Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: results from an international registry

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Decreased 6-min walk distance and reduced diffusion capacity are associated with decreased survival in patients with sarcoidosis-associated pulmonary hypertension <http://bit.ly/2UQfWJh>

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ABSTRACT

Introduction: Sarcoidosis-associated pulmonary hypertension (SAPH) is associated with reduced survival in single-centre studies. The international Registry for SAPH (ReSAPH) with long-term follow-up was established to enrich our knowledge of this complication of sarcoidosis. This analysis aims to elucidate factors associated with reduced transplant-free survival in SAPH patients.

Methods: ReSAPH contains prospectively collected outcomes of SAPH patients since the time of registry enrolment. Information analysed includes right heart catheterisation data, pulmonary function testing, chest radiography, Scadding stage and 6-min walk distance (6MWD), among others. Cox regression models were used to identify independent predictors of transplant-free survival.

Results: Data from 215 patients followed for a mean $\pm$ SD 2.5 $\pm$ 1.9 years were available for analysis. In the 159 precapillary patients, the Kaplan–Meier-adjusted 1-, 3- and 5-year transplant-free survival was 89.2%, 71.7% and 62.0%, respectively. Kaplan–Meier-adjusted 1-, 3- and 5-year transplant-free survival in the incident group was 83.5%, 70.3% and 58.3%, respectively, and in the prevalent group was 94.7%, 72.2% and 66.3%, respectively. Patients with reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (<35% predicted) and 6MWD <300 m in the precapillary cohort had significantly worse transplant-free survival. Reduced 6MWD and preserved forced expiratory volume (FEV_1)/forced vital capacity (FVC) ratio were identified as independent risk factors for reduced transplant-free survival in the precapillary cohort.

Conclusion: Reduced D_{LCO} (<35% pred) and 6MWD (<300 m) at the time of registry enrolment were associated with reduced transplant-free survival in the overall precapillary cohort. Preserved FEV_1 /FVC ratio was identified as an independent risk factor for worsened outcomes.

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Introduction

Sarcoidosis is a multisystem disease prevalent throughout the world [1, 2]. Lung involvement in sarcoidosis is seemingly invariable, with up to 95% of patients manifesting some form of pulmonary disease during the course of their lifetime. Sarcoidosis-associated pulmonary hypertension (SAPH) is a complication associated with significant morbidity and increased mortality [3].

From 2010 to 2013, the reported incidence of sarcoidosis in the United States ranged between 7.6 and 8.4 per 100 000 insured patients with an expected prevalence of ~60.0 per 100 000 [4]. The reported prevalence of SAPH is between 6% and 20% at rest and up to 43% with exercise [3, 5–9], with rates of 75% in those listed for lung transplantation [4].

SAPH is categorised as group 5 pulmonary hypertension [10, 11]. Although SAPH occurs more frequently in patients with fibrotic disease, it has been described in those without parenchymal involvement [12]. In addition to fibrotic distortion of the pulmonary vasculature from parenchymal fibrosis, other factors may be related to the granulomatous changes of the pulmonary vasculature found on both arterial and venous sides. Additionally, extrapulmonary factors such as extrinsic mechanical compression of the large pulmonary arteries by hilar lymphadenopathy or fibrosing mediastinitis may play a role, as well as their associated comorbidities, including obstructive sleep apnoea, liver disease and heart failure [13].

Since SAPH is relatively rare, the most practical way to further explore this previously underappreciated entity is through the inception of prospective registries. Therefore, an observational international Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH) was established to prospectively collect data on patients with both incident and prevalent SAPH. We have previously reported the baseline characteristics of the ReSAPH population [14] and now provide an analysis of outcomes for the precapillary subset of patients.

Materials and methods

Patients with a diagnosis of sarcoidosis based on the American Thoracic Society/European Respiratory Society (ERS)/World Association of Sarcoidosis and Other Granulomatous Diseases criteria [15], data from at least one follow-up visit and a haemodynamic diagnosis of pulmonary hypertension were enrolled in an 11-centre observational registry [14], initiated in October 2011. All patients were required to have at least one right heart catheterisation (RHC) demonstrating a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, in accordance with the 2015 European Society of Cardiology/ERS guidelines definition [10]. Incident cases were defined as the diagnosis of pulmonary hypertension within 1 year of entry into the registry, whereas prevalent cases were historically diagnosed more than a year prior. All information was recorded in a secure web-based electronic database (REDCap) [16]. Local institutional review board approval was obtained prior to entering any patient into the database. The authors used the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist in preparing this report [17].

