Connective Tissue Disease–associated Pulmonary Arterial Hypertension in the Modern Treatment Era

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***Rationale*: Pulmonary arterial hypertension in association with connective tissue disease (CTD-PAH) has historically had a poor prognosis, with a 1-year survival rate among patients with systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) of 45%. However, more therapies have become available.**

***Objectives*: To investigate the survival and characteristics of all patients diagnosed with CTD-PAH in the U.K. pulmonary hypertension service.**

***Methods*: National registry of all incident cases of CTD-PAH diagnosed consecutively between January 2001 and June 2006.**

***Measurements and Main Results*: Patients with CTD-PAH (429; 73% SSc-PAH) were diagnosed by a catheter-based approach. One- and 3-year survival rates were 78 and 47% for patients with isolated SSc-PAH. Survival was worse for those with respiratory disease–associated SSc-PAH (3-yr survival, 28%; $P = 0.005$) whereas survival among patients with exercise-induced SSc-PAH was superior (3-yr survival, 86%; $P = < 0.001$). Age, sex, mixed venous oxygen saturation, and World Health Organization functional class were independent predictors of survival in isolated SSc-PAH. Nineteen percent of patients with exercise-induced SSc-PAH and 39% of patients with isolated SSc-PAH who were in functional classes I and II had evidence of disease progression. The prevalence of diagnosed SSc-PAH is 2.93 per 1 million. The 3-year survival rate of 75% for those with pulmonary arterial hypertension associated with systemic lupus erythematosus (SLE-PAH) was significantly better than that for patients with SSc-PAH ($P = 0.01$).**

***Conclusions*: Survival of patients with SSc-PAH in the modern treatment era is better than in historical series. A significant proportion of patients with mild functional impairment or exercise-induced SSc-PAH have evidence of disease progression. Survival of patients with respiratory disease–associated pulmonary hypertension is inferior. SLE-PAH has a better prognosis than SSc-PAH.**

Keywords: pulmonary hypertension; connective tissue disease; systemic sclerosis; systemic lupus erythematosus; survival

Connective tissue disease–associated pulmonary arterial hypertension (CTD-PAH) has historically had a poor prognosis, with a 1-year survival rate before the availability of advanced therapies of 45% in patients with systemic sclerosis (SSc) (1). The management of CTD-PAH in the United Kingdom has, however, changed significantly. First, all three groups of advanced therapies—prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors—used in idiopathic PAH have also been shown to improve pulmonary hemodynamics and functional status in patients with CTD-PAH (2–7). Second, the diagnosis, prescribing, and management of all adult CTD-PAH has been centralized to five pulmonary hypertension (PH) centers. This has produced a unique chance to investigate the characteristics, treatments, and survival of all patients with CTD-PAH within a single country.

Previous studies have largely concentrated on SSc-associated PAH (SSc-PAH), with a disease prevalence estimated to be between 7.5 and 12% (8, 9). This has led to the introduction of screening programs. In systemic lupus erythematosus (SLE) estimated survival has ranged from relatively good to being worse than in idiopathic PAH (10, 11). Even less is known about PAH in other forms of connective tissue disease.

Using pooled data from the five PH centers in the United Kingdom we have performed a cohort study of all incident cases diagnosed during a 5.5-year period starting in 2001, the year when the centers were commissioned. We hypothesized that the prognosis in SSc-PAH has improved during the modern treatment era. Using this unique national registry we also aimed to determine incidence, prevalence, and prognostic factors in SSc-PAH, together with outcomes in rarer forms of CTD-PAH. Some of the results of this study have been previously reported in the form of an abstract (12).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Systemic sclerosis (SSc)–associated pulmonary arterial hypertension (PAH) has historically had a poor outcome. Little is known of outcomes in exercise-induced and respiratory disease–associated SSc-PAH, or in PAH due to other connective tissue diseases.

What This Study Adds to the Field

Survival of patients with SSc-PAH in the modern treatment era is better than in historical series. Survival of patients with respiratory disease–associated pulmonary hypertension is inferior. SLE-PAH has a better prognosis than SSc-PAH.

