Development and validation of a patient reported outcome measure for systemic sclerosis: the EULAR Systemic sclerosis Impact of Disease (ScleroID) questionnaire

Mike O. Becker*[1], Rucsandra Dobrota*[1], Alexandru Garaiman[1], Kim Fligelstone[2], Ann Tyrell Kennedy[2], Annelise Roennow[2], Yannick Allanore[3], Patricia E. Carreira[4], László Czirják[5], Christopher P. Denton[6], Roger Hesselstrand[7], Gunnel Sandqvist[7], Otylia Kowal-Bielecka[8], Cosimo Bruni[9], Marco Matucci-Cerinic[9], Carina Mihai[1,10], Ana Maria Gheorghiu[10], Ulf Müller-Ladner[11], Joe Sexton[12], Tore K Kvien[12], Turid Heiberg≠[13], Oliver Distler≠[1]

*≠equal contributions

1. Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
2. Federation of European Scleroderma Associations (FESCA)
3. Department of Rheumatology, University Paris Descartes and Cochin Hospital, Paris, France
4. Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain
5. Department of Immunology and Rheumatology, Medical School, University of Pécs, Pécs, Hungary
6. Centre for Rheumatology, University College London, Royal Free Campus, London, United Kingdom
7. Department of Rheumatology, Lund University, Lund, Sweden
8. Department of Rheumatology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland
9. Department of Experimental and Clinical Medicine, Division of Rheumatology AOUC, University of Florence, Florence, Italy
10. Department of Internal Medicine and Rheumatology, Cantacuzino Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
11. Department of Rheumatology and Clinical Immunology, Justus-Liebig University Giessen, Campus Kerckhoff, Bad Nauheim, Bad Nauheim, Germany
12. Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway
13. Regional Research Support, Oslo University Hospital, Oslo, Norway

Corresponding author:
Prof. Dr. med. Oliver Distler
Department of Rheumatology, University Hospital Zurich, Gloriastr. 25, 8091 Zurich
E-Mail: Oliver.Distler@usz.ch; Phone +41 44 255 29 70; Fax: +41 44 255 89 79

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ABSTRACT

Objectives:

Patient reported outcome measures (PROMs) are important for clinical practice and research. Given the high unmet need, our aim was to develop a comprehensive PROM for systemic sclerosis (SSc), jointly with patient experts.

Methods:

This EULAR-endorsed project involved 11 European SSc centres. Relevant health dimensions were chosen and prioritized by patients. The resulting ScleroID questionnaire was subsequently weighted and validated by OMERACT criteria in an observational cohort study, cross-sectionally and longitudinally. As comparators, SSc-HAQ, EQ-5D, SF-36 were included.

Results:

Initially, 17 health dimensions were selected and prioritized. The top 10 health dimensions were selected for the ScleroID questionnaire. Importantly, Raynaud`s phenomenon, impaired hand function, pain and fatigue had the highest patient-reported disease impact. The validation cohort study included 472 patients with a baseline visit, from which 109 had a test-retest reliability visit and 113 a follow-up visit (85% female, 38% diffuse SSc, mean age 58 years, mean disease duration 9 years). The total ScleroID score showed strong Pearson correlation coefficients with comparators (SSc-HAQ, 0.73; Patient's global assessment, VAS 0.77; HAQ-DI, 0.62; SF-36 physical score, -0.62; each $p<0.001$). The internal consistency was strong: Cronbach's alpha was 0.87, similar to SSc-HAQ (0.88) and higher than EQ-5D (0.77). The ScleroID had excellent reliability and good sensitivity to change, superior to all comparators (intra-class correlation coefficient 0.84; standardized response mean 0.57).

Conclusions:

We have developed and validated the EULAR ScleroID, which is a novel, brief, disease specific, patient-derived, disease impact PROM, suitable for research and clinical use in SSc.

KEYWORDS: SCLERODERMA, SYSTEMIC; PATIENT REPORTED OUTCOME MEASURES; QUALITY INDICATORS, HEALTH CARE; IMMUNE SYSTEM DISEASES

KEY MESSAGES:

What is already known about this subject?

- PROMs are important to integrate the patient`s view into routine care
- They are an integral part of clinical trials and required for registration of novel treatments
- A brief and specific validated PROM for overall SSc is lacking

What does this study add?

- It develops and validates the ScleroID, a disease specific PROM that captures patient experience and SSc complexity in an easy to apply format for clinical care and clinical trials.

How might this impact on clinical practice or future developments?

- ScleroID can be used to integrate patient experience to improve decision making in clinical practice
- Further studies are needed to validate ScleroID as a potential PROM for future clinical trials in SSc..

INTRODUCTION

Systemic sclerosis (SSc) is characterized by a chronic and frequently progressive course and by a high patient-to-patient variability [1]. SSc has one of the highest morbidities and case-specific mortalities amongst the connective tissue diseases [2, 3]. Overall, general health (as measured by the SF-36 and EQ-5D questionnaires), as well as quality of life and functional abilities (as measured by the Health Assessment Questionnaire Disability Index, HAQ-DI) are significantly reduced in SSc [4-6].

