

# Poor survival in patients with scleroderma and pulmonary hypertension due to heart failure with preserved ejection fraction

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## Abstract

Pulmonary hypertension due to heart failure with preserved ejection fraction (PH-HFpEF) has been poorly studied in patients with systemic sclerosis (SSc). We sought to compare clinical characteristics and survival of SSc patients with PH-HFpEF (SSc-PH-HFpEF) versus pulmonary arterial hypertension (SSc-PAH). We hypothesized that patients with SSc-PH-HFpEF have a similar poor overall prognosis compared with patients with SSc-PAH when matched for total right ventricular load. The analysis included 117 patients with SSc-PH (93 with SSc-PAH versus 24 with SSc-PH-HFpEF) enrolled prospectively in the Johns Hopkins PH Registry. We examined baseline demographics and hemodynamics at diagnostic right heart catheterization (RHC), two-dimensional echocardiographic characteristics, six-minute walking distance (6MWD), treatment modalities, and laboratory values (serum NT-proBNP, creatinine, uric acid, and sodium), and assessed survival. Demographics and clinical features were similar between the two groups. Baseline RHC showed significantly higher pulmonary and right heart pressures in the SSc-PH-HFpEF compared with the SSc-PAH group. Trans-pulmonary gradient (TPG), however, was equally elevated without significant difference between the groups. SSc-PH-HFpEF patients had left atrial enlargement on echocardiography compared with SSc-PAH patients. No significant differences were found between groups for 6MWD, NT-proBNP, and other laboratory values. Although overall median survival time was 4.6 years with no difference in mortality rate between the two groups (SSc-PH-HFpEF versus SSc-PAH: 75% versus 59%;  $P = 0.26$ ), patients with SSc-PH-HFpEF had a twofold increased risk of death compared with SSc-PAH patients after adjusting for hemodynamics. Concomitant intrinsic pulmonary vascular disease and HFpEF likely contribute to very poor survival in patients with SSc-PH-HFpEF.

## Keywords

scleroderma, pulmonary hypertension, left heart disease, HFpEF

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## Introduction

Pulmonary arterial hypertension (PAH) is a dramatic complication of systemic sclerosis (SSc) that occurs in approximately 7–12% of patients and is a leading cause of death in this population.<sup>1–3</sup> PAH is defined by a mean pulmonary artery pressure (mPAP)  $\geq 25$  mmHg, pulmonary vascular resistance (PVR)  $\geq 3$  Woods units, and pulmonary artery wedge pressure (PAWP)  $\leq 15$  mmHg as obtained during right heart catheterization (RHC) at rest.<sup>4</sup> While SSc-associated

PAH (SSc-PAH) is considered a Group 1 disease of the pulmonary hypertension (PH) classification, it is not uncommon to encounter SSc patients with PH (mPAP  $\geq 25$  mmHg) with a PAWP  $> 15$  mmHg at rest.<sup>5</sup> These patients, in the absence of significant lung parenchymal disease (e.g. lung fibrosis),

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are then classified as PH due to left heart disease (SSc-PH-LHD), or Group 2 of the PH classification.<sup>4</sup> The underlying cause of LHD is further characterized based upon: (1) the presence or absence of valvular disease; and (2) left ventricular function: heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF). In particular, the prevalence of PH-HFpEF within the SSc population with PH (SSc-PH-HFpEF) may be significant, in the range of 20–45% in recent studies.<sup>6,7</sup>

Several studies have previously shown that SSc-PAH is a distinctive entity within Group 1 diseases. Despite seemingly better hemodynamic measurements at rest, patients with SSc-PAH have a threefold higher risk of death and poorer response to therapy compared to patients with idiopathic PAH (IPAH).<sup>8,9</sup> The hemodynamic characteristics and natural history of SSc-PH and HFpEF patients have been much less studied. We have recently shown that elevated PAWP presents an increased pulsatile load on the right ventricle (RV) in the setting of PH; however, the hemodynamic significance of this observation, and particularly the exact impact of elevated PAWP on survival in SSc patients with concurrent PH, remain unknown.<sup>10</sup>

In this context, we hypothesized that patients with SSc-PH-HFpEF have a similar prognosis compared to patients with SSc-PAH when matched for total RV load (resistive and pulsatile components). We therefore sought to evaluate the survival and baseline hemodynamics in a cohort of patients with SSc associated PH (SSc-PH) followed prospectively at our center.

## Methods

### Patient population

This study includes patients with SSc-PH, either PAH or PH-HFpEF, diagnosed and evaluated by the Johns Hopkins Pulmonary Hypertension (PH) program between January 2000 and January 2015, with at least six months of follow-up. The study was approved by the Johns Hopkins University Institutional Review Board and all patients signed informed consent.

The diagnosis of SSc was confirmed by rheumatologists with expertise in SSc at the Johns Hopkins Scleroderma Center. Included patients have either met the 1980 American College of Rheumatology criteria for the diagnosis of scleroderma<sup>11</sup> or had at least three of five features of CREST syndrome (calcinosis, Raynaud's phenomenon [RP], esophageal dysmotility, sclerodactyly, telangiectasias). Date of onset of scleroderma was defined as the date of first non-Raynaud sign attributable to scleroderma.

The diagnosis of PH was confirmed by RHC at rest with  $\text{mPAP} \geq 25$  mmHg. PAH was differentiated from PH-HFpEF by  $\text{PAWP} \leq 15$  mmHg. All patients had echocardiography demonstrating left ventricular EF ( $\text{LVEF}$ )  $\geq 50\%$ . Furthermore, based on the diastolic pulmonary vascular

pressure gradient (DPG), the group of patients with SSc-PH-HFpEF was further divided into two subsets, isolated post-capillary PH (Ipc-PH;  $\text{DPG} < 7$  mmHg and  $\text{PVR} < 3$  Wood units) and combined pre- and post-capillary PH (Cpc-PH;  $\text{DPG} \geq 7$  mmHg and  $\text{PVR} \geq 3$  Wood units).<sup>4</sup> Patients with other potential causes of PH (reduced ejection fraction or valvular disease, human immunodeficiency virus [HIV], primary biliary cirrhosis or portal hypertension, chronic thromboembolic disease, sickle cell disease, significant chronic obstructive pulmonary disease [COPD], significant interstitial lung disease [ILD], or overlap syndrome) were excluded. Significant COPD was defined as a forced expiratory volume in 1 s ( $\text{FEV}_1$ ) to forced vital capacity (FVC) ratio  $< 70\%$  and a  $\text{FEV}_1$  of  $< 60\%$  predicted. Significant ILD was defined based on the results of a combination of pulmonary function tests and chest radiography or computed tomography (CT).<sup>12–14</sup> Patients with total lung capacity (TLC)  $< 60\%$  predicted were excluded, and those with  $\text{TLC} \geq 70\%$  predicted were included. Patients with a TLC in the range of 60–70% predicted were included if their CT or chest radiography scan showed only minimal interstitial fibrosis (Fig. 1).

