Research Article

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Pulmonary Hypertension in Early Systemic Sclerosis a Study of a Cohort of Patients in Bogota, Colombia

Luis Javier Cajas[1]*, Julia Recalde Reyes[2] and Javier AleFebdro Correa[2]

[1]Rheumatologist - Universidad Nacional de Colombia -Hospital Universitario Nacional HUNInterna, Colombia

[2]Medicine- Rheumatology Fellowship. Universidad Nacional de Colombia, Colombia

***Author for Correspondence:**
ljaviercs.77@hotmail.com

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Abstract

Objectives: Pulmonary hypertension (PH) is a significant cause of morbidity and mortality in patients with systemic sclerosis (SSc), presenting various etiologies. SSc manifests even before cutaneous involvement (early SSc) or, in some cases, does not develop SSc without scleroderma (ssSSc). Cases of PH have been reported even in early stages of the disease. This study aims to determine the prevalence of PH in these patients and to identify its causes and risk factors.

Methods: Data from a cohort of SSc patients in Bogotá, Colombia, were analyzed, excluding those with cutaneous sclerosis. Those meeting the ACR/EULAR criteria were considered as ssSSc, while those not meeting these criteria but meeting the VEDOSS criteria were considered as early SSc (eSSc). High probability of PH was considered when the pulmonary systolic pressure was greater than 39 mmHg or the peak tricuspid regurgitation velocity (PTRV) was >3.4 m/s, with a PASP between 33 and 39 mmHg or PTRV between 2.9 and 3.4 m/s, combined with two other suggestive findings of PH. PH was classified as type 2 if left ventricle ejection fraction <50%, coronary disease, or moderate to severe diastolic dysfunction; type 3 if extensive interstitial disease on tomography >20%, forced vital capacity (FVC) <70%, or DLCO<60%; type 4 if embolism-related abnormalities were detected on scintigraphy or tomography. Patients not meeting these criteria were classified as type 1 PH. We search for the proportion of patients with PH and risk factors associated.

Results: Out of a total of 353 patients, 71 (20%) had early SSc, and 51 (14.4%) had SSc without scleroderma. The prevalence of PH was 26%, with 25% in early SSc with intersticial lung disease (eSSc-ILD) and 27% in ssSSc. Seventy two percent and 50% were classified as group 1 in each category. Two patients were classified as group 2 and 3, but no patients with type 4 PH were found. There was no relationship found between gender, years of RP, digital ulcers, telangiectasias, or other clinical or antibody variables with the presence of PH, especially the presence of anti-centromere antibodies (p=0.5) and abnormalities in capillaroscopy (p=0.96), both in all PH groups and exclusively in type 1 group.

Conclusion: PH can occur or is highly probable in approximately a quarter of patients, in early stages of the disease or in the absence of cutaneous involvement, showing a variety of etiologies. No associated risk factors were identified.

Keywords: Pulmonary hypertension • Systemic sclerosis

Introduction

Early systemic sclerosis refers to the early stages of the disease, where prompt diagnosis is crucial for initiating appropriate treatment and preventing disease progression; it is characterized by three red flags: RP, puffy fingers, and antinuclear antibody positivity [1]. Early diagnosis and treatment are essential for improving patient outcomes, as SSc can progress to irreversible fibrosis and organ damage. The 2013 American College of Rheumatology (ACR)/European League

