Hopelessness is associated to severity of both digital vasculopathy and lung disease in systemic sclerosis patients: a prospective one-year study

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Abstract

Objective

Systemic sclerosis (SSc) is an autoimmune fibrosing disease with multi-organ involvement, significantly impacting quality of life. This study assessed the burden of hopelessness and its clinical and psychosocial correlates in SSc patients.

Methods

76 SSc patients were followed prospectively over one year. Clinical assessments included Medsger Severity Score (MSS), disease activity (revised EUSTAR Activity Index), modified Rodnan skin score (mRSS), and digital ulcer (DU) presence and severity (DUCAS), Hand disability (HAMIS), Raynaud diary, and Raynaud's Condition Score (RCS). Psychosocial measures included the Beck Hopelessness Scale (BHS), 36-Item Short Form Survey (SF-36), Hospital Anxiety and Depression Scale (HADS), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Body Image Scale (BIS). Patients were stratified by BHS into mild (≤8) and moderate/severe (>8) hopelessness.

Results

SSc patients had significantly higher BHS scores than controls ($p<0.001$). Moderate/severe hopelessness was linked to more severe disease (MSS: BHS>8 = 6 [4-10] vs. ≤8 = 3 [2-5], $p=0.008$) and worse MSS lung scores over time ($p<0.05$). BHS>8 was also associated with poorer HAMIS, RCS, and ADL function. Multivariate analysis showed significant associations between hopelessness and MSS lung scores (Coeff = 0.490, CI [0.030–0.957], $p=0.037$), RCS (Coeff = 0.180, CI [0.029–0.329], $p=0.019$), and BIS (Coeff = 0.229, CI [0.165–0.292], $p<0.001$). In SSc patients with active DU, hopelessness correlated with DUCAS (Coeff =0.636, CI [0.033–1.239], $p=0.039$).

Conclusion

Hopelessness is common in SSc and linked to lung severity and digital vasculopathy, highlighting the importance of targeting hand function and pulmonary disease to improve psycho-social wellbeing.

Key words

systemic sclerosis, hopelessness, vasculopathy, lung disease

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Introduction

Systemic sclerosis (SSc) is a chronic multi-organ disease characterised by autoimmunity, vasculopathy and fibrosis, with one of the highest mortality rates among connective tissue diseases (1, 2). The life of SSc patients is characterised by severe limitation in their activity of daily living (ADL), and changes in their physical appearance, due to organ fibrosis and vasculopathy (3). The cutaneous involvement has a significant effect on the physical and mental perception of the patient's health status. For these reasons, the assessment of both psychological aspects and quality of life of these patients by Patient Reported Outcome Measurements (PROMs) has been strongly encouraged in SSc (4).

One distinctive feature of the psychological distress experienced by patients with chronic diseases, such as SSc, is a deep loss of hope for the future, often referred as hopelessness (5). This cognitive pattern is characterised by a negative outlook on the future, reflecting a deficiency in the main elements of hope. Indeed, while patients with high levels of hope may identify adaptive strategies (both physical and psychological) to manage their condition, those experiencing hopelessness tend to stick to unattainable goals, persisting with ineffective approaches and fostering a sense of powerlessness. Hopelessness avoids the exploration of alternative paths, as patients may be reluctant to abandon their current goals. After a specific mental strategy proves to be unsuccessful, hope serves as a cognitive resource, facilitating the identification of alternative pathways to achieve desired goals. In contrast, patients with hopelessness exhibit diminished problem-solving capacity and are less likely to explore or identify novel strategies (6).

This construct has been extensively studied across a wide range of physiological and pathological conditions, including aging and end-of-life care in the elderly, HIV infection, and cancer (7-10). Within the realm of rheumatic diseases, available literature provides limited data on the prevalence of hopelessness; specifically, one study reported its prevalence being 14% among a group of women with rheumatoid arthritis (11).

The prevalence and incidence of hopelessness in SSc and its relationship with the clinical characteristics of the disease have not yet been investigated. The goals of this study were to assess the prevalence of hopelessness in a cohort of SSc patients compared to healthy controls (HC) and to evaluate, over a 12-month follow-up period, its association with clinical variables, including digital ulcers (DU), Raynaud's phenomenon, disease activity and severity, hand function and psychosocial measures.

