

Prevalence and risk factors of interstitial lung disease in early systemic sclerosis and systemic sclerosis sine scleroderma: a cross-sectional study

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Abstract

Introduction: Interstitial lung involvement (ILD) is one of the main complications in patients with systemic sclerosis (SSc), representing a significant cause of mortality. According to previous reports, ILD can appear in many patients from early stages (eSSc) to patients with established disease without skin involvement (ssSSc).

Methods: Patients were included in the ssSSc group if they met the ACR/EULAR 2013 classification criteria and had a Rodnan skin score 0. In the eSSc group, if they did not meet the former criteria but fulfilled the VEDOSS criteria. Patients must have undergone a high-resolution chest CT scan within the last six months. Experts in this complication reviewed the images, and the percentage of patients with ILD in each group was determined. A univariate and multivariate analysis was performed to determine potential risk factors for ILD, including conventional risk factors and clinical findings in both groups. Odds Ratios and their 95% confidence intervals were estimated. Statistical significance was considered when p was less than 0.05.

Results: Data from 353 patients with SSc: 65 (18.4%) with ssSSc, and 75 (21.2%) eSSc (VEDOSS patients) were included in the study. The proportion of patients with ILD was 38% in the ssSSc group and 20% in VEDOSS patients group ($p=0.03$). Regarding risk factors, anticentromere antibody positivity was found to have a protective effect (OR 0.17, 95% CI 0.03-0.44, $p=0.001$), and anti-SCL-70 antibody presence was identified as a risk factor for ILD (OR 35.8, 95% CI 2.6-492, $p=0.007$). No association was found with male gender, digital ulcers, puffy fingers, or capillaroscopic findings.

Conclusions: ILD in patients with SSc can occur from early stages or without skin involvement, thus an active search for ILD is warranted, as it can be present in 1 out of 5 patients with these disease subsets.

Keywords: Systemic sclerosis; Interstitial lung disease; Early diagnosis

Introduction

Systemic sclerosis (SSc) is a disease characterized by skin fibrosis, vasculopathy, and heterogeneous involvement of internal organs. Among autoimmune diseases, it has one of the highest mortality burdens, making the early detection of complications that increase this risk necessary^{1,2}.

Currently, lung diseases, including interstitial and vascular pulmonary involvement, are considered the main cause of death in systemic sclerosis, with mortality rates increasing from 6% in 1972 to 33% in 1997^{2,3,4}. It presents diverse clinical courses, ranging from stability with immunosuppressive use to slow or rapid progression, with survival inversely proportional to the degree or extent of lung involvement⁵.

Given the high morbidity and mortality associated with interstitial lung disease (ILD) in systemic sclerosis, high-resolution chest tomography (HRCT) has been proposed as a strategy for its early detection. Between 75% and 90% of patients show interstitial lung abnormalities on HRCT, demonstrating the high prevalence of this involvement^{6,7}.

Another strategy is identifying risk factors that could predict which patients may develop ILD. Risk factors identified in patients with established skin fibrosis include diffuse and rapid cutaneous involvement, male gender, African American and Asian ancestry, and positive SCL-70 antibody status^{1,8}. Additionally, observations in patient cohorts such as the European League Against Rheumatism Scleroderma Trial and Research Group (EUSTAR) have shown that internal organ involvement, including ILD, can occur even without cutaneous fibrosis, appearing 3 to 5 years earlier than skin symptoms (Raynaud's phenomenon or puffy fingers)^{9,10}.

This finding has influenced the diagnostic approach, leading to early detection criteria called the "Very Early Diagnosis of Systemic Sclerosis" (VEDOSS), which includes clinical findings such as Raynaud's phenomenon, "puffy fingers," antinuclear antibodies (ANA), alterations in capillaroscopy and systemic sclerosis-specific antibodies¹¹.