Against Rheumatism (EULAR) criteria have been helpful in classifying patients with systemic sclerosis (SSc), but they lack sensitivity for early stages of the disease [1], It has even been described that this domain can occur years after the diagnosis of the disease [2], however, not everyone will develop skin involvement, which is why it is difficult to differentiate ssSSc of eSSc. To address this, criteria for a very early diagnosis of SSc (VEDOSS) have been proposed by the EULAR Scleroderma Trial and Research group (EUSTAR). VEDOSS criteria include the anteriorly mentioned red flags such as RP, puffy fingers, and antinuclear antibody positivity, along with SSc-specific antibodies positivity and/or abnormal nailfold capillaroscopy [3]. Early diagnosis of SSc is important to detect subclinical internal organ involvement and initiate treatment at a potentially reversible stage [1]. In the literature, the terms very early SSc and early SSc have been often used interchangeably to indicate the preclinical phases of SSc with signs of RP, but not skin or internal organ involvement. These terms include very early SSc (veSSc), early SSc (EaSSc), preclinical systemic sclerosis (PreSSc), and undifferentiated connective tissue disease at risk for systemic sclerosis (UCTD-risk-SSc). However, veSSc and eSSc have distinct clinical meanings. To avoid confusion, we refer to veSSc as the stages prior to a definite diagnosis of SSc and to eSSc as the first phases of SSc with an already definite, but recent SSc diagnosis (<3 years) [4,5] or when it already has organic involvement, such as esophageal, being the earliest in most reports [6]. PH is one of the main causes of death in patients with SSc; especially those with diffuse cutaneous SSc. PH can also develop in early stages of SSc, even before the appearance of skin thickening or other signs of organ involvement. Therefore, regular screening and early detection of PH are crucial for patients even with eSSc [1]. PH occurs up to 25% of patients with SSc with symptoms and 12% in asymptomatic and is the leading cause of death in these patients. PH-SSc is a poor prognostic factor in SSc, with a median survival of 3 years after diagnosis [7]. Studies have reported early onset (within 5 years of SSc diagnosis since first non-Raynaud symptoms) of PAH in diffuse cutaneous systemic sclerosis (dcSSc) patients. Moreover, early onset of Systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is associated with more severe vascular disease than late onset SSc-PAH [8,9]. Wangkaew S, et al. [10]; studied in a cohort study; the incidence, predictors, and survival of pulmonary hypertension (PH) determined by echocardiography in Thai patients with early-onset systemic sclerosis (SS); they recruited 133 patients with SS of less than 3 years duration from the first non-RP symptom, and clinically and echocardiographically evaluated them at the beginning of the study and then annually. During the mean follow-up period of 4.2 years, 20 patients developed PH; all associated with interstitial lung disease (ILD) or left heart disease, with no cases of isolated PAH. The incidence rate of PH was 3.95 per 100 person-years. Predictive factors for PH were a higher NYHA functional class, the presence of telangiectasias, and a larger left atrial diameter. RP and higher oxygen saturation were protective factors. Survival after the diagnosis of PH at 1, 3, and 5 years was 88.9%, 82.3%, and 48.0%, respectively, indicating a poor prognosis. PH was the main cause of death in 83% of deceased cases. Data derived from the EUSTAR cohort demonstrated that patients who have SSc without scleroderma have a high rate of interstitial disease, approximately 40%; the identification of this manifestation is angular due to its association with mortality. This study could not demonstrate the association with pulmonary hypertension; however the data noted are exclusively from echocardiogram [11]. In summary, PH in early forms of systemic sclerosis has significant clinical significance due to its impact on prognosis, cardiovascular complications, and quality of life. Early detection and appropriate management of PH are essential for optimizing outcomes and improving the well-being of patients with SSc. This study aims to determine the prevalence of PH in these patients and to identify its causes and risk factors.

Methods

Patients: We retrospectively retrieved data on patients treated at the outpatient service of Rheumatology unit between 2017 and 2024. The medical records of patients diagnosed with systemic sclerosis were reviewed within the service's database. They were classified according to whether they met the ACR/EULAR classification criteria in 2013 as established disease if they presented skin thickening, otherwise as scleroderma sine scleroderma (ssSSc) if they did not. In case they did not meet the necessary score of the ACR/EULAR criteria, did not have cutaneous thickening, and met VEDOSS criteria, they were considered patients with early-stage disease, eSSc. Patients with other autoimmune pathologies, insufficient clinical data preventing disease stage classification, and insufficient data regarding pulmonary function and echocardiography were excluded.