Material and methods

This prospective observational study was conducted at the Immuno-rheumatology Unit of the Campus Bio-Medico University Hospital Foundation in Rome and the Vascular Medicine and Autoimmunity Unit CRIIS, ASL Roma 2. The study was approved by the IRB of the Campus Bio-Medico University Hospital Foundation in Rome (N. 2023.020). This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All participants provided written informed consent prior to inclusion in the study.

Study population

From January 2023 to May 2023, 76 adult SSc patients, fulfilling the 2013 ACR/EULAR criteria, were consecutively enrolled (12).

Exclusion criteria were: age <18 years, psychiatric disorder within the DSM V, history of solid organ and/or blood cancer within the last five years or were currently undergoing cancer treatment (non-melanoma skin cancers adequately treated within the three months from enrolment were included), history of chronic renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, haematological, rheumatological (other than SSc and Sjögren's syndrome + SSc overlap syndromes), genitourinary or metabolic disease, history of chronic/recurrent (*e.g.* HBV, HCV, COPD) or severe infections, non-scleroderma digital ulcers, acute HIV positivity, pregnancy or breastfeeding, major surgery (general anaesthesia and/or hospitalisation for more than 24 hours) in the past two

months or planned major surgery during the study period.
35 HC, matched for age and sex, were randomly selected and included to provide baseline measures of hopelessness and psychosocial measures.

Assessment of disease status
Clinical assessments were performed at baseline (T0), 6 months (T1) and 12 months (T2). SSc disease activity was assessed by evaluating the following parameters: modified Rodnan Skin Score (mRSS), presence of DU, DU-severity (DUCAS) (13), DU-related pain (DUVAS), years of intravenous iloprost therapy for Raynaud's phenomenon, hand functionality (HAMIS scale) (14), Medsger Severity Score (MSS) (15), revised EUSTAR activity index (rEUSTAR-AI) (16), nailfold capillaroscopy, presence of tender joints, swollen joints, calcinosis cutis and tendon frictions rubs. Furthermore, PROMs, including the Raynaud's phenomenon diary, the Raynaud's condition score (RCS) (17), the Patient Global Assessment (PtGA), were assessed at each timepoint and changes in the therapeutic regimen were assessed at timepoints T1 and T2.

Assessment of hopelessness and psychological state
The validated Italian version of the Beck Hopelessness Scale (BHS) was used to assess hopelessness at T0, T1 and T2 (18). This item includes 20 true or false statements evaluating negative thoughts, feelings, and beliefs about the future, with a total score ranging from 0 to 20. A score of 8 or higher indicates an increased risk of depression and suicidal ideation (19, 20).
At T0, T1 and T2 , patients were asked to complete the following questionnaires related to quality of life (Functional Assessment of Chronic Illness Therapy-Fatigue scale - FACIT-F), Short Form Health Survey-36 (SF-36), body image perception (Body Image Scale - BIS), and the presence of anxiety and depressive symptoms (Hospital Anxiety and Depression Scale - HADS) [21–24] Physical Component Score (PCS) and Mental Component Score (MCS) were derived from weighted contributions of all eight SF-36 domains, with greater weight from physical and mental health domains, respectively.

Table I. SSc patient (n=76) cohort characteristics at baseline.

Age	58 [51-68]
Female	74 (97.4%)
Months from first Raynaud's phenomenon	110 [60-240]
Months from SSc diagnosis (ACR/EULAR 2013 Criteria)	78 [28.5-132]
Cutaneous disease subtype	
dcSSc	22 (28.9%)
lcSSc	49 (64.5%)
sine	2 (2.6%)
Interstitial lung disease	26 (34.2%)
Pulmonary hypertension	9 (11.8%)
History of digital ulcers (previous and/or current)	47 (61.8%)
History of calcinosis cutis (previous and/or current)	15 (19.7%)
mRSS	6 [3-12]
Nailfold capillaroscopy (scleroderma pattern)	
Early	17 (22.4%)
Active	33 (43.4%)
Late	23 (30.3%)
Presence of telangiectasias	25 (32.9%)
Intravenous iloprost therapy for Raynaud's phenomenon	70 (92.1%)
Years of intravenous iloprost therapy	4 [2-7.5]
rEUSTAR-AI	1.34 [0.336- 2,773]
Medsger Severity Scale	5 [2-7]

dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; mRSS: modified Rodnan Skin Score; rEUSTAR-AI: revised EUSTAR Activity Index.

