



## REVIEW

# Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus

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**ABSTRACT:** Pulmonary arterial hypertension (PAH) is a severe manifestation of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE). Due to improvements in the understanding of the pathogenesis of these diseases, improved methodological rigour in the conduct of epidemiological studies and the advent of successful therapies, our understanding of SSc-PAH and SLE-PAH has evolved considerably. In this review we will review the current evidence regarding the prevalence, prognostic factors and survival estimates for SSc-PAH and SLE-PAH. In doing so, we will compare and contrast these two diseases, highlight clinically useful features, discuss methodological limitations of existing data, and draw attention to areas where research is needed.

**KEYWORDS:** Lupus, pulmonary hypertension, scleroderma, systemic lupus erythematosus, systemic sclerosis

Pulmonary arterial hypertension (PAH) is a severe manifestation of many of the sero-positive connective tissue diseases (CTDs). It has long been recognised as a manifestation of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) [1, 2]; however, it can occur in other connective tissue diseases, including SSc-SLE overlap syndrome [3], mixed connective tissue disease (MCTD) [4–6], inflammatory myositides (dermatomyositis and polymyositis) [7, 8], Sjögren's syndrome [9] and rheumatoid arthritis [10]. In patients suspected of having PAH, Doppler echocardiography has been recommended to detect pulmonary hypertension (PH) and evaluate for left ventricular systolic and diastolic dysfunction, left-sided ventricular enlargement or valvular heart disease [11]. Right heart catheterisation is required to confirm the presence of PAH, establish a specific diagnosis and determine the severity of PAH [11]. Using catheterisation derived haemodynamics, PAH is defined as a mean pulmonary artery pressure ( $\bar{P}_{pa}$ )  $\geq 25$  mmHg and a pulmonary capillary wedge pressure of  $\leq 15$  mmHg [12].

Of the CTDs associated with PAH, SSc-PAH and SLE-PAH are the most common [13]. Typically, these patients are grouped together in studies of PAH-specific therapies under the category of CTD [14, 15]. Together, advances in our knowledge of

the mechanism of SSc-PAH and SLE-PAH, improved methodological rigour in the conduct of SSc-PAH and SLE-PAH observational studies, and the introduction of successful PAH specific therapies have resulted in a progressive evolution in our understanding of SSc-PAH and SLE-PAH. It has been suggested that SSc-PAH and SLE-PAH are heterogeneous diseases with variable responses to therapy. As such, categorisation of these patients together may not be appropriate and may affect the outcome of studies [16].

The most frequently observed and reported aetiology of PH in SSc is PAH. However, PH in SSc can be the result of a number of other aetiologies, such as pulmonary veno-occlusive disease (PVOD) [17], left ventricular systolic and diastolic dysfunction (heart failure with preserved ejection fraction) [18], and pulmonary fibrosis [19]. DORFMULLER *et al.* [20] demonstrated the frequent presence of PVOD-like pathologic changes in the veins and pre-septal venules of the pulmonary vasculature of SSc-PAH patients. These other aetiologies probably play a role in the differing response to therapy and prognosis of SSc-PH compared to SLE-PH and idiopathic PAH [21].

In this review we will synthesise the current knowledge of the prevalence, prognostic factors and

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survival estimates for SSc-PAH and SLE-PAH. In doing so, we will compare and contrast the two diseases, highlight clinically useful features, discuss methodological limitations of existing data, and draw attention to areas where research is needed.

### SCLERODERMA-ASSOCIATED PAH

SSc is an autoimmune disease characterised by immune activation leading to inflammation, fibrosis and vasculopathy. It is currently hypothesised that, in a genetically susceptible individual, exposure to an environmental stimulus results in immune activation and release of immune mediators. Transforming growth factor (TGF)- $\beta$  stimulates fibroblast proliferation, leading to increased collagenase and collagen synthesis, resulting in the fibrotic manifestations of SSc [22]. Fibroblast stimulation also results in increased vascular endothelial growth factor, which leads to aberrant neoangiogenesis. In the setting of SSc lung disease, macrophage activation leads to increased production of TGF- $\beta$ , tumour necrosis factor- $\alpha$ , platelet-derived growth factor and fibronectin, resulting in the radiographic and clinical features of lung fibrosis and nonspecific inflammatory pneumonia. Advanced pulmonary vasculopathy histologically appears as smooth muscle hypertrophy, adventitial and intimal proliferation, *in situ* thrombosis and/or plexiform lesion(s). Together, these vascular changes result in a low-flow, high-resistance vessel and produce the clinical manifestations of PAH.

