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New Classification Criteria for SLE

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Abstract

Purpose of review: To compare the recently published European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) classification criteria for SLE with the Systemic Lupus International Collaborating Centers (SLICC) criteria and the earlier ACR criteria, focusing on their key concepts.

Recent findings: While the SLICC criteria introduced numbers of new criteria items, the new EULAR/ACR criteria added only non-infectious fever, based on an early SLE cohort study and an SLE patient survey, and condensed hematological, mucocutaneous and neurological items. Whereas the SLICC criteria maintained the overall structure familiar from the ACR criteria, the EULAR /ACR criteria use anti-nuclear antibodies (ANA) as an obligatory entry criterion, have weighted criteria and group these in domains. Where the SLICC criteria greatly increased sensitivity, losing some specificity, the EULAR/ACR criteria increased specificity again, for excellent classification criteria performance.

Summary: Despite differences in structure and statistical performance, the EULAR/ACR and SLICC criteria agree on the importance of both immunological and clinical findings, on the high impact of lupus nephritis by histology, and on most clinical items.

Keywords

Systemic lupus erythematosus; classification criteria; diagnosis; autoantibodies; lupus nephritis

Introduction

Classification criteria are essential for science, defining a group of patients sufficiently homogenous to make meaningful clinical trials and translational studies possible. Beyond this, however, useful classification criteria will shape our concept of the disease. This was definitely true for the 1982 SLE classification criteria system of the American College of Rheumatology (ACR), with 11 criteria, at least four of which had to be positive for classification [1]. In 1997, these criteria were amended to include two of the three current standard tests for anti-phospholipid antibodies, namely anti-cardiolipin antibodies and lupus

anticoagulant [2]. At the same time, the LE cell phenomenon was released into history. Further progress led to an increase in information pertinent to SLE classification. Prominent examples were routine measurement of serum complement levels [3–5] and renal biopsy having become the standard approach for managing patients with (suspected) lupus nephritis [6,7]. While useful, the ACR criteria did not keep up with better understanding of the clinical manifestations and laboratory findings in SLE (Figure 1). This prompted the need for new SLE classification criteria.

With close to ten years between them, the criteria of the Systemic Lupus International Collaborating Centers (SLICC)[8] and the new European League Against Rheumatism (EULAR)/ACR criteria [9,10] took different approaches, namely maintaining the structure, but adding several new items and two new concepts for the SLICC criteria and changing the structure and overall reducing items for the EULAR/ACR criteria.

Published in 2012, the SLICC criteria increased sensitivity, included many new items and stressed two important concepts, first that SLE required at least one clinical and at least one autoimmune measure and secondly, the special role of lupus nephritis in that, when biopsy proven, it could “stand alone” [8]. In 2019, this was followed by the EULAR/ACR criteria, which stressed specificity, condensed the list of items and changed the overall structure by using anti-nuclear antibodies (ANA) as an obligatory entry criterion and by adding individual weights for all criteria items [9,10].

The EULAR/ACR criteria in many ways reiterate many advances in the SLICC criteria, including similar definitions and similar requirement of autoimmune measures. Some of this may have been parallel development, given that SLE experts worldwide luckily communicate and thus evolve concepts together. More likely, however, SLICC concepts had already reshaped ideas on SLE of many of the SLE experts working on the EULAR/ACR classification criteria, much the same as the ACR criteria had previously exerted such influence. The focus of this review will be the key concepts in the classification criteria.

Sensitivity as a critical issue

At a sensitivity of 83% in all three cohorts [1,8–10], the revised ACR criteria for SLE performed well as compared to other criteria, but still excluded one in six SLE patients. This sensitivity was sufficient for some scientific purposes. When, however, the ACR classification criteria became the central measure of accepting or not accepting a diagnosis of SLE, this limited sensitivity gap turned into a serious problem. Despite the ACR and EULAR steadfastly and appropriately reiterating the point that classification criteria are not for diagnosis [11,12], the complexity of SLE invites reliance on classification criteria, and when there is limited experience with SLE, in particular. The SLICC criteria, in contrast, have not been limited to research use only.