METHODS

Patient Population

Details of all incident cases of CTD-PAH diagnosed consecutively at a U.K. PH center between January 1, 2001 and June 31, 2006 were entered into local databases at the time of diagnosis. One investigator

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(R.C.) subsequently visited each site to examine patient records to confirm the diagnosis and to record clinical data. Patients given a diagnosis of PAH at rest were excluded from the study cohort if mean pulmonary artery pressure ($\overline{Ppa}$) was less than 25 mm Hg, pulmonary capillary wedge pressure was greater than 15 mm Hg, or pulmonary vascular resistance (PVR) was less than 240 dyn · second · cm^{-5}. Exercise-induced PAH was defined as a $\overline{Ppa}$ of at least 30 mm Hg with a pulmonary capillary wedge not more than 15 mm Hg on exercise. Subsequent disease progression in patients with exercise-induced PAH was defined as development of PAH at rest at subsequent right-heart catheterization. In patients with baseline PAH at rest, progression was defined as both a 20% fall in walk distance and an increase in World Health Organization (WHO, Geneva, Switzerland) functional class or, when subsequent catheterization data were present, a 20% increase in both $\overline{Ppa}$ and PVR.

Patients with either a forced vital capacity of less than 60% predicted or, when no spirometry results were found, moderate or severe fibrosis (more than one third of lung fields involved) on high-resolution computed tomography were defined as having respiratory-associated PH. No specific nationwide treatment algorithm was used; advanced therapies were commenced as thought appropriate at each center. Combination therapies were used when allowed and clinically indicated. Patient follow-up was as per clinical need. To calculate survival an end point of either date of death or transplant or a censor date of January 26, 2007 was used. Date of diagnosis was taken as the date of initial diagnostic right-heart catheterization. If this could not be located in the hospital records then date of first visit was used. Mortality status was ascertained from PH center records, by contacting general practitioners, and by using the National Health Service strategic tracing service. As this study was designed and conducted to define current care, formal ethics approval was not required. The national Patient Information Advisory Group was fully informed regarding the use of patient data.

Statistical Analysis

Analysis was performed with the SPSS statistical package (SPSS, Chicago, IL). Mean and standard deviation or confidence interval were used to describe parametric data, whereas the median and interquartile range were used for nonparametric data. Comparison between unpaired quantitative data was performed by independent *t* or Mann-Whitney *U* test. Qualitative data were compared by χ^2 test. Factors associated with survival in isolated SSc-PAH were examined by multiple Cox regression analysis. Additional detail on the methods of the regression analysis is provided in the online supplement. Two types of walk tests were in use and therefore, to combine these into a single variable for modeling, distances were converted to a *z*-score corresponding to the number of standard deviations from the mean. Survival estimates were performed by Kaplan-Meier analyses with comparisons performed by log-rank test. As cause of death could not always be confidently ascribed; all-cause mortality was used in survival statistics. A *P* value less than 0.05 was taken as significant throughout.

RESULTS

Study Population

The patients included in the study cohort are shown in Figure 1. The maximal duration of follow-up was 6 years, with a mean follow-up of 3.3 years. Data were recorded primarily for clinical purposes and therefore baseline demographics were not complete in all cases. Right-heart catheterization details were located in 98% of cases, gas transfer in 71% of cases, and forced vital capacity in 79% of cases. Exercise capacity was recorded in 82% of patients, using the 6-minute walk test in 56% and incremental shuttle walking test in 26% of cases. Baseline pulmonary hemodynamics of patients with isolated SSc-PAH and isolated SLE-associated pulmonary arterial hypertension (SLE-PAH) were not significantly different, although patients in the latter group were younger and had better exercise tolerance and gas transfer (T_{LCO}; Table 1).