For each incident patient, the first RHC identifying pulmonary hypertension was used for diagnosis and to calculate transplant-free survival. For prevalent patients, survival time was calculated as time from registry entry. For example, a prevalent patient diagnosed 1 year prior to registry entry and followed for 5 years from diagnosis had survival time left-truncated at year 1 and right-censored at year 4 (48 months). RHC values recorded included the mean right atrial pressure (RAP), mPAP and systolic (sPAP) and diastolic (dPAP) pulmonary artery pressures, as well as the pulmonary capillary wedge pressure (PCWP) and thermodilution cardiac output. Pre-capillary SAPH was defined as an mPAP ≥ 25 mmHg with a PCWP of ≤ 15 mmHg [10]. Calculated pulmonary vascular resistance (cPVR) was calculated as $\text{mPAP} - \text{PCWP} / \text{cardiac output}$.

Demographics collected included age, sex, race and duration of sarcoidosis. When available, the most recent chest radiograph at the time of entry into the study was reviewed and staged [18] by the enrolling investigator. Scadding staging was not centrally adjudicated. Physiological studies recorded included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), FEV₁/FVC ratio, single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) and 6-min walk distance (6MWD) [15, 19, 20].

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Investigators were asked to record historical and current use of pulmonary hypertension therapy, but no direction was given regarding choice of treatment. Duration of therapy was not captured. Demographics of patients on and off pulmonary arterial hypertension (PAH) therapy were compared. Predefined cut-points of 6MWD, D_{LCO} , mPAP and cPVR were examined for their association with transplant-free survival [21–23].

The participating clinical centres were University of Cincinnati Medical Center (Cincinnati, OH, USA), Cleveland Clinic (Cleveland, OH), Inova Fairfax Hospital (Falls Church, VA, USA), University of Alabama (Birmingham, AL, USA), Temple University (Philadelphia, PA, USA), University of Southern California (Los Angeles, CA, USA), University of Utah (Salt Lake City, UT, USA), Mayo Clinic (Rochester, MN, USA), Erasmus University Medical Centre (Rotterdam, the Netherlands), The Christ Hospital (Cincinnati, OH), the Royal Brompton Hospital (London, UK) and King Saud University (Riyadh, Saudi Arabia).

Statistical analysis

Statistical analysis was performed using STATA 11.0 (Stata Corp., College Station, TX, USA), and SAS (version 9.4; Cary, NC, USA). Data are presented as mean $\pm$ SD or n (%), where appropriate. Between-group differences were compared using t-test, Chi-squared test, Fisher's exact test or the Mann–Whitney–Wilcoxon rank-sum test, as appropriate. Time to survival was calculated from the date of the first identifying RHC for incident patients and the date of SAPH diagnosis for prevalent patients. The Kaplan–Meier method was used to estimate the cumulative probability of outcomes, and between-group differences were compared using the log-rank test. Univariate Cox proportional hazard models were used to assess association between baseline covariates and all-cause mortality (presented as hazard ratio (HR) and 95% confidence intervals). Univariate parameters were considered for inclusion in multivariate models with $p < 0.10$. For final multivariate models, $p < 0.05$ was considered statistically significant. For expected collinear terms (*i.e.* sPAP, dPAP, mPAP), those with the lowest p -value were deemed most statistically significant and included in multivariate models. Kaplan–Meier analysis was used to assess differences in cumulative survival. Transplanted patients were considered right-censored at the time of transplant. All statistical tests involving group comparisons were two-tailed, with p -values < 0.05 considered statistically significant.

Results

Description of baseline data for the precapillary cohort

There were 215 patients enrolled over a 6-year period (last date of entry September 12, 2017) (figure 1). The majority of patients (159 (73.9%) out of 215) had precapillary pulmonary hypertension, with 60% of patients enrolled from the USA, 24% from Western Europe and 16% from Saudi Arabia. A list of participating centres is included in the materials and methods section. The mean age of the overall precapillary cohort (referred to as the “precapillary cohort” from here on) was 56.9 ± 10.6 years with 72.3% female, 56% African American and 31.4% Caucasian and a mean duration between the time of initial

FIGURE 1 Registry for Sarcoidosis-Associated Pulmonary Hypertension (ReSAPH) flowchart. mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure.