Although common in the setting of SSc, the vasculopathic manifestations can vary across individual patients [23]. Vasculopathy of the small blood vessels can present as telangiectasia. Telangiectasias are composed of vasodilated venules without evidence of neovascularisation or inflammation [24]. They not only occur externally on the skin, but also on the tongue, buccal mucosa, oesophageal lumen and stomach. The pathogenesis of telangiectasia has largely been studied in the setting of hereditary haemorrhagic telangiectasia (HHT). Patients with HHT demonstrate genetic mutations in the TGF- $\beta$  receptor complex, most notably endoglin (a TGF- $\beta$  binding protein) and activin receptor-like kinase 1. Telangiectasias are more frequently found in SSc patients with elevated soluble endoglin, and pulmonary artery pressure ( $P_{pa}$ ) is positively correlated with elevated endoglin levels [25]. It is hypothesised that the presence of telangiectasia is an expression of an aberrant vascular process. It may reflect an attempt to increase blood perfusion to hypoxic tissues that is a result of the loss of normal circulation in the affected tissue [26].

The presence of telangiectasia in SSc patients should prompt a few considerations. First, it has been suggested that increased numbers of telangiectasias may be a marker for PAH. Using a 0 to 2 scoring system (0: none; 1: <10; and 2:  $\geq 10$  telangiectasias) to evaluate the presence of matted telangiectasia in 11 body areas, a 10-point increase in telangiectasia score has an adjusted odds ratio of PAH by right heart catheterisation of 12.4 (95% CI 1.78–85.9;  $p=0.01$ ) [26]. A second consideration is that the luminal telangiectasia can be friable, and put these patients at increased risk of gastrointestinal bleeding [27]. In its most severe form, it can result in gastric antral vascular ectasia (GAVE or “watermelon stomach”). We have reported a case of GAVE unmasked by the use of prostaglandin E1 (alprostadil) resulting in upper gastrointestinal bleeding necessitating blood transfusion [28]. The presence of luminal telangiectasias and GAVE may be relevant if one is contemplating anticoagulation of patients

with SSc-PAH. Vasculopathy of the small cutaneous vessels can also be observed in the nail folds. Indeed, the presence of abnormal nail fold capillaries manifesting as enlarged capillaries or “drop out” of capillaries can be a useful diagnostic clue to the presence of an underlying connective tissue disease in the aetiology of PAH. Evaluation of abnormal nail fold capillaries can be easily undertaken in the clinic by visual inspection of the nail fold, or with the use of capillaroscopy.

Vasculopathy of the medium sized vessels can present as Raynaud’s phenomenon: cold or stress induced, triphasic discoloration of any acral region of the body (fingers, nose, penis, toes or ears). Persistently decreased perfusion can lead to digital pulp loss, pitting, digital shortening, ulceration or gangrene. Raynaud’s phenomenon is a sensitive criterion in the diagnosis of SSc occurring in >90% of SSc patients. As such, it can be useful in the evaluation of SSc-PAH; if absent, the diagnosis of SSc is unlikely. However, Raynaud’s phenomenon is not a specific finding as it can occur in other CTDs (SLE, MCTD and inflammatory myositides) and idiopathic PAH. When recruiting a PAH patient with Raynaud’s phenomenon for participation in a clinical trial, and when SSc is the suspected underlying diagnosis, classification criteria should be used to ensure that a better defined cohort of SSc patients are classified as SSc [29]. The widely used SSc classification criteria [29] has been criticised [30, 31], and should not be used as diagnostic criteria [32]. Revised classification criteria for the recruitment of SSc patients into clinical trials are currently being developed through a joint initiative between the European League Against Rheumatism and the American College of Rheumatology [33].

With improved methodological rigour and the availability of PAH specific therapies, our understanding of the epidemiology of PAH has evolved over the past four decades. Early echocardiographic-based prevalence estimates were as high as 43–59% [34, 35], but more recent estimates range between 21% and 26.7% [36, 37]. More rigorous right heart catheterisation-based prevalence estimates are lower and range between 7% and 29%, with the majority of estimates at the lower end (table 1) [34, 38–41]. Prevalence estimates vary substantially due to variability in patient selection (academic/community practice, disease subtype, symptomatic/nonsymptomatic and presence/absence of other issues such as interstitial lung disease), method (echocardiogram or cardiac catheterisation) and threshold of pulmonary pressures used for diagnosis. It has been argued that studies may underestimate the true prevalence since clinically severe or symptomatic patients are referred to academic centres [46].