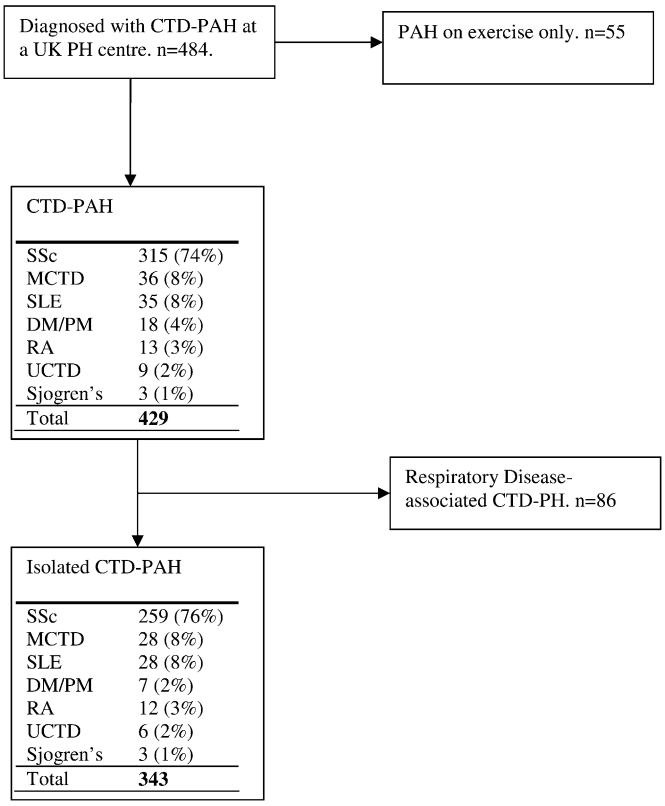

Figure 1. Study cohort. CTD-PH/PAH = connective tissue disease–associated pulmonary hypertension/pulmonary arterial hypertension; DM/PM = dermatomyositis/polymyositis; MCTD = mixed connective tissue disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease; UK-PH = U.K. pulmonary hypertension center.

SSc-PAH

One-, 2-, and 3-year survival for patients with isolated SSc-PAH was 78, 58, and 47%, respectively. The survival in isolated SSc-PAH was superior to that seen in respiratory disease–associated PH (Figure 2). There was no significant difference in the pulmonary hemodynamics of these two groups, although patients in the latter group had lower gas transfer and exercise tolerance and were more likely to be nonwhite (*see* Table 1).

Therapies for SSc-PAH

Sixty-two percent of patients with isolated SSc-PAH received advanced monotherapy, 28% combination therapy, and 10% no advanced therapy. Patients who were commenced on a single therapy and subsequently had an additional therapy added in were classed as having received combination therapy. Of those receiving a single monotherapy 68% received an endothelin receptor antagonist, 17% a prostanoid, and 15% a phosphodiesterase-5 inhibitor.

Predictors of Mortality in Patients with Isolated SSc-PAH

Univariate analysis showed that patients under the age of 60 years had better survival as compared with patients 70 years of age or older (Table 2). WHO functional class III or IV was associated with more than two times the risk of death as compared with class I or II ($P = 0.002$). Patients with higher mean right atrial pressure, $\overline{Ppa}$, PVR, and total pulmonary resistance had a higher risk of death. Higher cardiac index, mixed venous oxygen saturation ($S\bar{v}_{O_2}$), gas transfer, and walk

TABLE 1. BASELINE DEMOGRAPHICS

	Isolated SSc-PAH	*Respiratory-associated SSc-PH*		*Isolated SLE-PAH*	
	(*n* = 259)	(*n* = 56)	*P* Value*	(*n* = 28)	*P* Value†
Age, yr	63.9 (10.5)	57.9 (11.4)	<0.001	42.0 (12.9)	<0.001
Female, %	82	77	0.34	96	0.06
Ethnicity (white/nonwhite), %	96/4	80/20	<0.001	70/30	<0.001
$\overline{Ppa}$, mm Hg‡	42.0 (17)	40.0 (17.5)	0.57	48.0 (16)	0.10
CI, L/min/m^2	2.43 (0.73)	2.38 (0.72)	0.66	2.63 (0.63)	0.20
PVR, dyn · s · cm^{-5}‡	715 (597)	705 (592)	0.71	715 (377)	0.90
$S\bar{v}_{O_2}$, %	64.1 (9.9)	62.7 (10.5)	0.35	65.0 (7.9)	0.66
T_{LCO}, %	41.5 (14.8)	29.1 (10.1)	<0.001	59.2 (12.1)	<0.001
WHO I and II/III/IV, %	16/68/16	5/55/40	<0.001	15/70/15	0.99
6MWT, m‡	231 (216)	146 (124)	0.03	340 (194)	0.03