A disease-specific, patient-reported outcome measure (PROM) for use in clinical trials and in clinical practice in SSc that covers the different disease features of this multi-organ autoimmune disease is lacking [7]. The European Medicines Agency (EMA) recommends that sufficient evidence needs to be provided on the patient benefit by PROMs before granting approval of a new therapeutic agent [8], and PROMs need to be included as outcome measures in therapeutic RCTs. Thus, the lack of sensitive, disease specific PROMs covering the overall disease is currently one of the greatest challenges for drug development in this devastating disease. In addition, published data show that systematic use of PROMs in clinical practice improves patient-physician communication and decision making, as well as patients' satisfaction [9].

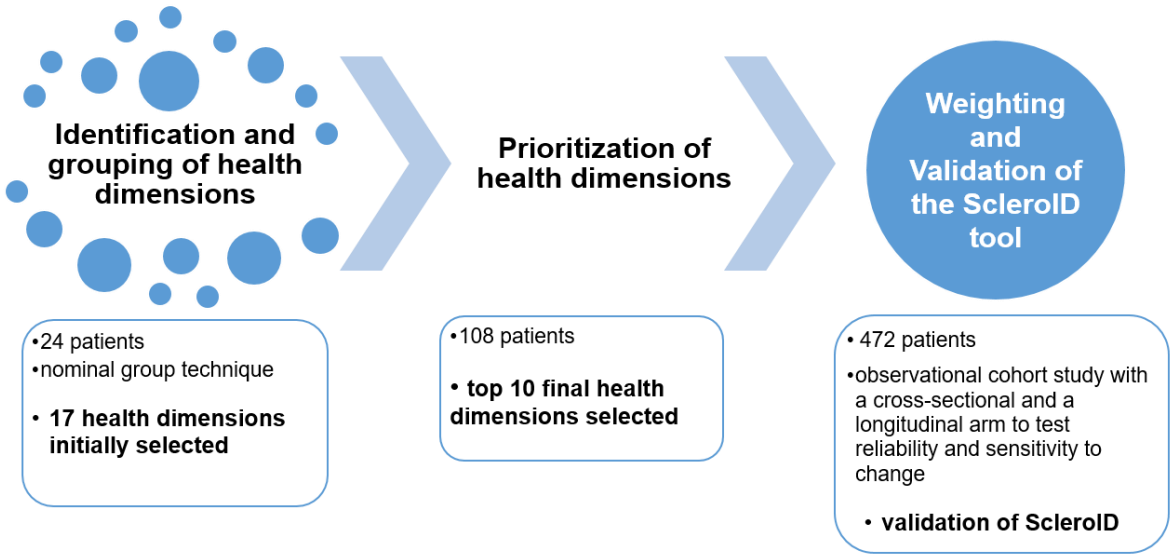
Research in the field of other autoimmune diseases provides the basis for the successful development of disease-specific PROMs. For rheumatoid arthritis, the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire [10, 11], and for psoriatic arthritis, the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire [12], were designed to capture the burden of disease that is most important to patients. Furthermore, the RAID has been successfully used to identify thresholds for symptom states acceptable for patients, as well as evaluating onset of response to medication [13, 14].

In this study, we aimed to develop a novel, patient-derived PROM for SSc that is able to cover the global disease burden - the EULAR ScleroID. Furthermore, we validated the ScleroID by the Outcome Measures in Rheumatology (OMERACT) filter in a large, multi-centric, clinical cohort study [15].

METHODS

The development of the EULAR ScleroID follows approaches used in the EULAR-endorsed RAID and PsAID questionnaires, as well as in the Pancreatic Cancer Disease Impact Score (PACADI) [10-12, 16, 17], with some modification given the differences between these diseases and SSc. Validation of the EULAR ScleroID follows the internationally recommended methodology of the OMERACT filter [15] (supplement). This is a longitudinal, multicentric project, involving 11 European expert SSc centres and patient research partners. The project workflow and process are presented in Figure 1. The project was approved by the ethics committee in each participating centre.

Figure 1. General ScleroID project workflow and procedure



Patient and public involvement

Patient research partners were involved in all the stages of the ScleroID project, starting with project design (KF, ATK), to the identification of the relevant health dimensions, and development and validation of the ScleroID including item reduction by weighting. These steps are detailed in the sections below. Furthermore, the dissemination of the study has been supported by the patient organisation Federation of European Scleroderma Associations (FESCA) by invited presentations of the preliminary results at patient congresses.

Part 1: Development of the ScleroID questionnaire

Identification, prioritization and selection of the health dimensions for the ScleroID

First, 24 patients with SSc participated in a nominal group technique exercise and selected candidate health dimensions with the highest impact on their disease status . First, the expert investigators (RD, MB, TH) presented a review of the literature on PROMs used in SSc. The patient representatives thereafter suggested health dimensions on which the disease has an important impact, according to their personal perception. On day one, 66 health dimensions were collected. On the second day, these were discussed and grouped by the patients according to the main concept that they are referring to, under neutral moderation by TH. Finally, 17 candidate dimensions were unanimously selected (further details in the supplement/Annex 2).
Subsequently, the identified health dimensions were evaluated by a larger group of SSc patients from all 11 participating centres. The objective of this exercise was to optimize face validity and to prioritise the dimensions. The health dimensions were translated by the investigators and patient research partners into each language (supplement). Patients were presented with the list of candidate health dimensions in a random order and asked to rank them according to a decreasing order of importance. The top 10 dimensions based on median ranking were selected by the steering committee (MB, RD, KF, ATK, TH, OD) for the final ScleroID. The limitation to 10 dimensions was chosen based on ranking and aiming for a better feasibility of the final questionnaire and focussing on the most relevant health dimensions reported by the SSc patient research partners.

