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Predictive Factors for Pulmonary Involvement in Systemic Scleroderma: A Single-Center Retrospective Study in Morocco

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Abstract | **Original Research Article**

Introduction: Pulmonary involvement is the leading cause of morbidity and mortality in systemic scleroderma (SSc). Identifying predictive factors would enable targeted monitoring and early management. ***Materials and Methods:*** This is a single-centre retrospective study including 71 patients with SSc (ACR/EULAR 2013 criteria), followed between January 2012 and December 2024. Patients with pulmonary involvement were compared to those without pulmonary involvement. Univariate and then multivariate logistic regression analysis was performed to identify independently associated factors. ***Results:*** Pulmonary involvement was found in 35 patients (49.3%). Diffuse interstitial pneumonia was the main involvement (100% of cases), with a predominance of the non-specific interstitial pneumonia pattern (69%). Pulmonary arterial hypertension was observed in 20% of patients. In univariate analysis, digital ulcers ($p = 0.03$), diffuse skin involvement ($p = 0.009$) and the presence of anti-SSA antibodies ($p = 0.02$) were significantly associated with pulmonary involvement. In multivariate analysis, only the presence of anti-SSA antibodies remained independently associated (OR 5.84; 95% CI 1.09–31.2; $p = 0.039$). ***Conclusion:*** The presence of anti-SSA antibodies could be a predictive marker of pulmonary involvement in SLE. Prospective multicentre studies are needed to confirm these findings.

Keywords: Systemic sclerosis, Pulmonary involvement, Interstitial lung disease, Anti-SSA antibodies, Risk factors, Predictive markers.

INTRODUCTION

Systemic scleroderma (SSc) is an autoimmune disease characterized by vascular dysfunction, immune activation, and progressive organ fibrosis. Among visceral complications, pulmonary involvement is currently the leading cause of disease-specific mortality [1].

It manifests primarily as diffuse interstitial pneumonia (DIP) and pulmonary arterial hypertension (PAH). Despite therapeutic advances, the respiratory course remains unpredictable and heterogeneous across patients. Identifying clinical or immunological factors associated with pulmonary involvement would allow for early risk stratification. However, data remain variable across the populations studied [2, 3].

The objective of this study was to identify factors associated with pulmonary involvement within a Moroccan cohort of patients with SSc.

MATERIALS AND METHODS

Study Type and Duration: A single-center retrospective study conducted in the Department of Internal Medicine at the Hassan II University Hospital Center in Fez, between January 2012 and December 2024.

Study population: All patients with systemic sclerosis meeting the 2013 ACR/EULAR criteria were included.

Patients were divided into two groups:
- Group 1: SSc with pulmonary involvement
- Group 2: SSc without pulmonary involvement

Pulmonary involvement was defined by:
- The presence of interstitial abnormalities on high-resolution chest CT, and/or
- Restrictive respiratory dysfunction (FVC < 80% of predicted).

PAH was suspected on echocardiography (PAPs > 35 mmHg).

Data analysis: A data collection form was used to gather data from medical records.

Statistical analysis was performed in collaboration with the Laboratory of Epidemiology, Clinical Research, and Community Health at the Faculty of Medicine and Pharmacy in Fez.

Patient characteristics were described using descriptive statistics: qualitative variables were expressed as counts and percentages, while quantitative variables were presented as means ± standard deviation.

The comparison of systemic and immunological involvement between patients with systemic sclerosis with or without pulmonary involvement was performed using Student's t-test for quantitative variables, and the chi-square test or Fisher's exact test, depending on the sample size, for qualitative variables.

A univariate analysis identified factors associated with the development of pulmonary involvement. Variables with a p-value < 0.20 in the univariate analysis were then included in a multivariate logistic regression model to determine the factors independently associated with pulmonary involvement. The threshold for statistical significance was set at $p < 0.05$.

RESULTS

We included 71 patients with systemic sclerosis in our study. Pulmonary involvement was found in 35 patients, representing 49.3% of the study population. The mean age of the patients was 49 years, ranging from 21 to 77 years. The population was predominantly female, with a female-to-male sex ratio of 9.14.

Among patients with pulmonary involvement, the predominant symptoms were dyspnea in 71% of patients, followed by chronic dry cough in only 22.8% (Table 1).

Table 1: Distribution of patients according to clinical symptoms

Symptom	N (patients)	%
Asymptomatic	10	28.5%
Dyspnea stage I–II (NYHA)	20	57%
Dyspnea stage III–IV (NYHA)	5	14%
Cough	8	22.8%

Three types of pulmonary involvement were observed in our series. All patients presented with diffuse interstitial pneumonia, while pulmonary arterial hypertension (PAH) was found in 20% of cases. Pleurisy was reported in only one patient.