Bellando et al. conducted a five-year multicenter analysis of the EUSTAR cohort in patients with Raynaud's phenomenon and VEDOSS criteria, finding that having at least one additional criterion besides Raynaud's phenomenon increased the likelihood of progressing to established SSc by 58% to 94%, depending on the detailed finding¹². This result is crucial for understanding early systemic sclerosis (eSSc), which includes meeting VEDOSS criteria but not the ACR/EULAR 2013 classification criteria, regardless of internal organ involvement indicated by gastrointestinal issues (primarily gastroesophageal reflux), lung impairment (carbon monoxide diffusion capacity [DLCO] <80%, pulmonary hypertension), diastolic heart dysfunction, or digital ulcers. These

additional variables increase diagnostic sensitivity and improve prognosis within the first five years post-diagnosis^{12,13,14}.

With these concepts, the prevalence of early systemic sclerosis has been found to vary from 6% to 50% depending on the cohort, with up to 47% progressing to systemic sclerosis within five years^{15,16,17}.

Another concept that involves internal organ fibrosis without skin changes is systemic sclerosis sine scleroderma (ssSSc), a less common presentation with a prevalence of 4% to 8%. Patients with ssSSc meet the ACR/EULAR 2013 classification criteria but have a Rodnan skin score of 0. In this variant, ILD prevalence is recorded between 25% and 72% based on pulmonary function tests or HRCT findings^{10,18,19,20}.

There is no consensus regarding differentiating the early forms of the disease (eSSc) from the established forms without skin involvement (ssSSc). One proposal sought differentiation according to the time of evolution of the disease, more significant or less than five years^{21,22}, without being universally accepted since it has yet to have external validation or in large cohorts of patients. This lack of clarity in differentiating the two forms of the disease has generated significant differences in the inclusion of patients in studies.

We need more descriptions of ILD in early systemic sclerosis or systemic sclerosis sine scleroderma patients, considering the heterogeneity in the reported prevalences in the case of ssSSc, which may be related to inclusion criteria, the lack of information in other populations such as Latin Americans, and the limited study of risk factors associated with these specific populations.

The primary objective of this study is to determine the proportion of ILD in early systemic sclerosis (eSSc) and systemic sclerosis sine scleroderma (ssSSc) and analyze potential risk factors for its development.

Materials and Methods

Patients

An analytical cross-sectional study was carried out. It included patients over 18 years old with early systemic sclerosis (eSSc) or systemic sclerosis sine scleroderma (ssSSc) and, therefore, with a Rodnan score of 0, who attended the rheumatology outpatient clinic at a university hospital between 2019 and 2023. Patients meeting the 2013 ACR/EULAR criteria without skin thickening were considered to have ssSSc, while those not meeting the classification criteria but meeting the VEDOSS criteria were considered to have eSSc. Regarding the early forms of the disease;

there is a "very early" form and an "early" form, differentiated by the presence of involvement beyond Raynaud's phenomenon or puffy fingers, including esophageal involvement, which is one of the earliest manifestations. Considering that not all patients underwent digestive endoscopy or esophageal motility tests, we could not distinguish between very early and early disease, and all patients were grouped under eSSc or VEDOSS patients.

Patients included in the study had a diagnosis of eSSc (VEDOSS patients) or ssSSc, regardless of disease duration, with at least one high-resolution chest CT (HRCT) conducted six months before consultation. This timeframe assumes that imaging control and significant changes in abnormal findings are uncommon in shorter periods, provided no new symptoms exist. Exclusion criteria included a diagnosis of systemic sclerosis fulfilling the 2013 ACR/EULAR criteria with skin involvement, poly autoimmunity, and other conditions that could cause ILD or inadequate imaging quality to clarify the ILD diagnosis. Additionally, patients with symptomatic deterioration in the six months before imaging or at the time of imaging request were excluded, as changes in CT findings may be attributed to factors other than ILD.

