ORIGINAL ARTICLE

Onset and progression factors for Systemic Sclerosis-associated interstitial lung disease: Data from a North African cohort

Facteurs d'apparition et de progression de la pneumopathie interstitielle diffuse associée à la sclérodermie systémique: Données d'une cohorte nord-africaine

Houssem Abida[1,2], Zeineb Meddeb[1,2,3], Meriem Affes[1,4], Saoussen Hantous[1,4], Siwar Sbaihi[1,6], Sana Toujani[1,2], Cherifa Abdelkefi[1,2], Mariem Jebri[1,5], Henda Neji[1,4], Kamel Bouslama[1,2], Lamia Ben Hassine[1,5], Saloua B'chir Hamzaoui[1,2], Amira Elouni[1,2], Thara Larbi[1,2]

1. Faculty of Medicine of Tunis, University of Tunis El Manar, 1068, Tunis, Tunisia
2. Internal medicine department, Mongi Slim University Hospital, Tunis, Tunisia,
3. Laboratory of Genetics, Immunology, and Human Pathology, Faculty of Sciences of Tunis, University of Tunis El Manar, Tunis, Tunisia
4. Radiology department, Abderrahmen Mami University Hospital, Tunis, Tunisia
5. Internal medicine department, Charles Nicolle University Hospital, Tunis, Tunisia
6. Radiology department, Mohamed Taher Maamouri University Hospital, Nabeul, Tunisia

Abstract

Introduction: Screening for interstitial lung disease (ILD) at the onset of systemic sclerosis (SSc) as well as during follow-up is mandatory. The aim of our study was to define the risk factors of SSc-ILD onset and progression in a Tunisian population.

Methods: This was a bicentric, descriptive, retrospective study that included patients with SSc. Data from the initial evaluation and from a 3-year follow-up (FUT) were collected. The patients' chest tomography (CT) scans were reinterpreted by a radiologist specialized in thoracic imaging using the Goh score.

Results: Forty-nine patients were included. ILD was diagnosed at FUT in 31 patients (63%), of whom 35% had progressive disease. The most common radiological pattern was nonspecific interstitial pneumonia (68%). The mean values for the global extension and overall severity score of ILD at FUT were 33.3% and 5.61, respectively. Factors associated with ILD onset included: A higher modified Rodnan skin score (p=0.008; OR=1.16, 95% CI [1.04–1.3]), pulmonary hypertension (p=0.004; OR=9.35, 95% CI [1.093–30.011]), esophageal involvement (p=0.044; OR=3.650, 95% CI [0.494–26.945]), anti-topoisomerase I antibodies (p=0.001; OR=9.344, 95% CI [2.352–37.123]) and a lower hemoglobin level (p=0.04; OR=8.576, 95% CI [1.481–15.912]). ILD progression factors included: a lower forced vital capacity (p=0.002; OR=0.797, 95% CI [0.637–0.998]), anti-topoisomerase I antibodies (p=0.015), elevated C-reactive protein (p=0.038; OR=5.07, 95% CI [1.09–30.3]), an indeterminate radiological pattern (p=0.048).

Conclusion: A higher mRSS, esophageal involvement, pulmonary hypertension, anti-topoisomerase I antibodies and anemia were factors associated with ILD onset. Progression risk factors were reduced baseline respiratory volumes and biological inflammatory syndrome.

Key-words: Systemic sclerosis, Interstitial lung disease, onset, progression, chest tomography

Résumé

Introduction: La recherche de la pneumopathie interstitielle diffuse (PID) au diagnostic de la sclérodermie systémique (SSc) et au cours du suivi est indispensable. Le but de notre étude était de définir les facteurs associés à son apparition et de progression dans une population tunisienne.

Méthodes: Etude descriptive et rétrospective, incluant des patients atteints de SSc. Les données de l'évaluation initiale et d'un suivi à 3 ans (TAEM) ont été recueillies. Les tomodensitométries thoraciques (TDM) ont été réinterprétées par un radiologue spécialisé en imagerie thoracique selon le score de Goh.

Résultats: Quarante-neuf patients ont été inclus. Une PID a été diagnostiquée à TAEM chez 31 patients (63 %), dont 35 % présentaient une forme progressive. Le pattern radiologique le plus fréquent était la pneumopathie interstitielle non spécifique (68 %). Les facteurs d'apparition de la PID comprenaient : un score de Rodnan plus élevé (p=0,008 ; OR=1,16), une hypertension pulmonaire (p=0,004 ; OR=9,35), une atteinte œsophagienne (p=0,044 ; OR=3,650), la présence d'anticorps anti-topoisomérase I (p=0,001 ; OR=9,344) et un taux d'hémoglobine plus bas (p=0,04 ; OR=8,576). Les facteurs de progression incluaient : une capacité vitale forcée plus basse (p=0,002 ; OR=0,797), les anti-topoisomérase I (p=0,015), une CRP élevée (p=0,038 ; OR=5,07) et un pattern radiologique indéterminé (p=0,048).

