EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Physiological Predictors of Survival in Patients with Sarcoidosis Associated Pulmonary Hypertension: Results from an International Registry

Oksana A. Shlobin, Vasilis Kouranos, Scott D. Barnett, Esam H. Alhamad, Daniel A. Culver, Joseph Barney, Francis C. Cordova, Eva M. Carmona, Mary Beth Scholand, Marlies Wijsenbeek, Sivagini Ganesh, Elyse E. Lower, Peter J. Engel, John Wort, Laura Price, Athol U. Wells, Steven D. Nathan, Robert P. Baughman

Please cite this article as: Shlobin OA, Kouranos V, Barnett SD, *et al*. Physiological Predictors of Survival in Patients with Sarcoidosis Associated Pulmonary Hypertension: Results from an International Registry. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.01747-2019).

The early view version of this article has been updated after first being published on 5 March 2020, to address some minor corrections to the presented survival rates.

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Physiological Predictors of Survival in Patients with Sarcoidosis Associated Pulmonary Hypertension: Results from an International Registry

Short Title: Predictors of outcomes in sarcoidosis-associated pulmonary hypertension.

Authors:
Oksana A. Shlobin MD (1)
Vasilis Kouranos (2)
Scott D. Barnett (1)
Esam H. Alhamad (3)
Daniel A. Culver (4)
Joseph Barney (5)
Francis C. Cordova (6)
Eva M Carmona (7)
Mary Beth Scholand (8)
Marlies Wijsenbeek (9)
Sivagini Ganesh (10)
Elyse E. Lower (11)
Peter J. Engel (12)
John Wort (2)
Laura Price (2)
Athol U Wells (2)
Steven D. Nathan (1)
Robert P. Baughman MD (11)

Affiliations
1. INOVA Fairfax Hospital, Falls Church, VA, USA
2. Royal Hospital Brompton, London, UK
3. King Saud University, Riyadh, Saudi Arabia
4. Cleveland Clinic, Cleveland OH, USA
5. University of Alabama, Birmingham, AL, USA
6. Temple University, Philadelphia PA USA
7. Mayo Clinic, Rochester Minn, USA
8. University of Utah, Salt Lake City, Utah, USA
9. Erasmus University Medical Centre, Rotterdam, NL
10. University of Southern California, Los Angeles, CA, USA
11. University of Cincinnati Medical Center, Cincinnati, OH, USA
12. The Christ Hospital, Cincinnati, OH, USA

Address Correspondence to:
Oksana A Shlobin MD
Medical Director, Pulmonary Hypertension Program
Inova Fairfax Hospital
3300 Gallows Road
Falls Church VA 22042
Oksana.shlobin@inova.org

Word Count:
Abstract = 246
Manuscript = 2,999

References: 41

Tables and Figures:
Tables = 6
Figures = 6

Funding
Gilead Pharmaceuticals provided an unrestricted educational grant to support the registry. The research database at the University of Cincinnati is funded by the National Institutes of Health (NIH) Clinical and Translational Science Award (CTSA) program, grant 1UL1TR001425-01. The CTSA program is led by the NIH's National Center for Advancing Translational Sciences (NCATS).
SDB, VK, OAS and AUW performed all data analysis and OAS was responsible for drafting the manuscript. OAS, VK, RPB, AUW, and SDN all provided significant input into the writing of the manuscript. All authors contributed to patient entry and supervising data entry at each of their sites. All authors reviewed the final manuscript.

Short Sentence
Decreased six minute walk distance and reduced diffusion capacity are associated with decreased survival in patients with sarcoidosis associated pulmonary hypertension

Abbreviations

6MWT six minute walk test

6MWD six minute walk distance

CO cardiac output

cPVR calculated pulmonary vascular resistance

DL_{CO} diffusing capacity for carbon monoxide

FEV_1 forced expiratory volume at 1 second

FVC forced vital capacity

dPAP diastolic pulmonary artery pressure

mPAP mean pulmonary artery pressure

PH pulmonary hypertension

RA right atrial pressure

RHC right heart catheterization

SAPH sarcoidosis associated pulmonary hypertension

sPAP systolic pulmonary artery pressure

Abstract

Introduction Sarcoidosis associated pulmonary hypertension (SAPH) is associated with reduced survival in single center studies. An 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 enrollment. Information analyzed includes right heart catheterization data, pulmonary function testing, chest x-ray Scadding stage, six minute walk distance (6MWD) among others. Cox regression models were used to identify independent predictors of transplant-free survival.

Results Data from a total of 215 patients followed for a mean of 2.5 ± 1.9 years were available for analysis. In the 159 pre-capillary patients, the KM adjusted 1, 3 and 5 year transplant free survival was 89.2%, 71.7% and 62.0%, respectively. In the incident and prevalent groups, KM adjusted 1, 3 and 5 year transplant free survival was 83.5%, 70.3% and 58.3% and 94.7%, 72.2%, and 66.3%, respectively. Patients with reduced DL_{CO} (<35% predicted) and 6MWD <300m in the pre-capillary cohort had significantly worse transplant-free survival. Reduced 6MWD and preserved FEV_1/FVC ratio were identified as independent risk factors for reduced transplant-free survival in the pre-capillary cohort.

Conclusion Reduced diffusion capacity (<35% of predicted) and 6MWD <300m at the time of registry enrollment were associated with reduced transplant-free survival in the overall precapillary cohort. Preserved FEV_1/FVC ratio was also identified as an independent risk factor for worsened outcomes.

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 an increased mortality (3).

From 2010 to 2013, the reported incidence of sarcoidosis in the Unites States ranged between 7.6-8.4 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 rate of 75% for those listed for lung transplantation(4).

