There is a need for new systemic sclerosis subset criteria. A content analytic approach.

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ABSTRACT

Objectives. Systemic sclerosis (SSc) is heterogeneous. The objectives of this study were to evaluate the purpose, strengths and limitations of existing SSc subset criteria, and identify ideas among experts about subsets.

Methods. We conducted semi-structured interviews with randomly sampled international SSc experts. The interview transcripts underwent an iterative process with text deconstructed to single thought units until a saturated conceptual framework with coding was achieved and respondent occurrence tabulated. Serial cross-referential analyses of clusters were developed.

Results. Thirty experts from 13 countries were included; 67% were male, 63% were from Europe and 37% from North America; median experience of 22.5 years, with a median of 55 new SSc patients annually. Three thematic clusters regarding subsetting were identified: research and communication; management; and prognosis (prediction of internal organ involvement, survival). The strength of the limited/diffuse system was its ease of use, however 10% stated this system had marginal value. Shortcomings of the diffuse/limited classification were the risk of misclassification, predictions/generalizations did not always hold true, and that the elbow or knee threshold was arbitrary. Eighty-seven percent use more than 2 subsets including: SSc sine scleroderma, overlap conditions, antibody-determined subsets, speed of progression, and age of onset (juvenile, elderly).

Conclusions. We have synthesized an international view of the construct of SSc subsets in the modern era. We found a number of factors underlying the construct of SSc subsets. Considerations for the next phase include rate of change and hierarchal clustering (e.g. limited/diffuse, then by antibodies).

Introduction

Systemic sclerosis (SSc) is a family of conditions unified by the presence of immune activation, systemic vasculopathy and fibrosis. These may result in internal organ involvement, variable disease trajectory and survival. Classification criteria for subsets of patients with SSc are widely used in clinical research.(1) Sixteen clinically based criteria sets have been proposed ranging from 2 to 6 subsets, usually based on the extent of skin involvement(2-18) The most frequently used are those proposed by LeRoy et al in 1988 which classify SSc patients as limited or diffuse cutaneous subtypes.(6) Subset classification may be used to identify patients with differential disease evolution, response to therapy, and prognosis.(7, 11, 19, 20) In a new era of earlier identification of disease(21-23), autoantibody profiling(24, 25), genetic markers(26), biomarkers(27) and personalized medicine(22), the construct of 'subsets in SSc' may have evolved.

Development of new *subset criteria* for SSc is being undertaken, led by the international steering committee of American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for SSc. An important first step is to evaluate the current construct underpinning the meaning and utility of SSc subset criteria. It is also important to understand the strengths and limitations of previous iterations of SSc subset criteria so that a new iteration of SSc subset criteria will build upon the strengths and address the limitations.

The aim of this study is to evaluate the construct of SSc subsets in the modern era. Specifically, the objectives of this study are to evaluate the meaning and purpose of SSc subset criteria; determine the strengths and limitations of existing SSc subset criteria, and identify potential areas for improvement. An accurate understanding of the construct underlying SSc subsets will inform the study design of the new iteration of SSc subset classification criteria development.

Methods

Study design. We conducted a cross-sectional study, with face-to-face interviews, to determine the purpose, strengths, limitations and areas of improvement for SSc subset criteria.

Sample. Our previous work found that the most valid and reliable beliefs are elicited from individuals who have a greater depth of knowledge and experience.(28) Thus we interviewed experts in SSc. SSc experts were defined as individuals who participate in a referral center for or conduct human research in SSc. A list of attendees at the Systemic Sclerosis World Congress (n=771) was used to identify SSc experts (those who publish in SSc and/or have a SSc program) (n=69). Each SSc expert was assigned a number. SSc experts were randomly sampled from the SSc expert list using a computerized random number generator. Subjects were contacted using a standardized letter by email inviting them to participate in a recorded interview. This recruitment strategy has been successfully used in previous work.(29) An interview time was arranged. Each participant was assigned a study identification code to maintain anonymity. Characteristics of the participants collected included sex, pediatric/adult rheumatology/other, years in practice, number of new SSc patients seen per year, participation in SSc research, and location of practice. There is no consensus on the sample size for a belief elicitation study.(28) Using central limit theorem, an a priori sample size of 30 was chosen to assume a normal distribution to the mean values of summarized data. This conservative approach provides a larger and more robust sample size than usually recommended for content analytic studies.(30) Institutional research ethics approval was obtained and participants provided written informed consent.

