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RESEARCH ARTICLE

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Pulmonary hemodynamics and transplant-free survival in sarcoidosis-associated pulmonary hypertension: Results from an international registry

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Abbreviations: 6MWD, 6 min walk distance; APS, advanced pulmonary sarcoidosis; CI, cardiac index; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; ESC/ERS, European Society of Cardiology/European Respiratory Society; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, Interstitial lung disease; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; ReSAPH, Registry of sarcoidosis-associated pulmonary hypertension; RHC, right heart catheterization; SAPH, sarcoidosis-associated pulmonary hypertension; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; WASOG, World Association of Sarcoidosis and other Granulomatous Disorders; WU, Woods units.

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Abstract

Pulmonary hypertension (PH) is a risk factor for mortality in patients with sarcoidosis. Severe PH in chronic lung disease has previously been defined as mean pulmonary arterial pressure (mPAP) ≥ 35 mmHg or mPAP 25 ≥ mmHg with cardiac index (CI) ≤ 2 L/min/m^2. However, there is no clear definition denoting severity of sarcoidosis-associated PH (SAPH). We aimed to determine pulmonary hemodynamic cut-off values where transplant-free survival was worse among patients with SAPH. This was a retrospective cohort analysis of the Registry of SAPH database focusing on pulmonary hemodynamic predictors of transplant-free survival among patients with precapillary SAPH. Cox regression was performed to determine which pulmonary hemodynamic values predicted death or lung transplantation. Kaplan–Meier survival analysis was performed on statistically significant predictors to determine pulmonary hemodynamic cut-off values where transplant-free survival was decreased. Decreased transplant-free survival occurred among SAPH patients with mPAP ≥ 40 mmHg and SAPH patients with pulmonary vascular resistance (PVR) ≥ 5 Woods units (WU). Transplant-free survival was not decreased in patients who fulfilled prior criteria of severe PH in chronic lung disease. We identified new cut-offs with decreased transplant-free survival in the SAPH population. Neither cut-off of mPAP ≥ 40 mmHg nor PVR ≥ 5 WU has previously been shown to be associated with decreased transplant-free survival in SAPH. These values could suggest a new definition of severe SAPH. Our PVR findings are in line with the most recent European Society of Cardiology/European Respiratory Society guideline definition of severe PH in chronic lung disease.

KEYWORDS
mean pulmonary artery pressure, pulmonary vascular resistance, ReSAPH, sarcoidosis-associated pulmonary hypertension, transplant-free survival

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease that commonly affects the lungs and has a highly variable course and prognosis.[1] A subset of patients with pulmonary sarcoidosis progress despite optimal pharmacologic management and develop advanced pulmonary sarcoidosis (APS), which carries high morbidity and mortality.[1] This high-risk phenotype includes sarcoidosis-associated pulmonary hypertension (SAPH).[2] Anywhere from 5.7% to 28.3% of all sarcoidosis patients develop SAPH, and almost 74% of patients with sarcoidosis referred for lung transplantation have SAPH.[3,4] In patients with sarcoidosis, pulmonary hypertension (PH) is an independent risk factor for mortality, conferring up to an 8-10-fold increase in mortality.[3]

Hemodynamic evaluation of SAPH via right heart catheterization (RHC) is paramount. Patients with SAPH without left ventricular (LV) dysfunction, defined as pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, have significantly lower survival compared to those with LV dysfunction. Patients with pulmonary vascular resistance (PVR) ≥ 3 Woods units (WU) also had significantly lower survival than those with PVR < 3 WU.[5]

Severe PH in chronic lung disease has previously been defined as mean pulmonary arterial pressure (mPAP) ≥ 35 mmHg or mPAP ≥ 25 with cardiac index (CI) ≤ 2 L/min/m^2.[6] However, there has been conflicting data on the significance of mPAP ≥ 35 mmHg and impact on survival among patients with SAPH. Indeed, a recent analysis of the Registry of SAPH (ReSAPH) database demonstrated that severe PH, defined as mPAP ≥ 35 mmHg, was not predictive of transplant-free survival.[7]

Additional factors that may influence outcomes in SAPH include treatment with pulmonary vasodilator therapy and coexistent cardiac sarcoidosis. Pulmonary vasodilator therapy may benefit those with precapillary SAPH; prospective studies examining pulmonary vasodilator therapy in SAPH show varying benefits in pulmonary hemodynamics, 6-min walk distance (6MWD), or quality of life, but not mortality. Of note, a recent retrospective study found that pulmonary vasodilator therapy was associated with reduced risk of mortality among patients with SAPH.[8] Given these varying findings, the indications for treatment of SAPH and specific treatment regimens have not been standardized, though the 2022 World Association of Sarcoidosis and other Granulomatous Disorders statement on the diagnosis and management of SAPH does advocate for consideration of treatment of SAPH with pulmonary vasodilator therapy in appropriate patients under the management of a multidisciplinary team.[2,9] Coexistent cardiac sarcoidosis can impact both LV and right ventricular function, which can in turn lead to the develop of SAPH.[2]

