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Application and performance of disease activity indices proposed for patients with systemic sclerosis in an international cohort of patients with juvenile systemic sclerosis

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Abstract

Objectives: Juvenile systemic sclerosis is a rare childhood disease. Three disease activity indices have been published for adult patients with systemic sclerosis: the European Scleroderma Study Group Index, a modified version of the European Scleroderma Study Group Index and the revised European Scleroderma Trials and Research index. The objective of this study was to determine the feasibility and performance of the three disease activity indices in a prospectively followed cohort of patients with juvenile systemic sclerosis.

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Methods: The analysis cohort was selected from the prospective international inception cohort enrolling juvenile systemic sclerosis patients. The correlation of the disease activity indices with the physicians' and the patients' global assessment of disease activity was determined. The disease activity indices were compared between patients with active and inactive disease. Sensitivity to change between 6- and 12-month follow-up was investigated by mixed models.
Results: Eighty percent of the 70 patients had a diffuse cutaneous subtype. The revised European Scleroderma Trials and Research index was highly correlated with the physician-reported global disease activity/parents-reported global disease activity (r = 0.74/0.64), followed by the European Scleroderma Study Group activity index (r = 0.61/0.55) and the modified version of the European Scleroderma Study Group activity index (r = 0.51/0.43). The disease activity indices significantly differed between active and inactive patients. The disease activity indices showed sensitivity to change between 6- and 12-month follow-up among patients who improved or worsened according to the physician-reported global disease activity and the parents-reported global disease activity.
Conclusion: Overall, no disease activity score is superior to the other, and all three scores have limitations in the application in juvenile systemic sclerosis patients. Furthermore, research on the concept of disease activity and suitable scores to measure disease activity in patients with juvenile systemic sclerosis is necessary in future.

Keywords
Systemic sclerosis, disease activity, juvenile systemic sclerosis

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Introduction

Juvenile systemic sclerosis (jSSc) is a rare chronic multisystemic connective tissue disease with disease onset in children and adolescents younger than 18 years. The estimated prevalence is 3 per 1,000,000 children,[1] and the yearly incidence is estimated to be 0.27 per 1,000,000 children.[2] JSSc is one of the most severe rheumatologic diseases in childhood due to its significant morbidity and mortality.[3] A major hallmark of jSSc is the combination of inflammation, fibrosis and vasculopathy.[4]

The clinical presentation and course of jSSc can be evaluated by measuring disease activity (DA) and damage at a given time. Both components reflect disease severity of jSSc and describe the total impact of the disease on organ function.[5,6] DA is the component that varies over time and is potentially influenceable by an intervention. In contrast, DA captures organ damage that is irreparable and typically not reversible by treatment. Currently, no evaluated instrument exists to assess DA in patients with jSSc. Several composite scores for DA have been developed for adult patients with systemic sclerosis (SSc) in recent years. Valentini et al.[6] published on behalf of the European Scleroderma Study Group (EScSG), the EScSG activity index (EScSGI) in 2001. A modified version of the EScSGI (the mEScSGI) was published by Minier et al.,[7] including additional pulmonary and vascular organ outcome measures.[8] A third DA measure was published by the European Scleroderma Trials and Research group (EUSTAR), which developed a revised disease activity index (rEUSTARi).[9] The EScSGI includes mainly information from patients' self-assessment (vascular, skin and cutaneous parameters) and was developed in a cohort of SSc patients with long disease duration.[10] In contrast, rEUSTARi was developed in a cohort that included SSc patients with short disease duration, and includes, for example, articular involvement and tendon friction rub.[9]

The objective of our study was to determine the performance and applicability of the three disease activity indices (DAIs): EScSGI, mEScSGI and rEUSTARi, in a multicentre cohort study enrolling patients with jSSc to critically evaluate the potential applicability of the composite scores in patients with jSSc.

Materials and methods

Patients

The cohort evaluated was the juvenile systemic sclerosis inception (jSSci) cohort, an international multicentre observational cohort study in which specialised paediatric and adolescent rheumatology centres from Europe (25), Asia (5), North America (6) and South America (6) enrolling jSSc patients and follow them longitudinally every 6 months. The study coordination and management is based at the Hamburg Centre for Paediatric and Adolescent Rheumatology. The jSSci is an ongoing cohort study. The first patient was enrolled into the cohort in January 2008.

