The Hospital Anxiety and Depression Scale in patients with systemic sclerosis: a psychometric and factor analysis in a monocentric cohort

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Competing interests: page S-41.

ABSTRACT

Objective. *To evaluate the feasibility, validity, reliability, and responsiveness of the Hospital Anxiety and Depression Scale (HADS) and to analyse its model structure in patients with systemic sclerosis (SSc).*

Methods. *In this study, 316 SSc patients were included; of these, 159 participated in the responsiveness analysis. Psychometric properties were tested in analogy to the Outcome Measures in Rheumatology (OMERACT) filter and an exploratory and confirmatory factor analysis was performed to examine the structure of HADS.*

Results. *The HADS showed adequate feasibility, validity, reliability, and responsiveness to clinically relevant worsening of the disease. For our population of SSc patients, the HADS model with two sub-scales, HADS-A and HADS-D, and a general scale HADS-S, measuring anxiety, depression, and distress, respectively, was most appropriate. The rates of anxiety, depression, mixed anxiety-depressive disorder (MADD) and distress identified by HADS were 32.2%, 25.9%, 18.5%, and 49.5%, respectively, in our cohort.*

Conclusion. *The psychometric properties of the HADS make it useful for screening in SSc, where anxiety, depression, MADD, and distress represent a significant burden to patients.*

Introduction

Systemic sclerosis (SSc) is a rare acquired chronic disease characterised by vasculopathy, inflammation as well as skin and organ fibrosis resulting from the excessive deposition of extracellular matrix (1). Depending on the extent of skin involvement, SSc is classified into diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) (2). The diagnosis itself of chronic disease, and the occurrence of interstitial lung disease, gastrointestinal symptoms, pulmonary arterial hypertension, digital ulcers, skin fibrosis with joint contractures and gradual changes in physical appearance pose a relevant psychological burden to patients (1). This may lead to psychological distress and ultimately psychiatric disorders such as anxiety and depression, as well as psycho-organic syndromes with disturbances of cognition and orientation (3-5).

Two studies have assessed the prevalence of depression and anxiety in SSc by using the hospital anxiety and disease scale (HADS), but presently there are no data on its feasibility, validity, reliability, and responsiveness to change in SSc patients (6, 7).

Hence, the objectives of the present study were to: a) examine the feasibility, validity, reliability, and sensitivity to clinical change of HADS in individuals with SSc, b) investigate the factor structure of HADS as an overall validity measurement, c) estimate the burden of anxiety, depression and distress quantified by HADS in our cohort.

Patients and methods

Data collection and population

Consecutive patients with all questionnaire data available and fulfilling the ACR/EULAR 2013 classification criteria for SSc (8), yearly followed up longitudinally (2013–2020) in our clinic were included in the cross-sectional/longitudinal analyses, respectively:

a) The responsiveness analysis involved patients, in which we recorded a worsening or improvement of the disease in the previous 12±3 months. Worsening of disease was defined either as occurrence of any of the following

Table I. A. Clinical characteristics of patients with SSc (overall, and stratified by the disease worsening group).

