# Survival in patients with pulmonary arterial hypertension associated with systemic sclerosis from a Swedish single centre: prognosis still poor and prediction difficult

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# Survival in patients with pulmonary arterial hypertension associated with systemic sclerosis from a Swedish single centre - prognosis still poor and prediction difficult.

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ABSTRACT

Objectives: To describe the survival rate in a cohort of systemic sclerosis (SSc) patients with pulmonary arterial hypertension (SSc-PAH) and to evaluate possible predictors for SSc-PAH in a cohort of SSc patients.

Methods: 30 patients with SSc-PAH and 150 SSc patients without PAH were included. Survival and survival on therapy were calculated. Clinical features at baseline were correlated to the risk for development of PAH during follow-up.

Results: The one, two, three and four year survival rates were 86, 59, 39 and 22% respectively from diagnosis of PAH. Hazard ratio for total mortality (95% CI) in the SSc-PAH group was 3.2 (1.8-5.7) compared to SSc without PAH ($p<0.001$). Risk factors at baseline for the development of PAH were limited skin involvement, low diffusing capacity of the lung for carbon monoxide ($DL_{CO}$), high N-terminal pro brain natriuretic peptide (NTProBNP), increased estimated systolic pulmonary arterial pressure (ESPAP), and the presence of teleangiectases. Severe peripheral vascular disease requiring iloprost treatment during follow-up was associated with an 8-fold increased risk of PAH.

Conclusion: Despite modern treatment and yearly screening by echocardiography, the survival in SSc-PAH is still low in our cohort. The identified risk factors should be assessed to select patients eligible for right heart catheterization to make an earlier diagnosis.

## INTRODUCTION

Pulmonary complications have been recognised as the leading cause of death in systemic sclerosis (SSc, scleroderma) [1, 2]. Both pulmonary fibrosis and pulmonary arterial hypertension (PAH) may be lethal although mild forms also exist. The identification of pulmonary fibrosis, which often develops very early in disease, has been facilitated by the wide use of high resolution computed tomography (HRCT) of the lungs, whereas it's still debated which patients might benefit the most from any possible therapy. On the other hand PAH, which is often recognised later in disease, is more difficult to diagnose given the need for invasive measurement by right heart catheterization (RHC). In addition, also SSc patients without pulmonary involvement have a reduced exercise capacity [3].

SSc complicated by PAH (SSc-PAH) is classified as associated with connective tissue disease (A-PAH, 1.4.1) in the updated clinical classification of pulmonary hypertension of Dana Point 2008 [4, 5]. Treatment with prostanoids, endothelin receptor antagonists (ERA) and phosphodiesterase type-5 inhibitors (PDE-I) as well as guidelines for the treatment has been available for several years. Since the introduction of modern treatment there have been reports of improved survival in SSc-PAH especially from highly specialised centres that also included patients into the pivotal trials. Williams *et al* reported one and two year survival rates of 81 and 71% in SSc-PAH patients diagnosed 2002 or later [6]. The follow-up of the ItinérAIR-Sclérodermie study showed a 3-year survival of 56% in SSc-PAH patients as compared to 91% in the whole SSc cohort [7]. Mathai *et al* highlighted the impact of concurrent pulmonary fibrosis in SSc-PAH by publishing one, two and three year survival rates of 87, 79 and 64% in the absence of pulmonary fibrosis and 82, 46 and 39% in the presence of concurrent pulmonary fibrosis [8].

A possible way of improving the survival would be by earlier therapeutic intervention, which would require better screening tools or better predictors for development of SSc-PAH or a

lower threshold for conducting RHC. A reduction of nailfold capillary density has been observed in PAH patients but it is unknown if this actually precedes or accompanies the development of PAH [9]. The presence of anti-centromere antibodies (ACA) [10], ischemic ulcers of the fingers [11], low diffusing capacity of the lung for carbon monoxide ($DL_{CO}$) [12, 13], high N-teminal pro-brain natriuretic peptide (NTProBNP) [12, 14], and increased numbers of teleangiectases [15] have been associated with the development of SSc-PAH whereas cyclic treatment with iloprost infusion has been reported to be preventive in a preliminary study [16].