Data collection and pulmonary hypertension classification: All patients should have the following data: Demographic data (age, sex, race), clinical data (puffy fingers, years of Raynaud, ulcers, telangiectasias, calcinosis, arthritis, dyspnea, reflux symptoms,) autoantibodies, data from echocardiogram (pulmonary artery systolic pressure (PSAP), tricuspid regurgitation velocity (PTRV), left ventricular ejection fraction

(LVEF), diastolic disfunction, atrial fibrillation), lung function tests (forced vital capacity (FVC) or corrected carbon monoxide diffusing capacity (DLCO), high resolution chest tomography. If lung scintigraphy or left cardiac catheterization data were available, they were also considered. High probability of PH was considered when the pulmonary systolic pressure was greater than 39 mmHg or the peak tricuspid regurgitation velocity (PTRV) was >3.4 m/s, with a PASP between 33 and 39 mmHg or PTRV between 2.9 and 3.4 m/s, combined with two other suggestive findings of PH. PH was classified as type 2 if left ventricle ejection fraction <50%, coronary disease, or moderate to severe diastolic dysfunction; type 3 if extensive interstitial disease on tomography >20%, forced vital capacity (FVC) <70%, or DLCO<60%, Chronic obstructive pulmonary disease (COPD) classified as moderate to severe or moderate to severe sleep apnea syndrome; type 4 if embolism-related abnormalities were detected on scintigraphy or tomography. Patients not meeting these criteria were classified as type 1 PH.

Objectives: The main objective was to determine the proportion of patients with pulmonary hypertension detected through echocardiography in patients with early forms of systemic sclerosis or established disease without cutaneous involvement. As secondary objectives, to determine the types of pulmonary hypertension in each group and the existence of differences in clinical features or characteristics between the eSSc or ssSSc patient groups with or without PH.

Statistical analysis: Qualitative variables are described as means with their standard deviations (SD) or medians with their interquartile range (IQR), depending on their normal or non-normal nature, respectively, and categorical variables with their relative and absolute frequencies. For the primary objective, the number of patients with a high probability of pulmonary hypertension is described in each group. For the secondary objectives, differences in characteristics were assessed using chi-square tests or logistic regression depending on the nature of the variable. A p-value of less than 0.05 was considered statistically significant. This study obtained approval from an ethics committee according to the legal requirements of the site where it was conducted. Patients were informed and provided signed consent for the use of their data and images.

Results

Data from 353 patients diagnosed with systemic sclerosis and sufficient data for their classification in the database were obtained, of these 71 patients with eSSc and 51 with ssSSc, for a total of 122 patients to be analyzed. The vast majority of these patients were women (96%), with an average age of 51 years and 9 years of onset of Raynaud's phenomenon. 38.5% of the patients reported dyspnea, with the most frequent symptom being associated with the gastrointestinal tract. The most frequent antibody was anti-centromere with 67%. The complete characteristics of the population are found in (**Table 1**). According to echocardiography findings, 26% of patients had a high probability of pulmonary hypertension, which was very similar between the groups, 25% in eSSc and 27% in ssSSc (p=0.79). Regarding the classification of the type of pulmonary hypertension that associated with lung disease represented 31% of the cases, 3 associated with extensive interstitial lung disease with significant alteration of lung function, 3 associated with COPD, and 4 due to sleep apnea syndrome. In eight patients (25%) of the cases, PH was associated with left heart disease, the majority due to significant diastolic dysfunction and one due to systolic dysfunction with reduced ejection fraction secondary to coronary artery disease. Two of the patients met criteria to classify them as both Group 2 and Group 3 PH. There were no patients with data of chronic thromboembolic disease as the cause of PH. The remaining 16 patients were therefore considered as having Group 1 PH, being the majority group with 43.7%. We found no differences between the probable causes of PH among the groups. The results are fully shown in (**Table 2**). In the analysis of possible differences between the groups of patients with eSSc and ssSSc and pulmonary hypertension with

Table 1: Clinical characteristics of patients.