SAPH is categorized as Group 5 pulmonary hypertension (10, 11). Although SAPH occurs more frequently in patients with fibrotic disease, it also has been described in those without parenchymal involvement (12). In addition to fibrotic distortion of the pulmonary vasculature from parenchymal fibrosis, other contributors may be related to the granulomatous changes of the pulmonary vasculature found on both the arterial and venous sides. Extrapulmonary factors such as extrinsic mechanical compression of the large pulmonary arteries by hilar lymphadenopathy or fibrosing mediastinitis may also play a role, as well as associated comorbidities including obstructive sleep apnea, 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 ATS/ERS/WASOG criteria (15), at least one follow up visit data and a hemodynamic diagnosis of PH were enrolled in an eleven center observational registry (14), initiated in October 2011. All patients were required to have at least one right heart catheterization (RHC) demonstrating a mean pulmonary artery pressure (mPAP) ≥25 mmHg, in accordance with the 2015 ESC/ERS guidelines definition (10). Incident cases were defined as the diagnosis of PH within one 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 study is registered at ClinTrials.gov (NCT01467791). 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 PH 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 (RAP), systolic (sPAP), diastolic (dPAP), and mean pulmonary artery (mPAP) pressures, as well as the pulmonary artery occlusion pressure (PAOP) and thermodilution cardiac output (CO). Pre-capillary SAPH was defined as an mPAP$\geq$25 mmHg with a PAOP of ≤15 mmHg (10). Pulmonary vascular resistance (cPVR) was calculated as mPAP-PAOP/CO.

Demographics collected included age, gender, race, and duration of sarcoidosis. When available, the most recent chest x-ray at the time of entry into the study was reviewed and staged (18) by the enrolling investigator. Scadding staging was not centrally adjudicated. Physiologic studies recorded included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1 to FVC ratio (FEV_1/FVC), the single breath diffusing capacity for carbon monoxide (DL_{CO}) and six minute walk test distance (6MWD) (15, 19-20). Investigators were asked to record historic and current use of PH therapy but no direction was given regarding choice of treatment. Duration of therapy was not captured. Demographics of patients on and off PAH therapy were compared. Predefined cut-points of 6MWT, DL_{CO}, mPAP and cPVR were examined for their association with transplant free survival (21, 22, 23).

Participating Clinical Centers

Site	City, Country
University of Cincinnati Medical Center	Cincinnati, USA
Cleveland Clinic	Cleveland, USA
Inova Fairfax Hospital	Falls Church, USA
University of Alabama	Birmingham, USA
Temple University	Philadelphia, USA
University of Southern California	Los Angeles, USA
University of Utah	Salt Lake City, USA
Mayo Clinic	Rochester, USA
Erasmus University Medical Centre	Rotterdam, Netherlands

The Christ Hospital	Cincinnati, USA
Royal Hospital Brompton	London, United Kingdom
King Saud University	Riyadh, Saudi Arabia

Statistical Analysis

Statistical analysis was carried out using STATA 11.0 (Stata Corp., College Station, TX), and SAS (ver. 9.4, Cary, NC, USA). Data are presented as mean±SD or frequency and percent, where appropriate. Between-group differences were compared with Student's *t*-test, chi-square 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 right heart catheterization (RHC) for incident 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 with 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 and 95% confidence intervals). Univariate parameters were considered for inclusion in multivariate models with $p<0.10$. For final multivariate models, a $p<0.05$ 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 MV 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 2-tailed with p-values <0.05 considered statistically significant.

Results

Description of baseline data for the pre-capillary cohort

There were 215 patients enrolled over a 6 year period (last date of entry 9/12/17) (Figure 1). The majority of patients (159/215 (73.9%)) had precapillary PH, with 60% of patients enrolled from the USA, 24% from Western Europe and 16% from Saudi Arabia. A list of participating centers is included in the Material and Methods. The mean age of the overall precapillary cohort (referred to as the "pre-capillary cohort" from here on) was 56.9±10.6 years with 72.3% female, 56% African American, 31.4% Caucasian and a mean duration between the time of initial sarcoidosis diagnosis and SAPH of 12.6±11.8 years (Table 1). A total of 125 (78.6%) patients had documentation of radiographic Scadding staging (Table 2).

A comprehensive hemodynamic profile was available in 148 (93.1%) of the patients (no CO documented in 11 patients) (Table 1). The mean mPAP of the cohort was 36.9±9.2 mmHg (Figure 2a), mean PAOP 9.3±3.2 mmHg and mean CO of 5.4±1.7 L/min. The mean cPVR was 5.9±3.4 (Figure 2b) while the mean TPR was 7.8±3.9 Wood units (WU).

The mean FVC of the group was 62.4±19.7% predicted with a mean DL_{CO}% predicted of 40.0 ± 15.9. Airflow obstruction (FEV_1/FVC<70%) was identified in 58/159 (36.5%) of patients (Table 1). Patients were limited functionally with a mean 6MWD of 302.6±119.3 meters (Table 2), with no correlation between the mPAP and 6MWD (r=-0.11 [p<0.187]) (Figure 3). A total of 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 vs prevalent pre-capillary 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 vs 46.9%) (Table 1). In 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 enrollment into the registry was 15.2 ± 9.7 months. In the incident group, the average time from SAPH diagnosis to the registry enrollment was 3.7 ± 6.1 months. Pulmonary function tests (PFTs) demonstrated similar restriction, however the incident cohort demonstrated less obstruction by FEV_1/FVC ratio (75.2±16.1 vs. 66.6±16.2, p=0.001), and a higher mean DL_{CO} (12.1±13.3 vs. 6.8±4.6, p=0.003). The severity of PH was similar between groups, although the sPAP was slightly higher numerically in the prevalent cohort (56.2±14.1 vs 60.2±15.7, p=0.0939). The prevalent group was much more likely to be treated with PAH specific therapy and receive a lower dose of prednisone.

