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PAPER

The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: Strengths, weaknesses, and opportunities for improvement

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The American College of Rheumatology classification criteria were developed to operationalize the definition of systemic lupus erythematosus (SLE) to allow comparison of clinical research from different centers, but also serve to facilitate education and to guide clinical practice. The classification criteria have been critical to research, but should be viewed as a temporary step until improved understanding of the pathogenesis of SLE emerges. Criteria have inherent limitations, including bias towards more severe and longer duration disease, equal weighting of features that vary in clinical significance, and exclusion of patients with SLE from research because they do not meet criteria. For some SLE research questions, it may be appropriate to include patients diagnosed with SLE who do not meet criteria, if these patients' manifestations and criteria are documented explicitly. SLE disease activity, cumulative organ damage, disease duration, criteria ever met, and criteria met at time of enrollment are important data that should be presented in clinical studies of SLE regardless of the number of criteria met. The criteria should be reevaluated periodically, utilizing patients and controls with a range of diseases and disease severity. A simplified weighting system may more accurately reflect clinical practice.

Keywords: systemic lupus erythematosus; classification criteria; diagnostic criteria; classification; clinical trials

Introduction

Classification criteria were developed to operationalize the definition of systemic lupus erythematosus (SLE), a disorder characterised by heterogeneous clinical and laboratory features. In addition to allowing more direct comparisons of studies, the criteria serve as tools for education and as a guide for clinical practice. They were not, however, intended to be utilized as diagnostic criteria in individual patients. This paper reviews the background, strengths, and weaknesses of the classification criteria for SLE, and proposes ways to improve the criteria and their use.

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Background of the SLE classification criteria

Diseases may be classified according to their symptoms, anatomy, pathophysiology and/or etiology. As medical knowledge advances, classification usually moves from descriptive labels based on symptoms to systems derived from etiology. Sydenham first distinguished scarlet fever from measles on descriptive grounds two centuries before the etiologic agents were recognized.[1] Because the etiology of SLE is not known, patients with SLE are classified predominantly on descriptive grounds. As understanding of the etiology and pathogenesis of SLE improves, so will diagnosis and classification.[2] For instance, the discovery of antiphospholipid antibodies has identified a subgroup of SLE with a distinct phenotype and probably a common etiology and pathogenesis.

Influenced by the Jones criteria for acute rheumatic fever, subspecialty organizations began to develop criteria for the diagnosis and classification of diseases in the mid-twentieth century.[3] The American Rheumatism Association (ARA, later the American College of Rheumatology (ACR)) published criteria for the diagnosis of rheumatoid arthritis in 1958 to standardize the definition of the disease.[4] In 1958, Winslow and colleagues devised a classification system for SLE utilizing major and minor criteria, for the purposes of studying pleuritis in SLE.[5]

Recognizing that 'uniform classification of defined groups of patients is necessary in order to assemble and compare data from different sources concerning natural history, evaluation of therapy, and epidemiologic description,' the Diagnostic and Therapeutic Criteria Committee of the ARA published the preliminary criteria for classification of SLE in 1971. The criteria were based upon evaluation of 74 manifestations of SLE in a group of 245 'unequivocal' SLE patients submitted from 52 rheumatologists from 59 hospitals and clinics in the United States and Canada. Contributors were selected 'on the basis of their interest and experience in the recognition and differential diagnosis of SLE.'[6] The SLE patients were compared with 234 rheumatoid arthritis patients and 217 medical patients with diagnoses other than rheumatic disease. The resultant criteria required 4 of 14 well-defined criteria for classification of SLE.[7] Though subject to some criticism,[8] the criteria were generally well accepted. More than 11 investigators independently evaluated the criteria in their patients with SLE, and found that 71.1–96% of their SLE patients met these criteria.[9–14] Though control groups have varied, most studies have found high specificity ($>90\%$) among patients with other rheumatic diseases. One study found 100% specificity of the criteria in 100 normal women.[6]