Variable	Total N=122	Early SSc N=71	ssSSc N=51	p
Women	117 (96%)	67(94%)	50(98%)	0.13
Age in years (SD)	57(14.8%)	57 (14.9%)	57.8 (14.9)	0.73
Years of Raynaud (SD)	9 (7.8)	7.7 (6.7)	10.7 (9)	0.04
Puffy fingers (%)	67	38	93	<0.001
Ulcers (%)	14.8	10	21.5	0.07
Telangiectasias (50%)	50	23	92	<0.001
Calcinosis (%)	7.3	2.8	13.7	0.02
Arthritis (%)	46.2	50.7	40	0.24
Dyspnea (%)	38.5	35.2	43.1	0.37
Reflux symptoms (%)	60.8	51.4	74	0.01
Capillaroscopy (%)				
Normal	27.5	38.9	5.1	
Early	39.1	33.3	44.5	
Active	27.5	22.2	33.3	
Late	5.8	5.5	6	
Abnormal	40.9	30.9	54.9	0.008
Auto antibodies (%)				
Centromere	67.1	61.9	75.5	0.14
SCL-70	8.2	7	9.8	0.58
ANAS	24.5	32.3	13.7	0.01

ANAS: Antinuclear antibodies; **SD:** Standard deviation; **SSc:** Systemic sclerosis; **ssSSc:** sin scleroderma systemic sclerosis

Table 2: Proportion and types of pulmonary hypertension in each group of patients.

	Total N=32	Early SSc N=18	ssSSc N=14	p
Pulmonary hypertension (%)	26.2	25.3	27.4	0.79
PASP mmHg (SD)	48.3 (14.6)	52 (14.3)	43.7(14)	0.14
Type 3 PH (%)	10 (31.2)	4 (22.2)	6 (42.8)	0.21
Type 2 PH (%)	8 (25)	5 (27.2)	3 (21)	0.78
Type 1 PH (%)	16 (43.7)	8 (44.4)	8 (57.1)	0.19

PASP: Pulmonary artery systolic pressure; **PH:** Pulmonary hypertension; **SSc:** Systemic sclerosis; **ssSSc:** sin scleroderma systemic sclerosis

those who did not have echocardiographic findings of pulmonary hypertension, no disparities were found in both clinical and paraclinical features, especially anti-centromere antibody (p=0.53), digital ulcers (0.85), or capillaroscopic alterations (p=0.9).

