Frailty assessment in patients with systemic sclerosis

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Abstract

Objective

To evaluate the prevalence of frailty, a clinical syndrome characterised by reduced physiological reserve which exposes affected individuals to the worst consequences of acute clinical episodes, in SSc patients, and to identify associated demographic and clinical factors.

Methods

Frailty, comorbidities, SSc-related-activity, -organ damage and -overall patient-reported impact were assessed in 169 consecutive outpatients with SSc aged over 60 years by Primary Care Frailty Index (PC-FI), age-adjusted Charlson Comorbidity index (CCI), revised EUSTAR activity index, Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI), and Sclero-ID, respectively. Information and data on hospitalisations were recorded during follow-up visits, scheduled according to clinical necessity, in 85 patients.

Results

Frailty was observed in 51.3% of patients, with 31.9% classified as mildly frail, 10.7% as moderately frail, and 7.7% as severely frail. Frail SSc patients, as compared with non-frail, were older, had a longer disease duration, higher CCI, SCTC-DI, Sclero-ID and exhibited more severe SSc complications. Multivariate analysis identified that disease duration and SSc-related organ damage as independent factors associated with PC-FI scores. Patients who died or required hospitalisation during follow-up were older, with higher PC-FI and CCI than the other SSc patients, though their SSc disease activity and damage did not differ significantly.

Conclusion

Over half of SSc patients exhibited frailty, which correlated with both SSc-related organ damage and comorbidities. PC-FI appears to predict death and hospitalisations in SSc patients, highlighting frailty assessment as a potential tool for health programme planning.

Key words

systemic sclerosis, frailty, multimorbidity, organ damage accrual

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Introduction

Systemic sclerosis (SSc) is characterised by vasculopathy, autoimmunity, and fibrosis affecting the skin and internal organs with substantial heterogeneity in organ involvement, disease severity and prognosis across patients (1, 2). Although SSc is considered a rare disease, several studies observed an increase in its incidence and prevalence in recent years in Italy and other countries (2, 3).

The age of onset for SSc varies greatly, but it is more common in the middle age. The mortality rate is higher in SSc than in the general population (2); however, survival rate in Italian SSc patients diagnosed after 2009, particularly within 2 years after disease onset, was found to approach that of the Italian general population (4). Consequently, a large proportion of SSc patients currently followed in Clinics is older than 60 years. Notably, in a long-term observational study of SSc patients we demonstrated a progressive accrual of organ damage due to SSc, often accompanied by age-related comorbidities (5).

Based on these epidemiological observations we aimed to investigate the presence of the clinical syndrome known as frailty in aged SSc patients. Frailty is characterised by decreased physiological reserves across organ systems, which increases susceptibility to adverse outcomes from acute events such as infections and cardiovascular incidents (6) and is associated with increased risk of disability, hospitalisations, and death (7). It has been suggested that identifying frail patients at risk for poor outcomes and complex care needs may support better standards of care for older adults (8).

Since not much information on frailty among SSc patients is available (9-11), we sought to estimate its prevalence in a cohort of consecutive patients and to identify associated demographic and clinical factors.

For this purpose, we took advantage of a recently developed and validated index, the Primary Care Frailty Index (PC-FI), based on Italian routinely collected primary care data in individuals ≥60 years old (8).

Patients and methods

Patient selection

The study evaluated consecutive patients with SSc older over 60 years old fulfilling the 2013 ACR/EULAR classification criteria (12), and prospectively followed in an Italian EUSTAR centre with long-term experience in SSc patients, who were included at the time of scheduled visits or infusions. Patient management was performed according to common guidelines. Screening for pulmonary arterial hypertension (PAH) was performed by multiparametric evaluation with tools changing during time, such as the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2009 guidelines, or the DETECT algorithm (13). Follow-up visits were scheduled according to clinical necessity. Clinical, laboratory and demographic data were retrieved from clinical charts. Information and data on hospitalisations were recorded during follow-up visits. If enrolled patients did not attend scheduled visits, they, or their relatives, were contacted. Mortality, need for hospitalisation and their causes were ascertained also by hospital or administrative records. The main cause of death or hospitalisation was classified as SSc-related, or non-SSc-related, as previously described (5).