Classically, it was believed that PAH occurred later in the disease course of SSc, and occurred more frequently in patients with the limited subtype of SSc. However, these notions are being challenged. In a retrospective cohort of 78 SSc-PAH patients, 55% had a PAH diagnosis within 5 yrs of the first non-Raynaud’s phenomenon symptom. Furthermore, there was no difference in the frequency of early onset PAH between SSc patients with the limited or diffuse subtypes [47]. AVOUAC *et al.* [45] have refined classical thinking by proposing that there are two subsets of SSc patients who are at risk of developing PH: 1) patients with the limited subtype, in the late stage of the disease with a diffusing capacity of the lung for carbon monoxide per unit of alveolar volume ( $DL_{CO}/VA$ ) are at risk of PAH; and 2)

**TABLE 1** Prevalence of systemic sclerosis-associated pulmonary arterial hypertension

Prevalence	Diagnostic threshold	Ref.
<b>Echocardiogram based</b>		
43%	$P_{pa,sys} \geq 35$ mmHg	[34]
35%	$P_{pa,sys} > 30$ mmHg	[42]
59%	$P_{pa,sys} \geq 40$ mmHg	[35]
16%	$P_{pa,sys} > 40$ mmHg	[43]
26.7%	$P_{pa,sys} \geq 40$ mmHg	[37]
21% limited, 26% diffuse	$P_{pa,sys} > 30$ mmHg or $> 35$ mmHg	[36]
<b>Right heart catheterisation based</b>		
2.93 per million <sup>#</sup>	$\bar{P}_{pa} \geq 25$ mmHg at rest with $P_{pcw} < 15$ mmHg	[44]
5%	$\bar{P}_{pa} > 25$ mmHg at rest with $P_{pcw} \leq 15$ mmHg	[45]
7%	$\bar{P}_{pa} > 32$ mmHg	[38]
16%	$\bar{P}_{pa} \geq$ mmHg at rest with $P_{pcw} \leq 12$ mmHg	[39]
29%	$\bar{P}_{pa} \geq 20$ mmHg or $P_{pa,sys} \geq 35$ mmHg	[34]
12%	$\bar{P}_{pa} > 25$ mmHg	[40]
7.85% <sup>*</sup>	$\bar{P}_{pa} \geq 25$ mmHg at rest or $\geq 30$ mmHg during exercise, with $P_{pcw} < 15$ mmHg	[41]

$P_{pa,sys}$ : pulmonary artery systolic pressure;  $\bar{P}_{pa}$ : mean pulmonary artery pressure;  $P_{pcw}$ : pulmonary capillary wedge pressure. <sup>#</sup>: general population; <sup>\*</sup>: 95% CI 5.7–10.

males with the diffuse subtype and a decreased  $DL_{CO}/VA$  are at risk of PH secondary to interstitial lung disease.

PAH is a leading cause of death in SSc patients [48]. Early survival estimates published in 1996 reported a median survival of 12 months, and 1-, 2-, 3- and 5-yr survival of 50, 44, 40 and 4%, respectively [49]. However, survival estimates have improved over time. Using data from the same centre in 2011, 1-, 2- and 3-yr survival have improved to 81, 72 and 64%, respectively, with a median survival of 4.9 yrs [50]. Other groups have also independently demonstrated a gradual improvement in survival over time (table 2) [44, 51]. The improvement in survival may be due to the availability of PAH specific therapies, namely prostaglandins [58], endothelin receptor antagonists [59] and phosphodiesterase-5 inhibitors [60]. Alternately, heightened awareness of PAH complicating SSc may have led to earlier referral for evaluation and

treatment. This could result in lead-time and length-time biases, thereby affecting the interpretation of survival rates. Despite the progressive improvement in survival, the long-term ( $> 5$  yr) survival remains poor. Patients with SSc continue to do worse than their other PAH counterparts. In the REVEAL registry (Registry to Evaluate Early And Long-term PAH disease management), SSc was independently associated with worse prognosis [61].

We conducted a systematic review of prognostic factors for survival in PAH in patients with SSc [62]. Human leukocyte antigen (HLA) DRw6 [63], HLA DRw52 [63], elevated mean right atrial pressure [40], higher mixed venous oxygen saturation [44], peripheral vascular resistance [40, 55, 56], stroke volume index [55], pulmonary artery capacitance [55], age [44, 64], sex [44, 64], functional class [44, 55, 56], estimated glomerular filtration rate  $< 60$  mL per min per  $1.73 \text{ m}^2$  and signs of right

**TABLE 2** Survival in systemic sclerosis-associated pulmonary arterial hypertension

Survival %					Ref.
1-yr	2-yr	3-yr	5-yr	Median	
Not reported	60	Not reported	Not reported	Not reported	[52]
50	44	40	4	12 months	[49]
Not reported	50	Not reported	10	Not reported	[53]
81	63	56	Not reported	3 yrs	[40]
81	71	NR	Not reported	Not reported	[54]
78	58	47	Not reported	Not reported	[44]
86	68	56	Not reported	Not reported	[51]
85	72	67	36	4 yrs	[55]
80	56	51	Not reported	Not reported	[56]
82	Not reported	Not reported	Not reported	Not reported	[57]
81	72	64	49	4.9 yrs	[58]
Not reported	72	Not reported	48	Not reported	[16]

heart failure [56] are reported predictors of survival (table 3). In patients with SSc-PH and interstitial lung disease, a lower DLCO (HR 0.95, 95% CI 0.92–0.98) and presence of pericardial effusion (HR 3.96, 95% CI 1.56–10.06) were associated with survival [65]. Many of these findings are comparable to prognostic factors for survival in idiopathic PAH [66]. The presence of anti-centromere [44, 64] and anti-SCL-70 [44, 64] antibodies are not associated with survival.