The criteria were revised in 1982 by the ARA Diagnostic and Therapeutic Criteria Committee. Eighteen academic investigators recognized as experts in the field of SLE submitted data regarding ten consecutive SLE patients, and for each patient the next age-, race- and sex-matched patient with non-traumatic, nondegenerative connective tissue disease seen at that hospital or clinic. Cluster analysis was applied to thirty potential variables in 177 SLE patients and 162 controls to determine which combination of features best distinguished patients with SLE from patients without SLE. Eleven criteria were chosen, including tests for antinuclear antibody (ANA) and antibodies to native DNA or Smith antigen; criteria for Raynaud's phenomenon and alopecia from the previous criteria were not included.[15] In 1997, the criteria were updated to include the presence of antiphospholipid antibodies (Table 2).[16] Meanwhile, criteria have been formally developed for 19 other rheumatic disorders.[17]

Table 1 Preliminary criteria for the classification of systemic lupus erythematosus[7]

The proposed criteria are based on 14 manifestations which include 21 items, as follows. For the purposes of classifying patients in clinical trials, population surveys, and other such studies, a person shall be said to have SLE if any four or more of the following 14 manifestations are present, serially or simultaneously, during any interval of observation:

1 Facial eythema (Butterfly rash)	Diffuse erythema, flat or raised, over the malar eminences and/or bridge of the nose: may be unilateral
2 Discoid lupus	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions; may be present anywhere on the body
3 Raynaud's phenomenon	Requires a two-phase color reaction, by patient's history or physician's observation
4 Alopecia	Rapid loss of large amounts of the scalp hair, by patient's history or physician's observation
5 Photosensitivity	Unusual skin reaction from exposure to sunlight, by patient's history or physician's observation
6 Oral or nasopharygeal ulceration	
7 Arthritis without deformity	One or more peripheral joints involved with any of the following: a) Pain on motion b) Tenderness c) Effusion or periarticular soft tissue swelling (Peripheral joints are defined for this purpose as feet, ankles, knees, hips, shoulders, elbows, wrists, metacarpophalangeal, proximal interphalangeal, terminal interphalangeal and temporomandibular joints)
8 L.E. cells	Two or more classical L.E. cells seen on one occasion or one cell seen on two occasions, using an accepted published method
9 Chronic false-positive STS	Known to be present for at least six months and confirmed by TPI or Reiter's tests
10 Profuse protinuria	Greater than 3.5 g per day
11 Cellular casts	May be red cell, hemoglobin, granular, tubular or mixed
12 One or both:	a) Pleuritis—Good history of pleuritic pain; or rub heard by a physician; or X-ray evidence of pleural thickening or fluid b) Pericarditis—Documented by EKG or rub
13 One or both:	a) Psychosis b) Convulsions—By patient's history or physician's observation in the absence of uremia and offending drugs
14 One or more:	a) Hemolytic anemia b) Leukopenia—WBC less than $4000/mm^3$ on two or more occasions c) Thrombocytopenia—Platelet count less than $100\,000/mm^3$

Table 2 Revised SLE classification criteria[15]

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any of four or more criteria are present, serially or simultaneously, during any interval of observation

1 Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2 Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3 Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient's history or physician's observation
4 Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5 Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6 Serositis	a) Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion *or* b) Pericarditis–documented by ECG or rub or evidence of pericardial effusion
7 Renal disorder	a) Persistent proteinuria greater than 0.5 g per day or greater than 3+ if quantitation not performed *or* b) Cellular casts—may be red cell, hemoglobin, granular, tubular or mixed
8 Neurologic disorder	a) Seizures—in the absence of offending drugs or known metabolic derangements; eg uremia, ketoacidosis, or electrolyte imbalance *or* b) Psychosis—in the absence of offending drugs or known metabolic derangements, eg uremia, ketoacidosis, or electrolyte imbalance
9 Hematologic disorder	a) Hemolytic anemia—with reticulocytosis *or* b) Leukopenia—less than 4000/mm^3 total on two or more occasions *or* c) Lymphopenia—less than 1500/mm^3 on two or more occasions *or* d) Thrombocytopenia—less than 100 1000/mm^3 in the absence of offending drugs
10 Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer *or* b) Anti-SM: presence of antibody to Sm nuclear antigen *or* c) Positive finding of antiphospholipid antibodies based on: 1 An abnormal serum level of IgG or IgM anticardiolipin antibodies *or* 2 A positive test result for lupus anticoagulant using a standard method *or* 3 A false positive serologic test for syphilis known to be positive for at least six months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11 Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug induced lupus syndrome.'