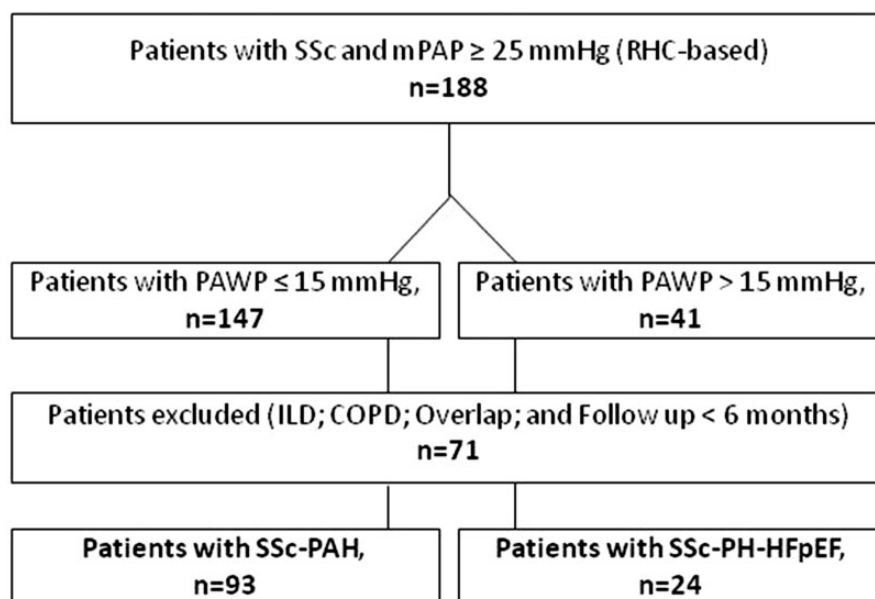
### Data collection

Data were collected prospectively in the Johns Hopkins PH Program registry. Demographic data and SSc-characterizing features (date of first RP, first non-Raynaud symptom, and serum autoantibodies) were obtained from clinical reports.

Baseline hemodynamic measurements were obtained at the first RHC defining PH. Hemodynamic data included: heart rate (HR), right atrial pressure (RAP), systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), PAWP, cardiac output (CO), pulmonary artery oxygen saturation ( $\text{PA O}_2$  sat%). Additionally, pulmonary pulse pressure ( $\text{PP} = \text{sPAP} - \text{dPAP}$ ), pulmonary artery capacitance ( $\text{PA}_C = \text{SV} / \text{PP}$ ),  $\text{PVR} = (\text{mPAP} - \text{PAWP}) / \text{CO}$ , trans-pulmonary gradient ( $\text{TPG} = \text{mPAP} - \text{PAWP}$ ), dPAP to PAWP gradient ( $\text{DPG} = \text{dPAP} - \text{PAWP}$ ), effective arterial elastance ( $\text{Ea} = \text{sPAP} / \text{SV}$ ), resistance-compliance time ( $\text{RC-time} = \text{C}_{\text{PA}} * \text{PVR}$ ), cardiac index ( $\text{CI} = \text{SV} / \text{body surface area}$ ), and stroke volume index ( $\text{SVi} = \text{CI} / \text{HR}$ ) were calculated.<sup>15</sup>

Baseline echocardiograms, pulmonary function tests (PFTs), six-minute walking test (6MWT), and specific serum measurements (uric acid, NT-proBNP, creatinine [Cr], and sodium) were considered for analysis when performed in the range of  $\pm 3$  months from the diagnostic RHC.

Survival was assessed from the date of diagnosis of PH by RHC. The primary outcome of death was determined from the clinical and hospital records as well as the Social Security Death Index (SSDI). Participants were censored at the time of their last clinic visit or contact with our center up to August 31, 2015.



**Fig. 1.** Algorithm of selection of patients. Highlighted boxes indicate patients included. There were 71 patients excluded (ILD/COPD = 58, Overlap = 2, Follow-up < 6 months = 11).

SSc, systemic sclerosis; PH, pulmonary hypertension; RHC, right heart catheterization; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; FU, follow-up; SSc-PAH, scleroderma-associated pulmonary arterial hypertension; SSc-PH-HFpEF, scleroderma-associated pulmonary hypertension due heart failure and preserved ejection fraction.

### Statistical analysis

Continuous variables are shown as mean  $\pm$  standard deviation (SD) or median (interquartile range [IQR]) as appropriate. Group comparisons were made using Student's *t* test or Wilcoxon rank test, as appropriate, for continuous variables and  $\chi^2$  statistics or Fisher's exact test, as appropriate, for categorical variables. A *P* value < 0.05 was considered significant.

Time-to-event analysis was performed using the Kaplan-Meier product limit estimator. Comparisons between groups were assessed by Log-Rank Test. To test the hypothesis that outcomes differed between SSc-PH-HFpEF and SSc-PAH, and to examine modifiers of the relationship between disease type and outcome, univariable and bi-variable Cox regression hazard models were constructed and the risk of mortality was adjusted for the relevant prognostic factors.<sup>9,16–19</sup> The proportional hazards assumption was examined for all covariates using a continuous time-varying predictor and generalized linear regression of scaled Schoenfeld residuals on function of time.<sup>20,21</sup> Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

## Results

### Study population

One hundred and seventeen patients with SSc-associated PH met the inclusion criteria described in the "Methods" section. Of these patients, 93 were diagnosed with SSc-PAH

and 24 with SSc-PH-HFpEF. Demographic characteristics are shown in Table 1. There were no differences between the two groups in gender, race, and SSc type. There was a majority of white women with limited cutaneous SSc (lcSSc). The median duration of SSc and symptoms of RP was 13.6 years (range = 5.9–19.8) and 17.6 years (range = 10.8–30.6), respectively. The median time of follow up after the PH diagnosis was three years (range = 1.5–5.7).