The inclusion criteria for the jSSci cohort are the following: (1) patients who fulfil the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc[11] and (2) patients aged less than 16 years at the time of the first non-Raynaud sign of disease and aged less than 18 years at the time of enrolment. The patients are prospectively followed every 6 months with a standardised case report

form. The informed consent and case report forms are available in the native language of each participating study centre.

Measures

Sociodemographic, clinical and laboratory parameters; the results of physical and organ examinations and physician- and patient-related outcome measures were collected at enrolment and thereafter every 6 months on a standardised case report form. Patients were classified into diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous subset (lcSSc)[12] by the treating paediatric rheumatologist. The treating physician assessed skin involvement using the modified Rodnan Skin Score (mRSS).[13] Gastrointestinal involvement was assessed by the treating clinician who reported about the following symptoms: diarrhoea (>3 stools/day), constipation (stooling more than once every 3 days) and reflux symptoms, by evaluation with barium swallow, oesophageal scintigraphy and endoscopy and colon scintigraphy. Cardiac involvement was assessed by an abnormal echocardiogram finding such as pericardial effusion, abnormal ejection fraction, left ventricular (LV), or right ventricular (RV) diastolic dysfunction or abnormal electrocardiography (ECG) finding. Renal involvement was defined by meeting any of the criteria: a history of prior hypertension, hypertension was present at the baseline visit, or when a positive urinary sediment with significant proteinuria or renal crisis occurred prior or at the time of enrolment. Musculoskeletal involvement was clinically assessed by total joint count and assessment of muscle strength. Forced vital capacity (FVC) and diffusing lung capacity for carbon monoxide (DLCO) were recorded as a percentage of the predicted value for the patient's demographics.

In addition, the physician reported about global (G) disease activity (PGA) and global disease damage (PGD) on a visual analogue scale (VAS) ranging from 0 to 100. The digital ulcer clinical assessment score (DUCAS) was collected since 2018. The patients or their parents (Pa) reported global disease activity (PaGA), global disease damage (PaGD), ulceration activity and Raynaud activity, assessed on a VAS ranging from 0 to 100. Functional limitations were assessed using the childhood health assessment questionnaire (CHAQ).[14] Both the physicians and the patients or parents evaluated globally the overall jSSc disease course compared to the last visit (much better, a little better, almost the same, a little worse or much worse). More details about the cohort and the instruments can be found in Foeldvari et al.'s study.[15]

The three DAIs were calculated according to the published scoring algorithms. The description of single items, their scoring and their distribution at the 12-month follow-up are reported in Supplemental Table 1. The presence of hypocomplementaemia (a component of the EScSGI and the mEScSGI) and the patient's reported 17-area thickness score (a component of the mEScSGI) were not available for assessment in our cohort. The score components for these measures were set to zero in the corresponding scores.

The EScSGI, the mEScSGI and the rEUSTARi were calculated at the 6- and 12-month follow-up because some individual index components require the change in the parameter since the last visit, and this information was not available for the baseline visit. Established cut-offs from adult SSc for the EScSGI (≥ 3)[6] and the rEUSTARi (≥ 2.5)[9] were applied to define jSSC patients as active. Such a cut-off was not available for mEScSGI.

Statistics

Spearman correlation coefficients were used to determine the association between the DA scores and the PGA, the PGD, the PaGA, the PaGD, the DUCAS and the CHAQ. We hypothesised that higher levels of DA scores are associated with higher levels in the PGA, the PaGA and the DUCAS, while we expected weaker correlations for the PGD, the PaGD and the CHAQ reflecting damage. The single components of the three DA scores were correlated with the PGA, the PGD, the PaGA and the PaGD by polychoric correlation coefficients, an appropriate association measure for ordinal variables. The change in DA scores was modelled by generalised linear mixed models in the patients whose DA improved or worsened according to the physicians' or the patients'/parents' evaluation. Standardised regression coefficients were calculated to compare the magnitude of change between the three DA scores. Mann–Whitney U-test was used to compare the DA scores between patients with a PGA < 10 to patients with a PGA ≥ 10 and comparing patients with a PaGA < 10 to patients with a PaGA ≥ 10. The effect size (Cohen's d) was calculated to quantify the group differences. All statistical analyses were performed with STATA 12.1.[16]