In addition to pulmonary involvement, cutaneous involvement was consistent, found in all patients (100%), of whom 63% had diffuse cutaneous sclerosis compared to only 37% of patients with limited cutaneous involvement. Joint manifestations were observed in 23 patients. Esophageal involvement was the most common gastrointestinal manifestation, affecting 18 patients, while cardiac involvement was reported in 7 patients. Regarding the immunological profile, antinuclear antibodies were present in the majority of patients. Anti-Scl70 and anti-SSA antibodies were the most common, found in 13 and 9 patients, respectively, which prompted their statistical analysis.

Radiologically, nonspecific interstitial pneumonia (NIP) was the predominant radiological pattern, found in 69% of patients, whereas the pattern of typical interstitial pneumonia (TIP) was less common, found in only 31% of patients.

Pulmonary function tests primarily revealed a restrictive syndrome with a significant decrease in forced vital capacity (FVC):

The mean FVC was 59% ± 0.17 of the predicted value, with 80% of patients having a value below 70%, indicating moderate to severe restrictive ventilatory impairment in the majority of cases. Consistent with this, the mean FEV1 was also reduced to 58% ± 0.18, with 73% of patients below 70%. It is noted that only 20% of patients had a normal FVC (≥ 80%), and 27% for FEV1. These low proportions underscore the frequent and significant respiratory impairment in the study population.

The distribution of patients according to the severity of FEV1 is as follows: approximately 30% of patients have an FEV1 < 50%, indicating severe impairment. Meanwhile, the intermediate categories (FEV1 between 50% and 79%) comprise a relative majority, with a balanced distribution between 20% and 25% in each range. Less than 20% have preserved respiratory function (FVC ≥ 80%).

With regard to treatment, 65.7% of patients with pulmonary involvement received induction therapy with cyclophosphamide. Among them, nearly 70% received maintenance therapy with azathioprine.

Univariate analysis identified several factors significantly associated with pulmonary involvement. These included digital ulcerations ($p = 0.03$), diffuse skin

involvement (p = 0.009), and the presence of anti-SSA antibodies (p = 0.02). (Table 2)

Table 2: Univariate analysis

Variable	Pulmonary involvement (N=35)	No pulmonary involvement (N=36)	p-value
Digital ulcers	20	11	0.03
Digital necrosis	7	2	0.074
Cardiac involvement	7	11	0.674
Sclerodactyly	31	25	0.073
Diffuse cutaneous involvement	21	10	0.009
Anti-SSA antibodies	10	2	0.02
Inflammatory syndrome	16	15	0.747

In multivariate analysis, only the anti-SSA antibody remained an independent risk factor for pulmonary involvement, with an odds ratio of 5.84 (95% CI: 1.09–31.2; p = 0.039). This means that the presence of this autoantibody increases the risk of developing pulmonary involvement by nearly sixfold, independent of other clinical or immunological variables. This is a strong signal that warrants consideration in the follow-up of these patients.

DISCUSSION

Pulmonary involvement in scleroderma manifests primarily in two major clinical forms: pulmonary interstitial disease (PID) and pulmonary arterial hypertension (PAH). IPD is currently one of the leading causes of morbidity and the leading cause of mortality in patients with systemic sclerosis due to its progression to progressive pulmonary fibrosis and chronic respiratory failure. [4]

In our cohort, the prevalence of pulmonary involvement was 49.3%, which falls within the range reported by major international registries, notably the EUSTAR cohort (35–50%). The variations observed across different studies—lower in some Northern European series (14.7% in Denmark) and higher in Asian meta-analyses (up to 70%)—could be explained by methodological differences (systematic screening by high-resolution CT versus symptomatic diagnosis), genetic characteristics, or varying diagnostic delays. Thus, the frequency observed in our population appears consistent with data from Mediterranean and European registries. The table below shows the prevalence of pulmonary involvement by cohort (Table 3).

Table 3: Prevalence of pulmonary involvement by study

Study	Patients (n)	Study period	Type	Prevalence
Morocco	86	2011–2021	Retrospective	66.3%
Tunisia	56	1985–2013	Retrospective	64.81%
East Asia	5250	-	Meta-analysis	56%
Denmark	1869	2000–2016	Registry	14.7%
EUSTAR	5000	2004–2020	Multicenter registry	35–50%
Our series	35/71	2012–2024	Retrospective	49.3%

Radiologically, nonspecific interstitial pneumonia (NIP) was the predominant pattern (69%), which is consistent with the majority of international studies. Bouros *et al.,* and Goh *et al.,* reported 71% and 65% of NIPL, respectively, while the SLS II trial by Tashkin *et al.,*[12] found a comparable proportion (62%). These results reinforce the notion that scleroderma-associated pulmonary fibrosis most often progresses in a homogeneous manner, consistent with the NIPL pattern.