Other potential prognostic factors remain controversial due to the presence of conflicting studies (table 4).  $P_{pa}$  has been evaluated in three studies. MACGREGOR *et al.* [64] reported that at baseline systolic  $P_{pa}$  was associated with survival. They also reported that the association between an increasing  $P_{pa}$  and survival was suggestive, but not statistically significant. MUKERJEE *et al.* [40] reported survival differences in patients with  $\bar{P}_{pa} < 32$  mmHg, 32–44 mmHg and  $> 45$  mmHg. Yet recently, LAUNAY *et al.* [65] found no difference in survival in patients with a  $\bar{P}_{pa} \leq 35$  mmHg *versus*  $> 35$  mmHg. Differences in the measurement of  $P_{pa}$  (systolic *versus* mean), timing (baseline *versus* after treatment) and categorisation of  $P_{pa}$  may account for the differences in the study findings. The subtype of

SSc (limited *versus* diffuse) [64, 67], the presence of interstitial lung disease [40, 44, 49, 51] and duration of SSc prior to development of PAH [44, 55, 68] are also controversial prognostic factors with conflicting studies.

There are several reasons for the discrepancies in the literature. The conduct and interpretation of prognostic studies of survival in SSc-PAH face a number of challenges. Frequently, factors appear to prognosticate survival in univariate analyses. However, the relationship does not remain in multivariate models. This can occur when potential factors are related, and represent facets of the same construct (*e.g.* haemodynamic parameters). Furthermore, the methodological quality of the SSc-PAH prognostic studies is variable. The attributes of participants, prognostic factors and outcome measures are well reported, whereas attributes of study attrition, confounding and the analytic methods used are not well reported [62]. These issues may introduce bias in the evaluation of effect. Finally, the small sample sizes may result in insufficient power to detect a true relationship. As such, further evaluation of prognostic factors in SSc-PAH in studies that meet the current rigours of measurement science is needed.

**TABLE 3** Prognostic factors associated and not associated with systemic sclerosis-associated pulmonary arterial hypertension

Prognostic factor	Estimate	Ref.
<b>Factors associated with survival</b>		
HLA DRw6	RR 54.52 (p=0.01)	[63]
HLA DRw52	RR not reported (p=0.02)	[63]
Elevated mean $P_{ra}$	HR 20.7 (p=0.0001)	[40]
Higher mixed venous oxygen saturation	HR 0.17, 95% CI 0.09–0.33	[44]
PVR	No difference in Kaplan–Meier curves in patients with a change in PVR <20%, 20–34% or $\geq 35\%$ (p=0.8)	[40]
	HR 1.10, 95% CI 1.03–1.18 (p<0.01)	[51]
	PVR index: HR 1.05, 95% CI 1.01–1.09 (p<0.01)	[56]
	HR 1.20, 95% CI 1.02–1.41 (p=0.02)	
SVI	HR 0.94, 95% CI 0.89–0.99 (p=0.02)	[55]
Pulmonary artery capacitance	HR 0.43, 95% CI 0.20–0.91 (p=0.03)	[55]
Functional class	Lower functional class has better survival:	[44]
	HR 2.26, 95% CI 1.02–4.97	[56]
	NYHA classes III/IV: HR 4.54, 95% CI 1.37–8.33 (p=0.01)	[55]
	WHO classes III/IV have worse survival than classes I/II: log rank test p=0.02	
Sex	Males have worse survival: HR 2.02, 95% CI 0.65–6.20*	[64]
	Females have better survival: HR 2.20, 95% CI 1.36–3.55	[44]
Age yrs	Age >50 yrs has worse survival: HR 2.34, 95% CI 0.54–10.2†	[64]
	Younger age has better survival: HR 0.66, 95% CI 0.34–1.29	[44]
Estimated glomerular filtration rate*	HR 2.63, 95% CI 1.29–5.37 (p<0.01)*	[55]
Signs of right heart failure	HR 2.56, 95% CI 1.02–14.28 (p=0.04)	[56]
<b>Factors not associated with survival</b>		
Anti-centromere antibody	HR 1.67, 95% CI 0.66–4.26	[64]
	No effect on survival: data not reported	[44]
Anti-Scl-70	HR 0.28, 95% CI 0.03–1.99	[64]
	No effect on survival: data not reported	[44]

HLA: human leukocyte antigen;  $P_{ra}$ : right atrial pressure; PVR: pulmonary vascular resistance; SVI: stroke volume index; NYHA: New York Heart Association; WHO: World Health Organization. #:  $< 60$  mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>; \*: estimate was suggestive but not statistically significant; †: estimate from univariate analysis. Multivariate models including different haemodynamic parameters estimate HR 2.56–3.41.