Frailty index

Frailty was measured by the PC-FI, an index developed using data from >300,000 primary care patients ≥60 years old in Italy, and validated in a Swedish population-based cohort, which includes 25 health deficits (8). The PC-FI is calculated as the ratio between the number of health deficits affecting a person and the total number of deficits considered by the assessor. The following cut-offs were proposed to define absent, mild, moderate and severe frailty: <0.07, 0.07–0.14, 0.14–0.21, and ≥0.21 (8).

SSc disease activity

SSc activity was measured using the revised EUSTAR activity index (14).

SSc-related organ damage

Organ damage was evaluated through the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI) (15).

Table I. Clinical and demographical features of SSc patients included in the study, and comparisons between non-frail (PC-FI=0) and frail patients (PC-FI≥0.07), and between patients with moderate/severe frailty (PC-FI≥0.14) and the remaining patients. Continuous variables are presented as median and interquartile range (IQR).

	All SSc patients >60 years (n=169)	PC-FI=0 (n=84)	PC-FI≥0.07 (n=85)	*p*-value	PC-FI<0.14 n=138	PC-FI≥0.14 n=31	*p*-value
Females (%)	154 (91.1)	78 (92.9)	76 (89.4)	0.5900	127 (92)	27 (87.1)	0.4813
Age (years)	71 (64-77)	68.5 (63-73)	74 (68-79)	**<0.0001**	69 (64-76)	76 (71-83)	**<0.0001**
Disease duration (years)	13 (6-21)	10 (6-16)	18 (9-27)	**0.0004**	12 (6-19.5)	19 (12-28)	**0.0063**
Anti-topo 1 + (%)	38 (22.5)	19 (22.6)	19 (22.3)	0.9670	33 (23.9)	5 (16.1)	0.4763
Anti-centromere + (%)	98 (58)	47 (55.9)	51 (60)	0.5940	78 (56.5)	20 (64.5)	0.4151
dcSSc	21 (12.4)	9 (10.7)	12 (14.1)	0.5025	17 (12.3)	4 (12.9)	1.0000
mRSS	2 (2-4)	4 (2-6)	2 (2-4)	**0.0293**	3 (2-5)	2 (2-4)	0.0677
Current digital ulcers	26 (15.4)	8 (9.5)	18 (21.2)	**0.0358**	16 (12.3)	10 (32.3)	**0.0040**
Joint contractures	26 (15.4)	7 (8.3)	19 (22.3)	**0.0115**	18 (13)	8 (25.8)	0.0751
ILD at HRCT	61/106 (57.5)	28/49 (57.1)	33/57 (57.9)	0.9378	47/84 (55.9)	14/22 (63.6)	0.5163
LVEF at ECHO (%)	60 (55-62)	60 (60-65)	60 (55-60)	**0.0003**	60 (57-64)	60 (55-60)	**0.0006**
FVC (% predicted)	106 (92-121)	109 (93-122)	105 (85-119)	0.0545	108 (94-122)	102 (71-115)	**0.0006**
PAH confirmed by RHC	8 (4.7)	0 (0)	8 (9.4)	**0.0066**	1 (0.7)	7 (22.6)	**<0.0001**
Scleroderma renal crisis	3 (1.8)	0 (0)	3 (3.5)	0.2456	1 (0.7)	2 (6.4)	0.0869
Oesophageal involvement	124 (73.4)	60 (71.4)	64 (75.3)	0.5697	100 (72.5)	24 (77.4)	0.5727
Gastrointestinal involvement	57 (33.7)	24 (28.6)	33 (38.8)	0.1587	45 (32.6)	12 (38.7)	0.5162
Immunosuppressive treatments	43 (25.4)	20 (23.8)	23 (27.1)	0.6277	39 (28.3)	4 (12.9)	0.1087
Prostanoids	46 (27.2)	22 (26.2)	24 (28.2)	0.7652	36 (26.1)	10 (32.3)	0.4854
Glucocorticoids	54 (31.9)	20 (23.8)	34 (40)	**0.0240**	40 (30)	14 (45.2)	0.0809
HAQ-DI	0.62 (0.25-1.25)	0.50 (0.25-0.87)	0.87 (0.37-1.72)	**0.0023**	0.50 (0.25-0.97)	1.62 (1.12-2.37)	**<0.0001**
CCI	5 (4-6)	4 (3-5)	6 (4-7)	**<0.0001**	4 (4-5)	6 (6-9)	**<0.0001**
Sclero-ID	3.9 (2.2-5.8)	3.2 (1.7-4.9)	4.9 (2.5-6.4)	**0.0029**	3.3 (1.6 -5.4)	5.1 (3.4-7.2)	**0.0002**
SCTC-DI	4 (2-7)	3 (0.5-7)	5 (3-7.5)	**<0.0001**	3 (1-6)	6 (5-10)	**<0.0001**
EUSTAR activity index	1.17 (0.25-1.34)	1 (0.17-1.33)	1.17 (0.50-1.42)	0.0545	1.17 (0.25-1.33)	1.17 (0.66-1.42)	0.3354