	Overall	DU improvement	DU worsening	FVC improvement	FVC worsening	GIT improvement	GIT worsening
Number of patients	316	17	12	72	67	25	68
Age (median [IQR])	60.86 [49.88, 69.56]	53.25 [48.93, 60.92]	57.92 [49.77, 63.70]	60.95 [51.99, 68.45]	61.82 [54.73, 69.49]	60.89 [54.10, 66.89]	61.00 [53.10, 71.47]
Male gender (%)	53 (16.8)	5 (29.4)	6 (50.0)	12 (16.7)	8 (11.9)	1 (4.0)	10 (14.7)
SSc subset, lcSSc (%)	198 (77.0)	6 (37.5)	3 (30.0)	48 (76.2)	50 (82.0)	18 (72.0)	43 (78.2)
Disease duration (median [IQR])	7.77 [4.03, 13.83]	7.71 [5.33, 13.38]	9.13 [6.69, 18.71]	7.58 [4.64, 15.83]	9.08 [5.13, 15.90]	11.84 [7.32, 23.41]	7.81 [5.37, 15.47]
Raynaud`s phenomenon (%)	284 (93.7)	17 (100.0)	10 (90.9)	65 (92.9)	59 (93.7)	24 (100.0)	61 (93.8)
Current digital ulcerations (%)	26 (8.7)	0 (0.0)	11 (100.0)	7 (10.1)	7 (10.9)	6 (26.1)	9 (13.6)
Modified Rodnan skin score (median [IQR])	2.00 [0.00, 6.00]	9.00 [2.00, 12.00]	8.00 [6.75, 12.50]	2.50 [0.00, 7.00]	2.00 [0.00, 5.00]	3.00 [2.00, 7.00]	2.00 [0.00, 6.00]
Joint synovitis (%)	44 (14.1)	1 (5.9)	2 (16.7)	8 (11.1)	8 (12.1)	4 (16.0)	4 (6.1)
Joint contractures (%)	112 (35.8)	8 (47.1)	7 (58.3)	35 (49.3)	26 (38.8)	13 (52.0)	27 (40.9)
Dyspnea, stages 3 and 4 (%)	36 (11.9)	1 (5.9)	1 (9.1)	5 (7.1)	7 (10.6)	1 (4.2)	4 (6.0)
LVEF < 45 % (%)	5 (1.6)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.5)	0 (0.0)	0 (0.0)
Pulmonary hypertension by echocardiography (%)	36 (12.1)	1 (5.9)	1 (9.1)	2 (3.0)	5 (8.2)	1 (4.2)	3 (4.8)
Interstitial lung disease (%)	126 (42.9)	10 (58.8)	7 (63.6)	33 (47.1)	27 (42.9)	10 (41.7)	25 (40.3)
FVC% (median [IQR])	94.00 [83.00, 107.00]	96.00 [85.00, 109.00]	89.50 [83.00, 99.00]	102.00 [87.75, 112.00]	93.00 [78.50, 103.00]	96.00 [86.75, 107.50]	98.50 [86.00, 114.50]
DLCO% (median [IQR])	72.00 [55.00, 85.00]	78.00 [71.25, 91.00]	72.00 [66.00, 81.75]	69.00 [58.00, 87.00]	67.50 [52.75, 79.25]	76.50 [65.00, 86.25]	71.00 [57.50, 88.00]
Gastrointestinal symptoms (%)	195 (61.7)	12 (70.6)	8 (66.7)	45 (62.5)	40 (59.7)	17 (68.0)	53 (77.9)
ANA positive (%)	311 (99.0)	17 (100.0)	11 (100.0)	71 (100.0)	66 (98.5)	25 (100.0)	68 (100.0)
ACA positive (%)	147 (47.7)	6 (35.3)	2 (18.2)	29 (41.4)	29 (43.3)	13 (52.0)	40 (58.8)
Anti-Scl70 positive (%)	71 (23.2)	4 (23.5)	6 (54.5)	22 (31.0)	13 (19.4)	7 (28.0)	11 (16.4)
Anti-RNA-Polymerase III Ab positive (%)	32 (10.9)	3 (17.6)	3 (30.0)	6 (8.5)	9 (13.8)	3 (12.5)	7 (10.6)
CK elevation = Yes (%)	32 (10.6)	2 (12.5)	1 (9.1)	9 (12.9)	6 (9.1)	1 (4.3)	7 (10.4)
EScSG-AI (median [IQR])	0.50 [0.50, 2.00]	1.00 [0.00, 1.50]	1.50 [1.00, 3.00]	1.00 [0.50, 2.00]	1.00 [0.50, 2.00]	1.00 [0.50, 2.00]	1.00 [0.50, 2.00]
HADS-A score (median [IQR])	5.00 [2.00, 8.00]	9.00 [9.00, 10.00]	5.50 [4.50, 11.00]	10.00 [9.00, 11.00]	5.00 [2.00, 7.00]	10.00 [9.00, 11.00]	10.00 [9.00, 10.25]
HADS-D score (median [IQR])	4.00 [1.00, 8.00]	9.00 [8.00, 9.00]	4.50 [1.00, 10.25]	8.00 [7.00, 9.00]	4.00 [2.00, 9.00]	9.00 [8.00, 10.00]	9.00 [7.00, 10.00]
HADS-S (median [IQR])	8.00 [4.00, 16.00]	18.00 [17.00, 18.00]	11.50 [7.00, 18.75]	18.00 [17.00, 19.00]	11.00 [4.00, 16.00]	19.00 [18.00, 20.00]	18.00 [17.75, 20.00]
Anxiety* (%)	7 (2.4)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Depression* (%)	33 (11.5)	1 (20.0)	0 (0.0)	6 (15.0)	0 (0.0)	3 (21.4)	3 (6.4)
MADD* (%)	7 (2.4)	0 0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)

ACA: anti-centromere antibodies; ANA: antinuclear antibodies; anti-Scl70 antibodies: antitopoisomerase I antibodies; CK: creatine kinase; CRP: C reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ECG: echocardiography; EScSG-AI: European Scleroderma Study Group Activity Index 2001; FVC: forced vital capacity; HADS-A: anxiety sub-scale of Hospital Anxiety and Depression Scale; HADS-D: depression scale of Hospital Anxiety and Depression Scale; HADS-S: distress sub-scale of Hospital Anxiety and Depression Scale; LVEF: left ventricular ejection fraction; MADD: mixed anxiety-depressive disorder; mRSS: modified Rodnan skin score; RNP: ribonucleoprotein.
* diagnosed by a psychiatrist.

events: decline in forced vital capacity (FVC) ≥10%, or FVC ≥5% and diffusing capacity for carbon monoxide (DLCO) ≥15%, new diagnosis of interstitial lung disease (ILD) on high-resolution computed tomography (HRCT), new-onset pulmonary hypertension (PH) and new active digital ulcerations (DU) (9). In addition to these events, an increase in European Scleroderma Study Group activity index 2001 (EScSG-AI) >3 points, an increase in modified Rodnan skin score (mRSS) >5 points and >25% and an increase of 0.12 points in UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument (GIT) were considered to indicate clinically relevant change (9-12).

Improvement of the disease was defined as an increase in forced vital capacity (FVC) ≥10%, or FVC ≥5% and diffusing capacity for carbon monoxide (DLCO) ≥15%, complete healing of DU, decrease of EScSG-AI >3 points, decrease in modified Rodnan skin score (mRSS) >5 points and >25% and an decrease of 0.18 points in UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract Instrument (GIT) (12).

b) The cross-sectional analysis included data from the most recent follow-up visit of the patients, who participated in the responsiveness analysis. The rest of patients participated with the most recent follow-up visit to this analysis.

c) The test-retest reliability included the patients which returned the HADS questionnaire after 10 (±4) days from their follow-up visit.

Ethical approval for this data collection and analysis was issued by the cantonal ethics committee (BASEC Nr.-2016-01515 and BASEC Nr. 2018-02165).

Table I. B. Clinical characteristics of patients with SSc (overall, and stratified by the disease worsening group).