Table II. Comparison between SSc and sex- and age-matched healthy controls.

	SSc (n=76)	Healthy Controls (n=35)	*p*-value
Beck hopelessness scale	8 [3-12]	4 [2-5]	<0.0001
FACIT-F	33 [25-41]	44.5 [40-47]	<0.0001
HADS	14 [10-18.5]	8 [5-11]	<0.0001
Short Form Health Survey 36 (SF-36)			
Physical functioning	60% [12.5-90]	95% [90-100]	<0.0001
Role-physical limitations	25% [0-100%]	100% [100-100]	<0.0001
Role-emotional limitations	66% [33-100]	100% [100-100]	0.0001
Vitality	45 [25-60]	65% [55-75]	<0.0001
Mental health	56% [44-68]	72% [60-84]	<0.0001
Social functioning	50% [25-75]	87% [62-100]	<0.0001
Pain	50% [33-78]	90% [67-100]	<0.0001
General health	30% [15-45]	70% [55-75]	<0.0001
Health change	37.5% [5-50]	50% [50-50]	0.0044

FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue scale; HADS: Hospital Anxiety and Depression Scale

Statistical analysis
Data are presented as median [25th–75th percentiles] for continuous variables, while categorical variables were expressed as percentages. Differences between continuous variables were investigated using the Mann-Whitney-U test. A mixed linear model was applied to assess the association between the BHS (dependent variable) and demographic, clinical and psychometric variables (independent variables). Statistical significance was set at $p<0.05$, and 95% confidence intervals were calculated. Analyses were conducted using Stata (v. 18.0, College Station, Texas, USA) and RStudio (v. 4.3, Boston, MA, USA).
The sample size for this study was based on the primary objective of estimating the prevalence of clinically significant hopelessness among SSc patients. In the absence of SSc-specific data, an estimated prevalence of 30.9% was adopted from reported findings in the general adult population, consid-

Table III. SSc population stratified by Beck Hopelessness Scale (BHS) score at different timepoints (T0, T1, T2).