**TABLE 4** Controversial prognostic factors for survival in systemic sclerosis (SSc)-associated pulmonary arterial hypertension (PAH)

Prognostic factor	Estimate	Inference	Ref.
<b>P<sub>pa</sub></b>	Baseline systolic P <sub>pa</sub> >60 mmHg:	Yes	[64]
	HR 3.60, 95% CI 1.42–9.15	Suggestive but not significant	[64]
	Increasing P <sub>pa</sub> : HR 5.36, 95% CI 0.4–37.8	Yes	[40]
	3-yr survival in patients with $\bar{P}_{pa}$ <32 mmHg, 32–44 mmHg and >45 mmHg	No	[65]
	75, 61 and 33%, respectively		
	(Kaplan–Meier estimate p<0.01)		
<b>Limited sub-type</b>	$\bar{P}_{pa}$ ≤35 mmHg versus >35 mmHg showed no difference		
	(Kaplan–Meier estimate log rank test p=0.08)		
	HR 2.37, 95% CI 0.68–8.20	Suggestive but not significant	[64]
<b>Interstitial lung disease</b>	Limited and diffuse SSc have equally poor survival: 10–20% at 5 yrs	No	[67]
	(test of significance not reported)		
	No difference in Kaplan–Meier curves in SSc-PAH patients with and without fibrosis	No	[40]
	(p=0.3)	No	[49]
	No difference in median survival in SSc-PAH with and without fibrosis: 55 months	Yes	[44]
	(95% CI 3–58 months) versus 11.5 months (95% CI 4–26 months); log rank p=0.20	Yes	[51]
<b>Time between SSc onset and observed PAH</b>	3-yr survival 47% versus 28%; p=0.005	Yes	[65]
	HR 5.15, 95% CI 1.73–15.3 (p<0.01)		
	3-yr survival SSc-PH-ILD 47% versus SSc-PAH 71% (p=0.07)		
	5.24 versus 9.93 yrs (p<0.01)	Yes	[68]
	HR 0.99 95% CI 0.95–1.03 (p=0.60)	No	[55]
	Data not reported	No	[44]

P<sub>pa</sub>: pulmonary artery pressure;  $\bar{P}_{pa}$ : mean pulmonary artery pressure; PH: pulmonary hypertension; ILD: interstitial lung disease.

Several studies of PAH-specific therapies have included SSc-PAH patients, in addition to other forms of PAH (idiopathic PAH, SLE-PAH and repaired PAH) [69, 70]. Collectively, improvements in haemodynamics, time to clinical worsening and functional capacity have been demonstrated. However, investigators have demonstrated a treatment effect of lesser magnitude in SSc-PAH patients compared to idiopathic PAH patients [69, 70]. For example, RUBIN *et al.* [70] demonstrated an improvement in 6-min walk test (6MWT) distance in bosentan treated idiopathic PAH patients (increase of 46 m in bosentan group versus a decrease of 5 m in placebo group); whereas bosentan prevented deterioration in 6MWT distance in SSc-PAH patients (increase of 3 m in the bosentan group versus a decrease of 40 m in the placebo group). Similarly, in a trial evaluating inhaled iloprost compared to placebo, OLSCHESKI *et al.* [69] demonstrated a 12-m improvement in 6MWT distance in the iloprost treated SSc-PAH patients compared to a 58.8-m improvement in the iloprost treated idiopathic PAH patients. The SSc-PAH patients, however, did achieve comparable improvements in the Mahler Dyspnoea Index and measures of quality of life as idiopathic PAH patients [69].