	ILD wrosening	MRSS improvement	MRSS worsening	PH worsening	EScSG-AI improvement	EScSG-AI wrosening	*p*-value
Number of patients	9	30	7	8	26	21	
Age (median [IQR])	66.14 [53.37, 70.02]	59.97 [52.10, 69.64]	56.95 [48.95, 61.67]	67.65 [60.37, 72.77]	59.31 [53.97, 68.33]	60.90 [54.89, 65.00]	0.505
Male gender (%)	2 (22.2)	6 (20.0)	2 (28.6)	0 (0.0)	5 (19.2)	4 (19.0)	0.064
SSc subset, lcSSc (%)	8 (88.9)	12 (46.2)	3 (42.9)	3 (50.0)	13 (54.2)	10 (55.6)	<0.001
Disease duration (median [IQR])	8.73 [4.82, 34.76]	6.54 [2.88, 9.63]	9.67 [5.40, 10.23]	15.00 [7.08, 33.70]	7.37 [3.38, 14.48]	6.91 [5.52, 25.40]	0.512
Raynaud`s phenomenon (%)	8 (88.9)	29 (96.7)	6 (100.0)	8 (100.0)	25 (96.2)	20 (95.2)	0.966
Current digital ulcerations (%)	1 (11.1)	2 (6.7)	3 (60.0)	0 (0.0)	5 (21.7)	5 (26.3)	<0.001
Modified Rodnan skin score (median [IQR])	5.00 [2.00, 8.00]	4.00 [2.25, 7.00]	18.00 [10.50, 22.50]	2.50 [1.50, 4.75]	6.00 [3.25, 12.25]	5.00 [0.00, 10.00]	<0.001
Joint synovitis (%)	0 (0.0)	3 (10.3)	1 (14.3)	0 (0.0)	1 (3.8)	5 (25.0)	0.501
Joint contractures (%)	4 (44.4)	15 (51.7)	5 (71.4)	5 (62.5)	16 (64.0)	11 (52.4)	0.057
Dyspnea, stages 3 and 4 (%)	1 (11.1)	3 (10.0)	0 (0.0)	2 (25.0)	4 (15.4)	3 (14.3)	0.814
LVEF < 45 % (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.995
Pulmonary hypertension by echocardiography (%)	1 (11.1)	4 (13.8)	0 (0.0)	8 (100.0)	3 (11.5)	2 (11.1)	<0.001
Interstitial lung disease (%)	9 (100.0)	18 (60.0)	3 (50.0)	5 (71.4)	9 (34.6)	12 (57.1)	0.013
FVC% (median [IQR])	89.00 [71.00, 103.00]	94.00 [80.00, 109.50]	90.00 [78.50, 106.50]	96.00 [86.00, 112.25]	89.50 [78.00, 105.25]	97.00 [84.25, 111.00]	0.431
DLCO% (median [IQR])	84.00 [56.50, 90.00]	71.00 [62.25, 82.25]	69.00 [65.50, 82.50]	55.00 [50.00, 70.00]	68.00 [55.75, 73.00]	69.00 [62.50, 88.50]	0.19
Gastrointestinal symptoms (%)	5 (55.6)	14 (46.7)	2 (28.6)	2 (25.0)	13 (50.0)	10 (47.6)	0.023
ANA positive (%)	8 (88.9)	30 (100.0)	7 (100.0)	8 (100.0)	26 (100.0)	21 (100.0)	0.244
ACA positive (%)	2 (22.2)	6 (20.0)	0 (0.0)	4 (50.0)	8 (32.0)	5 (23.8)	0.001
Anti-Scl70 positive (%)	3 (33.3)	9 (30.0)	6 (85.7)	1 (12.5)	7 (26.9)	6 (28.6)	<0.001
Anti-RNA-Polymerase III Ab positive (%)	1 (11.1)	6 (20.0)	1 (14.3)	0 (0.0)	7 (26.9)	5 (23.8)	0.274
CK elevation = Yes (%)	1 (11.1)	1 (3.6)	1 (16.7)	2 (25.0)	4 (16.7)	6 (28.6)	0.455
EScSG-AI (median [IQR])	0.50 [0.00, 2.00]	1.00 [0.50, 2.00]	3.25 [1.88, 3.50]	1.50 [0.50, 2.12]	2.00 [1.12, 2.38]	3.50 [3.00, 4.00]	<0.001
HADS-A score (median [IQR])	6.00 [3.00, 7.00]	10.00 [9.00, 10.00]	6.00 [3.00, 9.00]	2.00 [1.50, 8.25]	10.00 [9.00, 11.25]	5.00 [2.00, 8.00]	<0.001
HADS-D score (median [IQR])	4.00 [2.00, 9.00]	9.00 [8.00, 10.00]	3.00 [2.50, 9.50]	4.50 [1.75, 7.25]	8.00 [7.00, 9.00]	4.00 [3.00, 6.00]	<0.001
HADS-S (median [IQR])	8.00 [4.00, 19.00]	18.00 [18.00, 19.00]	13.00 [5.50, 16.50]	6.50 [3.00, 15.25]	18.00 [17.00, 19.25]	10.00 [5.00, 15.00]	<0.001
Anxiety* (%)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0.843
Depression* (%)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	3 (21.4)	0 (0.0)	0.081
MADD* (%)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0.843

ACA: anti-centromere antibodies; ANA: antinuclear antibodies; Anti-Scl70 antibodies: antitopoisomerase I antibodies; CK: creatine kinase; CRP: C reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; ECG: echocardiography; EScSG-AI: European Scleroderma Study Group Activity Index 2001; FVC: forced vital capacity; HADS-A: anxiety sub-scale of Hospital Anxiety and Depression Scale; HADS-D: depression scale of Hospital Anxiety and Depression Scale; HADS-S: distress sub-scale of Hospital Anxiety and Depression Scale; LVEF: left ventricular ejection fraction; MADD: mixed anxiety-depressive disorder; mRSS: modified Rodnan skin score; RNP: ribonucleoprotein.
* diagnosed by a psychiatrist.

