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Multi-center Delphi Exercise Reveals Important Key Items for Classifying Systemic Lupus Erythematosus

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Abstract

Background—The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) embarked on a project to re-evaluate classification criteria for systemic lupus erythematosus (SLE). The first phase of the classification project involved generation of a broad set of items potentially useful for classification of SLE and their selection for use in a subsequent forced-choice decision analysis.

Methods—A large international group of expert lupus clinicians was invited to participate in a 2-step process to generate, rate and select items based on their importance in diagnosing early and established SLE, respectively, via a web-based survey.

Results—135 and 147 experts were invited to participate in the item generation and item reduction process, respectively. Out of 145 items generated, item reduction resulted in 40 candidate items moving forward to the next phase. Key features for classifying both early and established SLE included characteristic autoantibodies, specific renal features, and skin

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manifestations. A small majority (51%) stated that one organ system would be sufficient for classifying SLE, but that additional typical laboratory features (ANA, dsDNA) would be required. Notably, 85% of the expert group would positively classify SLE if renal pathology alone showed lupus nephritis.

Conclusion—The Delphi exercise resulted in a set of 40 candidate criteria for the classification of SLE for subsequent assessment. This study comprised the largest panel ever involved in the development of SLE classification criteria, providing a broadly representative view of the current approach to classification SLE.

Systemic lupus erythematosus (SLE) has long been considered the prototype autoimmune disease. The typical rash, multi-organ involvement and diverse production of autoantibodies all support its conception as a single disease. However, the diversity and heterogeneity of clinical presentation of SLE and other related conditions commonly presents a diagnostic challenge to practitioners and poses a risk of misclassification for researchers enrolling patients into clinical studies. Multiple attempts have been made to capture the heterogeneous clinical and laboratory findings in this complex disease and establish SLE classification criteria.¹ The 1982 revised criteria set of the American College of Rheumatology represented a milestone in this effort and served the specific purpose of classifying established SLE for the purposes of clinical studies, rather than as diagnostic criteria for diagnosing SLE in clinical practice. Thirty years later, in 2012 the Systemic Lupus International Collaborating Clinics (SLICC) group revisited the classification criteria for SLE. This set of criteria reached higher sensitivity as compared to the ACR criteria, at the expense of decreased specificity.² Several reports of SLE cohorts support the validity of these criteria and suggest that they may be an improvement over the ACR classification criteria.^{3,4,5}

One limitation of both sets of criteria is suboptimal performance in early disease. Rheumatologists see many patients in the early phases of SLE, where they may have to treat SLE even though the classification criteria of the disease may not be formally met. This may not represent a major problem in daily practice since the criteria are for classification and not diagnosis.⁶ In the context of research studies, however, many patients with early or limited SLE may be excluded, and as a result, patients with early SLE are presumably underrepresented in major clinical trials. Another issue is the necessity of ANA-positivity as a prerequisite for the classification of SLE and whether classification of SLE with without ANA allows potential enrollment of patients with distinct non-SLE conditions.

To address these issues, an ACR-EULAR initiative is being undertaken to re-evaluate existing criteria and develop updated classification criteria in a multistep process that combined expert-based and novel, data-driven methods. The ultimate goal of the initiative is to develop classification criteria with enhanced performance characteristics, including improved sensitivity among patients with early SLE.⁷ The objective of this study, the initial phase of the multistep process, was to generate a comprehensive list of candidate criteria that should be considered for the classification of SLE. We then reduced the list of candidate criteria to a more manageable number based on appropriateness. Here we present the results

of an international Delphi exercise that generated an initial list of candidate items for use in classifying SLE and differentiating SLE from other diseases.

METHODS

Design

This cross-sectional study of international SLE experts had 2 parts, item generation and item reduction. A web-based survey was used for both parts.⁸

Committee and Expert panel

The EULAR/ACR steering committee for the classification of SLE consisted of six members each from North America and Europe. Snowball sampling was used to identify international SLE experts. SLE experts were defined as individuals with expertise in the care of lupus patients, and/or expertise in clinical or translational lupus research. Experts were purposefully sampled to ensure representation from various geographic areas.

