A Delphi exercise and cluster analysis to aid in the development of potential classification criteria for systemic sclerosis using SSc experts and databases

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ABSTRACT

Objectives. *Since the 1980 ACR classification criteria for systemic sclerosis (SSc) do not identify 20% with SSc, revised criteria are necessary.*

Methods. *Suggested new criteria from the literature were sent in random order to 96 SSc experts. A 3-round Delphi Consensus eliminated criteria. Then cluster analysis reduced items. The Canadian Scleroderma Research Group (CSRG) database was used to determine the prevalence of each item.*

Results. *Seventy-one of 96 (71%) completed all 3 rounds; 47 items were expanded to 76 in round 2. Thirty items had at least 50% consensus and 18 had >75% agreement to include (a priori cut point). Clustering occurred for 4 categories: proximal to MCP skin involvement, vascular abnormalities, autoantibodies and tissue damage. Proximal to MCPs skin involvement identified 80% of patients. Adding one item from each of the other 3 categories or 1 or more items from 2 of 3 remaining categories increased the proportion of patients classified to 94% in CSRG patients. Categories included (1) Vascular (dilated capillaries, telangiectasia, Raynaud's phenomenon [RP]), (2) Autoantibodies (anticentromere [ACA] or antitopoisomeraseI [Topo1]) and (3) Fibrosis/damage (esophogeal dysmotility dysphagia, sclerodactyly, digital ulcers). In the CSRG, 98% were identified if using proximal skin involvement; or sclerodactyly plus one of: RP, ACA or Topo1.*

Conclusions. *This is a first step toward developing new SSc classification criteria. A Delphi exercise alone cannot suffice for item reduction. Also, validation prospectively in SSc patients and diseases that mimic SSc is needed in order to calculate sensitivity and specificity of future criteria.*

Introduction

Systemic sclerosis (scleroderma, SSc) is an uncommon multisystem, chronic, connective tissue disease of variable clinical expression and disease subsets. The current criteria for the classification of SSc published in 1980 by the American College of Rheumatology (ACR) (1), fail to include a significant proportion of patients that experts agree have SSc; specifically those with limited cutaneous SSc (lcSSc), SSc sine scleroderma and early disease. In the Canadian Scleroderma Research Database (CSRG), 12% of patients do not meet the ACR criteria for SSc but are identified by rheumatologists as having SSc (2, 3). Some patients who have Raynaud's phenomenon (RP), sclerodactyly alone, esophageal dysmotility, telangiectasia, calcinosis and scleroderma-related autoantibodies (*e.g.* anti-centromere [ACA]) are not classified as having SSc using the current ACR criteria unless they also meet minor criteria (digital pitting scars or tuft resorption or pulmonary fibrosis). There are also some patients who have SSc features with significant organ complications such as pulmonary arterial hypertension (PAH) who do not meet current criteria (4).

It is now possible to incorporate new clinical and biological measures to increase the sensitivity and specificity of the criteria for classification. With the use of improved statistical methodologies and carefully defined clinical measures, updated and internationally validated criteria can be developed. Based on a review of the current SSc literature, Walker *et al.* outlined the ideal classification system as one that is: (1) easy to apply; (2) allows for early identification of disease; (3) subclassifies disease to aid in prognosis and treatment; (4) incorporates clinical and diagnostic variables; and (5) under-

goes international validation (2). Thus, these principles can serve as guidelines for the development of new classification systems and will be applied to SSc in this study.

The purpose of this study was to obtain consensus on prior and potential new items for SSc criteria and determine the frequency of the items and clustering of items in the CSRG database where there has been a long disease duration in most SSc patients. The CSRG cohort started enrolling prevalent patients (over representing those with mild and long standing disease) (5). This makes an ideal group in which to test new items for classification of SSc as the 1980 criteria do not classify a proportion of the lcSSc group (1-3, 6).

Methods

Ethics approval

All CSRG sites have been approved and patients have provided written consent. This project also received ethics approval from the University of Western Ontario's (London, Ontario, Canada) Ethics Board.