TABLE 1 Precapillary cohort demographics

	Precapillary SAPH	Incident SAPH	Prevalent SAPH	p-value [#]
Subjects	159	81 [50.9]	78 [49.1]	
Age years	56.9±10.6	57.0±11.2	56.7±10.0	0.862
Sex				
Female	115 [72.3]	61 [75.3]	54 [69.2]	
Male	44 [27.7]	20 [24.7]	24 [30.8]	0.392
Race				
Caucasian	50 [31.4]	24 [29.6]	26 [33.3]	
African/American	89 [56.0]	38 [46.9]	51 [65.4]	
Other	20 [12.5]	19 [23.4]	1 [1.3]	0.001
Time between initial sarcoidosis diagnosis and SAPH years	14.1±10.9	12.9±12.0	15.3±9.7	0.167
Baseline oxygen saturation %	93.6±4.5	93.5±4.5	94.7±4.3	0.152
FVC L	2.04±0.76	2.0±0.8	2.1±0.8	0.495
FVC % pred	62.4±19.7	60.4±18.5	64.3±20.9	0.225
FEV₁ L	1.4±0.6	1.4±0.5	1.3±0.5	0.340
FEV₁ % pred	55.2±19.9	57.0±18.6	53.4±21.2	0.266
FEV₁/FVC ratio	70.9±16.7	75.2±16.1	66.6±16.2	0.001
D_{LCO} mL·min⁻¹·mmHg⁻¹	9.3±10.1	12.1±13.3	6.8±4.6	0.003
D_{LCO} % pred	40.0±15.9	41.7±15.5	38.4±16.1	0.263
6MWD m	302.6±119.3	296.2±127.3	311.8±108.4	0.469
RAP mmHg	6.4±4.6	6.4±5.0	6.4±4.1	0.967
sPAP mmHg	58.15±14.9	56.2±14.1	60.2±15.7	0.094
dPAP mmHg	23.4±8.0	22.7±8.5	24.2±7.5	0.244
mPAP mmHg	36.9±9.2	35.8±8.9	38.1±9.6	0.118
PCWP mmHg	9.3±3.2	9.3±3.1	9.3±3.4	0.952
cPVR Woods units	5.9±3.4	5.4±3.0	6.3±3.7	0.101
Cardiac output L·min⁻¹	5.4±1.7	5.4±1.5	5.4±1.9	0.894
SAPH therapy	115 [72.3]	48 [59.3]	67 [86.0]	0.003
Sarcoid therapy	122 [76.7]	58 [71.6]	64 [82.1]	0.512
Prednisone daily dose mg	12.7±9.9	15.8±11.4	10.1±7.4	0.002
Survival	117 [74.1]	56 [70.0]	61 [78.2]	0.195
Follow-up years	2.4±1.9	2.4±1.8	2.4±1.6	0.999

Data are presented as n, n (%) or mean±SD, unless otherwise stated. Bold type represents statistical significance. SAPH: sarcoidosis-associated pulmonary hypertension; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; cPVR: calculated pulmonary vascular resistance. #: statistical comparisons compare incident and prevalent precapillary SAPH groups.

TABLE 2 Pulmonary function tests, 6-min walk distance (6MWD) and radiography staging in the precapillary cohort

Pulmonary function tests	
FVC % pred	62.4±19.7
FEV ₁ % pred	55.2±19.9
FEV ₁ /FVC % pred	70.9±16.7
D _{LCO} % pred	40.0±15.9
Radiography Scadding staging	
Subjects	125
I	3 [2.4]
II–III	31 [24.8]
IV	82 [65.6]
6MWD m	302.6±119.3

Data are presented as mean±SD, n or n (%). FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide.

FIGURE 2 Distribution of a) mean pulmonary artery pressure (mPAP) and b) calculated pulmonary vascular resistance (cPVR) in the precapillary cohort.

sarcoidosis diagnosis and SAPH of 12.6 ± 11.8 years (table 1). 125 (78.6%) patients had documentation of radiographic Scadding staging (table 2).

A comprehensive haemodynamic profile was available in 148 (93.1%) of the patients (no cardiac output documented in 11 patients) (table 1). The mean mPAP of the cohort was 36.9 ± 9.2 mmHg (figure 2a), mean PCWP 9.3 ± 3.2 mmHg and mean cardiac output 5.4 ± 1.7 L·min⁻¹. The mean cPVR was 5.9 ± 3.4 Wood units (WU) (figure 2b), while the mean TPR was 7.8 ± 3.9 WU.