We hypothesize that there are pulmonary hemodynamic cut-off points at which transplant-free survival, defined as death or recipient of lung transplant, is decreased among patients with precapillary SAPH. Our objective was to identify potential cut-off points among pulmonary hemodynamic values of right atrial pressure (RAP), mPAP, PCWP, confidence intervla (CI), and PVR in patients with pre-capillary SAPH that confer worsened transplant-free survival.

METHODS

Study population and design

This was a retrospective cohort study of patients with SAPH registered in the ReSAPH database, an ongoing 11-center observational registry initiated in October 2011.[10] As ReSAPH is an ongoing registry, different numbers of patients are analyzed based on the date of analysis (data lock was January 1, 2022 for this study). Patients with a diagnosis of sarcoidosis, data from at least one follow-up visit, and a diagnosis of PH were enrolled. To be part of the registry, all patients with a diagnosis of sarcoidosis were required to have at least one RHC with mPAP ≥ 25 mmHg, as defined by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.[11] Although the registry included patients with postcapillary PH, this study focused upon patients with precapillary PH defined by the 6th PH World Symposium, namely with PVR ≥ 3 WU and PCWP ≤ 15 mmHg.[12] Severe PH was defined as mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with CI ≤ 2 L/min/m^2, consistent with prior definition of severe PH in chronic lung disease.[7]

By virtue of the inclusion requirements of the ReSAPH, all patients have mPAP ≥ 25 mmHg. Baseline characteristics, pulmonary function testing data, 6MWD, chest radiograph Scadding stage, and RHC data including RAP, mPAP, PCWP, PVR, and CI calculated via thermodilution were collected from the ReSAPH database. Patient outcomes of death, lung transplantation, or alive without lung transplantation at 1 year from RHC, 5 years from RHC, and overall (defined as last available follow up), were collected from the ReSAPH database. The authors used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist in the preparation of this manuscript. This study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975.

Statistical analysis

All continuous variables are presented as mean (standard deviation) or median (interquartile range) unless otherwise stated. Cox regression was performed to identify which continuous pulmonary hemodynamic variables significantly predicted the outcome of death or lung transplantation. Subsequent Kaplan–Meier survival analyses were performed on variables with significant association to determine cut-off values that discriminated transplant-free survival. Multicollinearity analysis performed to determine the degree of correlation between identified cut-offs. Bootstrapping was utilized to perform statistical internal validation of the identified cut-offs among the cohort. Cox regression analysis was performed with identified cut-offs as well as pertinent additional variables was performed to determine independent, significant predictors of death or lung transplantation. Cox regression analysis was also performed to assess if the previously defined cut-offs for severe PH are associated with the outcome of death or lung transplantation. Continuous variables with missing data, such as CI, 6MWD, and diffusing capacity for carbon monoxide (DL_{CO}), were dichotomized, with patients missing the data compared to in the analysis; nonsignificant results of patients with missing data were not reported. CI was dichotomized by the mean value of CI in the cohort. 6MWD was dichotomized at a cut-off of 300 m, based on prior ReSAPH analyses.[7,13] DL_{CO} was dichotomized at a cut-off of 40% predicted, which is the threshold for severely reduced DL_{CO}. Statistical analysis was performed using IBM SPSS Statistics, Version 25.

TABLE 1 Baseline and clinical characteristics of patients with precapillary SAPH ($N = 169$).