	T0			T1			T2		
	BHS ≤ 8	BHS > 8	*p*-value	BHS ≤ 8	BHS > 8	*p*-value	BHS ≤ 8	BHS > 8	*p*-value
MSS total	4 [2-7]	5 [3-8]	0.101	**3 [2-5]**	**6 [4-10]**	**0.008**	4 [2-5]	4 [3.75-6]	0.128
MSS - Skin	**1 [1-1]**	**1 [1-2]**	**0.032**	1 [1-1]	1 [1-1]	0.547	1 [1-1]	1 [1-1]	0.803
MSS - Lung	**0 [0-1]**	**1 [0-2]**	**0.032**	**1 [0-1]**	**2 [0-2]**	**0.022**	**1 [0-2]**	**2 [1-2]**	**0.013**
rEUSTAR-AI	1.21 [0.38-2.57]	1.50 [0.59-3.00]	0.607	1 [0.27-2.75]	1.8 [1.2-4]	0.08	**0.89 [0.25-2.18]**	**2.38 [1.17-4.46]**	**0.014**
mRSS	6 [3-12]	6 [2-15]	0.665	6 [3-13]	6 [4-10]	0.921	5 [3-11]	5 [2-13]	0.968
Therapy variation	NA	NA	NA	**6.67%**	**27.03%**	**0.031**	13.79%	17.14%	0.713
Digital ulcers at visit	13.89%	5.88%	0.443	6.67%	23.68%	0.865	17.24%	27.78%	0.316
DUCAS	0 [0-0]	0 [0-0]	0.157	4 [3.5-4.5]	4 [3.5-4.5]	1	4 [3-4]	4 [3.5-4]	1
DUVAS	0 [0-0]	0 [0-0]	0.233	8 [7-9]	7 [2-8]	0.633	8 [7-8]	7 [3-8]	1
HAMIS scale	**0 [0-5]**	**4 [0-11]**	**0.032**	0 [0-2.8]	0 [0-5]	0.383	0 [0-2]	3 [0-5]	0.055
RCS	**3 [1-5]**	**6 [4-8]**	**0.003**	**1 [0-1]**	**3 [1-7]**	**<0.001**	**1 [1-6]**	**5 [3-6]**	**0.009**
Raynaud's phenomenon diary									
Pain (Yes)	44.74%	45.95%	0.916	30%	45%	0.214	27.59%	36.11%	0.465
Paraesthesia (Yes)	68.42%	62.16%	0.569	36.67%	52.63%	0.189	55.17%	72.22%	0.153
Impairment in ADL (Yes)	26.32%	43.24%	0.124	**13.33%**	**36.84%**	**0.029**	**10.35%**	**33.33%**	**0.029**
PtGA	6 [3-8]	7 [5-8]	0.141	**3.5 [1.2-5.8]**	**5 [5-7]**	**0.001**	**5 [3-6]**	**6 [5-7]**	**0.011**
FACIT-F	**39 [33-46]**	**26 [21-33]**	**<0.001**	**41.5 [37.25-47]**	**28 [22-34]**	**<0.001**	**44 [37-47]**	**25 [22-35]**	**<0.001**
HADS-anxiety	**5 [3-7]**	**10 [6-12]**	**<0.001**	**5 [4-7]**	**9 [7-12]**	**<0.001**	**5 [2-7]**	**9 [6-12]**	**<0.001**
HADS-depression	**5 [2-7]**	**10 [6-14]**	**<0.001**	**5 [4-7]**	**9 [6-11]**	**<0.001**	**5 [2-6]**	**10 [9-12]**	**<0.001**
HADS-total	**10 [6-14]**	**18 [14-22]**	**<0.001**	**11 [8-14]**	**18 [13-23]**	**<0.001**	**10 [4-12]**	**19 [14-24]**	**<0.001**
BIS	**6 [2-10]**	**19 [12-26]**	**<0.001**	**7 [1.5-13.3]**	**15.5 [8.25-21.75]**	**0.001**	**5 [1-13]**	**17 [10-26]**	**<0.001**
SF-36									
Physical functioning	**0.80 [0.60-0.95]**	**0.55 [0.30-0.80]**	**0.006**	**0.85 [0.59-0.95]**	**0.48 [0.26-0.6]**	**<0.001**	**0.8 [0.55-0.95]**	**0.8 [0.2-0.8]**	**0.009**
Role-physical limitations	**0.50 [1-0.25]**	**0 [0-0.50]**	**0.002**	**1 [0.25-1]**	**0 [0-0.44]**	**0.001**	**0.5 [0-1]**	**0 [0-0.5]**	**0.009**
Role-emotional limitations	**1 [0.41-1]**	**0.33 [0-0.67]**	**<0.001**	**1 [0.33-1]**	**0.33 [0-0.67]**	**0.002**	**1 [0.33-1]**	**0.17 [0-0.67]**	**0.008**
Vitality	**0.58 [0.46-0.70]**	**0.35 [0.20-0.50]**	**<0.001**	**0.58 [0.5-0.7]**	**0.35 [0.20-0.45]**	**<0.001**	**0.65 [0.5-0.7]**	**0.35 [0.24-0.5]**	**<0.001**
Mental health	**0.64 [0.56-0.76]**	**0.75 [0.50-0.88]**	**<0.001**	**0.7 [0.6-0.76]**	**0.52 [0.44-0.64]**	**<0.001**	**0.68 [0.56-0.84]**	**0.46 [0.32-0.56]**	**<0.001**
Social functioning	**0.75 [0.50-0.86]**	**0.50 [0.25-0.62]**	**<0.001**	**0.75 [0.62-0.87]**	**0.5 [0.37-0.62]**	**<0.001**	**0.75 [0.5-0.9]**	**0.5 [0.38-0.62]**	**<0.001**
Pain	**0.71 [0.45-0.86]**	**0.45 [0.23-0.65]**	**0.006**	**0.72 [0.48-1]**	**0.45 [0.23-0.7]**	**<0.001**	**0.67 [0.45-0.78]**	**0.45 [0.23-0.45]**	**<0.001**
General health	**0.40 [0.35-0.55]**	**0.25 [0.15-0.35]**	**<0.001**	**0.45 [0.35-0.65]**	**0.3 [0.1-0.3]**	**<0.001**	**0.5 [0.3-0.6]**	**0.25 [0.2-0.35]**	**0.006**
Health change	0.50 [0.50-0.50]	0.50 [0.25-0.50]	0.106	**0.5 [0.5-0.75]**	**0.5 [0.2-0.5]**	**0.002**	**0.5 [0.5-0.75]**	**0.5 [0.25-0.5]**	**0.032**
PCS	**42.95 [33.32-50.73]**	**32.73 [29.23-41.94]**	**0.013**	**45.95 [37.72-53-82]**	**31.30 [25.78-38.34]**	**<0.001**	**41.15 [35.00-51.06]**	**34.53 [26.69-40.81]**	**0.008**
MCS	**46.08 [43.15-56-27]**	**35.28 [31.39-42.55]**	**<0.001**	**48.77[40.31-51.79]**	**39.72 [33.17-45.00]**	**<0.001**	**49.79 [44.50-55.25]**	**34.68 [29.04-44.95]**	**<0.001**