The predominance of PINS is of major clinical interest, as it is generally associated with a more favorable prognosis than common interstitial pneumonia (CIP), although certain fibrotic forms may progress to severe disease. In contrast, the Tunisian series by Klii *et al.,* reported a predominance of CIP (65%), highlighting inter-population heterogeneity. These differences may reflect recruitment biases, later diagnosis, or inconsistent radiological criteria. (Table 4)

Table 4: Predominant type of interstitial lung disease by series

Study	Country	n	Pattern	NSIP (%)
Our series	Morocco	35	NSIP predominant	69%
Goh *et al.,*2008	UK	215	NSIP	65%
Bouros *et al.,*2002	Greece	80	NSIP	71%
Tashkin *et al.,*2016	USA	142	NSIP	62%
Klii *et al.,*2020	Tunisia	152	UIP predominant	35%
Sanchez-Cano *et al.,*2020	Spain	281	Mixed	58%

In our cohort, the observed functional severity (mean FVC of 59% ± 17, with nearly 30% of patients having an FVC < 50%) suggests that the diagnosis of lung disease was often made at an already advanced stage. This underscores the importance of early systematic screening, regardless of symptoms, especially since nearly 30% of patients were asymptomatic at the time of diagnosis.

Univariate analysis revealed an association between pulmonary involvement and several systemic manifestations, notably digital ulcerations and diffuse skin involvement. These results are consistent with the hypothesis that the severity of peripheral vascular involvement may reflect systemic microvascular involvement, including the pulmonary bed. However, in multivariate analysis, only the presence of anti-SSA antibodies remained significantly associated with pulmonary involvement (OR 5.84; 95% CI 1.09–31.2; p = 0.039).

The association between anti-SSA antibodies and scleroderma-associated PID is the central finding of our study. This observation is consistent with recent data in the literature suggesting that certain autoantibody profiles may be associated with more severe organ involvement and a poorer prognosis, particularly in overlap forms of systemic sclerosis [15].

In a cohort of 156 patients, Watanabe *et al.,*[16] reported an independent association between anti-SSA antibodies and interstitial lung disease (OR 2.67; p = 0.024). Similarly, analysis of the EUSTAR database [17] confirmed the role of anti-SSA as an independent risk factor for pulmonary fibrosis (p = 0.006).

Several pathophysiological mechanisms may be considered. Anti-SSA antibodies may reflect increased humoral immune activation, promoting persistent interstitial inflammation and secondary fibroblast activation. They are also frequently observed in overlap forms with Sjögren's syndrome, a condition itself associated with an increased risk of interstitial lung disease. It is, however, difficult to determine whether they constitute a direct causal factor or merely a marker of a more severe autoimmune phenotype. Our results should nevertheless be interpreted with caution. The wide confidence interval (1.09–31.2) reflects the small sample size and the low number of anti-SSA-positive patients, posing a risk of overestimating the effect. Our OR, which is higher than those reported in some studies (2–3), could be explained by this statistical limitation or by population-specific characteristics.

Our data suggest that the presence of anti-SSA antibodies may serve as an indicator warranting increased vigilance. In these patients, close respiratory monitoring—including pulmonary function tests and chest imaging—may be considered. However, only prospective validation will determine whether these autoantibodies should be incorporated into a risk stratification algorithm.

Our study has several limitations: its retrospective nature, its small sample size, and the lack of systematic measurement of DLCO, a key parameter in the evaluation of scleroderma-associated pulmonary fibrosis. Furthermore, the absence of longitudinal follow-up prevents us from assessing fibrotic progression or long-term prognostic impact. Nevertheless, to our knowledge, this study is one of the first Moroccan analyses specifically exploring factors associated with pulmonary involvement in SSc, with an internal comparison between patients with and without respiratory involvement.

CONCLUSION

Pulmonary involvement is a common complication of systemic sclerosis in our cohort, with a prevalence of 49.3%. Nonspecific interstitial pneumonitis is the predominant radiological presentation. Several clinical manifestations were associated with pulmonary involvement in univariate analysis, but only the presence of anti-SSA antibodies remained independently associated after multivariate adjustment.

These results suggest that anti-SSA antibodies may be associated with a phenotype at risk for pulmonary involvement. However, given the retrospective nature and small sample size of the study, this association should be interpreted with caution. Prospective multicenter studies, including longitudinal follow-up, are needed to clarify the true prognostic value of these autoantibodies.

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