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Prognostic factors for lung function in systemic sclerosis: prospective study of 105 cases.

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Objectives: To identify prognostic factors for SSc-ILD and to clarify the possible causative role of manometric esophageal involvement.

Methods: Consecutive SSc-patients underwent pulmonary function tests (PFT) and esophageal manometry. They were included in this study if PFT were repeated more than 12 months after baseline. The primary endpoint was a decrease ≥10% in forced vital capacity (FVC). The secondary endpoints were a decrease ≥15% in carbon monoxide diffusing capacity (DLCO) and a decrease ≥20% in FVC.

Results: Of the 105 patients (45 diffuse SSc, median disease duration 2.0 years), 23 (23%) had a FVC below 80%, 60 (59%) had a DLCO below 80%, and 57 (54%) had severe esophageal hypomotility at baseline. Over 72±46 months, 29 patients (28%) displayed a decrease ≥10% in FVC, 39 of 98 patients (40%) displayed DLCO decline, and 19 patients (18%) displayed a decrease ≥20% in FVC. In multivariate analysis, diffuse SSc was a significant predictor for a decrease ≥10% in FVC (p=0.01). No other predictor of a decrease in pulmonary function was identified.

Conclusion: Only diffuse SSc was predictive of a decrease in pulmonary function in this early-SSc cohort. This does not support preliminary data suggestive of a causative role of oesophageal involvement.

Key words:

Diffuse scleroderma, Esophageal manometry, Gastro-esophageal reflux, Interstitial lung disease, Prognostic factors, Systemic sclerosis.

Interstitial lung disease (ILD) occurs in up to 75% of patients with systemic sclerosis (SSc) (1), but progresses to severe restrictive lung disease in only about 13% of these patients (2). Pulmonary volume seems to decrease principally in the first four years of the disease (2). In recent series, ILD has been identified as one of the leading causes of death in SSc (3,4), being implicated in about 30% of SSc-related deaths (3). The therapeutic management of this condition therefore remains a major challenge. Studies assessing the efficacy of immunosuppressive drugs, such as cyclophosphamide, for the treatment of SSc-related ILD (SSc-ILD) have mostly generated disappointing results (5). In particular, a recent randomized controlled trial failed to demonstrate clearly that oral cyclophosphamide treatment for one year was effective, showing only a modest increase in forced vital capacity (FVC) at 12 months (6), which was no longer detectable at 24 months (7). These results may be accounted for by the lack of identification of a subgroup of SSc-patients at high risk of pulmonary progression (5).

A possible causative role of gastro-esophageal reflux (GER) in promoting idiopathic lung fibrosis (8,9) as well as SSc-ILD (10-12) was raised by previous studies. In particular, Marie *et al.* (11) suggested that the level of gastro-esophageal dysmotility was associated with the frequency and the severity of pulmonary involvement. However, conflicting results have been obtained in other studies (13,14). Indeed, in a previous cross-sectional study investigating the prevalence of Barrett's esophagus in our cohort of SSc-patients, no significant association was found between gastro-esophageal involvement and ILD, assessed both by CT-scan and pulmonary function tests (PFT) (14).

In this study, we investigated the possible link between SSc-ILD and manometric esophageal involvement, and investigated the prognostic factors for a decrease in pulmonary function, using a prospective follow-up design.

Patients and Methods

Our cohort of SSc-patients has been described elsewhere (14). The patients included in this previous study and new patients attending consultations in our department until January 2006 were included in a prospective follow-up study after the baseline evaluation of esophageal and systemic involvements. The inclusion criteria were esophageal manometry and PFT at baseline, and second PFT more than 12 months after the initial assessment. The prospective data were collected according to routine care assessments based on at least annual systemic follow-up. The exclusion criteria were being lost to follow-up, assessment only once at our tertiary care centre, with no second PFT or less than one year of follow-up data available. All patients gave informed consent and the study was approved by local ethical committee.

The end of the study period corresponded, for each patient, to the last admission for routine follow-up including PFT, available in January 2008. The following treatments administered during the study period that might interfere with the study results were listed: proton pump inhibitors (PPI), oral or intravenous cyclophosphamide treatment during at least six months, and steroids (intravenous, or oral at a daily dose exceeding 10 mg/d prednisone-equivalent). The overall severity of the disease was assessed with the revised Medsger scale (15). An

increase in Medsger scale class between baseline and the end of the study was interpreted as an overall deterioration of the disease.