MSS: Medsger Severity Score; rEUSTAR-AI: revised EUSTAR-Activity Index; DU: digital ulcers; DUCAS: DU clinical assessment score; DUVAS: DU Visual Analog Scale; DUCAS: DU Clinical Assessment Score; HAMIS: HAnd Mobility In Scleroderma; RCS: Raynaud Condition Score; ADL: Activity of Daily Living; BIS: Body Image Scale; PCS: Physical Component Summary; MCS: Mental Component Summary.

ered appropriate given the psychosocial burden of SSc (25). Using a 95% confidence level and a precision of ±10%, the required sample size was calculated as 81 patients. The present SSc patient sample (n=76) provides a margin of error of approximately ± 10.3%, which is acceptable for the study's aims.

Results

A total of 76 patients (Table I) were included in the study, with 97.4% being female and a median age of 58 years [52–68]. The one year follow up was completed by 65 (85.5%) patients, with one patient lost to follow-up due to SSc-related death. At baseline (T0), 28.9% out of patients had diffuse cutaneous systemic sclerosis (dcSSc), and SSc-ILD (confirmed at thoracic HRCT) was present in 34.2% out of patients. Nailfold capillaroscopy at baseline was available for 73 patients, with 'sclerodema active' being the most common pattern (n=33; 43.4%) (Table I). 61.8% out of patients had a history of DU at baseline; 7 (9.2%) patients had active digital ulcers at T0, 11 (15.5%) at T1 and 15 (20.0%) at T2.

Values of hopelessness and psychosocial measures

At baseline, compared to HC, SSc patients had significantly higher levels of hopelessness (8 [3–12] *vs*. 4 [2–5]; *p*=<0.001), anxiety and depressive symptoms (HADS) (14 [10–18.5] *vs*. 8 [5–11]; *p*<0.001), and fatigue (FACIT-Fatigue scale) (33 [25–41] *vs*. 44.5 [40–47], *p*<0.001). All domains of the SF-36 were significantly lower in patients compared to HC (Table II).

Subgroup analysis (BHS ≤8 vs. BHS >8)

The different clinical and psychometric parameters were subsequently evaluated in relation to hopelessness levels at each time point (T0, T1, T2). Patients were divided using the BHS cutoff of 8, defining moderate/severe hopelessness (BHS >8) and mild hopelessness (BHS ≤8) (Table III), above which there is an increased risk of suicide and depression.

Subjects with moderate/severe hopelessness (BHS>8) had more severe disease, as evidenced by higher total MSS at all time points (Table III), with statistical significance at T1 (BHS>8 = 6 [4–10] *vs*. BHS≤8 = 3 [2–5], *p* = 0.008). At baseline, patients with BHS>8 showed more severe involvement in the MSS skin and lung domains (Table III). The MSS lung domain consistently reflected this trend across all time points: at T0, BHS>8 = 1 [0–2] *vs*. BHS ≤8 = 0 [0–1], *p*=0.032; at T1, BHS>8 = 2 [0–2] *vs*. BHS ≤8 = 1 [0–1], *p*=0.022; and

Table IV. Mixed-effects model with BHS as the dependent variable.