Feasibility, validity, reliability and discrimination capacity of HADS - Outcome measures in rheumatology filter criteria

The psychometric properties of HADS were assessed in analogy to the OMERACT (Outcome Measures in Rheumatology) filter, which encompasses the following three pillars (13):

1. Truth:

a) *content and face validity* - a psychologist reviewed the items and evaluated if these criteria were fulfilled, additionally, the percentage of missing answers, floor and ceiling effects were computed; b) *construct validity* examined by Spearman's correlations between HADS scores and Short Form 36 (SF-36), (Scleroderma Health Assessment Questionnaire (SHAQ) and Sense of coherence - 13 (SOC-13); considered ranges for correlation were: poor $0<|r|<0.29$, fair $0.30<|r|<0.59$, moderate $0.60<|r|<0.80$, very strong $0.8<|r|<1$; c) *internal consistency reliability* assessed by computing Cronbach's alpha coefficient (α) and split-half reliability ($\lambda 4$) was additionally considered as measure of validity (for α and $\lambda 4$ considered ranges were: unacceptable $0< \alpha \mid \lambda 4 <0.49$, poor $0.5< \alpha \mid \lambda 4 <0.59$, questionable $0.6< \alpha \mid \lambda 4 <0.69$, acceptable $0.7< \alpha \mid \lambda 4 <0.79$, good $0.8< \alpha \mid \lambda 4 <0.89$, excellent $0.9< \alpha \mid \lambda 4 <1$) (14,15).

2. Discrimination:

a) sensitivity-to-change over one year was assessed by computing Cohen's *d* coefficient using HADS scores of two visits of patients with change. Prior to computing Cohen's *d* coefficient, HADS-S, HADS-A and HADS-D were categorised according to the available literature. Cut-offs for Cohen's *d* were: *d* (0.01) = very small, *d* (0.2) = small, *d*

Table II. Cases number and rates of anxiety, depression, MADD and distress detected by HADS and diagnosed by a psychiatrist (overall and stratified by gender and SSc subset).

		Gender			SSc subset		
	Overall	Female	Male	*p*-values	Diffuse cutaneous SSc	Limited cutaneous SSc	*p*-values
Number of patients	316	263	53		59	198	
Anxiety, n (%)	100 (32.2)	85 (32.8)	15 (28.8)	0.691	21 (35.6)	59 (30.4)	0.555
Mild cases, n (%)	61 (19.6)	55 (21.2)	6 (11.5)	0.157	9 (15.3)	42 (21.6)	0.375
Moderate cases, n (%)	26 (8.4)	18 (6.9)	8 (15.4)	0.083	7 (11.9)	12 (6.2)	0.243
Severe cases, n (%)	13 (4.2)	12 (4.6)	1 (1.9)	0.609	5 (8.5)	5 (2.6)	0.098
Depression, n (%)	81 (25.9)	69 (26.4)	12 (23.1)	0.74	23 (39.0)	42 (21.5)	0.012
Mild cases, n (%)	44 (14.1)	39 (14.9)	5 (9.6)	0.429	13 (22.0)	20 (10.3)	0.033
Moderate cases, n (%)	19 (6.1)	16 (6.1)	3 (5.8)	1	5 (8.5)	13 (6.7)	0.853
Severe cases, n (%)	18 (5.8)	14 (5.4)	4 (7.7)	0.74	5 (8.5)	9 (4.6)	0.416
MADD, n (%)	58 (18.5)	50 (19.2)	8 (15.4)	0.657	18 (30.5)	28 (14.4)	0.009
Distress, n (%)	154 (49.5)	130 (50.2)	24 (46.2)	0.704	32 (54.2)	93 (47.9)	0.485
Anxiety diagnosed by psychiatrist, n (%)	7 (2.4)	7 (2.9)	0 (0.0)	0.494	2 (3.7)	4 (2.3)	0.924
Depression diagnosed by psychiatrist, n (%)	33 (11.5)	30 (12.5)	3 (6.2)	0.321	8 (14.8)	19 (10.7)	0.565
MADD diagnosed by psychiatrist, n (%)	7 (2.4)	7 (2.9)	0 (0.0)	0.494	2 (3.7)	4 (2.3)	0.924

MADD: mixed anxiety-depressive disorder; n: number of cases.

(0.5) = medium, *d* (0.8) = large, *d* (1.2) = very large, and *d* (2.0) = huge (16-18).
b) *test-retest reliability* at 10 (± 4) days was assessed by computing intra-class correlation coefficient (ICC). A value of ICC less than 0.40 is interpreted as a poor test-retest reliability, between 0.40 and 0.59: fair, between 0.60 and 0.74: good, and between 0.75 and 1.00: excellent, respectively (19).
3. Feasibility:
It examined the applicability of HADS (20).

Measures

The Hospital Anxiety and Depression Scale (HADS) has in total 14 items (scored from 0 to 3), which constitute the overall distress scale (HADS-S). In the original version, by grouping the items 1, 3, 5, 7, 9, 11, 13 and items 2, 4, 6, 8, 10, 12, 14, an anxiety subscale (HADS-A) and a depression subscale (HADS-D) are obtained, respectively. Cut-off score values are available for the categorisation of severity: scores 8-11 represent mild cases, 12-15 moderate cases, and 15-21 severe cases (21 is the highest score possible) for the subscales HADS-A and HADS-D; scores of higher then 9 represent distress (42 is the highest reachable score) for the HADS-S scale (16, 21). Patients with scores of both HADS-A and HADS-D >8, were defined as having a mixed anxiety-disorder (MADD).