Conclusion: Un score de Rodnan élevé, une atteinte œsophagienne, une hypertension pulmonaire, des anti-topoisomérase I et une anémie étaient associés à l'apparition de la PID. Les facteurs de progression étaient une diminution des volumes respiratoires de base et un syndrome inflammatoire.

Mots-clés: Sclérodermie Systémique, Pneumopathie interstitielle diffuse, Apparition, progression, tomographie thoracique

Correspondance

Houssem Abida

Internal medicine department, Mongi Slim University Hospital, Tunis, Tunisia, Faculty of Medicine of Tunis, University of Tunis El Manar, 1068, Tunis, Tunisia

Email: abida.houssem@yahoo.fr

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Introduction

Interstitial lung disease (ILD) is one of the most common manifestations of Systemic Sclerosis (SSc) and is part of its classification criteria items for the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) [1]. Its onset represents a turning point in the disease's history, as it is the leading cause of mortality, with a mortality rate reaching up to 40% [2,3]. Furthermore, the onset of ILD significantly alters patients' quality of life and functional autonomy [4].
According to studies, ILD usually appears within the first three to four years after disease onset. However, a significant proportion of patients develop ILD before or after this suggested period [6]. Besides, the progression of ILD and response to treatment vary from patient to patient. Although it may remain clinically and radiologically stable, it has the potential to progress rapidly and exhibit resistance to all forms of immunosuppressive therapy [3,5]. The main concern in such cases is the progression to chronic respiratory failure, which may require long-term oxygen therapy or even lung transplantation.These factors highlight the importance of systematic screening at disease onset and regular follow-up monitoring. Indeed, early diagnosis of ILD allows management in limited and potentially reversible lesions. It also allows preventing or delaying disease progression.
ILD onset and progression appear to be associated with specific patient clusters categorized as low and high risk [6]. These clusters are defined by epidemiological, clinical, biological, and radiological parameters. These parameters were suggested by studies conducted in some national or regional cohorts [6]. Identifying these clusters guides clinicians to implement personalized monitoring strategies and initiate early adapted treatment for ILD [7]. To address this need, our study aimed to identify predictive factors for the onset and progression of SSc-ILD in a cohort of Tunisian (North African) patients.

Methods

Patients

We included patients evaluated in the internal medicine departments of Mongi Slim University Hospital and Charles Nicolle University Hospital between 2000 and 2020 who met the 2013 ACR/EULAR classification criteria for SSc [1] or had a diagnosis of sclerolupus overlap syndrome, defined as concurrent SSc and systemic lupus erythematosus (SLE) based on the 2019 ACR/EULAR criteria [8]. Eligible patients had undergone at least two thoracic computed tomography (CT) scans, with an interval of 2 to 3.5 years between scans. Patients with any additional systemic disease, other than SLE in the context of SSc-SLE overlap syndrome, were excluded.

Clinical data collection

Baseline was defined as the date of the first consultation in the referring center, and follow-up time (FUT) as the time of the second radiological assessment (between 2 and 3,5 years). We collected baseline information on demographics, clinical, biological and imaging findings of all patients. Regarding the disease, detailed baseline data regarding cardio-pulmonary, articular, vascular, digestive and cutaneous assessment were included. Pulmonary assessment at FUT was also obtained.

Definitions

Restrictive lung disease (RLD) was defined by a Total Lung Capacity (TLC) <80% with a normal Forced expiratory volume exhaled in the first second (FEV1)/Forced Vital Capacity (FVC) ratio. In the absence of plethysmography, RLD was considered in the presence of FVC below 80% and a normal FEV1/FVC ratio. A decrease in DLCO was defined as a value below 80% of the predicted value.

Chest tomography

Scans were reinterpreted by a radiologist specialized in thoracic imaging from the radiology department of Abderrahmen Mami University Hospital. Interpretation was done on a dedicated console using parenchymal (1600 Hounsfield Units (HU) centered on -600 HU) and mediastinal (350/55 HU) windows. Analysis was conducted in axial, coronal, and sagittal planes, with maximum and mini intensity reconstructions.
In each CT-scan, we noted main parenchymal and extra-parenchymal lesions. We also described their distribution in axial and cranio-caudal planes. These findings allowed us to define radiological patterns: Non-Specific Interstitial Pneumonia (NSIP), Usual Interstitial Pneumonia (UIP) and indeterminate pattern [9]. We finally used the Goh score to assess ILD extent [10].

