

Systemic sclerosis: To subset or not to subset, that is the question

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Abstract

Systemic sclerosis (SSc) is a heterogeneous disease with variability in autoantibody profiles, skin and internal organ involvement, disease trajectory, and survival. The ability to identify more homogeneous subsets of SSc patients has informed patient care and been an essential aspect of SSc research. In this article, the historic evolution of subsetting systems in SSc are described including clinically based SSc subsetting systems, their utility, strengths, and limitations. There is a shifting paradigm of SSc subsets, including biologic classification of SSc subsets and fully data-driven approaches to SSc subset classification, taking into consideration the needs of the SSc global community in the modern era and the ability to prognosticate patients with SSc.

Keywords: Scleroderma, systemic sclerosis, subsets, validation, prognosis

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Introduction

The heterogeneity of systemic sclerosis (SSc) disease manifestations (including symptoms, signs, radiographic findings and serology) impacts disease trajectory, quality of life, disability and prognosis. Efforts have been undertaken to identify more homogeneous subsets of SSc patients. The ability to identify subsets of SSc impacts both clinical care and the ability to perform valid and reproducible research. In this article, the historic evolution of subsetting systems in SSc are described including clinically based SSc subsetting systems, their utility, strengths, and limitations.

Clinical and research consequences

Clinically based systemic sclerosis subsets

The need for systemic sclerosis (SSc) subset criteria has long been recognized. Over the last few decades, over a dozen SSc subsetting systems ranging from two to six subsets have been proposed (Table 1) (1-14). Often various subsets of SSc were used for local purposes and primarily based on the extent of skin involvement. Goetz et al. (5) used two-subset criteria to classify a case series of patients in South Africa. They were among the first to identify gastrointestinal manifestations. Winterbauer (14) described SSc patients with CRST (calcinosis, Raynaud's phenomenon [RP], sclerodactyly, telangiectasia) as a benign subset of SSc. Investigators later added esophageal dysmotility, the "E" of CREST syndrome. This description was intended for clinical practice and is easy to use. However, most patients with SSc have CREST features. Tuffanelli et al. (13) classified patients as acrosclerosis and diffuse on the basis of extent of skin involvement and presence of RP.

The most frequently used SSc subset criteria were proposed by LeRoy et al. (7) in 1988, with over 1000 citations. The criteria of LeRoy et al. (7) were used to identify homogeneous groups of subjects for research, improve the nomenclature of SSc, and identify patients at risk of internal organ involvement. Subsetting SSc patients into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) were developed by an expert panel. These criteria have face validity and the prognosis in the two groups is different (more skin involvement in the dcSSc subset is related to a higher chance of organ involvement such as pulmonary fibrosis and worse outcomes including increased mortality) (15). The convergent and divergent validity of the criteria have been demonstrated in several studies. dcSSc is associated with tendon friction rubs, anti-nucleolar antibody, anti-topoisomerase I, renal crisis, cardiac involvement, interstitial lung disease (ILD), and poor prognosis. lcSSc is associated with anti-centromere antibody and less organ involvement (16). Both subsets have Raynaud's, digital ulcers, gastrointestinal involvement, telangiectasia, and calcinosis. Hu-

man leukocyte antigen DR1 occurs more commonly in patients with lcSSc (17). The criteria perform better at SSc expert centers and have been successfully applied in tertiary-care settings around the world (18). The criteria have good predictive validity for survival (3, 4, 16, 19), but poorly predict the development of restrictive lung disease (20, 21).

In recent years, subsetting with respect to demographic features (such as age, sex, and ethnicity) or overlap with another systemic autoimmune rheumatic disease has been considered (Table 2) (22-26). Improved understanding of the etiology, disease manifestations, disease trajectory, and prognosis among these subsets has pragmatic clinical implications. This has facilitated the practice of personalized medicine with specific baseline investigations, monitoring, and therapy of these subsets.