The Short Form 36 (SF-36) has 36 items, which can be grouped into the Mental Health subscale (SF-36-MH) and the Mental Component Summary subscale (SF-36-MCS) offering information about how well a respondent is mentally (22, 23).

The Scleroderma Health Assessment Questionnaire (SHAQ) is a version of the Health Assessment Questionnaire (HAQ) adapted to SSc. It has five additional visual analogue scales, assessing Raynaud's phenomenon, digital ulcers, gastrointestinal symptoms, pulmonary symptoms, and overall symptoms of systemic sclerosis (24).

The sense of coherence-13 (SOC-13) questionnaire assesses comprehensibility, manageability and meaningfulness (25).

The UCLA Scleroderma Clinical Trial Consortium GIT 2.0 (GIT) includes 34 items and 7 multi-item scales (reflux, distention/bloating, diarrhoea, fecal soilage, constipation, emotional well-being, and social functioning) and a total GIT score to assess the gastrointestinal symptoms severity in SSc (26).

Factor analysis

To evaluate the factor structure of the HADS an exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were conducted. Before EFA was done, various assumptions on inter-correlations of the HADS items were tested (27). The recommendation from the Consensus-based Standards for the selection of health Measurement Instruments (at least 100 participants and more than seven times the number of items of the outcome measures examined are necessary for a factor analysis study) was met (28).
The confirmatory analysis was performed for the suggested factor structure model in the EFA, and for the "best fitted" models available in the literature (21, 29-35).
A root mean square error of approximation (RMSEA) below 0.08, along with comparative fit index (CFI) above 0.95, a goodness of fit index (GFI) over 0.9, and a standardised root mean square residual (SRMR) <0.08 are the minimum required features reported for a good model fit (36).

Statistical analysis

All analyses were performed in R language 4.0. Demographic and clinical characteristics were presented as frequencies for factor variables or mean (± standard deviation) for normally distributed continuous variables. A diagnosis of depression or an anxiety disorder made by a psychiatrist, where available, was recorded.

Results

Patient characteristics

Of the 316 patients (aged 60.86 [IQR: 49.88, 69.56], 16.8% male, 77% with lcSSc, disease duration 7.77 [IQR: 4.03, 13.83] years), 159 patients had disease worsening or improvement within 12 (±3 months): 139 of the FVC, 93 of the GIT, 29 of the DU, 9 of the ILD, 37 of the mRSS, 8 of PH and 47 of EScSG-AI criterion. Twenty patients returned an additional HADS questionnaire and thus participated to the test-retest reliability analysis. At inclusion 26/316 (8.7%) had active digital ulcers, 126/316 (42.9%) had interstitial lung disease and 36/316 (12.1%) pulmonary hypertension evaluated by echocardiography. The median mRSS, FVC, DLCO and EScSG-AI were 2, 94%, 72%, and 0.5, respectively. HADS-A, HADS-D and HADS-S median scores were 5, 4 and 8, respectively (Table I).

In our cohort HADS identified 100 (32.2%) patients with anxiety, 81 (25.9%) with depression, 58 (18.5%) with MADD, and 154 (49.5%) with distress. Only seven (2.4%), 33 (11.5%) and seven (2.9%) patients of our cohort were referred to a psychiatrist with a confirmed diagnosis of anxiety, depression and MADD, respectively (Table II). The distribution of anxiety, depression, and distress among gender and SSc subsets was similar, the mild form of anxiety or depression being predominant in our cohort (Table II, Fig. 1).

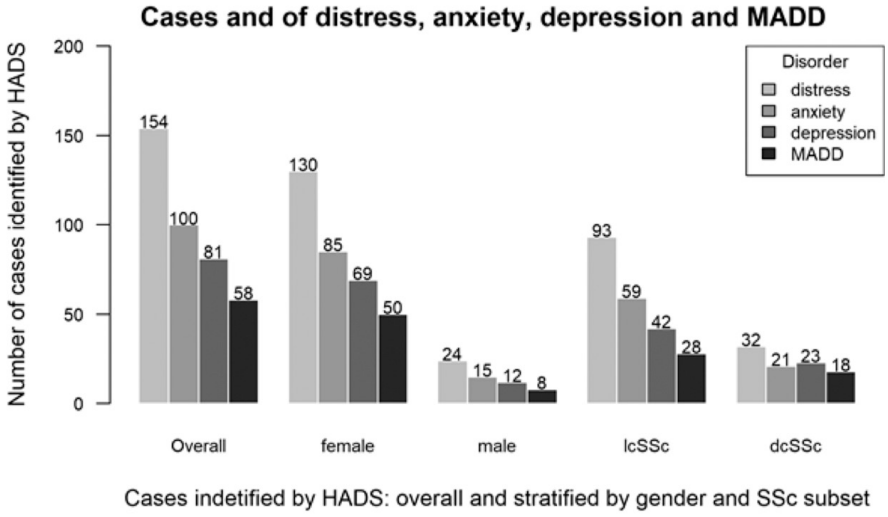

Fig. 1. Cases and rates of anxiety, depression, distress and MADD stratified by gender and SSc subset.