dcSSc: diffuse cutaneous disease; mRSS: modified Rodnan skin score; ILD: interstitial lung disease; HRCT: high resolution computed tomography; EF: ejection fraction; FVC: forced vital capacity; HAQ-DI: Health Assessment Questionnaire-Disability Index; CCI: Charlson Comorbidity Index; Sclero-ID: EULAR Systemic Sclerosis Impact of Disease; SCTC-DI: Scleroderma Clinical Trials Consortium Damage Index.

Table II. Prevalence of frailty in 169 SSc patients older ≥60 years.

Absent frailty	84 (49.7%)
Mild frailty	54 (31.9%)
Moderate frailty	18 (10.7%)
Severe frailty	13 (7.7%)

Patient reported outcome measure

The overall patient reported impact of SSc was evaluated by the Sclero-ID, a validated disease-specific questionnaire (16).

Comorbidities

The age-adjusted Charlson Comorbidity index (a single index accounting for both age and medical comorbidity) (17) was calculated at the same time point.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and were compared using the Student's *t* test or Mann-Whitney test, as appropriated. Categorical variables were compared using Chi-Square or Fisher exact test. Correlations were evaluated by the Spearman test. For the multivariable analysis, logistic regression models with *a priori* selection of variables were used.

Ethical statement

Ethics approval was obtained from the local ethics committee, and patients included in the database gave their written informed consent. The study was conducted in accordance with Helsinki Declaration principles.

Results

Among 281 consecutive outpatients with SSc evaluated over an 8-month period, 169 (60.1%) were older than 60 years. Their demographic and clinical features are reported in Table I. Median age was 71 years.

The median PC-FI of these patients was 0.08 (0.04-0.12). In detail, 84 patients (49.7%) were considered non-frail, whereas 54 (31.9%), 18 (10.7%) and 13 (7.7%) were considered as having mild, moderate or severe frailty, respectively (Table II).

Frail SSc patients, as compared with non-frail, were older, with longer disease duration and higher CCI, SCTC-DI, Sclero-ID and HAQ-D scores. Additionally, they had lower left ventricle ejection fraction, more frequent joint contractures, current digital ulcers and PAH, and were more frequently treated with glucocorticoids (Table I).

At the time of this study, glucocorticoids were used in around 30% of the entire cohort (Table I), mostly at low-dose (median dosage of prednisone-equivalent among users was 4.3mg/d (2.5–5.0); most frequent indications were interstitial lung disease (35%), arthritis (20%), myositis (8%), or non-SSc-related indications (24%)). On the other hand, no differences were observed as far as sex, SSc-specific autoantibodies, disease subset, disease activity as measured by the revised EUSTAR activity index; modified Rodnan skin score was slightly lower than in non-frail patients. Moreover, SSc patients with moderate/severe frailty (PC-FI≥0.14) had lower Forced

Table III. Correlations between PC-FI and other variables.