	Univariate			Multivariate		
BHS	Coeff.	*p*-value	CI [95%]	Coeff.	*p*-value	CI [95%]
Age	0.090	0.010	0.022 to 0.158	0.094	0.001	0.040 to 0.148
Sex	-4.537	0.123	-10.302 to 1.229	-2.515	0.265	-6.941 to 1.911
lcSSc	-0.482	0.652	-2.579 to 1.615			
dcSSc	-3.012	0.121	-6.817 to 0.794			
Months from SSc diagnosis (ACR/EULAR 2013 criteria)	0.013	0.007	0.003 to 0.022			
Months from first Raynaud's phenomenon	0.011	0.007	0.003 to 0.196			
Digital ulcers history	0.558	0.574	-1.387 to 2.504			
Calcinosis history	2.072	0.083	-0.272 to 4.416			
Years of intravenous iloprost therapy	0.268	0.016	0.049 to 0.486			
ILD	0.648	0.492	-1.199 to 2.494			
Pulmonary hypertension	1.417	0.338	-1.483 to 4.317			
Upper GI involvement	1.144	0.242	-0.774 to 3.061			
Lower GI involvement	1.836	0.053	-0.022 to 3.693			
Telangiectasia	1.263	0.215	-0.734 to 3.260			
rEUSTAR-AI	-0.001	0.899	-0.020 to 0.018			
mRSS	-0.014	0.783	-0.115 to 0.087			
MSS total	0.168	0.106	-0.036 to 0.371			
Lung (MSS)	**0.836**	**0.001**	**0.323 to 1.348**	**0.494**	**0.037**	**0.030 to 0.957**
Presence of digital ulcers	0.478	0.507	-0.934 to 1.890			
Number of digital ulcers	-0.035	0.910	-0.635 to 0.566			
DUCAS	0.721	<0.001	0.343 to 1.110			
DUVAS	0.263	0.017	0.046 to 0.480			
Raynaud's condition score	**0.255**	**0.003**	**0.088 to 0.423**	**0.1796**	**0.019**	**0.029 to 0.329**
PtGA	0.218	0.076	-0.022 to 0.458			
FACIT-fatigue	-0.024	<0.001	-0.295 to -0.189			
HADS anxiety	0.473	<0.001	0.330 to 0.617			
HADS depression	0.712	<0.001	0.573 to 0.850			
HADS total	0.388	<0.001	0.311 to 0.466			
HAMIS	0.078	0.174	-0.035 to 0.191			
BIS	**0.241**	**<0.001**	**0.174 to 0.309**	**0.2287**	**<0.001**	**0.165 to 0.292**
Short Form Health Survey 36 (SF-36)						
Physical functioning	-5.494	<0.001	-7.663 to -3.325			
Role-physical limitations	-2.818	<0.001	-4.243 to -1.392			
Role-emotional limitations	-0.350	0.303	-1.016 to 0.316			
Vitality	-10.787	<0.001	-13.286 to -8.288			
Mental health	-10.480	<0.001	-13.454 to -7.505			
Social functioning	-5.514	<0.001	-7.830 to -3.197			
Pain	-5.480	<0.001	-7.790 to -3.170			
General health	-9.123	<0.001	-12.087 to -6.160			
Health change	-3.113	0.008	-5.422 to -0.804			
PCS	-0.121	<0.001	-0.173 to -0.070			
MCS	-0.075	<0.001	-0.116 to -0.034			

at T2, BHS >8 = 2 [1–2] *vs*. BHS ≤8 = 1 [0–2], *p*=0.013.

Regarding disease activity, the rEUSTAR-AI was higher in patients with moderate/severe hopelessness across all time points, reaching statistical significance at T2 (BHS>8 = 2.38 [1.17–4.46] *vs*. BHS≤8 = 0.89 [0.25–2.18]; *p*=0.014). Furthermore, hand disability, as measured by HAMIS, was significantly higher in SSc patients with moderate/severe hopelessness at baseline (BHS> 8 = 4 [0–11] *vs*. BHS≤8 = 0 [0–5]); *p*=0.032). At the same time, mRSS did not show significant association to moderate/severe hopelessness in the cohort (Table III).

During follow-up, several SSc-related PROMs were found to be consistently, significantly worse in patients with moderate/severe hopelessness. These included the RCS, which was consistently worse across all time points, as well as PtGA and impairment in activities of daily living (ADL) (Table III).

At all timepoints, SSc patients with moderate/severe hopelessness also showed worse scoring in the PCS, MCS, FACIT-F, HADS-Anxiety, HADS-Depression and worse BIS (Table III). Finally, therapy variation at T1, defined as start of new/increased immunosuppressive and/or vasoactive treatment in the last 6 months, were significantly more frequent in subjects with moderate/severe hopelessness levels (BHS>8 = 27.03% *vs*. BHS ≤8 *vs*. 6.67%; *p*=0.031).

