


SHORT REPORT

Performance of the EULAR Systemic sclerosis Impact of Disease (ScleroID) questionnaire as a patient-reported outcome measure for patients with diffuse systemic sclerosis

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ABSTRACT

Objective Systemic sclerosis Impact of Disease (ScleroID) is the first comprehensive patient-reported outcome measure (PROM) specifically developed for systemic sclerosis (SSc). We investigated the performance of ScleroID in patients with diffuse cutaneous SSc (dcSSc), as a prerequisite for its use in randomised controlled trials (RCTs) testing potentially disease-modifying drugs.

Methods All patients with dcSSc from the large, multicentric, ScleroID cohort were included. SSc-Health Assessment Questionnaire (HAQ), EuroQol-5 Dimensions and 36-item Short Form Health Survey (SF-36) were used as comparators. The study includes a longitudinal arm with a reliability visit at 7±3 days and a 12 months follow-up visit. The performance of ScleroID in dcSSc was assessed according to the Outcome Measures in Rheumatology filter.

Results In total, 152 dcSSc patients were analysed (29% male, median age 54 years). ScleroID reflected well the disease impact of dcSSc, showing a good construct validity with high Spearman's correlation coefficients with comparators (SSc-HAQ, 0.79, 95% CI (0.69, 0.86); HAQ-Disability Index, 0.72 95% CI (0.60, 0.80); SF-36 physical score, -0.69 95% CI (-0.77, -0.60)). The internal consistency was strong (Cronbach's alpha 0.87, split-half reliability coefficient 0.88).

In the longitudinal arm, 44 patients had a reliability visit and 113 had a follow-up visit, of whom 19/113 (17%) reported a significant change (11 improved, 8 worsened). ScleroID showed a good consistency and discriminative ability with excellent test-retest reliability (intraclass correlation coefficient 0.89, 95% CI (0.84, 0.92)) and moderate sensitivity to change (standardised response mean -0.63 in the improved subgroup and 0.48 in the worsened subgroup), but superior to the comparators.

Conclusion The European Alliance of Associations for Rheumatology (EULAR) ScleroID performs well for patients

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systemic sclerosis Impact of Disease (ScleroID) has been successfully validated as a patient-reported outcome measure (PROM) for systemic sclerosis (SSc) in an unselected cohort of patients.

WHAT THIS STUDY ADDS

⇒ In this post hoc analysis of the data from the original ScleroID study, we could show its superior performance to comparators (SSc-Health Assessment Questionnaire, EuroQol-5 Dimensions, 36-item Short Form Health Survey) in diffuse cutaneous SSc (dcSSc) patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This analysis provides evidence for further use of ScleroID as a disease-specific PROM in clinical trials and routine care for patients with dcSSc.

with dcSSc. This supports its inclusion and regular assessment as PROM in RCTs.

INTRODUCTION

Diffuse cutaneous systemic sclerosis (dcSSc) is the most severe form of SSc, often associated with multiple organ involvement and significant morbidity and mortality. There is a pressing, unmet need for efficient therapies, which drives the development and testing of novel therapeutic agents in randomised controlled trials (RCTs) in SSc.¹ Due to their

increased morbidity and mortality, dcSSc patients are most frequently recruited into clinical trials.

Patient-reported outcome measures (PROMs) play an important part of patient-centred medicine and hence are key outcome measures for RCTs.^{2,3} In RCTs, PROMs allow assessment of health-related quality of life, treatment effect and safety as perceived by patients. PROMs are mandatory for all RCTs and are highly relevant for regulatory authorities when evaluating applications for marketing authorisation of new therapeutic agents.^{1,2,4,5}

However, selecting the ideal PROM to reflect the outcome of interest in SSc-RCTs is often difficult, on one side due to the paucity of specific and validated PROMs, on the other side due to the heterogeneity of the disease, both in terms of clinical manifestations and disease progression.^{1,6} Most SSc-RCTs relied on a set of generic, legacy PROMs that showed good performance in SSc, such as the Health Assessment Questionnaire Disability Index (HAQ-DI) and its adaptation, the Scleroderma HAQ, the medical outcomes study 36-item Short Form Health Survey (SF-36)⁷ and the EuroQol-5 Dimensions (EQ-5D).⁸

Most of the available and validated SSc-specific PROMs focus on particular aspects of the disease. Examples include instruments such as the Raynaud Condition Score, the Scleroderma Skin Patient-Reported Outcome or the new Hand Disability in Systemic Sclerosis-Digital Ulcers tool.^{1,9,10}

To date, none of the RCTs in SSc meeting their primary endpoint in interstitial lung disease have shown a meaningful change in PROMs when they were used as secondary outcome measures for treatment effect.¹ This might be attributed to limitations of the investigational drug itself but also due to the insufficient sensitivity to change of the PROMs available.¹ This highlights the need for developing better PROMs, which can reflect how patients feel, cope with and respond to the use of an investigational product in clinical trials.¹¹ Considering the predominant focus of RCTs on patients with dcSSc, a validated PROM to reflect the disease burden experienced by patients with dcSSc is crucial.