Interview. A 10-minute interview was conducted individually with each expert. Using a standardized semi-structured interview template, experts were asked open-ended questions investigating their beliefs about the purpose and limitations of SSc subset criteria. Appendix 1. The investigator used probes (e.g. can you tell me more about that?) to facilitate elaboration of an expert's

comments. The interview was recorded using a dictaphone and transcribed verbatim.

Analysis. Participant characteristics were double entered into a computerized database and summarized using descriptive statistics. Hsieh and Shannon's qualitative content analytic approach was used to analyze the interview data.(31) Independently, 2 investigators (SRJ, MS) read all the transcripts repeatedly to achieve immersion and obtain a sense of the whole data set. The transcripts were re-read word by word to derive codes by first highlighting the exact words from the text that appear to capture key thoughts or concepts. The investigators made notes of the initial analysis, and created labels for codes that are reflective of the thoughts. The codes were organized into meaningful clusters. The incidence of codes and rank order frequency are reported. The results of the 2 independent analyses were compared. The aggregate results were presented to an independent, international group of SSc experts (n=6) for comment and identification of conceptual links amongst the themes to develop an analytical thematic schema. This research triangulation enhances the credibility of the findings and ensures the analysis reflects the full breadth and depth of the data.(32) Descriptive statistics were used to summarize the data. Quantitative analyses were conducted using RStudio (version 0.97.248).

RESULTS

SSc experts. Thirty experts from 13 countries were successfully recruited. The participants were predominantly male (67%), European (63%) and practiced adult rheumatology (87%) with a median of 22.5 (interquartile range 17.3) years in practice seeing SSc patients. Two investigators were involved in previous SSc subset classification criteria development. Table 1 summarizes participant characteristics.

Meaning of SSc subsets. The term SSc subsets meant 'distinguish patients' into 'distinct groups' using terms 'differentiate', 'stratify', 'separate', 'divide' and

'characterized subgroups.' There was no ambiguity in the meaning of SSc subset criteria.

Purpose of SSc subsets. The purpose of SSc subset criteria fell into 3 thematic clusters. Under the cluster *Management*, experts stated that SSc subsets should 'guide intensity of investigations at baseline'; 'intensity of monitoring over time'; inform management, treatment/therapeutics, 'aggressiveness of therapy' and inform 'response to treatment'. A second thematic cluster *Prognosis* was identified, with 2 sub-clusters: '*internal organ involvement*' and '*survival*.' Experts stated that SSc subsets should inform prognosis, namely 'outcomes', 'course of disease', 'changes over time', 'disease progression'; 'function as prognostic indicators' or 'assist with risk stratification, ideally informing time to organ failure'. A third thematic cluster *Research and Communication* was identified. Experts stated that SSc subsets be used 'during study sample selection to reduce the heterogeneity of disease.' SSc subsets can be used to 'educate' patients, trainees and medical colleagues about SSc. It facilitates communication among health professionals in the patient's circle of care (see Figure 2).

Strengths of Limited/Diffuse classification system. 100% of experts endorsed using the limited/diffuse cutaneous subset system. Experts stated the strengths of the limited/diffuse subset system are its 'ease of use' and 'simple to understand.' It 'has prognostic value,' 'informs what to look for,' 'useful for management' and 'applicable for research.' However, 10% of experts stated that this system has little or no value. One expert stated, 'I put it in the note to communicate to other physicians…. I have more tools and am more comprehensive in how we evaluate patient.' Another expert stated 'I hate these criteria, the skin is the wrong thing.'