Transplant-free survival analysis of the pre-capillary cohort

There were 41 patients (25.8%) who died and 9 (5.7%) who 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 Kaplan-Meier adjusted 83.5%, 70.3% and 58.3%. In the prevalent subgroup, the 1, 3 and 5 year transplant free survival was Kaplan-Meier adjusted 94.7%, 72.2%, 66.3%. There was no difference in transplant-free survival between the two subgroups (p=0.202) (Figure 4).

In the pre-capillary cohort, transplant-free survival was not associated with any demographic characteristics including age, gender or race. Similarly, neither the presence of parenchymal nor fibrocystic disease on chest X-Ray was associated with outcomes. Severe PH (defined as mPAP≥35mmHg) and median cPVR≥4.4 were not predictors of worse outcome. However, severe gas transfer impairment (DL_{CO}< 35% predicted) and 6MWD<300m were strong predictors of decreased transplant-free survival (p=0.015 and p<0.001, respectively (Figure 5)). In the prevalent cohort, 6MWD<300m 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<300m were strong predictors of decreased transplant-free survival (p<0.037 and p<0.002, respectively) (Figure 6B). When the most recent definition of PH (11) was applied to the cohort, exclusion of 20 patients with cPVR<3 did not change the above

associations (graphs not provided). The use of PAH specific medications at time of enrollment in the study was also not associated with improvement in transplant-free survival; however patients receiving PAH specific agents appeared to be have more severe SAPH, with lower DL_{CO}%s, higher RAPs, sPAPs, mPAPs and cPVRs (Table 4).

Univariate predictors of transplant-free survival in the pre-capillary 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 DL_{CO} (HR 0.97; 95% CI 0.94-0.99, p=0.012) (Table 5). The only hemodynamic 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 FEV_1/FVC ratio (HR 1.02; 95% CI 1.00-1.05, p=0.061). Data for incident and prevalent groups is presented in Table 5a.

Multivariate predictors of transplant-free survival in the pre-capillary cohort

A final multivariate Cox proportional hazards model was created with the independent predictors of outcomes from each domain described above. Statistically significant parameters with univariate HRs whose p values were <0.10 were considered for inclusion in the model. For expected collinear terms, such as hemodynamic parameters, variables with the lowest p-value were included in the final model. In the final multivariate model, the FEV_1/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 DL_{CO}, 6MWD and sPAP in the incident and 6MWD in the prevalent groups (Table 5a) were statistically significant predictors of transplant-free survival. None of the variables reached statistical significance as predictors of outcomes in either subgroup (Table 5b) in the multivariate analysis, although in the prevalent cohort, 6MWD was nearly statistically significant (p<0.055).

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 center retrospective studies (3, 5, 6, 9, 11, 21-30). To address this issue, we established a multicenter 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 were previously reported (14). The present paper 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 PH 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, 33-34), 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 PH 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 FEV_1/FVC ratio and 6MWD withstood the scrutiny of a multivariate analysis to emerge as independently associated with outcomes in the analyzed cohort. The demonstrated association of a lower FEV_1/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 FEV_1/FVC ratios.

There are no published guidelines for treating SAPH. The limited supportive evidence for treating SAPH emanates mostly from single center and/or retrospective studies (34-41). As previously noted in this cohort, US-based centers are less likely to use PAH therapies than non-US centers (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 enrollment 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 possible 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 (41).

In the previously published French registry which enrolled patients with severely affected hemodynamics, the 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 likely twofold: survival bias in the prevalent cohort due to enrichment with less severe cases and lead-time bias as the prevalent subgroup was further along in their 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 (41). The ReSAPH cohort had relatively preserved hemodynamics that reflect well preserved RV function, with only 19% of our patients having RA pressures>10 mmHg, while only 28% had cardiac indices<2.5L/min/m^2. In the present analysis, severity of PH, 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-analyze the data. A possible explanation for this apparent lack of association might be severity bias; specifically, only including patients with mPAPs ≥25 mmHg in the registry and not allowing a wider spectrum of mPAPs 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 hemodynamic 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 (34). Moreover, none of these studies included patients with stage IV fibrocystic disease, which represents the majority of the ReSAPH patient population. In neither the ReSAPH nor French (8) registries, was the use of steroid therapy associated with better outcomes.

In sarcoidosis, the presence of PH 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 endpoint 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 (36, 39), there are other studies that attest to its utility as a responsive surrogate for therapeutic efficacy (38, 40).

In summary, this study is the largest registry to date of both incident and prevalent patients with pre-capillary 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 previously reported 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 physiologic (FEV_1/FVC ratio and diffusion capacity) and functional (6MWD) parameters. These same factors might help to inform future SAPH clinical trials with regards to enrichment (DL_{CO} and FEV_1/FVC) and outcomes (6MWD).