Data Analysis Process

Patients were divided into two main clusters according to the presence (ILD+) or absence (ILD-) of ILD on any of the CTs during study time.
ILD+ patients were divided into 2 subgroups according to the progression of ILD :
• **Stable ILD Group:** Defined by the absence of all the INBUILD study criteria items for progressive interstitial lung disease with autoimmune manifestations (IPAF) [11].
• **Progressive ILD Group:** Included patients whose ILD met one or more of the following progression criteria: meeting INBUILD trial criteria [11], exhibiting an ILD extent greater than 20% on the Goh staging system at any CT scan, showing worsening of dyspnea stage in the 6–12 months before initial assessment or during the first 6–12 months of follow-up, or having a baseline FVC less than 60% of the predicted value, with at least two of the last three criteria required.

Statistical Analysis

Data was analyzed using SPSS software version 24.0. Comparisons of two means were performed using Student's t-test, and for small sample sizes, the Mann-

Whitney non-parametric test was used. Comparisons of more than two means (>2) were carried out using one-way ANOVA, and for small sample sizes, the Kruskal-Wallis non-parametric test was employed. In case of significant differences, pairwise comparisons were conducted using the Bonferroni method. Comparisons of percentages were done using Pearson's chi-square test or Fisher's exact test. The relationship between two quantitative variables was examined using Pearson's correlation coefficient. To identify risk factors independently associated with complications, a multivariate analysis was performed using stepwise logistic regression or the entry method. The multivariate analysis allowed the calculation of adjusted Odds Ratios, measuring the independent effect of each factor. In all statistical tests, the significance level was set at 0.05.

Ethical Considerations

Strict anonymity of individual data was maintained throughout the study. Only the principal investigator knew the identities of the patients. The study protocol was submitted to the ethics committee of Mongi Slim Hospital, which approved the conduct of this work (Approval N°15/2022).

Results

Patients characteristics at baseline

A total of 87 patients were identified. Forty nine patients fulfilled our inclusion criteria (fig.1).

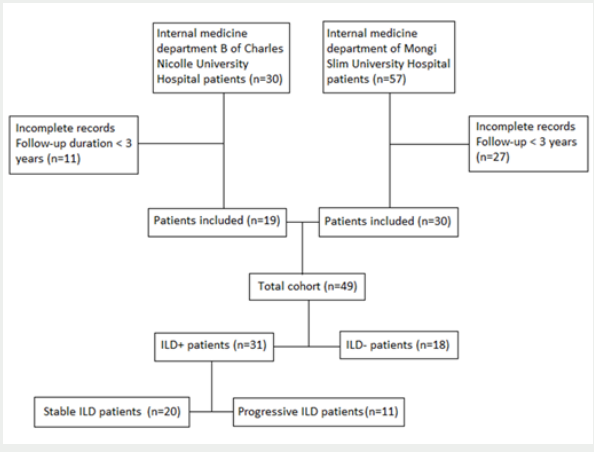


Figure 1. Cohort patients flowchart

A total of 31 patients developed ILD at FUT (63%). Among them, eleven patients presented progressive ILD (35%).

Baseline demographic, clinical, biological, immunological and imaging characteristics are detailed in table 1. On biological assessment, twenty patients had anemia (41%). Antinuclear antibodies were positive in 47 patients (96%).

Table 1. Demographic, clinical, biological and imaging characteristics of the study patients at baseline assessment