Age of onset can distinguish juvenile onset, usual age of onset, and geriatric onset SSc. Geriatric onset SSc is more frequently associated with malignancy, justifying cancer screening at the time of SSc diagnosis in the elderly (27). Compared with SSc patients diagnosed before the age of 30 years, geriatric onset SSc patients have a lower frequency of digital ulcers (54% vs 34%, $p < 0.001$) but a higher frequency of cardiac conduction system abnormalities (9% vs 21%, $p = 0.004$).

Main Points

- Over the last few decades, over a dozen SSc subsetting systems ranging from two to six subsets have been proposed.
- Subsetting with respect to demographic features (e.g. age, sex, ethnicity) or overlap with another systemic autoimmune rheumatic disease has also been considered.
- Metabolomics, proteomics, genomics, transcriptomics, and epigenomics are novel approaches that may improve our understanding of the biologic complexities that arise in SSc
- The ability to subset SSc into more homogeneous groups of patients with comparable etio-pathogenesis, molecular pathways, disease manifestations, disease trajectory, and response to therapy and/or prognosis will undoubtedly guide appropriate management and resource utilization.
- A valid and reliable SSc subset system should aid in cohort enrichment for patients most likely to derive a therapeutic benefit from novel therapeutic agents.

Male sex is also associated with increased risk of mortality (hazard ratio (HR) 1.16, $p = 0.003$) in patients with SSc above that observed for males in the general population (23). Males with SSc more frequently have diffuse SSc (45% vs 30%, relative risk [RR] 1.44, 95% CI 1.18-1.75) and ILD (ILD; 41% vs 33%, RR 1.24, 95% CI 1.01-1.52) (23). Males have an increased unadjusted (HR 1.57, 95% CI 1.19-2.06) and adjusted (HR 1.40, 95% CI 1.06-1.85) mortality (23), a shorter time from SSc diagnosis to pulmonary arterial hypertension (PAH) diagnosis (mean \pm standard deviation 1.7 ± 14 versus 5.5 ± 14.2 years), and an increased frequency of renal crisis (19% vs 8%, RR 2.33, 95% CI 1.22-4.46) (24). Among SSc-PAH patients, men appear to have decreased 1-, 2-, 3-, and 5-year survival (83.2%, 68.7%, 53.2%, 45.6%) compared with females (85.7%, 75.7%, 66.4%, 57.4%) (24).

Compared with white SSc patients, East Asians less frequently have calcinosis (29% vs 9%, $p = 0.002$) and esophageal hypomotility (88% vs 69%, $p = 0.002$) (25). Black SSc patients more frequently have ILD (31% vs 53%, $p = 0.007$), and North American Indigenous patients more frequently have diffuse disease (35% vs 56%, $p = 0.02$) (25).

SSc patients with another overlapping systemic autoimmune rheumatic disease express differences in disease manifestations, forming another clinically relevant subset (26, 28, 29). For example, SSc-systemic lupus erythematosus (SLE) patients are younger at diagnosis (37.9 years vs 47.9 years, $p < 0.001$), more frequently East Asian (5.5% vs 20%) or South Asian (5.1% vs 12%), have lupus anticoagulant (6% vs 0.3%, $p < 0.001$), anticardiolipin antibody (6% vs 0.9%, $p < 0.001$), and elevated pulmonary artery pressures (52% vs 31%, $p < 0.001$) (26). SSc-SLE patients less frequently have calcinosis (13% vs 27%, $p = 0.007$), telangiectasia (49% vs 75%, $p < 0.001$), and dcSSc subset (12% vs 35%, $p < 0.001$) (26).

Importantly, attention has been paid to the subset of SSc patients with very early disease (Table 1). The Very Early Diagnosis of Systemic Sclerosis (VEDOSS) criteria identify this subset of patients based on the presence of RP, puffy fingers, antinuclear antibodies, AND capillaroscopy OR SSc-specific antibodies (1). They may have SSc or have not yet developed SSc. They have recent onset of symptoms (other than RP which may be present for longer than other symptoms). VEDOSS patients may be a subset of SSc with fewer symptoms, which may warrant early detection, early intervention, and recruitment into prevention trials and may be prognostic depending on what features are present very early in the disease (30).