Definition of Interstitial Lung Disease

In HRCT, ILD was considered present if reticulation, ground-glass areas without a more probable explanation, honeycombing, or traction bronchiectasis were identified by an experienced physician (radiologist, pulmonologist, or rheumatologist) in interstitial diseases. Disease was considered extensive if it affected more than 20% of the lung area, as calculated by the Goh method.²⁷

Objectives

The primary objective is to determine the proportion of patients with early-stage systemic sclerosis and systemic sclerosis sine scleroderma with interstitial lung disease. Secondary objectives included analyzing potential risk factors for ILD in these groups, differences between the two groups, and whether there are differences within the early-stage group based on whether the onset of Raynaud's phenomenon was more or less than five years ago.

Statistical Analysis

Qualitative variables were described as means with their standard deviations (SD) or medians with their interquartile ranges (IQR), depending on whether they followed a normal or non-normal distribution, respectively. Categorical variables were described with their relative and absolute frequencies. Univariate analysis of the correlation between clinical findings and the

presence of ILD and differences between the groups was conducted using chi-square or Mann-Whitney tests, depending on the nature of the variables. Subsequently, a multivariable logistic regression analysis was performed, adjusted for both conventional risk factors and other factors found in this study. Given the sample size and the occurrence of variables with zero events, a penalized logistic regression using the Firth method was conducted to allow additional variables in the analysis when necessary. Odds ratios (OR) and their 95% confidence intervals were estimated. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using Stata 17®.

This study has ethics committee approval by legal requirements for a no-risk study. There was no intentional intervention or modification of variables in the participants, and data were collected by reviewing medical records without identifying subjects or addressing sensitive behavioral aspects.

Results

Data were collected from 353 patients diagnosed with systemic sclerosis. Of these, 65 patients (18.4%) met the classification criteria for systemic sclerosis without skin involvement. They were thus classified as having ssSSc, while 75 patients (21.2%) did not meet the classification criteria but met the VEDOSS criteria and were therefore classified as having eSSc or VEDOSS patients. No distinction was made between very early and early disease, as only a portion of the subjects underwent testing for possible gastroesophageal reflux disease.

Ninety-five percent of the population were women, including patients with Raynaud's phenomenon. The most common additional clinical manifestations were puffy fingers in 63% of patients, followed by dysphagia/heartburn symptoms in 56% and telangiectasias in 50%. Table I provides a summary of group characteristics.

Significant differences were found in the proportion of reported symptoms and clinical signs, such as years since the onset of Raynaud's phenomenon (10 years; $p=0.007$), finger edema (81.6%; $p<0.001$), telangiectasias (77.7%; $p<0.001$), digital ulcers (21.4%; $p=0.02$), calcinosis (13.8%; $p=0.01$), dyspnea (44.6%; $p=0.05$), dysphagia/heartburn (68.5%; $p=0.04$), and capillaroscopy abnormalities (49.2%; $p<0.004$), with all these variables being more frequent in the ssSSc group. Capillaroscopy was performed in only half of the included patients (53%). No differences were found in the frequency of specific antibodies, anticentromere ($p=0.27$), or SCL-70 ($p=0.23$).

The proportion of patients with interstitial lung disease (ILD) was 20% in VEDOSS patients group and 38% in the ssSSc group, a statistically significant difference ($p=0.03$). No differences were observed between the groups in lung function values. Spirometry was performed in 70% VEDOSS patients and 66% with ssSSc, and DLCO in 37% and 30%, respectively (Table II).

The proportion of patients with severe ILD, with an extent greater than 20%, was higher in patients with systemic sclerosis without scleroderma (9.3% vs. 5.3%), but this difference was not statistically significant ($p=0.4$).

No statistically significant differences were found between patients with a duration of Raynaud's phenomenon greater than or less than 5 years (Table III).