Development of the ScleroID questionnaire

The experts (MB, RD, TH, OD) developed one question with numeric rating scales to assess each of the selected top 10 health dimensions. The ScleroID questionnaire was subsequently translated into all applicable languages following the protocol detailed in the supplement.

Part 2: Weighting of the dimensions and validation of ScleroID

Study design

A cross-sectional international observational cohort study with longitudinal reliability and sensitivity to change arms was performed. Patients above 18 years of age fulfilling the ACR/EULAR 2013 classification criteria for SSc were prospectively included[18]. Patients with severe comorbidities not related to SSc were excluded (e.g. concomitant inflammatory disease, organ failure, recent acute cerebrovascular event, serious psychiatric or neurological disease). The ethical approval for the study was obtained by all participating centres and all patients signed written informed consent.

The sample target for the cohort study was 500 patients for the cross-sectional arm and 100/150 patients for reliability/sensitivity to change longitudinal arms, respectively, based on previous experiences with RAID and PsAID. As comparator questionnaires for the ScleroID, the most frequently used global PROMs applied in SSc were selected (supplement).

Data collection

Clinical and demographic data were collected according to EUSTAR standards [19] (supplement). In addition, patients completed the ScleroID questionnaire, the selected comparators (SSc-HAQ, EQ-5D, SF-36), patient's global assessment on a visual analogue scale (VAS), specific questions on the state of disease and a minimal clinically important difference question (supplement, Table S1) at all visits (supplement) [20-25]. For the weighting procedure, in order to assess the relative impact of the health dimensions, patients were asked to distribute 100 points between the 10 dimensions of the ScleroID according to the perceived impact on their health (supplement). This was the basis for calculation of the ScleroID score (see statistical methods). Patients considered to be in a stable state by the physician and with no foreseeable change in treatment or medical intervention in the next 10 days following the baseline visit were included into the reliability arm, and asked to complete the reliability questionnaire at 7±3 days after the baseline visit (annex). Patients considered to have active disease by the treating physician were included into the sensitivity to change arm and completed the respective questionnaire at the 12 months visit and/or at the 6 months visit, if available (annex).

Statistical analysis

The calculation of the ScleroID score was based on the ranking of the weights, as performed in RAID, PsAID and PACADI[10-12, 16, 17]. Mean and median weights were calculated for each health dimension, after which mean and median ranks were computed for the whole cohort. These represent the basis for calculating the final weight, which is multiplied by the value on the numeric rating scale (NRS) for each dimension/item and summed up for the final ScleroID score, which is then divided by 100.

The validation of ScleroID psychometric properties was performed according to the OMERACT filter, which assesses three main features: feasibility, truth and discrimination [15]. Feasibility addresses the applicability of the ScleroID questionnaire. Truth encompasses face validity (does the measure make sense), and content validity (e.g. distribution of the score, floor/ceiling effect). As other measures of truth, internal consistency using Cronbach`s alpha and construct validity (concurrent validity) with Pearson correlations to other scores (SSc-HAQ, SF-36, EQ-5D) were calculated. Construct validity was also investigated using a confirmatory factor analysis (supplement). In addition, we assessed reliability and sensitivity to change. In the reliability arm, patients, who reported themselves as “stable”, were included in the test-retest reliability (reproducibility) analysis by assessing the intraclass correlation coefficient and agreement by Bland-Altman plot. In the sensitivity to change arm, patients reporting themselves as “not stable” were included in the sensitivity to change (responsiveness) analysis by the standardised response mean (SRM, which is the difference in the baseline and follow-up mean values divided by the standard deviation of the change scores). Confidence intervals were obtained by bootstrapping.

RESULTS

Part 1: Development of the ScleroID questionnaire

Identification and prioritization of health dimensions for the ScleroID

In the initial nominal group exercise, 24 patient research partners selected 17 health dimensions reflecting the impact of SSc (Table 1). An additional cohort of 108 patients (Supplementary Table S2) subsequently prioritized these health dimensions. The selected health dimensions and their prioritization are summarized in Table 1.

Table 1. Initially selected candidate health dimensions and their prioritisation ranking by importance.