Definition of abbreviations: 6MWT = 6-minute walk test; CI = cardiac index; $\overline{Ppa}$ = mean pulmonary artery pressure; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; PVR = pulmonary vascular resistance; SLE-PAH = systemic lupus erythematosus–associated pulmonary arterial hypertension; SSc-PH/PAH = systemic sclerosis–associated pulmonary hypertension/pulmonary arterial hypertension; T_{LCO} = percentage predicted gas transfer; WHO I, II, III, and IV = World Health Organization functional classes.

Values represent mean (standard deviation) or percentage unless otherwise indicated.

* Isolated SSc-PAH versus respiratory-associated SSc-PH.

† Isolated SSc-PAH versus isolated SLE-PAH.

‡ Median (interquartile range).

distance were associated with a decreased risk of death. Multiple variable analysis showed that younger age, female sex, higher $S\bar{v}_{O_2}$, and lower WHO functional class were independent predictors of survival. The effects on survival of antinuclear, SCl-70, and anti-centromere antibody status, together with the time from onset of connective tissue disease to diagnosis of PAH, were also tested but were found to be nonsignificant in both univariate and multivariate analysis. Survival curves based on $S\bar{v}_{O_2}$ and WHO class are shown in Figures 3A and 3B.

SSc-PAH on Exercise

Survival of the 42 patients with isolated exercise-induced SSc-PAH compared with those with isolated SSc-PAH at rest is shown in Figure 4. Five patients with exercise-induced SSc-PAH subsequently died. PH and/or right-heart failure was recorded as the main cause of death in four patients. The fifth patient died of septicemia secondary to hepatic abscesses. Eight patients (19%) had evidence of disease progression with subsequent PAH at rest diagnosed at repeat right-heart catheterization ($\overline{Ppa}$, 35.2 ± 10.2 mm Hg; pulmonary capillary wedge pressure, 10.6 ± 2.0 mm Hg; cardiac index, 2.58 ± 0.49 L · min · m^{-2}; PVR, 478 ± 213 dyn · s · cm^{-5}). Mean time to PAH at rest was 838 ± 477 days from diagnosis. Seven (17%) patients required advanced therapies within 3 years of diagnosis.

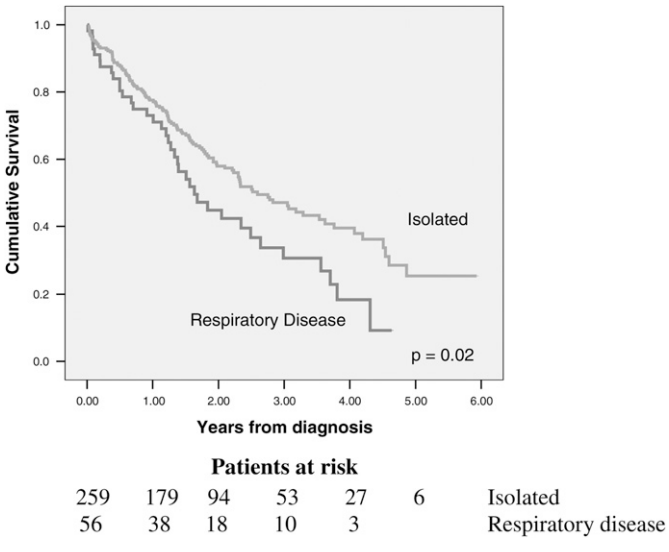

Figure 2. Survival from diagnosis of patients with systemic sclerosis and isolated or respiratory disease–associated pulmonary hypertension.

