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# More than Skin Deep: Bringing Precision Medicine to Systemic Sclerosis

**Christopher A. Mecoli, MD MHS**, **Ami A. Shah, MD MHS**

The Johns Hopkins University School of Medicine, Baltimore MD USA

Historically, patients with systemic sclerosis (SSc) have been classified by the extent of their skin involvement – diffuse cutaneous SSc, characterized by skin involvement of the torso and proximal limbs, and limited cutaneous SSc, with involved skin predominantly distal to the elbows and knees. Subgrouping based on cutaneous type is grounded in literature demonstrating differences in organ involvement and mortality [1]. However, this binary classification system does not capture the marked clinical heterogeneity known to exist within these two subgroups. Attempting to risk-stratify a given SSc patient's clinical trajectory, organ-specific complications, and response to medications based solely on cutaneous type is an imperfect approach in the modern era.

Over the past few decades, the value of SSc-specific and associated autoantibodies has been increasingly realized [2-3]. As more clinical-serologic associations have been discovered and validated, our ability to phenotype SSc patients has dramatically improved. This increased awareness, in conjunction with improved laboratory capabilities in autoantibody testing, has allowed for the majority of SSc cohorts around the world to have comprehensive and detailed serotyping. However, even within a given autoantibody subtype, there is often heterogeneity in clinical presentation and course - the power of combining both serology and skin subtype to predict outcomes has been illustrated by Cottrell et al, who demonstrated that within a given SSc-specific autoantibody group (e.g. Scl-70), different clinical trajectories exist based on cutaneous subtype [4].

In addition to utilizing cutaneous type and autoantibodies to help clinically phenotype SSc patients, a third component – time – is perhaps most critical of all. Epidemiologic issues relating to time are integral to characterizing SSc cohorts given the known fact that organ-specific complications do not occur evenly throughout the life of SSc patients [5]. These include minimizing immortal person-time (e.g. time during which the relevant outcome under study could not have been observed), accounting for SSc disease duration, and assessing the timing of events relative to one another. This concept has been eloquently shown by Herrick et al upon developing a model to predict progression of skin disease in SSc; whereas the baseline modified Rodnan skin score (MRSS) alone was a poor predictor, the model improved upon the addition of disease duration, and furthermore with

Corresponding Author: Ami A Shah, Associate Professor of Medicine, Deputy Director, Rheumatology Precision Medicine Centers of Excellence - Clinical Program, Director of Clinical and Translational Research, Johns Hopkins Scleroderma Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, Phone: 410-550-7715, Fax: 410-550-1363, Ami.Shah@jhmi.edu.

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incorporation of RNA polymerase III antibody status [6]. Similarly, the power of utilizing cutaneous subtype, autoantibody status and timing as filters through which to study the cancer-scleroderma relationship has illustrated the value of these tools to risk-stratify SSc patients for malignancy [7].

It is in this landscape that the work by Nihtyanova et al in this issue of *Arthritis and Rheumatology* bolsters the argument for incorporating cutaneous type, serology, and disease duration to subgroup SSc populations. Their study includes over 1300 SSc patients seen at the University College of London and stratifies them into one of 14 subgroups defined *a priori* based on different combinations of cutaneous skin type (limited or diffuse) and autoantibody status: anti-centromere (ACA), anti-topoisomerase (Scl70 or ATA), anti-RNA polymerase 3 (ARA), anti-U3RNP, anti-PmScl, anti-nuclear antibody (ANA) positive but extractable nuclear antigen (ENA) negative, and “other” including anti-U1RNP, Th/To, SL, Ku, Jo1, Ro, La, XR, PL7, hnRNP, Sm and ANA negative). For each of the 14 combinations, they performed time-to-event analyses of organ-specific complications and survival at 5, 10, 15, and 20 year follow-up. Upon collapsing similar strata, they discovered 7 distinct SSc subgroups: ACA+ limited cutaneous, Scl70+ limited cutaneous, Scl70+ diffuse cutaneous, ARA+, U3RNP+, limited with “other” antibodies, and diffuse with “other” antibodies. Based on these clinical subgroupings, the authors report markedly different incidence rates of scleroderma renal crisis (SRC), scleroderma heart disease, pulmonary hypertension (PH), clinically significant pulmonary fibrosis (csPF), and overall mortality.