In the assessment of risk factors for the development of ILD, adjusted for risk factors described in the literature (Table IV), only the presence of anticentromere antibodies was found to have a protective effect (OR 0.17, 95% CI 0.03-0.44, $p=0.001$), while the presence of anti-SCL-70 antibodies was identified as the most critical risk factor for ILD (OR 35.8, 95% CI 2.6-492, $p=0.007$) in both the total population and each group. Additionally, antinuclear antibodies unrelated to centromere or SCL-70 patterns were identified as a risk factor exclusively in the ssSSc group (OR 6.1, 95% CI 1.0-34.2, $p=0.03$).

Regarding the analysis of capillaroscopic findings in the group of patients who underwent the examination (53%), no presence of a scleroderma pattern in general or any stage (early, active, or late) was found to be a risk factor for the development of ILD in any of the groups.

Discussion

Our study found VEDOSS patients proportion of 21.2%, which is lower compared to 50% in the Spanish Scleroderma Registry (RESCLE)¹⁶ and 44% in the cohort by Valentini et al.²³.

Regarding interstitial lung involvement, Valentini and colleagues found that in a cohort of 115 patients with Raynaud's phenomenon, 70 presented a specific antibody or a scleroderma capillaroscopy pattern and were thus classified as having early disease. Among these, 51 presented symptoms suggestive of internal organ involvement, with dyspnea reported in 19 subjects (37%) and 23, compared to 15 subjects (27.5%) in our study. In the study by Bruni et al., a group of early scleroderma patients who met VEDOSS criteria showed lung involvement, with CT abnormalities in 32% and DLCO < 80% in 42% of patients, with an overall lung involvement of 27% of patients without digital ulcers²⁴. Blaja et al. reported in 102 patients with early scleroderma defined by finger edema, specific antibodies, or specific capillaroscopy findings or internal organ involvement, a lung involvement prevalence of 5.2% by HRCT or 7.5% with FVC <

80% and DLCO < 70%²¹. Our study found an ILD proportion of 20.6% by high-resolution chest tomography.

The main risk factors for ILD in patients with established systemic sclerosis or skin involvement are male gender, diffuse variant, presence of anti-topoisomerase I antibodies, and FVC < 70%^{1,25}. However, evidence on risk factors for lung involvement in VEDOSS patients is limited. In contrast to involvement in other organs, such as the esophagus, where Bruni et al. found an association with digital ulcers ($p < 0.01$), there was no statistically significant association between digital ulcers and lung involvement ($p = 0.30$)²⁴.

The study by Valentini et al. identified risk factors for internal organ involvement in the eSSc population without specifying factors for ILD involvement. These included the presence of any specific systemic sclerosis antibody combined with a scleroderma-compatible capillaroscopy pattern (OR 4.95, 95% CI 2.28-11.26), finger edema (OR 12.1, 95% CI 1.49-98.2), dysphagia/heartburn (OR 12.5, 95% CI 4.94-31.61), and anticentromere antibodies (OR 2.68, 95% CI 1.24-5.78)²³.

Our study did not identify a clinical finding significantly associated with lung involvement. However, we found that positivity for anti-topoisomerase I antibodies (OR 48.2, 95% CI 4.2-551, $p = 0.002$) was a risk factor, while anticentromere antibody positivity was protective (OR 0.19, 95% CI 0.37-0.99, $p = 0.05$).

The frequency of ssSSc has varied across cohorts. Diab et al. reported a prevalence of 1.9% with an ILD involvement of 25.9%¹⁹. In the Marangoni et al. cohort, ssSSc prevalence was 8.3% with 56.9% ILD involvement, and 31% of patients had FVC < 80%¹⁸. The German cohort by Hunzelmann et al. described a prevalence of 1.5% with 72.7% ILD involvement²⁰, while Simeón-Aznar et al. reported a prevalence of 7.5% with 63.7% lung involvement²⁶. In comparison, our study found an ssSSc prevalence of 18.4%, higher than reported in these other cohorts, with 38.4% lung involvement, falling within the range of worldwide findings. The variation in the proportion of patients with ssSSc may be due to the different criteria used to select patients or to demographic variations. As has been demonstrated, several autoimmune diseases have a higher prevalence in Latin America due to influential genetic, environmental, and healthcare access factors. However, there is no specific data on ssSSc compared to other world regions.