Preparation of Delphi Consensus Survey

A Delphi Consensus Exercise of three rounds was conducted internationally among rheumatologists and some dermatologistis with an expertise in SSc to develop potential items (to be refined later) for updating the SSc classification criteria. Individual and combinations of criteria that classified the greatest proportion of patients from the CSRG database were determined using cluster analysis. Initially, a preliminary list of 44 potential items was previously developed in a study by a CSRG sub-committee led by Jennifer Walker and Janet Pope based on a literature review of non-redundant, applicable and expert-supported items. For this study, the 44 items were refined by removing items that did not satisfy the primary requirements for classification criteria (2) and adding any other potential items so 47 items were present at baseline. Their face validity was evaluated by a designated committee of CSRG rheumatologists and the list was circulated in the Delphi format to three clinicians who are SSc experts to assess the clarity of instructions, definitions, flow, format and ease of use of the survey form.

Study participants

SSc experts included members of the CSRG (7) and Scleroderma Clinical Trials Consortium (SCTC), an international group of institutions comprised of individuals wishing to advance SSc research (http://www.sctc-online.org/membersh.htm). Other rheumatologists who did not belong to these groups were considered SSc experts by reputation were also sent the Delphi. The number of eligible rheumatologists for our study was 96. Eligible rheumatologists were invited to participate by email prior to the initiation of the Delphi.

The Delphi Exercise

The items of each Delphi survey were arranged in random order between participants and rounds, to avoid an order effect during item selection. Each version of the survey was randomly ordered to those who agreed to participate. Each round of the survey included a qualitative component in which rheumatologists could include additional comments or suggested items in the form of written feedback. For round one of the exercise, rheumatologists were asked to indicate whether each of 47 items should be included as potential SSc classification criteria, after selecting "yes", "no", or "not sure" from a drop down list of items in a column next to the items. Experts were asked to complete this task within three weeks. Items were retained if there was at least 30% consensus and the new items that respondents proposed were added.

A second survey was distributed for round 2 to participants who had returned the survey from round one. No items were eliminated from the survey for the second round; however additional items were added after considering the comments and suggestions from participants, producing a total of 71 items for the second round. Participants were again asked to indicate whether each of the items should be included as potential classification criteria by selecting "yes", "no", or "not sure". In round 2, participants were informed what the consensus for each item was from the previous round, and given the option to change their opinion for each item, considering this new information. For the second and third rounds, definitions of items from the literature were provided, in response to requests after the first survey. Items with at least 50% consensus were retained from round 2.

For completers of the 2nd round, a third survey was distributed. Participants who had missing responses on round 3 were asked to provide responses. For those who did not provide the missing values in return, we did not use their 3rd survey results in the subsequent analyses. Items with at least 75% consensus as potential SSc criteria were not discarded from round 3 (as *a priori* we had determined these cut-offs).

Cluster analysis

Cluster analysis was performed to reduce the final number of potential criteria to a more practical and non-redundant number for classification purposes. The VARCLUS procedure was used to perform the cluster analysis with a correlational matrix. However, because the Delphi responses were binary (1=yes, 0=no), a correlation matrix for binary values, and a tetrachoric correlation matrix were calculated; the latter using a programme called Tetmat (8).

Frequency analysis

Results from the Delphi were assessed in the CSRG patient database to quantitatively evaluate the items after clustering was performed (n=850 patients). All analyses utilised SAS version 9.1 for Windows version 5.1. To elucidate which criteria classified the most SSc patients, a programme (proc FREQ) was applied to all the combinations with the 'list' option to display the proportion of CSRG patients included within each subset (9). The programme could determine how many people mmeet each combination of items (from one to 18 items alone or with other items). If a patient in the database had missing data for an item, they were removed for analyses pertinent to the missing value(s).