Importantly, sensitivity drops further in early disease [13–15]. This is logical given that criteria items may accumulate over time, independent of each other, and that patients may present with “organ-dominant” SLE [16]. Beyond issues with diagnosis and therapy, reduced

sensitivity for early disease may even influence scientific results by condensing the patient population to the subset of patients with multi-organ, more long term, involvement.

Increasing sensitivity was therefore an important goal of the SLICC criteria [8]. This goal was addressed by the provision that lupus nephritis on histology in combination with positive ANA or antibodies to double-stranded DNA (dsDNA) was sufficient for classification, the first example of weighting criteria. SLICC also added items, such as alopecia or low serum complement (Tables 1 and 2). On clinical grounds, these changes were desirable anyway. Statistical fine-tuning (based on regression analyses) also led to new definitions for leukopenia, lymphopenia and arthritis, as well as to the splitting of hematology into three distinct items [8].

The SLICC criteria in this way achieved an unprecedented sensitivity of 94% in the derivation cohort and of 97% in the validation cohort [8]. This impressive sensitivity of 97% for the SLICC criteria was independently confirmed when the EULAR/ACR criteria were tested [9,10].

Moreover, sensitivity was also much improved in early SLE [13,14]. In the international early SLE cohort of the EULAR/ACR project the ACR criteria had a sensitivity of 66% only, which was improved to 84% in the SLICC criteria [15]. Similarly, a subanalysis of the EULAR/ACR criteria validation cohort showed a sensitivity of 56% in the first year of disease for the ACR criteria, and a much higher sensitivity of 89% for the SLICC criteria [17].

The EULAR/ACR criteria had the defined goal of also improving sensitivity versus the ACR criteria, with the provision to get close to SLICC criteria sensitivity, if possible [18]. With a sensitivity of 96%, vs. 97% for the SLICC criteria, with overlapping confidence intervals, as compared to 83% for the ACR criteria, this goal was reached [9,10]. Similarly, in the first year, the EULAR/ACR criteria reached 89% sensitivity, close to the SLICC criteria [17]. Analyzed in the SLICC case scenarios, the EULAR/ACR criteria had a sensitivity of 91% (95% CI 88%-94%) compared to 97% (95% CI 96%-99%) for the SLICC criteria [19] and 83% (95% CI 79%-87%) for the 1997 ACR criteria [8].

Specificity

While specificity is of lesser importance in diagnosis, which can always be revised in case the later course points to a differential diagnosis, patients can usually not post hoc be removed from a clinical trial or even a translational study. For classification, therefore, specificity is important. In the derivation sample, the SLICC criteria had a high specificity of 92%, as compared to 93% for the ACR 1997 criteria [8]. In the validation sample, however, specificity unfortunately dropped to 84%, while ACR criteria specificity was 96%. This decrease in specificity concomitant with the increase in sensitivity was confirmed in several other analyses [13,14,20,21]. The SLICC criteria still increased the sum of sensitivity and specificity from 1.79 to 1.81 in the SLICC [8] and from 1.76 to 1.80 in the EULAR/ACR validation cohorts [9,10], showing improved performance. When applied to the SLICC case scenarios, the EULAR/ACR criteria had a specificity of 89% and an overall agreement of

90% compared to the SLICC criteria with a specificity of 84% and an overall agreement of 91% [19].

The EULAR/ACR criteria project defined increasing specificity to the high level of the revised ACR criteria, while still increasing sensitivity, as the main statistical goal [18]. Throughout the EULAR/ACR classification criteria project, decisions in doubt were made in favor of specificity, even if they threatened to reduce sensitivity. This approach was successful [9,10], with the specificity of the revised ACR criteria reached in the derivation cohort (96% vs 95%) and in the validation cohort (93% vs 93%). This was due to several steps taken. From the first draft proposal, one step accordingly was to take ANA out of the specific criteria items and to reposition the ANA test to an entry criterion [18], as discussed later. Lymphopenia, another lower specificity item, was eliminated by the external experts in the nominal group technique (NGT) exercise [22]. Defining domains, within which only the highest-ranking item was counted [23–25], was another step towards higher specificity.