Univariate and multivariate data analysis

Univariate and multivariate analyses were conducted using a mixed-effects model with BHS as dependent variable. Univariate analysis (Table IV) revealed that hopelessness was significantly influenced by patient age (Coeff = 0.090, CI 95% [0.022; 0.158], *p*=0.01), months from SSc diagnosis (Coeff = 0.013, CI 95% [0.003; 0.022], *p*=0.007), time since the first Raynaud's phenomenon

(Coeff= 0.011, CI95% [0.003; 0.196], *p*=0.007), higher values of the MSS Lung domain (Coeff = 0.836, CI 95% [0.323; 1.348], *p*=0.001), higher levels of DUCAS (Coeff =0.721, CI95% [0.343;1.110], *p*<0.001), higher levels of DUVAS (Coeff = 0.263, CI95% [0.046; 0.480], *p*=0.017), higher values of the RCS (Coeff = 0.255, CI95% [0.088; 0.423], *p*=0.003), worse FACIT-Fatigue score (Coeff = -0.024, CI95% [-0.295; -0.189], *p*<0.001), higher values of HADS-anxiety (Coeff = 0.473, CI95% [0.330; 0.617], *p*<0.001) and HADS-depression (Coeff = 0.712, CI95% [0.573; 0.850], *p*<0.001), higher values of BIS (Coeff = 0.241, CI95% [0.174; 0.309], *p*<0.001), and all individual domains and composite scores of the SF-36 questionnaire (Table IV), except from the 'Role Emotional Limitations' (Table IV).

The multivariate analysis (Table IV) confirmed significant association between hopelessness levels and older patient age (Coeff = 0.094, CI95% [0.040; 0.148], *p*=0.001), higher values of the MSS lung domain (Coeff = 0.494, CI95% [0.030; 0.957], *p*=0.037), higher values of RCS (Coeff = 0.180, CI95% [0.029; 0.329], *p*=0.019), and BIS (Coeff = 0.229, CI95% [0.165; 0.292]; *p*<0.001) (Table III).

Finally, an additional multivariate analysis (Table IV) was performed on the subset of patients with active DU showing a statistically significant correlation between hopelessness levels and the following: DUCAS (Coeff = 0.636, CI95% [0.033; 1.239], *p*=0.039), BIS (Coeff =0.228; CI95% [0.136; 0.320], *p*=<0.001) and PCS (Coeff = -0.075, CI95% [-0.146; -0.004], *p*=0.038) (Table IV).

Table V. Multivariate analysis in the SSc-DU population: BHS as dependent variable.

BHS	Coeff.	*p*-value	CI [95%]
Age	**0.114**	**0.001**	**0.044 to 0.182**
Sex	-4.867	0.061	-9.960 to 0.226
Lung (MSS)	-0.041	0.899	-0.677 to 0.594
RCS	0.033	0.787	-0.205 to 0.270
BIS	**0.228**	**<0.0001**	**0.136 to 0.320**
Therapy variation	0.044	0.964	-1.870 to 1.957
PCS	**-0.075**	**0.038**	**-0.146 to -0.004**
MCS	-0.019	0.357	-0.061 to 0.022
DUVAS	-0.032	0.837	-0.340 to 0.275
DUCAS	**0.636**	**0.039**	**0.033 to 1.239**

Discussion

The results of this prospective study highlight the significant impact of SSc on patients' psychosocial well-being. While hopelessness has been associated to reduced quality of life, treatment adherence, and increased suicide risk in other chronic diseases (*i.e.* rheumatoid arthritis and systemic lupus erythematosus), the present study is the first to demonstrate elevated hopelessness levels in SSc patients compared to age- and sex-matched controls (8, 11, 26). Disease duration and age were also significant factors in determining hopelessness in SSc patients, with the age being a known factor for hopelessness in the general population (10). The disease duration, measured as both time from first Raynaud's phenomenon and from SSc (ACR/EULAR 2013 criteria) diagnosis, impacted on hopelessness levels of SSc patients.