Item generation

An initial list of candidate items was generated from review of the literature, explicitly including all items from existing SLE criteria sets. The international SLE panel was asked to review this list of candidate items regarding their usefulness in classifying SLE, for distinguishing SLE from non-SLE, for their importance in diagnosing early and established SLE and for diagnosing childhood-onset SLE. They were also queried regarding the importance of ANA in classifying SLE, the usefulness of specific autoantibodies and pathologic data for classifying SLE, and the utility of any additional specific laboratory or biomarker tests. Participants were asked to suggest additional items of value for classifying patients as having SLE, including clinical, laboratory or immunologic elements. Free text comment fields were provided for every question to facilitate the inclusion of additional items. These items were extracted from free text comments and considered further if they were mentioned by at least 3 experts.

Item reduction

The 145 items from the item generation process were subjected to a two-round, web-based Delphi process in order to reduce the number of items.

Delphi reduction round 1—Participants were asked to rate the usefulness of each candidate item for classification criteria. To reduce response burden due to the large number of candidate items, the expert panel was divided into 3 groups, and each group assessed one third of the candidate items, which were assigned to each group at random. Each group also received 9 items in common as an internal control. Using an online survey platform questionnaire (SurveyMonkey Inc., San Mateo, California, USA) the experts rated each item using a Likert scale (range 1–9, where 1 corresponded to “not at all appropriate” and 9 to “completely appropriate”) in response to 3 questions: 1. How appropriate is this manifestation for the classification of SLE? 2. How appropriate is this manifestation for the classification of SLE within the first year of a patient's disease? 3. [Answer only if you see children]: How appropriate is this manifestation for the classification of SLE in children? A

mean and median appropriateness score were calculated for each candidate item. To be retained, items had to fulfill two criteria, namely 1. Median appropriateness score greater than 3; AND 2. At least 25% of ratings in the "most appropriate" (7,8,9) category) for either questions 1 or 2 above. Because we anticipated a small number of pediatric answers, we analyzed these separately via thematic analysis (see below).

Delphi reduction round 2—Experts who responded to the first item reduction survey were invited to vote in a second item reduction survey. During this round, experts were presented with their own ratings of each item alongside the median ratings for the entire group, and a list of items eliminated based on the prior round. Experts were instructed to review their scores in relation to the median score and decide whether to change their score based on this information. Again, participants were asked to rate each candidate item on its usefulness as a classification criteria ("How appropriate is this manifestation for the classification of SLE?"). One third of the items were randomly assigned to one third of the expert group for scoring on a Likert scale; again, each group also received nine items in common as an internal control. Mean and median appropriateness score were calculated for each item. Items were selected to move forward based on two criteria, which were considerably stricter than in round 1, namely: 1. Mean appropriateness score greater than or equal to 6.5; AND 2. At least 50% of ratings in the "most appropriate" (7,8,9) category. Finally, two composite items were selected to move forward despite not meeting the above threshold because it was felt that these important manifestation of disease should be assessed during the nominal group technique exercise.

Appropriateness scores were analyzed across the 3 groups using t-tests (2-sided), in order to assess whether there were systematic differences in the responses of the 3 groups to the common items used as internal controls. Statistical analysis was performed using SAS (Version 9.2).

Thematic analysis

A qualitative content analytic approach was used to analyze the free text data.⁹ Independently, 2 investigators read all the free text data repeatedly to achieve immersion and obtain a sense of the whole data set. The investigators made notes to capture key thoughts or concepts. The concepts were organized into meaningful clusters. The aggregate results were presented to the SLE classification criteria steering committee for comment. This research triangulation enhances the credibility of the findings and ensures the analysis reflects the full breadth and depth of the data.¹⁰

RESULTS

SLE experts

Through snowball sampling, 135 panelists with expertise in clinical care and clinical and translational lupus research from various geographic areas were identified. For the item reduction process, an additional 12 experts, for a total of 147, were invited to complete the survey. 3 individuals did not respond to our solicitations. Overall, the mean age of the experts was 53 years and they were in clinical practice for a mean time of 23 years. On

average, each of these experts saw 168 individuals with SLE per year. The majority of the panelists were adult rheumatologists (81.6%), but the group also included dermatologists (7.5%), nephrologists (6.8%), pediatricians (3.4%), and non-clinical SLE researchers (0.7%). 53% were from North or Central America and 46% from Europe. Specific countries of origin are listed in Supplementary Table 2.