SSc-PAH with Good Functional Class

Although survival of patients with isolated SSc-PAH at rest who were in functional class I and II at baseline was superior to that of patients in classes III or IV, mortality was still appreciable (*see* Figure 3B). Three of the 41 patients refused clinical follow-up. Evidence of disease progression was found in 15 (39%) of the remaining patients during follow-up, and in 7 (88%, all of whom received advanced therapy) of the 8 patients who died and had follow-up. Disease progression was confirmed by hemodynamics in eight patients and by a combination of both a 20% fall in walk distance and an increase in WHO class in seven patients who had not undergone repeat right-heart catheterization. Mean time to clinical worsening was 840 ± 414 days from diagnosis.

Incidence and Prevalence Estimates

Assuming a U.K. population of 60 million, the incidence of CTD-PAH at rest, diagnosed within the U.K. PH Service, increased from 0.68 per million per year in 2001 to 1.55 per million per year in 2005. The population prevalence, on June 31, 2006, of patients diagnosed within the U.K. PH service was 4.23 per million for CTD-PAH at rest and 2.93 per million for SSc-PAH at rest.

Other Disease Types

One- and 3-year survival rates for isolated PAH associated with SLE were 78 and 74%, with polymyositis/dermatomyositis (PM/DM) they were 100 and 100%, with MCTD they were 89 and 63%, and with rheumatoid arthritis they were 83 and 66%, respectively. When compared with SSc-PAH, only the survival of SLE-PAH ($P = 0.01$; Figure 5) and PM/DM-PAH ($P = 0.03$) were significantly better. Of patients with SLE 75% were treated with advanced therapy whereas 86% received immunosuppression; 11% had an immunosuppressive started and 75% were already immunosuppressed. In contrast to patients with isolated PAH, the superior survival seen in patients with other forms of CTD when compared with SSc did not extend to those patients with respiratory disease–associated PH.

DISCUSSION

This article reports the findings of the largest ever study of connective tissue disease–associated pulmonary hypertension involving patients with a right-heart catheter-based diagnosis. It incorporates the vast majority of such patients within a single nation and, importantly, includes only incident cases. We have therefore been able to define the medium to long-term outcome in patients with both SSc-PAH and other less well studied forms of CTD-PAH. In an unselected cohort of patients with SSc-PAH we have demonstrated improved survival when compared with early historical data, where median survival was found to be less than 2 years (1, 13).

Although some later studies have demonstrated superior survival they have involved prevalent and selected patients

