Impact of interstitial lung disease on the survival of systemic sclerosis with pulmonary arterial hypertension

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To assess severity markers and outcomes of patients with systemic sclerosis (SSc) with or without pulmonary arterial hypertension (PAH-SSc/non-PAH-SSc), and the impact of interstitial lung disease (ILD) on PAH-SSc. Non-PAH-SSc patients from the Spanish SSc registry and PAH-SSc patients from the Spanish PAH registry were included. A total of 364 PAH-SSc and 1589 non-PAH-SSc patients were included. PAH-SSc patients had worse NYHA-functional class (NYHA-FC), worse forced vital capacity (FVC) (81.2 ± 20.6% vs 93.6 ± 20.6%, P < 0.001), worse tricuspid annular plane systolic excursion (TAPSE) (17.4 ± 5.2 mm vs 19.9 ± 6.7 mm, P < 0.001), higher incidence of pericardial effusion (30% vs 5.2%, P < 0.001), and similar prevalence of ILD (41.8% vs. 44.9%). In individuals with PAH-SSc, ILD was associated with worse hemodynamics and pulmonary function tests (PFT). Up-front combination therapy was used in 59.8% and 61.7% of patients with and without ILD, respectively.

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Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterized by fibrosis of the skin and internal organs and vasculopathy[1,2,3]. Pulmonary hypertension (PH)—of which pulmonary arterial hypertension (PAH) is the most frequent form in SSc—and interstitial lung disease (ILD) are the two leading contributing causes of early death[4]. When associated with connective tissue diseases (CTD) like SSc, PAH is classified as Group 1.4 of the PH classification[5]. Both PH and ILD may coexist[6,7], and when ILD is significant PH is classified as Group 3. However, this classification is challenging and difficult to incorporate into clinical practice with SSc patients.

Prevalence of PAH in SSc varies across studies between 5 and 19%[8,9,10]. Prevalence of clinically relevant ILD is 20%[11]. The prevalence of PAH confirmed by right heart catheterization (RHC) in this registry is ~ 4%[12,13]. REHAP (Registro Español de Hipertensión Arterial Pulmonar) is the Spanish registry of SSc patients, and has been running since 2006[14]. The prevalence of PAH confirmed by right heart catheterization (RHC) in this registry is ~ 4%[12,13]. REHAP patients had SSc (PAH-SSc) confirmed on RHC. RHC was only performed in 58 non-PAH-SSc patients ruling out this complication, and specifically in 6 out of 38 patients with sPAP > 40 mmHg by echocardiography. These were the populations analyzed. Autoantibody specificities were available in non-PAH-SSc patients, 687/1413 (48.6%) had anti-centromere antibody, 259/1386 (18.7%) had anti-topoisomerase I antibody and 42/353 (11.9%) had anti-RNA polymerase III antibody.

Impact of PAH on SSc patients. Table 1 summarizes the baseline demographic, clinical, and echocardiography data of patients according to presence of PAH. Compared to non-PAH-SSc patients, PAH-SSc patients were older, had worse New York Heart Association functional class (NYHA FC) and pulmonary function tests (PFTs) (as assessed by % of predicted forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO)); more patients had FVC/DLCO ≥1.4 and even ≥1.6. Furthermore, mean systolic pulmonary artery pressure (sPAP) was greater in PAH-SSc patients, more patients presented sPAP > 40 mmHg, any grade or moderate-severe degree of tricuspid regurgitation, pericardial effusion, or lower tricuspid annular plane systolic excursion (TAPSE) values. No differences were observed in the prevalence of ILD. Regarding medical treatment, most PAH-SSc patients (62.6%) received up-front combination therapy while 15.9% non-PAH-SSc patients received specific vasodilators for peripheral vasculopathy. These differences did not change when the population was compared according to the presence or absence of ILD (online supplementary table II and III).

Impact of ILD and the severity of FVC impairment on PAH-SSc. Of the 220 PAH-SSc patients who had high-resolution computed tomography (HRCT) scans, 92 (41.8%) had ILD. Patients’ characteristics are shown in Table 2. Compared with PAH-SSc without ILD patients, those with concomitant ILD had lower female proportion and more patients presented impaired PFTs, with FVC <60% and DLCO ≤55%. The extent or specific ILD patterns were not available. Nevertheless, in order to estimate the severity according to Goh’s criteria, 48 out of 88 (54.5%) PAH-SSc with ILD patients had extensive disease taking into account FVC <70%. Right atrial pressure (RAP), cardiac output (CO), cardiac index (CI), and mean pulmonary artery pressure (mPAP) were significantly lower. No significant differences were found on echocardiography, but mean TAPSE was lower. No differences were observed regarding treatment strategies in patients with concomitant ILD and...
those without. Up-front combination therapy was the most frequent treatment in both cases (59.8% of patients with ILD and 61.7% of patients without ILD). No differences in transplant-free survival were observed in PAH-SSc patients according to the presence of ILD (P = 0.444) (Fig. 2A). Nevertheless, 1-, 3- and 5-year transplant-free survival rates were 82.5%, 60.2%, and 35% vs. 84.1%, 58.9%, and 43.5%, respectively, with a tendency for shorter survival in PAH-SSc patients with concomitant ILD.

FVC was available in 88 out of 92 patients with PAH-SSc and ILD. Thirty-five (40%) of these patients had FVC < 60%. Patients' characteristics are shown in supplementary table V. Patients with FVC < 60% were younger at diagnosis and had lower mean FVC/DLCO compared to their counterparts with FVC ≥ 60%. No differences were observed in gender, NYHA FC or 6-min walk test (6MWT), hemodynamics, biomarkers, electrocardiogram, or echocardiographic variables. Up-front combination therapy was the preferred approach in both cases (51.4% in FVC < 60% group and 66.0% in FVC ≥ 60% patients), although there was a trend towards lower use of up-front combination therapy and greater use of monotherapy in patients with FVC < 60% (P = 0.042). For PAH-SSc patients, no differences in survival were found regarding FVC impairment (FVC < 60% vs FVC ≥ 60% patients) (P = 0.167) (Fig. 2B). However, there was a numerical reduction at 1-, 3- and 5-year survival rates in patients with FVC < 60% compared with FVC ≥ 60% (76.8%, 51.2% and 27.0% vs. 85.0%, 68.5% and 42.3%, respectively), with a trend to shorter survival.

Table 1. Baseline demographic, clinical, and echocardiography data of PAH-SSc (REHAP) and non-PAH-SSc patients (RESCLE). Significant values are in bold. DLCO diffusing capacity for carbon monoxide, FVC forced vital capacity, HRCT high-resolution computed tomography, ILD interstitial lung disease, LVEF left ventricular ejection fraction, NYHA FC New York Heart Association functional class, sPAP systolic pulmonary artery pressure, SD standard deviation, TAPSE tricuspid annular plane systolic excursion. *Statistical significant comparison after Bonferroni correction (p < 0.017) or £(p < 0.012).

| Parameter | PAH-SSc | Non-PAH-SSc | P value |
|-----------|---------|-------------|---------|
| Gender, female, n (%) | 364 | 316 (86.8) | 1589 | 1408 (88.6) | 0.366 |
| Age at diagnosis, years, mean (SD) | 364 | 62.7 (12.0) | 1589 | 51.3 (15.5) | <0.001 |
| NYHA FC, n (%) | 364 | 667 | |
| I–II | 107 (29.4) | 612 (91.7) | <0.001 |
| III–IV | 257 (70.6) | 176 (8.2) | <0.001 |
| ILD on HRCT, n (%) | 220 | 92 (41.8) | 939 | 422 (44.9) | 0.408 |
| Pulmonary function test | | | |
| FVC (%) predicted, mean (SD) | 329 | 81.2 (20.6) | 1295 | 93.6 (20.6) | <0.001 |
| <60%, n (%) | 50 (15.2) | 83 (6.4) | <0.001* |
| 60–<80%, n (%) | 105 (31.9) | 218 (17) | <0.001* |
| ≥80%, n (%) | 174 (52.9) | 994 (76.5) | <0.001* |
| DLCO (%) predicted, mean (SD) | 280 | 45.3 (17.7) | 1011 | 79.0 (36.6) | <0.001 |
| DLCO ≤55%, n (%) | 213 (76.1) | 156 (15.4) | <0.001 |
| FVC/DLCO, mean (SD) | 270 | 2.1 (1.0) | 1005 | 1.3 (0.4) | <0.001 |
| FVC/DLCO ≥1.6, n (%) | 183 (67.8) | 184 (18.3) | <0.001 |
| FVC/DLCO ≥1.4, n (%) | 210 (77.8) | 350 (34.8) | <0.001 |
| Electrocardiogram | | | |
| Arrhythmia/Atrial fibrillation, n (%) | 318 | 27 (8.5) | 691 | 46 (6.7) | 0.298 |
| Echocardiography | | | |
| LVEF (%), mean (SD) | 243 | 64.1 (8.5) | 1153 | 63.7 (6.7) | 0.526 |
| sPAP, mmHg, mean (SD) | 325 | 70.0 (21.3) | 673 | 27.5 (9.1) | <0.001 |
| sPAP >40 mmHg, n (%) | 314 (96.6) | 38 (5.6) | <0.001 |
| Tricuspid regurgitation, yes, n (%) | 304 | 278 (91.4) | 1129 | 520 (46.1) | <0.001 |
| Mild | 124 (40.8) | 507 (45.0) | 0.216 |
| Moderate | 116 (38.2) | 13 (1.2) | <0.001* |
| Severe | 38 (12.5) | 0 (0.0) | <0.001* |
| No | 26 (8.6) | 609 (53.9) | <0.001 |
| TAPSE, mm, mean (SD) | 169 | 17.4 (5.2) | 234 | 19.9 (6.7) | <0.001 |
| Pericardial effusion, n (%) | 297 | 89 (30.0) | 1115 | 58 (5.2) | <0.001 |
| PAH-targeted treatments at diagnosis | 364 | | 1589 |
| No treatment | 17 (4.7) | 1337 (84.1) | <0.001* |
| Monotherapy | 119 (32.7) | 176 (11.1) | <0.001* |
| Up-front combination | 228 (62.6) | 76 (4.8) | <0.001* |
Univariate and multivariate survival analysis in PAH-SSc and non-PAH-SSc patients. For both populations, factors associated to transplant-free survival on univariate analysis are shown in Table 3.

The multivariate survival analysis in PAH-SSc patients identified age at diagnosis (hazard ratio (HR) 1.02 [95% CI 1.00–1.03]; \( P = 0.036 \)), NYHA FC III-IV (HR 1.63 [95% CI 1.10–2.42]; \( P = 0.015 \)), and pulmonary vascular resistance (PVR) (HR 2.41 [95% CI 1.37–4.25]; \( P = 0.002 \)) as poor prognostic indicators, whereas DLCO per 10%—predicted increase (HR 0.87 [95% CI 0.78–0.97]; \( P = 0.009 \)) and up-front combination therapy (HR 0.54 [95% CI 0.38–0.77]; \( P < 0.001 \)) were the only factors associated to better prognosis (Table 4). The multivariate analysis in non-PAH-SSc patients showed that older age at diagnosis (HR 1.09 [95% CI 1.07–1.11]; \( P < 0.001 \)) worsened prognosis, while FVC per 10%—predicted increase (HR 0.80 [95% CI 0.72–0.88]; \( P < 0.001 \)) and DLCO per 10%—predicted increase (HR 0.92 [95% CI 0.85–1.00]; \( P = 0.048 \)) were associated with greater survival.

Discussion

By linking two nationwide registries this study, the largest conducted to date, further highlights the huge impact that PAH has on SSc patients. Approximately half of the patients were diagnosed with ILD independently of the presence of PAH. In PAH-SSc patients, ILD was found to worsen PFTs and hemodynamics but did not have a direct significant impact on survival, regardless of the severity of the ventilatory restrictive pattern. Older age, worse NYHA FC stages, higher PVR, and reduced DLCO at the time of diagnosis were independently linked to poor prognosis. Current treatment strategies (i.e., greater use of up-front combination therapy) are likely to have had an impact on survival of PAH-SSc patients even when they experienced mild-moderate ILD.

PAH-SSc patients had higher sPAP and tricuspid regurgitation velocity, were older, had worse NYHA FC, lower DLCO and elevated FVC/DLCO ratio (>1.6 and 1.4), and greater prevalence of pericardial effusion; all of them well known clinical features of SSc-associated PAH. The devastating effect of PAH on SSc was reflected by a reduction of nearly 60% in 5-year transplant-free survival (41.1% vs. 93.9% in non-PAH-SSc patients). Three-year survival rate of PAH-SSc patients in our study (59.1%) was similar to that reported by other registries and a meta-analysis performed by Lefèvre et al. 24. Only in the large prospective PHAROS study 3-year survival rate was higher (75%)30. This has been attributed to earlier diagnosis of PAH as reflected by the greater percentage of patients with NYHA FC I-II (59% vs. ~30% in the above-mentioned registries and in our series). Availability of new PAH-targeted therapies and treatment strategy changes during follow-up are also likely to affect survival. However, in the meta-analysis published by Lefèvre et al.35 survival did not change between studies over time, and disease's severity at baseline was the most important prognostic factor. Up to 60% of PAH-SSc patients in our series received up-front combination therapy in contrast to the 43% in the French registry and the 34% in
the REVEAL registry, both contemporary\textsuperscript{24,27}. Subsequent evidence endorsed up-front combination treatment\textsuperscript{31}, and current guidelines recommend this strategy for most of the patients\textsuperscript{32}. Even though the increased use of

| Table 2. Demographic, clinical, and hemodynamic data of patients with PAH-SSc according to the presence of ILD. Significant values are in bold. BNP B-type natriuretic peptide, CI cardiac index, CO Cardiac output, DLCO diffusing capacity for carbon monoxide, FVC forced vital capacity, IQR interquartile range, ILD interstitial lung disease, LVEF left ventricular ejection fraction, mPAP mean pulmonary artery pressure, NTproBNP N-terminal pro B-type natriuretic peptide, NYHA FC New York Heart Association functional class, PVR pulmonary vascular resistance, RAP right atrial pressure, sPAP systolic pulmonary artery pressure, SD standard deviation, \( \text{SvO}_2 \) mixed venous oxygen saturation, TAPSE tricuspid annular plane systolic excursion, 6MWT 6-min walking test. *Statistical significant comparison after Bonferroni correction (\( p < 0.017 \)). |

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Approximately half of the patients with PAH presented ILD, with 40% showing a moderate-severe restrictive ventilatory pattern. PAH-SSc patients with ILD had lower FVC, DLCO, TAPSE, and CI. Recently, Chauvelot et al. analyzed 128 patients from the French prospective PH registry: 66 with SSc-PH-ILD and 62 with SSc-PAH. Patients with SSc-PH-ILD had lower FVC and lower DLCO. Use of first-line PAH-specific therapies was similar in both groups and included endothelin receptor antagonists (80%), phosphodiesterase 5 inhibitors (13%), or a combination of both (6%). Only 3 patients received a prostacyclin analog as initial treatment.

In our study, PAH-SSc patients with ILD and FVC ≥ 60% presented with FVC/DLCO ≥ 1.6 more frequently, indicating a more prominent vascular involvement in this subgroup. The threshold determining the extension of ILD leading to one or another classification PH group is blurred and remains to be defined. Thus, when patients present with precapillary PH and mild ILD they are classified into PH Group 1, and when they have more severe ILD they are classified into PH Group 3 (PH-ILD). Despite this fact, a significant proportion of patients present with intermediate severity of ILD and with different degrees of PH, which make PH classification and the following treatment decision especially challenging.

In this cohort, the worse hemodynamics and pulmonary capacity at PAH-SSc diagnosis associated with concomitant ILD did not turn into worse transplant-free survival, although a trend to higher 5-year survival was observed in patients with lower FVC. Previous studies have reported increased mortality in patients with PAH-SSc and ILD3,26,34, but most of them merged PAH-SSc patients with mild ILD (PH group 1) with PH-ILD patients. As in our series, Volkmann et al. reported similar 3-year survival rates in PAH-SSc patients with and without ILD (50% and 60%, respectively)35, which were associated with early use of aggressive treatment (i.e., prostanoid therapy was used in 52% of patients with ILD). Recently, Young et al. have described a prospective cohort of 93 patients with ILD, identifying a PH prevalence of 29 (31.2%) with a 3-year survival of 91%. Such optimal survival may be explained by the intensive PH screening program and the extensive use of vasodilator therapy (82.8% of the patients with PH). Conversely, the survival in the French registry was significantly shorter in patients with SSc-PH-ILD compared to those with SSc-PAH. In SSc-PH-ILD patients, the survival rates at 1, 2, and 3 years were 91.9%, 78.8%, and 58.5%, respectively, compared to 95.9%, 91.3%, and 78.6% in SSc-PAH patients (P = 0.04)

A more conservative approach with higher use of PAH monotherapy at diagnosis was observed for patients with ILD and FVC < 60%. This was probably due to safety concerns associated with the use of PAH-targeted therapies in patients with PH-ILD as these latter patients have traditionally been excluded from PAH clinical trials.

Facing the reality that we still cannot precisely classify PH-SSc when associated with ILD, there is increasing evidence suggesting that early use of pulmonary vasodilator treatment improves outcomes, and worldwide registries confirm a widespread off-label use of these drugs in real life, reflecting that treating PAH is a priority for clinicians irrespective of the severity of ILD. Our results reinforce this idea and indicate that treating PAH-SSc aggressively from onset improves outcomes regardless of the presence of ILD.

In PAH-SSc patients, prognostic factors identified in univariate survival analysis were similar to prior meta-analysis30, although lower FVC or DLCO, increased FVC/DLCO ratio ≥ 1.4, and lower use of up-front combination therapies at the time of PAH diagnosis were also identified as indicators of poorer survival. Interestingly, the presence of ILD or reduced FVC were not identified as risk factors in the multivariate analysis, whereas older age, worse NYHA FC, elevated PVR or reduced DLCO, and monotherapy at PAH diagnosis were associated to up-front combination therapy in our study was not correlated with better global survival compared to the registries mentioned above, this strategy was independently associated with greater survival in our cohort.
worse prognosis. Conversely, in the French PH registry only the presence of ILD, chronic kidney disease, and 6-min walk distance at baseline were associated with greater mortality. Concerning the age at PAH diagnosis, the French national study conducted between 2006 and 2017, has described an improvement in survival in patients ≤ 70 years but not in older ones. That may be explained by the higher proportion of patients that, in the later years, has been treated with pulmonary vasodilator up-front combination therapy both in the first 4 months

| Table 3. | Factors associated to survival in univariate analyses. Significant values are in bold. † Parameter not included in the multivariate analysis as it was available in less than 60% of non-PAH-SSc patients. ‡ Parameter not included in the multivariate analysis as it was available in less than 60% of PAH-SSc patients. * All death patients in non-PAH-SSc had TAPSE ≥ 18 mm. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | PAH-SSc          |                | Non-PAH-SSc      |                |                  |                  |
|                | HR (95% CI) | P value | HR (95% CI) | P value |                  |                  |
| Gender, female | 0.96 (0.63–1.45)| 0.846 | 0.42 (0.29–0.60) | < 0.001 |                  |                  |
| Age at diagnosis, years | 1.02 (1.00–1.03) | 0.010 | 1.08 (1.07–1.09) | < 0.001 |                  |                  |
| NYHA FC III–IV† | 1.98 (1.40–2.80) | < 0.001 | 2.95 (1.78–4.89) | < 0.001 |                  |                  |
| ILD on HRCT | 1.20 (0.85–1.71) | 0.304 | 1.60 (1.11–2.32) | 0.013 |                  |                  |
| 6MWT, per 10-m increase | 0.97 (0.96–0.98) | < 0.001 | NA | NA |                  |                  |

| Table 4. | Factors associated to survival in multivariate analyses. Significant values are in bold. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | PAH-SSc          |                | Non-PAH-SSc      |                |                  |                  |
|                | HR (95% CI) | P value | HR (95% CI) | P value |                  |                  |
| Age, years | 1.02 (1.01–1.03) | 0.033 | Age, years | 1.09 (1.07–1.11) | < 0.001 |                  |                  |
| NYHA FC III–IV† | 1.63 (1.10–2.42) | 0.015 | FVC, per 10%-predicted increase | 0.80 (0.72–0.88) | < 0.001 |                  |                  |
| PVR, Wood units | 2.41 (1.37–4.25) | 0.002 | DLCO, per 10%-predicted increase | 0.92 (0.85–0.99) | 0.048 |                  |                  |
| DLCO, per 10%-predicted increase | 0.87 (0.78–0.97) | 0.009 |                  |                  |                  |                  |
| Up-front combination therapy | 0.54 (0.38–0.77) | < 0.001 |                  |                  |                  |                  |
Several limitations have to be recognized in the interpretation of this study, some of them (e.g., only using variables common to both registries, not analyzing treatments during follow-up nor the last one reported) have already been noted. RHC was not performed for the selection of non-PAH-SSc patients due to it is an invasive procedure, and it is indicated after cautious doctor’s decision. ILD-targeted therapy was not available in PAH-SSc cohort that may also influence on survival of this patients. Both registries are voluntary, which leads to a lack of information on variables that may impact prognosis. To mitigate this limitation, multivariable analysis was carried out using only variables available in > 60% of patients.

Conclusion
The largest assessment ever of the impact of PAH on SSc confirms the very relevant clinical and prognostic repercussion of PAH on SSc. When associated with ILD, PAH-SSc presents with worse hemodynamic features and PFTs, but not poorer survival independently of ILD severity. Baseline treatment with pulmonary vasodilator up-front combination therapy was established in a majority of PAH-SSc patients regardless of the presence of ILD and was independently associated with longer survival.

Materials and methods

Patients. Study design, inclusion and exclusion criteria, and data collection of RESCLE and REHAP registries have been published elsewhere. All methods were carried out in accordance with relevant guidelines and regulations and the study was approved by the Hospital Vall d’Hebron Institutional Review Board [PRAMI]280/2018]. In brief, RESCLE is a voluntary nationwide registry of patients with SSc diagnosed on the 2013 ACR/EULAR criteria for SSc and/or on the modified LeRoy and Medsger classification criteria. The onset of scleroderma was defined as the first symptom related to SSc including Raynaud’s phenomenon. Both prevalent and incident non-PAH-SSc patients from RESCLE registry were included in the analysis, and excluding PH-SSc patients. REHAP is also a voluntary nationwide registry designed to prospectively collect exhaustive information on the demographics, management, and outcome of patients newly and previously diagnosed with PAH by RHC. PAH was defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest with a pulmonary artery wedge pressure ≤ 15 mmHg and pulmonary vascular resistances ≥ 3 Wood units at RHC. For the purposes of this study, only prospectively recruited incident patients with SSc-associated PAH (PAH-SSc) from REHAP registry were included in this analysis.

Data collected. Baseline data from RESCLE and REHAP registries at the time of diagnosis of SSc and PAH respectively were collected. The following variables, considered potential risk factors for PAH in SSc, were common to both registries and included in the analyses: (1) Demographics: age at the time of diagnosis (SSc or PAH) and gender; (2) Clinical: New York Heart Association functional class (NYHA FC) and time since SSc diagnosis (only for RESCLE patients); (3) Pulmonary function test (PFT): predicted forced vital capacity (FVC %), predicted diffusing capacity for carbon monoxide (DLCO %) and the FVC%/DLCO% ratio > 1.6. We also evaluated a less restrictive cut-off value of 1.4, which has been associated to PH in patients with ILD. ILD was defined as the presence of an interstitial pattern on high-resolution computed tomography (HRCT) in REHAP, and by HRCT or chest x-ray in RESCLE. Comparative analyses were performed only in patients with HRCT-confirmed ILD; (4) Echocardiography assessments: left ventricular ejection fraction (LVEF), systolic PAP (sPAP), degree of tricuspid regurgitation, pericardial effusion, and tricuspid annular plane systolic excursion (TAPSE); (5) Causes of death, which were homogenized as both registries had different approaches of capturing these data (online supplementary table I). For the definition of independent prognostic factors in PAH-SSc and to analyze the impact of ILD on PAH-SSc, we also selected prognostic variables including 6-min walk test (6MWT), hemodynamic parameters (cardiac output [CO], cardiac index [CI], mean pulmonary artery pressure [mPAP], pulmonary vascular resistance [PVR], right atrial pressure [RAP], and mixed venous oxygen saturation [SvO2]), and biomarkers (N-terminal pro B-type natriuretic peptide [NTproBNP] or B-type natriuretic peptide [BNP]).

Patient demographics, clinical variables, cardiac, and pulmonary assessments were prospectively recorded by participating physicians according to a standard protocol. Both registries required all patients to provide written informed consent in order to participate. The Institutional Review Boards of the participating hospitals approved the respective registries.

Statistical analyses. Continuous variables were summarized as the mean ± SD or the median and interquartile range (IQR) as appropriate and compared using Student’s t-test or Mann–Whitney U test, respectively. Categorical variables were compared using the chi-square and Fisher’s exact tests as appropriate. P values < 0.05 (2-tailed) were considered significant. Bonferroni correction was applied in multiple comparisons. Patients lost to follow-up were censored on the day of their last visit. Time-to-event analyses were performed using the Kaplan–Meier method until date of lung transplantation or death. Transplant-free survival was estimated since the time of SSc diagnosis in non-PAH-SSc patients, and since PAH diagnosis in PAH-SSc patients. Factors associated with worse prognosis were identified using the Cox proportional hazards models. Variables collected in > 60% of patients that were found to be significant in univariate analysis (P < 0.05) were incorporated into a step-wise multivariate model.

Data availability
The data that support the findings of this study are available on request from the corresponding author.
References

1. Denton, C. P. & Khanna, D. Systemic sclerosis. Lancet 390, 1685–1699. https://doi.org/10.1016/S0140-6736(17)30933-9 (2017).

2. Kowal-Bielecka, O. et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann. Rheum. Dis. 76, 1327–1339. https://doi.org/10.1136/annrheumdis-2016-209909 (2017).

3. Steen, V. D. & Medsger, T. A. Changes in causes of death in systemic sclerosis, 1972–2002. Ann. Rheum. Dis. 66, 940–944. https://doi.org/10.1136/annrheumdis.2006.066068 (2007).

4. Simonneau, G. et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur. Respir. J. https://doi.org/10.1183/13993003.01913-2018 (2019).

5. Chang, B., Wigley, F. M., White, B. & Wise, R. A. Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. J. Rheumatol. 30, 2398–2405 (2003).

6. Trad, S. et al. Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease. Arthritis Rheum. 54, 184–191. https://doi.org/10.1002/art.21538 (2006).

7. Mathai, S. C. et al. Survival in pulmonary hypertension associated with systemic sclerosis: Impact of interstitial lung disease. Arthritis Rheum. 60, 569–577. https://doi.org/10.1002/art.24267 (2009).

8. Hachulla, E. et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: A French nationwide prospective multicenter study. Arthritis Rheum. 52, 3792–3800. https://doi.org/10.1002/art.21433 (2005).

9. Mukerjee, D. et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: Application of a registry approach. Ann. Rheum. Dis. 62, 1088–1093. https://doi.org/10.1136/ard.62.11.1088 (2003).

10. Hsu, V. M. et al. Development of pulmonary hypertension in a high-risk population with systemic sclerosis in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort study. Semin. Arthritis Rheum. 44, 55–62. https://doi.org/10.1016/j.semarthrit.2014.03.002 (2014).

11. Aounac, J. et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J. Rheumatol. 37, 2290–2298. https://doi.org/10.3899/jrheum.100245 (2010).

12. Coghlan, J. G. et al. Systemic sclerosis and its pulmonary complications in The Netherlands: An epidemiological study. Ann. Rheum. Dis. 68, 961–965. https://doi.org/10.1136/annrheumdis.2008.091710 (2009).

13. Michelfelder, M. et al. Interstitial lung disease increases mortality in systemic sclerosis patients with pulmonary arterial hypertension without affecting hemodynamics and exercise capacity. Clin. Rheumatol. 36, 381–390. https://doi.org/10.1007/s10067-016-3504-6 (2017).

14. Chaisson, N. E. & Hassoun, P. M. Systemic sclerosis-associated pulmonary arterial hypertension. Chest 144, 1346–1356. https://doi.org/10.1378/chest.12-2396 (2013).

15. Weatherald, J. et al. Screening for pulmonary arterial hypertension in systemic sclerosis. Eur. Respir. Rev. https://doi.org/10.1183/16000617.0023-2019 (2019).

16. Le Pacque, J. et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: Impact of pulmonary arterial hypertension therapies. Arthritis Rheum. 63, 2456–2464. https://doi.org/10.1002/art.30423 (2011).

17. Condiffe, R. et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am. J. Respir. Crit. Care Med. 179, 151–157. https://doi.org/10.1164/rcrm.200806-953OC (2009).

18. Alba, M. A. et al. Early- versus late-onset systemic sclerosis: Differences in clinical presentation and outcome in 1037 patients. Medicine (Baltimore) 93, 73–81. https://doi.org/10.1097/MD.0000000000000018 (2014).

19. Garcia-Hernandez, F. J. et al. Pulmonary hypertension in Spanish patients with systemic sclerosis. Data from the RESCLE registry. Clin. Rheumatol. 38, 1117–1124. https://doi.org/10.1007/s10067-018-4390-x (2019).

20. Pestana-Fernandez, M. et al. Long-term efficacy and safety of monotherapy versus combination therapy in systemic sclerosis-associated pulmonary arterial hypertension: A retrospective cohort study from the Nationwide Spanish Scleroderma Registry (RESCLE). J. Rheumatol. https://doi.org/10.3899/jrheum.180595 (2019).

21. Escribano-Subias, P. et al. Survival in pulmonary hypertension in Spain: Insights from the Spanish registry. Eur. Respir. J. 40, 596–603. https://doi.org/10.1183/13993003.00101211 (2012).

22. Chung, L. et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 146, 1494–1504. https://doi.org/10.1378/chest.13-3014 (2014).

23. Hurdman, J. et al. ASPIRE registry: Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. Eur. Respir. J. 39, 945–955. https://doi.org/10.1183/09031936.00078411 (2012).

24. Hooper, M. M. et al. Mortality in pulmonary arterial hypertension: Prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur. Respir. J. 50, https://doi.org/10.1183/13993003.00740-2017 (2015).

25. Weatherald, J. et al. Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension. Eur. Respir. J. https://doi.org/10.1183/13993003.008678-2018 (2018).

26. Hachulla, E. et al. Survival improved in patients aged 5-70 years with systemic sclerosis-associated pulmonary arterial hypertension during the period 2006 to 2017 in France. Chest https://doi.org/10.1016/j.chest.2019.10.045 (2006).

27. Lefèvre, G. et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: A systematic review and meta-analysis. Arthritis Rheum. 65, 2412–2423. https://doi.org/10.1002/art.38029 (2013).

28. Kolstad, K. D., Li, S., Steen, V., Chung, L. & Investigators, P. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry (PHAROS). Chest 154, 862–871. https://doi.org/10.1016/j.chest.2018.05.002 (2018).

29. Galie, N. et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N. Engl. J. Med. 373, 834–844. https://doi.org/10.1056/NEJMoa1413687 (2015).

30. Galie, N. et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur. Heart J. 37, 67–119. https://doi.org/10.1093/eurheartj/ehv317 (2016).

31. Chauvel, L. et al. Hemodynamic response to treatment and outcomes in pulmonary hypertension associated with interstitial lung disease versus pulmonary arterial Hypertension in Systemic sclerosis: Data from a study identifying prognostic factors in pulmonary hypertension associated with interstitial lung disease. Arthritis Rheum. 73, 295–304. https://doi.org/10.1002/art.41512 (2021).

32. Lee, M. H. & Bull, T. M. The role of pulmonary arterial hypertension-targeted therapy in systemic sclerosis. F1000Res https://doi.org/10.12688/f1000research.20313.1 (2019).

33. Volkmann, E. R. et al. Improved transplant-free survival in patients with systemic sclerosis-associated pulmonary hypertension and interstitial lung disease. Arthritis Rheum. 66, 1900–1908. https://doi.org/10.1002/art.38623 (2014).
36. Young, A. et al. Prevalence, treatment, and outcomes of coexistent pulmonary hypertension and interstitial lung disease in systemic sclerosis. *Arthritis Rheum.* **71**, 1339–1349. https://doi.org/10.1002/art.40862 (2019).
37. Nathan, S. D. et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur. Respir. J.* https://doi.org/10.1183/13993003.01914-2018 (2019).
38. van den Hoogen, F. et al. 2013 classification criteria for systemic sclerosis: An American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum.* **65**, 2737–2747. https://doi.org/10.1002/art.38098 (2013).
39. LeRoy, E. C. & Medsger, T. A. Jr. Criteria for the classification of early systemic sclerosis. *J. Rheumatol.* **28**, 1573–1576 (2001).
40. Valenzuela, A., Nandagopal, S., Steen, V. D. & Chung, L. Monitoring and diagnostic approaches for pulmonary arterial hypertension in patients with systemic sclerosis. *Rheum. Dis. Clin. N. Am.* **41**, 489–506. https://doi.org/10.1016/j.rdc.2015.04.009 (2015).
41. Yaqub, A. & Chung, L. Epidemiology and risk factors for pulmonary hypertension in systemic sclerosis. *Curr. Rheumatol. Rep.* **15**, 302. https://doi.org/10.1007/s11926-012-0302-2 (2013).
42. Morrison, K. et al. Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: Results from a large multicenter cohort study. *BMC Pulm. Med.* **16**, 134. https://doi.org/10.1186/s12890-016-0296-z (2016).
43. Steen, V. & Medsger, T. A. Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum.* **48**, 516–522. https://doi.org/10.1002/art.10775 (2003).
44. Eid, D. & Mohamed-Hussein, A. A. R. Evaluation of FVC/DLCO ratio as a predictor for pulmonary hypertension in patients with interstitial lung diseases. *Eur. Respir. J.* **50**, 25 (2017).
45. Steen, V. D., Graham, G., Conte, C., Owens, G. & Medsger, T. A. Jr. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum.* **35**, 765–770. https://doi.org/10.1002/art.1780350709 (1992).

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