The shortcomings of the limited cutaneous and diffuse cutaneous SSc system grouped into 4 thematic clusters. Under thematic cluster "Misclassification" experts expressed concern relating to the observation that 'all diffuse starts as

limited, and limited can extend to diffuse.' 'Everyone starts as limited,' and this system requires 'expert clinicians and expert centers' to prevent misclassification. A second thematic cluster was 'predictions or generalizations do not always hold true.' Participants observed that 'pulmonary arterial hypertension can occur in both types,' and 'some patients don't behave the way they are supposed to.' The beliefs that the 'diffuse type has a worse prognosis,' 'anticentromere is associated with limited and Scl70 (Topoisomerase1) is associated with diffuse' are not always true. This system is 'not good enough for predicting organ involvement,' and 'doesn't work for lung.' A third thematic cluster related to the use of the elbow as a cutaneous threshold as participants felt that it is an 'absolute breakdown without context,' is 'arbitrary,' and that the 'forearm are diffuse in action. A fourth thematic cluster related to dependence on the skin for classification. Participants expressed the 2 subset system 'does not account for progression or regression,' does not reflect the intermediate subtype, and 'only includes observed skin thickening. Participants opined that 'in early disease the skin is not the major organ,' and 'skin alone is not useful.' Other comments included 'limited is not well defined,' 'the system does not capture disease severity or disease activity,' 'is missing antibodies,' does not account 'for rate of physiologic change,' and is an 'oversimplification.'

Number and types of subsets. Eighty-seven percent of experts use more than 2 SSc subsets. In practice, the participants endorsed using 2 to 10 subsets. Figure 5. SSc sine scleroderma was considered a subset (n=7), whereas others explicitly stated SSc sine scleroderma is not a separate subtype (n=2). Overlap patients were considered a distinct subset (n=6). Some participants subset SSc by autoantibody or antinuclear antibody pattern (n=6), explicitly describing centromere, topoisomerase, RNA polymerase, nucleolar pattern and U1RNP antibodies. Some participants subset SSc by rate of skin progression (n=3) distinguishing 'rapidly progressive' from 'slowly progressive.' Experts subset SSc based on stage of disease, distinguishing 'early' versus 'late' or 'established.' Experts also subset based on age of onset distinguishing 'juvenile onset' and

'geriatric onset.' Other described subsets included 'pre-SSc or undifferentiated,' 'single organ dominant,' intermediate,' 'fibrotic or vasculopathic with or without inflammation,' and considered gene expression and interferon signatures.

DISCUSSION

We have found that the concept of SSc subsets exists as a multidimensional and complex latent construct. It cannot be easily measured but is considered to be real by international SSc experts. Ontology is the philosophical study of the nature of being, and the categories of being and their relations. Our work addresses the ontological questions: 'what is it?' and 'what is it for?' SSc subset criteria have wide ranging utility as they may inform patient care, predict internal organ involvement and survival; are needed to identify more homogeneous groups of patients for SSc studies and inform medical communication. The limited and diffuse cutaneous SSc subset system has been extensively adopted over the past 25 years. However, limitations to their use have been identified. Our findings suggest there is a need for new systemic sclerosis classification criteria.

Our results provide important considerations for the next phase of criteria development. Experts continue to be influenced by the degree of skin involvement. Skin involvement is a manifestation that is relatively easy to measure, is low cost and can be ascertained in any setting. However, an emerging concept not included in previous iterations of SSc subset criteria is the rate of skin change. Methods of assessing rate of skin change have been proposed.(33-35) The next iteration of subset criteria should consider the feasibility of incorporating rate of change and its predictive validity for informing response to therapy, internal organ involvement and survival. The time from disease onset may also affect cutaneous subsetting, and will need to be accounted for.