Information on SSc-related antibodies was available for 105 patients (89.7%). Of these, 99 patients (84%) had anti-nuclear antibodies (ANA) and six patients had no autoantibodies. ANA were found to be anti-centromere (ACA) specific in 58 (49%) patients and anti-Scl-70 specific in six (5%, all with PAH). Of the remaining 35 patients, eight had speckled, 11 had nucleolar, two had homogenous, and six had undefined ANA patterns.

Systemic hypertension, hypothyroidism, coronary artery disease (CAD), and obstructive sleep apnea (OSA) were the most common major co-morbidities in the study population, with higher frequency of OSA in SSc-PH-HFpEF patients. At the time of RHC, the body mass index (BMI) was significantly higher in the SSc-PH-HFpEF group (SSc-PAH versus SSc-PH-HFpEF:  $25.8 \pm 6$  versus  $32 \pm 8$  kg/m<sup>2</sup>; *P* < 0.05), while the World Health Organization (WHO) functional status was similar between the two groups (class I–II: 47% versus 42%, class III–IV: 52% versus 54%; SSc-PAH versus SSc-PH-HFpEF, *P* = 0.6).

One hundred and seven (91.5%) patients received PH-specific therapy following RHC. There was a larger

**Table 1.** Demographic and clinical characteristics.

	All (n = 117)	SSc-PAH (n = 93)	SSc-PH-HFpEF (n = 24)
Gender			
Male	20 (17)	16 (17)	4 (16)
Female	97 (83)	77 (83)	20 (84)
Race			
White	101 (86)	81 (87)	20 (83)
Other	16 (14)	12 (13)	4 (14)
SSc type			
LcSSc	106 (90)	85 (91)	21 (87)
dcSSc	11 (10)	8 (9)	3 (13)
BMI (kg/m <sup>2</sup> )	27 ± 6.7	25.8 ± 6	32 ± 8*
Age at PH diagnosis (years)	62.3 ± 11.9	61 ± 12	63 ± 10
Duration of Raynaud (years)	17.6 [10.8–30.6]	17.6 [11.3–32.6]	15.6 [8.3–30.1]
Duration of SSc (years)	13.6 [5.9–19.8]	13.6 [5.9–23.5]	13.3 [4.8–22.4]
Duration of follow-up (years)	3.1 [1.5–5.7]	3.1 [1.5–6]	2.7 [1.4–5.3]
Autoantibodies (n = 105)			
Anti-nuclear (ANA) +	99 (84)	82 (88)	17 (71)
Anti-centromere +	58 (49)	47 (50)	11 (46)
Anti-SCL70 +	6 (5)	6 (7)	0
Other pattern	35 (30)	29 (31)	6 (25)
Major co-morbidities			
Systemic Hypertension	24 (20)	19 (21)	5 (21)
Diabetes mellitus	4 (3)	3 (3)	1 (4)
Arrhythmias	8 (7)	7 (8)	1 (4)
CAD	11 (9)	7 (8)	4 (16)
OSA	13 (11)	7 (7)	6 (25)*
Hypothyroidism	23 (19)	19 (20)	4 (17)
Hyperlipidemia	10 (9)	7 (8)	3 (13)
WHO Functional Class			
I	10 (9)	9 (10)	1 (4)
II	43 (37)	34 (37)	9 (38)
III	51 (44)	40 (43)	11 (46)
IV	10 (9)	8 (9)	2 (8)
Treatment			
PDE5i	87 (74)	77 (83)	10 (42)
ERA	76 (65)	63 (68)	13 (54)
Prostaglandins <sup>†</sup>	34 (29)	27 (29)	7 (29)
Low dose CCB <sup>‡</sup>	12 (10)	10 (10)	2 (8)
Oxygen supplement	29 (25)	23 (25)	6 (25)
Diuretics	86 (73)	67 (72)	19 (79)
Oral anticoagulation	31 (26)	20 (21)	11 (46)**
PH-specific medications			
No	10 (9)	4 (4)	6 (25)*
Yes	107 (91)	89 (96)	18 (75)
Deaths	73 (62)	55 (59)	18 (75)

Data are expressed as n (%), mean ± SD or median [IQR].

\**P* < 0.05.\*\**P* < 0.01.<sup>†</sup>Inhaled prostaglandins in 17 patients.<sup>‡</sup>5[5,10] median[min,max] of Amlodipine dose equivalent (in mg).

BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers (used for RP); dcSSc, diffuse cutaneous SSc; ERA, endothelin receptor antagonists; LcSSc, limited cutaneous SSc; OSA, obstructive sleep apnea; PDE5i, phosphodiesterase 5 inhibitors; WHO, World Health Organization.