The objectives of this study were to describe the survival rate in our cohort of SSc-PAH patients and to evaluate possible predictors for SSc-PAH in a cohort of SSc patients.

## METHODS

The study comprised 30 patients diagnosed as SSc-PAH during the time period of July 1st 2002 to September 30th 2009. The first time point was selected because it coincides with the time when we entered into a deeper collaboration with the Department of Cardiology which resulted in an improved screening program and a subsequent use of RHC when needed. The patients underwent yearly echocardiography to measure estimated systolic pulmonary arterial pressure (ESPAP) and were considered for RHC if ESPAP > 36 mmHg unless explained by left sided heart disease. All patients in this study fulfilled the ACR criteria for SSc [17]. For each of these 30 SSc-PAH patients 5 controls without PAH were identified from the total SSc cohort. Cases and controls were matched by year of first examination in our department. The disease was classified as diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) according to the extent of skin involvement [18]. Skin involvement was determined by the modified Rodnan skin score (mRss) [19]. The disease onset was defined as the first non

Raynaud's manifestation. The 6 minutes walking test (6MWT) was performed in accordance with the American Thoracic Society guidelines [20].

Pulmonary function tests were done on all patients using a body plethysmograph (Erich Jaeger GmbH, Hoechberg, Germany). ESPAP was calculated by the modified Bernoulli equation using the peak velocity of the jet of the tricuspid regurgitation registered on the echocardiography whenever possible.

Nailfold capillary microscopy was performed by one of the co-authors (MW) using 20 x magnification [21].

Prediction of PAH by pulmonary function tests, mRss, nailfold capillary density, serum-NTProBNP, ESPAP, ACA , teleangiectases, ulcers and pitting scars at baseline was calculated as well as association between PAH and the ever occurrence of teleangiectases, ulcers and iloprost treatment.

All patients with PAH were examined by HRCT. Patients with severe interstitial lung disease were excluded whereas patients with none or mild interstitial lung disease disproportional to PAH-symtoms and signs were included.

RHC was performed by experienced clinicians according to standard techniques, using a Swan-Ganz catheter. Mean right atrial pressure, systolic, diastolic, and mean pulmonary arterial pressure (mPAP), as well as pulmonary capillary wedge pressure (PCWP) were measured. Cardiac output (CO) was measured using the thermodilution method and the cardiac index (CI) was calculated as CO/body surface area ($L/min/m^2$). Pulmonary vascular resistance (PVR) was calculated as (mPAP-PCWP)/CO. The Venice criteria for diagnosis were used when this study was performed and based on current guidelines PAH was defined as mPAP ≥25mm Hg at rest or ≥30mm Hg during exercise, with PCWP ≤15mm Hg and PVR >3WU [22].

Statistics

Differences between groups were analysed using the Mann-Whitney U test or the $\chi^2$ test. Results are presented as mean (SD) or odds ratio (OR) with 95% CI. Survival was estimated with the Kaplan-Meier method, differences in estimated survival was analysed using the Log Rank test, and hazard ratio was estimated with a proportional hazards model.

## RESULTS

### Treatment

After diagnosis of PAH the patients' initial treatment was oral single therapy in 24 cases (23 ERA, 1 PDE-I), oral combination therapy in 5 cases (ERA and PDE-I) and in one case the therapy wasn't started until after the last date of follow-up because of a need for further examinations. At the end of follow-up (September 30$^{th}$ 2009 or death of the patient) 13 patients were still on oral single therapy (12 ERA, 1 PDE-I), 12 on oral combination therapy, one on combination of ERA and prostanoid (epoprostenol iv), and 3 on combination ERA, PDE-I and prostanoid (one each of iloprost inhalation, epoprostenol iv and remodulin iv). Initial haemodynamic findings were worse in patients who started with combination therapy compared to those starting on mono therapy with lower mean (± SD) CI (2.0 ± 0.4 vs 2.8 ± 0.9 L/min/m$^2$; $p<0.05$) and higher mean (± SD) PVR (11.5 ± 3.9 vs 7.9 ± 4.0 WU; $p<0.05$).