The mean FVC of the group was $62.4 \pm 19.7\%$ predicted with a mean D_{LCO} $40.0 \pm 15.9\%$ pred. Airflow obstruction ($FEV_1/FVC < 70\%$) was identified in 58 (36.5%) out of 159 patients (table 1). Patients were limited functionally, with a mean 6MWD of 302.6 ± 119.3 m (table 2), with no correlation between the mPAP and 6MWD ($r = -0.11$, $p < 0.187$) (figure 3). 122 (76.7%) of patients were on sarcoidosis-specific treatment at the time of study entry, whereas PAH-specific treatment was reported in 115 (72.3%) of patients (table 3).

Comparison of incident versus prevalent precapillary subgroups at baseline

Demographics were similar between the incident ($n=81$, 50.9%) and prevalent groups ($n=78$, 49.1%), except for race, with a higher percentage of African Americans in the latter group (65.4% *versus* 46.9%) (table 1). In the prevalent group, the average time from SAPH diagnosis to entry into the registry was 60.4 ± 46.5 months and the average time from most recent RHC and enrolment into the registry was 15.2 ± 9.7 months. In the incident group, the average time from SAPH diagnosis to registry enrolment was 3.7 ± 6.1 months. Pulmonary function tests demonstrated similar restriction; however, the incident cohort demonstrated less obstruction by FEV_1/FVC ratio (75.2 ± 16.1 *versus* 66.6 ± 16.2 , $p=0.001$), and a higher mean D_{LCO} (12.1 ± 13.3 mmol·min⁻¹·mmHg⁻¹ *versus* 6.8 ± 4.6 mmol·min⁻¹·mmHg⁻¹, $p=0.003$). The severity of pulmonary hypertension was similar between groups, although the sPAP was slightly higher numerically in the prevalent cohort (56.2 ± 14.1 mmHg *versus* 60.2 ± 15.7 mmHg, $p=0.0939$). The prevalent group was much more likely to be treated with PAH-specific therapy and receive a lower dose of prednisone.

FIGURE 3 Mean pulmonary artery pressure (mPAP) *versus* 6-min walk distance (6MWD) in the precapillary cohort.

TABLE 3 Pulmonary artery hypertension-specific agent use[#] in the precapillary cohort

PDE-5i	86 [53.4]
Sildenafil	66 [76.7]
Tadalafil	20 [23.3]
ERA	56 [34.8]
Ambrisentan	18 [32.1]
Bosentan	38 [67.9]
PDE-5i + ERA combination	28 [17.6]
PDE-5i + ERA + prostanoid combination	10 [6.3]

Data are presented as n (%). PDE-5i: phosphodiesterase-5 inhibitor; ERA: endothelin antagonist. [#]: current or historical use.

Transplant-free survival analysis of the precapillary cohort

41 (25.8%) patients died and nine (5.7%) were transplanted. Overall, the Kaplan–Meier-adjusted 1-, 3- and 5-year transplant-free survival was 89.2%, 71.7% and 62.0%, respectively. In the incident subgroup, the Kaplan–Meier-adjusted 1-, 3- and 5-year transplant-free survival was 83.5%, 70.3% and 58.3%. In the prevalent subgroup, the Kaplan–Meier-adjusted 1-, 3- and 5-year transplant-free survival was 94.7%, 72.2% and 66.3%, respectively. There was no difference in transplant-free survival between the two subgroups ($p < 0.202$) (figure 4).

In the precapillary cohort, transplant-free survival was not associated with any demographic characteristics, including age, sex or race. Nor was the presence of parenchymal nor fibrocystic disease on chest radiography associated with outcomes. Severe pulmonary hypertension (defined as mPAP ≥ 35 mmHg) and median cPVR ≥ 4.4 WU were not predictors of worse outcome. However, severe gas transfer impairment ($D_{LCO} < 35\%$ pred) and 6MWD < 300 m were strong predictors of decreased transplant-free survival ($p = 0.015$ and $p < 0.001$, respectively) (figure 5). In the prevalent cohort, 6MWD < 300 m was found to be a predictor of decreased transplant-free survival ($p < 0.009$) (figure 6a). In the incident cohort, both severe gas transfer impairment and 6MWD < 300 m were strong predictors of decreased transplant-free survival ($p < 0.037$ and $p < 0.002$, respectively) (figure 6b). When the most recent definition of pulmonary hypertension [11] was applied to the cohort, exclusion of 20 patients with cPVR < 3 WU did not change the above associations (graphs not provided). The use of PAH-specific medication at time of enrolment in the study was not associated with improvement in transplant-free survival; however, patients receiving PAH-specific agents appeared to be have more severe SAPH, with lower D_{LCO} percentages and higher RAP, sPAP, mPAP and cPVR (table 4).