**Table 2.** Right heart catheterization.

	All (n = 117)	SSc-PAH (n = 93)	SSc-PH-HFpEF (n = 24)
<b>Baseline hemodynamics</b>			
HR (bpm)	80 ± 14	80 ± 14	81 ± 18
RAP (mmHg)	9 ± 4	8 ± 4	12 ± 3*
sPAP (mmHg)	65 ± 18	65 ± 18	70 ± 20*
dPAP (mmHg)	24 ± 8	23 ± 8	30 ± 9*
mPAP (mmHg)	39 ± 11	40 ± 10	43 ± 12*
PAWP (mmHg)	12 ± 5	10 ± 3	19 ± 2*
CI (L/min/m <sup>2</sup> )	2.6 ± 0.8	2.6 ± 0.8	2.7 ± 1.0
CO (L/min)	4.7 ± 1.7	4.6 ± 1.4	5.3 ± 2.4
PA O <sub>2</sub> saturation (%)	66 [61–72]	66 [61–71]	64 [60–73]
PP (mmHg)	40 ± 12	40 ± 12	41 ± 12
<b>Measures of RV load</b>			
PAC (mL/mmHg)	1.7 ± 0.9	1.6 ± 0.9	1.9 ± 1.0
TPG (mmHg)	28 ± 11	28 ± 11	25 ± 12
DPG (mmHg)	13 ± 8	13 ± 8	11 ± 9
PVR (wood units)	6.8 ± 4.4	7.1 ± 4.4	5.7 ± 4.5
Ea	1.26 ± 0.5	1.25 ± 0.75	1.30 ± 1.05*
RC time (s)	0.51 ± 0.17	0.53 ± 0.17	0.44 ± 0.13*
SVi (mL/m <sup>2</sup> /beat)	34.2 ± 10.9	34.2 ± 10.4	34.3 ± 13.1

Data are expressed as n (%), mean ± SD or median [IQR].

\* $P < 0.05$ .

CI, cardiac index; CO, cardiac output; dPAP, diastolic pulmonary artery pressure; DPG, diastolic pulmonary gradient; Ea, arterial elastance; HR, heart rate; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAC, pulmonary artery capacitance; PAWP, pulmonary artery wedge pressure; PP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RC, resistance-compliance; RV, right ventricle; sPAP, systolic pulmonary artery pressure; SVi, stroke volume index; TPG, trans-pulmonary gradient.

percentage of patients with SSc-PAH who received PAH-specific therapy compared to SSc-PH-HFpEF patients (SSc-PAH versus SSc-PH-HFpEF, 95.7% versus 75%;  $P < 0.05$ ). Treatment during the follow-up period showed higher usage of phosphodiesterase 5 inhibitors (PDE5i) in patients with SSc-PAH, and higher usage of oral anticoagulants in patients with SSc-PH-HFpEF. All other treatments (endothelin receptor antagonists [ERA], prostaglandins, oxygen supplement, low dose calcium channel blockers [used for RP], and diuretics) were equally used in the two groups.

### Hemodynamic data

Baseline hemodynamic data are shown in Table 2. Traditional hemodynamic measurements showed significantly higher pulmonary and right atrial pressures in patients with SSc-PH-HFpEF compared with those with SSc-PAH (SSc-PH-HFpEF versus SSc-PAH: mean sPAP [mmHg], 70 ± 20 versus 65 ± 18; mean dPAP [mmHg], 30 ± 9 versus 23 ± 8; mean RAP [mmHg], 12 ± 3 versus 8 ± 4;  $P < 0.05$ ). While PVR tended to be lower in

SSc-PH-HFpEF patients, TPG was equally elevated without significant difference between the two groups (SSc-PH-HFpEF versus SSc-PAH: mean PVR [Wood units], 5.7 ± 4.5 versus 7.1 ± 4.4; mean TPG [mmHg], 25 ± 12 versus 28 ± 11;  $P = 0.1$ ). Despite trends toward higher resistive load, the effective arterial elastance (Ea), a measure of total RV afterload, was statistically lower in the SSc-PAH group (SSc-PH-HFpEF versus SSc-PAH: 1.30 ± 1.0 versus 1.25 ± 0.8;  $P < 0.05$ ).

### Echocardiography, PFT, 6MWT, and laboratory data

Echocardiography, PFT, and 6MWT data are shown in Table 3. On echocardiography, patients with SSc-PH-HFpEF had an increased prevalence of left atrial enlargement compared to SSc-PAH patients (SSc-PH-HFpEF versus SSc-PAH: mean LA diameter [cm], 4.0 ± 0.7 versus 3.7 ± 0.5;  $P < 0.05$ ), whereas patients with SSc-PAH tended to have more RV dysfunction although this did not reach significance (SSc-PH-HFpEF versus SSc-PAH: moderate-severe RV dysfunction, 5.3% versus 24.7%;  $P = 0.1$ ). There were no significant differences in PFT, 6MWT, or laboratory parameters (including serum sodium, Cr, and NT-proBNP) between PH-HFpEF and PAH scleroderma patients (Table 3).

### Survival and predictors of mortality

The overall median survival time for the entire cohort was 4.6 years and there were 73 (62%) deaths observed: 18 (75%) in the SSc-PH-HFpEF group and 55 (59%) in the SSc-PAH group. The Kaplan–Meier survival curves are shown in Fig. 2. Although the SSc-PH-HFpEF group had a higher crude mortality than the SSc-PAH group, the difference was not statistically significant (log rank test:  $P = 0.26$ ). Univariable and bi-variable Cox proportional hazards analyses were performed as shown in Table 4. There was a non-significant increased risk of death in the SSc-PH-HFpEF group (HR 1.47 [95% CI = 0.79–2.70;  $P = 0.2$ ]) on the univariable analysis. In bivariable analyses, adjusting for a singular demographic and clinical variable at a time, such as age at diagnosis of PH, sex, and WHO FC, no significant association between disease type and outcome was found. However, after adjusting for hemodynamic prognostic factors (PVR, TPG, DPG, Ea, and 1/PAC “multiplicative inverse of PAC”), significant statistical associations between disease type and outcomes were observed, with a nearly twofold increased risk of death in the SSc-PH-HFpEF group (Table 4).