### Survival in patients with SSc-PAH

The patients' clinical characteristics at diagnosis of PAH are described in table 1. Only examinations from the same week as RHC are included.

#### *Survival and survival on drug*

The one, two, three and four year survival rates were 86, 59, 39 and 22% respectively (figure 1, graph A). Median survival was 2.5 years. Corresponding survival on oral therapy, *ie* time to

death or transition into prostanoid treatment, were 78, 48, 31 and 20%, with a median of 2.0 years. Finally, corresponding survival on single oral therapy, *ie* time to death, transition into prostanoid therapy or a combination of ERA and PDE-I, were 54, 19, 12 and 8% (figure 1, graph B) with a median of 1.3 years.

Differences in survival between different WHO-classes were not significant due to the small numbers.

**Survival in patients with SSc**

Counting from diagnosis of SSc, the 5, 10 and 15 year survival rates in the 30 patients with PAH were 67, 43 and 24%, and 87, 72 and 70% in the 150 patients without PAH (figure 2). Median survival from SSc diagnosis was >20 years in patients without PAH and 8.0 years in patients who developed PAH. Hazard ratio for total mortality (95% CI) in the SSc-PAH group was 3.2 (1.8-5.7) compared to SSc without PAH ($p<0.001$).

Median time from SSc diagnosis to diagnosis of PAH was 3.2 years (figure 3, graph A). Two different groups were identified, those who had PAH already at referral (n=11), and those who developed PAH during follow-up (n=19). No difference in survival between these two groups was noticed illustrating no benefit of already having SSc and belonging to a screening cohort. None of the features described in table 1 differed between the 11 patients with PAH at referral and the 19 patients who were later diagnosed with PAH illustrating similar disease severity.

Median time from first non-Raynaud's manifestation to diagnosis of PAH was 9.6 years (figure 3, graph B) and the graph illustrates that PAH may occur at any time during the disease process, which is further illustrated by the median time from start of Raynaud's phenomenon to diagnosis of PAH which was 13.1 years (figure 3, graph C).

**Prediction of PAH in SSc patients**

Pulmonary functions VC and $DL_{CO}$ at first visit were associated with PAH, but only $DL_{CO}$ could predict PAH. Both NTProBNP and ESPAP at first visit were predictive of PAH. The mRss or capillary density at first visit could not predict PAH but the patients who already had PAH at first examination indeed had lower capillary density than patients who didn't develop PAH (table 2).

Although odds ratio (OR) for PAH in ACA positive patients was 2.0, which was not significant whereas patients with the lcSSc phenotype were more inclined to develop PAH. The presence of teleangiectases at the first visit was associated with an almost three fold increased risk of PAH.

Less severe vascular manifestations such as presence of one or many ischemic ulcers of the fingers or one or many pitting scars resulted in a two fold increased risk of PAH which wasn't significant, whereas severe vascular disease requiring iv iloprost treatment had an OR of 8.3 for PAH (table 3).

DISCUSSION

This paper illustrates the severe prognosis for patients affected by SSc-PAH in a Swedsh single centre. Despite modern treatment with prostaniods, ERA and PDE-I the median survival is less than 3 years after diagnosis. The survival was much worse than in the study of Williams *et al* which only included patients with 6MWT > 150 m and total lung capacity > 70p%, but also slightly worse than the ItinérAIR-Sclérodermie study whose composition is likely more similar to ours [6, 7].