The use of autoantibody profiling and nailfold capillaroscopy is increasingly being proposed to subset SSc patients.(18, 36) Given their importance, they are now items in the American College of Rheumatology European League Against Rheumatism classification criteria for systemic sclerosis.(37) The limited and diffuse cutaneous system includes centromere and topoisomerase antibodies, yet is not always consistent. A wider array of scleroderma-specific antibodies has been studied. RNA polymerase3 antibodies have been associated with renal crisis. However, the inclusion of a greater number of scleroderma specific antibodies in SSc subset criteria will need to tempered against their broad availability and cost. Furthermore, there appears to be geographic variation in the prevalence of antibodies, notably the prevalence of RNA polymerase III antibodies in the US versus southern Europe.(38) The impact of geographic variability on the operating characteristics of subset criteria including autoantibodies will need to be evaluated. Similarly, the possible role and contribution of nailfold capillaroscopic SSc patterns may need to be considered. The identification of early, active, and late nailfold capillaroscopic SSc patterns may inform subsetting.

The appropriate number of subsets is another important consideration. The majority of experts believe there are more than 2 subsets. Previous iterations of criteria have proposed up to six subsets. However, a 2 subset system has been shown to have the best predictive validity for prognosticating future outcomes in SSc.(1) New systems of subset classification will need to consider if the inclusion of additional subsets confers incremental value.(17)

Investigators are encouraged to think carefully about how we approach development of classification criteria for subsets of disease. Classical ‘philosophic realism,’ an underpinning of psychometric science, says that the notion of subsets within a disease is a real thing that we cannot directly observe and therefore called a latent variable or construct.(39) We use combinations of symptoms, signs and test results to indicate the construct (i.e. define the

subsets). The items that define the construct should be highly correlated and interchangeable.(40) The final system of subset classification should be reflective of the underlying, real, latent construct. However, it may be that subsets within a disease don't exist as real and independent entities but rather constructed in the minds of experts.(40) Under this approach of 'philosophic constructivism' the items chosen to define subsets form the construct. As a consequence, the use of different items to define subsets may result in different outcomes.(40) For example, defining subsets by autoantibodies, extent of skin involvement or rate of change may differentially predict future organ involvement or survival. Researchers have been advised to investigate how constructivism should be considered when evaluating the validity of and choosing measures to inform patient care or the conduct of research.(40) Combining items of different attributes in a hierarchical form (e.g. extent of skin involvement and autoantibodies) may address this issue. Figure 6.

One may argue that there may not be 1 subset classification system that serves all purposes. Subclassification will create more homogeneous groups, but the groups may need to be different based on the intended purpose (to understand pathophysiology, prevention or prognosis). The question then, is which is needed most by clinicians? Our findings suggest the international expert community prefers subset criteria to be associated with future outcomes, namely response to therapy and prognosis. For example, experts in this study stated it would be 'helpful to identify patients who have a poor prognosis' and 'warrant more aggressive therapy', thereby conferring more personalized medicine. Ideally subset criteria would help facilitate giving the right drug to the right patient. Once subsets are identified, it is important to evaluate predictors of trajectory, and then ascertain if these predictors can guide treatment. However, it should be remembered that subset classification based on pathophysiology and prognosis may not be stable over time as future outcomes can change.

Strengths of this study include interview of a large number of SSc experts, and

broad representation of SSc experts from both Europe and North America. We have included the perspective of pediatric rheumatology, dermatology and gastroenterology, which was a limitation of the 2013 ACR EULAR SSc classification criteria.(41) However, since we randomly sampled participants from the list of SSc experts attending the Systemic Sclerosis World Congress; and the meeting was predominantly attended by SSc experts from Europe and North America, no SSc experts currently practicing in Asia, Africa or South America were included in this study. In order to develop SSc subset classification criteria that are generalizable globally, it is advised to include the perspectives of these regions in the subsequent phases of criteria development.