Factor analysis

EFA supported a two-factor model, one composed by the items 1, 3, 5, 7, 9, 11, 13, which evaluates anxiety (HADS-A subscale), and the other one including the other 7 items (2, 4, 6, 8, 10, 12, 14), which evaluates depression (HADS-D subscale) (Fig. 2, upper panels). This model was identical to the original model developed by Zigmond and Snaith (20).

Then, this model together with Moorey, Razavi, Dunbar, Brandberg, Friedman and one bifactor, two group factors structure models were analysed for fit indices (Table III). All models, except Razavi and Moore, showed an adequate fit, including the Zigmond and Snaith model, which was suggested by the EFA. Of these, the bifactor, two group factors model showed the best fit indices of all eight (Table IV, Fig. 2 - lower panel). This represents a model of the HADS with two subscales (HADS-A and HADS-D) and a general item scale (HADS-S), capable of assessing anxiety, depression and distress (Table III).

OMERACT filter criteria

- Truth

The EFA and CFA suggested a model of HADS fitted for SSc patients, composed of HADS-A, HADS-D and HADS-S. The expert evaluation concluded that the questions are capable to identify anxiety, depression and distress, respectively. The percentage of the missing answers ranged from 0.93% (item 14) to 2.22% (item 1), with an overall missingness of only 1.41%. Moreover HADS-A and HADS-D represent the original model of HADS developed to evaluate anxiety and distress in non-psychiatric clinics, face validity being adequate also by definition (21). Thus, the *face and content validity* are deemed adequate.

Construct validity: all three scales showed a moderate to very strong correlation to each other, as well as with SF-36-MH and SF-36-MCS (Spearman's r=-0.70 to -0.84). There was a fair to moderate correlation with the SHAQ (Spearman's r=0.43 to 0.62) and a strong correlation with SOC-13 (-0.68 to -0.73). *Internal consistency reliability* was excellent for the HADS-S (Cronbach's α=0.91; split-half reliability λ4=0.92), and very good to excellent for HADS-A and HADS-D (Cronbach's α=0.85 to 0.89; split-half reliability λ4=0.87 to 0.91).

- Discrimination

Sensitivity-to-change: HADS-A showed a large to very large effect size (ES) for progression of ILD as assessed on HRCT, new onset of PH, and increase and decrease in EScSG-AI, FVC, MRSS, and improvement in DU status (Cohen's *d*=1 to 1.41), and a small to medium for worsening of the DU, and worsening and improvement of GIT score (Cohen's *d*=0.35 to 0.71). HADS-D performed similarly to HADS-A in the sensitivity to change analysis. Compared to these subscales, HADS-S and the other evaluated questionnaires (SF36-MH, SF36-MSC and SOC-13) showed a small to very small ES for changes in all dimensions, except for MRSS worsening, where a medium to large ES was recorded (Cohen's *d*=0.77 to 1.13).

Test-retest reliability: all three HADS scales showed an ICC=0.73 corresponding to a good test-retest reliability.

- Feasibility

HADS is a one-page, easily administered self-reported measure, developed to identify cases of anxiety, depression and distress among patients in non-psychiatric patient populations. It takes 2 to 5 min to complete it (16, 21), making it a highly applicable tool (Table IV).