Our study found risk factors for ILD in ssSSc, including anti-topoisomerase I antibody positivity (OR 19.8, 95% CI 1.3-285), positivity for ANAs in patterns other than centromere (mostly granular or nucleolar) (OR 6.1, 95% CI 1.0-34.2), and anticentromere antibody positivity as a protective factor (OR 0.05, 95% CI 0.007-0.37). Positivity for ANAs in patterns other than centromere, such as granular AC-4, has been associated with the presence of anti-SS-A/Ro and Ku; AC-5 with U1 RNP and RNA polymerase III; and nucleolar AC-8 with PM/SCL and Th/To.

Several of these are closely associated with the presence of ILD in this disease, which may indicate that these patterns require a more intensive investigation for pulmonary complications.^{1,28,29}

Regarding the severity of interstitial lung disease, estimated by an extension as more significant than 20% per the Goh method, which is critical in deciding treatment initiation, we found a prevalence of 9.3% in the ssSSc group and 5.3% in the VEDOSS patients group. This suggests that skin involvement severity does not always correlate with the extent of lung disease and that severe lung involvement requiring treatment can occur even in the early stages. The cohorts reviewed did not report ILD extension assessment for comparison.

No statistically significant differences were found in clinical findings, capillaroscopy, antibodies, or lung disease presentation in groups with symptom onset less or more than 5 years, suggesting that in VEDOSS patients and ssSSc groups, disease duration does not necessarily influence ILD presentation, similar to findings by Blaja et al.²¹

The proportion of patients with ILD was significantly different between the eSSc group (20%) and the ssSSc group (38%) ($p=0.03$). This may have important implications when considering patient screening, requiring stricter criteria in the ssSSc group and prognosis since ILD occurs in more advanced stages of the disease with greater systemic involvement. In such cases, the risk of progression may be higher, or the response to treatment may be lower, which warrants further study.

Study limitations include the cohort's lack of smoking status documentation, which has been identified as a risk factor for developing ILD and, therefore, may also be a determinant in the early forms, and only 70% of patient's results for carbon monoxide diffusion, forced vital capacity, and capillaroscopy, which could be confounding factors when adjusting for ILD and its functionality. Regarding capillaroscopy, the limitation lies in the insufficient sample size to demonstrate an association between vascular abnormalities and ILD. The low frequency of DLCO (diffusing capacity for carbon monoxide) testing is attributed to the logistical challenges in our setting, where the test may take longer to perform than a chest CT scan. This complicates the analysis based on disease severity but does not affect the frequency of ILD occurrence, as the gold standard was applied across all patients in the study. Regarding the interpretation of the tomography, we had some limitations because of the lack of assessment of the inter-reader correlation.

As an additional limitation, we note that systemic sclerosis has a long and heterogeneous course involving multiple organ systems. Thus, including patients based exclusively on ACR/EULAR or VEDOSS criteria to achieve a more homogeneous population may exclude certain patient groups, primarily those in the early stages of the disease. Additionally, risk factors may differ

depending on whether the disease is very early or early, which we were unable to classify in this group, for example, as has been demonstrated, gastrointestinal involvement may impact the development of lung disease. Future studies should evaluate this, assessing the presence of symptoms and endoscopic or functional esophageal findings. We recommend further studies in this field, incorporating these variables more precisely to enable more robust statistical adjustments in regression models. Additionally, prospective studies are needed to evaluate the progression of this complication in this specific patient group.

Conclusions

The study suggests that lung involvement in patients with systemic sclerosis can frequently be present in patients without skin involvement.