### Ipc-PH versus Cpc-PH

Patients defined as Cpc-PH in the SSc-PH-LHD group had a worse functional status at presentation compared to Ipc-PH (WHO FC III–IV: Cpc-PH versus Ipc-PH: 73% versus 25%;  $P = 0.03$ ). On RHC, patients with Cpc-PH had higher



**Table 3.** Baseline echocardiography, PFT, 6MWT, and LAB.

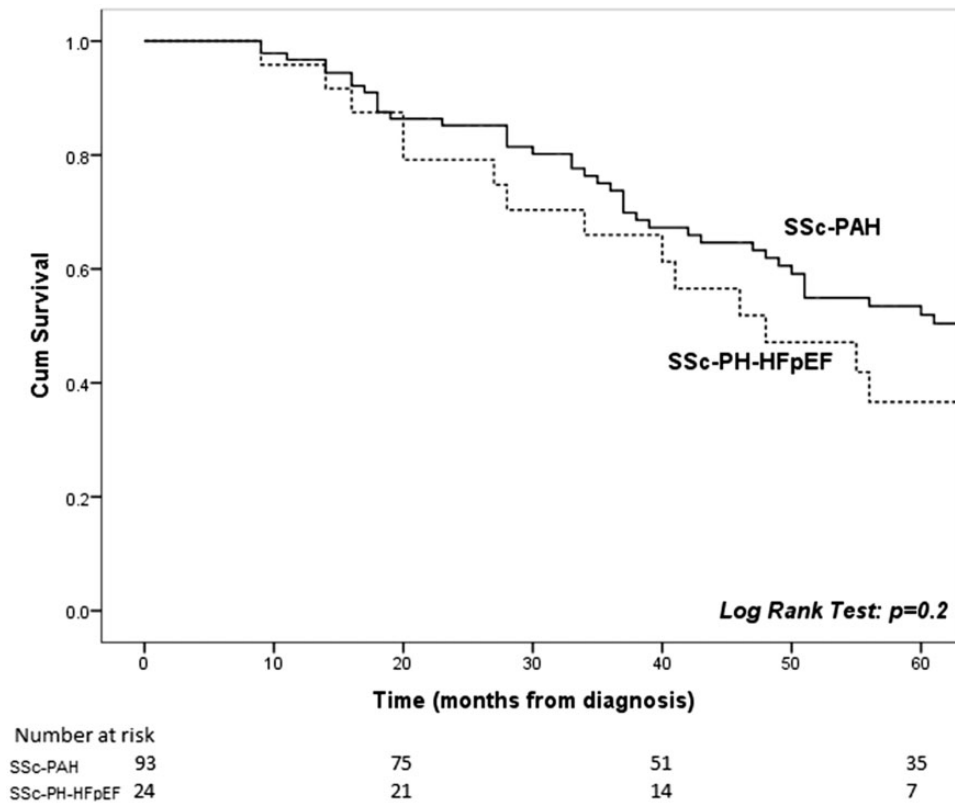
	All (n = 97)	SSc-PAH (n = 77)	SSc-PH-HFpEF (n = 20)
<b>Echocardiogram</b>			
LA diameter (cm)	3.7 ± 0.6	3.7 ± 0.5	4.0 ± 0.7*
LA dilation			
None/mild	86 (91)	71 (95)	15 (79)**
Moderate/severe	8 (971)	4 (5)	4 (21)**
RA dilation			
None/mild	56 (59)	45 (60)	11 (55)
Moderate/severe	39 (41)	30 (40)	9 (45)
RV dilation			
None/mild	65 (67)	54 (70)	11 (55)
Moderate/severe	32 (33)	23 (30)	9 (45)
RV dysfunction			
None	71 (74)	53 (69)	18 (95)
Mild	5 (5)	5 (6)	0
Moderate	11 (12)	10 (13)	1 (5)
Severe	9 (9)	9 (12)	0
Diastolic dysfunction			
No	74 (77)	57 (74)	17 (90)
Yes	22 (23)	20 (26)	2 (10)
Pericardial effusion			
No	54 (56)	42 (55)	12 (60)
Yes	42 (44)	34 (45)	8 (40)
eRVSP (mmHg)	66 ± 18	65.1 ± 18	68 ± 18
LVEF (%)	62 ± 5.5	62.8 ± 5.5	62.3 ± 5.4
	All (n = 109)	SSc-PAH (n = 88)	SSc-PH-HFpEF (n = 21)
<b>PFT</b>			
FEV <sub>1</sub> (predicted %)	79 ± 19	80 ± 19	72 ± 21
FVC (predicted %)	82 ± 19	83 ± 18	77 ± 22
DLCO (predicted %)	56 ± 18	54 ± 18	62 ± 20
FVC/DLCO (predicted %)	1.6 ± 0.6	1.6 ± 0.6	1.3 ± 0.4**
	All (n = 95)	SSc-PAH (n = 77)	SSc-PH-HFpEF (n = 18)
<b>6MWT</b>			
6MWD (m)	308 ± 126	313 ± 128	285 ± 115
% Predicted	64 ± 23	65 ± 22	57 ± 26
<b>LAB</b>			
Hb (g/dL) (n = 106)	12.2 ± 2	12.1 ± 1.8	12.6 ± 2.3
Uric acid (mg/dL) (n = 64)	7.0 ± 2.2	6.9 ± 2.3	7.8 ± 2
Creatinine (mg/dL) (n = 111)	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.3
Sodium (mmol/L) (n = 107)	139 ± 3	139 ± 3	139 ± 3
NT-proBNP (pg/mL) (n = 89)	673 [340–2573]	623 [340–2608]	1201 [333–2563]

Data are expressed as n (%), mean ± SD or median [IQR].

\*P &lt; 0.01.

\*\*P &lt; 0.05.

6MWD, six-minute walking distance; DLCO, diffusing capacity of lungs for carbon monoxide; eRVSP, estimated RV systolic pressure; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced expiratory volume; LA, left atrium; LVEF, left ventricular ejection fraction; PFT, pulmonary function test; RV, right ventricle.



**Fig. 2.** Kaplan–Meier survival graphs. Patients with SSc-PH-HFpEF (scleroderma-associated pulmonary hypertension due to heart failure with preserved ejection fraction) (dotted line) compared with those with SSc-PAH (scleroderma-associated pulmonary arterial hypertension) (solid line).

RAP, mPAP, and PVR and lower SV/PP, when compared to Ipc-PH patients (Table 5). Survival was significantly better in patients with Ipc-PH (Fig. 3).

## Discussion

In this study, we found that while patients with SSc-PH-HFpEF had similar demographic and clinical characteristics as those patients with SSc-PAH, SSc-PH-HFpEF patients had worse hemodynamic impairment. Further, contrary to our hypothesis, SSc-PH-HFpEF patients had a nearly two-fold increased risk of death compared to SSc-PAH when controlling for hemodynamic parameters known to have prognostic value. These findings suggest that in SSc, PH related to HFpEF is a clinically relevant and distinct entity with a poor prognosis.