Item generation

120 experts responded to the initial survey, for an overall response rate of 88%. This initial survey resulted in a list of 196 candidate items. Combining very similar and overlapping items resulted in a condensed candidate list of 159 items. Sixteen of these contained one or more closely related concepts which were grouped into a single item (e.g. “fevers,” “fatigue,” and “weight loss,” were collapsed into a single item labelled “constitutional symptoms (fever, fatigue, OR weight loss)”), resulting in 153 unique items. Eight items were felt to be too difficult (or unavailable) for widespread use in clinical practice (see Supplementary Table 3). In keeping with the goal of developing classification criteria of practical utility, these items were eliminated from the list, leaving 145 candidate items (see Supplementary Table 4).

Item reduction

123 out of 147 experts responded to the round 1 item reduction survey, for an overall response rate of 84%. This exercise resulted in 90 candidate items being retained (see Supplementary Table 5). There was no statistically significant difference in appropriateness scores between groups using the internal control items (data not shown). 112 out of 123 experts responded to the round 2 item reduction survey, for an overall response rate of 91%. The round 2 item reduction survey resulted in 40 candidate items being retained (Table 1).

Thematic analysis

Additional themes from the serial surveys of expert panelists are described below.

Presence of ANA as a significant parameter for diagnosing SLE—Experts were asked whether they would make the diagnosis of SLE in the presence or absence of anti-nuclear antibodies on at least two occasions, and using immunofluorescence and/or ELISA. 23% of experts would be comfortable classifying SLE in the absence of ANA by immunofluorescence assay (IF) while 58% would not (19% were unsure). In contrast, if ANA testing relied on ELISA, 39% of the experts were willing to make the diagnosis in the absence of ANA while only 28% would not (Figure 1). Some experts noted that they would diagnose SLE in the absence of a positive ANA if historical positive values were available, that there was a subgroup of anti-Ro-positive patients that may test ANA negative, or that the variable and sometimes inferior quality of commercial ELISA testing did influence their answer. Nevertheless, the majority of the experts would only be willing to make the diagnosis of SLE in the absence of ANA on immunofluorescence in very few and special cases (unequivocal histology and subgroup of anti-Ro-positive patients).

Anti-dsDNA and anti-Sm antibodies are the autoantibodies considered most characteristic of SLE—When provided with a list of possible autoantibodies that might

prove helpful in diagnosing SLE, 99% of experts viewed anti-dsDNA antibodies and anti-Sm antibodies as the most typical serologic findings of SLE. 61% stated that antiphospholipid antibodies would be helpful in making the diagnosis, 46% for anti-Ro antibodies, 37% for anti-RNP, and 34% for anti-La, respectively. Anti-C1q antibodies were also suggested as a novel laboratory finding (Figure 1). Positive ANA alone was sufficient for 75% of the experts, while 25% would additionally require a specific immunofluorescence pattern.

Novel laboratory parameters may be important for classifying SLE in the future—Experts were asked to suggest additional, novel laboratory parameters that they found important for classifying SLE. A large number of such candidate items were initially suggested (Supplementary Table 3). Items suggested most frequently included high circulating levels of IP10, MCP1 and TNF; a type I interferon signature, high Th17 markers, plasma cell expansion and increased serum BlyS. Other laboratory markers that were mentioned by at least 3 experts each included plasma cell expansion, hypergammaglobulinemia, lymphopenia, and anti-chromatin antibodies.