Demographic and toxic exposure data	
Sex ratio (Men/Women)	0.36
Mean age at diagnosis (years)	47 [range: 18-86]
Mean of body mass index (Kg/m^2)	24.06 [range: 14.1-35.6]
Obesity (n,%)	6 (12%)
Overweight (n,%)	9 (18%)
Ever-smoker (n,%)	11 (22%)
Silica exposure (n,%)	9 (18%)
Skin involvement	
Raynaud phenomenon (n,%)	47 (96%)
Digital ulcers (n,%)	29 (59%)
Skin sclerosis (n,%)	42 (86%)
Modified Rodnan Skin Score (mean)	12.28 [range: 0-36]
Limited/Diffuse/sine phenotypes (n)	22/20/7
Giant capillaries on Nailfold capillaroscopy (n/N$^{*,\%}$)	17/29 (59%)
Esophageal involvement	
Dysphagia (n,%)	27 (55%)
Pyrosis (n,%)	20 (41%)
Peptic esophagitis on Oesogastroduodenoscopy (n/N,%)	24/46 (52%)
Esophageal hypoperistalsis on Esophageal manometry (n/N,%))	12/13 (92%)
Esophageal dilatation on Chest tomography (CT) (n,%)	22 (45%)
Mean esophageal diameter on CT-(mm) (n,%)	28.41 [range: 12,5-49]
Pulmonary hypertension (PAH)	
Suggestive features of PAH on heart echocardiography (n/N,%)	14/46 (29%)
Mean of systolic pulmonary arterial pressure on heart echocardiography (mmHg)	35.19 [range:17-100]
precapillary PAH on right heart catheterization (n/N)	4/19 (21%)
Pulmonary artery diameter > 29 mm on CT (n,%)	12 (25%)
Pulmonary artery/Aorta ratio > 1 on CT (n,%)	9 (18%)
Mosaic perfusion pattern on CT (n,%)	2 (4%)
Right heart cavities dilatation on CT** (n/N,%)	3/12 (25%)
Arthralgia	27 (55%)
Biological and immunological data	
Hemoglobin level (mean) (g/dl)	12.29 [range: 7.3-15.6]
Increase of CRP***level (n,%)	8 (16%)
Increase of Erythrocyte Sedimentation Rate	21 (43%)
Anti-topoisomerase I antibodies (n/N,%)	27/48 (56%)
Anti-centromere antibodies (n/N,%)	4/43 (9%)
Anti-Th/To antibodies (n/N,%)	4/27 (15%)
Anti-fibrillarine antibodies (n/N,%)	1/25 (4%)
Anti-RNA Polymerase III antibodies (n/N,%)	1/23 (4%)
Pulmonary functional tests findings	
Mean of FEV1****(%)	72.04 [range: 31-106]
Mean of FVC***** (%)	67.50 [range: 31 – 105]
Mean of TLC****** (%)	66 [range: 45 – 104]
Restrictive syndrome (n,%)	21 (43%)
Decrease of DLCO******* (n/N,%)	⅘ (80%)

N: number of patients for whome the assessement was performed, Contrast agent injection was performed for 12 patients, **CRP:** C-reactive protein, **FEV1:** Forced Expiratory Volume in one second, **FVC:** Foced vital capacity , **TLC:** Total lung capacity, **DLCO:** Diffusing capacity of the lungs for carbon monoxide

Ground glass opacities were the most frequent lesions found on CTs at both baseline (96%) and follow-up (97%). For patients with ILD, NSIP was the most frequent radiological pattern found in 21 patients (68%) (Table 2).

Table 2. Pulmonary imaging findings at baseline and follow-up

	Baseline assessment (n,%*)	Follow-up assessment (n,%*)
Parenchymal lesions		
Ground glass opacities (n,%)	25 (96%)	30 (97%)
Septal thickening (n,%)	22 (85%)	26 (84%)
Traction bronchectasias et bronchiolectasias (n,%)	22 (85%)	25 (81%)
Intralobular reticulations (n,%)	17 (65%)	18 (48%)
Condensations (n,%)	10 (38%)	17 (55%)
Honey combing lesion (n,%)	6 (23%)	7 (23%)
Radiological patterns		
Non Specific Interstitial Pneumonia (n,%)	17 (65%)	21 (68%)
Usual Interstitial Pneuonia (n,%)	6 (23%)	6 (10%)
indeterminate pattern (n,%)	3 (12%)	4 (13%%)
Goh score		
Mean of global ILD extent (%)	33.10 [range: 3-77]	33.26 [range: 5-85]
Mean of reticulations proportion (%)	33.22 [range: 5-56]	34.91 [range: 7-70]
Mean ground glass proportion (%)	43.07 [range: 10-100]	43.99 [range: 0.66-100]
Mean global ILD severity score	5.76 [range: 1.25-13]	5.57 [range: 2-13]
Non parenchymal abnormalities		
Mediastinal lymphadenopathies (n,%)	8 (26%)	
Pericardial effusion (n,%)	15 (48%)	
Pleural effusion (n,%)	1 (3%)	

*Percentage calculated compared to ILD+ patients

Comparison of ILD+ and ILD- patients

No significant differences were observed when comparing patients by sex, age at diagnosis, exposure to toxic agents, or body weight. PFT results were comparable between the two groups. On chest CT, patients with ILD showed a higher prevalence of pericardial effusion (p=0.000) and mediastinal lymphadenopathy (p = 0.018). Skin sclerosis, as assessed by the modified Rodnan Skin Score (mRSS), was significantly associated with ILD onset (p = 0.002). Esophageal dilatation on CT correlated with the presence of ILD (p = 0.015). CT signs suggestive of pulmonary hypertension (PH) were significantly associated with ILD (table 3). Regarding laboratory findings, elevated erythrocyte sedimentation (ESR) rate was more frequently observed in ILD-positive patients (p = 0.026), while C-reactive protein (CRP) levels were similar between the groups. Mean hemoglobin levels were significantly lower in ILD-positive patients (p = 0.04). The presence of anti-topoisomerase I and anti-Th/To antibodies was associated with ILD (p = 0.001 and p = 0.031, respectively), whereas anti-centromere antibodies were associated with the absence of ILD (p = 0.006). Details of the univariate analysis comparing the two patient groups are presented in Table 3.