In PH-related to LHD (i.e. post-capillary PH), the most common form of PH in the Western world,<sup>22</sup> the elevation in pulmonary vascular pressures can result from several mechanisms. These include passive transmission of pressures from the left atrium, changes in vascular compliance due to elevated left atrial pressure,<sup>10</sup> and changes in the pulmonary vascular tone or vascular remodeling. As demonstrated by Lam et al. in the Olmstead County cohort, over 80% of HFpEF patients had elevated RV systolic pressure on echocardiography consistent with PH. In addition, these patients

with HFpEF-PH had significantly poorer outcomes compared to patients with HFpEF alone.<sup>22</sup> Further, as noted by Mohammed et al., HFpEF patients with echocardiographic evidence of RV dysfunction, measured either semi-quantitatively or by the tricuspid annular plane systolic excursion (TAPSE), had increased risk of hospitalization and both cardiovascular and all-cause mortality compared to HFpEF patients without RV dysfunction.<sup>23</sup> Taken together, these data from large epidemiologic studies highlight the high prevalence and clinical impact of PH in the setting of HFpEF.

However, scant data exist on PH related to HFpEF in the setting of SSc. While it is well recognized that diastolic dysfunction (i.e. HFpEF) is the most common cardiac manifestation in SSc perhaps reflecting primary myocardial fibrosis,<sup>24,25</sup> the prevalence and characteristics of RHC-determined PH-HFpEF in the setting of SSc is not well described in the literature. Fox et al. reported, in a cohort of 107 patients with SSc who underwent RHC for evaluation of possible PH, that 24 of the 53 (45%) participants with PH (mPAP > 25 mmHg) had PAWP > 15 mmHg at rest, consistent with LHD.<sup>6</sup> While the proportion of patients with PH related to LHD in our cohort was significantly less (20.5%), these differences may be related to our study criteria in which patients with reduced LV systolic function were systematically excluded; this information was not

**Table 4.** Risk of mortality, bivariate analysis.

Predictor	$\beta$ (95% CI)
Group, SSc-PH-HFpEF	
Unadjusted HR,	1.47 (0.79–2.70)*
Adjusted for,	
Hemodynamics:	
PVR, per Wood unit	1.79 (1.03–3.11) <sup>†</sup>
TPG, per mmHg	1.84 (1.05–3.20) <sup>†</sup>
DPG, per mmHg	1.66 (0.96–2.87) <sup>†</sup>
I/PAc, per I/(mL/mmHg)	3.11 (2.00–4.81) <sup>†</sup>
Ea	1.99 (1.56–2.55) <sup>†</sup>
Treatment:	
PH specific therapy <sup>‡</sup> , yes	1.75 (0.69–4.90)
Warfarin, yes	1.50 (0.93–2.53)
Demographics:	
Age, per year	1.18 (0.68–2.06)
Sex, male	1.35 (0.79–2.32)
Race, not white	1.31 (0.76–2.25)
Clinical status:	
WHO FC, III–IV	1.17 (0.67–2.04)
6MWD, per % predicted	1.53 (0.76–3.06)

\* $P = 0.2$ .<sup>†</sup> $P < 0.05$ .<sup>‡</sup>Endothelin receptor antagonists, phosphodiesterase 5 inhibitors, prostaglandins.

I/PAc, multiplicative inverse of pulmonary artery capacitance; 6MWD, six-minute walking distance; CI, confidence interval; DPG, diastolic pulmonary gradient; Ea, arterial elastance; HR, hazard ratio; PVR, pulmonary vascular resistance; SSc-PH-HFpEF, pulmonary hypertension due heart failure with preserved ejection fraction associated with systemic sclerosis; TPG, trans-pulmonary gradient; WHO FC, World Health Organization Functional Class.

specified in the Fox study. Furthermore, the proportion of SSc patients with PH related to LHD at rest observed in the current study is similar to two prior RHC-based studies, including a systematic review.<sup>7,26</sup>

While in general, there were no differences in demographic characteristics between the SSc-PAH and SSc-PH-HFpEF groups in our study, it is noteworthy that the SSc-PH-HFpEF patients had significantly higher BMI and were more likely to have OSA. Similar characteristics have been reported in previous studies.<sup>27,28</sup> The high prevalence of OSA in the SSc-PH-HFpEF group (and thus possibly an element of group 3 PH) could have contributed to the worse outcome in this group. Clinically, patients who were in WHO FC I–II formed almost half (46%) of our cohort with equal distribution among the two groups. This relative higher proportion of patients with WHO FC I–II at the time of diagnosis of PH, compared with other similar cohorts,<sup>29</sup> is however consistent with our previous study,<sup>19</sup> suggesting a tendency for earlier referral of SSc patients to the PH clinic at our center in recent years.

Further, as expected, echocardiographic evidence of LA dilation was more common in the SSc-PH-HFpEF group

**Table 5.** Characteristics of SSc-PH-HFpEF patients.

	lpc-PH (n = 9)	Cpc-PH (n = 15)
Demographics		
Gender		
Male	2 (22)	2 (13)
Female	7 (78)	13 (87)
SSc type		
lcSSc	7 (78)	14 (93)
dcSSc	2 (22)	1 (7)
WHO Functional Class III–IV	2 (25)	11 (73)*
BMI (kg/m <sup>2</sup> )	31.4 ± 8.9	32.4 ± 7.5
Age at PH diagnosis (years)	67 ± 5	62 ± 12
Baseline hemodynamics		
HR (bpm)	73 ± 12	86 ± 20
mPAP (mmHg)	34 ± 4	49 ± 10*
RAP (mmHg)	10 ± 3.5	14 ± 2*
PAWP (mmHg)	18 ± 2	19 ± 2
TPG (mmHg)	16 ± 6	30 ± 11*
DPG (mmHg)	2 ± 3	16 ± 7*
CI (L/min/m <sup>2</sup> )	3.1 ± 1.2	2.4 ± 0.9
CO (L/min)	6.2 ± 3.1	4.7 ± 1.8
PA O <sub>2</sub> saturation (%)	72 ± 6	62 ± 7*
PVR (Wood units)	2.9 ± 1.8	7.4 ± 4.8**
Ea	0.7 ± 0.3	1.7 ± 1.1*
Compliance (SV/PP)	2.6 ± 0.9	1.3 ± 0.5*
SV (mL/m <sup>2</sup> /beat)	84 ± 34	56 ± 20*
Survival		
Survival (median ± SE) (years)	7.4 ± 1.5	3.3 ± 0.9*
Deaths	4 (44)	14 (93)