Classical features are considered most often for the classification of SLE by experts—When asked for clinical findings helpful for classifying SLE in addition to ACR and SLICC criteria, experts most often mentioned Raynaud's syndrome, transverse myelitis, aseptic meningitis, capillaroscopic changes, palatal ulcers, biopsy proven skin changes (as opposed to typical rash) and ultrasound proven arthritis. For distinguishing SLE from non-SLE, experts felt that ANA, anti-dsDNA-antibodies, hypergammaglobulinemia, hypocomplementemia, high-interferon alpha signature, and high BlyS levels represented important laboratory findings. In addition, renal pathology, malar rash, and urine sediment were frequently considered. When asked to rate classical clinical features in their importance for making the diagnosis of SLE, there was a strong consensus on skin symptoms such as malar rash and acute cutaneous lupus, with more than 70% of the experts finding those parameters helpful in both early and established SLE. Renal findings (including proteinuria > 0.5 g/L, urine protein/creatinine ratio and cellular casts), pleuritis, pericarditis, non-erosive arthritis, hematological features, and typical autoantibodies were identified as the strongest factors. Strikingly, the only item rated significantly different for early versus established SLE was chronic cutaneous lupus, but this was under-represented in early disease (51% vs. 70%). Joint tenderness (38 and 39%) and nasal (35 and 38%) and oral ulcers (45 and 46%) were most similar between early and established SLE.

A majority of experts would rely on histopathology to make the diagnosis of SLE—When experts were asked whether they would classify SLE based only on one pathological finding, 48% responded with yes, while 40% stated that in addition to the biopsy they would need at least one distinct laboratory finding (i.e. autoantibodies). There was consensus that the pathology would need to be from a renal rather than a skin biopsy. 12% of experts would not make the diagnosis based a single pathological finding. An important related question referred to the number of organ systems needed to qualify for systemic disease. Here 37% indicated 2 organ systems would be necessary and 22% indicated 1 organ system with additional conclusive laboratory findings. There was a

consensus that disease manifestations included as criteria should conclusively reflect involvement of specific organ systems (e.g. renal pathology) and or laboratory abnormalities, as opposed to less specific findings such as fever or arthritis. 30% stated that one organ system would be sufficient without additional findings. An additional 7% voted for 3 organ systems and 4% for 4 organ systems.

Pediatricians utilize similar criteria for classifying childhood-onset SLE—Six physicians who care for pediatric patients rated criteria for the classification of childhood-onset SLE. Similar to consideration of adult SLE, these experts found skin features such as malar rash, photosensitivity and oral ulcers in addition to renal symptoms, pericarditis and pleuritis, and classical laboratory findings most helpful for classifying pediatric SLE. The difference in relative importance for pediatric lupus compared with (established) adult SLE was most significant for seizures (83% vs 62%) and oral ulcers (100% vs 46%). In line with finding such differences, 50% of the pediatric rheumatologists in this study did not feel that there was a need for separate criteria for childhood-onset SLE.

Impact of thematic analysis on criteria reduction

Based on thematic analysis of the comments from the expert panelists, the following additions were made to the final Delphi item list: 1) A composite neuropsychiatric lupus item was created. While none of the individual neuropsychiatric SLE items met the retention threshold, several related items were highly rated and based on individual comments during the Delphi exercise, it was felt that this important organ manifestation should be considered in the next phase of SLE criteria development. Participants in the next phase will be informed that CNS lupus items did not meet the pre-determined Delphi cutoff. 2) Raynaud's phenomenon was retained as a candidate item for the same reason. 3) 2 items – high-titer positive ANA on Hep 2 cells and lymphopenia $<1000/\text{mm}^3$ on 2 or more occasions were added because they were identified as important variants of other criteria that did meet the retention cutoff. Finally, ANA and complements were identified as special items that serve as “entry criteria” for the classification of SLE: consideration of the other items on the list should be based on the assumption that patients had a positive ANA and/or a low complement (C3).

DISCUSSION

This first phase of a multi-phase process to develop criteria for the classification of SLE was designed to produce a broadly inclusive, non-redundant, and practical list of candidate criteria. Existing and novel criteria were rated by a large and diverse panel of international experts. As this group comprised the largest panel ever involved in the development of SLE classification criteria, the candidate criteria list provides a broadly representative view of the current approach to classification and diagnosis of SLE.