Table 3. Univariate comparison of ILD+ and ILD- Systemic Sclerosis patients

	ILD+ (n=31)	ILD- (n=18)	p-value
Sex-ratio (Men/women)	8/23	5/13	NS*
Age at disease onset (years)	46.26	38.61	NS
Age at diagnosis (years)	50.32	41.11	NS
Exposure to silica (n/N**,%)	5/26 (19%)	4/17 (24%)	NS
Ever-smoker (n,%)	7 (23%)	4 (22%)	NS
Chest investigations			
Restrictive disease on PFTs*** (n/N,%)	15/27 (56%)	6/14 (43%)	NS
Decrease of DLCO**** (n/N,%)	4/4 (100%)	1/1 (100%)	NS
Mediastinal lymphadenopathies (n,%)	8 (26%)	0 (0%)	0.018
Pericardial effusion (n,%)	15 (48%)	0 (0%)	0.000
Skin involvement			
Raynaud phenomenon (n,%)	30 (97%)	17 (95%)	NS
Digital ulcers (n,%)	20 (60%)	9 (50%)	NS
Mean of modified Rodnan Skin Score	15.67	6.29	0.002
Diffuse cutaneous phenotype (n,%)	15 (48%)	5 (28%)	NS
Limited cutaneous phenotype (n,%)	14 (45%)	8 (44%)	NS
Sine Scleroderma phenotype (n,%)	2 (7%)	5 (28%)	NS
Giant capillaries on nailfold capillaroscopy (n/N,%)	8/15 (53%)	9/14 (64%)	NS
Esophageal involvement			
Pyrosis (n,%)	16 (52%)	4 (22%)	0.044
Dysphagia (n,%)	16 (52%)	6 (33%)	NS
Peptic esophagitis (n,%)	16 (57%)	8 (44%)	NS
Esophageal hypoperistalsis (n/N,%)	8/9 (89%)	4/4 (100%)	NS
Esophageal dilatation on CT***** (n,%)	18 (58%)	4 (22%)	0.015
Mean of esophageal diameter (mm)	30.33	17.29	0.009
Pulmonary hypertension			
Pulmonary artery diameter > 29 (mm) (n,%)	11 (36%)	1 (6%)	0.019
Right ventricular dilatation on CT (n,%)	1/10 (10%)	2/2 (100%)	0.007
PA/Ao******ratio > 1 on CT (n,%)	8 (26%)	1 (6%)	NS
Mean fo systolic pulmonary artery pressure (mmHg)	34.20	36.82	NS
Arthralgia (n,%)	16 (52%)	11 (61%)	NS
Biological and immunological findings			
Increased CRP******* level (n,%)	7 (23%)	1 (6%)	NS
Increased ESR******** level (n,%)	17 (55%)	4 (24%)	0.026
Hemoglobin level (g/dl)	11.88	13.01	0.04
Anti-centromere antibodies (n,%)	0/27 (0%)	4/16 (25%)	0.006
Anti-Th/To antibodies (n,%)	1/29 (3%)	⅜ (38%)	0.031
Anti-topoisomerase I antibodies (n,%)	23 (74%)	4/17 (24%)	0.001
Anti-RNA Polymerase III antibodies (n,%)	0/16 (0%)	⅛ (13%)	NS
Anti-fibrillarin antibodies (n,%)	1/17 (6%)	0/8 (0%)	NS

NS: Non significant, **N:** Number of patients for which the information was assessed, **PFT:** Pulmonary functional tests, **DLCO:** Diffusing capacity of the lungs for carbon monoxide, **CT:** Chest tomography, **PA/Ao:** Pulmonary artery/Aorta, **CRP:** C-reactive protein, **ESR:** Erythrocyte sedimentation rate

Multivariate analysis confirmed the correlation between mRSS (OR=1.16; 95%CI [1.04-1.3]), PH (OR=9,35; 95%CI [1,093-30,011]), anemia (OR= 8,576; 95%CI [1,481-15,912]) and anti-topoisomerase 1 abs (OR=9,344; 95%CI [2,352-37,123]) with ILD onset (Table 4).