Less obvious, a strategic decision had significant impact on the specificity of the criteria. Most features of SLE are mimicked by other conditions. The ACR criteria system had therefore already defined exclusion criteria for seizures, psychosis and thrombocytopenia [1]. The SLICC criteria defined exclusions for a total of 10 items [8]. Even this list of exclusions was not complete. Instead of a list, for the EULAR/ACR criteria, one attribution rule that limits the items taken into account for SLE to those not more likely explained by another condition [24,25] replaces individual exclusions. This is in line with what clinicians do in their daily routine. It may, however, need more experience and can cause problems when calculating EULAR/ACR classification criteria performance from older databases that do not contain such information. Basically though, researchers should never count a classification criterion as “SLE” if they know it is due to another condition.

One relevant example is lupus arthritis. By defining it as non-erosive arthritis [1], the revised ACR criteria in fact tried to exclude rheumatoid (and psoriatic) arthritis. This became more disputed over time, when novel imaging technique showed lupus arthritis to be more commonly (somewhat) erosive than previously thought [26,27]. Moreover, rheumatoid arthritis lupus overlap disease, termed “rhupus” [28,29], was recognized as an issue for classification. The SLICC criteria accordingly did not include any exclusionary criteria for lupus arthritis [8]. The EULAR/ACR criteria attribution rule, in contrast, will exclude arthritis that is more likely rheumatoid arthritis, such as in anti-CCP positive individuals (although anti-CCP antibodies can occur in SLE [30]), or due to other conditions.. Classification as rheumatoid arthritis SLE overlap disease is still possible, provided the other SLE criteria items reach the classification threshold. This approach greatly increased lupus arthritis specificity.

The importance of Immunology

SLE by nature is a systemic autoimmune disease [31,32]. For classification criteria (or diagnosis, for that matter), SLE without findings in the autoimmune serology therefore is a potentially dangerous construct. This was also underlined by the phase II belimumab trials that found success in serologically active SLE patients only [33]. Accordingly, the SLICC

criteria for SLE classification demand at least one of six immunological criteria [8], as listed in Table 1. Moreover, a histology compatible with lupus nephritis is sufficient for classification only if accompanied by positive ANA or anti-dsDNA-antibodies.

In the EULAR/ACR criteria this principle is taken one step further in making positive ANA an obligatory entry criterion [9,10,18]. Antibodies to nuclear acids and their binding proteins are a hallmark of SLE, and all these usually lead to positive ANA [34,35]. Accordingly, ANA have very high sensitivity for SLE, but limited specificity, given their occurrence in other connective tissue diseases, all sorts of autoimmune disease, and even in healthy individuals. Behaving differently from all other items made ANA less suitable as a specific item, but omitting it would have deprived the criteria of an important concept.

While ANA as an obligatory entry criterion makes classification impossible for any SLE patient who never had positive ANA, this decision is based on data showing that truly and persistently ANA-negative SLE is an uncommon situation [36]. Missing this small subset of patients would still be a problem for diagnosis, but not so much for classification. To limit a negative impact, in addition to complying with the old principle that criteria items are counted also historically and with no need to occur simultaneously, a low titer of 1:80 was chosen from the systematic literature search and meta-regression analysis [18] and alternative test systems are accepted [9,10]. However, ANA-negative SLE definitely exists, reaching 6.2% in the SLICC inception cohort [37], and was also reported in biopsy proven lupus nephritis [38], which might exclude a lupus nephritis subset from clinical trials.

In sharp contrast to ANA, antibodies to the Smith antigen (Sm) and to dsDNA are highly specific, if less sensitive. These two antibodies have remained in place from the revised ACR criteria [1,8]. For the EULAR/ACR criteria, an increasing range of less specific anti-dsDNA tests made it necessary to define anti-dsDNA test specificity at 90% compared to appropriate disease controls [9,10]. In SLICC, this was accomplished by higher cut-offs for ELISA assays [8].