No.	Health dimensions	Mean rank	Median rank	Order by median rank	%Patients giving rank 1 to the dimension	%Patients giving rank 1-3 to the dimension	%Patients giving rank 1-10 to the dimension
1	**Raynaud**	5.8	5	1	19.4	36.1	84.3
2	**Hand function**	6.7	5	1	8.3	25.0	78.7
3	**Upper GI symptoms**	7.2	6	2	7.4	24.1	73.1
4	**Pain**	6.9	6	2	10.2	25.9	75.9
5	**Fatigue**	6.7	6	2	9.3	26.9	78.7
6	**Lower GI symptoms**	7.8	7	3	10.2	24.1	69.4
7	**Limitation of life choices and activities**	8.3	8	4	4.6	20.4	66.7
8	**Body mobility**	8.7	8,5	5	2.8	11.0	65.7
9	**Breathlessness**	8.6	9	6	12.0	27.8	52.8
10	**Digital ulcers**	9.5	10	7	1.9	17.6	54.6
11	Anxiety	10.2	10	7	2.8	9.3	50.9
12	Dryness	10.1	10	7	1.9	9.3	54.6
13	Appearance	10.3	11	8	3.7	9.3	49.1

14	Concentration difficulties	10.9	12	9	1.9	9.3	39.8
15	Cough	11.3	13	10	1.9	10.2	38.9
16	Depression	11.6	13	10	0.9	7.4	35.2
17	Calcinosis	12.5	14	11	0.9	6.5	31.5

*Patients from the prioritization cohort were asked to rank the dimensions in order of their importance by giving a rank from 1 (most important) to 17 (least important). Each rank could only be used once. The top 10 dimensions with the lowest median rank (highest importance) were selected for the questionnaire. The 10th to 12th dimension had an equal median rank but the 10th dimension had a higher role for more patients (% giving top rank, last 2 columns) and was consequently chosen in favour of dimensions 11 and 12. Dimensions included in the final ScleroID questionnaire are bolded.

Abbreviations: No, number; GI, gastrointestinal.

Selection of health dimensions and development of the ScleroID questionnaire

The steering committee agreed unanimously to include the ten health dimensions rated with the highest priority into the ScleroID questionnaire. One question with appropriate anchors to assess each of the selected ten health dimensions was developed by the steering committee (MB, RD, KF, ATK, TH, OD). These questions formed the ScleroID questionnaire (Table 2), which was also agreed upon by the patient research partners.

Table 2. The ScleroID (Systemic Sclerosis Impact Of Disease) questionnaire.

The EULAR Scleroderma Impact of Disease Score (ScleroID)

How much have the different aspects of systemic sclerosis affected you during the last week?
Please mark your responses on the scale by choosing the appropriate number for each of the following dimensions:

Raynaud's phenomenon:

Circle the number that best describes the severity of your Raynaud's phenomenon during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Hand function:

Circle the number that best describes your hand function limitations due to your systemic sclerosis during the last week:

No limitation	0	1	2	3	4	5	6	7	8	9	10	Extreme limitation

Upper gastrointestinal tract symptoms (e.g. swallowing difficulties, reflux, vomiting):

Circle the number that best describes the severity of your upper gastrointestinal tract symptoms due to your systemic sclerosis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Pain:

Circle the number that best describes the pain you felt due to your systemic sclerosis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Fatigue:

Circle the number that best describes the impact of overall fatigue due to your systemic sclerosis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Lower gastrointestinal tract symptoms (e.g. bloating, diarrhea, constipation, anal incontinence):

Circle the number that best describes the severity of lower gastrointestinal tract symptoms during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Limitations of life choices and activities (e.g. social life, personal care, work):

Circle the number that best describes how severe the limitations of life choices and activities due to your systemic sclerosis were during the last week:

No	0	1	2	3	4	5	6	7	8	9	10	Extreme

Body mobility:

Circle the number that best describes how much your body mobility was affected due to your systemic sclerosis during the last week:

Not affected	0	1	2	3	4	5	6	7	8	9	10	Extremely affected

Breathlessness:

Circle the number that best describes how severe your breathlessness due to systemic sclerosis was during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Digital ulcers:

Circle the number that best describes how much your digital ulcers affected you overall during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

Part 2: Weighting and validation of the ScleroID questionnaire

Cohort study

In total, 472 SSc patients from nine countries (France, Italy, Hungary, Poland, Romania, Spain, Sweden, Switzerland, United Kingdom) were included in the cross-sectional cohort study.

The majority of patients were female (84.8%), more than a third had diffuse cutaneous SSc (dcSSc, 37.5%) and the median age was 57 years. The various disease manifestations, including lung fibrosis (42.6%), pulmonary arterial hypertension (7%), gastrointestinal involvement (>60% of patients with oesophageal symptoms), articular involvement (4.4% with synovitis) and digital ulcers (24.0% with previous ulcers, 13.0% with current ulcers) were well represented, reflecting a typical SSc population (Table 3).

Table 3. Characteristics of the patients with SSc included in the weighting and validation cohort study.