Results

Patients

A total of 150 patients with jSSc were enrolled into the cohort up to April 2021. Of these patients, 70 could be included in the analyses due to available 12-month follow-up data. Fifteen patients dropped out of the study due to loss of contact with the transition to an adult rheumatologist, and for the other 65 patients, there were no 12-month follow-up data available at the time of data cut-off. The patients who were not included in our analyses ($n = 80$) had a significantly lower mRSS and PGA compared to the analysed 70 jSSc patients; otherwise, all other characteristics

Table 1. Sociodemographic and clinical characteristics of patients in the jSSc inception cohort at 6- and 12-month follow-up (N = 70).

	6-month visit	12-month visit
	N = 70	N = 70
Female gender, n (%)	55 (78.6%)	
Age at visit, years, median (p25–p75)	14.1 (10.4 to 16.8)	14.6 (10.9 to 17.3)
Ethnicity, n (%)		
Caucasian	61 (87.1%)	
African	5 (7.1%)	
Indian	2 (2.9%)	
Other	2 (2.9%)	
Diffuse subtype	57 (81.4%)	
Limited subtype	13 (18.6%)	
BMI, SDS, median (p25–p75)	−0.2 (−1.3 to 0.9)	−0.4 (−1.2 to 0.7)
Height, SDS, median (p25–p75)	−0.2 (−0.8 to 0.9)	−0.1 (−0.9 to 0.9)
Disease duration, years, median (p25–p75)	3.0 (1.5 to 4.8)	3.5 (2.0 to 5.4)
Age of onset of Raynaud's, years, median (p25–p75)	9.8 (5.9 to 12.5)	
Age of onset of non-Raynaud's, years, median (p25–p75)	10.7 (7.1 to 12.8)	
ANA positivity, n (%)	63 (91.3%)	
Anti-centromere antibodies, n (%)	0 (0.0%)	
Anti-Scl-70 antibodies, n (%)	27 (39.1%)	
Modified Rodnan skin score, median (p25–p75)	15.0 (8.0 to 23.0)	9.3 (5.0 to 24.0)
DUCAS score, median (p25–p75)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.5)
Gastrointestinal involvement, n (%)	20 (28.6%)	30 (43.5%)
Musculoskeletal involvement, n (%)	38 (55.1%)	40 (58.0%)
Cardiac involvement, n (%)	11 (15.7%)	13 (18.6%)
Pulmonary involvement, n (%)	35 (50.0%)	37 (52.9%)
Renal involvement, n (%)	3 (4.3%)	4 (5.7%)
Physician's global assessment of disease activity, VAS, median (p25–p75)	22.5 (12.5 to 42.5)	20.0 (10.0 to 30.0)
Physician's global assessment of damage, VAS, median (p25–p75)	30.0 (20.0 to 50.0)	30.0 (15.0 to 40.0)
Physician's global assessment of ulceration activity, VAS, median (p25–p75)	0.0 (0.0 to 15.0)	0.0 (0.0 to 10.0)
Patient's global assessment of disease activity, VAS, median (p25–p75)	35.0 (10.0 to 50.0)	30.0 (10.0 to 40.0)
Patient's global assessment of damage, VAS, median (p25–p75)	30.0 (20.0 to 50.0)	20.0 (10.0 to 40.0)
Patient's global assessment of Raynaud's activity, VAS, median (p25–p75)	20.0 (10.0 to 40.0)	10.0 (0.0 to 30.0)
Patient's global assessment of ulceration activity, VAS, median (p25–p75)	3.5 (0.0 to 20.0)	0.0 (0.0 to 10.0)
CHAQ	0.3 (0.1 to 0.8)	0.3 (0.0 to 0.8)
EScSG, median (p25–p75)	1.5 (0.5 to 3.0)	1.5 (0.5 to 3.0)
mEScSG, median (p25–p75)	1.5 (1.0 to 3.0)	1.5 (1.0 to 3.0)
rEUSTARi, median (p25–p75)	1.5 (0.9 to 3.0)	1.5 (0.6 to 3.0)

ANA: antinuclear antibodies; jSSc: juvenile systemic sclerosis; p25: 25th percentile; p75: 75th percentile; BMI: body mass index; SDS: standard deviation score; DUCAS: digital ulcer clinical assessment; VAS: visual analogue scale 0 (best possible value) to 100 (worst value); CHAQ: Childhood Health Assessment Questionnaire; EScSG: European Scleroderma Study Group; mEScSG: modified European Scleroderma Study Group activity index; rEUSTARi: revised European Scleroderma Study group activity index.

were comparable (Supplemental Table 2) between both groups.