As demonstrated by both cross-sectional subgroup analysis and uni-/multivariate analysis, moderate/severe hopelessness was significantly associated to the severity of lung involvement. Notably, the MSS lung domain score is based on the lung function tests values as markers of ILD severity and systolic pulmonary arterial pressure (sPAP) as marker of pulmonary hypertension severity, thus suggesting an association between SSc-related lung involvement and hopelessness. This finding underlines the profound impact of pulmonary complications, both ILD and pulmonary hypertension, on the psychological health of SSc patients (27). At the same time mRSS, a well-known prognostic factor, was not linked to increased hopelessness levels and the mRSS derived MSS skin domain was associated to moderate/severe hopelessness only at baseline.

In SSc, regional hand involvement is very common, characterising different clinical phenotypes (both lcSSc and dcSSc) and possibly affecting body image perception (2, 28, 29). In this SSc population, hand functionality (HAMIS scale) and severity of digital vasculopathy (RCS, DUCAS), which are reported clinical unmet needs, were associated at both univariate and multivariate analysis with increased hopelessness levels (28, 30, 31). Regarding patients with SSc-DU, DU severity (measured by DUCAS) was significantly associated with BHS in multivariate analysis. Moreover, the association between years of intravenous iloprost therapy for Raynaud's phenomenon and BHS at univariate analysis suggest the prominent impact of digital vasculopathy on this psychological domain. This underscores the substantial psychological burden associated with severe digital vasculopathy in SSc patients, as its manifestations, characterised by intense pain, constitute a primary factor in the development of depression within this population (32, 33). The link between pain and mood disorders, such as depression and hopelessness, presents an intriguing field for future research into the neurobiology of pain (5, 34).

Body image disturbance, has been previously described in SSc and has been linked to skin fibrosis, in particular facial involvement, and hand contractures (35). In this cohort, body image disturbance was significantly associated with hopelessness levels in multivariate analysis with significantly higher BIS values in patients with BHS >8 at all timepoints. These finding support the role of body image perception as a key factor in the development of depressive symptoms in SSc patients and highlights the need for aesthetic-regenerative medicine in SSc management (36). In the field of medical psychology, both body image disturbance and hopelessness have been associated to type D ('Distressed') personality (37). This personality is characterised by both negative affectivity and social inhibition and it has been shown to af-

fect negatively the prognosis in patients with cardiovascular diseases and coping strategies in cancer patients (38, 39). Assessment of personality should be considered in rheumatic disease, as a recent study showed that psoriatic arthritis patients with type D personality had higher frequency of metabolic syndrome, lower levels of physical activity and higher cardiovascular disease risk score (40). In the future, further studies looking into personality types and clinical characteristics among SSc patients could improve patient stratification. In this regard, patients with type D personality seem to show higher expression of inflammatory markers and endothelial dysfunction, although the mechanisms involved in these processes remain still unknown (41).

A limitation of this study is the relatively small sample size, which is attributable to the low incidence of SSc in the general population. At the same time the psychometric questionnaires, including the BHS, used in this study are inherently subject to the patient's personal interpretation, which may affect the generalisability of the results to a broader population. The assessment of Raynaud's phenomenon in this study was based on the validated, patient-reported RCS, which does not provide an objective measure of the severity of SSc-related vasculopathy. No association between the BHS and nailfold capillaroscopy pattern was found. Lastly, given the lack of pre-established treatment, the possible association between treatment and different outcomes cannot be uniquely ascertained due to a possible confounding by indication bias. Despite these limitations this study sheds light on a still largely unexplored clinical issue for SSc patients. Importantly, the prospective design, by enabling the observation of changes over time in the same study population, allows for a more accurate characterization of hopelessness, a psychological construct that may fluctuate in response to external factors, and should be considered a methodological strength.

In the present study SSc patients have been thoroughly assessed for disease severity and activity, including DU, thus allowing a strict correlation between clinical and psychological variables, in particular hopelessness.

In SSc patients, the high levels of hopelessness reaffirm the need for a combined clinical and psychological support in their daily management. Hopelessness is a very relevant psychological domain as scores of BHS >8 are associated to increase risk of self-harm and suicide. In this cohort, hopelessness was significantly associated with pulmonary disease and regional hand involvement (hand functionality, RP severity and DU); thus, highlighting these two as crucial treatment targets for overall well-being of SSc patients. Although lung function impairment has been often the primary outcome of RCT in SSc, this study highlights the importance of hand functionality as a key determinant of patients' quality of life, warranting greater attention from investigators in future clinical trials.

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