Addressing this unmet need, we have recently developed and validated the Systemic sclerosis Impact of Disease (ScleroID) questionnaire, which has received the endorsement of the European Alliance of Associations for Rheumatology (EULAR). This is the first comprehensive PROM specifically developed by SSc patients and experts to reflect the global disease impact of SSc, which showed a good performance in a large clinical validation study.¹² The development of ScleroID was specifically designed for SSc, based with adaptations on the previous, successful development of similar EULAR composite measures for rheumatoid arthritis and psoriatic arthritis.^{13–15}

In the current study, we report a novel, detailed analysis of the performance of ScleroID in the subset of patients with dcSSc, adhering to the guidelines established by Outcome Measures in Rheumatology (OMERACT), thus

adding important information for its future use in clinical trials.¹⁶

PATIENTS AND METHODS

The ScleroID development and validation study was a multicentric collaboration including 11 European expert SSc centres and patient research partners.¹² Briefly, the study included the cross-sectional analysis of a large baseline cohort consisting of 472 SSc patients, along with a longitudinal component featuring a reliability visit at 7±3 days (109 patients) and a 12-month follow-up visit (113 patients). At all visits, patients completed the ScleroID questionnaire as well as the SSc-HAQ, EQ-5D and SF-36.¹²

In the current study, we focus on analysing all patients diagnosed with dcSSc from the original ScleroID cohort.

The performance of ScleroID in dcSSc was assessed according to the OMERACT guidelines, including the major pillars of truth, discrimination and feasibility.^{16,17} Truth encompasses face and content validity ('Is the measure applicable and does it make sense?', floor/ceiling effect), construct validity ('Does the PROM measure what it should measure?') and internal consistency ('Do the PROM items cover all the aspects they are supposed to?'). Spearman correlations between ScleroID and the other established PROMs (SSc-HAQ, EQ-5D, SF-36), as well as Cronbach's alpha and the split-half reliability coefficient, were calculated accordingly.

Discrimination was assessed through test-retest reliability ('Are the results reproducible in a stable population?') by calculating the intraclass correlation coefficient (with the reference values below 0.50: poor, between 0.50 and 0.75: moderate, between 0.75 and 0.90: good, above 0.90: excellent¹⁸). Patients self-reported their perceived disease status at follow-up by answering a dedicated Likert-scale question (online supplemental methods). Sensitivity to change was consequently assessed to determine whether the tool could distinguish between different groups at follow-up, such as stable versus improved or worsened, using the standardised response mean (SRM).

RESULTS

Out of 152 dcSSc patients with baseline data analysed, 44 (29%) were male, with a median age of 54 years and a median disease duration of 7 years since the first non-Raynaud symptom. The self-reported disease status was good or very good in a third of patients, acceptable in almost half of the cohort and bad or very bad in 17% of patients (table 1). A detailed cohort description is shown in table 1.

Truth and feasibility

The ScleroID questionnaire was filled in completely by the great majority of dcSSc patients, with minimal percentages of missing data observed among the individual items (online supplemental figure S1). There was