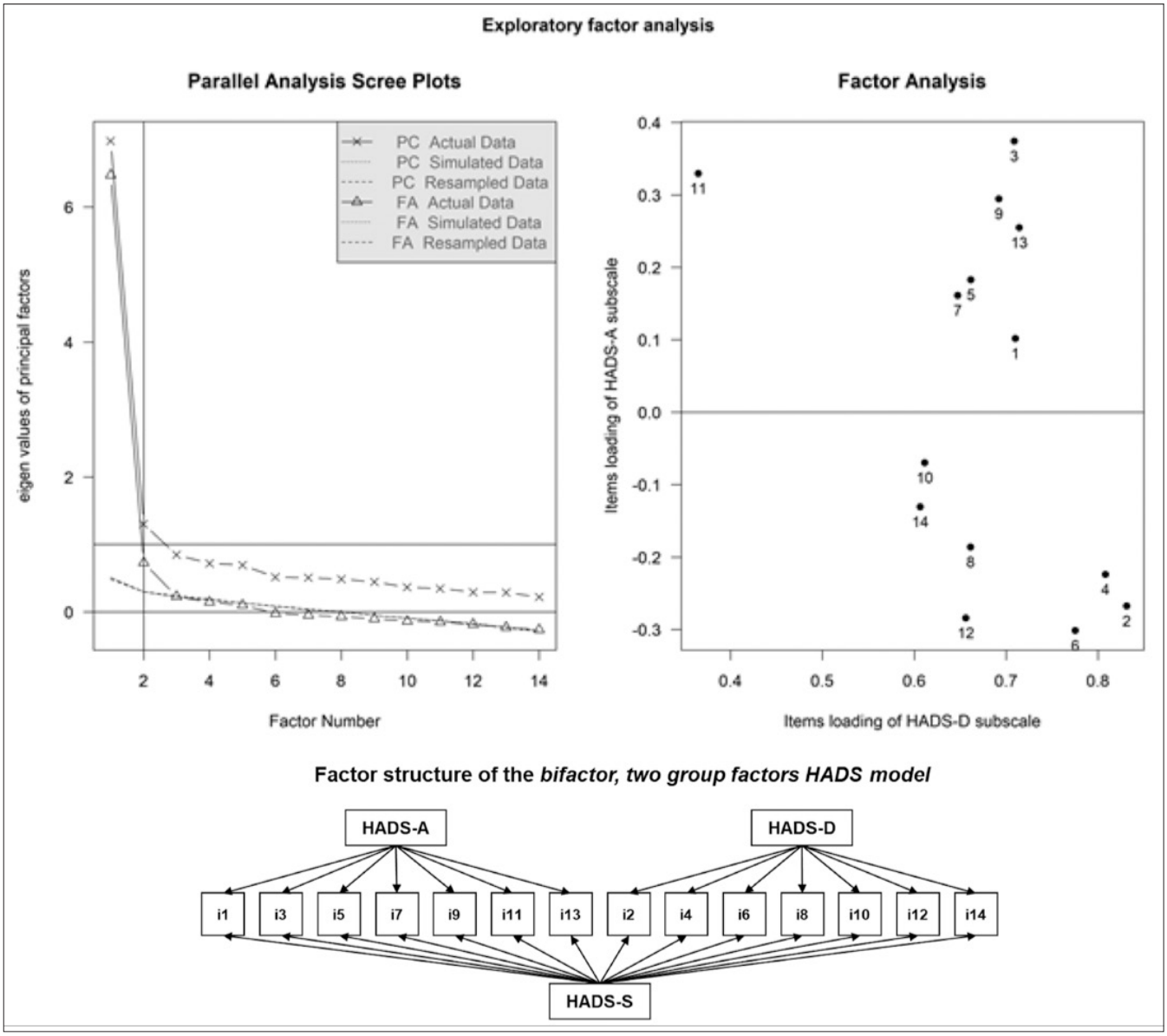

Fig. 2. Exploratory factor analysis and factor structure of the most suitable HADS model for SSc patients.
Parallel analysis scree plot: the solid line shows eigenvalues of actual data, while the dotted and dashed lines (placed on top of each other) show simulated and resampled data. The point of inflection – the point where the gap between simulated data and actual data tends to be minimum - occurs at a number of factors supported by our model (n=2) (upper-left panel).
Factor analysis: Distribution of item loadings of the model into the sub-scales (upper-right panel).
Factor structure of the *bifactor, two group factors HADS model*: the structure of model most suitable for SSc patients. It contains a scale that evaluates the anxiety (HADS-A: items 1, 3, 5, 7, 9, 11, 13), a scale that evaluate the depression (HADS-D: 2, 4, 6, 8, 10, 12, 14), and by grouping all items (from 1 to 14), the scale to measure distress is obtained (lower panel); i: item.

Discussion

Our present study is the first one to evaluate the psychometric properties and factor structure of the HADS in patients with systemic sclerosis. This tool was then used to estimate the anxiety, depression, MADD and distress in our cohort.

Factor structure

Over time, more structure models of HADS have been developed by grouping the items in different subscales capable of distinguishing between different forms of anxiety and depression (*e.g.* psychomotor anxiety, anhedonic depression, restlessness, agitation, etc.). Moreover, these models of HADS are related to a specific non-psychiatric disease (35). Therefore, it was advisable to perform an EFA and CFA for finding the best model of HADS fitted for SSc patients.

The EFA supported a model with two sub-scales, HADS-A and HADS-D, able to screen for anxiety and depression, respectively. The items of these sub-scales are grouped identical to the original model of HADS proposed by Zigmond and Snaith (21). Together with the other seven models, this model was evaluated in the CFA. Because the EFA suggested a model that had already been considered to be examined in CFA, *i.e.* the original model proposed by Zigmond and Snaith, neither

Table III. Confirmatory factor analysis - fit indices.

HADS-Model	CFI	RMSEA	SRMR	GFI	*p*-value
Razavi (all items included - HADS-S)	0.88	0.11	0.06	0.82	<0.0001
Moorey (anxiety: 1, 3, 5, 9, 11, 13; depression: 2, 4, 6, 7, 8, 10, 12, 14)	0.94	**0.08**	**0.05**	**0.91**	<0.0001
Zigmond & Snaith (anxiety: 1, 3, 5, 7, 9, 11, 13 - HADS-A; depression: 2, 4, 6, 8, 10, 12, 14 - HADS-D)	**0.95**	**0.07**	**0.05**	**0.92**	<0.0001
Dunbar (autonomic anxiety: 3, 9, 13; negative affectivity: 1, 5, 7, 11; anhedonic depression: 2, 4, 6, 7)	**0.96**	**0.07**	**0.04**	**0.93**	<0.0001
Friedman (psychomotor agitation: 1, 7, 11; psychic anxiety: 3, 5, 9, 13; depression: 2, 4, 6, 8, 10, 12)	**0.96**	**0.07**	**0.04**	**0.93**	<0.0001
Caci (anxiety: 1, 3, 5, 9, 13; restlessness: 7, 11, 14; depression: 2, 4, 6, 8, 10, 12)	0.94	**0.08**	**0.05**	**0.92**	<0.0001
Brandberg (anxiety: 3,5,9,12, restless:1,7,11,14, depression: 2,4,6,8,10,12)	**0.95**	**0.07**	**0.05**	**0.92**	<0.0001
Bifactor two group factors (anxiety: 1, 3, 5, 7, 9, 11, 13 - HADS-A; depression: 2, 4, 6, 8, 10, 12, 14 - HADS-D, all items included - HADS-S)	**0.97**	**0.06**	**0.03**	**0.94**	<0.0001

Good model fit if: RMSEA < 0.08, CFI > 0.95, GFI > 0.9, SRMR <0.08, HADS-A: anxiety subscale of Hospital Anxiety and Depression Scale; HADS-D: depression subscale of Hospital Anxiety and Depression Scale; HADS-S: distress scale of Hospital Anxiety and Depression Scale.

random sampling with replacement nor half-split the cohort at random were anymore necessary to avoid determination and confirmation of a model in the same cohort. The CFA showed that our explored model, consisting of HADS-A and HADS-D sub-scales had good fit indices, but was not the best model for SSc patients. The model with the best fitted indices in our CFA was the bifactor, two group factors model. This was obtained by adding to the HADS-A and HADS-D a general scale (HADS-S, the distress scale, all 14 items of the HADS). This would structure the questionnaire into HADS-A, HADS-D, on the one hand, and into HADS-S, on the other hand, allowing to screen for anxiety, depression, mixed-anxiety, (HADS-A and HADS-D) and additionally for overall distress (HADS-S) in SSc patients.