Age, Years (standard deviation)	58.3 (9.3)
Self-reported gender	
Female (*n*, %)	115 (68.0)
Male (*n*, %)	54 (32.0)
Self-Identified Race	
Black (*n*, %)	94 (55.6)
White (*n*, %)	62 (36.7)
Other (*N*, %)	13 (7.7)
RAP, mmHg (standard deviation)	7 (5.9)
mPAP, mmHg (standard deviation)	38 (10.6)
PCWP, mmHg (standard deviation)	9.6 (3.4)
PVR, WU (standard deviation)	6.4 (3.0)
CI, L/min/m^2 (standard deviation)	2.7 (0.7)
FVC, L (standard deviation)	2.1 (0.8)
FVC % predicted, % (standard deviation)	52.7 (30.6)
FEV1, L (standard deviation)	1.8 (0.6)
FEV1% predicted, % (standard deviation)	44.7 (28.1)
FEV1/FVC > 0.70, *n* (%)	90 (53.3)
DL_{CO} % predicted, % (standard deviation)	29.1 (19.1)
DLCO <40% predicted, *n* (%)	89 (52.7)
DLCO >40% predicted, *n* (%)	45 (26.6)
DLCO Unavailable, *n* (%)	35 (20.7)
6MWD, m (standard deviation)	289.4 (155.8)
6MWD <300 m, *n* (%)	83 (49.1)
6MWD >300 m, *n* (%)	59 (34.9)
6MWD Unavailable, *n* (%)	27 (16.0)
Radiograph scadding stage	
0, *n* (%)	2 (1.2)
I, *n* (%)	3 (1.8)
II, *n* (%)	12 (7.1)
III, *n* (%)	22 (13.0)
IV, *n* (%)	102 (60.3)
Unavailable, *n* (%)	28 (16.6)
Duration of SAPH diagnosis before enrollment in registry, months (standard deviation)	22.9 (21.8)
Treated with pulmonary vasodilator therapy, *n* (%)	154 (91.1)
Prednisone dose, mg (standard deviation)	10.6 (9.8)
Treated with additional anti-inflammatory agent, *n* (%)	116 (68.6)
Number of organs with sarcoidosis involvement (standard deviation)	1.9 (1.1)
Concomitant cardiac sarcoidosis, *n* (%)	26 (15.4)
BNP, ng/L (standard deviation)	437.9 (1142.7)
LVEF on TTE, % (standard deviation)	58.3 (7.6)
RVSP on TTE, mmHg (standard deviation)	57.0 (19.0)
Exertional desaturation, *n* (%)	95 (56.2)

Note: Exertional desaturation defined as decrease in pulse oximetry by > 5% with exertion during a 6 min walk test.

Abbreviations: 6MWD, 6-min walk distance; BNP, brain-natriuretic peptide; CI, cardiac index; DL_{CO}: diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; SAPH, sarcoidosis-associated pulmonary hypertension; WU, woods units.

RESULTS

The ReSAPH database contained 169 patients with pre-capillary SAPH. Most patients were women and self-identified as black (Table 1). All patients had RHC with mPAP, PVR, and PCWP available in the database. The RAP was missing in 8 patients, and the CI was missing in 36 patients. Mean pulmonary hemodynamic values among this cohort were as follows: RAP was 7 mmHg, mPAP was 38 mmHg, PCWP was 9.6 mmHg, PVR was 6.4 WU, and CI was 2.7 L/min/m^2. The mean duration of SAPH diagnosis before inclusion in the ReSAPH registry was 22.9 months (Table 1). Spirometry showed reduced forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1); mean DL_{CO} was severely reduced. Mean 6MWD was less than 300 m. The majority of patients had Scadding Stage IV radiographs, indicative of pulmonary fibrosis (Table 1).

The 1-year transplant-free survival among pre-capillary SAPH patients was 89.4%, with 14 patients (8.2%) dying and 4 patients (2.4%) receiving lung transplant. The 5-year transplant-free survival was 63.9%, with 49 patients (29.0%) dying and 12 (7.1%) patients receiving lung transplant. The overall transplant-free survival (RHC date to time of last follow-up visit) was 60.9%, with 54 patients (32.0%) dying and 12 patients (7.1%) receiving lung transplant. Cox regression only found mPAP and PVR (as continuous variables) to have any significant association with the outcome of death or lung transplantation (Table 2).

Kaplan–Meier survival analysis was performed for mPAP and PVR given their significance in the initial cox

TABLE 2 Cox regression to determine associations of right heart catheterization variables with outcome of mortality or lung transplantation.

	1-year outcome	5-year outcome	Overall outcome
RAP (mmHg)	HR 0.97, 95% CI 0.86−1.10, $p = 0.65$	HR 0.97, 95% CI 0.91−1.04, $p = 0.37$	HR 0.98, 95% CI 0.92−1.04, $p = 0.39$
mPAP (mmHg)	HR 1.03, 95% CI 0.99−1.08, $p = 0.19$	**HR 1.03, 95% CI 1.01−1.05, $p = 0.011$**	HR 1.02, 95% CI 0.99−1.04, $p = 0.07$
PCWP (mmHg)	HR 0.96, 95% CI 0.83−1.11, $p = 0.56$	HR 1.02, 95% CI 0.94−1.11, $p = 0.65$	HR 1.02, 95% CI 0.95−1.10, $p = 0.59$
CI < 2.7 L/min/m^2 (mean value in cohort)[a]	HR 0.61, 95% CI 0.21−1.83, $p = 0.38$	HR 1.02, 95% CI 0.58−1.73, $p = 0.21$	HR 0.93, 95% CI 0.55−1.58, $p = 0.79$
PVR (WU)	HR 1.09, 95% CI 0.96−1.24, $p = 0.19$	**HR 1.07, 95% CI 1.01−1.15, $p = 0.047$**	HR 1.05, 95% CI 0.98−1.12, $p = 0.19$

