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Prognostic factors for severe pulmonary involvement in systemic sclerosis

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ABSTRACT

Background. Lung involvement is the main disease related death cause in patients with systemic sclerosis (SSc). The most frequent lung manifestations in SSc are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH).
Objectives. Evaluation of lung involvement in patients with SSc and identification of predictive factors for severe lung involvement.
Patients and methods. All patients with SSc of the EUSTAR100 center, having at least two visits between 2004 and 2016, were included. Survival status, cause of death, dyspnea, ILD on thorax radiography or high resonance thorax computer tomography (HRCT) and lung function tests were recorded during the entire follow-up. Severe lung involvement was defined as severe or end-stage lung involvement on the Medsger severity scale at any time during follow-up, or death. Cox proportional hazards regression was used in univariate and multivariate analysis to identify prognostic factors.
Results. 89 patients were included (12.4% males, mean age±SD 49.2±12.2 years, disease duration 4.1±7.5 years), with a follow-up duration up to 13 years. 14 deaths were reported, half due to lung involvement (4 deaths due to ILD, 3 deaths due to PAH). Pulmonary involvement was identified in a large proportion: at first visit 28/55 present ILD on thorax radiography, 7/12 on HRCT scans; at the most recent visit 41/71 present ILD on X-ray, 18/24 on HRCT scans. At least 10% decrease of pulmonary diffusion capacity for carbon monoxide (DLCO) and of forced vital capacity (FVC) was observed in 18/32 and 8/35 respectively; 24/48 developed severe or end-stage pulmonary involvement on the Medsger scale or have died. Risk factors for severe lung involvement were age>60 years, disease duration<3 years and diffuse cutaneous subset.
Conclusion. SSc often presents unfavourable disease course, mostly due to pulmonary involvement. While half of the deaths reported were due to lung involvement, only about half of the patients presenting ILD-typical findings on Rx develop end-stage lung involvement or death. It is of great importance to screen at baseline for ILD and PAH, following up annually, even while patients are asymptomatic.

Keywords: systemic sclerosis, prognostic factors, lung involvement

INTRODUCTION AND OBJECTIVES

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease with variable course. ILD and PAH are the most common types of lung involvement in SSc patients, as well as the main SSc-related mortality and morbidity causes in these patients (1).

SSc-ILD is characterized by inflammation or fibrosis of the lung parenchyma, possibly leading to impaired gas exchange, respiratory failure and eventually death. Its pathogenesis is not completely understood, with an immunological injury to pulmonary capillaries playing a potential role (2).

Dyspnea is the main symptom in SSc-ILD, but as it is neither sensitive nor specific, screening strategies for lung involvement are recommended in all SSc patients. The evaluation of respiratory symptoms, HRCT and pulmonary function tests (PFT) is

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a well accepted method for SSc-ILD diagnosis, while transthoracic echocardiography (TTE) is of high importance in PAH screening (3).

This study aims to asses the proportion of patients presenting lung involvement, identify the main death causes as well as prognostic factors for worsening of lung function, in a Romanian single-center cohort of patients with SSc.

PATIENTS AND METHODS

All patients diagnosed with SSc by expert opinion, who attended the EUSTAR100 center between January 2004 and March 2016, presenting at least 2 visits in the clinic were included in this study. All patients have signed informed consent for the recording and analysis of medical data. Patients were screened annually by X-ray, PFT and TTE; HRCT was recommended if PFV showed abnormalities and right heart catheterization recommandation if PAH was suspected.

We defined severe or end-stage lung involvement on the Medsger severity scale or death (4). Candidate risk factors were selected by clinical judgement among baseline parameters and included: male sex, age > 60 years, disease duration < 3 years, anti-centromere antibodies, anti-topoisomerase I antibodies, mRSS > 14, history of digital ulcers, diffuse cutaneous subset, FVC < 70%, DLCO < 80% of predicted, and proteiuria. Risk factors were assessed by univariable Cox proportional hazards regression, with a p value < 0.05 considered as statistically significant.

RESULTS

Demographic data

The study cohort comprised 89 patients (12.35% men, mean age 49.2±12.2 years, disease duration 4.1±7.5 years), with a follow-up duration up to 13 years. The female:male ratio was about 7:1, with age at diagnosis for men 43±17.74 years, while for women 44.45±14.55 years. 44.94% of patients were classified as diffuse cutaneous subset, with age at diagnosis for diffuse cutaneous subset 41.45±12.73 respectively 46.57±16.19 years for limited subset.