The mean disease duration was 3.6 years (SD 3.0), and the mean age at Raynaud's onset was 9.4 years (SD 4.0) at the 6-month follow-up. Fifty-five patients (79%) were female, and 57 (81%) had the diffuse cutaneous subtype. The mean PGA was 30.8 (SD 22.8) at the 6-month follow-up and slightly decreased at the 12-month follow-up (mean 26.3, SD 18.7). Detailed patient characteristics are reported in Table 1.

DA scores

At the 6-month follow-up, the mean levels of the EScSGI, the mEScSGI and the rEUSTARi were 1.9 (SD 1.5, median 1.5), 2.0 (SD 1.2, median 1.5) and 1.9 (SD 1.5, median 1.5), respectively. The distribution of the scores was slightly skewed and did not show a floor effect (Figure 1).

At the 6-month follow-up, the correlation between the EScSGI and the mEScSGI was $r = 0.87$ ($p < 0.001$; Figure 2), between the EScSGI and the rEUSTARi was

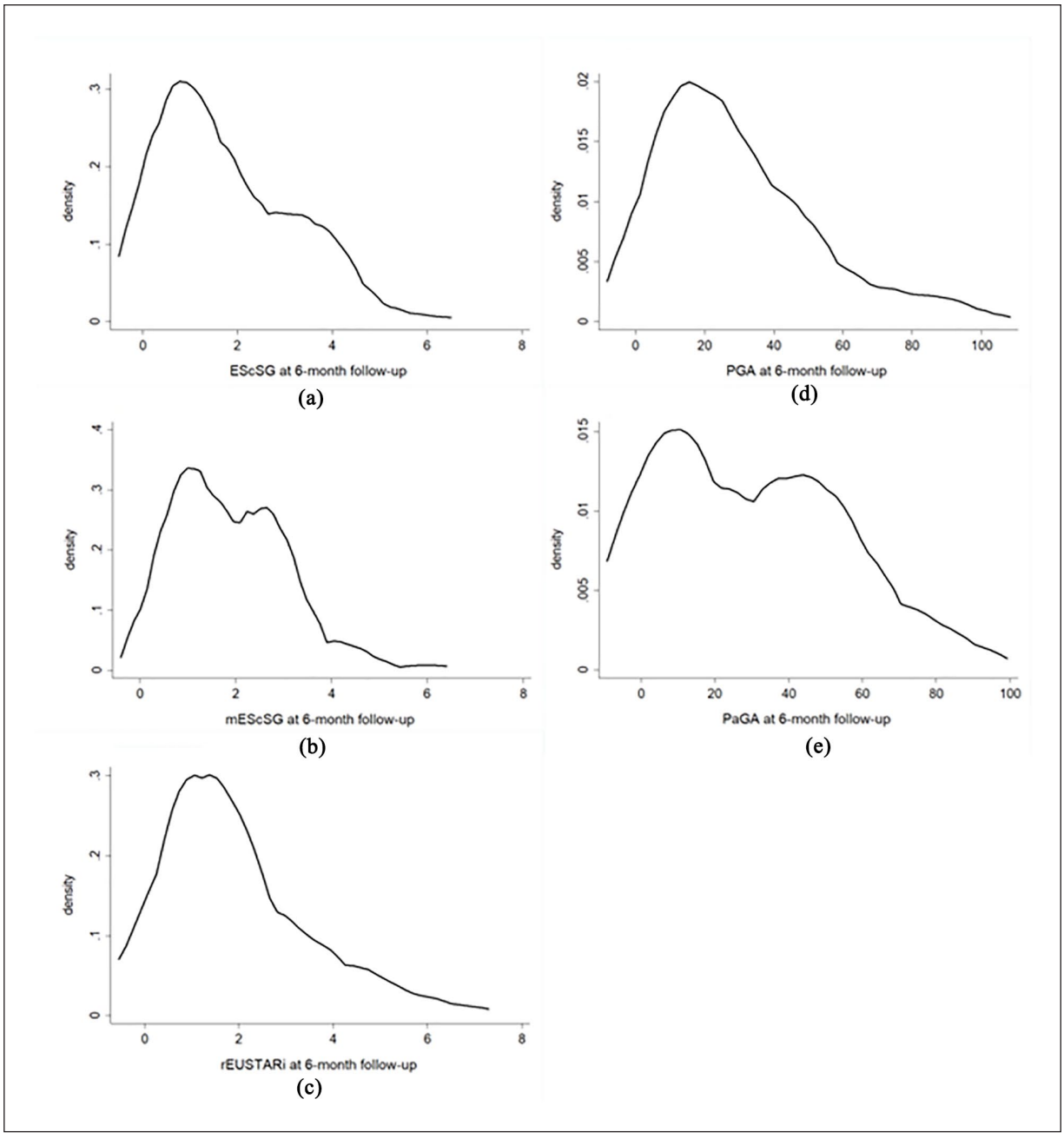

Figure 1. Distribution of (a) EScSGi, (b) mEScSGi, (c) rEUSTARi, (d) PGA and (e) PaGA at 6-month follow-up (Kernel density plot).

$r = 0.78$ ($p < 0.001$) and between the mEScSGI and the rEUSTARi was $r = 0.72$ ($p < 0.001$). The classification was in agreement between the EScSGI and the rEUSTARi in 73% of the patients (n = 58/70); 38 (54.3%) patients were classified as inactive by the EScSGI and the rEUSTARi, and 13 (18.6%) patients were