Abbreviations: 95% CI, 95% confidence interval; CI, cardiac index; HR, hazard ratio; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

[a]CI was dichotomized in the analysis given the amount of missing data; patients with missing CI were included in the cox regression analysis as a comparison group.

regression. Initial survival analysis compared stratified groups chosen based on patient cohort distribution and to aid in identifying significant changes in transplant-free survival across the mPAP and PVR distributions; mPAP was stratified to mPAP < 30 mmHg, mPAP ≥ 30 mmHg to <40 mmHg, and mPAP ≥ 40 mmHg, while PVR was stratified to PVR ≥ 3 WU to <5 WU, PVR ≥ 5 WU to <7 WU, and PVR ≥ 7 WU.

Comparison of the stratified mPAP groups showed a separation with seemingly lower transplant-free survival probability among patients with mPAP ≥ 40 mmHg as compared to the two lower mPAP groups, though this was not statistically significant (logrank $p = 0.06$). Given this pattern, subsequent survival analysis was performed comparing mPAP ≥ 40 mmHg (65 patients) and mPAP < 40 mmHg (104 patients), showing significantly lower 1-year (logrank $p = 0.012$), 5-year (logrank $p = 0.003$), and overall transplant-free survival probability (logrank $p = 0.016$) among SAPH patients with mPAP ≥ 40 mmHg (Figure 1). Transplant-free survival rates and median survival time among the mPAP groups are shown in Supporting Information: Table 1. Univariate cox regression analysis showed that mPAP ≥ 40 mmHg was significantly associated with increased risk of death or lung transplantation at 1 year (HR 3.56, 95% CI 1.24−10.25, logrank $p = 0.019$), 5 years (HR 2.08, 95% CI 1.26−3.45, $p = 0.004$), and overall (HR 1.80, 95% CI 1.11−2.92, $p = 0.018$).

Comparison of the stratified PVR groups roughly showed a separation with seemingly lower transplant-free survival probability among patients in PVR groups with PVR at least 5 WU as compared to the lower PVR group (logrank $p = 0.004$). Given this pattern, subsequent survival analysis was performed comparing PVR ≥ 5 WU (102 patients) and PVR < 5 WU (67 patients), showing significantly lower 5-year (logrank $p = 0.002$) and overall transplant-free survival probability (logrank $p = 0.006$) among SAPH patients with PVR ≥ 5 WU (Figure 2). Transplant-free survival rates and median survival time among the PVR groups are seen in Supporting Information: Table 2. Univariate cox regression showed that PVR ≥ 5 WU was significantly associated with increased risk of death or lung transplantation at 5 years (HR 2.64, 95% CI 1.41−4.97, $p = 0.003$) and overall (HR 2.18, 95% CI 1.24−3.85, $p = 0.007$).

Multicollinearity analysis showed both mPAP and PVR to have a variance inflation factor of 1.54, suggesting a moderate correlation between the two that likely does not impact the reliability of regression findings. Bootstrapping analysis with 1000 samples and 95% bias-corrected and accelerated CIs of the univariate cox regression model for the cut-offs of mPAP ≥ 40 mmHg and PVR ≥ 5 WU at 1 year, 5 years, and overall showed similar significance to the original univariate cox regression model, suggesting internal statistical validity (Supporting Information: Table 3).

In addition to the mPAP and PVR cut-offs of 40 mmHg and 5 WU respectively, univariate cox regression analysis (Table 3) demonstrated 6MWD < 300 m (HR 3.57, 95% CI 1.95−6.54, $p < 0.001$), severely reduced DL_{CO} (<40% predicted; hazard ratio [HR] 2.19, 95% CI 1.11−4.30, $p = 0.02$), and FEV1/FVC > 0.70 (HR 1.07, 95% CI 0.65−1.75, $p = 0.02$) to be associated with increased risk of death or lung transplantation. As the duration of SAPH diagnosis before enrollment in the registry increased, the risk of death or lung transplantation decreased

