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

JANET E. POPE

J Rheumatol 2015;42;11-13
http://www.jrheum.org/content/42/1/11

1. Sign up for TOCs and other alerts
   http://www.jrheum.org/alerts

2. Information on Subscriptions
   http://jrheum.com/faq

3. Information on permissions/orders of reprints
   http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
The 1980 preliminary criteria for scleroderma (systemic sclerosis; SSc) have worked well for decades. 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. In other cohorts, similar operational characteristics (sensitivity and specificity) have been reported. The 2013 SSc classification criteria may need some explanation and clarification. The footnote in Table 1 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. 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 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. 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 criteria can classify more patients that experts would label as having SSc. A patient with sclerodactyly, RP, positive ant centromere 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, ant centromere 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 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, 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. 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
considered important to first classify a patient as SSc before
assigning to a stratum to help predict behavior or prognosis.
Criteria deliberately avoided subsets because it was
because SSc subsets correlate with prognosis. The 2013
involvement in the current SSc classification 1,2,3. The
of 3 minor criteria) and by scoring items other than skin
needed for SSc classification; some experts would classify
between sensitivity and specificity regarding the 9 points
within SSc and potential mimicker databases7. It is
noteworthy that the sensitivity and specificity of the criteria
in the Norwegian cohort were nearly identical to per-
formance characteristics in the cohort from which the
criteria were originally derived4. 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 sensi-
tivity 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 classifi-
cation 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 points2,3,9. 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 classification1,2,3. 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 clinics10.
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.

JANET E. POPE, MD, MPH, FRCPC,
Professor of Medicine,
University of Western Ontario,
Schulich School of Medicine and Dentistry,
Department of Medicine, Division of Rheumatology,
St. Joseph’s Health Care,
London, Ontario, Canada.

Address correspondence to Dr. Pope, St. Joseph’s Health Care,
268 Grosvenor St., London, Ontario N6A 4V2, Canada.
E-mail: janet.pope@sjhc.london.on.ca
Dr. Pope was the co-convenor of the American College of
Rheumatology/European League Against Rheumatism SSc classification
committee.

REFERENCES
1. Preliminary criteria for the classification of systemic sclerosis
2. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M,
Tyndall A, et al. 2013 classification criteria for systemic sclerosis:
an American College of Rheumatology/European league against
72:1747-55.
3. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M,
Tyndall A, et al. 2013 classification criteria for systemic sclerosis:
an American College of Rheumatology/European League Against
Rheumatism collaborative initiative. Arthritis Rheum
2013;65:2737-47.
Molberg O. Performance of the 2013 ACR/EULAR classification
criteria for systemic sclerosis (SSc) in large, well defined cohorts of
SSc and mixed connective tissue disease. J Rheumatol 2015;
42:60-3.
5. Alhajeri H, Hudson M, Fritzler M, Pope J, Canadian Scleroderma


J Rheumatol 2015;42:11–13; doi:10.3899/jrheum.141103