New items and improved definitions

All three SLE criteria sets [1,8–10] demand at least one clinical criterion for classification, to make sure a disease is classified. For the SLICC criteria, great care was taken to fully depict clinical progress in SLE. This led to a variety of important additions [8], in particular among the mucocutaneous and neuropsychiatric manifestations and, by the inclusion of nephritis by histology, for renal involvement (Table 2). Likewise, the immunological items were amended, particularly including decreased complement levels and positive anti- β 2-glycoprotein-I antibodies, but also a positive Coombs test without hemolysis.

The work of the SLICC group was so thorough in this regard that the EULAR/ACR expert Delphi exercise [39] led to no new items. The one single additional item, non-infectious fever, emerged from both the early SLE cohort study [15] and the patient survey [40], and was then defined as $>38.3^{\circ}\text{C}$ [24]. Importantly, infections need to be excluded, as per the above-mentioned attribution rule, but even more critically in SLE patient management [41,42].

All of the three criteria systems put significant effort into appropriately defining criteria items. Psychosis in the ACR criteria subsumes two concepts today, namely psychosis and “acute confusional state” or “delirium” per SLICC and EULAR/ACR definitions, respectively. While the ACR and the SLICC criteria definitions were developed within the project, the EULAR/ACR criteria tended to use existing definitions from other fields [24].

In hematology, SLICC definitions importantly changed views as compared to the ACR criteria. The ACR criteria had defined leukopenia and lymphopenia as values twice $<4,000$ and $<1,500/\text{mm}^3$, respectively [1]. This was investigated in the SLICC criteria approach, leading to leukopenia $<4,000/\text{mm}^3$ and lymphopenia $<1,000/\text{mm}^3$ at least once [8]. While lymphopenia is not part of the EULAR/ACR criteria, the superior performance of the SLICC leukopenia definition was confirmed in the EULAR/ACR criteria derivation cohort [4, 5]. Similarly, the SLICC definition of synovitis as swelling/effusion or tenderness and morning stiffness in at least two joints was superior to frank synovitis [9,10], in line with our current understanding of lupus arthritis [43].

In some cases, more differentiation within the EULAR/ACR criteria was a direct consequence of the strategic decision to give all criteria individual weights. Slightly different weights led to a difference between “low C3 or C4” and “low C3 and C4”, between “pleural or pericardial effusion” and “acute pericarditis” and between International Society of Nephrology/Renal Pathology Society (ISN/RPS)[44] “class II or V” and “class III or IV” nephritis, each splitting a SLICC item into two EULAR/ACR items.

Accuracy versus simplicity

Feasibility is an important issue for classification criteria. The easier to memorize, the faster new criteria will influence the field. In this regard, the relative simplicity of the any four in eleven items principle of the revised ACR criteria set a high mark, even if it was in fact a total of 20 for the 1982 [1], and 21 for the 1997 criteria [2].

The counterweight is scientific accuracy. This can be found in two flavors in this century’s SLE criteria set. The SLICC criteria amended the list of items considerably to 42 positions in 17 criteria, and added exclusions to 10 of these items [8]. On the other hand, the simple ACR structure was kept, adding only the necessity of an immunological item to the now four in 17 criteria and the additional provision of lupus nephritis by histology mentioned above.

The EULAR/ACR criteria in contrast changed the overall structure, specifically giving individual weights to each item [4, 5], derived from a multi-criteria decision analysis [25] and depicted in Tables 1 and 2. While this could allow classification based on only two criteria (e.g. lupus arthritis and positive anti-dsDNA antibodies for example) in the presence of positive ANA, it also made the criteria system more complicated. Accordingly, the list of items had to be reduced (Tables 1 and 2). In addition, the attribution rule eliminated the necessity for exclusions.

Conclusions

Serving as scientific tools and as blueprints for better studying SLE, SLE classification criteria have evolved from the 1982 and 1997 revised ACR criteria to the SLICC and, most recently, EULAR/ACR 2019 criteria. Each built on the previous sets by adding new information, trying to maintain feasibility at the same time. The EULAR/ACR criteria have excellent statistical performance for classification. The excellent sensitivity of the SLICC criteria and broad representation of SLE symptoms remain clinically important.