In cases of early scleroderma, an active search for interstitial lung involvement using high-resolution chest tomography is warranted, as this can be present in at least 1 in 5 patients.

Treatment in the early phases of the disease remains unclear due to the variability in expert opinions and findings from some studies, which consider very early and early scleroderma as a spectrum between early-stage systemic sclerosis that may progress versus a mild form of scleroderma that will not progress²¹, it is considered that assessing the severity of internal organ involvement could significantly impact therapeutic decisions and, in the future, lead to a change in treatment guidelines.

Tables and Figures

Table I. Description of early systemic sclerosis and sine scleroderma systemic sclerosis patients

Variable	Total N=123	eSSc VEDOSS patients N=58	ssSSc N=65	p value
Women (%)	95.9	94.8	96.9	0.55
Age (SD)	56.8 (14.3)	53.6 (16.7)	59.6 (11.6)	0.02
Years of Raynaud's (SD)	8.4 (7.8)	6.4 (6.2)	10.1 (8.6)	0.007
Puffy fingers (%)	63.7	29.0	81.6	<0.001
Telangiectasias (%)	50.8	21.0	77.7	<0.001
Digital ulcers (%)	14.7	7.0	21.4	0.02
Calcinosis (%)	8.1	1.7	13.8	0.01
Arthritis (%)	45.9	46.5	45.3	0.89
Dyspnea (%)	36.5	27.5	44.6	0.05
GER symptoms (%)	60.3	50.8	68.5	0.04
Capillaroscopy (%) (n=66)				
Early				
Active	37.8	36.0	39.0	0.8
Late	24.2	12.0	31.7	0.07
Abnormal	7.5	8.0	7.3	0.9
Abnormal	37.4	24.1	49.2	0.004
Auto antibodies (%)				
Centromere	68.6	63.7	73.0	0.27
SCL-70	8.2	5.1	11.1	0.23
ANA	27.2	34.4	20.6	0.08

SD: Standard deviation, GER: Gastroesophageal reflux, ANA: antinuclear antibody

Table II. Characteristics of lung disease in eSSc and ssSSc patients

	Total N=123	eSSc VEDOSS patients N=58	ssSSc N=65	P value
Interstitial lung disease in HRCT (%)	30	20.6	38.4	0.03
Extent >20% (%)	7.5	5.3	9.3	0.40
FVC % (SD)	95.7 (17)	95.4 (18.0) (n=41)	95.9 (16.2) (n=43)	0.9
DLCO adj % (SD)	84.6 (28.4)	85.2 (26.4) (n=22)	84.2 (16.6) (n=20)	0.9

HRCT: high resolution computed tomography, FVC: Force vital capacity, DLCO adj: Adjusted Diffusing capacity for carbon monoxide, SD: Standard deviation

Table 3. Differences between eSSc and Raynaud's phenomenon more or less than 5 years

	< 5 years N=30	>5 years N=28	p
Women (%)	93.3	96.4	0.59
Age (SD)	51.7 (17.7)	55.7 (15.6)	0.36
Puffy fingers (%)	25.0	36.3	0.50
Telangiectasias (%)	16.6	25.9	0.39
Digital ulcers (%)	10.0	3.7	0.51
Calcinosis (%)	0	3.5	0.54
Arthritis (%)	50.0	42.8	0.58
Dyspnea (%)	26.6	28.5	0.87
GER symptoms (%)	44.8	57.1	0.35
Capillaroscopy (%) (n=66)			
Early	40.0	30.0	0.61
Active	6.6	20.0	0.33
Late	6.6	10	0.76
Abnormal	26.6	21.4	0.64
Auto antibodies (%)			
Centrómere	60.0	67.8	0.53
SCL-70	10.0	0	0.08
ANA	36.8	35.1	0.87
Interstitial lung disease (%)	23.3	17.8	0.6
Extent >20% (%)	6.9	3.7	0.59
FVC % (SD)	90.6 (17.6)	101.5(17.0)	0.052
DLCO adj % (SD)	77.2 (32.7)	90.8 (23.9)	0.28