Roles of the SLE classification criteria

The primary purpose of the classification criteria was to operationalize the definition of SLE and thereby allow data from different sources to be compared. The committee that developed the criteria tried to balance maximal sensitivity and specificity. The criteria have been validated in a number of medical settings, and almost all studies involving lupus patients utilize the criteria as inclusion criteria.[6,9–13] The criteria, however, also play a role in medical education and in clinical practice. The criteria have been beneficial for teaching the major features of a disease. Most medical students and physicians-in-training are familiar with the SLE criteria, as are researchers and clinicians outside the field of rheumatology. The criteria act as a framework to '[raise] the diagnostic acuity of the inexperienced toward that of the expert'.[18]

While the 'seduction is irresistable,'[19] the classification criteria are not intended to be utilized to diagnose individuals patients, and they do not perform well in that capacity. They serve as a guide in clinical practice, but clinicians often diagnose SLE without regard to the criteria, based upon each patient's individual manifestations.[20,21] The risk of using classification criteria for clinical diagnosis was highlighted in a study of vasculitis by Rao and coworkers in 1998 regarding the use of the 1990 ACR vasculitis classification criteria for diagnosis. They demonstrated that among 198 patients referred for possible vasculitis, the vasculitis classification criteria had a 25% false negative rate, a 21% false positive rate, and a 50% misclassification rate, with low positive predictive value, using clinical diagnosis as the gold standard for diagnosis.[22] Hunder comments in an accompanying editorial, 'classification criteria work best in the study of groups of patients and work less well in the evaluation of individual patients'.[23]

The difficulty in using classification criteria in diagnosis arises from heterogeneity of the presentation among patients with suspected systemic rheumatic diseases. Furthermore, the prevalence of systemic rheumatic diseases such as SLE is low in most clinical settings. Therefore, despite the high

sensitivity and specificity of the criteria, their positive predictive value in all but specialized referral centers is low.

Problems with the SLE classification criteria

Despite their central role in SLE research, the criteria are imperfect and misclassify patients, excluding patients with SLE from studies if they meet less than four criteria and including patients with four or more criteria who may not have lupus. This may be particularly problematic when a patient with possible SLE also has manifestations of, or even meets criteria for, another rheumatic disease.

In addition, the criteria may not make studies more comparable as intended. Patients meeting criteria may have dramatically different clinical manifestations. Furthermore, the criteria are meant to be objective in classifying patients, but clinicians may have different thresholds for deciding whether a patient has a particular criterion: for example, a patient with a remote history of pleurisy may be judged to meet the serositis criterion by one clinician but not another. The threshold is also variable for serologic testing for ANAs and antibodies directed against double-stranded DNA or Smith antigens. These laboratory evaluations are not methodologically standardized, and therefore have variable operating characteristics.[24] Finally, the purposes of clinicians, educators, researchers and others using the criteria vary widely; no single set of criteria may ever satisfy the needs of them all.

Patients managed clinically with SLE may not meet criteria

Clinicians have voiced concern that a significant number of patients diagnosed with SLE in clinical practice do not meet criteria. Fries and colleagues reported that 27% of their patients diagnosed and managed with SLE at Stanford did not meet the 1971 criteria.[8] One of the best population studies of SLE was a study in Rochester, Minnesota, by Michet and colleagues, who identified 25 SLE patients who met criteria, and 21 patients who were suspected of having SLE and did not meet criteria.[25] The 1974 Kaiser Permanente study reported that nine of 73 cases of SLE did not meet criteria.[26] Calvo-Alén and colleagues reported that 22 of 112 patients clinically diagnosed with SLE did not meet criteria, and voiced concern that a significant subset of SLE patients in the community do not meet criteria: 'our data clearly indicate that these patients belong to the spectrum of SLE and thus probably share similar outcomes. Exclusion of this subset of patients in lupus studies may possibly create a selection bias.'[27]