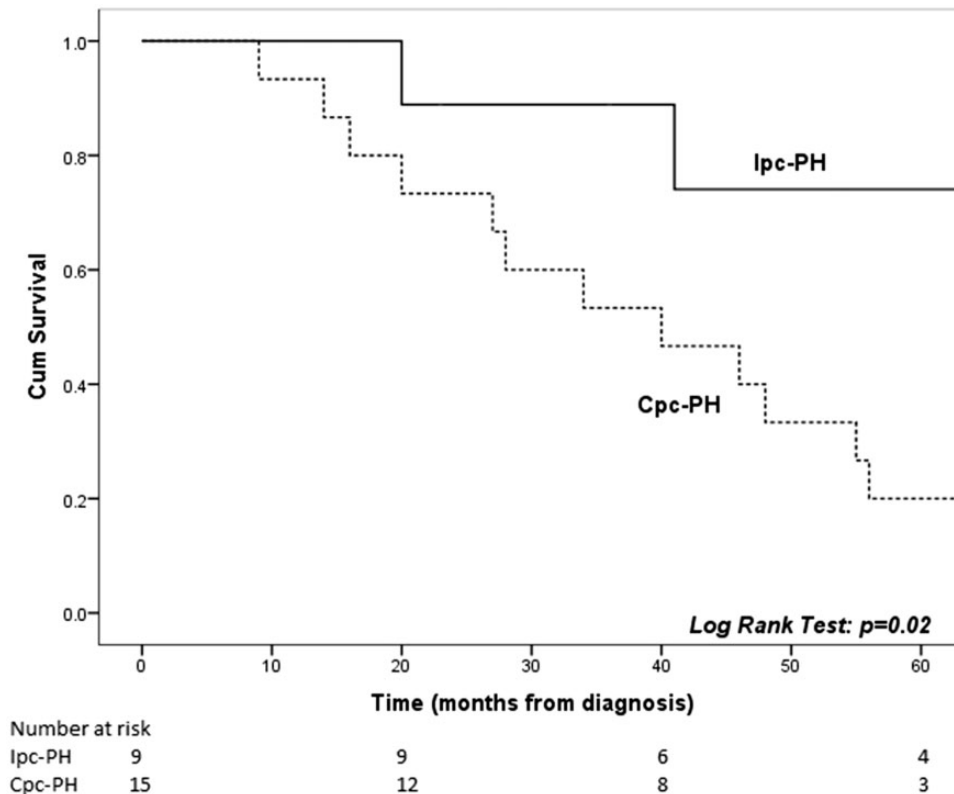
Data are expressed as n (%), mean ± SD or median ± SE.

\* $P < 0.05$ .\*\* $P < 0.01$ 

BMI, body mass index; CI, cardiac index; CO, cardiac output; Cpc-PH, combined pre- post-capillary PH; dcSSc, diffuse cutaneous SSc; Ea, arterial elastance; HR, heart rate; lpc-PH, isolated post-capillary PH; lcSSc, limited cutaneous SSc; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAWP, pulmonary capillary wedge pressure; PP, pulse pressure; PVR, pulmonary vascular resistance; SV, stroke volume; TPG, trans-pulmonary gradient; WHO, World Health Organization.

than the SSc-PAH group. Although our echocardiographic data showed that the majority of SSc-HFpEF patients (i.e. 90%) had normal diastolic parameters, these patients demonstrated significantly more enlarged left atria compared to the SSc-PAH group (21% versus 5 %,  $P < 0.05$ ). Doppler parameters of diastolic dysfunction are extremely load dependent and reflective of instantaneous left ventricular diastolic filling, while left atrial size is more representative of the chronic average left ventricle filling pressure. Hence, when increased, in the absence of other contributing pathology such as mitral valve disease, left atrial size is a long-term biomarker of diastolic dysfunction, regardless of Doppler findings,<sup>30</sup> with relevant prognostic value in terms





**Fig. 3.** Kaplan–Meier survival graphs. Patients with lpc-PH (isolated post-capillary PH; DPG < 7 mmHg and PVR < 3 Wood units) (solid line) compared with those with Cpc-PH (combined pre- post-capillary PH; DPG ≥ 7 mmHg and PVR ≥ 3 Wood units) (dotted line).

of cardiovascular risk and overall mortality.<sup>31,32</sup> Consistent with the findings by Fox et al., we found higher RAP in our SSc-PH-HFpEF patients compared with SSc-PAH. However, unlike prior studies, we found higher mPAP in the SSc-PH-HFpEF patients and no differences in TPG or DPG between groups. We hypothesize that the unexpected abnormally high mPAP and TPG in the SSc-PH-HFpEF group is likely the result of significant intrinsic pulmonary vascular disease in addition to the effect of added load from HFpEF in these patients. These findings are consistent with hemodynamic features observed in another cohort of patients with PH-LHD (without SSc) and HFpEF by Thenappan et al.<sup>33</sup>

Pulmonary complications (PH and ILD) are now the leading causes of mortality in patients with SSc.<sup>34</sup> Although patients with SSc can present with three different types of PH (PAH, PH-ILD, and PH-LHD), SSc-PAH has been the most commonly studied and targeted pharmacologically. However, in spite of advances in targeted therapy for PAH, prognosis in SSc-PAH remains unacceptably poor, and survival significantly lower, than in IPAH.<sup>8,35</sup> We excluded from this analysis patients with PH-ILD because of the confounding effect of ILD on median survival which is notoriously very poor for these patients (i.e. about 2.5 years).<sup>36</sup> The overall long-term survival of the patients with SSc-PH at our center remains poor, with a

median survival time of 4.6 years, but with consistent improvement in the last two decades from a previously reported three-year median survival.<sup>8,29</sup> This relative improvement may be explained by advances in targeted therapy or more likely early referral of these patients to our pulmonary hypertension clinic (i.e. lead-time bias), as discussed above.