FIGURE 4 Kaplan–Meier transplant-free survival curves for incident and prevalent subgroups.

FIGURE 5 Kaplan–Meier transplant-free survival curves for relationship with a) mean pulmonary artery pressure (mPAP) ≥ 35 mmHg, b) calculated pulmonary vascular resistance (cPVR) ≥ 4.4 Wood units (WU), c) diffusing capacity of the lung for carbon monoxide (D_{LCO}) threshold of 35% predicted and d) 6-min walk distance (6MWD) threshold of 300 m in the precapillary cohort.

Univariate predictors of transplant-free survival in the precapillary cohort

Transplant-free survival was strongly associated with a higher 6MWD (HR 0.95, 95% CI 0.92–0.97; $p=0.001$), age (HR 1.05, 95% CI 1.05–1.08; $p=0.009$) and D_{LCO} (HR 0.97, 95% CI 0.94–0.99; $p=0.012$) (table 5). The only haemodynamic parameter that trended towards statistical significance with transplant-free survival by univariate analysis was sPAP (HR 1.02, 95% CI 1.00–1.04; $p=0.051$) and a lower FEV₁/FVC ratio (HR 1.02, 95% CI 1.00–1.05; $p=0.061$). Data for incident and prevalent groups are presented in table 5.

Multivariate predictors of transplant-free survival in the precapillary cohort

A final multivariate Cox proportional hazards model was created with the independent predictors of outcomes from each domain described herein. Statistically significant parameters with univariate hazard ratios whose p -values were <0.10 were considered for inclusion in the model. For expected collinear terms, such as haemodynamic parameters, variables with the lowest p -value were included in the final model. In the final multivariate model, the FEV₁/FVC (HR 1.05, 95% CI 1.06–1.10; $p=0.019$) and 6MWD (HR 0.94, 95% CI 0.89–0.99; $p=0.003$) remained independent predictors of outcomes (table 6).

Subgroup analyses

Univariate and multivariate analyses of prevalent/incident subgroups of the overall cohort are shown in tables 5 and 6. In univariate analysis, the D_{LCO} , 6MWD and sPAP in the incident group and 6MWD in the prevalent group (table 5) were statistically significant predictors of transplant-free survival. None of the variables reached statistical significance as predictors of outcomes in either subgroup (table 5) in the multivariate analysis, although in the prevalent cohort, 6MWD was nearly statistically significant ($p<0.055$).

FIGURE 6 Kaplan-Meier transplant-free survival curves for relationship with i) mean pulmonary artery pressure (mPAP) ≥ 35 mmHg, ii) calculated pulmonary vascular resistance (cPVR) ≥ 4.4 Wood units (WU), iii) diffusing capacity of the lung for carbon monoxide (D_{LCO}) $< 35\%$ predicted and iv) 6-min walk distance (6MWD) threshold of 300 m in a) the prevalent subgroup of the precapillary cohort and b) the incident subgroup of the precapillary cohort.

TABLE 4 Comparison of demographics for the precapillary cohort on and off pulmonary artery hypertension (PAH)-specific therapy