The dilemma is difficult because the diagnosis of SLE is dependent upon clinical judgement, and this may or may not match the judgement of others. The prevalence of patients diagnosed with SLE may be much higher in the community than predicted by the criteria, but, even so, it is not clear if this represents more patients in the community with SLE, or more patients in the community misdiagnosed with SLE. Hochberg and colleagues reported that diagnosis of SLE by community-based physicians 'lacks precision.' They performed a telephone survey of 16 607 patients, and identified 15 patients who reported that their physician had given them a diagnosis of SLE. After review of their medical records, only six of the 15 cases were validated as SLE by expert SLE physicians.[28] In the lupus cohort at Johns Hopkins, an urban academic medical center that may attract more severe or atypical disease, 93% of the patients diagnosed clinically with SLE meet the criteria.[29] Other studies report that 83–97% of SLE patients meet the criteria, but without a gold standard for diagnosis, the exact proportion of patients with SLE who do not meet criteria is unknown.[14,30,31]

The variability in diagnosis, confounded by different sampling strategies, and geographic and racial variability, has resulted in almost a ten-fold difference in the estimates of the prevalence of SLE in the community, from 15 to 124 per 100 000 persons.[25,26,28,30,32,33]

Of note, the criteria were developed in patients from the United States, most of whom were Caucasian. It is known that the manifestations of SLE vary among different ethnic groups, and there has been little validation of the criteria in other populations.[34–36]

Patients diagnosed clinically with SLE but who do not meet criteria may differ from those who do

A series of articles have described subsets of patients with SLE who do not meet criteria, described by authors as 'latent lupus',[37] 'incomplete lupus',[38] 'lupus-like disease', and 'probable lupus'.[39] In these studies, the characteristics of patients who are clinically diagnosed and managed with SLE but who fail to meet criteria are described. Characteristics do not consistently appear in most of the studies, but two themes emerge:

- Patients diagnosed with SLE who do not meet criteria generally have less severe disease, have more insidious onset, and are more likely to be older at disease onset.

- As might be predicted, patients diagnosed with SLE who do not meet criteria are less likely to have involvement of organ systems included among the classification criteria. Because only the most characteristic organ system manifestations are included in the classification criteria, SLE patients whose disease is manifest in less typical organ systems may be less likely to meet the criteria.[8]

Alger and colleagues compared 31 SLE patients with Coomb's positive hemolytic anemia and/or thrombocytopenic purpura, with 62 SLE patients without these hematologic disorders. Fewer of the patients with hemocytopenias met the SLE classification criteria than those without hematologic problems, though the difference was not significant.[40] Lom-Orta and colleagues compared 31 patients diagnosed clinically with SLE who did not meet criteria, with 31 patients who did meet criteria, and found that the first group were more likely to be older, to be male, to have hematologic features such as hemolytic anemia and thrombocytopenia, and to have less arthritis, alopecia, serositis, facial erythema, central nervous system involvement, Raynaud's phenomenon, granular casts and oral ulcerations. Importantly, 23 of their 31 patients who did not initially meet criteria did so after an average of 27 months.[41] Baer and Pincus described five men with elderly-onset disease and minimal renal, neuropsychiatric and cutaneous involvement, in whom the diagnosis of SLE was delayed, and who did not meet the 1971 preliminary criteria. These patients did, however, meet the subsequent 1982 classification criteria.[42] In 1989, Greer and Panush compared 38 patients diagnosed clinically with SLE who had fewer than four criteria with 42 SLE patients who did meet criteria. The groups were similar in age, but patients who did not meet criteria were less likely to have renal disease, neuropsychiatric disease, serositis, hematologic abnormalities or autoantibodies other than ANA. After an average of 19 months, the patients continued to have evidence of systemic rheumatic disease, but only two met criteria and few required immunosuppressive therapy. In the Calvo-Alén study previously described, SLE patients who did not meet criteria were older and suffered from significantly less mucocutaneous disease, less arthritis, less leukopenia and lymphopenia, and were less likely to have double stranded DNA antibodies than those patients who met criteria.[27]

Patients who do not meet criteria for SLE but who have biopsy findings characteristic of SLE nephritis may represent a distinct subset of SLE.[8,43] Ascer and colleagues described 13 patients whom the authors believed had SLE with SLE glomerulonephritis, positive skin immunofluorescence, and positive ANA but no other features of SLE. The patients responded to corticosteroids and immunosuppressants, and after an average of 5.3 years none of the patients met the 1971 criteria.[44]