Characteristics	Overall	% of missingness
Age, years, median (IQR)	57 (48 to 65)	1.1
Female gender (n, %)	396 (84.8)	1.1
Time since RP onset, years, median (IQR)	11 (5.8 to 20)	26.3
Time since first non-RP manifestations, years, median (IQR)	9 (4.7 to 15)	5.5
Diffuse cutaneous SSc (n, %)	152 (37.5)	14.2
Limited cutaneous SSc (n, %)	253 (62.5)	14.2
mRSS, median (IQR)	4 (0 to 8)	26.5
Presence of Raynaud's phenomenon (n, %)	332 (94.6)	25.6
Digital ulcers (n, %)	47 (13)	23.5
Joint contractures (n, %)	124 (35.7)	26.5
Joint synovitis (n, %)	15 (4.4)	28.4
Oesophageal symptoms (dysphagia, reflux) (n, %)	232 (60.3)	18.4
Stomach symptoms (early satiety, vomiting) (n, %)	61 (17.6)	26.5
Intestinal symptoms (diarrhea, bloating, constipation) (n, %)	135 (33.8)	15.5
Malabsorption syndrome (n, %)	18 (7.4)	48.7
Dyspnea, NYHA stages III and IV (n, %)	27 (9.6)	40.7
FVC, % predicted, median (IQR)	95 (82 to 108)	40.5
FVC <80% predicted (n, %)	58 (20.6)	40.5
DLCO/SB, % predicted, median (IQR)	69 (55 to 81)	44.9
DLCO/SB, <70% predicted (n, %)	133 (51.2)	44.9
Lung fibrosis detected by HRCT (n, %)	78 (42.6)	61.2
Pulmonary hypertension (n, %)	19 (6.6)	39.4
PAPsys, mmHg, median (IQR)	28 (24 to 32)	54.4
LVEF, %, median (IQR)	60 (55 to 65)	35.4
ANA positive (n, %)	319 (96.7)	30.1
ACA positive (n, %)	118 (36.5)	31.6
Anti-Scl-70 AB positive (n, %)	112 (35.2)	32.6
Anti-RNA Polymerase III AB positive (n, %)	21 (7.6)	41.1
ESR, mm/h, median (IQR)	17 (10 to 30)	25.2
CRP, mg/l, median (IQR)	2 (0.9 to 5)	35
Immunosuppression (n, %)	59 (21.2)	41.1

ACA, anti-centromere antibodies; ANA, antinuclear antibodies; Scl70, anti-Scl70 antibodies, anti-topoisomerase I antibodies; DLCO, diffusing capacity of the lung for carbon monoxide; DLCO/SB, diffusing capacity of the lung for carbon monoxide/single breath; ESR, Erythrocyte sedimentation rate; F/M, Female/Male, FVC, forced vital capacity; HRCT, high resolution computer tomography; IQR, interquartile range LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; RP - Raynaud's phenomenon, RNA - ribonucleic acid; SSc, systemic sclerosis. Definitions of organ manifestations according to EUSTAR[19]

Weighting of the health dimensions and calculation of the ScleroID score

Overall, valid data on weighting was provided by 446 (94%) patients, and 462 (98%) patients provided complete data on the ScleroID questionnaire.

The health dimensions which were assigned the highest weights (and thus highest impact) by the patients were Raynaud's phenomenon, fatigue, hand function and pain, followed by upper and lower gastrointestinal (GI) symptoms (Table 4), confirming the results from the prioritisation.

Table 4. Weighting of the health dimensions according to their perceived impact by the patients participating in the cross-sectional cohort study (n=472).

Dimension	Weight Mean(SD)	Rank Mean(SD)	Top ranked	Upper 25%	Bottom 25%	Lowest ranked
Raynaud	20.9 (18.9)	7.8 (2.6)	39.0	65.9	28.0	16.7
Fatigue	12.9 (10.6)	7.6 (2.0)	23.7	58.5	25.6	18.2
Hand function	12.1 (10.4)	7.3 (2.3)	19.5	55.9	36.2	21.2
Pain	10.4 (8.7)	7.0 (2.3)	16.7	46.0	42.2	23.5
Upper.GI symptoms	8.0 (8.2)	6.4 (2.4)	12.3	37.3	50.6	36.0
Life choices	7.9 (8.2)	6.6 (2.3)	12.1	35.8	52.1	37.9
Lower GI symptoms	7.6 (9.1)	6.2 (2.5)	11.4	36	56.1	42.8
Body mobility	7.0 (6.7)	6.4 (2.3)	8.1	38.6	54.0	39.2
Dyspnoea	6.8 (8.8)	6.1 (2.4)	9.3	33.7	64.4	46.2
Digital ulcers	5.9 (9.8)	5.6 (3.0)	17.2	32.2	68.6	61.4

Column "Weight" gives the mean (SD) of the weight given to each dimension, column "Rank" gives the mean (SD) ranking of each dimension according to the patient distributed weights. The remaining four columns give the percentage of times the dimension was ranked as most important (top ranked), the percentage of times it was ranked as least important (lowest ranked), as well as in the upper and lower quartiles of importance. Abbreviations: GI, gastrointestinal.

The mean ranks given in Table 4 were re-scaled to sum up to 1 for the final weights. The ScleroID was calculated as a composite score of the selected 10 dimensions. For each dimension, the numeric rating scale (NRS) score was multiplied by the specific weight for this item and the weighted scores were summed up (see example in Table 5).