Randomised trials of PAH-specific therapies in SSc-PAH patients alone are limited. BADESCH *et al.* [58] reported a randomised, open-label trial comparing epoprostenol with conventional therapy versus conventional therapy alone in SSc-PAH patients. Using the 6MWT distance at 12 weeks as the primary outcome measure, they found a difference between treatment groups of 108 m (95% CI 55.2–180.0 m; p<0.001). They also demonstrated a haemodynamic improvement in the treatment group. The change

in  $\bar{P}_{pa}$  in the epoprostenol group and conventional treatment group were -5.0 mmHg and 0.9 mmHg, respectively (difference -6.0 mmHg, 95% CI -9.0– -3.0 mmHg). The mean changes in pulmonary vascular resistance were -4.6 mmHg·L<sup>-1</sup>·min<sup>-1</sup> and 0.9 mmHg·L<sup>-1</sup>·min<sup>-1</sup> in the epoprostenol and conventional treatment groups, respectively (difference -5.5 mmHg·L<sup>-1</sup>·min<sup>-1</sup>, 95% CI -7.3– -3.7 mmHg·L<sup>-1</sup>·min<sup>-1</sup>). There was no difference in survival between groups with four deaths in the treatment arm and five deaths in the control arm (p-value not significant) [58]. Using a comparison of natural history data [49], BADESCH *et al.* [71] reported improved long-term survival in the open-label extension study following the randomised trial. The probabilities of survival during the first and second year were 0.71 and 0.52, respectively. The probability of survival remained constant at 0.48 during the third and fourth years [71].

There is no evidence that immunosuppressives are effective in SSc-PH. SANCHEZ *et al.* [72] reported six SSc-PAH patients treated with monthly intravenous cyclophosphamide for ≥3 months with or without glucocorticoids. Response was defined as functional class I or II with sustained haemodynamic improvement after ≥1 yr of immunosuppressive therapy without the addition of PH-specific therapies. None of the patients achieved a response [72].

The 6MWT is a commonly used efficacy end-point in clinical trials including SSc-PH patients, and is a measure of exercise capacity accepted by the US Food and Drug Administration. However, evaluation of its psychometric properties for use as an outcome measure in SSc-PAH trials is limited. In patients with

SSc-PAH, the 6MWT has concurrent validity. Improvements in 6MWT distance are associated with improvements in dyspnoea, cardiac index,  $\bar{P}_{pa}$  and pulmonary vascular resistance [73]. The 6MWT has discriminant ability, differentiating patients receiving placebo and active treatment (36 m improvement in epoprostenol arm *versus* 15 m decline in placebo arm; 75 m improvement sildenafil arm *versus* 0 m placebo arm) [58, 73]. The greatest threat to the utility of the 6MWT as an outcome measure is its face validity, *i.e.* does it measure what it purports to measure. The 6MWT is not only a test of cardiopulmonary function, but also a test of musculoskeletal function. As such, SSc-PAH patients may have limitation in 6MWT distance resulting from arthritis, myositis, myopathy, digital ulceration, claudication or gangrene [74]. Furthermore, pain (*e.g.* arthralgia or myalgia) can also limit 6MWT distance [74]. SSc patients with arthritis experience more pain than patients with rheumatoid arthritis [75]. These SSc manifestations may mask any improvements in cardiopulmonary function and confound the measure of treatment effect.

### SLE-ASSOCIATED PH

PH is also a recognised manifestation of SLE. Prevalence estimates range from 0.005% to 14% [1, 76–84]. The wide range in prevalence estimates may be due to several factors. Early prevalence studies relied on detection of clinical symptoms. It was previously felt that routine screening of SLE patients was not justified due to the lack of effective therapy [85]. Furthermore, the accuracy of prevalence estimates was affected by the use of different diagnostic cut-offs for the diagnosis of PAH. The threshold of  $P_{pa}$  required for a diagnosis of PH in SLE was frequently higher than that used for SSc. In particular, the cut-off for the catheterisation-based diagnosis was high in the reported studies, *e.g.*  $\bar{P}_{pa} > 30$  mmHg as opposed to a conventional cut-off of  $> 25$  mmHg (table 5). Therefore, although SLE-PH is less frequent than SSc-PAH, PAH may be an under-recognised manifestation of SLE [3].

The diagnosis of SLE frequently occurs before the diagnosis of PAH, with a mean delay of 4.9 yrs ( $\pm 3.7$  yrs) [87]. The development of PAH in the setting of SLE has been associated with anti-ribonucleoprotein antibodies [88], the presence of Raynaud's phenomenon [1, 78, 72, 83], rheumatoid factor positivity [76, 82] and elevated levels of endothelin-1 [82]. More recently, FOIS *et al.* [85] reported that a systolic  $P_{pa} \geq 35$  mmHg was more common in subjects of African descent (50% *versus* 20%;  $p=0.03$ ); with longer disease duration ( $14 \pm 8$  *versus*  $9.5 \pm 8$  yrs;  $p=0.049$ ); with a history of peripheral nervous system involvement (25% *versus* 4%;  $p=0.02$ ); with pericarditis (58% *versus* 27%;  $p=0.04$ ); and with anti-smooth muscle antibodies (42% *versus* 11%;  $p=0.01$ ) and anticardiolipin antibodies (75% *versus* 31%;  $p=0.007$ ).