The classification criteria may bias towards more severe disease

Most studies have shown that patients who meet criteria have more severe and systemic disease than those who do not meet criteria, probably because the criteria rely on multiple specific and objective abnormalities. Lom-Orta's study discussed above demonstrated more severe disease in patients who met criteria.[41] In Rochester, Minnesota, Michet and colleagues found that SLE patients with four or more criteria had a reduced l0-year survival of 63%, while patients diagnosed clinically with SLE who did not meet criteria had the same l0-year survival as the general population, about 90%.[25] Greer and Panush found that patients who met criteria were more likely to have renal disease, neuropsychiatric disease, serositis, hematologic abnormalities and autoantibodies other than ANA, and concluded that patients with features of SLE who do not meet the classification criteria generally have a better prognosis with less visceral organ involvement.[38] Ganczarczyk and colleagues compared SLE patients who met criteria with patients who did not meet criteria but who had at least one SLE criteria and lupus-like disease. They found that patients who met criteria had more CNS and renal disease and were more likely to have double stranded DNA antibodies, positive Coomb's tests, elevated sedimentation, fever, headache, and fatigue. Most patients who did not meet criteria responded to nonsteroidal antiinflammatory drugs, and did not require corticosteroids.[37]

The only study that seems to contradict this is that of Calvo-Alén and colleagues, who found just as severe disease in their SLE patients who did not meet criteria. Their 22 patients had just as much major organ toxicity including nephritis and serositis, but tended to be older, and were less likely to have hematologic abnormalities. The authors attributed their findings to very restrictive diagnosis of SLE in patients who do not meet criteria, and a detailed chart review of all manifestations.[27]

SLE criteria select for patients with longer duration of illness

Because the criteria are cumulative, one might expect the classification criteria define more cases in patients

followed for a period of time, and fewer cases in patients early in the course of the disease or followed for shorter periods of time.[8] Indeed studies suggest that SLE patients who do not meet criteria eventually will meet criteria if followed long enough. Using the 1971 criteria, Cohen and Canoso reported that 67% of their SLE patients met criteria on first evaluation, 79% met criteria by six months, 89% met criteria by two years, and 94% met criteria by seven years.[11] Using the 1982 criteria, Levin and colleagues reported that 49.4% of patients diagnosed clinically with SLE met criteria at diagnosis, 72% met criteria after one year, and 85% met criteria by five years. Among those patients diagnosed with SLE who did not meet criteria at the time of diagnosis, 51% met criteria after one year, 83% met criteria after seven years, and 100% met criteria after twenty years.[14] In the study by Lom-Orta and colleagues described above, 23 of the 31 patients eventually met criteria in an average of 27 months.[41]

Other studies, however, have found that many patients who do not meet criteria at presentation may not meet criteria in follow-up. In Ganczarczyk's study, only 7 of the 22 patients met criteria after five years of follow-up, and the authors were unable to identify features to predict which of the patients would meet criteria.[37] Of Greer's 38 patients diagnosed clinically who did not meet criteria, only two patients eventually met criteria after an average of 19 months of follow-up or about five years of symptoms.[38] The reason for the differing findings is not clear, though it may reflect different case selection.

Patients with other systemic rheumatic disease may meet criteria for SLE

The criteria may not always distinguish SLE from other systemic rheumatic diseases well, particularly patients with antiphospholipid syndrome (APS). APS may develop in patients without (primary) or with (secondary) systemic illnesses such as SLE. APS antibodies are a criterion in the updated SLE classification criteria (Table 2). Patients, however, with primary APS may meet one or more of the criteria for SLE, including seizures, psychosis, hemolytic anemia, thrombocytopenia, false positive test for syphilis, and antiphospholipid antibodies, and may have other features of SLE not in the criteria such as cardiac valve vegetations or transverse myelitis. Vianna and colleagues compared 58 patients with primary APS with 56 patients with SLE and APS, and found very similar clinical and laboratory features in the two groups. 41% of the patients with primary APS had a positive ANA.[45] Therefore, differentiating primary APS from SLE may be difficult. The issue is further complicated by the fact that over time some patients with APS develop signs and symptoms that suggest that they do suffer from SLE.[46,47] Deciding whether a patient has SLE, APS, or both is a decision best made by the clinician; the ACR classification criteria may not distinguish such patients well. Similarly patients with an overlap of rheumatoid arthritis and SLE, sometimes referred to as 'rhupus,' may meet criteria for both diseases.[48] Patients with other rheumatic disorders and overlap syndromes may also meet criteria for SLE without a clinical diagnosis of SLE. Fries and colleagues found four or more of the 1971 SLE criteria in their Stanford database in 19.9% of patients with scleroderma, 18.1% of patients with Wegener's, 14.8% of patients with discoid lupus, 13.6% of patients with Felty's, 13.4% of patients with 'lupoid' hepatitis, 11.1% of patients with polyarteritis, and 9.9% of patients with rheumatoid arthritis.[8]