Patients who started on combination therapy without a period on mono therapy were more severely ill with lower CI and higher PVR. It is however difficult to evaluate these patients separately since PDE-I were not approved in the beginning of this study and an early start of

combination therapy was introduced in the end of the study when we had learned how rapidly some patients progressed.

It is well known that PAH associated with connective tissue diseases has a worse prognosis than idiopathic PAH. After 2 years from diagnosis less than 20% of our patients manage on oral single therapy illustrating that the pivotal trials, which mostly included patients with idiopathic PAH, only told us about short term outcome, whereas our study shows that continuous single therapy is an option only in few cases with SSc-PAH.

There is a striking difference in survival from diagnosis of SSc between patients with or without PAH and already from the diagnosis of SSc, up to 20 years later, death rates are 3.2 times as high in the patients who also have or develop SSc-PAH as compared to SSc patients without PAH. In addition, this is likely an underestimation, since some patients classified as not suffering from SSc-PAH probably had PAH which wasn't diagnosed during the years when the collaboration with the Department of Cardiology was less developed in our centre and the patients were not examined by RHC.

The graphs showing time from Raynaud's phenomenon, time from first non-Raynaud's manifestation and time from SSc diagnosis to PAH-diagnosis all illustrate that PAH may occur at any time during the disease and a constant vigilance is recommended once the SSc diagnosis has been established. To employ a screening program during this lengthy time period it needs to be simple. Today, echocardiography is recommended as screening tool, but there are several studies pointing out the high frequency of SSc patients with elevated ESPAP, both as a result of diastolic dysfunction and interstitial lung disease, and also the risk of both over and under estimation of the true pulmonary artery pressure [14, 23].

The surprising fact that neither PAH severity nor survival were better in the cohort yearly screened than in the patients with PAH at admittance implies that our screening tools either

must be more strongly applied or need to be improved and that the threshold for RHC should be lower.

To further improve the prediction we evaluated several possible risk factors for the development of PAH. Low $DL_{CO}$, high NTProBNP, high ESPAP, and the lcSSc subset at baseline were all associated with the subsequent development of PAH which makes it likely to improve the selection of patients with a greater need for either a tight screening by echocardiography or a lower threshold for examination by RHC. The goal of such screening or examination should be an earlier identification of PAH, earlier initiation of therapy and an improved survival. Another possible means of improving the survival could be an earlier identification of patients in need of more complicated therapy, either oral combination therapy or prostanoid therapy alone or in combination with ERA and/or PDE-I, a so called goal-oriented therapy [24]. In fact, the poor prognosis in our patients could be explained by the lack of treatment goals as only 10% improved in WHO-class despite a mean improvement in PVR of 1.4WU. Furthermore, 5 out of the 30 PAH-patients were older than 75 years at PAH diagnosis and were not eligible for treatment with prostanoid therapy.

Although its' underlying mechanisms are unclear, teleangiectases at baseline and during follow-up were a risk factor for PAH. A semi quantitative scoring as in the resent study by Shah *et al* [15] is possibly more predictive and seems very feasible from a clinical perspective.

From the point of pathogenesis it would be logical to evaluate signs of vascular damage. Both ulcers and pitting scars had an odds ratio above 2 ($p=0.17$ and $p=0.066$ respectively at the first visit). However, significance was not reached since our cohort contained too few patients and was thus likely underpowered. Both ulcers and pitting scars are however very common in SSc and were registered as dichotomous variables which are likely to include also less severe disease. We were thus hampered to distinguish between patients with one single ulcer or

pitting scar and those with recurrent or multiple ones. However, the need for iloprost treatment, a surrogate marker for severe vascular disease with many or recurrent ulcers, was associated with an 8-fold increased risk of developing PAH. The patients requiring iloprost treatment illustrate that severe peripheral vascular disease is associated with the development of vascular disease in the pulmonary circulation. We also noted an association between capillary density and PAH, but only when comparing patients who already had PAH with those who didn't develop PAH. It was thus not a predictor but rather an accompanying feature.