There are fewer data evaluating survival in SLE-PAH than SSc-PAH. Some estimates suggest a poor prognosis with a median survival of 13 months [77]; however, more recent survival estimates are more optimistic (table 6) [5, 57]. SLE-PAH patients have a shorter time from diagnosis to death compared to idiopathic PAH patients, with a reported hazard ratio of 2.6 (95% CI 1.1–6.1) [76]. PAH was the third most common cause of death in Korean SLE patients [89]. PAH has been reported as a common cause of death in Chinese and Korean patients, but not a common cause of death in North American or European cohorts [3], suggesting that ethnicity or access to care may be

**TABLE 5** Prevalence of systemic lupus erythematosus associated-pulmonary arterial hypertension

Prevalence	Diagnostic threshold	Ref.
<b>Echocardiogram based</b>		
2.8%	RVSP $> 45$ mmHg	[77]
4.9%	$P_{pa,sys} > 30$ mmHg	[78]
9%	Clinical findings <sup>#</sup>	[80]
10%	$P_{pa} > 55$ mmHg	[81]
11%	$P_{pa,sys} > 30$ mmHg and $\bar{P}_{pa} > 20$ mmHg	[82]
13%	$P_{pa,sys} \geq 35$ mmHg	[85]
14%	RVSP $> 30$ mmHg	[83]
14%	$P_{pa,sys} > 30$ mmHg	[86]
14%	RVSP $\geq 40$ mmHg	[84]
<b>Right heart catheterisation based</b>		
0.005%	$\bar{P}_{pa} > 40$ mmHg	[76]
5%	$\bar{P}_{pa} > 30$ mmHg	[77]
9.3%	$\bar{P}_{pa} > 40$ mmHg	[79]

RVSP: right ventricular systolic pressure;  $P_{pa,sys}$ : pulmonary artery systolic pressure;  $P_{pa}$ : pulmonary artery pressure;  $\bar{P}_{pa}$ : mean pulmonary artery pressure. <sup>#</sup>: cardiac thrust along the left sternal border with or without fourth heart sound and loud second component of the second heart sound, and right axis deviation  $\geq 110^\circ$ , R/S ratio in  $V_6 \leq 1$  and right bundle branch block with at least one of: large pulmonary arteries with pruned peripheral arterial tree, right atrial and/or ventricular hypertrophy on radiograph; or right ventricular dilation on echocardiogram.

prognostic factors for survival. Our recent systematic review of the literature [90] identified a number of clinical factors that may be associated with survival; magnitude of the elevation in  $\bar{P}_{pa}$  at diagnosis [78, 89, 91], thrombosis [89, 92, 93], thrombocytopenia [94], presence of an anti-cardiolipin antibody [89, 92, 93], concurrent pregnancy [95, 96], infection [77], Raynaud's phenomenon [93, 97], plexiform lesion [95] and pulmonary vasculitis [96]. Conversely, lupus central nervous system disease [89], lupus nephritis [89] and lupus disease activity [89, 98–100] have not been associated with survival in SLE-PH. It has been suggested that SLE-PAH patients have a better prognosis than SSc-PAH patients, where CONDLIFFE *et al.* [44] reported a 3-yr survival rate of 75% in SLE-PAH compared to 47% in SSc-PA patients in the UK ( $p=0.01$ ).

The role of immunosuppressive therapy in SLE-PH is controversial. Several small case reports/series have reported improvement with immunosuppressive therapy [87, 101–103]. However, others have reported clinical deterioration in SLE-PH despite immunosuppressive therapy [99, 104]. Recent observational studies suggest that a subset of SLE-PH patients will improve with immunosuppression. SANCHEZ *et al.* [72] report that five (38%) out of 13 SLE-PH patients treated with monthly intravenous cyclophosphamide  $600 \text{ mg} \cdot \text{m}^{-2}$  with or without glucocorticoids remained in New York Heart Association (NYHA) functional class I or II with sustained haemodynamic improvement after 1 yr of therapy. The same group later reported similar findings with four (44%) out of nine SLE-PH patients treated with monthly intravenous cyclophosphamide

**TABLE 6** Survival in systemic lupus erythematosus associated-pulmonary arterial hypertension

Survival %					Ref.
1-yr	2-yr	3-yr	5-yr	Median	
Not reported	Not reported	Not reported	50	5 yrs	[1]
Not reported	Not reported	Not reported	86	Not reported	[86]
50.5	Not reported	44.9	16.8	13 months	[77]
100	95.1	87.2	87.2	Not reported	[6]
78	Not reported	74	Not reported	Not reported	[45]
94	Not reported	Not reported	Not reported	Not reported	[57]

and glucocorticoids remaining in NYHA functional class I or II with a  $\bar{P}_{pa} < 40$  mmHg and/or a normal cardiac index [5]. It has also been observed that some SLE-PH patients can be transitioned from parental prostaglandin therapy to oral PH-specific treatment with continued improvement [105]. These outcomes contrast with SSc-PAH where, in general, immunosuppressive therapy is not effective and often requires the escalation of PH-specific therapy [72].

