Although only 21% of the patients in this study had renal involvement at the time of diagnosis, the overall prevalence of renal disease in this cohort was 29%, similar to the rate of renal involvement in our cohort as a whole (30%).

*** Major CV events were restricted to stroke in our population.

**** Causes of death included stroke (n = 1), sepsis (n = 3), cyclophosphamide induced acute respiratory distress syndrome (n = 1), pulmonary embolism (n = 1), suicide (n = 1).

Table 3. Effect of each variable on the SDI and renal damage

Model	Predictor	Estimate	Confidence Interval (95%)	p-value
Prediction of SDI[a]	EULAR/ACR set			(0.051)
	Anti-Ro-antibody negativity[c]	0.048	0.003-0.093	0.037
	Anti-La-antibody negativity[d]	0.047	0.006-0.088	0.025
	Anti-RNP-antibody negativity[e]	0.056	0.006-0.107	0.029
	All ENA-antibodies negativity[f]	0.069	0.006-0.132	0.033
	Adjusted for age + sex	0.045	0.004-0.086	0.031
Prediction of renal damage[b]	EULAR/ACR set			
	Anti-Ro-antibody negativity[c]	1.21	1.033-1.418	0.018
	Anti-La-antibody negativity[d]	1.178	1.042-1.331	0.009
	Anti-RNP-antibody negativity[e]	1.283	1.047-1.571	0.016
	All ENA-antibodies negativity[f]	1.266	1.022-1.567	0.031
	Removal of the renal domain	1.235	1.037-1.471	0.018
	Adjusted for age + sex	1.142	1.022-1.275	0.019
	ACR set			
	Anti-Ro-antibody negativity[c]	3.437	1.069-11.052	0.038
	Anti-RNP-antibody negativity[e]	3.507	1.127-10.91	0.03
	All ENA-antibodies negativity[f]	3.371	1.012-11.228	0.048
	SLICC set			
	Anti-La-antibody negativity[d]	1.6	1.024-2.49	0.038
	Anti-RNP-antibody negativity[e]	3.003	1.014-8.898	0.047

[a] Estimate presented is the coefficient for linear regression.
[b] Estimate presented is the odds-ratio for logistic regression.
[c] N = 54; [d] N = 86; [e] N = 53; [f] N = 34.