In conclusion, this study shows that the survival in SSc-PAH is still low in our cohort, despite modern treatment and yearly screening by echocardiography. The identified risk factors $DL_{CO}$, NTProBNP, ESPAP, the lcSSc subset, and the presence of teleangiectases at baseline should be assessed to select patients eligible for right heart catheterization to make an earlier diagnosis.

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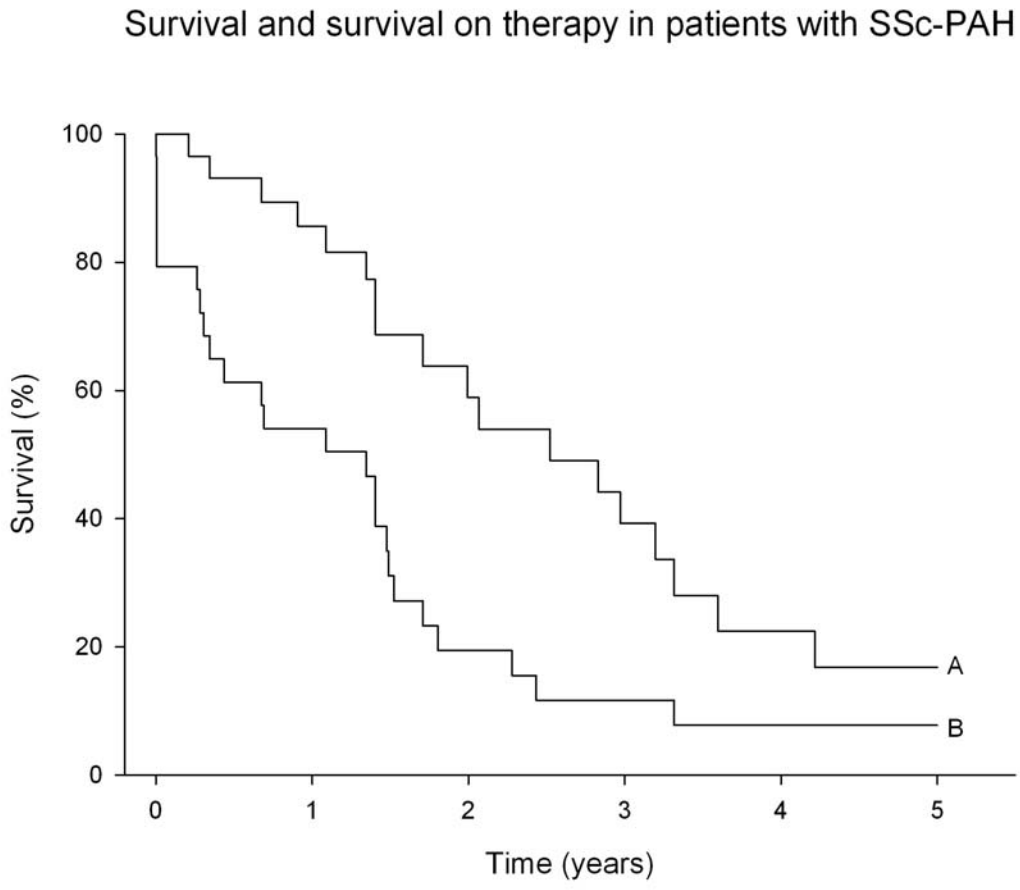
LEGENDS TO FIGURES

FIGURE 1

Title: Survival and survival on therapy in patients with SSc-PAH

Legend: Time from diagnosis of PAH by right heart catheterization to (A) death (illustrating survival); (B) death or transition into prostanoid or oral combination treatment (illustrating survival on single oral therapy).