TABLE 2. PREDICTORS OF MORTALITY IN ISOLATED SYSTEMIC SCLEROSIS–ASSOCIATED PULMONARY ARTERIAL HYPERTENSION*

		Univariate Analysis		Multiple Analysis	
Variable†	n	Univariate HR‡	*P* Value	Multiple HR‡	*P* Value
Age					
20–49 yr	30	0.61 (0.32, 1.16)	0.02	0.66 (0.34, 1.29)	0.018
50–59 yr	59	0.58 (0.34, 0.96)		0.40 (0.22, 0.71)	
60–69 yr	86	1.14 (0.76, 1.74)		0.81 (0.52, 1.27)	
>70 yr	84	Reference		Reference	
Sex					
Female	213	Reference	0.15	Reference	0.001
Male	46	1.39 (0.89, 2.15)		2.20 (1.36, 3.55)	
WHO					
I/II	41	Reference	0.002	Reference	0.044
III/IV	218	2.70 (1.45, 5.01)		2.26 (1.02, 4.97)	
$\overline{Pra}$, per 5 mm Hg		1.43 (1.22, 1.69)	<0.001	—	
$\overline{Ppa}$					
25–33 mm Hg	68	Reference	<0.001	—	
34–42 mm Hg	62	1.23 (0.69, 2.20)			
43–50 mm Hg	67	2.77 (1.65, 4.67)			
51–74 mm Hg	57	2.30 (1.34, 3.97)			
CI, per 0.5 L/min/m^2		0.77 (0.67, 0.89)	0.001	—	
PVR, per 100 dyn · s · cm^{-5}		1.10 (1.06, 1.14)	<0.001	—	
TPR					
277–560.0 dyn · s · cm^{-5}	64	Reference	<0.001	—	
561–865 dyn · s · cm^{-5}	61	2.55 (1.40, 4.65)			
866–1,233 dyn · s · cm^{-5}	62	2.51 (1.37, 4.61)			
1,234–3,032 dyn · s · cm^{-5}	62	4.69 (2.64, 8.34)			
$S\overline{v}_{O_2}$					
25.0–60.0%	61	Reference	<0.001	Reference	<0.001
60.1–66.0%	57	0.40 (0.24, 0.66)		0.36 (0.22, 0.59)	
66.1–70.0%	58	0.40 (0.25, 0.66)		0.38 (0.23, 0.63)	
70.1–95.0%	57	0.16 (0.09, 0.31)		0.17 (0.09, 0.33)	
Walk *z*-score					
−1.70 to −0.78	54	Reference	<0.001	—	
−0.79 to −0.007	54	0.56 (0.34, 0.91)			
−0.008 to 0.70	52	0.35 (0.20, 0.60)			
0.71 to 3.41	57	0.21 (0.11, 0.39)			
Missing§	42	0.63 (0.37, 1.05)			
$T_{L_{CO}}$					
13–31%	54	Reference	<0.001	—	
32–39%	52	0.83 (0.50, 1.37)			
40–49%	52	0.46 (0.26, 0.83)			
50–98%	47	0.42 (0.22, 0.78)			
Missing§	54	1.39 (0.86, 2.26)			
FVC					
60–73%	57	Reference	0.042	—	
74–89%	57	0.83 (0.49, 1.38)			
90–103%	61	0.72 (0.43, 1.22)			
104–147%	52	0.62 (0.34, 1.11)			
Missing§	32	1.52 (0.86, 2.69)			
Year of diagnosis					
2001/02	62	Reference			
2003–	197	0.96 (0.64, 1.43)	0.83		

Definition of abbreviations: HR = hazard ratio; $\overline{Pra}$= mean right atrial pressure; TPR, total pulmonary resistance.

* n = 259.

† Variables grouped where appropriate into quartiles.

‡ Hazard ratios are presented with 95% confidence intervals.

§ More than 10% of patients with missing data.

(4, 13, 14). Our survival rates concur with those seen previously in a smaller cohort of unselected incident cases (15). It is impossible to exclude the contribution of lead-time bias toward the improved survival we have demonstrated. However, even if the observed improvement is real the prognosis in SSc-PAH remains relatively poor, highlighting the need for more effective therapeutic strategies.

Survival of patients with respiratory-associated SSc-PH was significantly worse than that of patients with isolated SSc-PAH. Chang and colleagues previously found no significant difference in survival between 119 SSc patients with isolated PH and 112 SSc patients with a combination of restrictive lung disease and PH (16). A limitation of that study, however, was that no right-heart catheterization data were presented, with PH defined as an echocardiographically estimated systolic pulmonary artery pressure of less than 35 mm Hg. Patients with PH in association with hypoxic lung disease often have relatively mildly elevated pulmonary pressures with preserved or increased cardiac output (17). It is interesting to note that in the present study cohort, patients with both SSc and significant respiratory disease had disturbances in pulmonary hemodynamics that were disproportionate to the underlying lung disease and were more akin to

