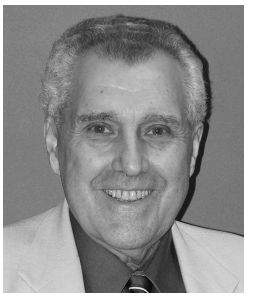
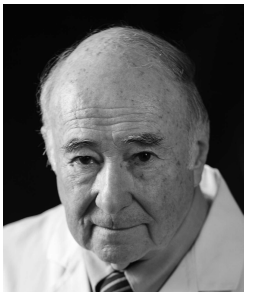
Editorial





Progress in the Evolution of Systemic Sclerosis Classification Criteria and Recommendation for Additional Comparative Specificity Studies

Sensitivity and specificity performance of the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for systemic sclerosis (SSc)[1,2] were assessed by Hoffmann-Vold, *et al* in this issue of *The Journal*[3]. Sensitivity was tested in 425 consecutive, representative patients with SSc seen at the Oslo University Hospital and compared to the original 1980 American Rheumatism Association (now ACR) preliminary criteria for definite SSc[4] and the subsequent 2001 criteria for early SSc proposed by LeRoy and Medsger[5]. Sensitivity (also called the true positive percent) is a binary classification measure of performance function, which indicates the proportion of all true cases in the study cohort who satisfy criteria. The 425 SSc cases analyzed in the Norwegian study satisfied either the 1980 ACR criteria for certain diagnosis or the 2001 LeRoy and Medsger criteria for early disease[3]. Specificity of the 2013 criteria was tested in a Norwegian nationwide cohort of 178 patients with mixed connective tissue disease (MCTD). Specificity (also called the true negative percent) indicates the proportion of the comparative or control subjects, like those having MCTD, who do not satisfy a criteria set.

SSc is a heterogeneous, multisystem, and multistage disorder marked by variable expression in its patterns of presentation and course of disease. Its pathogenesis is believed to differ from Raynaud disease and several of the other systemic connective tissue diseases (CTD), as do systemic lupus erythematosus (SLE) and idiopathic inflammatory myopathy (IIM). However, MCTD has frequent overlapping clinical features with SSc[6,7]. A vexing classification issue for SSc criteria development is how to deal with MCTD patients whose diagnosis depends heavily upon the presence of high titer antibody to U1RNP rather than a typical clinical profile[7]. Analytical complexity can arise in comparing case versus control patient subgroups defined by different criteria sets, i.e., SSc by mainly physician judgments and MCTD by anti-U1RNP antibody titer.

The 1980 criteria investigators[4] had analyzed patients with undifferentiated CTD (UCTD), many of whom had MCTD, as a potential comparison cohort, but decided to omit that subgroup. Distinguishing UCTD, and especially MCTD, from SSc seemed virtually impossible. The 2013 authors assigned both MCTD and UCTD to their control group of "scleroderma-like disorders"[1,2]. However, the proportions in the derivation and validation cohorts were relatively small, 9% and 10% for MCTD and 8% and 12% for UCTD, respectively[1,2]. A group of other scleroderma "mimicker" conditions were included in the derivation (18%) and validation (24%) samples[1,2]. One would infer that those conditions were excluded as scleroderma-like disorders when applying the criteria and deriving sensitivity and specificity performances (*footnote in Table 1[1,2]).

In the total 425 Norwegian SSc cases, the 2013 criteria were satisfied in 409 patients, yielding an overall sensitivity of 96%[3], confirming the 91% sensitivity derived in the ACR/EULAR criteria validation cohort[1,2]. The other aim of the Norwegian study, to assess specificity of the 2013 criteria against the MCTD cohort was, however, compromised. Data on 2 of the 8 items in the 2013 criteria were excluded from analysis — telangiectasias and abnormal nailfold capillaries[3]. Also, assessment of fingertip lesions was missing in 31 (18%) of the 178 MCTD patients[3]. Several publications on patients with MCTD[8,9,10] indicated high frequencies (46%–64%) of SSc capillary abnormalities and telangiectasias. The Norwegian patients with MCTD had very high proportions of Raynaud phenomenon (RP, 99%), and puffy fingers or sclerodactyly (82%). According to the 2013 criteria[1,2], most would have had 5 to 7 "points"[3] counting toward the 9-point requirement for classification as SSc[1,2]. Additionally, the Norwegian interstitial lung disease (ILD) item was more restrictive[3],