Table 5. Computation of the ScleroID score

Element	**Raynaud**	**Fatigue**	**Hand function**	**Pain**	**Life choices**	**Upper GI symptoms**	**Body mobility**	**Lower GI symptoms**	**Dyspnoea**	**Digital ulcers**
ScleroID weights	0.117	0.114	0.109	0.104	0.098	0.096	0.095	0.093	0.091	0.083
Example NRS scores	9	3	4	0	7	2	6	4	0	3
weights [x] scores	0.117x9	0.114x3	0.109x4	0.104x0	0.098x7	0.096x2	0.095x6	0.093x4	0.091x0	0.083x3
=	1.053	0.342	0.436	0	0.686	0.192	0.57	0.372	0	0.249
ScleroID =	3.9									

Example of computation of the ScleroID score for a given patient. The final score is computed using a weighted sum over the NRS (0-10) scores given to each dimension by the patient. The weights sum to 1, and are proportional to the mean ranks given to each dimension.

Performance of ScleroID by the OMERACT filter

Feasibility

The ScleroID showed feasibility in the application, given the low proportion of missing data: ten patients (2.1%) had missing items, compared to 36 and 37 patients with missing data for SF-36 physical/mental component summary (PCS/MCS), 8 for EQ-5D, 12 for HAQ-DI and 16 for SSc-HAQ (Table S3). The majority of participants (462 or 98%) had complete data on the ScleroID questionnaire. Missings were evenly distributed amongst the ScleroID items (no item had significantly higher missing values).

In daily practice, single items of questionnaires are frequently missing. We therefore assessed how imputation of single items affects the overall ScleroID score. When one missing item of the ScleroID score was imputed by the mean of the remaining cohort for this item, the error was minimal (up to 0.29/10 or <10%, Table S4).

Truth

Face validity was ensured by the involvement of patient research partners in all steps of the ScleroID development[26].

The ScleroID score range is 0 to 10, the actual median and interquartile range (IQR) in our patients was 3.2 (1.9-4.7) at baseline. The median and IQ for lcSSc patients was 3.3 (2.0-4.7) and for dcSSc patients 3.3 (1.7-4.8; Figure S2). In total, eight patients recorded a ScleroID score of 0, while the highest observed value was 9.4. There was no relevant floor or ceiling effect, which would be assumed if >15% of patients scored either the minimum or maximum value ([27], Figure S2). The ScleroID questionnaire showed a good construct validity when correlated with the comparators (SSc-HAQ 0.73; EQ-5D -0.48; Patient's global assessment, VAS 0.77; HAQ-DI 0.62; SF-36 PCS -0.62; each p<0.001, Table 6).

Table 6. Construct validity analysis by correlation between ScleroID and other established PROMs

Variable	**Pearson Correlation***
Physician's Global Assessment	0.28 (0.05)
Patient's Global Assessment	0.77 (0.03)
SF-36 Physical component score (PCS)	-0.62 (0.03)

SF-36 Mental component score (MCS)	-0.47 (0.03)
HAQ-DI	0.62 (0.03)
SSc-HAQ	0.73 (0.02)
EQ-5D (UK-weighted)	-0.48 (0.04)
VAS-GIT	0.38 (0.05)
VAS-Dyspnoea	0.38 (0.04)
VAS-Raynaud	0.42 (0.04)
VAS-Ulcers	0.37 (0.05)
*(bootstrap) standard errors of estimated correlation given in brackets. Abbreviations: SF-36: the short form (36) health survey; HAQ-DI: health assessment questionnaire disability index; SSc HAQ: systemic sclerosis health assessment questionnaire); EQ-5D: EuroQol five dimensional questionnaire. UK: United Kingdom; VAS: visual analogue scale.	

The internal consistency as another measure of construct validity was also strong: Cronbach's alpha for the ScleroID was 0.87, similar to the SSc-HAQ (0.88) and higher than for the EQ-5D (0.77, Table S2). We also performed a confirmatory factor analysis which suggested a bifactor model (one general factor with additional 2 or 3 factors) with good model fit indices (Table S6 and Figure S2). The omega indices, which are thought to be superior to Cronbach`s alpha[28, 29], suggested not only good model fit for the bifactor models (Table S7), but also supported our claim for sufficient unidimensionality to justify the use of a sum score (see also supplement).

Test-retest reliability

In total, 109 patients were included in the longitudinal reliability arm and completed a second visit at 7±3 days after baseline. The ScleroID had a very good test-retest reliability, with an intra-class correlation coefficient of 0.84 (ranging 0.61 to 0.79 for the individual items), superior to all comparators (Table S8; see also Bland-Altman plot for agreement in Figure S5).

Sensitivity to change

A total of 113 patients were included and had a median follow-up visit at 12.2 (IQR 11.5-13.1) months. The sensitivity to change for the ScleroID was estimated using the Standardized Response Mean (SRM) between baseline and follow-up, using only those patients (n=37) reporting disease status as not-stable (Table 7). The SRM is computed for all patients regardless of whether they report improved/worsened disease state, and then separately for those with improved and worsened state (Table 7). The ScleroID performed better than all other comparator PROMs in indicating overall change. This performance was even better in patients who experienced improvement (Table 7).