	Rho Spearman	*p*-value
CCI	0.487	<0.0001
SCTC-DI	0.440	<0.0001
Sclero-ID	0.296	0.0002
EUSTAR disease activity	0.196	0.012

PC-FI: Primary Care Frailty Index; CCI: Charlson Comorbidity Index; Sclero-ID: EULAR Systemic Sclerosis Impact of Disease; SCTC-DI: Scleroderma Clinical Trials Consortium Damage Index.

Table IV. Multivariable analysis. Logistic regression models with *a priori* selection of variables to evaluate factors potentially associated with PC-FI.

Variables	*p*-value	OR	95% CI
SSc disease duration (years)	0.0002	**1.076**	1.035 to 1.119
CCI	0.0006	**1.594**	1.220 to 2.083
SCTC-DI	0.0159	**1.147**	1.026 to 1.283
SSc disease subset (diffuse)	0.2308	0.487	0.150 to 1.580
Sex (female)	0.3433	0.517	0.132 to 2.025

PC-FI: Primary Care Frailty Index; CCI: Charlson Comorbidity Index; Sclero-Id: EULAR Systemic Sclerosis Impact of Disease; SCTC-DI: Scleroderma Clinical Trials Consortium Damage Index.

Table V. Clinical and demographical parameters of SSc patients included in the longitudinal study, and comparisons between patients who died or were hospitalised and patients with uneventful follow-up. Continuous variables are presented as median and interquartile range (IQR).

	SSc patients who died or were hospitalised (n=14)	SSc patients with uneventful follow-up (n=71)	*p*-value
Females (%)	13 (92.9)	64 (90.1)	0.75
Age (yrs)	76 (72-84)	69 (64-76)	**0.0009**
PC-FI	0.20 (0.12-0.28)	0.08 (0.04-0.12)	**0.0002**
Time of follow up (months)	3.5 (2.7-5)	5 (4-5)	0.21
Disease duration (yrs)	15 (10-20.5)	13 (6-25)	0.55
HAQ-DI	1.2 (0.1-2.5)	0.75 (0.5-1.4)	0.32
CCI	6 (3-5.7)	5 (4-6)	**0.0035**
Sclero-ID	5.45 (3.70-6.62)	4.25 (2.50-5.97)	0.18
SCTC-DI	5.5 (3-10)	6 (3-8)	0.62
EUSTAR disease activity	1.33 (1.08-2.12)	1.25 (1.00-1.96)	0.53

PC-FI: Primary Care Frailty Index; HAQ-DI: Health Assessment Questionnaire-Disability Index; CCI: Charlson Comorbidity Index; Sclero-ID: EULAR Systemic Sclerosis Impact of Disease; SCTC-DI: Scleroderma Clinical Trials Consortium Damage Index.

Vital Capacity (p=0.0006) than other SSc patients (Table I).

As expected, PC-FI was significantly correlated with CCI (Supplementary Fig. S1), but also with indexes measuring SSc-related damage, patient-reported disease burden, and, to a lesser degree, with disease activity (Table III). Multivariate analysis demonstrated that disease duration, SSc-related organ damage, and CCI were independently associated with PC-FI, whereas sex and disease subset were not (Table IV).

Longitudinal study

During the 8-month study period of the study 85 SSc patients (50.3%) attended at least one follow-up visit or died. Their median time of observation was 5 (3–5) months. Within this timeframe 2 patients (2.4%) died due to SSc-related cause and 12 (14.1%) needed for hospitalisation (in 4 cases for SSc-related causes).

Comparing these 14 patients with the remaining 71 SSc patients, they were older and had higher CCI and PC-FI scores while they did not differ as far as SSc-related disease activity, damage and patient-reported burden indexes (Table V).

Discussion

In this study we assessed the prevalence of frailty in SSc patients and identified demographic and clinical factors associated with it. More than half of the patients were found to suffer from frailty, which was associated with disease duration, SSc-related organ damage and comorbidities.