Discussion

The prevalence of pulmonary hypertension in our study was 26%; 25% affecting patients with early forms of systemic sclerosis and 27% in forms without skin involvement with a large majority of patients classified as group 1; In the study by Krikeerati, T et al. [8] , a cross-sectional study conducted in 409 adults with systemic sclerosis, patients received a follow-up of about two years and a definition of early pulmonary hypertension was obtained when the onset of pulmonary hypertension was within the first five years of the onset of the disease, 3409 patients were analyzed yearly and an incidence of 0.7 per 100 people year was found, (IC95% 0.5-1.1) [6]; The authors point out that early pulmonary hypertension was frequently associated (69.2%) with diffuse cutaneous forms of the disease and most of the patients were classified as pulmonary hypertension related to interstitial lung disease (69.2%) they also performed a logistic regression analysis and early pulmonary hypertension according to their defined criteria was associated with a WHO 2 functional class, cardiomegaly, a maximum velocity of the tricuspid regurgitation jet greater than 2.8 meters per second, also found a negative association of early pulmonary hypertension with gastrointestinal involvement with a calculated OR 0.08, (IC95% 0.01-0.56); It is important to highlight the relevant differences between the study by Krikeerati, T et al. [8] and ours in relation to the fact that the frequency of the phenomenon was not established in patients who met the operational definition of early or very early systemic sclerosis; however, it can be intuited that diagnosis within the first five years of the disease means that this study probably includes a significant proportion of patients with the early form of systemic sclerosis; in the search of the literature, reports and information regarding this problem in patients with early and very early systemic sclerosis are scarce and the aforementioned study is established as an important point of comparison, it is likely that the differences found in risk factors are related to an incipient and important vasculopathy in patients with very early systemic sclerosis and therefore the findings of differences in risk factors can be intuited. The study by J Sanchez et al [12] aimed to analyze whether patients with very early systemic sclerosis (SSc) develop evidence of pulmonary arterial hypertension (PAH) in an extended longitudinal study, 45 patients with very early SSc, defined by Raynaud's phenomenon (RP) and at least one of the following characteristics: nail bed capillaroscopy with SSc pattern, puffy fingers, SSc-specific autoantibodies. Screening tests for PAH, such as echocardiography, pulmonary function test, brain natriuretic peptide precursor (pro-BNP) levels, and, in cases of suspected PAH, right cardiac catheterization (RHC) were performed; PAH was not suspected in any of the patients, and none had to undergo RHC during follow-up. No difference from baseline or evidence of PAH was found by echocardiography. An isolated reduction in DLCO was observed in this very early SSc cohort that occurs in the early stages of the disease and progresses slightly at follow-up. The authors conclude that they found no evidence that PAH develops in people with very early SSc during follow-up. However, these patients may be at risk of developing PAH later in life. The article presents an observational study that evaluates the incidence and prognosis of PAH in patients with very early SSc. The study has some strength, such as the use of strict criteria to define very early SSc, longitudinal follow-up of patients, and the use of several PAH screening tests. However, it also has some limitations, such as small sample size, lack of a control group, variability in follow-up time, and possible underestimation of PAH by echocardiography. Compared to our study, that of J Sánchez et al. [12] has similar demographic characteristics in both studies, the majority of patients were women. In our study, 96% were women with a mean age at presentation of 57 years. In the study of J Sánchez et al., patients with very early SSc were defined by Raynaud's phenomenon (RP) and at least one of the following