Together, these findings suggest PH in the setting of SLE may not represent one homogenous condition, but may reflect the final common pathway in a few distinct pathologically based subsets [3, 106]. One subset may be those prone to thromboembolic disease. Features of this subset include the presence of the anti-phospholipid antibody syndrome, lupus anticoagulant/anti-cardiolipin antibodies [1] (note that the relationship between PH and the lupus anticoagulant is not reproducible [107]), increased risk of developing thrombotic arteriopathy and pulmonary embolism [88]. This subset of patients may benefit from concurrent anticoagulation. A second subset may be those with a pulmonary vasculopathy similar to SSc-PAH. This vasculopathy manifests as noninflammatory vascular remodelling, may contain the plexiform lesion and may be associated with the anti-ribonucleoprotein antibody. A third pathological based subset is one with an immune-mediated vasculopathy leading to pulmonary vasculitis: inflammation of the pulmonary artery that may be reversible with immunosuppression [106]. Indeed, some patients with SLE-PAH have been found to have circulating anti-endothelial cell antibodies [108]. This suggests B-cell activation may be part of the pathogenesis of SLE-PAH. Consequently, suppression of these antibodies may represent another rationale for concurrent immunosuppressive therapy. Similarly, immune complex deposition (large amounts of immunoglobulin (Ig)G and C1q, and small amounts of IgM and C3 in the intimal and medial layers) has been described in the pulmonary vessels of SLE-PH patients, again supporting a role for immunosuppression [76]. This inflammatory or "vasculitic" SLE-PAH subset classification is hypothesis generating and requires formal validation. If correct, this may explain why there has been a differential response to immunosuppressive therapy in observational studies [5, 72]. Correct identification of subsets may facilitate appropriate targeted therapy, allow treatment to start before irreversible vascular lesions occur [109] and identify those patients who can be stepped down to less aggressive therapy [110].

Clinical studies of PAH-specific therapy often include SSc-PAH and SLE-PAH under the all-encompassing category of CTD. DENTON *et al.* [15] reported the effect of bosentan at 48 weeks in 42 SSc-PH, five SLE-PAH patients and six MCTD patients. Functional class improved in 27% (95% CI 16–42%) and worsened in 16% (95% CI 7–29%) of patients. The Kaplan–Meier estimate for survival at 48 weeks was 92% (95% CI 85–100%) [15]. A *post hoc*, subgroup analysis of the SUPER-1 trial (12-week, double-blind evaluation of sildenafil 20, 40 or 80 mg *t.i.d.* or placebo) evaluated outcomes in 38 SSc-PAH, 19 SLE-PAH and 17 patients with other CTDs. Sildenafil-treated patients demonstrated mean increases in 6-min walk distance of 42 m (95% CI 20–64 m), 36 m (95% CI 14–58 m) and 15 m (95% CI –24–54 m) for 20, 40 and 80 mg, respectively, and a mean decrease of 13 m (95% CI –36–10 m) in the placebo group. Improvement of at least one functional class occurred in 29–42% of the sildenafil-treated patients compared to 5% of placebo-treated patients [14].

A few additional issues should be taken into consideration in the management of patients with SLE-PH. First, the use of a central venous line for epoprostenol infusion is associated with catheter infection and/or sepsis. In SLE-PAH patients treated with immunosuppressants, the risk of infection may be greater and, thus, may influence the treatment decision. Secondly, there is a risk of severe thrombocytopenia with epoprostenol in SLE-PAH. This may be of particular concern when thrombocytopenia precedes the start of epoprostenol therapy [111].

## CONCLUSION

Our understanding of the epidemiology of SSc-PAH has improved with increased precision in prevalence estimates and identification of prognostic factors. Short-term survival in SSc-PAH has improved with the introduction of PAH-specific therapies. However, long-term survival ( $\geq 5$  yr) remains discouraging, leaving room for newer advances in the understanding of pathophysiology and treatment. SLE-PAH is relatively understudied compared to SSc-PAH, and requires well-designed, appropriately powered studies. The current data suggests there are subsets of SLE-PH patients with a worse prognosis than SSc-PAH patients; however, there is also a subset of SLE-PAH patients who will respond to concomitant immunosuppressive therapy resulting in normalisation of cardiopulmonary haemodynamics. Research into these findings will undoubtedly lead to further refinement in our understanding of PH in the CTDs.

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## STATEMENT OF INTEREST

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