A Frailty Index to measure health status in patients with SSc was created in 2014 by the Canadian Scleroderma Research Group. This index considered 44 health deficits, recovered from patients self-reported questionnaires and clinical evaluation reports (including, among the others, some SSc-specific complications, like telangiectasias and scleroderma renal crisis), and was found to predict mortality in SSc patients (9). In a smaller cross-sectional study, the presence of the physical frailty phenotype was evaluated in 94 patients with SSc (10). This phenotype was defined using 5 components, mostly based on self-reported outcomes and items, such the time taken to walk 4.6 m, which are not routinely collected in SSc patients, and was found to be associated with disability, limitations in daily activities and hospitalisations in these patients (10). Available instruments dedicated to other rheumatic disorders, such as rheumatoid arthritis, also included items, *e.g.* handgrip strength, not routinely evaluated in SSc patients (18). Based on these considerations, we decided to use for our aims the PC-FI, an instrument developed and validated in the Italian primary care older population, which relies on routinely collected data and was proven to be reliable and easily implementable (8).

By using the PC-FI 49.7% of Italian SSc patients older than 60 years were classified as non-frail, 31.9% presented with mild frailty, 10.7% with moderate frailty, and 7.7% with severe frailty. Although this observation is consistent with findings seen in Italian primary care patients aged over 60 years (8), the prevalence of severe frailty in SSc seems to be higher than in the general population (of comparable median age of 71), in which only 3.8% of individuals were classified as severely frail (8). Indeed, besides age and comorbidity, several SSc-specific manifestations were associated with PC-FI, which was

proven to be significantly correlated with indexes of SSc-associated damage, patient-reported burden and disease activity. It is not unexpected that disease-specific manifestations contribute to frailty in SSc patients. For example, PAH might be associated with several items selected in the PC-FI as independent predictors for mortality and hospitalisation (*e.g.* oedema, oxygen prescription). Digital ulcers are associated with the risk of a lower limb segment amputation (19) and predict a worse disease course and decreased survival in patients with SSc (20). Even in milder cases, current digital ulcers, like joint contractures, might cause an impairment in the activities of daily living, which define another item considered by the PC-FI as independent predictor for mortality and hospitalisation (8). The association of frailty with the use of glucocorticoids is likely to be explained by the indications for treatment, such as interstitial lung disease, arthritis, myositis, myocarditis, *i.e.* disease manifestations correlated with disability and with other items included in the PC-FI.

In agreement with these observations, multivariate analysis suggested that in patients with SSc disease duration, disease-associated organ damage, and comorbidities are major drivers of frailty. We have previously demonstrated that SSc-associated organ damage progressively increases with disease duration (5). The independent role of disease duration suggested by multivariate analysis might confirm previous data suggesting that patients with long-standing SSc are particularly prone to suffer from frailty (10). This might be induced over time by the complex pathophysiology of SSc, that includes chronic autoimmune inflammation, vasculopathy and fibrosis leading to accumulation of deficits in multiple organ systems (10). Finally, our results confirm the independent impact of comorbidities on the prognosis of SSc patients that was recently highlighted by an Italian multicentre study (21).

It is well known that frailty and multimorbidity are two related conditions in older adults: most frail individuals are also multimorbid, but fewer multimorbid ones also present frailty (6). Indeed, in our population the correlation between frailty and multimorbidity indexes, although significant, was only fair-to-moderate (22), suggesting that these indexes reflect two distinct dimensions that do not entirely overlap. Our study is not without limitations, which are inherent to its nature of observational study from a monocentric cohort: the number of patients was relatively small, and we cannot exclude that selection bias may impact generalisability. Moreover, our longitudinal observation was performed on a short period of follow-up; despite this, we were able to observe the association of the baseline Frailty score with the evolution of this condition of frailty. Thus, our data might suggest that PC-FI can be applied to predict mortality and hospitalisation in SSc patients, as in the general population. To confirm its potential clinical utility, further larger multicentre longitudinal studies might be warranted to better define the value of frailty evaluation in SSc patients as this could lead in beneficial results, both for clinical decision making and the development of public healthcare programmes.

In conclusion, moderate-to severe frailty is quite prevalent in patients with SSc older than 60 years and it seems to be driven both by SSc itself and by comorbidities. Frailty assessment among patients with SSc might therefore provide useful information for health and social programme planning, stratifying patients according to their risk levels and helping in the identification of individuals who require special care (8), both for SSc-related manifestations and comorbidities.

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