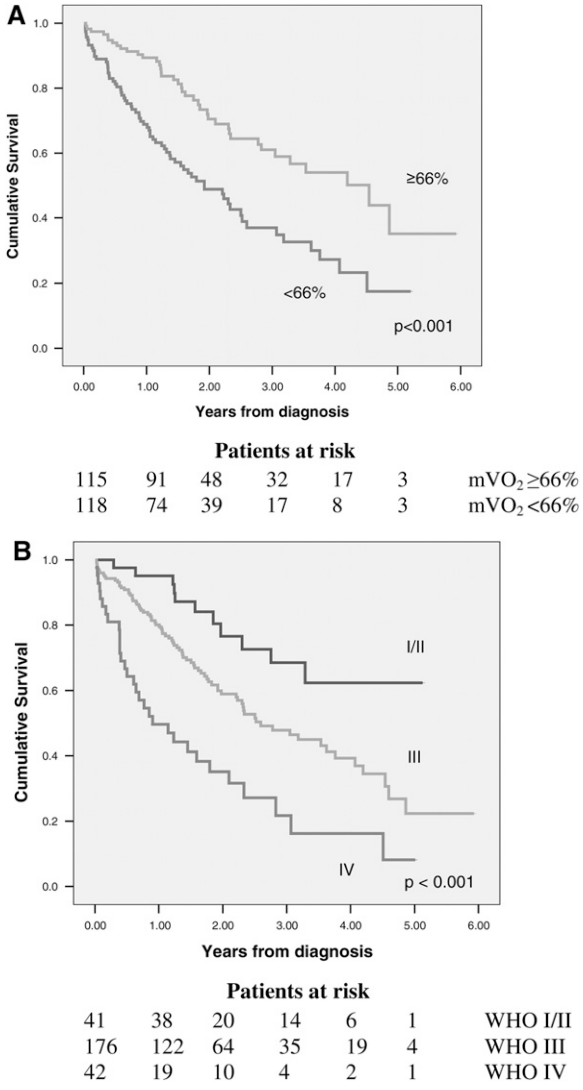

Figure 3. Survival from diagnosis of patients with isolated systemic sclerosis–associated pulmonary arterial hypertension (SSc-PAH) grouped by (*A*) median mixed venous oxygen saturation and (*B*) World Health Organization (WHO) functional class.

those seen in isolated SSc-PAH. Only three patients with respiratory-associated SSc-PH underwent transplantation during the study period. It is likely that this reflects the increased risk of transplantation in this group of patients related to factors such as gastroesophageal reflux disease and renal disease. However, the poorer outcome with standard therapy in this group of patients especially suggests that prompt referral for transplant assessment of suitable patients should be considered.

Age, sex, mixed venous oxygen saturation, and WHO functional class were identified as independent prognostic factors and may be useful in decision-making regarding advanced therapies. Several hemodynamic variables that correlated with each other were included for consideration in the multiple regression model. Parameters, such as PVR, which were significant in univariate but not multivariable analysis are therefore still of clinical relevance.

Although patients with exercise-induced SSc-PAH clearly had a better prognosis than patients with SSc-PAH at rest, mortality was not negligible, with the majority of these deaths being attributed to PH. Furthermore, evidence of disease progression

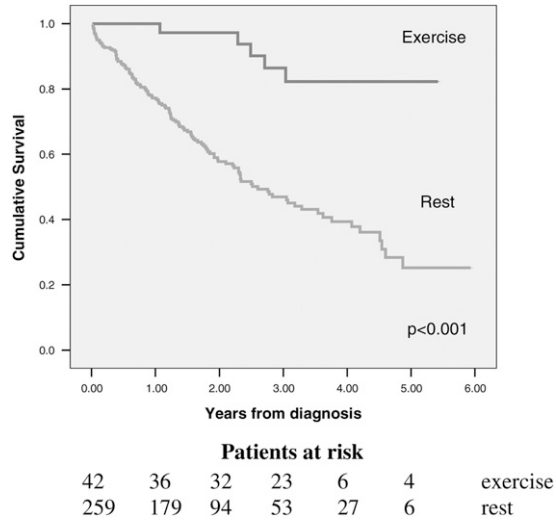

Figure 4. Survival from diagnosis of patients with isolated systemic sclerosis–associated pulmonary arterial hypertension at rest or on exercise.

to PAH at rest was found in almost one fifth of patients with SSc and exercise-induced PAH, and in 60% of those patients who died. It would therefore appear prudent to monitor patients with exercise-induced PAH to ensure that any deterioration in pulmonary hemodynamics is recognized early, allowing timely commencement of advanced therapy. Mortality of patients with isolated SSc-PAH at rest who were in WHO classes I and II was appreciable. Furthermore, more than one third of patients had evidence of disease progression during follow-up. The results of a randomized controlled trial into the effects of bosentan on patients in WHO functional class II (18% of whom had CTD-PAH) have been published (18). Both PVR and time to clinical worsening were improved in the treatment arm. Given the observed mortality in our study, patients with SSc-PAH in WHO class II may be a suitable group in which to study the effect of treatment on survival.