classified as active by the EScSGI and the rEUSTARi, while 27% (19/70) patients had divergent classification with 9 patients (12.9%) classified as active by the EScSGI/inactive by the rEUSTARi and 10 (14.3%) as inactive by the EScSGI/active by the rEUSTARi. The mean PGA was 51.0 (SD 22.7) in the patients classified as active by the EScSGI and the rEUSTARi and 17.0 (SD 11.2) in the patients classified as inactive by the EScSGI and the rEUSTARi (active EScSGI/inactive rEUSTARi: 25.0, SD 13.1; inactive EScSGI/active rEUSTARi: 33.8, SD 11.9) and significantly differed ($p < 0.001$) between the four groups.

Correlation of the DA scores

Correlation of the DA scores was calculated with the PGA, the PaGA and the DUCAS at 6-month follow-up (Table 2).

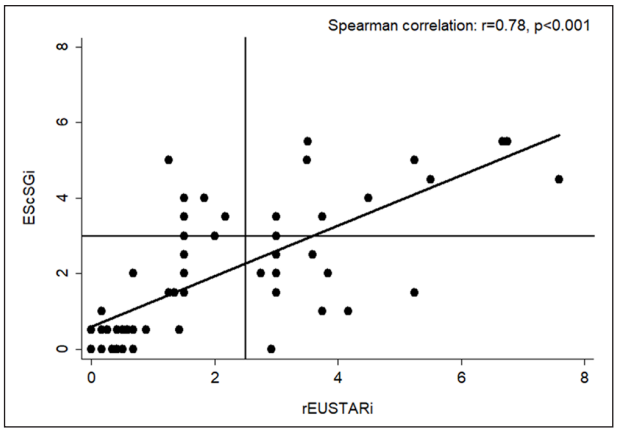

Figure 2. Correlation of EScSGi and rEUSTARi at 6-month follow-up. Inactive disease was defined by EScSGi ⩾ 3 (7) and rEUSTARi ⩾ 2.5 (9).

The rEUSTARi highly correlated with the PGA (r = 0.74, p < 0.001) followed by the EScSGI (r = 0.61, p < 0.001), whereas the correlation was weaker for the mEScSGI (r = 0.51, p < 0.001). The three DAIs showed slightly lower correlations with the PaGA and the DUCAS. The DAIs correlated with a smaller magnitude with the PGD and PaGD scores as well as with the CHAQ in comparison to the variables reflecting DA.