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Figure 1: Sensitivities (dotted) and specificities (solid) for the ACR 1997 criteria, the SLICC 2012 criteria and the EULAR/ACR 2019 criteria for SLE in the EULAR/ACR validation cohort [9,10](black) and the SLICC validation cohort [19](grey). The ACR 1982 criteria are added with their one validation cohort data (1).

Table 1.
Immunological criteria items evolving.

Please notice that the SLICC criteria demand at least one immunological criterion for classification. Domains of the EULAR/ACR 2019 criteria are separated by background color.

	ACR 1982	ACR 1997	SLICC	EULAR/ACR
Immunologic disorder	•Positive LE cell preparation •Anti-DNA •Anti-Sm •False positive serologic test for syphilis	-	-	-
		•Anti-DNA •Anti-Sm •Anti-phospholipid *	Anti-dsDNA	Anti-dsDNA (6)
			Anti-Sm	Anti-Sm (6)
			Anti-phospholipid *	Anti-phospholipid * (2)
	-		Low complement *	Low C3 and C4 (4)
				Low C3 or C4 (3)
	-		Positive Coombs test without hemolysis *	-
ANA	Antinuclear antibody [§]		ANA *	Entry criterion *

* Definitions apply.

[§] Exclusions apply.

Table 2.
Clinical criteria items evolving.

Domains of the EULAR/ACR 2019 criteria are separated by background color.

	ACR 1982	ACR 1997	SLICC	EULAR/ACR
ACLE	Malar rash		•Malar rash [§] •Bullous lupus •Toxic epidermal necrolysis variant •Maculopapular lupus rash •Photosensitive lupus rash [§] •SCLE	•Malar rash (6) •Maculopapular lupus rash (6)
SCLE	-			SCLE (4)
CCLE	Discoid rash		•Discoid rash [*] •Hypertrophic lupus •Lupus panniculitis •Mucosal lupus •LE tumidus •Chilblains lupus •Discoid lupus/lichen planus overlap	Discoid lupus (4)
Photosensitivity	Photosensitivity		- [‡]	- [‡]
Mucosal ulcers	Oral ulcers		•Oral ulcers ^{*§} •Nasal ulcers [§]	Oral ulcers (2)
Non-scarring alopecia	-		Non-scarring alopecia [§]	Non-scarring alopecia (2)
Arthritis	Non-erosive arthritis [*]		Arthritis [*]	Joint involvement [*] (6)
Serositis	•Pleuritis [*] •Pericarditis [*]		•Pleuritis [*] •Pericarditis [*]	Pleural or pericardial effusion [*] (5) Acute pericarditis [*] (6)
Renal disorder	•Proteinuria [*] •Cellular casts [*]		•Proteinuria [*] •RBC casts [*]	Proteinuria [*] (4)
Lupus nephritis histology	-		Compatible with lupus nephritis [‡]	ISN/RPS III/IV (10) ISN/RPS II/V (8)
Neurologic disorder	Seizures [§] Psychosis [§]		•Seizures [§] •Psychosis [§] •Acute confusional state ^{§§} •Mononeuritis multiplex ^{§§} •Myelitis •Neuropathy [§]	Seizure (5) Psychosis (3) Delirium (2)
Hematologic disorder	•Hemolytic anemia [*] •Leukopenia [*] •Lymphopenia [*] •Thrombocytopenia ^{*§}		Hemolytic anemia [*] •Leukopenia ^{*§} •Lymphopenia ^{*§} Thrombocytopenia ^{*§}	Hemolytic anemia [*] (4) Leukopenia [*] (3) - Thrombocytopenia [*] (4)

^{*} Definitions apply.

[§] Exclusions apply.

[‡] Sufficient for classification with positive ANA or anti-dsDNA antibodies.

[‡] Concept survives in definitions. ISN/RPS International Society of Nephrology/Renal Pathology Society classes.