All patients underwent esophageal manometry at baseline, as previously described (14). As Marie *et al.* (11), esophageal motility patterns were classified according to the Hurwitz's classification (16) in four stages. Hurwitz's stage 1 corresponds to normal esophageal motility; stage 2 corresponds to uncoordinated peristalsis with normal pressure wave amplitude; stage 3 corresponds to uncoordinated peristalsis with low pressure wave amplitude; stage 4 corresponds to aperistalsis and decreased low esophageal sphincter (LES) pressure. Severe esophageal hypomotility was defined as Hurwitz's stage 3 or 4.

PFT were carried out systematically at baseline and the last repeated PFT defined the end of the follow-up period. PFT results are expressed as a percentage of the standardized predicted value for age, sex and height. Restrictive lung disease was defined as FVC below 80%, and severe restrictive lung disease was defined as FVC at or below 50% (2).

As in previous studies assessing the functional deterioration in SSc-ILD (25), our endpoints included a decrease of at least 10% in FVC over the study period, which was our principal endpoint ("FVC decline"), and a decrease of at least 15% in carbon monoxide diffusing capacity (DLCO), which was a secondary endpoint ("DLCO decline"). Another secondary endpoint was a decrease of at least 20% in FVC ("severe FVC decline").

This study was longitudinal and observational. The associations between baseline levels of the variables studied and our three predefined endpoints were

evaluated after the end of the prospective follow-up period. Univariate and multivariate analyses were carried out. Differences between groups with a p value at or below 0.05 were selected for multivariate analysis. Survival was evaluated by the Kaplan-Meier method. Log-rank tests were used to assess differences in survival probabilities. Cox regression analysis was used to evaluate the association between baseline values and pulmonary outcome. Statistical significance was assumed if the null hypothesis could be rejected at $p<0.05$. Statistical analysis was performed with R® software (Lucent Technologies, version 2.5.0 for Windows).

During the study period, 47 patients (44.5%) underwent two computed tomography (CT)-scans separated by at least 24 months in Cochin hospital in routine, based on the physician's decision. An additional study assessing the concordance between PFT and CT-scan outcomes was carried out for this subgroup. Only high resolution CT-scan performed in the radiology unit of Cochin's hospital were considered for analyses. All CT-scans were assessed by the same trained radiologist, blind to the patient's clinical condition and the temporal order of the CT-scans for each patient, using a grading system described by Wells *et al.* (17). Grade 0 corresponds to a normal HRCT; grade 1 corresponds to predominant areas of ground-glass attenuation; grade 2 corresponds to equally extensive areas of ground-glass attenuation and reticulation; for grade 3, reticulations, microcystic spaces and bronchiectasis are predominant. We concluded that deterioration had occurred in cases of final CT-scan score higher than baseline score. The kappa coefficient was calculated to assess the concordance between our primary outcome and CT-scan deterioration.

Results

The baseline characteristics of the 105 recruited SSc-patients are reported in Table 1, and detailed for each cutaneous subtype of the disease.

After a mean follow-up duration of 71.8 ±46.4 months, 36 patients (35%) displayed an overall deterioration (Table 2). At baseline, 13% were receiving non steroidal anti-inflammatory drugs and 24% prokinetics. All patients received daily treatment with PPI throughout the study period. No patient received intravenous steroids or oral steroids at a dose exceeding 10 mg/d prednisone-equivalent. No patient was treated with oral cyclophosphamide during the study period, but four patients (4%) received intravenous cyclophosphamide at a dose of 0.7 g/m² monthly for at least six months to treat severe and progressive ILD.

Two FVC values (our first endpoint) were available for all patients. We did not have two DLCO values (baseline and follow-up) for seven patients, because restrictive lung disease was too severe (n=4) or due to technical problems (n=3). Two DLCO values (our secondary endpoint) were available for 98 patients (93%). PFT outcome in the overall cohort is shown in Table 2, and detailed for each cutaneous subtype. Of the four patients treated with intravenous cyclophosphamide, three displayed both a severe FVC decline and DLCO decline; the remaining patient displayed no decline in FVC or DLCO.

In univariate analysis, anti-topoisomerase I antibodies and diffuse cutaneous (dcSSc) subtype were associated with FVC decline (p=0.009 and p=0.001 respectively), and with severe decline of FVC (p=0.02 for both) (Table 3).