The analyses of the individual components of the scores showed that the variables relating to skin, including mRSS and skin involvement, and to vascular involvement, such as digital necrosis and ulceration, moderately or highly correlated with the PGA and the PaGA (Supplemental Table 3). In addition, the components defined by laboratory values (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) and pulmonary lung function testing (FVC% and DLCO%) correlated moderately with the PGA and the PaGA. The CHAQ was highly correlated with the PGD and PaGD rather than with the PGA and the PaGA.

Sensitivity to change

Sensitivity to change was considered either in patients who were rated by the physicians as improved (n = 28) or worsened (n = 10) as well as in patients who improved or worsened in the VAS of PGA (n = 49/n = 11, respectively) or the PaGA (n = 40/n = 17, respectively) between the 6- and 12-month follow-up. The three activity scores significantly decreased in patients with an improvement in the PGA and the PaGA (Table 3) in comparable magnitudes (standardised beta coefficients between −0.22 and −0.16). Sensitivity to change was also investigated in patients with worsening disease based on the physicians' ratings and in patients with a worse PGA or PaGA at the 12-month follow-up compared to the 6-month follow-up. The EScSGI significantly increased in these three patient groups. The mEScSGI and rEUSTARi did not significantly increase in these patients.

Table 2. Association of EScSGi, mEScSGi and rEUSTARi with measures of disease activity and damage assessed by the physicians and patients or parents at 6-month follow-up.

	r	p value
Physician's global assessment of disease activity, VAS		
EScSG	0.61	<0.001
mEScSG	0.51	<0.001
rEUSTARi	0.74	<0.001
Physician's global assessment of damage, VAS		
EScSG	0.40	0.002
mEScSG	0.33	0.011
rEUSTARi	0.52	0.002
DUCAS		
EScSG	0.58	0.001
mEScSG	0.55	0.002
rEUSTARi	0.64	0.013
Patient's global assessment of disease activity, VAS		
EScSG	0.55	0.000
mEScSG	0.43	0.001
rEUSTARi	0.56	0.044
Patient's global assessment of damage, VAS		
EScSG	0.49	<0.001
mEScSG	0.45	0.001
rEUSTARi	0.52	0.004
CHAQ		
EScSG	0.32	0.067
mEScSG	0.39	0.024
rEUSTARi	0.37	0.052

EScSGi: European Scleroderma Study Group Index; mEScSGi: modified version of the EScSGI; rEUSTARi: revised European Scleroderma Trials and Research index; r: Spearman correlation coefficient; VAS: visual analogue scale 0 (best possible value) to 100 (worst value); EScSG: Eurpoean Scleroderma Study Group; mEScSG: modified Eurpoean Scleroderma Study Group activity index; DUCAS: digital ulcer clinical assessment; CHAQ: Child Health Assessment Questionnaire.

We hypothesised that at 6-month follow-up, the patients with a PGA/PaGA < 10 (n = 26, 27.4%/n = 34, 38.6%; inactive) would have significantly lower values in the three scores than the patients with a PGA/PaGA ⩾ 10 (n = 69, 72.6%/n = 54, 61.4%; active). The distribution of the EScSGI, the mEScSGI and the rEUSTARi significantly differed between the inactive and the active patients (Figure 3). The largest effect size between the active and the inactive patients was shown in the rEUSTARi (PGA: d = 0.48; PaGA: d = 0.52) compared to the EScSGI and the mEScSGI.

Performance in jSSc subtype

The distribution of the EScSGI, the mEScSGI and the rEUSTARi was compared between the patients with limited and diffuse jSSc subtypes at the 12-month follow-up (Supplemental Figure 1). The three scores showed

Table 3. Sensitivity to change of EScSGi, mEScSGi and rEUSTARi between 6- and 12-month follow-up.