Results

Delphi analysis

Three rounds of the Delphi exercise were completed, having response rates of 80%, 74% and 72%, respectively (each based on a total of 96 eligible rheumatologists) (Fig. 1). Comments were made by 55% of respondents. After the first round, additional items were added to the second survey so the latter expanded the items to 76. The potential criteria items that produced a consensus rate of ≤50% in the second round were removed leaving 30 items for the third survey and 20 items were retained for further consideration after round 3. There was a gap in consensus between the top 20 items and lower 10, indicating that 75% consensus was a reasonable cut-off (Fig. 1). A total of seven Delphi responses were incomplete from the final round of the Delphi exercise and were excluded from the analyses.

We then removed scleroderma renal crisis because it is a rare event that occurred in 3% of patients in the CSRG, and anti-RNA polymerase III antibody because it is not a widely available test. After consensus was established for round three, the result was 18 items remaining as the most appropriate for the classification of SSc (Table 1).

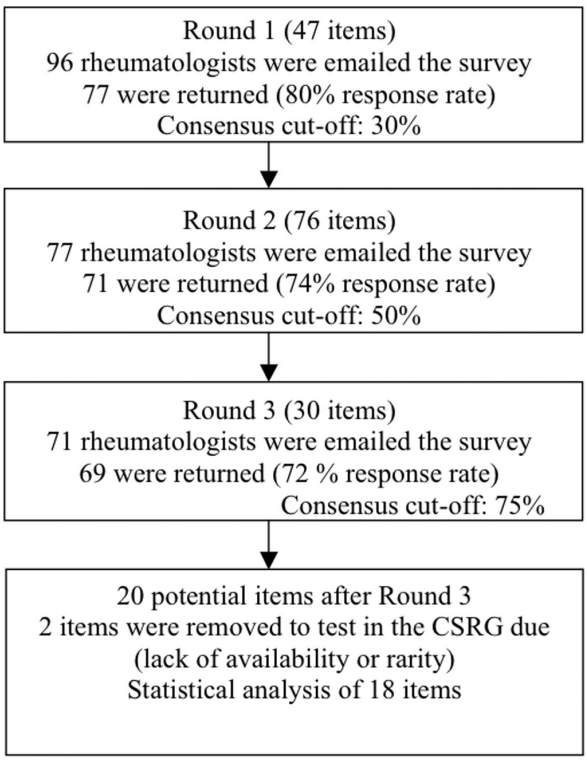

Fig. 1. Outline of Delphi Consensus Exercise. The number of items on each survey is listed in brackets as well as the corresponding response rates (all based on initial number of rheumatologists surveyed, 96, since only respondents were sent subsequent rounds).

Cluster analysis

The 18 items were arranged into 4 clusters using proc VARCLUS and a correlational matrix (actual correlations are not shown). The latent traits of these clusters were determined by the subject matter of each cluster and recommended guidelines for analysis (9). The first cluster was proximal skin involvement (proximal to the MCPs). Cluster 2 was identified as Damage / Fibrosis with items manifesting damage (10-12). Cluster 3 was identified as Vasculopathy. Cluster 4 contained Antibodies. ACA and Topo1 were the two items with100% agreement from the Delphi exercise.

Frequency analysis

Based on these results of the cluster analysis, combinations could be selected for assessment by frequency analysis to determine which criteria classified the greatest proportion of individuals, using the CSRG database. Figure 2 illustrates which combinations of criteria were selected and the proportion of patients from the CSRG database within each combination. Ninety-four percent could be included if one item from "Cutaneous Sclerosis" or one item from two categories of "Damage", "Capillary Involvement" and "Antibodies" were present. This cluster combination was selected from all possible combinations of clusters, to establish the point estimate that classified the greatest proportion of CSRG patients (other combinations and frequencies not shown).

These items could classify 94% proportion of individuals within the CSRG database whereas the old ACR criteria classified by major criterion 80% and using the full preliminary ACR criteria 12% could not be classified as SSc in the CSRG database.