Alternatives to the SLE classification criteria

Given the limitations of the SLE criteria, alternatives should be considered. For purposes of clinical care, the criteria may serve as a guide, but it is unlikely that they could ever match an experienced clinician's acumen for the individual patient. For the purposes of education, it is important to convey to clinicians, trainees, and patients that the criteria serve as guides to common and important manifestations, but that some patients may have SLE without four criteria, and that SLE is associated with manifestations other than those listed in the criteria. For purposes of research, there are ways the criteria or their use could be improved.

A number of alternatives to the present criteria have been proposed. Edworthy and colleagues developed classification trees by applying recursive partitioning methodology to the 339 subjects used in the development of the 1982 ARA classification criteria. The simple tree was 92% sensitive and specific, and the full tree was 97% sensitive and 95% specific, compared to the 1982 ARA criteria that were 96% sensitive and specific. These classification trees had similar sensitivity and specificity as the 1982 ARA criteria when tested in the Johns Hopkins Lupus Cohort,[49] but Davatchi analyzed the full classification tree in 135 SLE patients, and found 73% sensitivity, compared to 90% using the 1982 SLE classification criteria, in part due to their laboratory's higher cut-off for a positive ANA.[50] Currently these classification trees are not widely utilized.

In 1984 Clough developed weights for each criterion to improve the sensitivity and specificity of the classification criteria, as suggested by Leonhardt in 1964, Rupe in 1964, and Mustakallio in 1966.[51] Clough and colleagues compared 87 patients with clinically diagnosed SLE (independent of criteria) followed at Cleveland Clinic with 73 consecutive patients thought not to have SLE, in order to calculate the sensitivity and specificity of each criterion. From this they calculated the weighted importance of each criterion (Table 3). The probability of a patient having SLE increased with increasing total score, as delineated in their nomogram. A score of 2 predicted a 20% likelihood of SLE by Bayes' Theorem, and a score of 4 predicted a 95% likelihood of SLE. In their sample, the weighted criteria were more sensitive and specific than the 1982 classification criteria. They also discussed altering the weights depending upon the prevalence of SLE and each criterion in different clinics.[51] Somogyi and colleagues performed a similar exercise in 100 SLE patients and 100 controls, and also recommended the use of weighted or quantitative criteria.[52] Weighted criteria are not currently used in clinical studies, perhaps in part due to their complexity. Weighted criteria may be the most effective way, however, to improve the sensitivity and specificity of the classification criteria, since some of the criteria may be better able to distinguish SLE than others.[52–54] Weighted criteria and 'qualified lupus' may simulate how clinicians use the criteria in clinical practice.

Closely related to the notion of weighting is the suggestion to use major and minor criteria.[10] These have not been widely used, though it has been considered for clinical trials when patients are enrolled based on a major indication.

Schur has recommended subdividing patients according to their number of criteria. He classified patients with two criteria as possible SLE, patients with three criteria as probable SLE, patients with four or more criteria as definite SLE, and patients with many criteria as classic SLE. [55] This is an intuitive approach that resembles how clinicians might make judgements regarding the likelihood of SLE. If adapted as a reporting standard, it would enhance comparisons between patient populations. Graham Hughes recently proposed a new set of criteria, developed from his perception of SLE based on his clinical experience.[56]

Table 3 Weighted criteria[51]