characteristics: nail bed capillaroscopy with SSc pattern, swollen fingers, SSc-specific autoantibodies. In our study the variables that were most frequently found in this group of patients without skin involvement were a longer time of onset of Raynaud's phenomenon, puffy fingers, telangiectasias and symptoms of gastroesophageal reflux, especially for the SSc group. Both studies provide valuable information about systemic sclerosis in its early stages; It is interesting to find that although both studies analyzed demographically similar populations, no congruences were found in the frequency of occurrence of pulmonary hypertension, it is possible that this difference is based on additional factors that were not controlled in both studies, for example, the absence of right cardiac catheterization and the problem of sample size in the study of J Sánchez et al. It is also possible that there are differences in additional inflammatory biomarkers that are directly related to the magnitude of vascular damage and inflammation in these groups, which in theory, can support the differences between the frequency of pulmonary arterial hypertension between one study and another, more studies will be needed in this regard that eventually include the measurement of serum of these biomarkers. It is important to mention the role of echocardiography in the selection and screening of patients who should be taken for invasive study for the diagnosis of pulmonary hypertension; there are studies that have used echocardiography as a diagnostic method for pulmonary hypertension associated with systemic sclerosis: C Nagel et al [13] analyzed the sensitivity and specificity of stress Doppler echocardiography (SDE) in detecting pulmonary hypertension (PH) in patients with systemic sclerosis (SSc). The study included 76 patients with SSc, and SDE was performed at rest and during exercise. The results showed that SDE markedly improved sensitivity compared to echocardiography at rest alone. The sensitivity of echocardiography at rest was 72.7 % (95 % confidence interval (CI) 0.52-0.88), and specificity was 88.2 % (95 % CI 0.78-0.95). When a cutoff value for PASP was more than 45 mm Hg during low-dose exercise, SDE missed PH diagnosis in one of the 22 patients with PH and improved sensitivity to 95.2 % (95 % CI 0.81-1.0) but reduced specificity to 84.9 % (95 % CI 0.74-0.93). Reduction of specificity was partly due to concomitant left heart disease. The results of this prospective cross-sectional study using RHC as gold standard in all patients showed that SDE markedly improved sensitivity in detecting manifest PH to 95.2 % compared with 72.7 % using echocardiography at rest only; I Murata et al. [14] evaluated the prevalence and cause of pulmonary hypertension (PH) in 135 Japanese patients with systemic sclerosis. Doppler echocardiography was used to estimate pulmonary artery systolic pressure, and PH was diagnosed in 28 patients. The study found that PH in patients with proximal scleroderma was mainly due to pulmonary fibrosis, while an overlap of systemic lupus erythematosus (SLE) or polymyositis predisposed patients to PH due to arteriopathy. Wangkaew et al [10] investigated the incidence, predictors, and survival of pulmonary hypertension (PH) determined by Doppler echocardiography in Thai patients with early SSc; they used an inception cohort of patients with early SSc seen at the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital. All patients were assessed for clinical data and underwent Doppler echocardiography at the study entry and then annually. A total of 133 patients (81 female, 106 DcSSc, 103 anti-topoisomerase I-positive) with mean disease duration of 11.9 months were recruited. During the mean observational period of 4.2 years, 14 patients developed PH concurrent with ILD and 6 with left heart disease. The incidence rate for the development of PH was 3.95 per 100 person years. The multivariate Cox regression analysis indicated higher NYHA class (HR 6.90, 95% CI 2.28–20.94, $p = 0.001$), telangiectasia (HR 4.18, 95% CI 1.25–13.92, $p = 0.020$), and enlarged LA diameter (HR 1.16, 95% CI 1.05–1.28, $p = 0.005$) as predictors of PH. Raynaud's phenomenon (HR 0.22, 95% CI 0.06–0.84, $p = 0.026$) and high oxygen saturation (HR 0.80, 95% CI 0.65–0.99, $p = 0.047$) were protective factors. The survival rate after PH diagnosis at 1, 3, and 5 years were 88.9%, 82.3%, and 48.0%, respectively; In this regard, we can mention that compared to our study, that of Wangkaew et al. [10] included 133 patients, while our study included 353 patients. A larger sample size can provide greater accuracy and generalization of results; 2) 15% of patients in the Wangkaew et al study developed PH, while in our study, the prevalence was 26%. This could indicate a higher prevalence of PH in the population of the second study, or it could be the result of differences in methodology or patient characteristics; 3): Early Forms of Systemic Sclerosis (SSc): In the study of Wangkaew et al, all patients had early-onset SSc. In our study, 25% of patients with PH had early forms of SSc. This could suggest that PH is a common complication in the early stages of SSc; 4) Forms of SSc without Skin Involvement: our study reported that 27% of patients with PH had forms of SSc without skin involvement. The study of Wangkaew et al did not provide information on this aspect; 5) Patient Classification: In the study of Wangkaew et al, all patients with PH had interstitial lung disease (ILD) or left heart disease (LHD), and no cases of isolated arterial PH (group 1) were observed. In our study, the majority of patients with PH (72% in early forms of SSc and 50% in forms without skin involvement) were classified in group 1. This could

indicate differences in clinical characteristics or classification methodology between the two studies. In summary, although both studies provide valuable information about PH in patients with SSc, they also highlight the variability in the prevalence, clinical features, and outcomes of PH in different SSc patient populations. This underscores the need for further research in this field. The findings emphasize the importance of periodic screening for PH in patients with SSc, even in early stages or subtle forms of the disease, given the prognostic implications of this complication. Guidelines recommend annual screening through echocardiography in all asymptomatic patients [15].

Conclusion

In conclusion, these findings contribute to the evidence on the early development of PH in SSc and the need for effective strategies for timely detection. Discussions on the study methodology and comparisons with the literature can enhance the interpretation of these preliminary results.

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