	No PAH therapy	PAH therapy	p-value
Subjects	44 (27.7)	115 (72.3)	
Age years	58.7±9.7	57.1±9.7	0.325
Oxygen saturation index	94.5±3.5	93.8±4.8	0.432
FVC L	2.0±0.8	2.0±0.8	0.981
FVC % predicted	59.9±19.8	62.9±20.0	0.454
FEV ₁ L	1.3±0.6	1.4±0.5	0.660
FEV ₁ % predicted	53.0±21.1	55.3±19.7	0.546
FEV ₁ /FVC	67.7±17.5	71.2±16.6	0.303
D_{LCO} mmol·min ⁻¹ ·mmHg ⁻¹	14.6±19.2	7.9±5.5	0.003
D_{LCO} % predicted	43.7±18.1	38.8±15.1	0.207
6MWD m	305.2±137.8	296.2±111.5	0.790
RAP mmHg	4.9±2.4	6.6±4.7	0.008
sPAP mmHg	51.8±11.9	60.0±15.1	0.006
dPAP mmHg	21.8±10.0	23.9±7.3	0.204
mPAP mmHg	33.0±7.7	38.0±9.2	0.006
PCWP mmHg	9.5±3.1	9.2±3.3	0.728
LVEDP mmHg	14.8±1.3	16.8±29.6	0.889
Cardiac output	5.7±1.3	5.3±1.8	0.185
cPVR Woods units	4.5±2.2	6.4±3.6	0.005
Time between diagnosis of sarcoid and pulmonary hypertension years	14.2±11.1	10.3±10.6	0.092
Prednisone daily dose	15.8±13.5	12.2±8.7	0.110
Survival years	5.0±4.4	5.1±4.0	0.891

Data are presented as n [%] or mean±SD, unless otherwise stated. Bold type represents statistical significance. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{LCO} : diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; LVEDP: left ventricular end-diastolic pressure; cPVR: calculated pulmonary vascular resistance.

Discussion

The prevalence and impact of SAPH have only been recently appreciated. Due to the relatively low incidence of SAPH, prior reports have mostly emanated from single-centre retrospective studies [3, 5, 6, 9, 11, 21–30]. To address this issue, we established a multicentre international observational registry to capture the demographics, treatment and outcomes of SAPH across a wide geographic and ethnically diverse population. Demographic characteristics of the first 178 SAPH patients have been reported previously [14]. The present article builds further on that publication and is the largest report to date describing outcomes of patients with SAPH.

Multiple studies have demonstrated that development of pulmonary hypertension is associated with higher mortality in patients with sarcoidosis [1, 3, 5, 11, 25]. In this report, the outcomes of the overall cohort were similar to those previously described [22, 31–33], with a 3-year transplant-free survival of ~71%. There was no association between mortality and any demographic parameters. Earlier studies have suggested that the presence of pulmonary hypertension was associated with a higher prevalence of stage 4 parenchymal disease [30]. In this registry, Scadding staging was assessed on chest radiographs without central adjudication. With subsequent inherent limitations, of the 79% of SAPH patients with imaging available for Scadding staging, 65.6% had stage 4 disease. Only 2% of patients had stage 1 disease, suggesting that the lack of lung opacities on imaging is a fairly sensitive test for the absence of SAPH.

Although a number of factors was associated with survival in univariate analysis, only the FEV₁/FVC ratio and 6MWD withstood the scrutiny of a multivariate analysis to emerge as independently associated with outcomes in the analysed cohort. The demonstrated association of a lower FEV₁/FVC with improved outcomes is the first such description. A previous study [30] demonstrated no correlation between obstructive spirometric physiology and SAPH. We speculate that SAPH patients with evidence of obstruction may represent a subset with predominantly airway involvement with possibly less likelihood for contiguous vascular disease, thus portending a better outcome. An alternative explanation may be the reduced lung compliance among patients with higher FEV₁/FVC ratios.

TABLE 5 Univariate hazard ratios (95% CI) for survival in the precapillary cohort with incident and prevalent subgroups