Discussion

The use of a Delphi Consensus exercise among rheumatologists has allowed us to suggest a revised list of classification criteria, and proceed with replacing the 1980 ACR criteria (1) so that classification can be consistent across rheumatologists and research studies.

It is important to note the evolution of SSc criteria including subsets; which is beyond the scope of this article. For instance, in 1988, there was a proposal of a classification that introduced common SSc nailfold capillaroscopy abnormalities and specific antinuclear antibodies. Two subsets of SSc emerged from the discussions: diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) (6). In 2001, LeRoy and Medsger proposed criteria for an additional early or limited subset of SSc (lSSc) (13).

Delphi Consensus Exercise

The Delphi exercise has the ability to summarise the opinions of experts in a field that spans wide geographical distances, without the need for in-person meetings and travel. Three rounds were selected for the Delphi exercise because two rounds would not be sufficient to reduce items and achieve a sufficient consensus. Four rounds may have resulted in a greater loss-to-follow up and we did not believe a fourth round was necessary since the remaining 20 items after round 3 had high agreement to be tested for potential items used in SSc criteria. We attempted to limit the loss to follow-up after each round by

Table I. List of criteria from round three where consensus was ≥75%. Note two other highly ranked items were not tested as Scleroderma Renal Crisis they was too uncommon in the CSRG database and RNA polymerase III antibody is not widely available.

List of potential criteria	Response
Anti-Centromere Antibody (ACA)	Yes: 100%
Anti-Topoisomerase (Topo1) Antibody	Yes: 100%
Esophageal dysmotility / dysphagia	Yes: 95%
Sclerodactyly alone	Yes: 97%
Sclerodactyly and any other skin Involvement	Yes: 84%
Sclerodactyly and Typical sclerodermatous Skin changes proximal to MCP joints	Yes: 90%
Typical sclerodermatous skin changes Proximal to MCP's	Yes: 89%
Typical sclerodermatous skin changes distal to elbows or knees	Yes: 92%
Typical sclerodermatous skin changes Proximal to elbows or knees	Yes: 85%
Typical sclerodermatous skin changes on trunk	Yes: 88%
Finger tip ulcer or Digital tuft resorption	Yes: 90%
Loss of pulp space of the fingertip (whether by radiographic evidence or clinical)	Yes: 93%
Digital pits	Yes: 91%
Dilated blood vessels on nailfold capillaroscopy detected by the physician with a handheld device (with magnification if needed)	Yes: 82%
Capillary Loop Dropout	Yes: 77%
Raynaud's Phenomenon	Yes: 87%
Telangiectasia (large / well demarcated)	Yes: 75%
Calcinosis (cutis)	Yes: 80%

reminding participants that they will be included on the final publication only if they participate in all three rounds, and sent a reminder email after each round. Delphi exercises are at risk of having a large loss to follow-up (14). However, our response rate of 80%, 74% and 72% for rounds one, two and three, respectively, was greater than expected. We did not detect any respondent bias, as respondents and non-respondents were of similar characteristics (all were involved in patient care, teaching and research) and both groups had similar male to female ratios (data not shown).

There is no ideal cut-off or convention in the literature that indicates what value should be chosen as a consensus cut-off (15, 16). Thus we used our best judgment to select more stringent cut-offs with each round.

A limitation of this Delphi exercise is that participants were not able to discuss their opinions with each other directly, whereas they wrote in comments for each survey and more than half utilised this option. A criticism of the Delphi exercise is that it can be eminence based, in contrast to evidence-based. Another limitation is that there is no established sample size from which to reach a consensus that best reflects the truth. Delphi participants can span from 10 to 1500 individuals (17, 18). Thus we chose to select as many potential participants who could be SSc experts as possible, identifying 96 eligible rheumatologists, resulting in a final response rate of 72%. The use of a purposive sample was appropriate for this study because only a subset of rheumatologists can be considered SSc experts and thus a random sample would not be appropriate. These rheumatologists were more likely to be familiar with the current SSc classification and the limitations *a priori*.