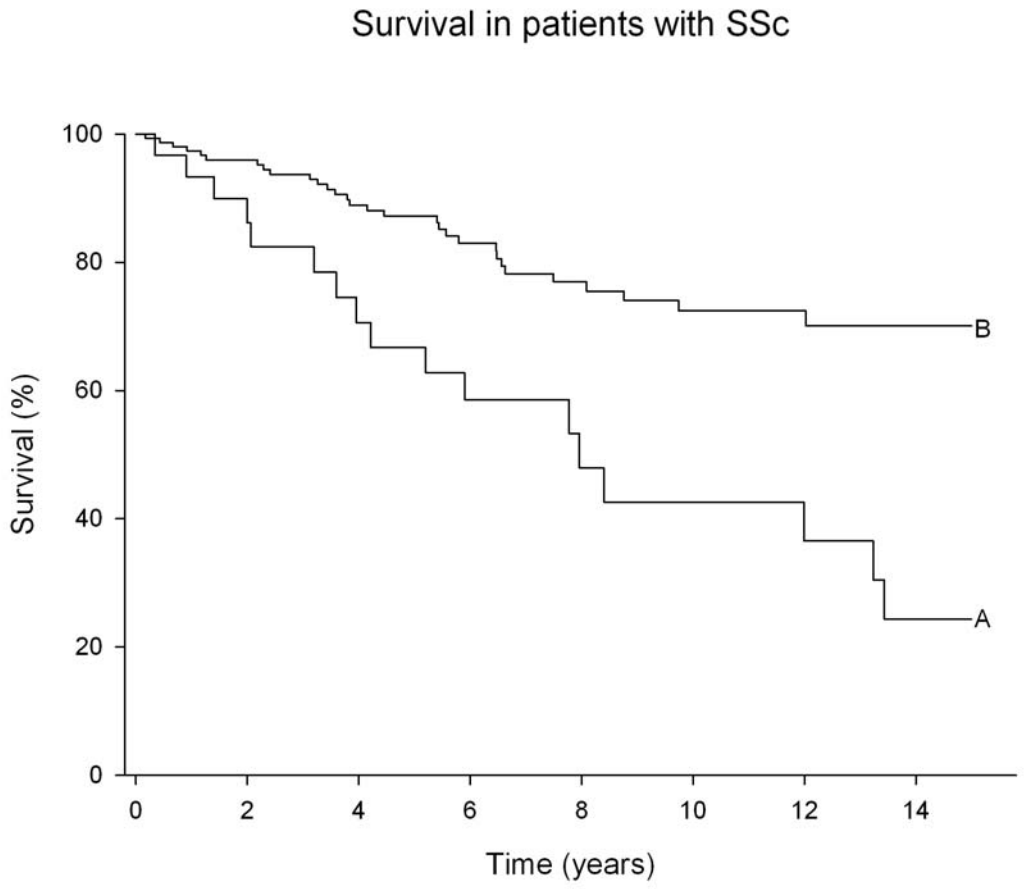



Time from diagnosis of PAH by right heart catheterization to (A) death;
(B) death or transition into prostanoid or oral combination treatment

FIGURE 2

Title: Survival in patients with SSc

Legend: Time from diagnosis of SSc to death subdivided by patients with (A) or without (B) development of PAH.