One challenge in developing classification criteria for rheumatic diseases is the need to distinguish classification from diagnostic criteria. The latter would be directed to an individual patient, while the purpose of classification is to define patients that are appropriate for enrollment in research studies. However, classification criteria are frequently used for diagnosis in practice.^{11,12} Items that function well as classification criteria are

common in SLE and have a high degree of specificity for the disease; thus, they are frequently useful for diagnosis. In addition, classification criteria are generally developed and considered by the same experts that publish and teach about diagnosing disease, and these experts frequently mingle these two uses.

ANAs are an illustrative and important example of this tension between classification and diagnosis that was apparent during the deliberations of the expert panel. A positive ANA is considered a fundamental aspect of SLE and this test has extremely high sensitivity for the diagnosis of SLE.¹³ However, in the initial phase of our process, when considering whether ANA positivity should be an absolute entry criterion for the classification of SLE, some experts noted that patients with definite SLE exist in whom the ANA is negative. Thus, while a majority of experts would require positive ANA for diagnosis of SLE, 27% were comfortable diagnosing SLE without positive ANA. In addition to the well-documented problems of ANA testing by ELISA,^{14,15,16,17} some experts noted that they would diagnose “ANA-negative SLE” if there had been a positive ANA in the patient’s history. (A separate Delphi exercise that focused on the performance of ANAs for classifying SLE was recently undertaken in a independent study.¹⁸) It was also notable that a majority of experts would diagnose SLE based on renal pathology alone, or on single organ system involvement if accompanied by laboratory findings such as positive ANA and anti-dsDNA antibodies. Thus, although SLE is conceived as a systemic illness and systemic features are widely used for diagnosis and in existing classification criteria, certain very specific features of the disease are clearly more useful for these purposes than others.

Although this international SLE expert panel initially identified a broad range of items, including both typical and unusual clinical manifestations, serologic and pathologic abnormalities, and a number of novel immune markers that have been implicated in the pathogenesis of SLE or indicators of disease activity, during the course of the Delphi process, many of these items were discarded. Among the highest scoring items, there was a clear preference for serologic evidence of autoantibody production, complement activation, and for objective indicators of immune-mediated nephritis. The significant overlap between this item list and existing classification criteria likely reflects the massive impact of the 1982 and revised 1997 ACR criteria on the education and training of the generations of SLE experts who took part in this Delphi exercise, as well as the persistent lack of more specific biomarkers.

Still, it is important to note that the expert panel identified a number specific immune biomarkers that may be useful for classification of SLE, such as high circulating levels of TNF; a type I interferon signature, or high Th17 markers, among others. The number and diversity of these candidate items suggest that recent and significant advances are being made in this area. These items were eliminated during the Delphi process because their measurement in a clinical setting is currently impractical. However, adoption of these kind of biomarkers in the future has the potential to align clinical classification of SLE with the underlying pathogenesis of the disease, potentially resulting in improved specificity as well as better assessment of the impact of new, targeted therapies for this disease. Testing of these biomarkers in defined groups of SLE patients for their performance in relation to established classification criteria is an important agenda item for future lupus research.

With regard to the issue of classification of early SLE, although some experts felt that some individual criteria are particularly useful for classifying early disease, there was not sufficient discrimination between the rating of any criteria for early vs. established disease to identify criteria for this purpose in these surveys. Future studies should address the issue of early diagnosis, specifically because classification criteria are used to determine enrollment in clinical studies.^{19,20} It is possible that a useful treatment for SLE might have the greatest impact in the early stages of the disease. Accordingly, inclusion of patients with well-established or later stages of disease might dilute the measured effectiveness of a treatment.

Finally, although the insight gained from experts that see pediatric lupus patients on the use of candidate criteria in this exercises was interesting, these criteria were not developed specifically to apply to childhood-onset SLE.