Table 7. Sensitivity to change of the ScleroID compared to other PROMs

Variable	SRM (all)	95% CI (all)	SRM (improved)	95% CI (improved)	SRM (worsened)	95% CI (worsened)
ScleroID	0.57 [36]	(0.31,0.86)	0.76 [20]	(0.42,1.23)	-2.31 [4]	(-25.14,-1.35)
Raynaud	0.08 [37]	(-0.26,0.4)	0.21 [20]	(-0.25,0.68)	-1.50 [4]	(-,-1.17)
Hand function	-0.20 [36]	(-0.57,0.11)	-0.22 [20]	(-0.77,0.22)	-0.78 [4]	(-3.5,-0.5)
Pain	0.01 [37]	(-0.23,0.45)	0.04 [20]	(-0.39,0.51)	0.00 [4]	(-1.5,1.5)
Fatigue	0.24 [37]	(-0.08,0.54)	0.40 [20]	(0,0.79)	-1.306 [4]	(-,-0.5)
Upper GI symptoms	0.56 [37]	(0.33,0.81)	0.58 [20]	(0.25,0.99)	- [4]	(-,-)
Lower GI symptoms	0.44 [37]	(0.09,0.82)	0.43 [20]	(-0.03,1.07)	- [4]	(-,-)
Life Choices	0.53 [37]	(0.25,0.87)	0.77 [20]	(0.33,1.51)	0.50 [4]	(0.5,1.5)
Body Mobility	0.35 [37]	(0.03,0.63)	0.54 [20]	(0.14,1)	0.00 [4]	(-1.5,1.5)
Dyspnea	0.50 [37]	(0.2,0.85)	0.65 [20]	(0.25,1.24)	0.00 [4]	(-1.5,1.5)
Digital ulcers	-0.09 [36]	(-0.43,0.23)	0.00 [20]	(-0.62,0.39)	-0.5 [4]	(-1.5,-0.5)
Patient's Global Assessment	0.29 [36]	(-0.04,0.66)	0.57 [20]	(0.22,1.02)	-0.20 [4]	(-1.5,1.5)
Physician's Global Assessment	0.09 [29]	(-0.26,0.47)	0.31 [17]	(-0.18,0.9)	-0.5 [4]	(-1.5,-0.5)
SF-36 Physical component score	-0.2 [37]	(-0.53,0.08)	-0.45 [20]	(-0.85,-0.07)	10.96 [4]	(9.25,128.35)
SF-36 Mental component score	-0.08 [37]	(-0.4,0.26)	-0.18 [20]	(-0.64,0.31)	-0.24 [4]	(-1.22,2.65)
HAQ-DI	-0.01 [36]	(-0.39,0.32)	0.10 [19]	(-0.34,0.61)	-0.78 [4]	(-2.6,-0.5)
SSc HAQ	0.15 [34]	(-0.23,0.45)	0.24 [18]	(-0.26,0.69)	-0.46 [4]	(-5.5,0.5)
EQ-5D	0.41 [37]	(0.09,0.74)	0.33 [20]	(-0.09,0.74)	1.42 [4]	(1.25,9.94)

DISCUSSION

Patient-reported outcome measures (PROMs) are being developed to capture the patient`s aspects of a disease, i.e. the specific patient experience beyond the disease manifestations that are in the physician`s focus, which are typically lethal or associated with high morbidity. Especially in SSc, which has a high morbidity and mortality as well as a high work disability, there is a discordance between the patient`s experience and the physician`s assessment, exemplified by differences in the patient`s and physician`s global assessment [30-32]. This was also observed in the present study, underlining the need to implement PROMs in the clinical assessment and shared decision making. Most PROMs used in SSc are legacy questionnaires adapted from other diseases and not SSc-specific instruments.

Hence, specific PROMs are needed, although some have tried to incorporate the patient`s view [7, 33].

We have developed and validated the ScleroID questionnaire as a global measurement tool to assess the disease burden in SSc patients. The questionnaire is simple and easy to apply, has high internal consistency and shows good correlation with the patient global assessment and the SSc-HAQ. Although weighting reflects patient experience, it does not significantly change the overall score. It is planned to develop a calculator (or app) to provide final scores. The ScleroID health dimensions have a high face validity due to the inclusion of SSc patient research partners throughout the development and validation process. Notably, main dimensions of the ScleroID questionnaire such as dyspnoea, pain, digital ulcers, gastrointestinal symptoms or fatigue were also associated with a high self-reported disability and high disease burden in other reports from the literature [5, 34].

The ScleroID questionnaire has a very good re-test reliability, which is even better than comparators and has better sensitivity to change than the comparators used. This is especially important as a high percentage of patients are relatively stable, but progression of the disease drives mortality and morbidity [35]. In addition, other frequently used major outcomes of SSc studies, such as the mRSS, show a relatively low sensitivity to change, which might partially explain the many randomized clinical trials with borderline significance using the mRSS as a primary outcome [36].