	EScSGi				mEScSGi				rEUSTARi			
	Beta	95% CI	p value	$beta_{st}$	beta	95% CI	p value	$beta_{st}$	beta	95% CI	p value	$beta_{st}$
Physician's rating 'improved', n = 28	−0.43	−0.96 to 0.10	0.108	−0.16	−0.45	−0.97 to 0.06	0.086	−0.18	−0.69	−1.29 to −0.09	0.025	−0.22
Improvement in Physician's global (VAS), n = 49	−0.44	−0.81 to −0.07	0.021	−0.17	−0.50	−0.87 to −0.13	0.008	−0.22	−0.58	−1.05 to −0.11	0.016	−0.20
Improvement in Patient's global (VAS), n = 40	−0.56	−0.97 to −0.14	0.009	−0.22	−0.48	−0.89 to −0.06	0.023	−0.20	−0.52	−1.05 to −0.02	0.041	−0.16
Physician's rating 'worsened', n = 10	1.18	0.05 to 2.30	0.041	0.41	0.68	−0.27 to 1.63	0.163	0.29	1.01	−0.23 to 2.25	0.111	0.22
Worsening in Physician's global (VAS), n = 11	1.20	0.13 to 2.28	0.028	0.33	0.79	−0.06 to 1.65	0.070	0.26	0.76	−0.77 to 2.27	0.330	0.17
Worsening in Patient's global (VAS), n = 17	0.81	0.06 to 1.56	0.035	0.25	0.30	−0.42 to 1.01	0.412	0.11	0.36	−0.74 to 1.47	0.518	0.10

EScSGi: European Scleroderma Study Group Index; mEScSGi: modified version of the EScSGi; rEUSTARi: revised European Scleroderma Trials and Research index; beta: regression coefficient from linear mixed model; $beta_{ST}$: standardised regression coefficient from linear mixed model; CI: confidence interval; VAS: visual analogue scale 0 (best possible value) to 100 (worst value).

Figure 3. Discriminative validity of EScSGi, mEScSGi and rEUSTARi between patients with (a) physician's global assessment of disease activity (PGA) and (b) patient's global assessment of disease activity < 10 or $\geqslant 10$ at 6-month follow-up.

significantly lower values for the patients with limited jSSc subtypes and limited variability (EScSGI: median 0.5, interquartile range (IQR): 0–0.5; mEScSGI: median 1, IQR: 0.5–1.5; and rEUSTARi: median 0.7, IQR: 0–1.3) compared to the patients with diffuse jSSc subtypes (EScSGI: median 1.5, IQR: 0.5–3.0; mEScSGI: median 1.5, IQR: 1.0–3.0; and rEUSTARi: median 1.5, IQR: 0.6–3).

Discussion

Measuring DA is a major challenge in patients with SSc, and inconsistent DA concepts have been discussed by Ross et al.[17] This is especially true for patients with jSSc. However, it is important to evaluate the state of the disease from the beginning of the disease because of the risk of early accrual of organ damage, to monitor the current disease status and, if necessary, to start or adjust treatment to avoid any irreversible fibrotic processes and organ damage. To date, three DAIs (the EScSGI, the mEScSGI and the rEUSTARi) have been proposed for use in adult SSc patients, but these DAIs have not yet been used in patients

with jSSc. We demonstrated the application and suitability of the three DAIs for patients with jSSc.

The rEUSTARi correlated slightly better with PGA as compared to the EScSGI. A similar result was recently published by Doyen et al.[10] who compared the performance of the EScSGI and the rEUSTARi in a cohort of 62 patients with diffuse cutaneous SSc. They reported that both indices were comparable to detect DA, and the rEUSTARi showed slightly better sensitivity. The main variable determining the rEUSTARi calculation in our cohort was the mRSS, followed by the presence of digital ulcers and elevated CRP levels. In our study, tendon friction rub contributed only marginally to the rEUSTARi because only three patients in our cohort had present tendon friction rub. In general, the rEUSTARi more strongly reflects skin involvement and disease characteristics related to joints[10] by including the mRSS and CRP as acute inflammation parameters.