Parameter	Precapillary	p-value	Incident	p-value	Prevalent	p-value
Subjects n	159		81		78	
Age years	1.04 (1.01–1.08)	0.023	1.03 (0.99–1.07)	0.131	1.06 (0.98–1.14)	0.137
Male	1.48 (0.78–2.80)	0.227	1.77 (0.76–4.15)	0.188	1.67 (0.62–4.31)	0.319
Race						
Caucasian	0.93 (0.31–2.85)	0.014	1.40 (0.42–4.68)	0.580	1.33 (0.49–3.61)	0.582
African American	0.68 (0.23–2.02)	0.490	0.75 (0.29–1.93)	0.522	Ref.	Ref.
Other	Ref.	Ref.	Ref.	Ref.		
FVC L, % predicted	0.99 (0.97–1.01)	0.222	0.99 (0.96–1.01)	0.264	0.99 (0.97–1.03)	0.729
FEV₁ L, % predicted	1.00 (0.98–1.01)	0.957	0.99 (0.97–1.01)	0.238	1.01 (0.98–1.03)	0.640
FEV₁/FVC ratio	1.03 (1.00–1.05)	0.041	1.00 (0.98–1.03)	0.832	1.03 (0.99–1.08)	0.113
D_{LCO} mL·min⁻¹·mmHg⁻¹, % predicted	0.98 (0.95–1.00)	0.060	0.96 (0.92–1.00)	0.035	0.98 (0.94–1.02)	0.236
6MWD m, per 10 m	0.95 (0.92–0.97)	0.003	0.95 (0.92–0.98)	0.004	0.92 (0.88–0.97)	0.002
RAP mmHg	0.96 (0.88–1.04)	0.313	0.94 (0.84–1.05)	0.292	0.99 (0.86–1.13)	0.861
sPAP mmHg	1.01 (0.99–1.03)	0.178	1.03 (1.01–1.06)	0.010	1.01 (0.98–1.04)	0.663
dPAP mmHg	1.01 (0.97–1.04)	0.625	1.01 (0.97–1.05)	0.602	1.02 (0.97–1.08)	0.480
mPAP mmHg	1.01 (0.98–1.04)	0.408	1.04 (1.00–1.08)	0.073	1.01 (0.97–1.06)	0.655
PCWP mmHg	1.03 (0.94–1.14)	0.546	1.04 (0.91–1.19)	0.603	1.03 (0.89–1.20)	0.669
cPVR	1.02 (0.93–1.11)	0.706	1.09 (0.97–1.22)	0.130	1.00 (0.88–1.15)	0.954
Cardiac output	0.91 (0.75–1.10)	0.319	0.86 (0.64–1.15)	0.306	0.93 (0.70–1.25)	0.643
PAH therapy	1.37 (0.59–3.19)	0.465	2.01 (0.74–5.45)	0.170	2.55 (0.52–12.32)	0.243
Sarcoid therapy	0.71 (0.31–1.63)	0.422	0.59 (0.22–1.57)	0.289	0.99 (0.22–4.46)	0.994
Prednisone daily dose mg	1.02 (0.99–1.06)	0.244	1.03 (0.98–1.07)	0.283	0.98 (0.91–1.05)	0.558

Bold type represents statistical significance. Statistically significant univariate hazard ratios were considered for the inclusion in multivariate models with $p < 0.10$. FVC: forced vital capacity; FEV₁: forced expiratory volume at 1 s; D_{LCO} : diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; cPVR: calculated pulmonary vascular resistance; PAH: pulmonary arterial hypertension.

There are no published guidelines for treating SAPH. The limited supportive evidence for treating SAPH emanates mostly from single-centre and/or retrospective studies [27, 33–39]. As previously noted in this cohort, US-based centres are less likely to use PAH therapies than non-US centres [14]. The majority of patients (~72%) were on therapy, similar to a recent French registry where nearly all subjects were treated with off-label medications [6]. The use of PAH-specific therapies at the time of enrolment into the study did not appear to be associated with improved transplant-free survival in this study. However, the length of treatment was not recorded, which may have impacted the results. In addition, treated patients appeared to have more severe SAPH at baseline, possibly implying that the outcomes would be worse without treatment. It is plausible that providers may feel more justified to treat more severe SAPH patients with off-label PAH therapies, thus reflecting an apparent “standard of care” that has evolved based on expert opinion with only one placebo-controlled trial [39].

In the previously published French registry, which enrolled patients with severely affected haemodynamics, 3- and 5-year survival were 74% and 55%, respectively [8]. These findings are quite similar to ours, despite our population representing a more diverse cohort, which includes both incident and prevalent subgroups. As expected, patients in the prevalent cohort had longer transplant-free survival. The explanation for this is probably two-fold: survival bias in the prevalent cohort due to enrichment with less severe cases and lead-time bias as the prevalent subgroup was further along the disease course. The goal of the registry was to capture as many patients with this rare complication of sarcoidosis as possible; therefore, the authors felt the study design was justified.