References

1. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885–1889.
2. Rybicki BA, Major M, Popovich J Jr, et al. Racial differences in sarcoidosis incidence: a five year study in a health maintenance organization. Am J Epidemiol 1997; 145:234–241.
3. Baughman RP, Engel PJ, Taylor L, et al. Survival in sarcoidosis associated pulmonary hypertension: the importance of hemodynamic evaluation. Chest 2010; 138:1078-1085.
4. Baughman RP, Field S, Costabel U, et al. Sarcoidosis in America. Analysis based on health care use. Ann Am Thorac Soc 2016; 13(08):1244–1252.
5. Shorr AF, Helman DL, Davies DB, et al. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J 2005; 25(5):783-788.
6. Huitema MP, Bakker ALM, Mager JJ, et al. Prevalence of pulmonary hypertension in pulmonary sarcoidosis; the first large European prospective study. Eur Respir J 2019; in press (https://doi.org/10.1183/13993003.00897-2019)
7. Shlobin OA, Nathan SD. Management of end-stage sarcoidosis: pulmonary hypertension and lung transplantation. Eur Respir J 2012; 39(6):1520-1533.
8. Boucly A, Cottin V, Nunes H, et al. Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension. European Respiratory Journal 2017; 50(4).
9. Handa T, Nagai S, Miki S, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. Chest 2006; 129(5):1246-1252.
10. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009; 54:S43eS54.
11. Frost A, Badesch D, Gibbs JSR et al. Diagnosis of pulmonary hypertension. Proceedings of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J Express 2018; in press.
12. Nunes H, Humbert M, Capron F, et al. Pulmonary hypertension associated with sarcoidosis: mechanisms, haemodynamics and prognosis. Thorax 2006; 61:68e74.
13. Shlobin OA, Baughman RP. Sarcoidosis-associated pulmonary hypertension. Semin Respir Crit Care Med 2017; 38:450–462.
14. Baughman RP, Shlobin OA, Wells AU, et al. Clinical features of sarcoidosis associated pulmonary hypertension: Results of a multi-national registry. Resp Med 2018; 139:72-78.
15. Judson MA, Costabel U, Drent M et al. The WASOG sarcoidosis organ assessment instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31:19-27.
16. Obeid JS, McGraw CA, Minor BL et al. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). J Biomed Inform 2013; 46(2):259-265.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The strengthening reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.J Clin Epidemiol 2008; 61(4):344-9.
18. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. Br Med J 1961; 2:1165-1172.
19. Hunninghake GW, Costabel U, Ando M et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16(Sep):149-173.
20. Borg G. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14:377-381.
21. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 2003; 124(3):922-928.
22. Arcasoy SM, Christie JD, Pochettino A, et al. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 2001; 120:873-880.
23. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 2008; 32:296-300.

24. Nardi A, Brillet P-Y, Letounmelin P, et al. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respi J 2011; 38: 1368-1373
25. Alhamad EH, Idrees MM, Alanezi MO, Alboukai AA, Shaik SA. Sarcoidosis-associated pulmonary hypertension: Clinical features and outcomes in Arab patients. Ann Thorac Med 2010; 5(2):86-91.
26. Gluskowski J, Hawrylkiewicz I, Zych D, Wojtczak A, Zielinski J. Pulmonary haemodynamics at rest and during exercise in patients with sarcoidosis. Respiration 1984; 46(1):26-32.
27. Keir GJ, Walsh SL, Gatzoulis MA, Marino PS, Dimopoulos K, Alonso R et al. Treatment of sarcoidosis-associated pulmonary hypertension: A single centre retrospective experience using targeted therapies. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31(2):82-90.
28. Kirkil G, Lower EE, Baughman RP. Predictors of mortality in sarcoidosis. Chest 2018; 153(1):105-113.
29. Patel MB, Mor-Avi V, Murtagh G, Bonham CA, Laffin LJ, Hogarth DK et al. Right heart involvement in patients with sarcoidosis. Echocardiography 2016; 33(5):734-41.
30. Sulica R, Teirstein A, Kakarla S, et al. Distinctive clinical, radiographic and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. Chest 2005; 128:1483-1489.
31. Baughman RP, Gerson M, Bosken CH. Right and left ventricular function at rest and with exercise in patients with sarcoidosis. Chest 1984; 85:301-306.
32. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct under-recognized entity. Eur Respir J. 2005; 26(4):586-93.
33. Hoeper MM, Behr J, Held M, et al. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonia. PLoS ONE 2015; 10(12):1-13.
34. Rodman DM, Lindenfeld J. Successful treatment of sarcoidosis-associated pulmonary hypertension with corticosteroids. Chest 1990; 97:500-502.
35. Fisher KA, Serlin DM, Wilson KC, et al. Sarocidosis-associated pulmonary hypertension: outcomes with long-term epoprostenol treatment. Chest 2006; 130:1481-1488.
36. Baughman RP, Judson MA, Lower EE, et al. Inhaled iloprost for sarcoidosis associated pulmonary hypertension. Clin Chest Med 2008; 29:549-571.
37. Millman N, Burton CM, Iversen M, et al. Pulmonary hypertension in end-stage pulmonary sarcoidosis: therapeutic effect of sildenafil? J Heart Lung Transplant 2008; 75:329-334.
38. Barnett CF, Bonura EJ, Nathan SD, et al. Treatment of sarcoidosis-associated pulmonary hypertension: Two center experience. Chest 2009; 135:1455-1461.
39. Baughman RP, Culver DA, Cordova FC et al. Bosentan for sarcoidosis associated pulmonary arterial hypertension (BoSAPAH): A double blind, placebo controlled trial. Am J Resp Crit Care Med 2012; 185:A3639.
40. Keir GJ, Walsh SL, Gatzoulis MA, Marino PS, Dimopoulos K, Alonso R et al. Treatment of sarcoidosis-associated pulmonary hypertension: A single centre retrospective experience using targeted therapies. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31(2):82-90.
41. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012; 142(2):448-456.

Table 1. Pre-capillary Cohort Demographics

	Pre-Capillary SAPH (n=159)	Incident SAPH (n=81, 50.9%)	Prevalent SAPH (n=78, 49.1%)	P*
Age (years)	56.9±10.6	57.0±11.2	56.7±10.0	0.862
Gender				
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**
Sarcoid to SAPH duration (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, % predicted)	2.04±0.76	2.0±0.8	2.1±0.8	0.495
FVC (% predicted)	62.4±19.7	60.4±18.5	64.3±20.9	0.225
FEV1 (L, % predicted)	1.4±0.6	1.4±0.5	1.3±0.5	0.340
FEV1 (% predicted)	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**
DL_{CO} (mL/min/mmHg)	9.3±10.1	12.1±13.3	6.8±4.6	**0.003**
DL_{CO} (mL/min/mmHg, %)	40.0±15.9	41.7±15.5	38.4±16.1	0.263
6MWTD (m) per 10m	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
PAOP (mmHg)	9.3±3.2	9.3±3.1	9.3±3.4	0.952
cPVR (WU)	5.9±3.4	5.4±3.0	6.3±3.7	0.101
CO	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**