OMERACT filter criteria

In the analysis performed with OMERACT filter criteria, HADS-A, HADS-D and HADS-S proved to be valid, reliable and easy-to-use tools to detect cases of anxiety, depression or general distress in SSc patients.

HADS-A and HADS-D changed significantly with occurrence of any

Table IV. HADS assessed by OMERACT filter criteria.

Pillar	HADS-A	HADS-D	HADS-S
Truth			
Face validity	adequate	adequate	adequate
Content validity	adequate	adequate	adequate
Missing answers	max: 2.22% -item 1 min: 1.05% - item 10	max: 1.75% - item 4 min: 0.93% - item 14	overall missing percentage: 1.41%
Floor and ceiling effect	absent ceiling (%) = 0.3 floor (%) = 9	absent ceiling (%) = 0.3 floor (%) = 9	absent ceiling (%) = 0.6 floor (%) = 0.3
Construct validity (Spearman's correlations with SOC-13, SF-36-MH, SF-36-MCS, and SHAQ)	strong, very strong, strong, moderate	strong, strong, strong, strong	strong, very strong, moderate
Internal consistency reliability (Cronbach's α, split-half reliability)	very good, very good	very good, excellent	excellent, excellent
Discrimination			
test-retest reliability	good	good	good
sensitivity to change (effect size)	large to very large for ILD and EScSG-A, large for PH events	large for PH, mRSS and EScSG-A events	large for mRSS events
Feasibility			
Applicability	good	good	good

worsening or improvement event, except an increase and decrease on GIT score. This suggests that activity of the disease has an impact on the psychological well-being of the patients. This could not be shown for either HAQ, SHAQ, SF-36-MH or SF-36-MCS, even though the latter two are also tools designed to assess mental well-being. The use of HADS as a screening tool for psychological deterioration concomitant with disease progression should be further investigated.

One plausible explanation for the small to medium effect size for a change in GIT score could be that the analysis was not anchored on a singular clinical event, but on patient reported outcome measure (GIT) which represents a composition of gastrointestinal events that may not improve or worsen simultaneously in the same direction.

Anxiety, depression, MADD and distress

Similar to other studies, very high rates of anxiety (23–64%) and depression (27–46%) were identified by HADS in SSc patients (6, 7) and by the Center for Epidemiologic Studies Depression Scale (CED-S) (37), Beck Depression Inventory (BDI) (38-40), Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Anxiety Rating Scale (HARS) (41). These high rates of anxiety and depression detected by HADS are also common among patients suffering from systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease or Sjögren's syndrome and comparable to cancer patients (6, 42).

Nevertheless, the diagnosis of depression according to the ICD-10/ DSM-IV criteria, BDI, MADRS or CED-S was more frequent than a diagnosis by HADS in patients with different rheumatic diseases, including SSc patients (60%, 46%, 43% or 34% *vs*. 26.1%, respectively) (6, 37, 40, 41). Also HARS identified a higher rate of anxiety in SSc patients than HADS-A (43% *vs*. 32.7%) (41). This suggests that HADS is not over-diagnosing psychiatric diseases compared to other instruments.

In our cohort, a small percentage of patients was actually referred to a psychiatrist. Therefore, we would recommend the use of the HADS-S, HADS-A and HADS-D, for which cut-off scores already exist, to efficiently screen SSc patients for a referral to a psychiatrist. It also implies that anxiety, depression and psychological distress might be under-recognised and need to be addressed appropriately, especially when poorer mental health is a risk factor for the physical symptom exacerbation (43).

Strengths and limitations of this study

Although only some cases of anxiety and depression detected in our cohort with HADS were confirmed cases by a psychiatrist, our study is currently the only one which evaluates the structure of the HADS and its psychometric properties for the use in SSc. By using a theory-driven approach for analysing factor structure (EFA and CFA) and a structured and methodological approach recommended by OMERACT, we were able to successfully validate HADS for the use in patients with SSc. Criterion validity could not be assessed. Nevertheless, the HADS meets adequately the criteria of the validity and reliability pillars of the OMERACT filter.

Selection bias might have been introduced, by including consecutive patients along with patients in which a worsening/improvement event occurred. Data allowing to conduct a stratified analysis for comorbidities that may influence the psychiatric well-being were not available. However, the anxiety and depression rates revealed by HADS in our study were similar to those stated by other studies and other questionnaires that measure anxiety and depression. Moreover, in absence of a criterion validity analysis, these percentages identified by HADS in our SSc cohort should not be seen as true prevalence for any psychiatric disorder.

In conclusion, the HADS, with two subscales, HADS-A and HADS-D, and a general scale, HADS-S, is a feasible, valid, reliable and responsive to clinical change tool, that is able to detect cases of anxiety, depression, MADD and distress, which represent a significant burden for SSc patients.

Competing interests

B. Maurer has received grants/research support from AbbVie, Protagen, Novartis Biomedical, speaker fees from Boehringer-Ingelheim as well as congress support from Pfizer, Roche, Actelion, Mepha and MSD. She has a patent mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143).

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The other co-authors have declared no competing interests.

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