To prevent participants from assuming the items were arranged in order of importance, or avoid our bias in organising the items according to importance, the items were presented in random order and participants received surveys with the items organised in different random order to avoid this order bias.

Potential items for SSc classification criteria such as ours are designed to have a high specificity since they test true disease against other diseases that may mimic SSc. This can result in a reduced positive predictive value when classification criteria are applied to the general population and the frequency of disease is much lower (19-23). Thus, potential criteria developed from the final items cannot be applied to the general population.

Cluster analysis

Cluster analysis was investigated as a means to reduce our criteria to a more appropriate lower number of items. Results of the cluster analysis were clinically meaningful because it organised the Delphi responses into the latent traits "tissue damage", "skin involvement", "capillary involvement" and "antibodies" although one could postulate that not all items in some of the clusters are truly pathophysiologically related. Some of the clusters may not make clinical sense but the clusters were obtained by statistical methods. For instance calcinosis may not be considered part of vasculopathy and is likely multi-factorial in its causes and could also be considered damage. Also some of the terms did not have a consensus definition such as dysphagia where the assumption was a scleroderma pattern (at the lower oesophagus but not excluding other areas) or telangiectasia where this could be interpreted as round well-demarcated or matte-like changes.

Frequency analysis

Since the current ACR criteria fail to classify 12% of SSc patients from the CSRG database (*i.e.* the unclassified cohort), our revised criteria aim to incorporate the unclassified cohort by including additional items such as antibodies (anti-centromere and topoisomerase 1) and dilated capillaries at the nailbeds.

Based on a cluster analysis, we were able to classify 94% of the CSRG database when either one characteristic of "cutaneous sclerosis" or two characteristics of either: "damage", "capillary involvement" or "antibodies" is/are satisfied. Combinations of items were determined empirically by identifying the greatest proportion of SSc patients that were classified with various subsets of items, so some of the findings could lack face validity. Two minor criteria would not always be considered SSc. Autoantibodies would have greater specificity when combined with another criteria whereas Raynaud's and dysphagia would be insufficient to classify SSc as many patients with CTD could have these features.

Others have suggested similar items for revising SSc criteria with the exception of Raynaud's phenomenon (2, 24), and another proposal with fewer but several similar items that included Raynaud's

The potential classification items for SSc include either Cutaneous Sclerosis or 1 from each of two categories Damage, Vasculopathy or Antibodies.

Proximal Skin Sclerosis
- Skin involvement proximal to the MCP joints

Damage / Fibrosis
- Pulmonary fibrosis
- Esophageal dysmotility / dysphagia
- Sclerodactyly (but not proximal to MCPs)
-Digital pits, tuft resorption

Vasculopathy
- Dilated nailfold capillaries, capillary drop out
- Raynaud's phenomenon
- Telangiectasia
- Calcinosis+

Systemic Sclerosis Antibodies (SSc Ab)*
- Anti-centromere antibody
- Anti-topoisomerase antibody

Potential items that define 96% of the Canadian Scleroderma Research Group (CSRG) patients

Criteria items	Frequency in the CSRG patients (%)
Former preliminary ACR criteria	
Major criterion SSc proximal to MCPs	80%
Major or minor criteria	88%
Add to criteria dilated nailfold capillaries + SSc Ab	94%
Sclerosis proximal to MCPs or sclerodactyly + SSc Ab or RP^	98%

Fig. 2. Potential SSc classification criteria based on the Delphi exercise and statistical analysis. The clustering analysis grouped the variables but some are not necessarily where experts would group them. Items were reduced to 11 from the clustering and matrix of frequency of patients included for permutations of the 18 items. For SSc Abs, RNA polymerase III was not included as it is not available in many labs as a routine part of the ENA testing. n=850 for CSRG patients.
^This analysis was done by an educated guess and not from clustering and correlational matrix. + Calcinosis may be damage and not vasculopathy but that is how the data clustered.