Note: values are mean ± SD or frequency (%). * Statistical comparisons compare Incident and Prevalent Pre-SAPH groups

6MWT six minute walk test, 6MWTD six minute walk test distance, cPVR calculated pulmonary vascular resistance, CO cardiac output, DL_{CO} diffusion capacity for carbon monoxide, FVC forced vital capacity, FEV_1 forced expiratory volume at 1 second, mPAP mean pulmonary pressure, RAP right atrial pressure, dPAP diastolic pulmonary artery pressure, sPAP systolic pulmonary pressure

Table 2. Pulmonary Function Tests, 6MWD and X-Ray Staging in the Pre-capillary Cohort

Characteristics	Mean Value ± SD
Pulmonary function tests	
FVC% predicted	62.4±19.7
FEV_1% predicted	55.2±19.9
FEV_1/FVC % predicted	70.9±16.7
DL_{CO} % predicted	40.0±15.9
Scadding X-Ray Staging (n=125)	
I, n (%)	3 (2.4%)
II-III, n (%)	31 (24.8%)
IV, n (%)	82 (65.6%)
6MWT	
6MWD, meters	302.6±119.3

FVC forced vital capacity, FEV_1 forced expiratory volume at 1 second, DL_{CO} diffusing capacity for carbon monoxide, 6MWT six minute walk test, 6MWD six minute walk test distance

Table 3. PAH Specific Agent Use* in the Pre-capillary Cohort

Medications	N (%)
PDE5i (sildenafil, tadalafil)	86 (53.4)
Sildenafil	66 (76.7)
Tadalafil	20 (23.3)
ERA (ambrisentan, bosentan)	56 (34.8%)
Ambrisentan	18 (32.1)
Bosentan	38 (67.9)
PDE5i + ERA combination	28 (17.6%)
PDE5i + ERA + prostanoid combination	10 (6.3%)

Note. PDE5i Phosphodiesterase 5 inhibitor, ERA endothelin antagonist
* Current or historical use

Table 4. Comparison of Demographics for Pre-capillary Cohort on and off PAH Specific Therapy.

	No PAH Therapy (44, 27.7%)	PAH Therapy (115; 72.3%)	p-value
Age	58.7±9.7	57.1±9.7	0.325
Oxygen Saturation, index	94.5 ± 3.5	93.8 ± 4.8	0.432
FVC	2.0±0.8	2.0±0.8	0.981
FVC%	59.9±19.8	62.9±20.0	0.454
FEV_1	1.3±0.6	1.4±0.5	0.660
FEV_1%	53.0±21,1	55.3±19.7	0.546
FEV_1/FVC	67.7±17.5	71.2±16.6	0.303
DL_{CO}	14.6±19.2	7.9±5.5	**0.003**
DL_{CO}%	43.7±18.1	38.8±15.1	0.207
6MWTD	305.2±137.8	296.2±111.5	0.790
RAP	4.9±2.4	6.6±4.7	**0.008**
sPAP	51.8±11.9	60.0±15.1	**0.006**
dPAP	21.8±10.0	23.9±7.3	0.204
mPAP	33.0±7.7	38.0±9.2	**0.006**
PAOP	9.5±3.1	9.2±3.3	0.728
LVEDP	14.8±1.3	16.8±29.6	0.889
TDCO	5.7±1.3	5.3±1.8	0.185
cPVR (Woods Units)	4.5±2.2	6.4±3.6	**0.005**
Duration between diagnosis of sarcoid and PH	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

Abbreviations: 6MWT six minute walk test, 6MWTD six minute walk test distance, cPVR calculated pulmonary vascular resistance, CO cardiac output, DL_{CO} diffusion capacity for carbon monoxide, FVC forced vital capacity, FEV_1 forced expiratory volume at 1 second, mPAP mean pulmonary pressure, RAP right atrial pressure, dPAP diastolic pulmonary artery pressure, sPAP systolic pulmonary pressure

Table 5. Univariate Hazard Ratios and 95% Confidence Intervals for Survival in the Pre-Capillary Cohort with Incident and Prevalent Subgroups

Parameter	Pre-Capillary (n=159)	p-value	Incident (n=81)	p-value	Prevalent (n=78)	p-value
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
FEV_1 (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
FEV_1/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
DL_{CO} (mL/min/mmHg, % 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 10m	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
PAOP (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
CO	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

Note. Values are mean ± SD or frequency (%). Statistically significant univariate hazard ratios were considered for the inclusion in multivariate models with $p<0.10$.
6MWD six minute walk distance, cPVR calculated pulmonary vascular resistance, CO cardiac output, DL_{CO} diffusing capacity for carbon monoxide, FVC forced vital capacity, FEV_1 forced expiratory volume at 1 second, mPAP mean pulmonary pressure, RAP right atrial pressure, dPAP diastolic pulmonary artery pressure, sPAP systolic pulmonary pressure

Table 6. Multivariate Hazard Ratios and 95% Confidence Intervals for Survival for Pre-Capillary Cohort with Incident and Prevalent Subgroups

Parameter	Pre-Capillary Cohort (n=159)	p-value	Incident (n=81)	p-value	Prevalent (n=78)	p-value
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*	*Ref*
FVC (L, % predicted)	--	--	--	--	--	--
FEV_1 (L, % predicted)	--	--	--	--	--	--
FEV_1/FVC ratio	1.05 (1.06-1.10)	**0.019**	--	--	1.04 (0.98-1.10)	0.228
DL_{CO} (mL/min/mmHg, % predicted)	0.98 (0.95-1.00)	0.080	0.98 (0.94-1.02)	0.297	--	--
6MWD (m), per 10m	0.94 (0.89-0.98)	**0.003**	0.97 (0.93-1.01)	0.173	0.94 (0.88-1.00)	**0.055**
RAP (mmHg)	--	--	--	--	--	--
sPAP (mmHg)			1.03 (1.00-1.07)	0.084	--	--
dPAP (mmHg)	1.04 (0.99-1.10)	0.141	--	--	--	--
mPAP (mmHg)	--	--	--	--	--	--
PAOP (mmHG)	--	--	--	--	--	--
cPVR	--	--	--	--	--	--
CO	--	--	--	--	--	--
PAH therapy	--	--	--	--	--	--

Note. Values are mean ± SD or frequency (percent). 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., dPAP, sPAP, mPAP), terms with the lowest p-value were deemed most statistically significant and included in MV models. '--' represents parameters not included in multivariate models based on $p>0.05$ in univariate model.