The neglected subset

The ability to subset SSc patients into limited and diffuse subsets has allowed a sustained program of research directed at the immuno-fibrotic manifestations of the dcSSc subset. This was done with the rationale that the diffuse subset of patients has more severe disease, have the most disease activity in the early phase, the intervention may be most effective in this subset of patients, and they have the most to gain (31). However, this has occurred at the expense of trials within the limited subset (32), as lcSSc is the more prevalent subset, comprising up to two thirds of most SSc registries (32). Furthermore, this subset carries as significant burden of disability and diminished quality of life (32, 33). Yet, they are routinely excluded from SSc clinical trials of novel therapeutic agents. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for SSc increase representation of this subset (32, 34). Without ignoring the diffuse subset, increased recruitment of the patients with the lcSSc subset into clinical trials may allow more emphasis on vasculopathic manifestations and the concept of remission (31).

What about novel SSc subset classifications in the near future?

Currently, an international collaborative effort is underway to develop new SSc subset criteria (35). In Phase 1, a cross-sectional study of international SSc experts from 13 countries was conducted to evaluate the purpose of SSc subsets in the modern era, assess the strengths and limitations of existing SSc subset criteria, and identify ideas among experts about subsets (21). The purpose of SSc subset criteria in the modern era fell into three themes. First, experts felt the subset system should inform research and communication. Subset criteria could be used during study sample selection to reduce heterogeneity of SSc patients within a trial. The use of SSc subset criteria could be used as a cohort enrichment strategy to identify those most likely to achieve the greatest magnitude of treatment benefit (21, 31). SSc subset criteria could be used to communicate with and educate other health care professionals. Second, SSc subset criteria may inform management. They could guide choice of baseline investigations, aggressiveness of monitoring over time, choice of therapy and response to therapy (21). Third, SSc subset criteria should inform prognosis, specifically with regards to internal organ involvement and survival (21).

Over 90% of global SSc experts use systems of subsetting SSc patients in their practice (21). Yet, the optimal number of subsets is another

Table 1. Comparison of systemic sclerosis subset systems.*

Authors	Classification scheme
Avouac et al. (1)	VEDOSS: RP, puffy fingers, antinuclear antibodies, AND capillaroscopy OR SSc-specific antibodies
Barnett et al. (2)	Three subsets: "limited," "moderate," and "extensive," based on skin involvement of the fingers only, limbs and face, and involvement of the trunk, respectively
Ferri et al. (3)	Four subsets: "sine scleroderma SSc" absence of cutaneous involvement with visceral involvement, nailfold capillary changes, and autoantibodies; "limited cutaneous" skin involvement of fingers with or without involvement of neck, face, and axillae; "intermediate cutaneous" skin involvement of upper and lower limbs, neck and face without truncal involvement, "diffuse cutaneous" distal, and truncal skin involvement
Giordano et al. (4)	Six subsets: I sclerodactyly only; II sclerodactyly & skin involvement of neck, lower eyelid or axillae; III skin involvement of hands and forearms±legs±face; IV group III and arm and/or thigh skin involvement; V group III and thorax; IV group and/or 4 and/or 5 plus abdomen Three subsets: "limited" skin involvement of fingers, face, neck, axillae; "intermediate" skin involvement proximal to fingers; "diffuse" truncal skin involvement
Goetz et al. (5)	Two subsets: "acrosclerosis" and "diffuse," based on skin thickening limited to extremities or includes trunk
Holzmann et al. (6)	Five subsets (Types I-IV) based on presence/absence of RP, sclerosis, extra-cutaneous manifestations, ANA
LeRoy et al. (7)	Two subsets: "diffuse cutaneous SSc" onset of RP within 1 year; truncal and acral skin involvement; tendon friction rubs; early incidence of ILD, renal failure, diffuse gastrointestinal disease, myocardial involvement; absence of anti-centromere antibodies, abnormal NC; lcSSc RP for years, skin involvement limited to hands, face, feet, and forearms or absent; late incidence of PAH, trigeminal neuralgia, calcinosis, telangiectasia; high incidence of anti-centromere antibodies, abnormal NC
LeRoy et al. (8)	Four subsets: LSSc consists of (1) objective RP plus any one of NC changes or SSc selective autoantibodies OR (2) subjective RP plus both NC changes and SSc selective autoantibodies; lcSSc criteria for LSSc plus distal cutaneous changes; dcSSc criteria for lcSSc plus proximal cutaneous changes; "diffuse fasciitis with eosinophilia" proximal cutaneous changes without criteria for LSSc or lcSSc
Maricq et al. (9)	Six subsets: diffuse, intermediate, digital, scleroderma sine scleroderma, undifferentiated connective tissue disease with scleroderma, CREST syndrome
Masi et al. (10)	Three subsets: digital skin involvement of fingers or toes but not proximal extremity or trunk; proximal extremity proximal extremities or face but not trunk; truncal thorax or abdomen
Rodnan et al. (11)	Three subsets: classical disease involving skin of the trunk, face & proximal extremities, and early involvement of esophagus, intestine, heart, lung and kidney; CREST syndrome; and overlap syndromes including sclerodermatomyositis and MCTD
Scussel-Lonzetti et al. (12)	Four subsets: "normal skin," "limited" skin involvement restricted to fingers, with RP, calcinosis, esophageal involvement and telangiectasia; "intermediate" skin involvement of arms proximal to metacarpal phalangeal joints but not trunk; "diffuse" skin involvement of the trunk
Tuffanelli et al. (13)	Two subsets: "acrosclerosis" RP, acral skin involvement, "diffuse SSc" no RP, skin involvement beginning centrally
Winterbauer (14)	CRST syndrome