GER: Gastroesophageal reflux, ANA: antinuclear antibody, FVC: Force vital capacity, DLCO adj: Adjusted Diffusing capacity for carbon monoxide, SD: Standard deviation

Table IV. Analysis of risk factors for ILD in early systemic sclerosis and sine scleroderma systemic sclerosis patients

	Total N=123 OR (IC 95%)	eSSc VEDOSS patients N=58 OR (IC 95%)	ssSSc N=65 OR (IC 95%)
Male	1,7 (0,18-16,2) P=0.62	2.0(0.09-41.5) p=0.65	0.6(0.36-10.3) p=0.73
Age	1 (0.99-1.05) P=0.10	1 (0.97-1.05) p=0.34	1 (0.97-1.05) p=0.34
Years of Raynaud's (SD)	0,8 (0.93-1.03) P=0.51	0,96 (0.86-1.03) p=0.54	0,96 (0.86-1.03) p=0.54
Puffy fingers (%)	0,78 (0,3-1,9) P=0.6	0.13 (0.06-2.6) P=0.6	0.48 (0.12-1.8) P=0.28
Digital ulcers	1.6 (0.58-4.6) P=0.34	0.41 (0.02-8.1) P=0.56	1.83 (0.55-6.0) P=0.32
Telangiectasias	1.0(0.47-2.2) P=0.93	0.8 (0.14-4.3) p=0.79	0.36 (0.1-1.2) p=0.10
Arthritis	1.1(0.54-2.5) p=0.46	1.1(0.33-4.2) P=0.78	1.19(0.43-3.2) P=0.73
GER symptoms	0.64(0.29-1.4) P=0.27	0.76(0.2-2.8) P=0.68	0.38(0.12-1.13) P=0.08
Centrómere auto antibodies	0.21(0.09-0.49) P=<0.001 0.17(0.03-0.44) P=0.001*	0.31(0.08-1.15) P=0.08 0.19(0.37-0.99) P=0.05*	0.09(0.02-0.35) P<0.001 0.05(0.007-0.37) P=0.003*
SCL-70 auto antibodies	28(3.39-231.1) P=0.002 35.8(2.6-492) P=0.007*	34.2(1.6-719) P=0.02 48.2(4.2-551) P=0.002*	12.2(1.4-113) P=0.02 19.8(1.3-285) P=0.02*
ANA	2.2(0.95-5.13) P=0.06	1.4(0.4-5.4) P=1.47	5.2(1.3-19.7) P=0.01 6.1(1.0-34.2) P=0.03*
Abnormal capillaroscopy	0.73(0.32-1.6) P=0.45	0.08(0.04-1.6) P=0.10	0.92(0.3-2.5) P=0.87
Dyspnea	4.0 (1.7-9.0) P=0.001 2.4(0.81-7.0) P=0.11**	3.6(0.9-13.6) P=0.059	3.6(1.2-10.5) P=0.01 7.4(1.2-42.8) P=0.02**

FVC <80%	3.1(1.0-9.3) P=0.04 1.1(0.25-5.0) P=0.86*	3.5(0.66-18.4) P=0.13	3.0(0.66-14.2) P=0.15
DLCO adj <80%	2.6 (0.85-8.1) 0.09	4.1(0.89-18.6) P=0.06	2.5(0.4-16.7) P=0.31

GER: Gastroesophageal reflux, ANA: antinuclear antibody, FVC: Force vital capacity, DLCO adj: Adjusted Diffusing capacity for carbon monoxide, SD: Standard deviation

*Adjusted to sex, age, Raynaud`s, digital ulcers, telangiectasias, arthritis, puffy fingers

** Adjusted to sex, age, Raynaud`s, digital ulcers, telangiectasias, arthritis, puffy fingers, SCL-70

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