6MWD six minute walk distance, cPVR calculated pulmonary vascular resistance, CO cardiac output, DL_{CO} diffusing capacity for carbon monoxide, FVC forced vital capacity, FEV_1 forced expiratory volume at 1 second, mPAP mean pulmonary pressure, RAP right atrial pressure, dPAP diastolic pulmonary artery pressure, sPAP systolic pulmonary pressure

Captions

Figure 1. ReSAPH Registry Flowchart

Figure 2. mPAP Distribution (a) and Calculated PVR Distribution (b) in the Pre-Capillary Cohort

Figure 3. mPAP vs 6MWD in the Pre-Capillary Cohort

Figure 4. Kaplan Meier Transplant-Free Survival Curves for Incident and Prevalent Subgroups

Figure 5. Kaplan Meier Transplant-Free Survival Curves for Relation to (a) mPAP≥35mmHg, (b) cPVR ≥ 4.4 Wood Units, (c) Gas Transfer Threshold of 35% predicted and (d) 6MWD Threshold of 300 meters in the Pre-capillary Cohort

Figure 6. 6A Kaplan Meier Transplant-Free Survival Curves for Relation to (a) mPAP≥35mmHg, (b) cPVR ≥ 4.4 Wood Units, (c) Gas Transfer Threshold of 35% Predicted and (d) 6MWD Threshold of 300 Meters in the Prevalent Subgroup of the Pre-capillary Cohort; 6B Kaplan Meier Transplant-free Survival Curves for Relation to (a) mPAP≥35mmHg, (b) cPVR ≥ 4.4 Wood Units, (c) Gas Transfer Threshold of 35% Predicted and (d) 6MWD Threshold of 300 Meters in the Incident Subgroup of the Pre-capillary Cohort