*Adapted from Johnson et al. (15).

VEDOSS: very early diagnosis of systemic sclerosis; SSc: systemic sclerosis; RP: Raynaud's phenomenon; ANA: anti-nucleolar antibody; ILD: interstitial lung disease; lcSSc: limited cutaneous systemic sclerosis; PAH: pulmonary arterial hypertension; LSSc: limited SSc; dcSSc: diffuse cutaneous SSc; MCTD: mixed connective tissue disease; CRST: calcinosis, Raynaud's phenomenon [RP], sclerodactyly, telangiectasia.

er important consideration. The majority of experts believe there are more than two subsets (21). Previous iterations of criteria have proposed up to six subsets; however, some experts believe there are as many as 10 subsets (21). A two-subset system has been shown to have very good predictive validity for determining future outcomes in SSc (15).

Biologic classification of SSc

Metabolomics, proteomics, genomics, transcriptomics, and epigenomics are novel approaches that may improve our understanding of the bio-

logic complexities that arise in SSc (36). This provides an opportunity to link high-dimensional data derived from diseased tissue with clinical observations and patient-reported symptoms (36). For example, based on skin gene expression, an "intrinsic" SSc subset system was proposed, categorizing subsets as inflammatory, fibroproliferative, limited, and normal-like (28, 37). Each subset was characterized by deregulated molecular pathways and specific cell types. SSc patients with the inflammatory intrinsic subtype may respond preferentially to immune suppressive agents such as mycophe-

nolate, cyclophosphamide, methotrexate, and biologics that are anti-inflammatory, whereas SSc patients with the fibroproliferative subtype may preferentially respond to antifibrotic medications (such as tyrosine kinase inhibitors) (36, 37). There have been calls for a new molecular taxonomy of rheumatic disease for the discovery of biomarkers to aid in patient classification, stratification, therapeutic decision-making, and prognosis (38).

SSc experts have advocated for the inclusion of novel biomarkers in disease classification (39).

Table 2. Categories of SSc subsets.

Distinguishing feature	Categories
Age of onset	Juvenile onset, usual age of onset, geriatric onset
Autoantibodies, antinuclear antibody pattern	Centromere, topoisomerase I, RNA polymerase III, U1RNP, nucleolar pattern
Ethnicity	Black, Caucasian, East Asian, South Asian, Arab, First Nation
Extent of skin involvement	Limited, diffuse, intermediate, scleroderma sine scleroderma
Skin molecular profile	Inflammatory, fibroproliferative, normal-like
Phenotypic predominance	Vasculopathic, fibrotic, inflammatory
Presence of other systemic autoimmune rheumatic diseases	Overlap: Sjogren’s syndrome, systemic lupus erythematosus, rheumatoid arthritis
Rate of progression	Rapidly progressive, slowly progressive
Sex	Male, female
Stage of disease	Pre-SSc, undifferentiated, very early, early, established, late

SSc: systemic sclerosis.