In PAH, it is typically the variables that reflect right ventricular failure, such as the cardiac index and right atrial pressures, that correlate most closely with outcomes [39]. The ReSAPH cohort had relatively preserved haemodynamics that reflect well-preserved right ventricular function, with only 19% of our patients having right atrial pressures >10 mmHg, while only 28% had cardiac indices <2.5 L·min⁻¹·m⁻². In the present analysis, severity of pulmonary hypertension, as measured by mPAP and PVR, was not demonstrated to be associated with worse outcomes. As the registry recruits more patients, we plan to re-analyse the data. A possible explanation for this apparent lack of association might be severity bias;

TABLE 6 Multivariate hazard ratios (95% CI) for survival for the precapillary cohort with incident and prevalent subgroups

Parameter	Precapillary cohort		Incident	Prevalent	
		p-value			p-value
Subjects n	159		81	78	
Age years	1.05 [0.98–1.08]	0.3031	#	1.10 [0.98–1.23]	0.092
Male	#	#	#	#	#
Race					
Caucasian	#	#	#	#	#
African American	#	#	#	#	#
Other	Ref.	Ref.	Ref.	Ref.	Ref.
FVC L, % predicted	#	#	#	#	#
FEV₁ L, % predicted	#	#	#	#	#
FEV₁/FVC ratio	1.05 [1.06–1.10]	0.019	#	1.04 [0.98–1.10]	0.228
D_{LCO} mL·min⁻¹·mmHg⁻¹, % predicted	0.98 [0.95–1.00]	0.080	0.98 [0.94–1.02]	#	#
6MWD m, per 10 m	0.94 [0.89–0.98]	0.003	0.97 [0.93–1.01]	0.94 [0.88–1.00]	0.055
RAP mmHg	#	#	#	#	#
sPAP mmHg			1.03 [1.00–1.07]	#	#
dPAP mmHg	1.04 [0.99–1.10]	0.141	#	#	#
mPAP mmHg	#	#	#	#	#
PCWP mmHg	#	#	#	#	#
cPVR	#	#	#	#	#
Cardiac output	#	#	#	#	#
PAH therapy	#	#	#	#	#

Bold type represents statistical significance. Statistically significant univariate hazard ratios were considered for the inclusion in multivariate models with $p < 0.10$. For multivariate models, $p < 0.05$ was considered statistically significant. For expected collinear terms (i.e. systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP)), terms with the lowest p-value were deemed most statistically significant and included in multivariate models. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; cPVR: calculated pulmonary vascular resistance; PAH: pulmonary arterial hypertension. #: parameters not included in multivariate models based on $p > 0.05$ in the univariate model.

specifically, only including patients with mPAP ≥ 25 mmHg in the registry and not allowing a wider spectrum of mPAP values might have muted any possible associations. Moreover, the fact that two-thirds of the patients were on PAH therapies might have further impacted any associations with outcomes. Interestingly, the French database, where even more patients were treated with PAH therapies, also failed to demonstrate an association between any haemodynamic parameter and survival [8].

Most patients in our cohort were treated with prednisone therapy. The treatment with anti-inflammatory medications has not demonstrated consistent benefit in SAPH, although response rates of 20–30% have been reported in small series [33]. Moreover, none of these studies included patients with stage IV fibrocystic disease, which represents the majority of the ReSAPH patient population. The use of steroid therapy was not associated with better outcomes in the ReSAPH nor French [8] registries.

In sarcoidosis, the presence of pulmonary hypertension is associated with decreased 6MWD [5, 9, 30]. In this analysis, the 6MWD was by far the strongest predictor of mortality, in the main cohort and both prevalent and incident subgroups. This association provides support for the use of the 6MWD as a functional and potentially modifiable surrogate end-point for future clinical trials in SAPH. Although some interventional studies of PAH therapies in patients with SAPH have failed to show a response in 6MWD to therapy [35, 38], there are other studies that attest to its utility as a responsive surrogate for therapeutic efficacy [27, 37].

In summary, this study is the largest registry to date of both incident and prevalent patients with precapillary SAPH. Although this analysis has inherent limitations of registry data including some missing data, it clearly demonstrates that functional impairment (as demonstrated by the 6MWD) and reduced diffusing capacity are associated with decreased survival in SAPH patients. The interesting association of an obstructive phenotype and improved outcomes has not been reported previously and needs to be examined further. Our description of outcomes in a diverse population of SAPH patients highlights a number of issues pertaining to this underappreciated entity that will hopefully form a foundation for future studies. Factors independently associated with outcomes included physiological (FEV₁/FVC ratio

and diffusing capacity) and functional (6MWD) parameters. These same factors might help to inform future SAPH clinical trials with regards to enrichment (D_{LCO} and FEV_1/FVC ratio) and outcomes (6MWD).

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