Table 1 Baseline cohort characteristics of patients with dcSSc

Variable	Value	Missingness of the variable
Total number of patients with dcSSc	152	NA
Age, years, median (Q1–Q3)	54.00 (44.0–61.0)	0%
Male gender, n (%)	44 (28.9)	0%
Time since RP onset, years, median(Q1–Q3)	8.0 (4.0–15.0)	17%
Disease duration*, years, median(Q1–Q3)	7.0 (3.2–12.0)	1%
Disease duration <3 years	23	1%
ANA positive, n (%)	102 (94.4)	13%
ACA positive, n (%)	5 (4.9)	13%
Scl-70 positive, n (%)	59 (55.7)	13%
Anti-RNA polymerase III positive, n (%)	15 (16.7)	15%
mRSS, median(Q1–Q3)	9.0 (5.0–15.0)	26%
Presence of RP, n (%)	123 (96.1)	16%
Digital ulcers—current, n (%)	23 (18.5)	9%
Digital ulcers—never, n (%)	63 (50.8)	9%
Joint contractures, n (%)	68 (55.7)	20%
Joint synovitis, n (%)	2 (1.6)	20%
Oesophageal symptoms (dysphagia, reflux), n (%)	91 (65.9)	9%
Stomach symptoms (early satiety, vomiting), n (%)	27 (22.0)	19%
Intestinal symptoms (diarrhoea, bloating, constipation), n (%)	54 (38.8)	9%
Malabsorption syndrome, n (%)	10 (10.8)	39%
Dyspnoea, NYHA stages I and II, n (%)	91 (86.7)	27%
Dyspnoea, NYHA stages III and IV, n (%)	14 (13.3)	27%
Pulmonary hypertension, n (%)	10 (10.6)	20%
Lung fibrosis detected by HRCT, n (%)	38 (67.9)	27%
FVC, % predicted, median (IQR)	87(75.5, 98.0)	41%
DLCO/SB, % predicted, median (Q1–Q3)	57.00 (48.5–71.5)	43%
Immunosuppression, n (%)	33 (32.7)	34%
ESR >25 mm/hour, n (%)	82 (68.3)	21%
CRP elevation, n (%)	31 (28.7)	29%
ScleroID score, median (Q1–Q3)	3.22 (1.7–4.7)	2%
Self-reported current disease status†		0%
Very good	14 (9.2%)	
Good	38 (25.0%)	
Acceptable	75 (49.3%)	
Bad	19 (12.5%)	
Very bad	5 (3.3%)	
Patients' global assessment	4 (2–6)	1%

*Disease duration was defined as the time since the first non-RP manifestation.

†The self-reported current disease status was assessed by the following question in the case report form: Think about all the ways in which the systemic sclerosis has affected you during the last week, how would you consider this state?

ACA, anticentromere antibodies; ANA, antinuclear antibodies; CRP, C reactive protein; dcSSc, diffuse cutaneous systemic sclerosis; DLCO/SB, diffusing capacity of the lung for carbon monoxide/single breath; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HRCT, high-resolution CT; mRSS, modified Rodnan Skin Score; NA, not applicable; NYHA, New York Heart Association; RP, Raynaud's phenomenon; ScleroID, Systemic sclerosis Impact of Disease.

no relevant ceiling or floor effect (online supplemental figure S2) and the individual scores of the ScleroID items

were distributed uniformly across the cohort (online supplemental figure S3).

Table 2 Performance of ScleroID in dcSSc by the OMERACT filter for truth and discrimination

Truth	
Construct validity—does the PROM measure what it is supposed to measure?	Spearman's correlation between ScleroID and: ▶ SSc-HAQ, 0.79, 95%CI (0.69, 0.86) ▶ HAQ-DI, 0.72, 95%CI (0.60, 0.80) ▶ SF-36 physical score, -0.69, 95%CI (-0.77, -0.60)
Internal consistency—do the PROM items cover all aspects they are supposed to?	Cronbach's alpha 0.87 (good) Split-half reliability coefficient 0.88
Discrimination	
Test-retest reliability—are the results reproducible in a stable population?	Intraclass correlation coefficient 0.89, 95%CI (0.84, 0.92) (excellent)
Sensitivity to change—can the PROM discriminate between groups in the setting of interest (worsened/improved)?	SRM -0.63 in the improved subgroup and 0.48 in the worsened subgroup; moderate, superior to the comparators (SSc-HAQ, EQ-5D, SF-36) Patients with no change: SRM -0.118
dcSSc, diffuse cutaneous systemic sclerosis; EQ-5D, EuroQol-5 Dimensions; HAQ-DI, Health Assessment Questionnaire Disability Index; OMERACT, Outcome Measures in Rheumatology; PROM, patient-reported outcome measure; ScleroID, Systemic sclerosis Impact of Disease; SF-36, 36-item Short Form Health Survey; SRM, standardised response mean.	

ScleroID showed a good construct validity with high Spearman's correlation coefficients with the other PROMs (SSc-HAQ, 0.79, 95% CI (0.69, 0.86); HAQ-DI, 0.72 95% CI (0.60, 0.80); SF-36 physical score, -0.69 95% CI (-0.77, -0.60)) (online supplemental table S1 and table 2).

Furthermore, the internal consistency was strong, according to Cronbach's alpha coefficient of 0.87 and to the split-half reliability coefficient of 0.88 (table 2).