In the item generation phase of the ACR/EULAR classification criteria for systemic sclerosis, novel markers such as anti-Ku antibodies and anti-Mi antibodies were proposed (40). Similarly, in the item generation phase of the EULAR/ACR classification criteria for SLE, type I interferon signature, plasma cell expansion, high circulating levels of TNF, IP10, and MCP1, high Th17 markers, and elevated serum BLYS were nominated as novel laboratory parameters (41). In both cases, novel biologic candidate criteria were not retained in the final classification criteria system because of concerns about feasibility and access (42, 43). Once issues of feasibility and access are addressed, clinical classifications systems might be complemented by biomarkers that stratify SSc into subgroups that are therapeutically relevant (38).

Data-driven SSc subset identification

Data-driven approaches for the identification of SSc subsets are also being considered (35, 44). Concerns have been raised that subsets based on clinically observed phenomenon may be biased, and that advanced statistical techniques may reveal novel subsetting systems that are data-driven. Using unsupervised cluster analysis in a combined cohort of the Canadian Scleroderma Research Group and the Australian Scleroderma Interest Group, three data-driven subsets were identified (44). Among patients with less than two years disease duration, subset 1 was characterized by a high proportion of digital ulcers (72%), pitting scars (85%), and anti-topoisomerase 1 antibodies (38%). Subset 2 had a majority of dcSSc (90%), with tendon friction rubs (36%) and anti-RNA polymerase 3 antibodies (100%). This subset had more severe skin involvement than the other subsets (mean modified Rodnan skin score (mRSS) 24.7 (standard deviation=9.8).

Subset 3 consisted of the limited cutaneous disease or scleroderma sine scleroderma (76%), were mostly female (90%), infrequently had digital ulcers (5%) or pitting scars (9%), and more anti-centromere antibodies (54%) (44).

A second unsupervised cluster analysis was conducted using the EULAR Scleroderma Trials and Research (EUSTAR) cohort of 6,927 patients who fulfilled the 1980 ACR classification criteria for SSc. The investigators identified two subsets. One comprised a majority with lcSSc (81%) and within the subset, half (54%) were positive for anti-centromere antibodies. Subset B had more dcSSc (61%) and half (54%) had anti-topoisomerase 1 antibodies. The investigators considered this a validation of the 1988 limited/diffuse subset system of LeRoy et al. (7), but subset B had both dcSSc and lcSSc patients. A further exploratory cluster analysis identified six subsets. Cluster 1 was composed of 89% lcSSc female patients, with an older age of onset, increased proportion of gastrointestinal involvement, low frequency of ILD and high frequency (79%) of anti-centromere antibodies. Cluster 2 had more lcSSc patients (71%), an increased frequency of suspected pulmonary hypertension on echocardiogram (39%), and ILD (85%). Cluster 3 was composed of lcSSc in 79% with a low frequency of gastrointestinal involvement and ILD. Cluster 4 had more limited cutaneous patients (63%) with high frequencies of cardiac, pulmonary, muscular, articular, digital ulcer, and gastrointestinal involvement. Cluster 5 had more diffuse cutaneous patients (72%) with gastrointestinal, articular, cardiac disease, and moderate lung involvement. Cluster 6 patients were characterized by a high frequency of dcSSc, male sex (22%), highest peak of mRSS (mean 27.2), and high frequencies of gastrointestinal, artic-

ular, muscular, renal, pulmonary, and cardiac disease and frequently were anti-topoisomerase 1 positive (77%). They found comparable predictive validity for mortality in the limited/diffuse cutaneous subset system (HR 2.03 [95% CI 1.61-2.56]), and subset A/B subset system (HR 2.47 [1.86-3.27]). Comparing mortality between cluster 1 and cluster 6, an increased risk of death (HR 6.14 (3.81-9.89)) was found for cluster 6.