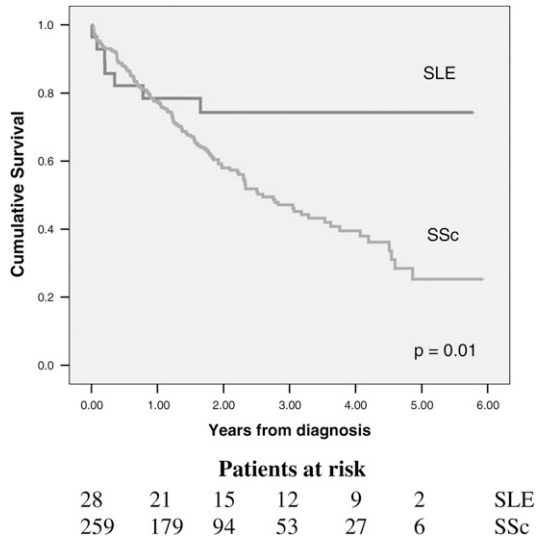

Figure 5. Survival from diagnosis of patients with isolated systemic sclerosis–associated pulmonary arterial hypertension and systemic lupus erythematosus–pulmonary arterial hypertension.

Two national studies estimated the prevalence of CTD-PAH to be 2.3 and 10 cases per million within the general population (19, 20). Our estimates of 4.23 per million for CTD-PAH and 2.93 per million for SSc-PAH are in rough agreement with these previous estimates.

There is a relative paucity of literature regarding the outcome of CTD-PAH in conditions other than SSc. Chung and colleagues retrospectively studied 20 patients with SLE-PAH, 55% of whom received advanced therapy and 45% of whom received immunosuppression (11). They found a median survival of 13 months. Even less is known regarding the outcome of patients with other forms of CTD-PAH. We have demonstrated that isolated SLE-PAH in the modern treatment era has a relatively good prognosis compared with SSc-PAH, although there was a group of patients with rapidly progressive SLE-PAH who died within 1 year of diagnosis. Sanchez and colleagues found that about 40% of patients with SLE-PAH responded to immunosuppression (21). We were unable to study the effect of immunosuppression on survival as the number of untreated patients was small. There were too few numbers with other CTD types to make many definite conclusions, although the good prognosis in patients with isolated PM/DM-PAH is noted.

The main limitations of this study are its observational, uncontrolled nature and the fact that much of the data was collected retrospectively, meaning that gaps in the data were unavoidable. As such, only inferences rather than firm conclusions can be made regarding possible effects of treatment. However, data regarding survival are robust and will not have been affected by the study design. Our estimates of prevalence did not include cases that were prevalent at the beginning of our inclusion period. However, because of the length of our study and the poor prognosis in CTD-PAH, the point prevalences at the end of our inclusion period are probably representative of the true prevalence of diagnosed and treated disease. These figures are likely to be conservative estimates of the true prevalences as they include only patients who had been diagnosed at a PH center. Few patients, however, will have been diagnosed and treated appropriately elsewhere because funding bodies in the United Kingdom will fund advanced therapies only if prescribed by one of the national PH centers. The comparison of survival between disease types is hampered by confounding variables such as differing ages of the specific disease populations. However, in the clinical setting it is useful to be able to compare the likely outcome of a typical patient with a rarer form of CTD-PAH with that of a typical patient with the more commonly seen SSc-PAH.

In conclusion, although survival in SSc-PAH may have improved when compared with historical data from before the modern treatment era it remains unacceptably poor. Further research into the use of advanced therapies specifically in CTD-PAH is needed. Patients with respiratory disease–associated PH have a poorer outcome. The clinical course of patients with both exercise-induced SSc-PAH and with SSc-PAH at rest who are in WHO functional classes I and II, although being superior to that of patients with PAH at rest in classes III and IV, reinforces the importance of monitoring these groups of patients for evidence of disease progression. Finally, we have demonstrated that the prognosis with current therapeutic regimens is significantly better in some of the other groups of CTD-PAH, especially SLE-PAH.

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