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requiring both radiographic evidence of pulmonary fibrosis and forced vital capacity < 70% predicted, while the 2013 criteria[1,2] required presence of only pulmonary fibrosis on chest radiography or "Velcro" crackles on auscultation not due to another cause[1,2]. If the missing items and comparable ILD definitions were to be included in deriving specificity of the 2013 criteria against MCTD patients[3], the false-positive rate would meaningfully increase. Thereby, specificity for that control condition would be diminished below the calculated 90%[3]. Additional critical studies of specificity performance of the published SSc criteria are indicated, including the influence of any exclusion criteria, if applied when analyzing scleroderma-like disorders[1,2].

It is accepted that limited cutaneous SSc (lcSSc) occurs more frequently than diffuse cutaneous SSc (dcSSc) in the general population. However, anatomical/topographic delineation boundaries of lcSSc versus dcSSc subsets may vary between clinical[11,12,13] and criteria studies[1,2,4,5]. A 1988 consensus proposal by LeRoy, *et al*[11] described lcSSc (then labeled lSSc) as "skin involvement limited to hands, face, feet, and forearms (acral), or absent." DcSSc (then labeled dSSc) was defined as "truncal and acral skin involvement"[11]. Of note, the 1988 article[11] did not categorize skin thickening of the upper arms or thighs, nor did it propose mutually exclusive topographical/anatomical definitions of lSSc versus dSSc. In 2001, LeRoy and Medsger proposed personal criteria for the classification of early and limited forms of SSc, which were not based upon a formal study[5]. Limited SSc without cutaneous involvement (lSSc) was then defined as RP plus abnormal nailfold capillaroscopy and/or SSc selective autoantibodies[5]. What is now labeled lcSSc was described as "cutaneous involvement distal (rather than limited) to the elbows, knees, and clavicles"[5]. DcSSc involvement needed to satisfy "criteria for lSSc plus proximal cutaneous changes"[5]. This brief proposal[5] was intended to outline constellations of criteria for diagnosis of SSc, introducing the noncutaneous form in conjunction with the distal (lcSSc) and proximal (dcSSc) extents of skin involvement. The limited SSc without skin involvement is sometimes referred to as either pre-SSc or sine scleroderma (ssSSc), depending upon the absence or presence of typical SSc organ involvement[3].

The 1980 ACR preliminary criteria established the term *proximal scleroderma* as typical sclerodermatous skin changes proximal to the metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints[4]. Sclerodactyly was defined as skin changes only distal to the MCP/MTP joints, i.e., limited to fingers and toes[4]. The Norwegian study illustrates the confusion that can arise from imprecise definitions, and therefore, varied use of these subgrouping terms. In correspondence with Hoffmann-Vold, the diffuse disease (dcSSc) cases (n = 97) in their report[3] included all accepted patients with skin thickening proximal to the MCP and MTP joints, i.e., proximal by 1980 criteria[4]. The complementary lcSSc subgroup (n = 294) excluded patients with proximal scleroderma by the 1980 criteria[4]. Two other SSc subgroups in that study[3] did not have cutaneous involvement, but satisfied criteria of LeRoy and Medsger[5]. The prescleroderma subset (n = 24) did not have typical internal organ manifestations, and the smallest subgroup (n = 10) was labeled as ssSSc, characterized as having 1 or more typical internal organ involvements[3].

Additional subtyping of cutaneous involvement has been proposed[12,13,14] as (1) sclerodactyly not extending beyond the MCP or MTP joints; (2) more proximal involvement, but distal to elbows/knees, considered as "intermediate"; and (3) cutaneous changes proximal to elbows/knees. The most widely accepted clinical definition for dcSSc is skin thickening proximal to the elbows or knees at any time during the disease course. In the future, we recommend that the SSc research community achieve consensus on the precise clinical definitions of anatomical delineations for cutaneous involvement in SSc to satisfy the purposes of both clinical studies and criteria development.