We used research triangulation in data analysis and provided raw data including quotations, i.e. indicators of qualitative research of high quality.(32, 42) Moving forward, investigators should take into consideration a few cautionary notes. First, investigators should be aware of the dangers associated with misclassification. Falsely classifying patients may have liability and cost consequences.(43) The false positive, false negative rates, positive and negative predictive value of the next iteration of subset classification criteria should be evaluated and compared against pre-existing subset criteria.(44)

In summary, we have synthesized an international view of the construct of SSc subsets in the modern era. A good ‘photograph’ of the present situation has been achieved. We found there are a number of factors underlying the construct of SSc subsets including disease trajectory, prediction of internal organ involvement, response to therapy, prognosis including survival. Data improving our understanding of the relevant domains and their relative importance will inform the study design of the next phase of SSc subset criteria development.

Conflicts of Interest

Maurizio Cutolo received research support from BMS, Actelion, Mundipharm, and Horizon.

Nemanja Damjanov has receiving Grants/Research support from Pfizer, MSD, Abbvie, Roche; has been Consultant for Pfizer, Abbvie and Roche; has been Speaker for Pfizer, MSD, Abbvie, Roche, Gedeon Richter, and Boehringer Ingelheim.

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Table 1. Summary of participant characteristics

Characteristics	**n=30**
Male sex n (%)	**20 (67%)**
Geographic region	
Europe n (%)	**19 (63%)**
Sweden	**1**
United Kingdom	**4**
Italy	**2**
Germany	**5**
France	**1**
Netherlands	**1**
Switzerland	**1**
Hungary	**1**
Serbia	**1**
Spain	**1**
Poland	**1**
North America n (%)	**11 (37%)**
Canada	**1**
United States of America	**10**
Specialty	
Adult rheumatology n (%)	**26 (87%)**
Pediatric rheumatology n (%)	**1 (3%)**
Adult and pediatric rheumatology n (%)	**1 (3%)**
Dermatology n (%)	**1 (3%)**
Gastroenterology n (%)	**1 (3%)**
Number of years in practice seeing SSc patients median (IQR)	**22.5 (17.3)**
Number of new SSc patients seen per year median (IQR)	**55 (120)**
Conduct of SSc research n (%)	**30 (100%)**
Use of SSc subset criteria n (%)	**30 (100%)**

Figure 1. Circle graph illustrating the thematic clusters ‘Management’ for the purpose of systemic sclerosis subset criteria.

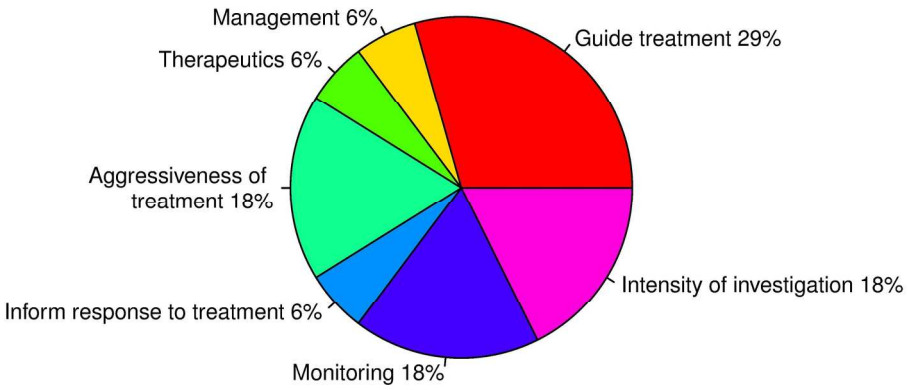
Figure 2. Circle graph illustrating the thematic cluster ‘Prognosis’ for the purpose of systemic sclerosis subset criteria.

Figure 3. Circle graph illustrating the thematic cluster ‘Types of outcomes’ for the purpose of systemic sclerosis subset criteria.