While prior studies in SSc patients have demonstrated a strong association between LV diastolic dysfunction as measured by echocardiography and outcomes, few studies have examined the impact of PH-HFpEF in this population.<sup>37</sup> Our study shows a lack of apparent difference in mortality between SSc-PH-HFpEF and SSc-PAH (SSc-HFpEF versus SSc-PAH: 75% versus 59 %;  $P=0.2$ ). Interestingly, we found that when controlling for hemodynamic measures, SSc-PH-HFpEF patients had poorer survival than those with SSc-PAH, with a nearly twofold increased risk of death (Table 4), possibly due to a combined pathologic process (LHD and pulmonary vascular disease) in these patients.

Of note, the increased risk of mortality in the SSc-PH-HFpEF group was not affected by either the use of PH specific therapy (PDE5i, ERA, and prostaglandins) and warfarin or the major clinical and demographic features. Considering the potential negative effect of pulmonary vasodilators on LHD, we cannot rule out a detrimental effect with the use of these drugs in this particular group.

Indeed, the finding of increased pulmonary pressures above what is expected from the mere increase in PAWP suggests the concurrent presence of pulmonary vascular disease in a portion of patients previously labeled as “out-of-proportion” or “reactive” PH-LHD. For this purpose, a DPG and/or PVR cutoff helps distinguish between isolated post-capillary PH (Ipc-PH; DPG < 7 mmHg and PVR < 3 WU) and combined pre- and post-capillary PH (Cpc-PH; DPG ≥ 7 mmHg and PVR ≥ 3 WU).<sup>4</sup> In our study, the average DPG was 2.1 in the Ipc-PH group and 15.8 in the Cpc-PH group. Compared with Ipc-PH, patients with Cpc-PH had more functional impairment (WHO FC III–IV in Cpc-PH versus Ipc-PH: 73% versus 25%;  $P=0.03$ ) and worse survival. In this regard, Gerges et al.<sup>16</sup> have demonstrated that DPG was a predictor of mortality in patients with elevated TPG. However, DPG is not associated with increased mortality either after heart transplant in patients with PH<sup>38</sup> or in a large cohort of patients with dilated cardiomyopathy and PH.<sup>39</sup> Recently, a study by Al-Naamani et al.<sup>18</sup> also did not find that DPG was predictive of mortality in 73 HFpEF patients. The incidence of Cpc-PH in their study was 36% compared with 63% in our study, which likely speaks to the high prevalence of significant pre-capillary disease in SSc-HFpEF participants. Notably, the DPG, TPG, and PVR in the Cpc-PH group was similar to the SSc-PAH group. Recently, Assad et al. have shown that patients with Cpc-PH and PAH share similar hemodynamic features (fixed RC time) as opposed to patients with Ipc-PH, suggesting the presence of pulmonary arterial remodeling in this group (i.e. Cpc-PH).<sup>40</sup>

## Limitations

Despite our relatively large cohort of SSc patients evaluated for PH (considering SSc is a rare disease and PH a relatively rare complication of this syndrome), this study has several limitations including the small sample size of the SSc-PH-HFpEF group ( $n=24$ ) and the fact that this is a single center experience. Regarding the number of patients with SSc-PH-HFpEF, it is remarkable that they represent a sizeable proportion (about 25%) of the entire cohort. This is likely explained by the age of the cohort and high prevalence of LHD in this age group combined with the propensity for underlying intrinsic myocardial dysfunction in SSc.<sup>41</sup> Another limitation is the possibility of misclassification of patients in this cohort. Misclassification could be related to the arbitrary cutoff for PAWP to discriminate between PAH and PH-HFpEF (i.e. 15 mmHg), knowing that measurements of PAWP are prone to many technical difficulties.<sup>42</sup> Pericardial constraint, from significant RV failure and RV volume overload, could have also contributed to elevated PAWP in the absence of significant LHD, leading to a reclassification of SSc-PAH to PH-HFpEF. Additionally, our practice to diurese patients to ensure euvolemia before performance of the RHC raises the likelihood of erroneous inclusion of PH-HFpEF patients in the PAH group. In this

respect, it is noteworthy that Robbins et al.<sup>43</sup> reported a significant portion of patients (22%) initially classified as PAH to be truly PH-LHD after a fluid load, which prompted the investigators to recommend the routine use of fluid challenge in the PH diagnosis algorithm in an attempt to unmask occult PH-LHD. Thus, maximizing fluid status prior to RHC and avoiding routine fluid challenge in our clinical practice may have contributed to an underestimation of PH-HFpEF. Taken together these observations clearly underscore the likely high prevalence of PH-HFpEF in the SSc population.

From a statistical standpoint, when examining potential modifiers of the relationship between disease type (SSc-PH-HFpEF versus SSc-PAH) and outcome (e.g. death), we were limited to perform bi-variate regression (e.g. models of two variables) rather than multivariate analysis (e.g. models of three or more variables), due to a relatively low incidence of death in the SSc-PH-HFpEF group.

## Conclusions

In conclusion, our study indicates a relatively high prevalence of PH-HFpEF in a cohort of SSc patients evaluated for PH. These patients are characterized by poor survival and a twofold increased risk of death compared to SSc-PAH patients when adjusted for hemodynamic factors. The poor prognosis in SSc-PH-HFpEF patients raises the possibility of concomitant intrinsic pulmonary vascular remodeling in addition to left heart disease (HFpEF), explaining significant resistive and high total RV load in these patients. Therefore, patients with SSc associated with PH-HFpEF might require closer monitoring and a more aggressive treatment of LHD and related co-morbidities (e.g. OSA and obesity), with the cautious combination of PAH therapy (although their role in HFpEF remains quite controversial), in order to improve overall outcome.

## Conflict of interest

The authors declare that there is no conflict of interest.

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