Table 4. Interstitial lung disease onset and progression factors according to multivariate study

	p	Odds ratio	Confidence interval for an odds ratio of 95%	
			Inferior	superior
ILD onset factors				
Modified Rodnan Skin Score	0.008	1.16	1.04	1.3
Pyrosis	0.025	3.650	0.494	26.945
Pulmonary hypertension	0.004	9.350	1.093	30.011
Low hemoglobin levels	0.004	8.576	1.481	15.912
Anti-topoisomerase 1	0.001	9.344	2.352	37.123
ILD progression factors				
Baseline Forced Vital Capacity	0.048	0.797	0.637	0.998
CRP*	0.038	5.07	1.09	30.3

***CRP:** C-reactive protein

Comparison of stable ILD and severe ILD patients

No significant differences were observed in epidemiological characteristics or toxic exposure between patient groups. Severe ILD was associated with a higher body mass index (BMI) (p=0.042). Respiratory assessment revealed that patients with progressive ILD exhibited more frequent respiratory symptoms, reduced lung volumes on PFTs and a higher prevalence of indeterminate ILD patterns. None of the Goh score items were associated with ILD progression in our cohort. Esophageal involvement, arthralgia, and PH were comparable between subgroups. Biological assessment showed a higher frequency of anti-topoisomerase I antibodies in patients with progressive ILD (p=0.015). CRP levels were associated with ILD progression (p=0.024) (Table 5). Multivariate study confirmed this last finding (OR= 5.07; 95%CI [1.09-30.3]) (table 4).

Discussion

To our knowledge, this is the first north african study identifying ILD onset and progression factors in SSc. Besides, this research studied the usefulness of the Goh score in initial assessment and follow-up. The present case series of 49 Tunisian SSc patients provided the following findings: (i) ILD was identified in 31 patients (63%), of whom 11 (36%) had severe disease based on predefined criteria. NSIP was the most frequent pattern (68%) followed by UIP (19%). Among extrapulmonary manifestations, cutaneous involvement was the most frequent one found in 96% of patients, followed by esophageal (76%) and articular involvement (55%).

Table 5. Univariate comparison of stable ILD and progressive ILD Systemic Sclerosis patients

	Stable ILD (n=20)	Severe ILD (n=11)	p-value
Sex-ratio (Men/Women)	6/14	2/0	NS*
Age at diagnosis (years)	52.50	46.36	NS
Silica exposure (n/N**,%)	4/18 (22%)	⅛ (13%)	NS
Ever-smoker (n,%)	6 (30%)	1/11 (9%)	NS
Mean of Body mass index (kg/m²)	22.94	27.85	0.042
Baseline ILD pattern			
Non specific interstitial pneumonia (n,%)	12 (60%)	6 (55%)	0.048
Usual Interstitial Pneumonia (n,%)	8 (40%)	1 (9%)	
Indeterminate pattern (n,%)	0 (0%)	4 (36%)	
Baseline Goh Score			
Mean of global ILD extent (%)	29.05	39	NS
Mean of reticulations extent (%)	29.6	41	NS
Mean of ground glass extent (%)	41.938	44.900	NS
Mean of global severity score	6.1	5	NS
Baseline extra-parenchymal findings			
Mediastinal lymphadenopathies (n,%)	7 (35%)	1 (9%)	NS
Pericardial effusion (n,%)	9 (45%)	6 (55%)	NS
Baseline respiratory functional assessment			
Forced vital capacity of PFT*** (%)	72.69	48.31	0.002
Skin involvement			
Raynaud phenomenon (n,%)	19 (95%)	11 (100%)	NS
Digital ulcers (n,%)	13 (65%)	7 (64%)	NS
Giant capillaries on nailfold capillaroscopy (n/N,%)	4/10 (40%)	⅘ (80%)	NS
Mean of modified Rodnan Skin Score	13.26	19.82	NS
Diffuse Cutaneous phenotype (n,%)	8 (40%)	7 (64%)	NS
Limited Cutaneous phenotype (n,%)	11/20 (55%)	3/11 (27%)	NS
Sine Scleroderma phenotype (n,%)	1/20 (5%)	1/11 (9%)	NS
Esophageal involvement			
Pyrosis (n,%)	9 (45%)	7 (60%)	NS
Dysphagia (n,%)	8 (40%)	8 (73%)	NS
Peptic esophagitis (n,%)	11/19 (58%)	5/9 (56%)	NS
Esophageal hypoperistalsis (n/N,%)	6/7 (86%)	2/2 (100%)	NS
Esophageal dilatation on CT*** (n,%)	11 (55%)	7 (64%)	NS
Mean of esophageal diameter (mm)	31.33	28.33	NS
Pulmonary hypertension			
Mean of systolic pulmonary artery pressure (mmHg)	34.4	33.86	NS
Arthralgia (n,%)	9 (45%)	7 (64%)	NS
Baseline biological and immunological findings			
Increase of CRP***** level (n,%)	2 (10%)	5 (45%)	0.024
Increased ESR****** (n,%)	12 (60%)	5 (45%)	NS
Hemoglobin level (g/dl)	11.64	12.3	NS
Anti-Th/To antibodies (n/N,%)	0/10 (0%)	1/9 (11%)	NS
Anti-topoisomerase I antibodies (n/N,%)	12 (60%)	11 (100%)	0,015
Anti-fibrillarin antibodies (n/N,%)	1/10 (10%)	0/7 (0%)	NS