Figure 4. Circle graph illustrating the thematic cluster “Research and Communication’ for the purpose of systemic sclerosis subset criteria.

Figure 5. Number of subsets

Figure 6. Illustrative example of hierarchical clustering for systemic sclerosis subsets



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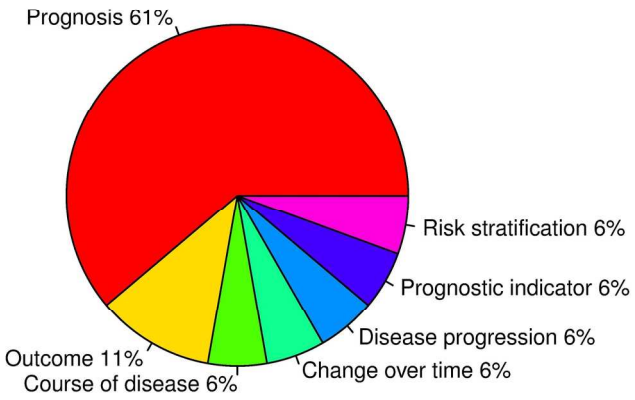

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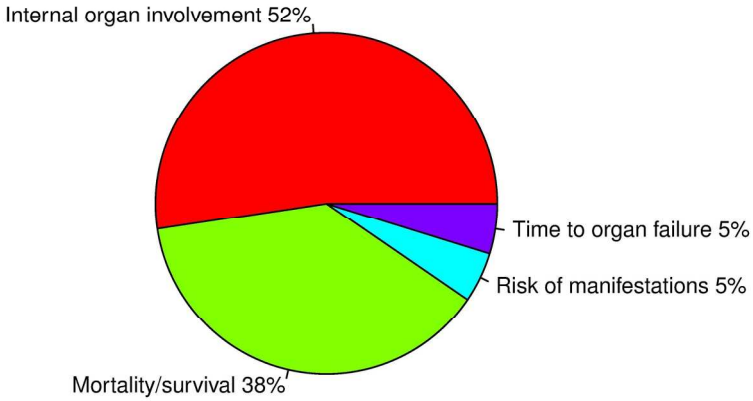

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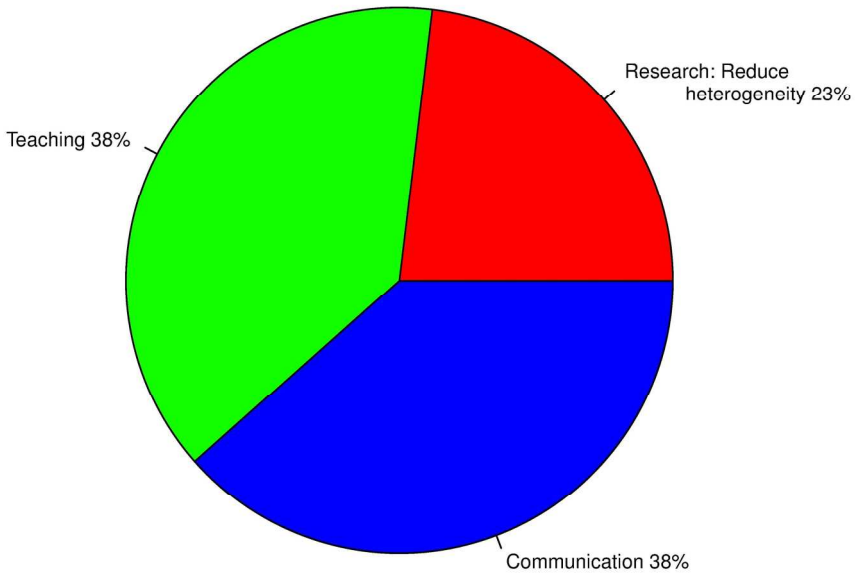