phenomenon (25). Some of the participating rheumatologists suggested that dilated capillaries and telangiectasia are somewhat sensitive and specific. Conversely, Raynaud's phenomenon, while considered to be highly sensitive, has a low specificity. This suggests that it is unlikely for an individual to have SSc if they do not have Raynaud's phenomenon. Again, this has not yet been tested prospectively. It is probable that when items are tested to try to revise SSc criteria, they will be reduced even further.
There are inherent limitations to relying on a database such as misclassification, and missing data and this cohort began as a prevalent cohort with 8 to 10 years of disease duration so there could be a survival bias. However, it is the lcSSc subset that do not always meet the ACR SSc criteria (1, 6), so this is the appropriate group to test other potential criteria. Missing data within the CSRG dataset is believed it to be random (26).
It was appropriate that a non-clinician analysed results. This has been implemented in previous Delphi studies to avoid bias while the Delphi technique is carried out and statistical analyses are performed (27). The value of improving the sensitivity of SSc criteria could allow for future therapies to initiated earlier and allow more patients to be classified with SSc who currently are excluded from studies; as they do not meet the ACR criteria.

The next steps
The ACR and EULAR have approved a proposal to update the classification criteria for systemic sclerosis using international experts and several databases. This project used the expanded list of potential items from the literature (from this exercise) and those added by experts (the round 2 list from this work) and also combined items from a European Delphi exercise; whereby a collaborative Delphi exercise with NA and European experts has been completed (28). The value of this paper is to acknowledge what the item reduction consisted of in this exercise and that consensus alone could not reduce items enough to have a small set of testable criteria such as 10 or fewer items and cluster analyses of the results and also testing the potential items in a SSc database did improve the proportion of patients who were classified with SSc from 88% with the previous preliminary ACR criteria to 94% with adding two more items (SSc antibodies and dilated nailfold capillaries). Thus, redefining the SSc classification criteria will be complex where statistical methods and expert opinion and testing of cohorts or prospective patients will be necessary.
Studying classification criteria items are not all inclusive as there are many other complications of SSc including renal crisis, pulmonary arterial hypertension, pulmonary fibrosis, both microvascular and macrovascular damage (29), inflammatory arthritis and myopathy. Detection and treatment of various complications differ among sites (30, 31).

Conclusions
In conclusion, the Delphi exercise was only able to reduce items to 20 which is likely too large to be used in any classification criteria and further reduction was used by clustering where redundant items were removed, but still 6% of SSc patients could not be classified using the clustered items. Thus, this is a small step in the process of defining new criteria, but the Delphi items have been in-

Supplemental figure

Frequencies of Items for Potential SSc Criteria in the Canadian Scleroderma Research Group (CSRG) Database

In CSRG Total SSc n=850 Original ACR criteria (1 major or 2 minor)	88%
New items	
1 of Major skin involvement or 1 from 2 categories Damage/Fibrosis, Vascular, SSc Antibodies	94%
Some suggested items for classification of SSc Skin	
Sclerodacyly with continuous skin involvement proximal to MCPs	42%
Skin fibrosis anywhere proximal to MCPs	46%
Truncal	25%
Proximal to elbows/knees	24%
Sclerodactyly	91%
Damage / Fibrosis	
Pulmonary fibrosis	35%
Esophageal dysmotility/dysphagia	77%
Digital ulcers/pits	45%
Vascular	
Raynaud's	95%
Dilated capillaries	64%
Telangiectasia	81%
Calcinosis	31%
SSc Antibodies	
Anticentromere antibody	34%
Antitopoisomerase I	16%

cluded in the next phase of developing more robust classification criteria. The ACR and EULAR have a joint committee that is developing SSc classification criteria and the items from this Delphi exercise can potentially be used to inform experts about potential domains or criteria which will be studied further. Also comparative patients (SSc mimickers) and prospectively collected SSc cases will be needed to determine the sensitivity and specificity of future SSc classification criteria.

SSc Delphi Participants

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[#]Part of the Canadian Scleroderma Research Group, who responded to Delphi and enrolled patients in CSRG database to test the potential criteria.

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