*N: Number of patients for whom the assessment was available
**NS: Non significant
***PFT: Pulmonary functional tests
****CT: Chest tomography
*****CRP:C-reactive protein
******ESR: Erythrocyte sedimentation rate

PH was found in 29% of patients; (ii) baseline factors associated to the onset of ILD were: higher mRSS (p=0.008), esophageal involvement (p=0.009), PH (p=0.004), mediastinal lymphadenopathies (p=0.018), pericardial effusion (p=0.000), Anti-topoisomerase I abs (p=0.001), absence anti-centromere abs (p=0.006), anemia (p=0.004) and increase of ESR (p=0.026); (iii) baseline factors associated to the worsening of ILD were: higher BMI (p=0.042), reduced pulmonary volumes on PFT, (p=0.048), indeterminate radiological ILD pattern (p=0.048), the presence of anti-topoisomerase abs (p=0.015) and increase of CRP (p=0.038).

In our study, none of the epidemiological parameters studied was associated with ILD onset or progression. Most data does not suggest a link between age and the onset of ILD [5]. For ILD progression, some reports, such as the analysis of the Singaporean cohort, found a correlation between the age of onset of SSc and the severity of ILD [12]. When it comes to gender, and unlike the feminine predominance of SSc in general, SSc-ILD seems to be more frequent and more severe in men [2,5]. This association may be attributed to the higher occupational silica exposure in men, which contributes to the development of fibrotic processes, particularly pulmonary fibrosis [13].

Regarding ILD progression, a French team in 2018 showed a more rapid and significant decline in TLC and FVC values in the high-exposure group to silica [14]. This result was not found in our study, which could be related to insufficient quantification of silica exposure in the medical history. We found that higher BMI correlated with more severe ILD. This can be explained by the fact that obesity can be a cause of a restrictive disease on PFT and worsening of functional tests. An example is the Venezuelan study showing that BMI variation was inversely proportional to the 6-minute walk test [15]. It is noteworthy that malnutrition is a well-established predictor of the onset and progression of ILD in the literature [15], in contrast to our findings.

Regarding the scan data, indeterminate patterns were associated with a more severe prognosis in univariate analysis. Besides, none of the Goh score items were associated with ILD progression in our cohort.

Some studies suggest that radiographic fibrosis scores predict survival in systemic sclerosis-associated ILD [16,17], with similar survival rates between UIP and NSIP patients. These authors recommend focusing on the extent of each radiological element, such as ground-glass opacities, reticulations, and honeycombing, rather than radiological patterns in SSc.

ILD extent has also been shown to be correlated with dyspnea levels [18], FVC values [19,20], and DLCO [20]. As a result, some authors recommend that in radiological follow-up of patients, it is better to assess the initial extent of ILD rather than the pattern, as an extent greater than 20% appears to have significant negative prognostic value [21,22].

In addition to parenchymal lesions, we demonstrated an association between mediastinal lymphadenopathy and the onset of ILD. Existing literature suggests that lymphadenopathy may serve as a marker of two distinct processes. First, it may reflect active inflammatory lung disease, such as ILD, with Renaud et al. reporting a positive correlation with the Goh score. Second, lymphadenopathy may indicate exposure to silica and resultant pneumoconiosis [23]. However, this latter association was not observed in our cohort, possibly due to the limited number of patients with mediastinal lymphadenopathy, which may have restricted the statistical power of the analysis.

Furthermore, we showed that pericardial effusion was associated with ILD onset in univariate analysis . The explanation behind this is that the vasculopathy described above, affecting the parietal pleura, is systemic and thus also present in the pulmonary parenchyma, contributing to fibrosis at this level.