By definition, the 425 patients selected in the Norwegian study fulfilled either the 1980 ACR classification criteria for SSc[4] and/or the LeRoy and Medsger modified criteria for the classification of early SSc[5]. Accordingly, sensitivity was 100% for the LeRoy and Medsger criteria in the 3 non-dcSSc subgroups[3]. The 2013 criteria also performed excellently in the lcSSc subset, being satisfied in 292 of the 294 patients (99%) with lcSSc[3]. In the 24 pre-SSc patients, sensitivity was 75%, and in the 10 with ssSSc, it was 20%. In a preceding study of ssSSc[15], no difference was recognized from lcSSc. Combining the lcSSc, ssSSc, and prescleroderma patients in the Hoffmann-Vold study[3], the 2013 criteria were satisfied in 312 of 328 cases, or a sensitivity of 95%.

Sensitivity of the new 2013 criteria was recently reported in an independent Canadian Scleroderma Research Group cohort of 724 SSc subjects who were diagnosed according to an experienced rheumatologist[16]. Sensitivity of the 2013 criteria was 98.3% versus 88.3% for the 1980 criteria. Among patients who did not have skin involvement proximal to the MCP joints, the differential (97% vs 60%) was greater[16], which are patients with earlier disease known to have been missed by the 1980 criteria[5,17]. The LeRoy and Medsger criteria[5] were developed to classify early SSc. The 2013 criteria have effectively combined and integrated the major criterion of proximal SSc from the 1980 set as a fully sufficient qualification (9 points), all of the 3 minor criteria from the 1980 set (sclerodactyly, digital pitting scars, and bilateral pulmonary fibrosis), plus the subsequent items from the LeRoy and Medsger criteria (RP, SSc-type nailfold capillary pattern, and SSc selective antibodies). The 2013 criteria further incorporated pulmonary arterial hypertension in the absence of ILD (2 points) and telangiectasia (2 points). Thus, evolution of SSc criteria has been complementary, with improvements in sensitivity to recognize patients with early, limited, or mild disease within the full scope of SSc. However, further research is needed on speci-

ficity of the available criteria against scleroderma-like conditions[1,2,4,5].

By way of historical background, the 1980 criteria effort was completed before the 1988 editorial of LeRoy and colleagues[11], which distinguished features of limited versus diffuse disease. However, the lc versus dc clinical distinction was widely recognized long before 1988 by the 1980 criteria investigators[4]. As contributors to, and being very familiar with, the 1980 criteria study data, we estimate that about half of the 264 patients with definite SSc submitted from 29 US medical centers had dcSSc, for an lc:dc ratio of about 1. In the Norwegian study[3], the 294 patients with SSc labeled as lc had a frequency 3 times greater than the 97 cases reported as dc, but actually proximal, by the 1980 criteria[4]. The lc and dc distribution was not reported in the 2013 criteria study[1,2]. The 1980 criteria were proposed as preliminary for certain or definite disease[4]. The sensitivity (97%) and specificity (98%) performances were excellent in the more advanced SSc case subset (n = 264) compared to SLE (n = 172), IIM (n = 120), and RP (n = 121) patients. However, it was soon appreciated[17] and later confirmed[18] that about 20% of patients with lcSSc did not satisfy the 1980 criteria set. One of the aims of the multinational committee that developed the 2013 criteria[1,2] was to improve sensitivity and "to encompass a broader spectrum of SSc."

The 2013 criteria[1,2] represent a welcome combination and integration of the preceding 1980 ACR criteria for definite disease[4] and the LeRoy and Medsger criteria for early SSc[5], yielding an overall 96% sensitivity in the 425 patients[3]. Hence, progress has clearly been achieved in the development of classification criteria for SSc over the past 35 years, particularly recognition of nailfold capillary abnormalities in limited disease[18] and SSc-associated serum autoantibodies[1,2]. New insights into the key vasculopathy, immune activation, and fibrosis pathophysiologic abnormalities in SSc and its subtypes will likely inform future classification efforts. Further specificity studies of the published criteria sets[1,2,4,5] also promise to improve predictive ability of the respective items.

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