Comparison to other PROMs

In contrast to other validated PROMS that have not been developed specifically for SSc (such as PROMIS-29,[37-39]) or have only been adapted to SSc (such as the SHAQ,[39, 40]), the ScleroID questionnaire was specifically developed, with involvement of SSc patient research partners. Although other specific PROMs for SSc have been developed, the Symptom Burden Index (SBI) and the Systemic Sclerosis Questionnaire (SySQ) did not involve the target population for dimension/item generation. The Scleroderma Assessment Questionnaire (SAQ), which is based on the SysQ, had only partial involvement of patients [41, 42]. However, these questionnaires have only been partially validated, mostly lacking a discriminant validity analysis, and are partly not validated in English (SysQ and SAQ). The recently published PROM CSF-17 (Cochin Scleroderma Functional scale 17), a 17 item PROM that focused on mobility and general task aspects of SSc, was also developed with involvement of SSc patients [43]. It has been evaluated in a smaller cohort than the ScleroID and in French only, with data on discriminant validity (sensitivity to change) still missing.

Limitations of the study

Although patients with diverse disease manifestations participated in the nominal group exercise, disease-related or demographic data were not prospectively collected at this early stage. Patients included in the cross-sectional analysis had to fulfil the ACR/EULAR 2013 classification criteria for SSc but there were no recommendations concerning disease subtype or organ involvement. The final selection of participants by the centres has an impact on the weighting of the ScleroID dimensions and the cross-sectional part included mainly patients with longstanding disease. However, our cohort reflects other observational cohorts such as the EUSTAR registry etc, indicating that it is a representative SSc population. Although SSc patients often acquire expert knowledge about their disease and are aware that the questionnaire evaluates SSc-related burden, it might be difficult at times to distinguish symptoms related to SSc from common, unrelated symptoms, e.g. as in the case of GI problems. This is however common to all PROMs.

Another potential limitation is the relative paucity of patients who experience change of their disease status, who then enter the sensitivity to change analysis. As this change was anchored by the patients themselves, there were no prior data to guide selection of these patients.

The ScleroID was designed as an overall measure of disease impact. It was derived from patients under routine clinical care and as such, it is still to be validated in clinical trials aiming at overall disease modification. If the ScleroID questionnaire can also be used for clinical trials focusing on organ-specific disease progression is subject to further analysis.

In summary, the ScleroID questionnaire is a unique, easy to apply, SSc-specific PROM that has been successfully validated in a large European clinical cohort using multiple translations. It should be further validated for clinical trials and in large registries and has the potential to measure disease impact that will be more meaningful for patients and health authorities than currently used approaches.

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CONTRIBUTORSHIP

The authors as listed on the title page of the manuscript have all made substantial contributions which qualifies them as authors. All authors contributed to critical revisions and approved the final version of the manuscript.

MB: design of the study, acquisition of data, analysis, interpretation of data, drafting and revising the article.

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AG: analysis, interpretation of data, drafting and revising the article.

KF: design of the study, acquisition of data, interpretation of data, revising the article.

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GS: acquisition of data, analysis, interpretation of data, revising the article.

OKB: acquisition of data, analysis, interpretation of data, revising the article.

CB: acquisition of data, analysis, interpretation of data, revising the article.

MMC: acquisition of data, analysis, interpretation of data, revising the article.

CM: acquisition of data, analysis, interpretation of data, revising the article.

AMG: acquisition of data, analysis, interpretation of data, revising the article.

UML: acquisition of data, interpretation of data, revising the article.
JS: design of the study, analysis, interpretation of data, revising the article.
TKK: design of the study, analysis, interpretation of data, revising the article.
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OD has/had consultancy relationship and/or has received research funding in the area of potential treatments of scleroderma and its complications from (last three years): Abbvie, Acceleron Pharma, Alexion, Amgen, AnaMar, Arxx Therapeutics, Baecon Discovery, Bayer, Boehringer Ingelheim, Catenion, Drug Development International Ltd, CSL Behring, ChemomAb, GSK, Horizon (Curzion) Pharmaceuticals, Inventiva, Italfarmaco, iQvia, Lilly, Medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Sanofi, Serodapharm, Target Bio Science and UCB In addition, he has a patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143).

DATA AVAILABILITY STATEMENT

Upon request, and subject to review by the steering committee, access can be granted to the anonymized raw data and the R code. De-identified data will be made available via secure data transfer. Data requests may be sent to the ScleroID steering committee, represented by Dr Oliver Distler, Department of Rheumatology, University Hospital Zurich, University of Zurich, Switzerland. E-mail oliver.distler@usz.ch.

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PREVIOUSLY PRESENTED WORK

Part of this work has previously been presented, as follows:

Presentations:

- The EULAR Systemic Sclerosis Impact of Disease score – a new patient-reported outcome measure under development, 4th Scleroderma World Congress, Patient Congress, Lisbon, Feb 18th – 20th, 2016
- Poster EULAR 2016
- Poster ACR 2016
- Abstract book EULAR 2017
- Poster ACR 2017
- Poster Patients' Congress SWC 02/2018 Bordeaux
- Abstract book EULAR 2018

- Meetings:
    - Working group patients and PIs inkl. teleconference – Rome, 06/2015
    - Task force meetings
- EULAR 06/2016 London
- ACR 11/2016 Washington
- EULAR 06/2017 Madrid
- EULAR 2020 Online E-Congress

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