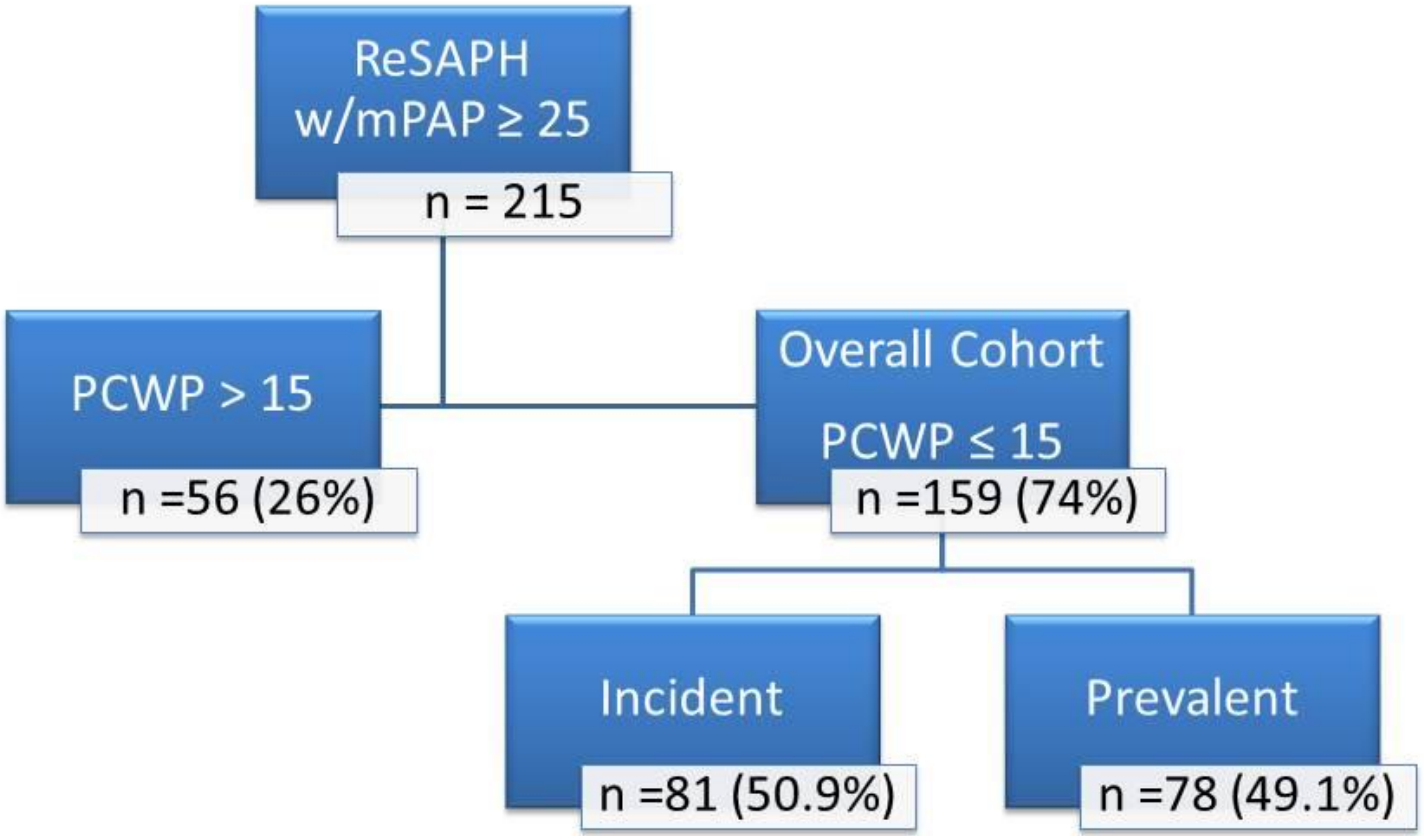
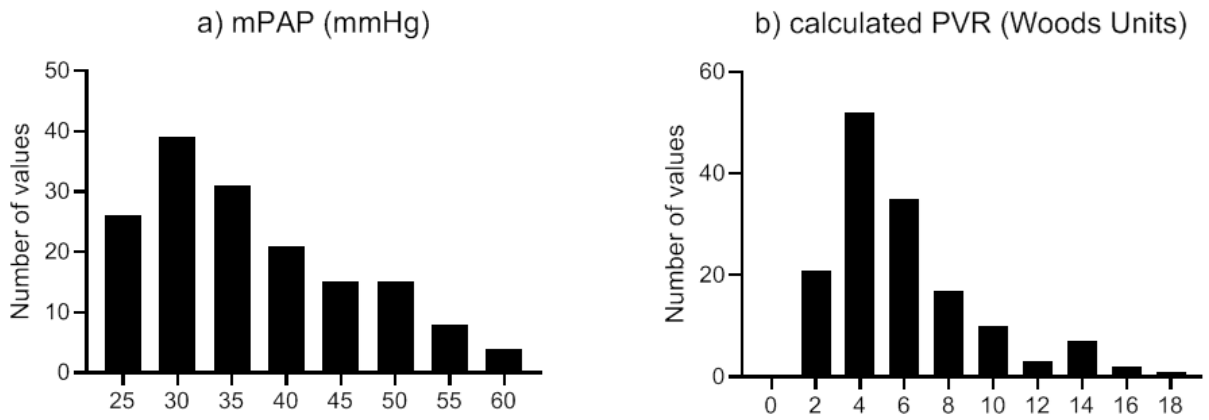
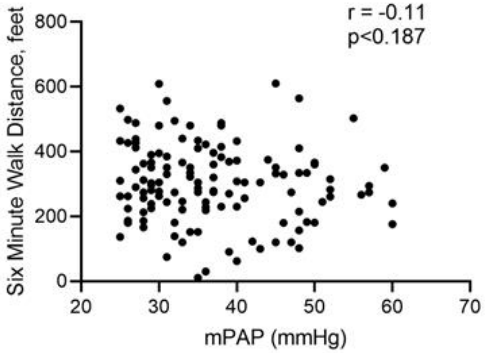
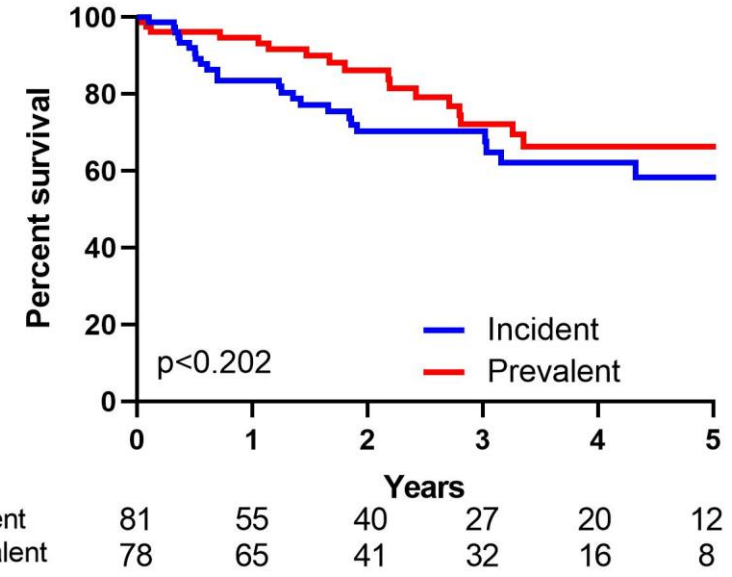


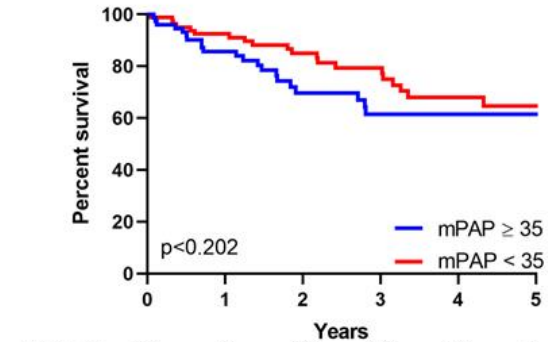
Figure 1. Flow Chart for ReSAPH Cohort


a) mPAP (mmHg)
Number of values
50
40
30
20
10
0
25
30
35
40
45
50
55
60
b) calculated PVR (Woods Units)
Number of values
60
40
20
0
0
2
4
6
8
10
12
14
16
18

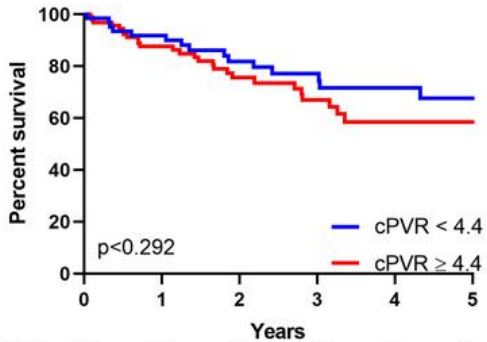

r = -0.11
p<0.187
Six Minute Walk Distance, feet
800
600
400
200
0
20
30
40
50
60
70
mPAP (mmHg)