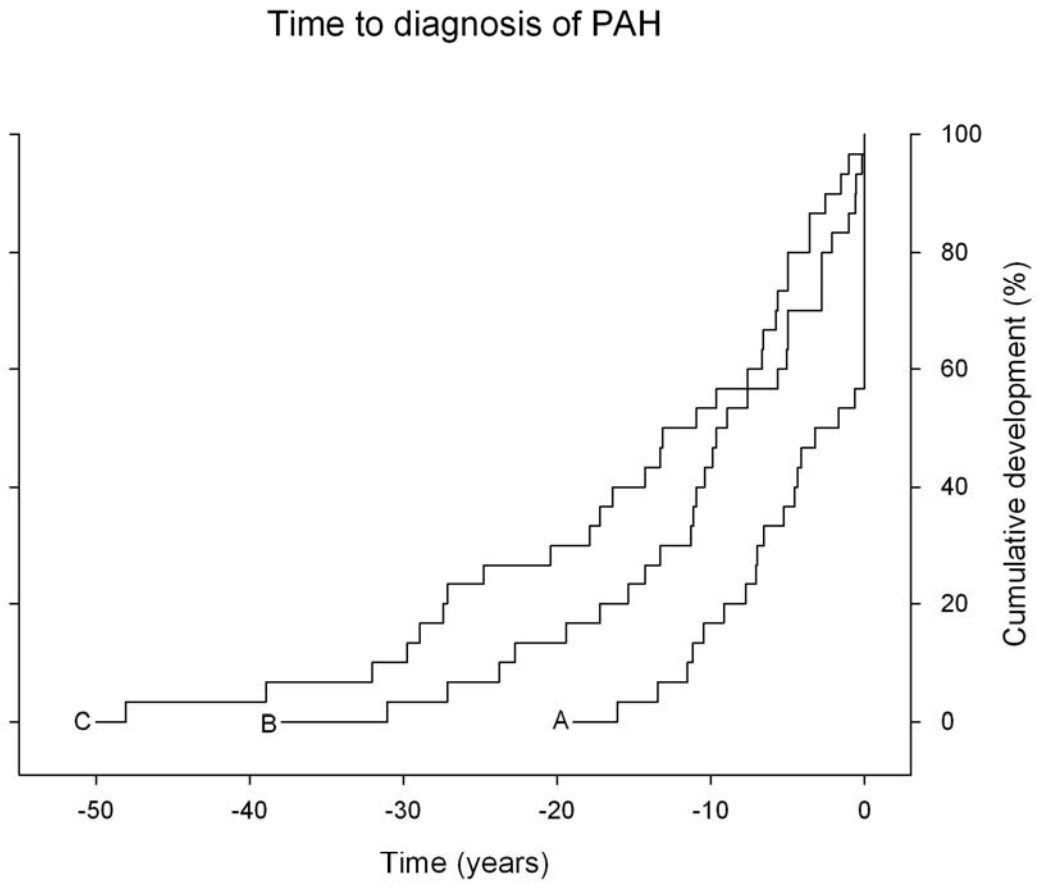



Time from diagnosis of SSc to death subdivided by patients with (A) or without (B) development of PAH

FIGURE 3

Title: Time to diagnosis of PAH

Legend: Time from (A) diagnosis of SSc; (B) first non-Raynaud's manifestation; (C) start of Raynaud's phenomenon, to diagnosis of PAH.




Time from (A) diagnosis of SSc;
(B) first non-Raynaud's manifestation;
(C) start of Raynaud's phenomenon
to diagnosis of PAH

TABLES

Table 1

*Clinical characteristics of 30 SSc-PAH patients at diagnosis of PAH either at first visit or at follow-up.*

| PAH diagnosed | at first visit | during follow-up |
|---|---|---|
| WHO-FC (I / II / III / IV) | 0/4/3/4 | 0/3/13/3 |
| | Mean (SD) | |
| 6MWT (m,) | 219 (201) | 262 (138) |
| NTProBNP (ng/L) | 3140 (2786) | 2447 (1839) |
| ESPAP (mmHg) | 69 (11) | 63 (17) |
| VC (p%) | 73 (19) | 73 (22) |
| $DL_{CO}$ (p%) | 33 (13) | 41 (10) |
| mPAP (mmHg) | 41 (6.8) | 44 (13) |
| TPG (mmHg) | 33 (7.9) | 37 (12) |
| PCWP (mmHg) | 7.9 (5.0) | 7.1 (5.6) |
| RAP (mmHg) | 7.0 (6.3) | 7.1 (6.5) |
| CO (L/min) | 4.9 (1.7) | 4.5 (1.3) |
| CI ($L/min/m^2$) | 2.7 (0.8) | 2.7 (0.9) |
| PVR (WU) | 7.3 (2.3) | 8.9 (4.9) |

WHO-FC: WHO-functional class; 6MWT: 6 minutes walking test; NTProBNP: N-terminal pro-brain natriuretic peptide: ESPAP: estimated systolic pulmonary arterial pressure; VC: vital capacity; p%: % of predicted; $DL_{CO}$: diffusing capacity of the lung for carbon monoxide; mPAP: mean pulmonary arterial pressure; TPG: transpulmonary gradient; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; WU: Woods Units.