DISCRIMINATION

In the longitudinal follow-up, 44 patients with dcSSc underwent a test-retest reliability visit at 7±3 days. ScleroID showed excellent consistency, with a calculated intraclass correlation coefficient of 0.89, 95% CI (0.84, 0.92).

In total, 113 patients had a 12-month follow-up visit, of whom 19/113 (17%) reported a meaningful change (11 improved, 8 worsened). ScleroID showed a moderate sensitivity to change, nonetheless superior to the other PROMs, as shown in table 2 and, in more detail, in table 3. Considering the sensitivity to change separately, depending on the direction of change, ScleroID showed a global SRM of -0.63 in the patients who improved, respectively, an SRM of 0.48 in those who worsened (and an SRM of -0.12 for patients with no change; table 3). The superiority to the other PROMs in terms of SRM was evident in both improved and worsened subgroups (table 3). The ScleroID values changed overall from baseline median 3.22 (IQR 1.7–4.7) to 3.27 (IQR 2.27–4.77) (patients who improved: 2.73 (IQR 1.74–3.88) to 1.78 (IQR 0.56 to 2.53) and patients who worsened: 4.77 (IQR 3.09–5.34) to 5.48 (IQR 4.71–5.90).

DISCUSSION

This in-depth analysis, specifically focusing on dcSSc patients, shows overall very good performance of ScleroID in this subgroup of individuals with more severe disease

Table 3 Sensitivity to change for the ScleroID between baseline and follow-up (SRM)

PROM	SRM (improved)	SRM (worsened)	SRM (stable)
ScleroID			
Raynaud score	-1.317	0.259	0.000
Hand function score	-0.855	0.403	-0.070
Pain score	-0.605	0.225	0.152
Fatigue score	-0.661	0.496	0.020
Upper GI score	0.231	-0.195	-0.097
Lower GI score	0.194	0.170	-0.134
Life choices score	0.210	0.177	-0.129
Body mobility score	0.000	0.279	-0.271
Dyspnoea score	0.422	0.277	0.013
Digital ulcers score	-0.249	0.526	-0.367
ScleroID total score	-0.634	0.483	-0.118
SF-36 Physical Component score	0.478	-0.352	0.261
SF-36 Mental Component score	0.567	0.138	0.120
HAQ-DI score	-0.441	-0.327	-0.187
SSc-HAQ score	-0.511	-0.244	-0.112
EQ-5D score	0.988	0.133	0.010
Thresholds: SRM <0.2–0.5 low, 0.5–0.8 moderate, >0.8 large responsiveness, respectively. ²⁰			
EQ-5D, EuroQol-5 Dimensional Questionnaire; GI, gastrointestinal tract; HAQ-DI, Health Assessment Questionnaire Disability Index; PROMs, patient-reported outcome measures; ScleroID, Systemic Sclerosis Impact of Disease; SF-36, Short Form (36) Health Survey; SRM, standardised response mean; SSc, systemic sclerosis.			

manifestations. The questionnaire is feasible to apply in a clinical setting and has the ability to reflect/capture the impact of dcSSc from the patients' own perspective across all relevant disease-related health dimensions. The good correlation with other established/validated PROMs and the strong internal consistency provide evidence of this.

Furthermore, the ScleroID questionnaire showed a good discriminative ability in the longitudinal analysis. First, it showed very good reproducibility in stable patients at repeated measurements. In addition, the sensitivity to change at 12 months follow-up was higher than for the other PROMs, with a moderate SRM, consistent in the improving/worsening subgroups. However, the low number of patients with a self-reported change at follow-up impairs a reliable evaluation of the sensitivity to change of the individual items of ScleroID based solely on these data. This limitation remains for exploration in future studies, particularly in the setting of a clinical trial, where besides the global disease impact, specific effects on certain health domains might be of particular interest.

Overall, the good performance of ScleroID in this cohort of patients with dcSSc further supports the findings from the unselected, original SSc validation cohort and from a large, unselected, monocentric cohort.^{12 19}

Our study is the first to analyse the performance of ScleroID in patients with dcSSc. Strengths of our study further include the multicentre, large cohort of patients with SSc, the thorough design and methodology following the OMERACT filter and the inclusion of several, widely used PROMs as comparators (SSc-HAQ, EQ-5D and SF-36). The data presented in this study support the decision of including ScleroID as a PROM in clinical trials focusing on patients with dcSSc and its evaluation in clinical practice.

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