TABLE 1. *Demographic and clinical data of the patients at enrolment (n = 89)*

Age, years	49.2±12.2
Age at diagnosis, years	44.27±14.88
Disease duration since diagnosis	4.1±7.5
Male sex	11 (12.35%)
Diffuse cutaneous subset	40 (44.94%)
mRSS, mean; q1;q3	8.78 ± 8.647; 2; 13
Interstitial lung disease	35 (39.32%)
Heart involvement	27 (30.3%)
Gastrointestinal involvement	74 (83.14%)
Raynaud's phenomenon	100%
Renal crisis history	1 (1.12%)
Musculo-articular involvement	35 (39.32%)

Disease evolution and prognostic factors

Lung involvement was identified in a large proportion: at first visit 28/55 presented ILD on thorax radiography (Rx), 7/12 on HRCT scans; at the last

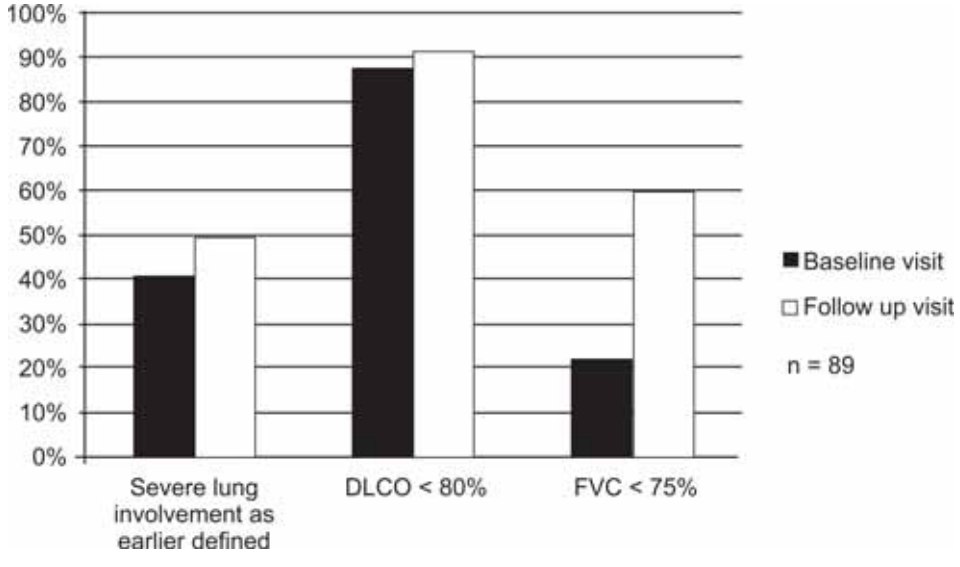

FIGURE 1. *Lung involvement at baseline and follow-up visit. Severe lung involvement was defined by the Medsger severity criteria (4)*

visit 41/71 present ILD on X-ray, 18/24 on HRCT scans. At least 10% decrease of DLCO and FVC was observed in 18/32 and 8/35, respectively: 24/48 developed severe or end-stage pulmonary involvement on the Medsger scale or died. There were 14 reported deaths, in 7 cases death being considered as due to lung involvement (4 deaths due to ILD, 3 deaths due to PAH).

Six of 28 patients who had specific ILD findings on Rx presented dyspnea at baseline; at the last visit the proportion has risen to almost 50% (19/41).

Risk factors for severe pulmonary involvement were age > 60 years, disease duration < 3 years and diffuse cutaneous subset.

TABLE 2. *Risk factors for severe pulmonary involvement (univariable Cox proportional hazards regression). HR=hazards ratio, CI=confidence interval*

Risk factors for severe pulmonary involvement			
	HR	95% CI	p
Age > 60 years	3.718	1.435-9.631	0.007
Disease duration < 3 years	45.941	5.01-421.284	0.001
Diffuse cutaneous subset	2.846	1.125-7.199	0.027

DISCUSSIONS

A wide clinical variety is observed in the course of SSc-ILD, with only 21% of patients with specific ILD findings on Rx presenting dyspnea at baseline, respectively 46% during follow-up. This shows that patients may be asymptomatic or minimally symptomatic at early stages of mild lung involvement, experiencing symptoms with increase of disease duration, disease worsening or older age. It is thus neccesary to screen at baseline for ILD and PAH, following up annually, even if patients are asymptomatic.

While ILD is a common feature in SSc and the main SSc related death cause (in our study 46.6% of patients present Rx modifications at last visit), only about half of the patients presenting typicalILD findings on Rx developed severe or end-stage lung involvement or died. This might be due to the close screening for lung involvement and starting of immunosupressive treatment with either cyclophosphamide or mycophenolate mofetil as soon as SSc-ILD was diagnosed, respectively with azathioprine as an alternative. There is an underlying necessity of further analysis of potential risk factors at baseline for the worsening of lung function.

Diffuse cutaneous subset, older age and early disease where found to be risk factors for worsening of SSc-lung disease in our study, with similar results found in the reviewed literature. A large study conducted on 900 SSc patients identified male sex, afro-american ethnicity, early disease and primary cardiac involvement due to SSc as risk factors for severe lung involvement (defined by an FVC<50% of predicted) (5). Different results regarding potential risk factors for SSc-ILD worsening coud be explained by the variability used to define SSc-ILD and number of patients included in the studies.

Limitations of our study were deficiencies in data collecting for the follow up tests, which were carried out in other facilities (with only 37% and 40% of patients having both at baseline and at last visit DLCO respectively FVC data), lack of firm classification criteria for SSc-ILD and the limited number of patients included in our study.

CONCLUSIONS

SSc often presents an unfavourable disease course, mostly due to pulmonary involvement. While half of the deaths reported were due to lung involvement, only about half of the patients presenting typical findings on Rx develop end-stage lung involvement or death. It is of great importance to screen at baseline for ILD and PAH, following up annually, even while patients are asymptomatic. Risk factors for worsening of lung function were age > 60 years, disease duration < 3 years and diffuse cutaneous subset.

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