Editorial

Systemic Sclerosis Classification: A Rose by Any Other Name Would Smell As Sweet?

The 1980 preliminary criteria for scleroderma (systemic sclerosis; SSc) have worked well for decades[1]. The monumental thinking of the authors is to be applauded. However, over time things have changed. There are more patients with SSc who are on the mild end of the spectrum and who are in the limited cutaneous SSc (lcSSc) subset; this may be due to the evolution of the disease, more recognition because of available commercial autoantibodies, earlier diagnosis, or all these reasons.

The 2013 criteria also incorporate the 3 main features of SSc (although not all patients have all features): vasculopathy, fibrosis, and autoantibodies. Raynaud phenomenon (RP) is included as a feature even though it does not distinguish from other patients with RP, but because SSc without RP is so rare, RP adds statistical value to the criteria[2,3]. In other cohorts, similar operational characteristics (sensitivity and specificity) have been reported[4,5,6].

The 2013 criteria can classify more patients that experts would label as having SSc. A patient with sclerodactyly, RP, positive anticentromere antibody, and proven pulmonary arterial hypertension would be classified as having SSc by the 2013 criteria but not by the 1980 criteria. The same applies for someone with sclerodactyly, RP, anticentromere antibodies, dysphagia, dilated nailfold capillaries, and calcinosis. However, a patient with only sclerodactyly, gastroesophageal reflux disease, dilated lower esophagus, dysphagia, RNA polymerase III, and scleroderma renal crisis would not meet either set of SSc criteria. But as soon as the scleroderma progressed beyond the fingers, the patient would satisfy both classifications.

The 2013 SSc classification criteria may need some explanation and clarification. The footnote in Table 1[2,3] would allow one to infer that those (SSc-mimicking) conditions were excluded as scleroderma-like disorders when applying the criteria and deriving sensitivity performance; however, patients who did not have SSc were used as controls (mimickers), thus precluding application of the criteria; i.e., the classification is not applied if the patient does not have sclerodactyly (ever) but has fibrotic skin involvement elsewhere, thus excluding application of the criteria to eosinophilic fasciitis and morphea. The SSc mimickers were collected both prospectively using cases and controls at sites and retrospectively from databases[2,3,7], but the validation for the final 2013 criteria was from the prospective cases and controls including patients in whom the criteria would not be applied, so common sense and clinical judgment are needed to use the criteria.

Expert opinion was also used to help reduce the items to be tested in the 2013 SSc classification criteria, and state-of-the-art methodology was used to have data-driven and eminence-determined item reduction[8,9]. The diagnoses within the controls were what would be expected to confuse a clinician whether a patient has SSc or not, so the operational characteristics should be similar in other external studies, and ongoing validation cohorts are needed. The 2013 criteria included only North American and European patients, so other cohorts may be different (those in Asia, Australia, Africa, etc.).

Sensitivity and specificity for the 2013 criteria were tested on patients who were serially collected (half had early SSc) in clinics with expertise in SSc. The definitions for items may be imprecise, such as puffy fingers and telangiectasia, in a scleroderma-like pattern (the latter is nearly circular reasoning).

It was thought by experts in the 2013 criteria (using Delphi and other exercises) that some patients with mixed connective tissue disease (MCTD) could be classified as having SSc (overlaps were allowed), and some patients with current undifferentiated connective tissue disease could meet several criteria for SSc (and perhaps be classified with SSc depending on manifestations). The problem of differentiating these 2 groups from SSc is acknowledged and was dealt with using the above framework. Whether MCTD is considered a separate entity is open for debate; however, patients with MCTD plus many features of SSc and a 2013 criteria score ≥ 9 points would be classified as having SSc and would presumably have prognoses (when adjusting for activity and severity of

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each SSc item) comparable to other similar patients who do not have the other features of MCTD, such as those with systemic lupus erythematosus or Sjögren features.

When trying to determine the real-world sensitivity and specificity of criteria, there are often missing data. That was the case in the Norwegian cohort[4] published in this issue of *The Journal*. This was also true when face validity was compared with some of the proposed SSc criteria items within SSc and potential mimicker databases[7]. It is noteworthy that the sensitivity and specificity of the criteria in the Norwegian cohort were nearly identical to performance characteristics in the cohort from which the criteria were originally derived[4]. Data on 2 common features in the 2013 criteria set were not available for study in the MCTD cohort, so specificity of the 2013 criteria in this MCTD patient group is likely underestimated; and other controls were not used, which could change the true sensitivity and specificity. Sensitivity and specificity of any criteria will also depend on the sample studied (i.e., only applied when there is a high index of suspicion of SSc and not applied when a better explanation for the signs and symptoms is present). Also the gold standard is physician diagnosis because there is no laboratory test to diagnose SSc. It is important to note that the Norwegian study compared different groups to determine sensitivity and specificity. Independent studies that assess how classification criteria function are important to highlight the strengths and limitations of published criteria.

Disease classification operates on a spectrum that may be a continuum with an arbitrary cutoff above which disease is classified; patients also may take time to meet criteria (undifferentiated connective tissue disease evolving into MCTD and meeting criteria for SSc). There were tradeoffs between sensitivity and specificity regarding the 9 points needed for SSc classification; some experts would classify patients with fewer criteria and occasionally would not classify patients with SSc despite having the required 9 or more points[2,3,9]. There were tradeoffs between a simple, useful classification scheme and a comprehensive one. Important SSc features were removed, such as scleroderma renal crisis and calcinosis because they were redundant or too rare. Both the 1980 and the 2013 SSc classification include SSc sine skin involvement (in the former, meeting 2 of 3 minor criteria) and by scoring items other than skin involvement in the current SSc classification[1,2,3]. The absolute criterion of skin involvement of the fingers and proximal to the metacarpophalangeal joint (MCP) was maintained (suggesting all fingers, bilaterally; and proximal MCP involvement was contiguous in the 2013 criteria).

Determining criteria for SSc subsets is an important next step because SSc subsets correlate with prognosis. The 2013 criteria deliberately avoided subsets because it was considered important to first classify a patient as SSc before assigning to a stratum to help predict behavior or prognosis. Schemata to consider: extent of skin involvement (anatomical location, maximum ever); antibodies; or organ involvement. Previous criteria for the lcSSc and diffuse cutaneous SSc (dcSSc) subsets are used in many clinics[10]. There are limitations to these criteria even though they correlate with some organ involvement and mortality because autoantibodies may also help predict prognosis and are not in the current 2 subsets. Also, a patient with early disease may be considered to have lcSSc, but skin can later evolve to dcSSc; likewise, as skin regresses, dcSSc can convert into lcSSc. Subtypes could also include disease overlap, sine skin involvement, and patients with very early disease. Phenotypes could be divided by genotypes, protein, or gene expression or other molecular differences, but these techniques are not ready for clinical use. The next task for SSc classification researchers will be to develop new subset criteria.

It is likely that in the future, the 2013 criteria will become outdated as medicine evolves and our understanding about the pathogenesis of SSc broadens and perhaps, even some day, the SSc that we understand today will have many diagnoses within it. However, currently the criteria aid in the classification of more patients that experts would otherwise label as having SSc, particularly the lcSSc subset, patients with mild disease, and early stages of disease.

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