Baseline FVC <70% was another candidate predictor (p=0.04), but caution is required in the interpretation of this result because only seven patients had a baseline FVC <70%. No association with FVC outcome was observed for the other variables considered: sex, ethnicity, age, SSc duration, and esophageal involvement. The results of the multivariate analysis are shown in Table 4. In the models concerning FVC decline, only dcSSc was a significant predictor, irrespective of SSc duration and baseline FVC. In the model concerning severe FVC decline, no significant predictor was identified.

In univariate analysis, two esophageal variables were identified as potential predictors of DLCO decline: severe esophageal hypomotility (p=0.009) and aperistalsis (p=0.02) (Table 5). However, these factors were not significant in multivariate analysis: HR=2.10 (CI 95%: 0.75-5.84), p=0.15 and HR=1.23 (CI 95%: 0.48-3.16), p=0.66, respectively. We were therefore unable to identify a predictor of DLCO decline in our cohort.

The whole population of SSc patients had at least one CT-scan during the study and CT-proven ILD was found in 52/105 and all patients with decline of FVC had ILD. In the subgroup of patients included in the study comparing PFT and CT-scan outcomes (two CT-scans separated by at least 24 months performed in Cochin hospital; n=47), the mean interval between CT-scans was 45.8 ±25.8 months. CT-scan scores at baseline were distributed as follows: grade 0, n=16 (34%); grade 1, n=16 (34%); grade 2, n=4 (9%) and grade 3, n=11 (23%). Eight patients displayed deterioration on CT-scans. Fifteen patients displayed a decline in FVC during the study period. The kappa coefficient for correlation between CT-

scan deterioration and FVC decline was 0.6, demonstrating reasonably good concordance between the two methods.

Discussion

This study was designed to evaluate the predictors of pulmonary function deterioration in non selected SSc-patients undergoing complete esophageal assessment at baseline. This is the larger prospective study aiming at the identification of potential link between esophageal involvement and ILD course. The dcSSc subtype was the only significant predictor of poor pulmonary outcome identified, irrespective of SSc duration, baseline FVC and overall deterioration of the disease. As decreased FVC in SSc-patients may be related to stiff chest wall and diaphragmatic dysfunction, we performed an additional analysis comparing PFT and CT-scan outcomes in about half the patients. We demonstrated that the two methods of assessment of ILD were reasonably well correlated in our cohort, as previously observed (18). Moreover, the frequency of FVC decline in this subgroup was similar to that in all patients, suggesting that this subgroup was representative of the entire cohort.

In SSc, the loss of esophageal peristalsis results from both fibrosis and vasculopathy affecting the esophageal smooth muscle and its innervation (19), frequently leading to severe GER. Some studies have suggested that GER may contribute to idiopathic pulmonary fibrosis (8,9) and SSc-ILD (10-12), through repeated microaspirations of gastric content into the respiratory tract. Other arguments supporting this hypothesis are the preferential localization of SSc-ILD in

the lower lung zones (18), and a frequent centrolobular localization of fibrosis in SSc patients with GER (20). However, the preliminary studies provide a low level of evidence due to their cross-sectional design or short follow-up periods, small numbers of patients and, in some studies, the absence of multivariate analysis. For example, Marie *et al*. (11) carried out a cross-sectional study in 43 patients, with a longitudinal study over two years in only 18 of them and univariate analysis only. Moreover, they identified an association between GER and DLCO, which depends on both ILD and vasculopathy, but no correlation with FVC, which better reflects ILD. More recently, in a cohort of forty patients, Savarino *et al.* identified a higher esophageal acid exposure (assessed by 24-h impedance pH monitoring) in SSc-patients with ILD than in SSc-patients without ILD (12). The design of this study differs from the one used in our own as it was a cross sectional one whereas we performed a prospective study; indeed, Savarino *et al* identified some associated factors with ILD including reflux episodes. However, only univariate analyses were provided, not allowing estimating the weight of the reflux on ILD among different associated factors. In addition SSc patients had to stop PPI before the study; this raises the role of the reflux during PPI therapy as the large majority of SSc patients receive long-term therapy with these drugs. Nevertheless, one of the important point in this study was the demonstration of the presence of nonacid reflux and also proximal extent of reflux episodes (12). This suggests that reflux-reducing, and not only acid-suppressive therapies, should be included in future studies aiming at the evaluation of the influence of esophageal involvement on ILD outcomes.