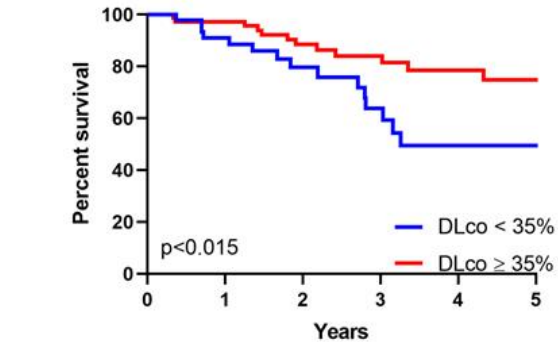
Incident	81	55	40	27	20	12
Prevalent	78	65	41	32	16	8



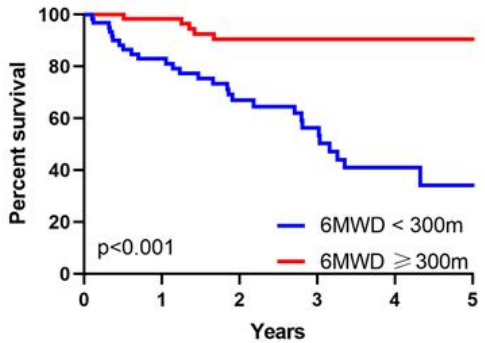
mPAP ≥ 35	75	54	30	20	13	5
mPAP < 35	84	67	51	38	24	16



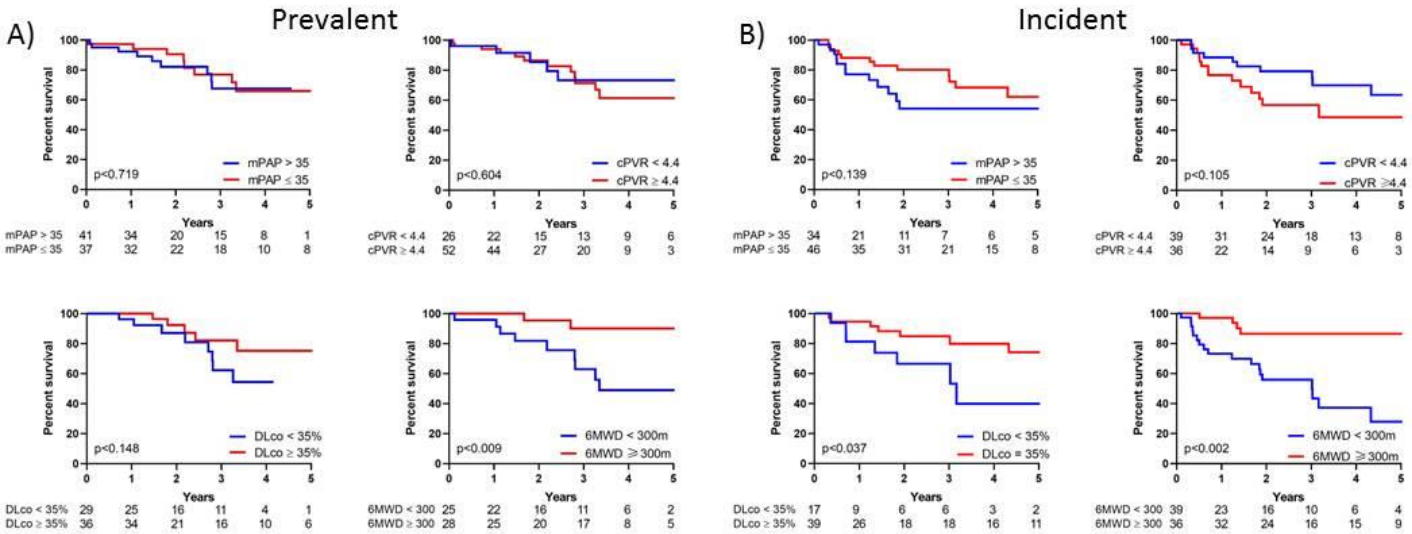
cPVR < 4.4	65	52	38	30	21	14
cPVR ≥ 4.4	94	69	43	28	16	7



DLco < 35%	47	38	24	15	6	2
DLco ≥ 35%	75	66	46	34	25	17



6MWD < 300	65	45	32	20	11	5
6MWD ≥ 300	64	55	41	31	22	14


A)
Prevalent
B)
Incident
Percent survival
Years
p<0.719
mPAP > 35
mPAP ≤ 35
mPAP > 35 41 34 20 15 8 1
mPAP ≤ 35 37 32 22 18 10 8
p<0.604
cPVR < 4.4
cPVR ≥ 4.4
cPVR < 4.4 26 22 15 13 9 6
cPVR ≥ 4.4 52 44 27 20 9 3
p<0.139
mPAP > 35
mPAP ≤ 35
mPAP > 35 34 21 11 7 6 5
mPAP ≤ 35 46 35 31 21 15 8
p<0.105
cPVR < 4.4
cPVR ≥4.4
cPVR < 4.4 39 31 24 18 13 8
cPVR ≥ 4.4 36 22 14 9 6 3
p<0.148
DLco < 35%
DLco ≥ 35%
DLco < 35% 29 25 16 11 4 1
DLco ≥ 35% 36 34 21 16 10 6
p<0.009
6MWD < 300m
6MWD ≥300m
6MWD < 300 25 22 16 11 6 2
6MWD ≥ 300 28 25 20 17 8 5
p<0.037
DLco < 35%
DLco ≥ 35%
DLco < 35% 17 9 6 6 3 2
DLco ≥ 35% 39 26 18 18 16 11
p<0.002
6MWD < 300m
6MWD ≥300m
6MWD < 300 39 23 16 10 6 4
6MWD ≥ 300 36 32 24 16 15 9