The distilled list of candidate classification criteria produced in this extensive Delphi process is the result of the first step in a multistep selection process that utilizes several criteria for analyzing candidate item acceptability and utility by lupus experts. Such a formalized multistep process has been used successfully for other diseases including systemic sclerosis.²¹ Subsequent phases of classification criteria development, including weighting and narrowing of the items, are needed to produce a working set of classification criteria. The development of a relatively small list of consensus items in this first phase provided a starting list for the nominal group technique in the next phase of this project.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- The Delphi exercise resulted in a set of 40 candidate criteria for the classification of SLE for subsequent assessment.
- This study comprised the largest panel ever involved in the development of SLE classification criteria, providing a broadly representative view of the current approach to classification SLE.

Figure 1.

International SLE expert panel responses to queries regarding ANA testing around the diagnosis of SLE (N=120).

SLE: systemic lupus erythematosus; ANA: Anti-nuclear antibody; IF: immunofluorescence; ELISA: enzyme-linked immunosorbent assay.

Table 1

Delphi appropriateness ratings of final list of candidate SLE classification items, rated on a scale of 1 to 9, sorted by mean rating (N=40).

Candidate item	Number of responses	Mean	Median	% Rated 7,8,9
anti dsDNA antibody	36	8.94	7.5	100%
lupus nephritis by renal biopsy with immune deposits	111	8.77	7	98%
acute, subacute, or chronic lupus rash (<i>can include malar, discoid, SCLE</i>)	37	8.65	8	100%
anti Smith antibody	38	8.55	7	97%
low C3 and C4	37	8.24	7.5	100%
ANA positive (any pattern) 1:160	110	8.10	6	86%
malar rash	37	8.00	6.5	86%
glomerulonephritis (<i>dysmorphic urinary RBC or urinary RBC casts (1 cast/hpf)</i>)	37	7.97	6	92%
active urine sediment (without UTI)	37	7.86	6.5	89%
discoid rash	37	7.84	7	86%
persistent proteinuria (>0.5g/day)	37	7.84	6.5	81%
rash with dermoepidermal interface changes and immunoglobulin and/or complement deposition on IF	37	7.78	7	92%
low C3	37	7.65	7	89%
presence of multiple autoantibodies	37	7.59	6	81%
ANA positive by Hep 2	110	7.59	5.5	81%
Arthritis	37	7.51	7	78%
SCLE	37	7.51	6	73%
serositis (<i>clinical signs, or pleural or pericardial effusion by imaging</i>)	37	7.32	6	78%
oral mucosal lesions on the hard palate	37	7.24	6.5	78%
pleural effusion	37	7.24	6	73%
thrombocytopenia (severe)	111	7.20	5	78%
autoimmune hemolytic anemia	37	7.11	7	68%
urinary RBC casts (1 cast/hpf)	37	7.03	6.5	73%
photosensitive rash	37	6.97	6	81%
positive lupus anticoagulant panel	37	6.97	6.5	70%
pleuritis	37	6.89	6.5	65%
leukopenia (<4000/mm ³ on 2 or more occasions)	109	6.87	5	68%
photosensitivity	37	6.86	6	70%
antiphospholipid antibodies (<i>LA, anticardiolipin, anti-B2GPI, or prolonged RVVT</i>)	36	6.83	6	72%
alopecia with associated scalp inflammation	111	6.83	5.5	62%
urine cellular casts	37	6.81	6	70%
lupus profundus	36	6.81	6	64%
lymphopenia (<1500/mm ³ on 2 or more occasions)	111	6.76	5.5	68%
thrombocytopenia	111	6.69	5.5	64%
pericardial effusion	37	6.57	5.5	54%
APLS (clinical signs/history + antibodies)	37	6.54	6	59%
ANA on Hep2 cells with a pattern compatible with SLE, titer 1:160	composite item			

Candidate item	Number of responses	Mean	Median	% Rated 7,8,9
lymphopenia (<1000/mm ³ on 2 or more occasions)	additional retained item			
Raynaud's phenomenon	additional retained item			
CNS dysfunction (<i>seizures, psychosis, chorea or acute confusional state</i>)	composite item			