In our study, esophageal involvement was assessed with a different method than Savarino *et al* (12). Manometry is considered as one of the most accurate methods for investigating esophageal motility (21). The prevalence of abnormal esophageal manometry results was similar to that previously reported for SSc-patients (80% in the study by Bassotti *et al*.) (22), as was mean LES pressure (15.8 mmHg according to Yarze *et al*.) (23). Some studies have shown that esophageal acid exposure in patients with low levels of esophageal motility may be better correlated with peristalsis abnormalities than with LES pressure (24). For this reason, we used Hurwitz's criteria, based on esophageal motility, to assess esophageal impairment.

In our cohort, no correlation between PFT deterioration and esophageal impairment was highlighted, taking into accounts both peristalsis and LES pressure. SSc is a multifactorial disease in which severe impairment tends to occur in several organs simultaneously (25). Consequently, GER is probably a confounding factor rather than a cause of ILD. The preferential localization of SSc-ILD in the lower lung zones (18) may instead be accounted for by the large number of vessels in these areas; vasculopathy is indeed thought to play a major role in the pathogenesis of lung fibrosis (26).

The main risk factors for the occurrence of ILD in SSc identified to date are dcSSc subtype, high skin fibrosis score and anti-topoisomerase I antibodies (25). In the Scleroderma Lung Study (SLS) (27), which was designed to assess the efficacy of cyclophosphamide for the treatment of SSc-ILD, similar baseline PFT profiles and PFT outcome were observed in the lcSSc and in the dcSSc subgroup.

However, only patients with ILD were recruited in the SLS, whereas consecutive patients with and without ILD were included in our study. Thus, the SLS was not designed to compare the prevalence and outcome of ILD in the two cutaneous subtypes of the disease.

The SLS (6) and a recent study by Goh *et al.* (28) identified two principal predictors of progression to restrictive lung disease in SSc: high fibrosis extension score on initial CT-scan (6) and baseline FVC, the 70% threshold being most strongly associated with pulmonary prognosis (29). In our cohort, the extension of ILD was not assessed on CT-scans, and our findings did not identify baseline FVC as a predictor of pulmonary function deterioration. The 70% threshold seemed to be associated with FVC decline in univariate analysis, but did not remain significant in multivariate analysis. This finding is probably due to too few patients having baseline FVC values below 70% in our cohort.

Finally, a poorer pulmonary outcome has previously been reported for black people (2,28), men (28) and greater age (28), whereas smoking does not seem to be correlated with mortality in SSc-patients (28). The small number of patients in these subgroups limited the statistical power of our analyses; we were unable to draw firm conclusions on this point.

Our study has several limitations. First, the systematic treatment of the patients with PPI may have masked the consequences of GER in the lung. However, a high frequency of esophageal mucosal abnormalities has previously been reported in SSc patients on long-term PPI treatment (29), demonstrating the persistence of severe GER. The pulmonary consequences of GER, if there are

any, might well have been observed despite this treatment. Moreover, it would have been unethical not to treat our patients with PPI for a long period, given the severe digestive complications of GER (14). Thus, our data represent the real outcome of SSc in patients. Follow-up data about NSAIDs and prokinetics were unfortunately not available and may account for outcomes. A second limitation concerns the lack of systematic assessment of ILD on CT-scans, but a comparison between PFT and CT-scan outcomes was performed in half the patients and showed reasonably good concordance between the two methods. Four percent of the patients received intravenous cyclophosphamide for at least six months. This may have affected the results of the study. Nevertheless, the number of patients concerned is very small, such treatment has not been demonstrated to be effective for this complication, and PFT outcome was no better in these patients than in the other patients. Another limitation is the lack of assessment of 24-hour intra-esophageal pH recording and mucosal damages that should be evaluated in the future to more closely determine the role of GER. Our study has also several strengths. Its prospective design limited bias. Consecutive patients were recruited, ensuring that our cohort was representative of the SSc population. The number of patients recruited, the six years of follow-up and the multivariate analysis guarantee a greater statistical power than previous studies assessing the potential link between manometric findings and ILD.

Conclusion

In this prospective longitudinal study assessing predictive factors for pulmonary function deterioration in SSc-patients, and the potential role of esophageal involvement, dcSSc subtype was the only significant predictor identified. These results do not support previous data suggesting a causative role for esophageal involvement in SSc-ILD. Further studies are required to better establish the relative weights of each of the prognostic factors for SSc-ILD identified to date in larger studies.