Criteria	*Score*[b]
Malar rash	1.0
Discoid rash	1.5
Photosensitivity	0.6
Oral ulcers	0.1
Arthritis	0.1
Serositis	0.6
Renal disorder	
(a) Proteinuria	1.0
(b) Cellular casts	1.5
Neurologic disorder	0.7
Hematologic disorder	1.5
Serology	
(a) Positive ANA, unknown DNA antibodies, unknown Sm antibodies	0.5
(b) Positive ANA, negative DNA antibodies, negative Sm antibodies	0.3
(c) Positive ANA, positive DNA antibodies, negative Sm antibodies	1.3
(d) Positive ANA, negative DNA antibodies, positive Sm antibodies	1.3
(e) Positive ANA, positive DNA antibodies, positive Sm antibodies	1.4
(f) Negative ANA, negative or unknown DNA antibodies, negative or unknown Sm antibodies	−1.8
Alopecia[a]	0.6
Raynaud' s phenomenon[a]	0.3

[a] Not present in 1982 SLE classification criteria.
[b] The probability of a patient having SLE increases with increasing score, as delineated in a nomogram in the referenced article. A score of 2 predicts a 20% likelihood of SLE by Bayes' Theorem, and a score of 4 predicts a 95% likelihood of SLE.

Opportunities for improving the SLE classification criteria and their use

Just as treatment under ideal conditions in randomized clinical trials should be confirmed under more generalizable and realistic conditions, studies of SLE should include the complete spectrum of patients seen in clinical practice. If the current criteria for SLE are utilized as the sole entry criteria for studies, a significant portion of SLE patients are excluded from study of the disease.

This issue is of particular importance to researchers conducting clinical trials, as enrollment of patients may be limited by small numbers of patients meeting study criteria.[18] SLE is an uncommon and heterogeneous disease, and researchers, limited only to those patients meeting criteria, struggle to find enough patients for the studies to provide adequate statistical power.

An alternative would be to admit patients into some clinical studies if they have SLE diagnosed by a rheumatologist but do not meet criteria, as long as their clinical manifestations are clearly described and therefore open to scrutiny by the scientific community. Regarding the entry of SLE patients into clinical studies even if they do not meet criteria, Calvo-Alén and colleagues wrote, 'We are, however, making the strong case for the inclusion of patients with clinically unequivocal SLE into outcome studies (many with clearly defined organ system involvement) if the true disease course, laboratory correlates, and disease

outcomes are to be determined.'[27] Hunder, in his editorial regarding the use and misuse of criteria in complex diseases, wrote, 'Because of the limitations of classification criteria, investigators may include patients whom they believe have the diagnosis in question regardless of whether they fulfill the criteria, as long as the investigators describe those who do not meet criteria and provide reasons for their inclusion.'[23] If studies include such patients the results should be analyzed with and without these patients to assess the impact of these patients on the study's results and conclusions.

This alternative may not be appropriate for all studies. Some studies, such as evaluation of potentially toxic treatments, should hold to the more rigorous four criteria minimum, while other studies should be able to include patients diagnosed and managed with SLE with less than four criteria. In a study evaluating the effectiveness of an intervention for a specific syndrome such as SLE nephritis, the important inclusion criteria should be the presence of lupus nephritis, regardless of whether the patient meets three or four criteria. There is a risk of allowing patients without SLE into SLE clinical studies if they do not meet criteria, but with careful documentation of study patients' SLE manifestations, the scientific community can make judgements regarding the quality of such research.

Detailed description of patient characteristics is the most important requirement that allows the reader to judge the patients themselves. Figure 1 demonstrates a standardized format in which SLE subjects could be described, and provides a literal picture of study patients. The figure demonstrates frequencies of each criterion and number of criterion in the Brigham and Women's Hospital Lupus Registry. Use of a standardized format would facilitate comparison of study patients with other SLE patients. As others have suggested and OMERACT has favored, we also recommend that the basic description of subjects include disease activity with one of the published disease activity measures, such as the BILAG, SLAM, SLEDAI, or ECLAM, cumulative organ damage measured by SLICC, and duration of illness.[57] It is important to note which criteria are atypical, which ones were ever present, and which were present at study entry.