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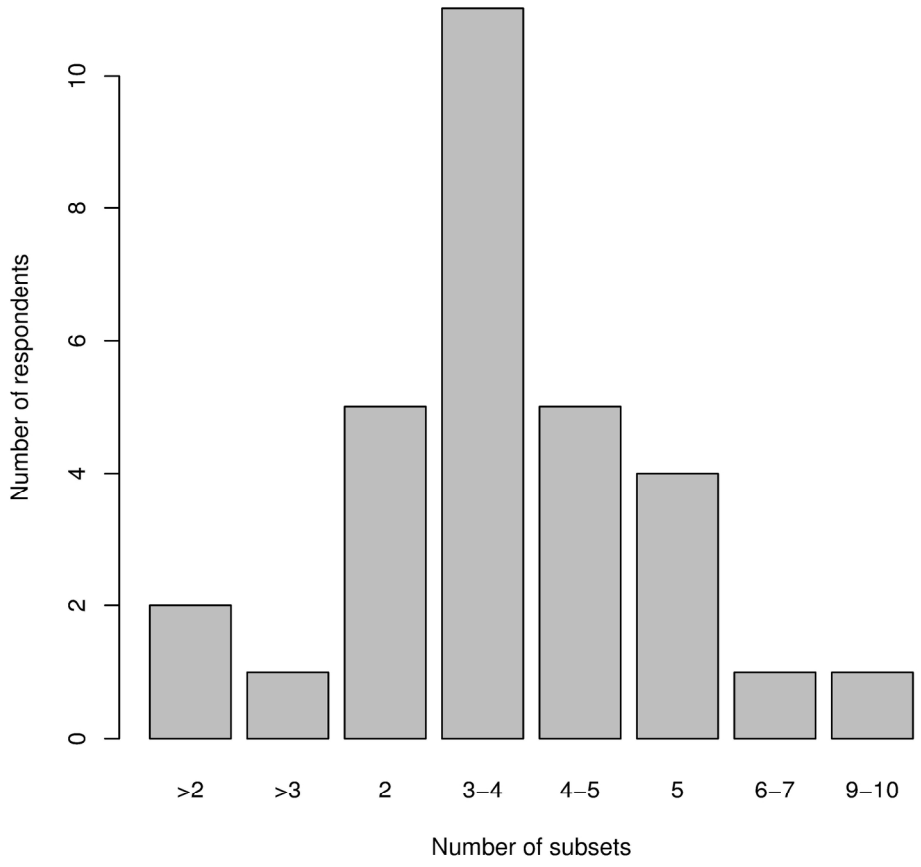

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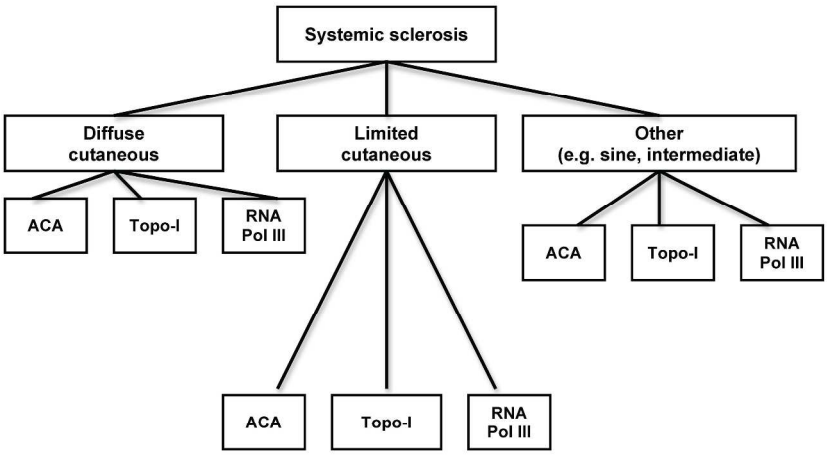

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