The strengths of the study are the inclusion of a large number of autoantibodies tested in a systematic manner, prospective follow-up of long duration, standardized clinical outcome measures, and rigorous analytic methods. Their study demonstrates the added value of incorporating antibodies to clinically phenotype SSc patients above and beyond cutaneous subtype. This is particularly apparent when comparing organ-specific outcomes and mortality between Scl70+ limited disease versus Scl70+ diffuse; whereas diffuse and limited Scl70+ patients had similar rates of csPF, the incidence of other organ-specific complications was increased >2-fold in the diffuse group, including mortality. With respect to organ-specific complications, this study highlights the clinical importance of the U3RNP+ subgroup, particularly its high risk of pulmonary hypertension (both Group 1 (PAH) and Group 3 (associated with ILD)) - one in three U3RNP+ patients developed PH over 15 years. Interestingly, patients with Scl70 or PM-Scl antibodies had the lowest hazard of PH development, even when accounting for PH secondary to ILD, and those with ACA had only average risk. In addition, ARA+ and ANA+ENA− patients have the highest initial skin scores, but also experience the most improvement – a factor that may be important to consider in the design of clinical trials focused on active diffuse cutaneous disease.

The proposed classification system has clear benefits in clinical practice, such as improved prognostication as well as informing disease monitoring strategies (e.g. frequency of hypertension screening for SRC, EKG for arrhythmia, or pulmonary function testing/ echocardiogram for csPF and cardiac scleroderma, respectively). For example, the knowledge that a patient with ACA+ limited disease has a 20-year incidence of csPF <10% might inform the treating provider that obtaining frequent PFTs may be unnecessary. In addition to direct impact on the clinical care of SSc patients, this classification framework

would allow for better comparisons across different SSc cohorts, as the frequency of different autoantibody subsets varies internationally [8]. The failure of validating research findings in different cohorts may in part be due to this geographic heterogeneity. For example, a cohort with a low prevalence (<10%) of ARA-positive SSc patients may not validate findings with regards to malignancy or SRC found in a different cohort where the ARA-positive prevalence is >20%. Lastly, these findings may inform optimal clinical trial study design in SSc. The differential severity and clinical course observed suggests that enrichment of high-risk subgroups – those who are most likely to progress - should be considered in trials focused on different organ-specific complications.

Moving forward, these results need to be validated in other SSc cohorts, including those with different racial and ethnic compositions. It remains to be seen whether race and ethnicity will impact this type of subgrouping, given certain racial groups such as African Americans are known to have more severe disease [9-10]. There also exist several unanswered questions regarding using this approach to classify SSc patients. For one, many patients were positive for >1 autoantibody (most notably anti-Ro antibodies); what impact this has on clinical trajectory and mortality warrants further study. We also need to better understand the influence that different treatment strategies have on these subgroups; for example, whether treatment of diffuse cutaneous disease impacted incidence rates of csPF. Lastly, the incorporation of other outcome measures, including SSc-specific patient reported outcomes, needs to be implemented and standardized, particularly given the current shortcomings of outcome measures pertaining to digital ischemia, calcinosis, and gastrointestinal symptoms.

These data illustrate that multiple measurements in combination, such as cutaneous subtype, autoantibody status and timing, improve predictive capability compared to a single measurement alone. The approach to incorporate and harmonize multiple clinical and biologic characteristics to subgroup SSc patients is the foundation of precision medicine. In the near future, dynamic genetic, plasma, serum, and/or cellular biomarkers will likely prove even more valuable for classification and provide insight into disease mechanism; the SSc community should anticipate this accordingly by storing biospecimens conducive to analysis. In an era of an increasing number of working groups, societies, and cohorts, standardization and validation will be paramount to success. Fortunately, many dedicated researchers and healthcare providers are focused on improving our ability to classify SSc patients, which will in turn advance research programs and, ultimately, clinical care.

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