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Table legends

Table 1. Baseline demographic characteristics, pulmonary function tests and esophageal profiles of the 105 patients, detailed for the diffuse cutaneous (dcSSc) and for the limited cutanous (lcSSc) subtypes.

Table 2. Overall and pulmonary outcomes during the study period (71.8 ±46.4 months).in the overall cohort, in the diffuse cutaneous (dcSSc) subgroup and in the limited cutaneous (lcSSc) subgroup.

Table 3. Comparison of baseline characteristics between patients with and without FVC decline during follow-up (71.8 ±46.4 months: univariate analysis.

Table 4. Multivariate analysis assessing candidate predictors of decrease in FVC during follow-up (71.8 ±46.4 months).

Table 5. Comparison of baseline characteristics between patients with and without DLCO decline during follow-up (71.8 ±46.4 months: univariate analysis (data available for 98 patients, 93.3%).

Table 1. Baseline demographic characteristics, pulmonary function tests and esophageal profiles of the 105 patients, detailed for the diffuse cutaneous (dcSSc) and for the limited cutanous (lcSSc) subtypes.

	all SSc patients (n=105)	**dcSSc patients (n=45)**	**lcSSc patients (n=60)**
Age, years: mean (SD)	52.7 (11.8)	52.2 (13.4)	53.1 (10.6)
Female, n (%)	90 (85.7)	33 (73.3)	57 (95.0)
Black, n (%)	8 (7.6)	5 (10.9)	3 (5.1)
SSc duration *, years: median (IQR)	2.0 (0.0-5.0)	2.0 (1.0-5.0)	1.0 (0.0-4.0)
Previous history of digital ulcers, n (%)	32 (30.5)	18 (39.1)	14 (23.7)
PAH ** (n=101), n (%)	1 (0.9)	1 (2.2)	0 (0.0)
Medsger stage ≥ 3 (n=104), n (%)	15 (14.4)	8 (17.4)	7 (11.9)
ANA ≥80, n (%):	89 (84.8)	40 (88.9)	49 (81.7)
- Anti-topoisomerase I antibodies, n (%)	30 (28.5)	30 (65.2)	0 (0.0)
- Anti-centromere antibodies, n (%)	21 (21.0)	0 (0)	21 (35.6)
- Anti-ribonucleoprotein (RNP), n (%)	8 (7.6)	3 (6.7)	5 (8.3)
FVC <80%, n (%)	23 (22.9)	15 (33.3)	8 (13.3)
FVC <70%, n (%)	7 (6.7)	5 (10.9)	2 (3.4)
FVC <50%, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
DLCO (n=102) <80%, n (%)	60 (58.8)	34 (73.9)	26 (44.1)
Abnormal esophageal manometry, n (%)	80 (76.2)	40 (88.9)	40 (66.7)

Hurwitz' s stage ≥3 (n=104), n (%)	57 (54.6)	30 (65.2)	27 (45.8)
Esophageal aperistalsis, n (%)	38 (36.2)	21 (45.6)	17 (28.8)
LES pressure, mmHg: <10mmHg, n (%)	52 (49.5)	26 (57.7)	26 (43.3)

IQR: interquartile range. SD: standard deviation. PAH: pulmonary arterial hypertension. * disease duration from the diagnosis of the first non-Raynaud symptom; ** pre-capillary PAH diagnosed by right heart catheterization; † diagnosed by histology.

Table 2. Overall and pulmonary outcomes during the study period (71.8 ±46.4 months).in the overall cohort, in the diffuse cutaneous (dcSSc) subgroup and in the limited cutaneous (lcSSc) subgroup.

	All SSc patients (n=105)	**dcSSc patients (n=45)**	**lcSSc patients (n=60)**
Results of final PFT			
FVC <80%	34 (32.4)	23 (50.0)	10 (16.9)
FVC ≤50%, n (%)	9 (8.5)	9 (19.6)	0 (0.0)
DLCO <80% (n=98), n (%)	81 (82.7)	33 (71.7)	48 (31.4)
PFT outcome, n (%)			
FCV decline ≥10%,	29 (27.6)	21 (45.7)	8 (13.6)
FCV decline ≥20%	19 (18.1)	13 (28.3)	6 (10.2)
DLCO decline ≥15%	39 (39.8)	14 (30.4)	25 (42.4)
FCV decline ≥10% or DLCO ≥15%	55 (52.4)	26 (56.5)	29 (49.2)
Overall severity at the end of the follow-up (n=104)			
Final Medsger stage ≥3, n (%)	39 (37.5)	25 (54.3)	14 (23.7)
Overall aggravation of SSc, n (%)	36 (34.6)	22 (27.8)	14 (23.7)

PFT: pulmonary function tests. FVC: forced vital capacity. DLCO: carbon monoxide diffusing capacity. SSc: systemic sclerosis.