Several limitations of EScSGI have been discussed by Hudson et al.[18] The main criticism refers to the validation cohort, of which about two-thirds had long disease duration (median disease duration since first Raynaud's phenomenon of 11 years) and who may have had accrual damage rather than DA.[19] Our analyses (median disease duration since first Raynaud's phenomenon of 3 years) showed that the EScSGI was more likely associated with the global assessments (GAs) of damage by the physician and the patient than the rEUSTARi. Medsger[19] demonstrated that DA was higher within the first 2 years after disease onset in patients with diffuse SSc. Hence, our cohort reflected an early disease stage in about half of the patients. The EScSGI includes the presence of hypocomplementemia, which was not assessed in our cohort; therefore, we could not analyse its contribution. However, it is unclear if this would have had much of an impact on the total score, since it is uncommon in SSc and it is debatable in the literature whether hypocomplementemia is an appropriate measure for DA in SSc.[9,20] The EScSGI includes three components defined by patient self-assessment while the rEUSTARi includes only one. This may explain the higher correlation of the EScSGI with the patient's GA of DA compared with the rEUSTARi.

The modified EScSGI[7] demonstrated weaker correlations and discriminative ability than the original EScSGI. The mEScSGI includes more pulmonary variables and also altered weighting of the single components compared to the original EScSGI. More than half of patients with jSSc are affected by pulmonary involvement.[21] Conversely, FVC% and DLCO% measurements may not show any meaningful change over time in jSSc patients with any abnormalities in pulmonary imaging.[22] The alteration in the weighting scheme, including a partial reduction of the weights of the original EScSGI components, may have caused weaker correlations and discriminative ability. It has also been discussed in the literature whether the inclusion of additional variables makes the mEScSGI less feasible[8] nor provides any advantages over the original EScSGI.[23]

All three DAIs showed sensitivity to change in patients who improved and worsened in the PGA and the PaGA between the 6- and 12-month follow-up with partially slightly higher effect sizes (standardised beta) for the rEUSTARi. However, not all the associations were statistically significant due to the small number of patients within a group. This suggests that the rEUSTARi may be suitable to capture changes in DA in a clinical trial in patients with jSSc.

We are aware of several limitations of our study. The major limitation is the lack of an independent measure of DA as gold standard in our cohort. The PGA and PaGA were selected as golden standard for the evaluation of the DAIs in our paediatric cohort. These are subjective measures because both were reported by the treating physicians and patients. The overall evaluation of PGA and PaGA is influenced by the single components of the three DAIs. The dependency of global DAIs from the single components of DAIs may results in slightly stronger correlation coefficients and larger effect sizes. Limited sample size restricts meaningful subgroup analyses. The proportion of patients with diffuse subtype is higher in our selected study population than expected for a typical jSSc cohort. Patients with a more severe disease course were more likely to provide follow-up data. Therefore, our results apply to somewhat more severely diseased patients. Two index components, the presence of hypocomplementaemia (in the EScSGI and the mEScSGI) and a patient-reported 17-area thickness score (mEScSGI), were not assessed in our cohort. The missing information on hypocomplementaemia may not influence our results, because it does not play a role in children and adolescents with jSSc. However, the missing patient-reported 17-area thickness score with its weight of 0.5 in the mEScSGI may influence the reported mean levels towards slightly lower means and slightly lower association measures (correlations and beta coefficients), in particular with patient-reported measures such as PaGA in our analyses. In addition, organ examinations were not performed according to a standardised protocol. This may have resulted in variability in the results of organ examinations between study centres, depending on the performed method.

In conclusion, we evaluated the performance and suitability of the three existing DAIs developed for adult patients with SSc in our cohort of patients with jSSc. To our knowledge, this is the largest cohort of jSSc patients worldwide prospectively followed according to a standardised study protocol. Overall, no DA score is superior to the other and all three scores have several weaknesses in jSSc patients. Furthermore, research on the concept of DA and suitable scores to measure DA in patients with jSSc is necessary in future. For example, the EUSTARi and the

rEUSTARi do not capture gastrointestinal and renal activity,[9] which limits their face and content validity in both SSc and jSSc.[17]

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: the editor/editorial board member of *Journal of Scleroderma and Related Disorders* is an author of this paper; therefore, the peer-review process was managed by alternative members of the board, and the submitting editor/board member had no involvement in the decision-making process.

Ethical approval

The study was approved by the ethical review board in Hamburg, Germany in 2007, and an amendment addressing the expanded inclusion criteria was approved in May 2014. All participating centres requested and received approval for the prospective registry from their local ethical review boards.

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Supplemental material

Supplemental material for this article is available online.

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