We found that PAH was also associated with ILD onset, which is consistent with existing literature. In fact, PAH typically arises in the context of ILD as a complication, driven by chronic hypoxemia and increased right heart flow. On a clinical level, skin sclerosis was associated with ILD onset. Multivariate analysis confirmed a significant association between higher mRSS and the onset of ILD in SSc (p=0.008), consistent with findings from national and international studies [24,25]. Furthermore, prior investigations suggest that diffuse cutaneous SSc is a predictor of poorer ILD prognosis [26].

We also demonstrated a significant association between esophageal involvement, assessed by morphological markers in univariate analysis (p=0.009) and functional markers in both univariate (p=0.044) and multivariate analyses (OR=3.65 ;p=0.025), and the onset SSc-ILD, consistent with prior investigations [27].

Morphologically, similar to findings in our cohort, previous studies have reported that increased esophageal diameter on CT scans is associated with the extent of ground-glass opacities and reticular patterns on follow-up thoracic CT scans [27,28].

We found no association between arthralgia and ILD presence or worsening. The role of inflammatory arthritis in the onset of ILD is debated. Some authors suggest that synovitis and active arthritis are predictive factors for ILD, similarly to other rheumatic diseases such as Rheumatoid Arthritis [29]. On the other hand, more recent studies have not found this link, such as the comparative study of the European EUSTAR cohort of Very Early Diagnosis of Systemic Sclerosis (VEDOSS)) [30]. In our study, hemoglobin levels were significantly lower in ILD+ patients compared to ILD- patients in both univariate (p=0.04) and multivariate analyses (OR=8.576 ; p=0.004). No significant difference was observed between patients with stable and progressive ILD. The multifactorial etiology of anemia complicates further characterization of this association. A 2019 Turkish study evaluating SSc patients using routine biomarkers reported comparable hemoglobin levels between ILD-positive and ILD-negative groups [31]. However, several studies have suggested that anemia may exacerbate organ involvement, particularly pulmonary and renal manifestations in SSc [32]. Consequently, some authors advocate incorporating

hemoglobin levels as a biomarker of disease activity and progression in SSc [32].

The literature presents conflicting findings regarding the association between CRP levels and systemic manifestations of SSc, particularly ILD. Earlier studies suggested a role for elevated CRP in the onset and progression of ILD, as well as PH, skin fibrosis, and arthritis [33]. However, more recent studies have not found this result [31]. In the EUSTAR cohort, persistent CRP elevation during follow-up was used to define a persistent inflammatory syndrome, which correlated with more severe progression of untreated ILD and a better response to immunosuppressive therapy [34]. Consistent with these findings, our study identified a significant association between elevated CRP levels and ILD progression in univariate (p=0.024) and multivariate analyses (OR=5.07 ;p=0.038), supporting the utility of CRP as an accessible biomarker for ILD in SSc. Nevertheless, the proportion of SSc patients with an inflammatory phenotype was small, suggesting that the clinical relevance of CRP may be limited for most patients.

In our study, anti-topoisomerase I antibodies were significantly associated with the onset of ILD in SSc in both univariate (p=0.001) and multivariate analyses (OR=9.344 ; p=0.001) and with ILD progression in univariate analysis (p=0.015), consistent with prior investigations [33]. Conversely, no patients with anti-centromere antibodies developed ILD, aligning with existing literature [35]. Anti-Th/To antibodies were associated with ILD onset in univariate analysis (p=0.031) but showed no correlation with ILD progression. However, these findings are limited by potential biases. First, anti-Th/To antibody testing was recently introduced in commercial line blot kits for SSc in Tunisia, resulting in incomplete testing across our cohort. Second, the small number of patients with anti-Th/To antibodies precluded robust statistical conclusions. The literature suggests that anti-Th/To antibodies are associated with less severe skin and esophageal involvement but may predict worse progression of other organ manifestations, including pulmonary involvement [36].

Our study has several limitations. First, the small sample size and retrospective design, coupled with missing data, restricted the robustness of our multivariate analyses. Second, while PH screening protocols were updated in the 2022 European Society of Cardiology guidelines, their retrospective application was challenging due to inconsistent historical data.

Conclusion

In our cohort, ILD onset and progression were associated with multiple clinical, biological, and imaging findings. These data underscore the importance of a standardized baseline assessment protocol for all SSc patients, aimed not only at accurately identifying those at risk of developing lung involvement but also at predicting disease progression. Such an approach would support early intervention and enable treat-to-target strategies designed to prevent chronic respiratory failure and its systemic complications. Establishing clear patient pathways based on these assessments is essential to ensure timely, personalized care and to optimize long-term outcomes in SSc-ILD.

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