Critique of existing subclassification of SSc

To date, the data-driven subset systems have limitations. They may be challenging to apply to the individual patient in the clinic (44). When compared with subsetting by extent of skin involvement or autoantibodies, LeClair et al. (44) found different subsetting methods predicted different outcomes. The more complex clustering approach failed to demonstrate superior predictive ability over existing approaches. None of the data-driven subsetting approaches have been externally or independently validated (45). Despite the availability of sophisticated statistical methods to support data-driven methods for stratification, clustering, and integration of multi-layered data, these approaches should be used with care, so that the literature does not contain studies that are not validated and yield variations of current subsetting without further refinement of prognosis or large overlap of clusters (38).

Considerations for future SSc subset criteria

The next generation of classification criteria will need to consider some unresolved issues. First, over the time period of a longitudinal study, some patients may change subsets (the “transitional” form) (46). Clinically, SSc presents as a spectrum with some patients expressing a few, mild symptoms, while others may have

severe, lethal complications. From a molecular perspective, some patients transition from inflammatory features to a more fibroproliferative phenotype (28). Genetic and serologic variables may influence progression of disease (47). The prevalence of this shift and implications for classification criteria should be considered (15). A solution could be to test incident patients who are followed over time and also validate the subsets in a large independent cross-sectional group of SSc patients.

Second, dependence on “extent of skin involvement” as the main criterion is being challenged. Data from the EUSTAR group suggest that autoantibody status is more closely associated with clinical manifestations than subset of disease (29). However, the presence of anti-topoisomerase 1 or anti-centromere antibody is not exclusively associated with particular disease manifestations. Thus, research is needed to ascertain if autoantibody profiling confers incremental predictive validity over the subset criteria of LeRoy (or others). For instance, a framework that divides patients into the extent of skin involvement and presence or absence of SSc-specific antibodies may or may not have added value beyond the lcSSc and dcSSc subsets. Alternatively, research is necessary to identify a combination of clinical and laboratory definitions for SSc subset classification criteria that confer improved validity and reliability (21).

The 1988 criteria of LeRoy et al. (15) are conceptually straight forward, are easy to implement, are widely used, and have stood the test of time. Future SSc subsets systems should be comparatively evaluated and demonstrate added value. Furthermore, the tradeoff between feasibility and content validity affects the incremental value of one classification subset over another. The feasibility of current subset criteria is limited to clinicians competent in SSc skin examination. The addition of capillaroscopy, antibodies, and vascular testing as criteria further limits the feasibility of the criteria in general rheumatology practice, but this is not necessarily a hindrance to apply in specialized clinics. Reliability is an essential quality of classification criteria as it represents the degree of consistency with repeated use. Inadequate reliability may result in misclassification of patients within and between studies, thereby threatening both the internal and external validity of the study results. The strength of a criterion set is threatened by a weak criterion. For example, poor inter- or intra-rater reliability in skin assessment or capillaroscopy may result in misclassification of subsets. Similarly, poor within- or between-laboratory testing of

molecular biomarkers may lead to misclassification of subsets. Molecular-based SSc subset classification systems will also need to take this into consideration. Standardized protocols for recruitment, sample taking, sample transport, and assays analysis will need to be developed to ensure results that are valid and reproducible (38).

Conclusion

To subset or not to subset, there is no question. The ability to subset SSc into more homogeneous groups of patients with comparable etio-pathogenesis, molecular pathways, disease manifestations, disease trajectory, and response to therapy and/or prognosis will undoubtedly guide appropriate management and resource utilization. A valid and reliable SSc subset system should aid in cohort enrichment for patients most likely to derive a therapeutic benefit from novel therapeutic agents. What remains to be seen is the ability to develop a subset system that is superior to the limited/dcSSc system. The next era of SSc criteria development will likely take into account advances in our understanding of the biology of the disease, its phenotypic expression, and the needs of the SSc global community.

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