*Table 2. Comparison between data from first visit of SSc patients with PAH at first visit, at subsequent visit, or without PAH.*

| | SSc without PAH | SSc-PAH at first visit | | SSc-PAH during follow-up | |
|---|---|---|---|---|---|
| n | 150 | 11 | | 19 | |
| | | Mean (SD) | p (vs patients without PAH) | | |
| Age, first non-Raynaud's symptom (yrs) | 50 (14) | 59 (10) | 0.018 | 47 (13) | 0.35 |
| Duration of symptoms at diagnosis (yrs) | 5.6 (7.9) | 3.6 (2.4) | 0.81 | 8.3 (8.0) | 0.054 |
| Age at diagnosis (yrs) | 56 (13) | 63 (12) | 0.055 | 55 (12) | 0.99 |
| VC (p%) | 89 (18) | 69 (19) | 0.015 | 84 (20) | 0.29 |
| $DL_{CO}$ (p%) | 70 (21) | 35 (12) | <0.001 | 53 (16) | <0.001 |
| mRss | 10 (9.6) | 8.1 (7.8) | 0.42 | 8.1 (6.2) | 0.54 |
| Capillary density (n/mm) | 4.8 (1.2) | 3.9 (1.2) | 0.046 | 4.6 (1.2) | 0.67 |
| NTProBNP (ng/L) | 696 (4149) | 2574 (2487) | <0.001 | 1859 (3785) | <0.001 |
| ESPAP (mmHg) | 29 (7.6) | 66 (15) | <0.001 | 42 (18) | 0.001 |

SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; VC: vital capacity; p%: % of predicted; $DL_{CO}$: diffusing capacity of the lung for carbon monoxide ; mRss: modified Rodnan skin score; NTProBNP: N-terminal pro brain natriuretic peptide: ESPAP: estimated systolic pulmonary arterial pressure.

*Table 3. Associations between clinical manifestations registered during follow up and PAH.*

| | SSc-PAH | SSc without PAH | OR (95% CI) | p |
|---|---|---|---|---|
| n | 30 | 150 | | |
| women / men | 24 / 6 | 114 / 36 | 1.3 (0.48-3.3) | 0.81 |
| lcSSc / dcSSc | 29 / 1 | 115 / 35 | 8.8 (1.2-66) | 0.011 |
| anti-centromere antibodies (yes / no) | 15 / 15 | 50 / 98 | 2.0 (0.89-4.3) | 0.10 |
| Teleangiectases at first visit (yes / no) | 18 / 10 | 57 / 93 | 2.9 (1.3-6.8) | 0.012 |
| Teleangiectases ever (yes / no) | 23 / 5 | 77 / 73 | 4.4 (1.6-12) | 0.003 |
| Ulcers at first visit (yes / no) | 5 / 20 | 15 / 135 | 2.2 (0.74-6.9) | 0.17 |
| Ulcers ever (yes / no) | 9 / 16 | 30 / 120 | 2.2 (0.91-5.6) | 0.12 |
| Pitting scars at first visit (yes / no) | 12 / 13 | 43 / 106 | 2.3 (0.96-5.4) | 0.066 |
| Pitting scars ever (yes / no) | 15 / 10 | 58 / 91 | 2.4 (0.99-5.6) | 0.078 |
| Iloprost treatment ever (yes / no) | 9 / 17 | 9 / 141 | 8.3 (2.9-24) | <0.001 |

SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; OR: odds ratio; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis.