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ORIGINAL CLINICAL SCIENCE

The spectrum of systemic sclerosis-associated pulmonary hypertension: Insights from the ASPIRE registry

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KEYWORDS:
systemic sclerosis;
pulmonary hypertension;
Interstitial lung disease;
left heart disease;
outcomes

BACKGROUND: There are limited data assessing the spectrum of systemic sclerosis-associated pulmonary hypertension (PH).

METHODS: Data for 912 systemic sclerosis patients assessed between 2000 and 2020 were retrieved from the Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre (ASPIRE) registry and classified based on 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines and multimodality investigations.

RESULTS: Reduction in pulmonary vascular resistance (PVR) diagnostic threshold to > 2 WU resulted in a 19% increase in precapillary PH diagnoses. Patients with PVR ≤2 WU had superior survival to PVR > 2–3 WU which was similar to PVR > 3–4 WU. Survival in pulmonary arterial hypertension (PAH) was superior to PH associated with lung disease. However, patients with mild parenchymal disease on CT had similar characteristics and outcomes to patients without lung disease. Combined pre- and postcapillary PH had significantly poorer survival than isolated postcapillary PH. Patients with mean pulmonary arterial wedge pressure (PAWP) 13–15 mm Hg had similar haemodynamics and left atrial volumes to those with PAWP > 15 mm Hg. Unclassified-PH had more frequently dilated left

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Abbreviations: SSc, systemic sclerosis; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; ILD, interstitial lung disease; LHD, left heart disease; CLD, chronic lung disease; PVOD, pulmonary veno-occlusive disease; RHC, right heart catheterization; CFES, combined fibrosis and emphysema syndrome, WHO FC, World Health Organization Functional Class; ISWD, Incremental Shuttle Walk Distance; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; CMR, cardiac magnetic resonance imaging; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction. RVEDV, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction; LAV, left atrial volume, IpcPH, isolated postcapillary PH; CpcPH, combined pre- and postcapillary PH

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atria and higher PAWP than PAH. Although Unclassified-PH had a similar survival to No-PH, 36% were subsequently diagnosed with PAH or PH associated with left heart disease. The presence of 2–3 radiological signs of pulmonary veno-occlusive disease was noted in 7% of PAH patients and was associated with worse survival. Improvement in incremental shuttle walking distance of ≥30 m following initiation of PAH therapy was associated with superior survival. PAH patients diagnosed after 2011 had greater use of combination therapy and superior survival.

CONCLUSION: A number of systemic sclerosis PH phenotypes can be recognized and characterized using haemodynamics, lung function and multimodality imaging.

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Pulmonary hypertension (PH) is a haemodynamic definition characterized by a mean pulmonary arterial pressure (mPAP) > 20 mm Hg and has many causes.[1] PH commonly develops in patients with systemic sclerosis (SSc), an autoimmune condition characterized by inflammation, fibrosis and vascular disease manifesting with skin thickening, Raynaud's phenomenon and varying degrees of internal organ involvement.[2]

Group 1 PH (Pulmonary arterial hypertension, PAH) results from a progressive pulmonary arterial vasculopathy leading to increased pulmonary vascular resistance (PVR) and pressure and occurs in 6.4–9% of patients with SSc.[3,4] Some patients with SSc and group 1 disease may develop remodeling of small pulmonary veins or venules (pulmonary veno-occlusive disease, PVOD).[5] Other forms of PH may also occur in association with SSc.[6] Group 2 PH is characterized by increased left atrial pressure and may develop in response to SSc-associated or comorbid left heart disease (PH associated with left heart disease, PH-LHD).[7] Group 3 PH (PH associated with chronic lung disease, PH-CLD) may also manifest in patients with SSc, especially in the presence of SSc-associated interstitial lung disease (ILD).[8]

Several therapies have been shown to result in haemodynamic and functional improvement in SSc-associated PAH (SSc-PAH).[9] However, there are limited data regarding characteristics and outcomes in other forms of PH associated with SSc (SSc-PH) and conflicting data on the impact of lung disease on outcomes in patients with SSc-PH.[10–12] We have therefore studied patient characteristics and outcomes across the spectrum of SSc-PH in a cohort of patients from a large registry.

Methods

The Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre (ASPIRE) registry, which enrolls consecutive patients at a large PH referral center in the UK, was interrogated to identify SSc patients assessed between 2000 and 2020. Haemodynamic, radiological, functional and lung function data were retrieved from clinical databases. Diagnostic criteria from the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines were adopted.[1] Repeat RHC was performed where clinically indicated. Computed Tomography (CT) reports from the time of diagnosis were interrogated to categorize the extent of any parenchymal lung disease as minor, mild, moderate or severe. Where no reports were available clinic letters were interrogated. The method of Goh et al was adapted so that extensive disease was defined by the presence of moderate-severe parenchymal lung disease or an FVC ≤70% in the presence of mild disease on CT.[13] Clinically significant COPD was defined by an FEV_1/FVC of < 0.7 and an FEV_1 < 60% predicted. Patients with no-PH or patients who were subsequently ascribed a different form of SSc-associated PH remained in their original group for the purpose of analysis including of PAH therapies. Where available, data regarding cardiac chamber size and function from cardiac magnetic resonance imaging (CMR) were retrieved.[14] Date of diagnosis was defined as date of first RHC demonstrating the presence or absence of PH. For the purpose of survival analysis, the censoring date was taken as the date of death (retrieved from the National Health Service central spine) or February 1, 2024. Ethical approval was obtained (REC 22/EE/0011) and the study complied with the ISHLT Ethics statement.

Statistical analysis

Data are presented as mean ± standard deviation or median (25th,75th centile) as appropriate. Paired data were compared using the paired t-test or Wilcoxon signed rank test. Unpaired data were compared using the independent *t*-test or Mann-Whitney *U* test. Multiple comparisons were performed using ANOVA or Kruskal-Wallis tests with Bonferroni post-hoc correction. Categorical data were compared using the χ^2 test. Prognostic factors were assessed using Cox regression analysis. Parameters with a *p*-value of < 0.2 at univariate analysis were entered into the multivariate analysis. Survival was estimated using the Kaplan-Meier method with differences between groups assessed by the Log-Rank test including selected pairwise comparisons. Survival curves were truncated at 10 years follow-up. A *p*-value of < 0.05 was used to define statistical significance. Analysis was performed using SPSS 26, Graphpad Prism and R version 4.3.1.

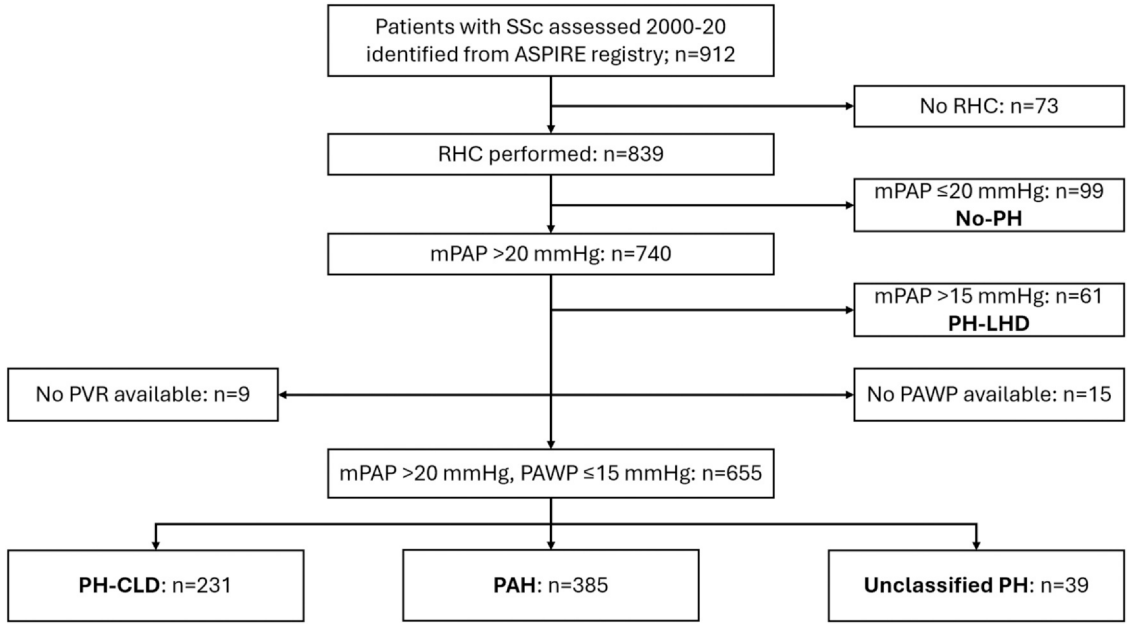

Fig. 1 Study flowchart. CLD, chronic lung disease; LHD, left heart disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SSc, systemic sclerosis.

Results

During the study period, 912 patients with SSc were identified as having been assessed for the presence of PH (Figure 1). Seventy-three patients did not undergo RHC, the majority of whom were deemed to be at low risk of PAH on the basis of non-invasive investigations. Ninety-nine patients (12% of those who underwent RHC) had a mPAP ≤20 mm Hg (No-PH). Twenty-four patients with a mPAP >20 mm Hg did not have either a pulmonary arterial wedge pressure (PAWP) or PVR available and so were excluded from further analysis. Sixty-one patients (7%) had a PAWP >15 mm Hg and were therefore defined as having PH-LHD. Of the remaining 655 patients, 385 (46% of those who underwent RHC) had precapillary PH without significant lung disease and were defined as having PAH. Two hundred and thirty one patients (27%) had precapillary PH in the presence of extensive lung disease (PH-CLD). Thirty-nine patients (5%) had an mPAP >20 mm Hg, PAWP ≤15 mm Hg but a PVR ≤2 WU and so were diagnosed with Unclassified-PH. Incremental shuttle walk distance (ISWD) data were available in 96%, DLco in 93% and mPAP in 100% of analysed patients.

Patient characteristics

The overall mean age was 66 ± 11 years while 85% of patients were female. Characteristics of the main groups are summarized in Table 1. Patients with Unclassified-PH or No-PH had a higher proportion in functional class (FC) II, lower emPHasis-10 scores and higher ISWD than the other 3 groups. FVC was significantly lower in PH-CLD and PH-LHD compared with other 3 groups. DLco was significantly lower in PH-CLD than in PAH and PH-LHD while it was significantly higher in patients with Unclassified-PH and No-PH. Pulmonary haemodynamics in patients with PAH and PH-CLD were similar. Compared with PAH, patients with PH-LHD had a similar mPAP but significantly higher PAWP, higher cardiac index and lower PVR. Survival according to diagnosis is demonstrated in Figure 2a and Figure S1a.

PAH and PH-CLD

Apart from a slightly lower PVR, patients with PH-CLD had similar abnormalities in exercise capacity, quality of life, pulmonary haemodynamics and CMR parameters to patients with PAH (Table 1). FEV_1, FVC and DLco were lower in patients with PH-CLD. Median survival was significantly worse in patients with PH-CLD compared with PAH (2.69 vs 3.98 years, $p = 0.0001$, Figure 3a and Figure S1a). Cox regression analysis identified male sex, higher age and lower DLco and ISWD, but not the form of precapillary PH, as independent predictors of worse survival in precapillary PH (Table S1 and Figure S1b).

Within the PH-CLD group, patients with combined fibrosis and emphysema syndrome (CFES)/emphysema had the lowest DLco, the highest proportion of males (45%) and the poorest survival (Table 2, Figure 3b). There was no significant difference in survival between the 43 patients with CFES and the 20 patients with moderate-severe emphysema ($p = 0.44$). Patients with precapillary PH with no-mild parenchymal lung disease had similar patient characteristics whereas patients with moderate-severe parenchymal lung disease had incrementally worse lung function (Table S2). Survival in patients with no-mild parenchymal lung disease was superior to that of patients with moderate-severe parenchymal lung disease (Figure S2).

Table 1 Characteristics of Main Diagnostic Groups

	PAH ($n = 385$)	PH-Lung ($n = 231$)	PH-LHD ($n = 61$)	Unclassified PH ($n = 39$)	No PH ($n = 99$)	p-value
Age (years)	66.8 ± 11	65.9 ± 11	65.8 ± 11	63.4 ± 11	64.4 ± 11	0.164
Female (%)	90	75	90	80	89	< 0.001
SSc form[a]: Limited/ Diffuse/Overlap (%)	89/5/6	72/21/7	78/11/11	87/5/8	70/14/16	< 0.001
WHO FC I/II/III/IV (%)	1/10/79/10	0/12/70/18	2/21/70/7	3/44/53/0	7/45/48/0	< 0.001
ISWD (m)	140 (65,260)[bc]	120(60,220)[bc]	140(80,255)[c]	255(115,420)[de]	260(140,120)[def]	< 0.001
emPHasis 10[g]	28 ± 13[bc]	30 ± 12[bc]	32 ± 12[b]	16 ± 14[def]	22 ± 12[de]	< 0.001
Lung Function:						
FEV_1 (%)	88.5 ± 19[ef]	70.4 ± 21[bcd]	74.2 ± 21[bcd]	88.7 ± 19[ef]	87.2 ± 21[ef]	< 0.001
FVC (%)	100.4 ± 22[ef]	78.6 ± 25[bcd]	78.1 ± 26[bcd]	99.5 ± 23[ef]	97.1 ± 22[ef]	< 0.001
FEV_1/FVC (%)	73.3 ± 9	75.3 ± 13	75.1 ± 12	74.3 ± 8	75.1 ± 10	0.221
DLco (%)	40.6 ± 12[bce]	31.9 ± 12[bcdf]	43.4 ± 16[bce]	56.8 ± 15[def]	54.9 ± 17[def]	< 0.001
Pulmonary Haemodynamics:						
mPAP (mm Hg)	40.4 ± 13[bc]	37.9 ± 12[bc]	38.5 ± 14[bc]	24.1 ± 2[cdef]	16.9 ± 2[bdef]	< 0.001
PAWP (mm Hg)	9.7 ± 3[bcf]	9.3 ± 3[bcf]	18.1 ± 3[bcde]	12.5 ± 2[cdef]	7.7 ± 3[bdef]	< 0.001
CO (L.min)	4.5 ± 1.5[bcf]	4.7 ± 1.4[bcf]	5.3 ± 1.7[bde]	6.8 ± 1.5[cdef]	5.2 ± 1.5[deb]	< 0.001
CI ($L.min.m^{-2}$)	2.6 ± 0.8[bcf]	2.8 ± 0.8[bc]	3.0 ± 0.9[bd]	3.5 ± 0.7[cdef]	3.1 ± 0.8[deb]	< 0.001
PVR (WU)	6.4 (3.7, 11.2)[bcf]	5.4(3.6,9.7)[bcf]	3.3(1.7,6.5)[bcde]	1.8 (1.7,1.9)[def]	1.8 (1.3,2.3)[def]	< 0.001
CMR[h]:						
LVEDV (ml)	122 ± 34[bf]	123 ± 34[bf]	144 ± 39[de]	164 ± 39[cde]	130 ± 31[b]	< 0.001
RVEDV (ml)	171 ± 59[c]	168 ± 61[c]	168 ± 63[c]	153 ± 37	126 ± 36[def]	< 0.001
RVSV (ml)	68 ± 22[b]	64 ± 21[b]	73 ± 23	85 ± 22[cde]	63 ± 17[b]	0.001
RVEF (%)	42 ± 12[bc]	40 ± 12[bc]	47 ± 15	56 ± 7[de]	51 ± 10[de]	< 0.001
LAV (ml)	69 ± 26[bf]	62 ± 22[bf]	86 ± 23[cde]	98 ± 20[cde]	66 ± 32[bf]	< 0.001
Maximal subsequent PH therapy (%)						< 0.001
none	11	11	24	64	94	
oral mono	32	38	53	15	4	
oral dual	41	37	15	13	2	
oral triple	3	1	2	0	0	
iv or neb prost	13	13	6	8	0	

CI, cardiac index; CO, cardiac output; DLco, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISWD, incremental shuttle walk distance; iv, intravenous; LAV, left atrial volume; LVEDV, left ventricular end diastolicvolume; mono, monotherapy; mPAP, meanpulmonary arterial pressure; neb, nebulized; PAWP, pulmonary arterial wedge pressure; prost, prostanoid; PVR, pulmonary vascular resistance; RVEDV, right ventricular enddiastolic volume; RVEF, right ventricular ejection fraction; RVSV, right ventricular stroke volume; WHO FC, World Health Organization Functional Class.

[a]Form of SSc not retrieved in 4% of cohort.
[b]$p < 0.05$ vs Unclassified PH.
[c]$p < 0.05$ vs No PH.
[d]$p < 0.05$ vs PAH.
[e]$p < 0.05$ vs PH-Lung.
[f]$p < 0.05$ vs PH-LHD.
[g]$n = 320$.
[h]$n = 380$.

Effect of changing PH diagnostic thresholds

World Symposia on PH (WSPH) from 2003 to 2013 and the 2015 ESC/ERS guidelines defined precapillary PH as mPAP ≥25 mm Hg, PAWP ≤15 mm Hg and PVR > 3 WU.[6] In view of population data suggesting that mPAP > 20 mm Hg is associated with worse survival, the 6th WSPH suggested a threshold of > 20 mm Hg to define PH.[15,16] In view of further data demonstrating that a PVR ≥2 WU is also associated with poorer survival, the 2022 ESC/ERS guidelines subsequently introduced a lower PVR threshold of PVR > 2 WU in defining precapillary PH.[1,17] Using these 3 diagnostic definitions of precapillary PH on the study cohort would result in 503 patients diagnosed with pre-capillary PH using the 2015 ESC/ERS criteria but only an additional 16 patients being diagnosed using the 6th WSPH criteria ($n = 519$). The 2022 ESC/ERS guidelines, however, resulted in an additional 97 patients being assigned a diagnosis of pre-capillary PH ($n = 616$, Figure S3).

PVR and unclassified-PH

We assessed survival in patients with precapillary or Unclassified-PH according to PVR. Survival of patients with a

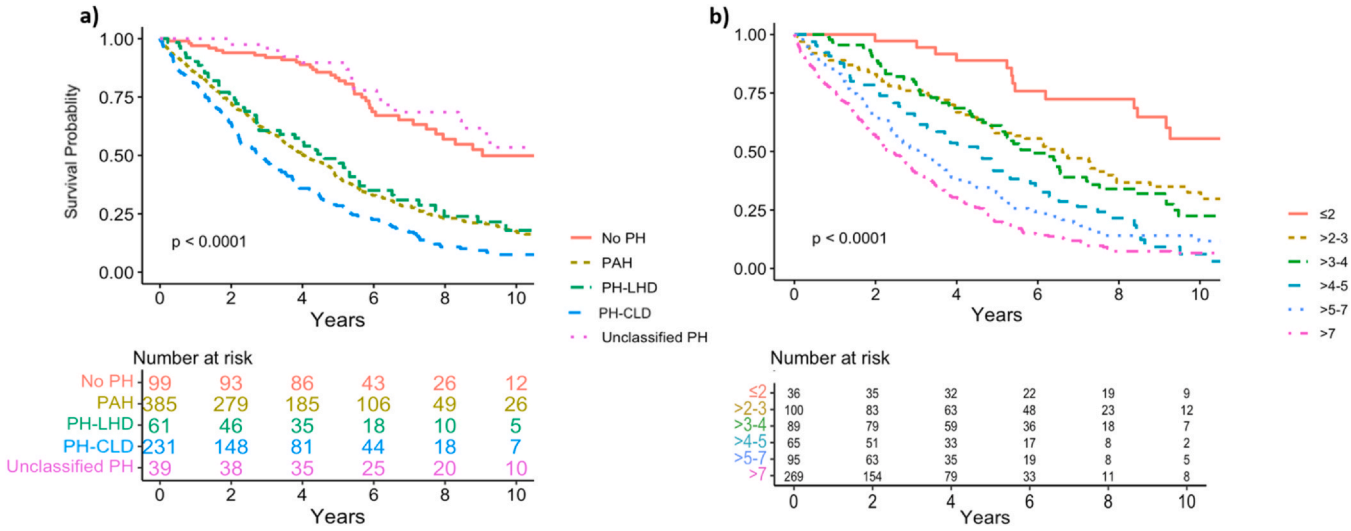

Fig. 2 Cumulative survival from diagnosis: (a) PH diagnosis of patients who underwent RHC. Significant paired *p*-values: PH-CLD vs all other groups: $p < 0.001$; PAH vs PH-CLD, No-PH and Unclassified-PH: $p < 0.001$; PH-LHD vs PH-CLD, No-PH and Unclassified-PH: $p < 0.001$. (b) Patients with precapillary or unclassified PH by PVR (WU). PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-CLD, PH associated with chronic lung disease; PH-LHD, PH associated with left heart disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; WU, Woods Units.

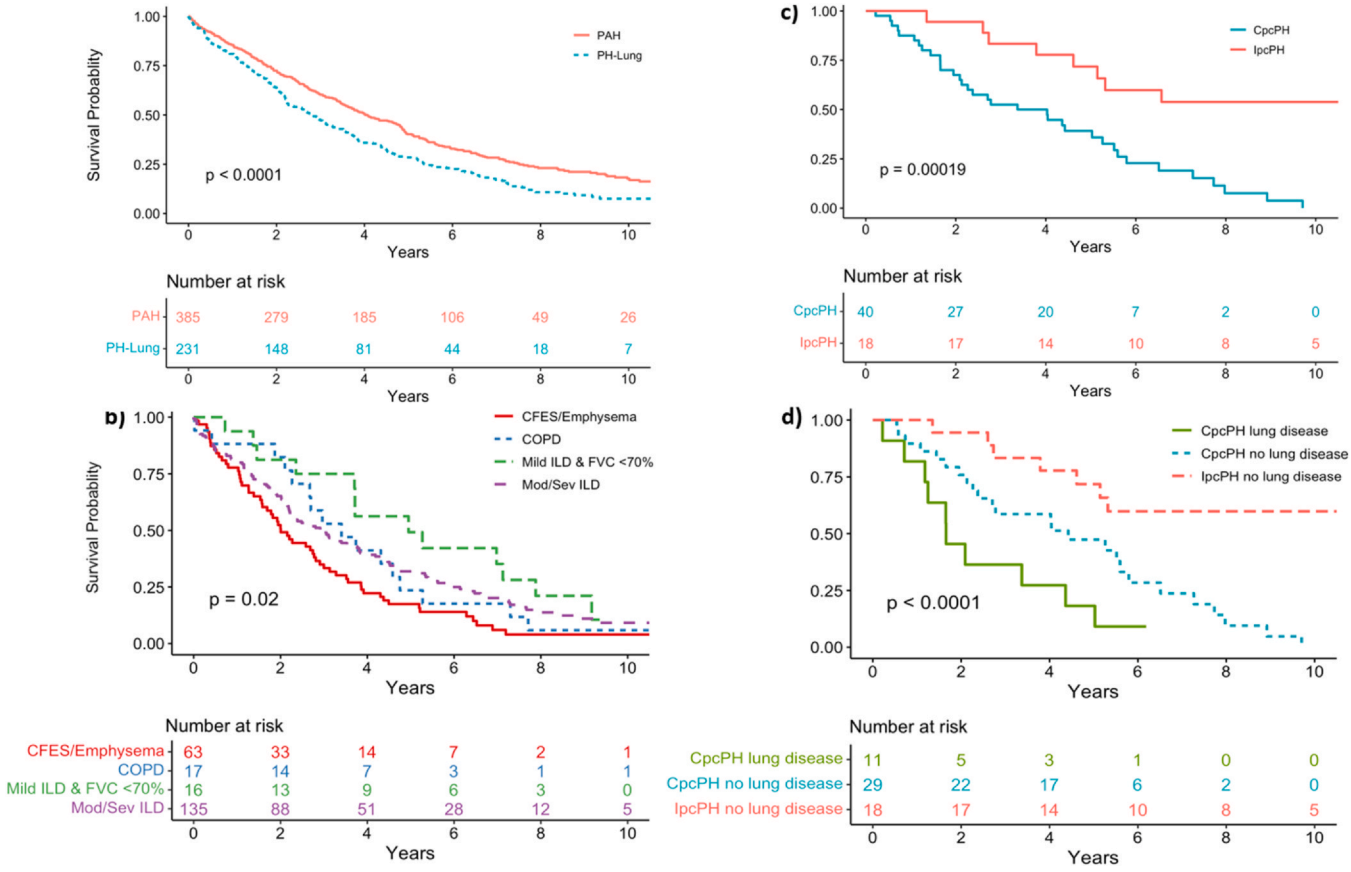

Fig. 3 Cumulative survival from diagnosis: (a) PAH vs PH-Lung; (b) Subgroups of PH-Lung; (c) Combined vs Isolated postcapillary PH; (d) PH-LHD with or without additional lung disease. CFES, combined fibrosis and emphysema syndrome; CpcPH, Combined pre- and postcapillary PH; ILD, interstitial lung disease; IpcPH, Isolated postcapillary PH; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-LHD, PH associated with left heart disease.

PVR ≤2 WU was superior to that of patients with a PVR >2–3 WU (median 9.5 vs 6.1 years, overall $p < 0.05$, Figure 2b). There was, however, no significant difference in survival between patients with a PVR >2–3 and >3–4 WU. Increasing levels of PVR were associated with progressively poorer survival.

Patients with Unclassified-PH had a haemodynamic picture distinct from other forms of PH or no PH, with mild

Table 2 Characteristics of PH-Lung Subgroups

	Moderate-severe ILD ($n = 135$)	Mild ILD & FVC < 70% ($n = 16$)	COPD ($n = 17$)	CFES/Emphysema ($n = 63$)	p-value
Age (years)	64.0 ± 12[a]	69.3 ± 10	71.7 ± 7[b]	67.4 ± 9	0.010
Female (%)	81	81	94	55	< 0.001
ISWD (m)	110 (40,180)	220 (160,280)	80 (0,160)	120 (40,200)	0.072
Lung Function:					
FEV_1 (%)	69.9 ± 22[a]	79.4 ± 14[a]	47.8 ± 6[bcd]	75.7 ± 21[a]	< 0.001
FVC (%)	70.9 ± 22[cd]	102.3 ± 14[ab]	73.8 ± 19[d]	89.7 ± 26[b]	< 0.001
FEV_1/FVC (%)	82.3 ± 8[cd]	63.1 ± 6[ab]	54.9 ± 9[d]	69.8 ± 13[b]	< 0.001
DLco (%)	32.3. ± 12	38.5 ± 9[c]	37.3 ± 15	28.2 ± 11[d]	0.004
Pulmonary Haemodynamics:					
mPAP (mm Hg)	37.4 ± 12	33.3 ± 11	38.7 ± 13	40.9 ± 12	0.195
PAWP (mm Hg)	9.2 ± 3	9.5 ± 3	11.2 ± 2	9.0 ± 3	0.111
CO (L.min)	4.8 ± 1.4	4.7 ± 1.4	4.6 ± 1.2	4.3 ± 1.4	0.127
CI ($L.min.m^{-2}$)	2.7 ± 0.7	2.8 ± 0.8	2.8 ± 0.8	2.6 ± 0.9	0.427
PVR (WU)	5.1 (2.9,8.3)	4.4 (2.5,6.3)	5.2 (2.25,8.15)	6.6 (2.2,10)	0.051

CFES, combined fibrosis andemphysema syndrome; CI, cardiac index; CO, cardiac output; DLco, diffusion capacity of the lung forcarbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; ISWD, incremental shuttle walk distance; mPAP, mean pulmonary arterialpressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascularresistance.

[a] $p < 0.05$ vs COPD (FEV1/FVC < 0.7 and FEV1 < 60% predicted).

[b] $p < 0.05$ vs moderate-severe ILD.

[c] $p < 0.05$ vs CFES/Emphysema.

[d] $p < 0.05$ vs Mild ILD & FVC < 70% predicted.

elevation in pulmonary pressure and higher cardiac output (Table 1). PAWP was higher than in patients with PAH, PH-CLD or No-PH while left atrial volume (LAV) and left ventricular end diastolic volume (LVEDV) were similar to those in PH-LHD but significantly higher than in PAH, PH-CLD and No-PH (Table 1). Survival was similar to No-PH and significantly superior to PAH, PH-CLD and PH-LHD (Figure 2a).

Progression to PAH in patients with no-PH and unclassified-PH

Of 99 patients with No-PH, 10 patients with No-PH underwent repeat RHC after a median of 4.05 years, of whom 6 developed precapillary PH and 1 PH-LHD. Of 39 patients with Unclassified-PH, 22 underwent repeat RHC at a median of 1.59 years. Nine (23% of Unclassified-PH) developed precapillary PH, 5 (13%) developed PH-LHD, 6 (15%) remained Unclassified-PH and 2 (5%) No-PH (Figure S4).

PH-LHD and PAWP thresholds

Patients with PH-LHD had higher LAV and LVEDV than patients with PAH (Table 1) while survival was similar (Figure 1). Of 61 patients with PH-LHD, 40 had PVR >2 WU (combined pre- and postcapillary PH, CpcPH), 18 had PVR ≤2 WU (isolated postcapillary PH, IpcPH) while 3 had no PVR available. Patients with CpcPH were older with similar spirometry but lower DLco, more severe pulmonary haemodynamics and inferior survival than those with IpcPH (Table 3, Figure 3c). CMR was performed in 32 patients and demonstrated that patients with CpcPH had similar LAV but lower LVEDV and right ventricular ejection fraction (RVEF) compared to patients with IpcPH (Table 3).

Eleven out of forty (28%) of CpcPH and 3/18 (17%) of IpcPH patients had moderate-severe parenchymal lung disease (CpcPH: 7 ILD, 4 emphysema, IpcPH: 3 ILD). Five-year survival of patients with and without moderate/severe lung disease was 18% and 43% in IpcPH and 33% and 72% in CpcPH ($p < 0.001$, Figure 3d).

Characteristics of patients with a PAWP of ≤12 mm Hg, 13–15 mm Hg and > 15 mm Hg were compared in the 824 patients with available PAWP. Patients in the 13–15 mm Hg group had higher CO and lower PVR than the ≤12 mm Hg group while CO and PVR were similar to the > 15 mm Hg subgroup (Table S3). In the 380 patients with baseline CMR data, LAV, LVEDV, and RVEF were significantly higher in the 13–15 mm Hg group than in the ≤12 mm Hg group but similar to the > 15 mm Hg subgroup.

Radiological features of PVOD

CT reports for PAH patients were interrogated for description of the 3 key radiological features of PVOD (centrilobular ground glass changes, interlobular septal thickening not due to interstitial lung disease and mediastinal lymphadenopathy).[18] The presence of ≥2 features was reported in 17/250 (7%) of patients with CT reports and was associated with more severe PH and lower DLco than those with 0–1 features (Table S4). Although survival was worse in patients with ≥2 features (Figure 4a) this was not independent of age, PVR and DLco.

Table 3 Characteristics of Patients with Isolated Postcapillary PH and Combined Pre-and Postcapillary PH[a]

	IpcPH ($n = 18$)	CpcPH ($n = 40$)	p-value
Age (years)	58.2 ± 11	69.3 ± 9	< 0.001
Female (%)	89	93	0.65
WHO FC I/II/III/IV (%)	6/47/47/0	0/8/81/11	0.002
ISWD (m)	210 (98,343)	140 (80,210)	0.06
Lung Function:			
FEV_1 (%)	76.2 ± 19	74.1 ± 23	0.37
FVC (%)	81.9 ± 19	77.7 ± 30	0.29
FEV_1/FVC (%)	77.7 ± 9	73.4 ± 13	0.11
DLco (%)	52.9 ± 14	40.3 ± 15	0.002
Pulmonary Haemodynamics:			
mPAP (mm Hg)	26.4 ± 3	43.8 ± 13	< 0.001
PAWP (mm Hg)	18.0 ± 2	18.1 ± 3	0.44
CO (L.min)	6.7 ± 1.2	4.6 ± 1.5	< 0.001
CI ($L.min.m^{-2}$)	3.8 ± 0.7	2.6 ± 0.7	< 0.001
PVR (WU)	1.2 (0.9, 1.6)	5.1 (3,7)	< 0.001
CMR[b]:			
LVEDV (ml)	162 ± 29	136 ± 42	0.04
LVEF (%)	56 ± 10	57 ± 10	0.46
RVEDV (%)	146 ± 41	175 ± 71	0.11
RVEF (%)	56.7 ± 10	43.2 ± 15	0.01
LAV (ml)	85 ± 18	86 ± 26	0.43

CI, cardiac index; CMR, cardiac magnetic resonanceimaging; CO, cardiac output; CpcPH, combined pre and postcapillary PH; DLco, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IpcPH, isolatedpostcapillary PH; ISWD, incremental shuttle walk distance; LAV, left atrialvolume; LVEDV, left ventricular end diastolic volume; LVEF, left ventricularejection fraction; mPAP, mean pulmonary arterial pressure; PAWP, pulmonaryarterial wedge pressure; PVR, pulmonary vascular resistance; RVEDV, rightventricular end diastolic volume; RVEF, right ventricular ejectionfraction; WHO FC, World Health Organization Functional Class.

[a]Three patients with PH-LHD had no PVR available.

[b]$n = 32$.

Response to PAH therapies

Baseline ISWD was an independent prognostic marker in PAH and PH-CLD (HR 0.998 (0.997, 0.99, $p < 0.001$)). Five hundred and forty-four patients who received PH therapies had baseline and follow-up (median 195 days) ISWD data available. First follow-up occurred 3–12 months following diagnosis in 387 of these patients whose median change in ISWD was 0 m (–40, +30), $p = 0.074$. The median change in ISWD in the 213 patients with PAH was 0 m (–47.5, +30), and in the 143 patients with PH-CLD was –4 m (–40, +40), p both > 0.05. Similarly, the median change in ISWD in the 28 patients with PH-LHD was 0 m (–40, 17.5), $p = 0.27$.

The 58 PAH patients (27%) who increased their ISWD by ≥30 m had similar age and lung function but slightly worse ISWD (120 m (75,195) vs 160 m (80, 270), $p = 0.047$) and PH (mPAP 45.1 ± 13 mm Hg vs 40.6 ± 12 mm Hg, $p = 0.008$) than those whose ISWD was stable (increased by < 30 m) or worsened. Survival in the group with ≥30 m improvement was, however, superior (5-year survival 70% vs 40%, $p = 0.046$, Figure 4b).

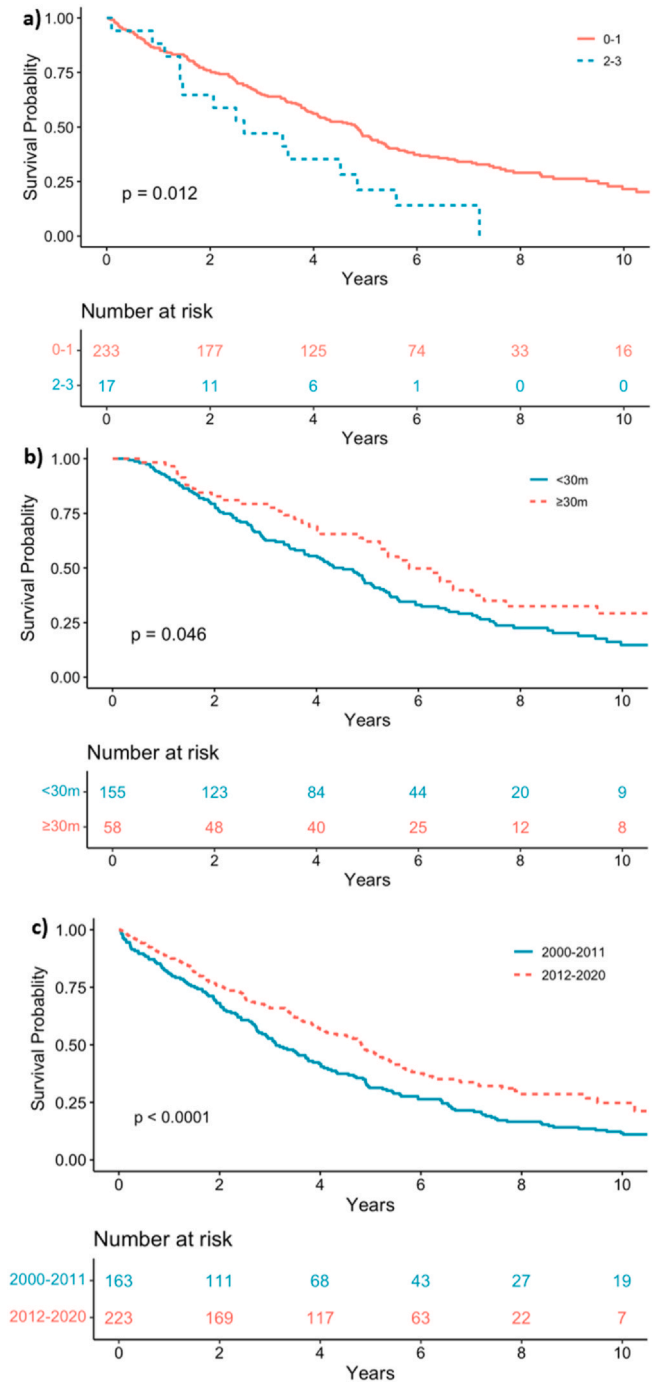

Fig. 4 Cumulative survival from diagnosis: (a) PAH patients with 0–1 or 2–3 radiological features of PVOD; (b) PAH patients with baseline and follow-up ISWD at 3–12 months following commencement of PAH therapy by those who increased ISWD by ≥30 m vs those who worsened/remained stable/increased by < 30 m; (c) PAH diagnosed 2000–11 vs 2012–20. ISWD, incremental shuttle walk distance; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease.

Treatment era

One hundred and sixty-three PAH patients were diagnosed between 2000 and 2011 and 223 between 2012 and 2020. The earlier group had similar FVC and DLco, slightly worse mPAP but higher CO and hence similar PVR

Table 4 Characteristics of PAH Patients Diagnosed during 2000–11 and 2012–20

	2000-11 ($n = 162$)	2012-20 ($n = 223$)	p-value
Age (years)	65.7 ± 10	67.6 ± 11	0.085
ISWD (m)	130 (35,225)	155 (60,250)	0.057
Lung Function:			
FVC (%)	98.0 ± 20	102.1 ± 23	0.078
DLco (%)	41.4 ± 10	39.9 ± 13	0.266
Pulmonary Haemodynamics:			
mPAP (mm Hg)	42.1 ± 13	39.1 ± 13	0.024
PAWP (mm Hg)	9.3 ± 3	10.1 ± 3	0.019
CO (L.min)	4.8 ± 1.5	4.2 ± 1.4	< 0.001
CI (L.min.m^{-2})	2.8 ± 0.8	2.5 ± 0.8	< 0.001
PVR (WU)	6.4 (2.9,9.9)	6.1 (2.2,10)	0.849
Maximal subsequent PH therapy (%)[a]:			< 0.001
none	3	3	
oral mono	51	18	
oral dual	28	63	
oral triple	1	4	
iv or neb prost	17	12	

CI, cardiac index; CO, cardiac output; DLco, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISWD, incremental shuttle walk distance; iv, intravenous; mono, monotherapy; mPAP, mean pulmonary arterial pressure; neb, nebulized; PAWP, pulmonary arterial wedge pressure; prost, prostanoid; PVR, pulmonary vascular resistance.

[a]In patients who fulfilled ESC/ERS 2015 definition of precapillary PH.

(Table 4). The proportion of patients fulfilling ESC/ERS 2015 definitions receiving combination therapy increased from 46% to 79% in the latter group ($p < 0.001$). Median survival was superior in the 2012–2020 group (4.8 vs 3.1 years, $p < 0.001$, Figure 4c). There was, however, no significant difference in survival in patients with PH-CLD diagnosed in the two treatment eras ($p = 0.15$).

Discussion

In this registry analysis we have provided a broad overview of patient characteristics and outcomes across the spectrum of SSc-associated PH. In keeping with previous studies, survival in PAH was superior to that in PH-CLD.[8,11,19,20] Both groups had similar age, exercise capacity, and pulmonary haemodynamics and subsequently received similar PH therapies. More patients with PH-CLD, however, were male and had worse spirometry and DLco. Although the majority of studies of PH-CLD in SSc have focussed on PH-ILD,[11,19,20] 27% of PH-CLD patients in the present study had CFES/emphysema which was associated with a lower DLco. Antoniou et al previously observed emphysema in 12% of 333 patients with SSc-ILD which was also associated with a lower DLco.[21] Interestingly, in their study CFES was present in 7.5% of lifelong non-smokers, suggesting that SSc may be a distinct risk factor for the development of emphysema.

The high prevalence of some degree of interstitial lung disease in SSc can result into a dilemma as to whether a patient has PAH or PH-CLD.[22] We therefore explored the impact of the extent of parenchymal lung disease on characteristics and survival and observed that patients with no/mild parenchymal lung disease had similar spirometry and DLco while these parameters were incrementally worse in patients with moderate and severe parenchymal lung disease. Furthermore, survival in the presence of moderate/severe disease was significantly worse than in none/mild disease. These observations support considering patients with mild lung disease on CT imaging as having PAH and are consistent with a previous cluster analysis by Launay et al in which the presence of extensive, but not limited, ILD was associated with poorer survival.[23]

Survival in PAH in the period 2012–2020 was superior to that observed in the earlier period of 2000–2011, despite similar lung function and PVR. It is notable that a significantly larger proportion of eligible patients received combination therapy in the latter group (79% vs 46%), although it is not possible to assign causality of the improved survival to changes in treatment. Of note, the magnitude of improvement in median survival in the current manuscript (3.1 to 4.8 years) was lower than in the paper of Hassan et al (4.0 to 8.8 years).[10] The reason for this difference is not entirely clear; patients in the later time period in both studies had similar haemodynamics while more patients in our study received combination therapy (79% vs 64%). It is possible that the cohorts differed in other ways. For example, DLco, which is an important prognostic factor in SSc-associated PAH, was not reported in the study of Hassan et al. Furthermore, different referral pathways and registry enrollment may have contributed to the observed differences. In the UK, all patients treated with targeted therapies for the management of PAH do so at a nationally designated specialist center while the ASPIRE registry enrolls all consecutively diagnosed patients. It is possible that in other healthcare systems sicker or frailer patients may be treated outside of quaternary specialist centers or may be less likely to consent to registry enrollment.

We have replicated observations that reducing the mPAP diagnostic threshold alone (from > 25 to > 20 mm Hg) resulted in only a small increase (3%) in the number of patients diagnosed with precapillary PH whereas additionally reducing the PVR threshold to > 2 WU resulted in a 19% increase in PH diagnoses.[24–26] We have further confirmed the prognostic importance of PVR in patients with elevated mPAP and normal PAWP and observed that survival in patients with PVR > 2–3 WU was inferior to that of patients with PVR ≤2 WU but similar to those with PVR > 3–4 WU.[27] In addition, we have observed that patients with Unclassified-PH have very similar survival to patients with No-PH. Furthermore, we noted that higher proportions of patients with Unclassified-PH were subsequently diagnosed with PAH and PH-LHD compared with patients with No-PH. Unclassified-PH was associated with LA volumes similar to that of PH-LHD and a mean PAWP that, although within the diagnostic threshold for precapillary PH, was higher than in precapillary PH. These data would suggest that a proportion of patients with Unclassified-PH may have occult left heart disease while a proportion may have "early" pulmonary vascular disease.

Although current ESC/ERS guidelines use a PAWP diagnostic threshold of > 15 mm Hg to define postcapillary PH, it is recognized that the upper limit of normal within the general population is 12 mm Hg.[28] We observed that patients with PAWP 13–15 mm Hg were similar to patients with PH-LHD in terms of CO, PVR and CMR parameters. The optimal PAWP for distinguishing pre- and postcapillary PH threshold merits further investigation.

Histopathological studies have previously reported venous obstructions in 75% of patients with CTD-PAH and 83% of patients with SSc-PH-ILD.[5,29] By their nature studies involving histopathology samples are highly selective of patients with severe, end-stage disease. Connolly et al identified ≥2 CT features of PVOD in 11% of patients with SSc-PAH and observed a trend towards poorer survival.[30] Our observations were similar with ≥2 CT features reported in 7% of patients and associated with lower DLco and poorer survival.

We observed no overall improvement in exercise capacity after initial PAH therapy initiation in either PAH, PH-CLD or PH-LHD. Chauvelot et al recently also observed no overall improvement in 6-minute walk distance (6MWD) following initial PAH therapy in both SSc-PAH and SSc-PH-ILD.[19] Despite this, they observed similar haemodynamic improvements in both groups. Patients with SSc tend to be older with musculoskeletal impairment to exercise and it is therefore possible that walk tests do not optimally reflect haemodynamic improvements in this group of patients. Indeed, a study of patients from the French national registry and from randomized controlled trials found weak correlations between CO and 6MWD and no association between changes in haemodynamics and CO.[31] We did, however, demonstrate superior survival in patients who improved their ISWD by > 30 m, similar to the minimum clinical important distance identified in idiopathic pulmonary fibrosis.[32]

There are a number of limitations to this study. Data was collected when clinically indicated meaning that follow-up RHC was not performed routinely. In addition, due to the time period of the study, NT-proBNP data was not collected during the majority of the study. Smoking status was also not collected. Kaplan-Meier survival analysis based on subsequent response to therapy may be vulnerable to bias and competing risk of death. CT findings were retrieved from routine radiological reports rather than being specifically reanalysed. Nevertheless, clinical reports of the nature and extent of parenchymal abnormalities identified subgroups of patients with shared characteristics and outcomes. Future work involving artificial intelligence-analysis of parenchymal appearances may further refine patient phenotyping.[33]

Conclusion

A number of SSc-PH phenotypes can be recognized and characterized using haemodynamics, lung function and multimodality imaging. Prospective evaluation of PAH therapies in defined SSc-PH phenotypes are warranted.

Author contributions

R. Condliffe conceived the study. H. Smith, A. Haque and R. Condliffe collected data and performed analysis. The remaining authors contributed additional data collection and approved the study manuscript.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2024.06.007.

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