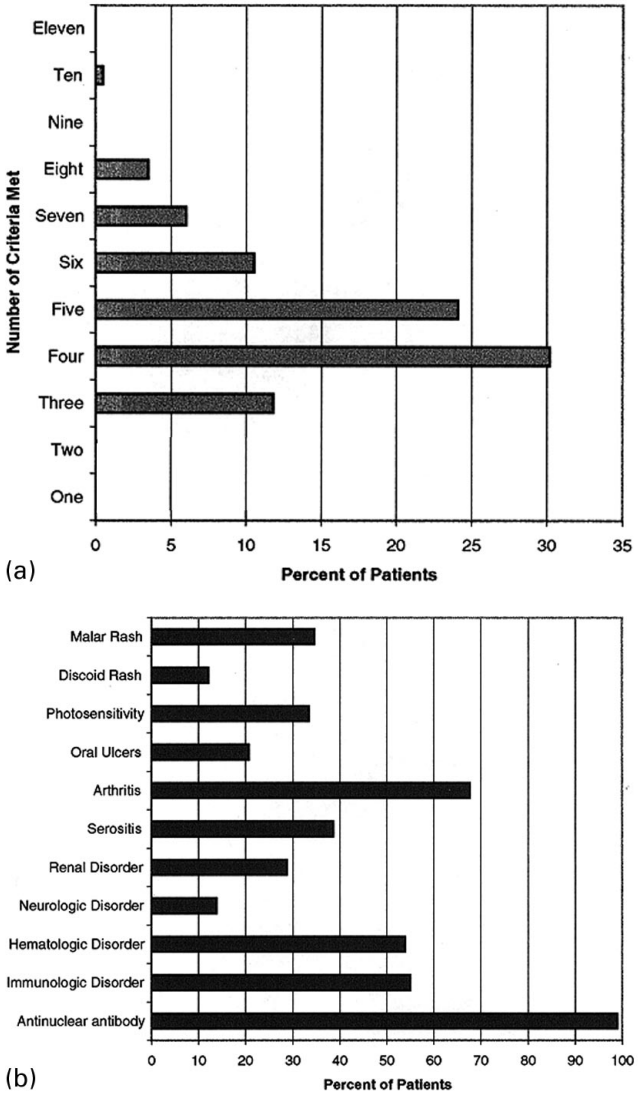

Figure 1 SLE study patient characteristics.

Reevaluating the criteria

Criteria are most useful if they remain dynamic, updated as medical science progresses, but not changed so frequently that they impede comparisons between studies.[19] Classification criteria may themselves delineate areas that deserve further scientific investigation. Hopefully, 'Disease criteria organize clinical knowledge, and improved knowledge improves disease criteria.'[58]

It is important that the criteria be periodically tested in patients thought by experts to have SLE, reevaluating the statistical analyses, and making improvements as indicated, to be sure that what experts and clinicians consider SLE is still in keeping with the criteria used in research. Ideally, community SLE patients as well as patients from academic centers should be included in this process. The sensitivity and specificity of the criteria should be evaluated not only in patients with systemic rheumatic diseases, but also in patients from the general population. Furthermore, the sensitivity and specificity of the criteria should be

evaluated in patients from a variety of ethnic backgrounds. Any revisions should be widely disseminated among rheumatologists and primary care physicians.

Conclusions and recommendations

The ACR classification criteria for SLE have been critical to clinical research, but should be viewed as a benchmark for our current understanding of the disorder's clinical features, a temporary mechanism to be utilized until better understanding emerges. The criteria have inherent limitations, including bias towards more severe and longer duration disease, equal weighting of features that vary in clinical significance, and exclusion of patients with SLE from research because they do not meet criteria. It may soon be time to rigorously reevaluate the SLE criteria so that they will better serve clinicians, teachers, researchers, and patients.

For SLE clinical research, and particularly trials of new agents, we recommend:

- Patients diagnosed with SLE who do not meet criteria should be included in some studies, if these patients' manifestations are explicitly reported, and the results of the study are analyzed with and without these patients.
- SLE disease activity, cumulative organ damage, disease duration, criteria ever met, and criteria met at time of enrollment are important data that should be presented in clinical studies of SLE regardless of the number of criteria met.
- The criteria should be revised periodically, utilizing patients and controls with a range of diseases and disease severity. A simplified weighting system may more accurately reflect clinical practice.

The ACR classification criteria for SLE, though not perfect, nor static, have served the field well. The criteria and their use should evolve over time to reflect and facilitate a better understanding of the disease.

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