Table 3. Comparison of baseline characteristics between patients with and without FVC decline during follow-up (71.8 ±46.4 months): univariate analysis.

	Patients with FVC decline (n=29)	**Patients without FVC decline (n=76)**	**p value**
Abnormal esophageal manometry, n (%)	27 (93.1)	53 (69.7)	0.06
LES pressure <10 mmHg, n (%)	17 (58.6)	35 (46.1)	0.81
Aperistalsis, n (%)	16 (55.2)	21 (27.6)	0.23
Hurwitz's stage ≥3, n (%)	21/28 (75.0)	36 (47.4)	0.08
Hurwitz's stage =4, n (%)	11 (37.9)	17 (22.4)	0.81
Baseline FVC <75%, n (%)	5 (17.2)	11 (14.5)	0.42
Baseline FVC <70%, n (%)	2 (6.8)	5 (6.6)	**0.04**
SSc duration, years, median (IQR)	2.0 (0.0 - 3.0)	1.5 (0.0 - 5.2)	0.20
Anti-topoisomerase I antibodies, n (%)	15 (51.7)	15 (19.7)	**0.009**
Diffuse cutaneous subtype, n (%)	21 (72.4)	24 (31.6)	**0.001**
Black, n (%)	4 (13.8)	4 (5.3)	0.60
Male, n (%)	5 (17.2)	10 (13.2)	0.42
Baseline age >50 years, n (%)	13 (44.8)	45 (59.2)	0.65
Overall aggravation of SSc, n (%)	15 (51.7)	21 (27.6)	0.26

LES: Lower esophageal sphincter. IQR: interquartile range. FVC: forced vital capacity. SSc: systemic sclerosis.

Table 4. Multivariate analysis assessing candidate predictors of decrease in FVC during follow-up (71.8 ±46.4 months).

Variable	HR (CI 95%)	p value
FVC decline ≥ 10%		
First model		
- Anti-topoisomerase I antibodies	0.92 (0.33 - 2.57)	0.88
- Diffuse cutaneous SSc	**4.22 (1.37 - 13.00)**	**0.009**
- Baseline FVC <75%	0.60 (0.21 - 1.71)	0.33
- SSc duration	0.61 (0.25 - 1.50)	0.28
Second model		
- Anti-topoisomerase I antibodies	0.99	0.99
- Diffuse cutaneous SSc	**3.41**	**0.02**
- Baseline FVC <70%	3.08	0.16
FVC decline ≥ 20%		
- Anti-topoisomerase I antibodies	1.54 (0.40 - 5.87)	0.52
- Diffuse cutaneous SSc	2.24 (0.54 - 9.24)	0.26

HR: hazard ratio. FVC: forced vital capacity. SSc: systemic sclerosis.

Table 5. Comparison of baseline characteristics between patients with and without DLCO decline during follow-up (71.8 ±46.4 months): univariate analysis (data available for 98 patients, 93.3%)

	Patients with DLCO decline (n=39)	**Patients without DLCO decline (n=59)**	**p value**
Abnormal esophageal manometry, n (%)	33 (84.6)	41 (69.5)	0.18
LES pressure <10 mmHg, n (%)	22 (56.4)	27 (45.8)	0.79
Aperistalsis, n (%)	21 (53.8)	12 (20.3)	**0.02**
Hurwitz's stage ≥3, n (%)	27 (69.2)	24/58 (41.4)	**0.009**
Hurwitz's stage =4, n (%)	16 (41.0)	9 (15.3)	0.06
Baseline FVC <75%, n (%)	4 (10.3)	10 (16.9)	0.85
SSc duration, years, median (IQR)	2 (0-4)	1 (0-5)	0.30
Anti-topoisomerase I antibodies, n (%)	10 (25.6)	14 (23.7)	0.06
Diffuse cutaneous SSc, n (%)	14 (35.9)	24 (40.7)	0.56
Overall aggravation of SSc, n (%)	14 (35.9)	18 (30.5)	0.59

LES: Lower esophageal sphincter. IQR: interquartile range. FVC: forced vital capacity. SSc: systemic sclerosis.