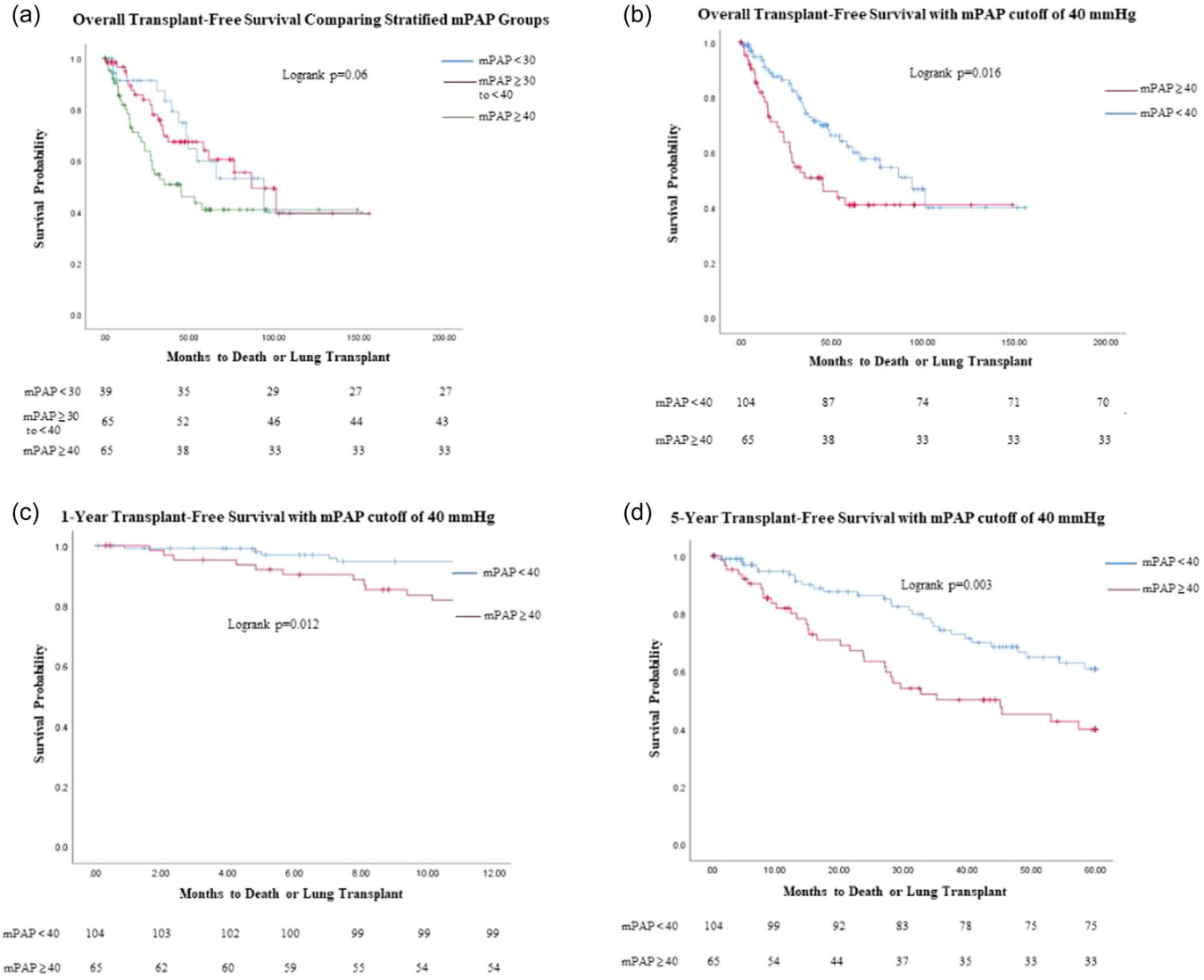

FIGURE 1 Kaplan–Meier survival analysis of mean pulmonary artery pressure. Kaplan–Meier analysis was performed to identify mPAP cut-off where transplant-free survival worsened. Number at risk displayed at bottom of each graph, with change in curves due to death or lung transplantation. (a) Comparison of overall transplant-free survival between mPAP < 30, mPAP ≥ 30 mmHg to <40 mmHg, and mPAP ≥ 40 mmHg. (b) Comparison of overall transplant-free survival between mPAP < 40 mmHg and mPAP ≥ 40 mmHg. (c) Comparison of 1-year transplant-free survival between mPAP < 40 mmHg and mPAP ≥ 40 mmHg. (d) Comparison of 5-year transplant-free survival between mPAP < 40 mmHg and mPAP ≥ 40 mmHg. mPAP, Mean pulmonary artery pressure.

significantly (HR 0.98, 95% CI 0.97–0.99, $p < 0.001$). Subsequent multivariable cox regression with these variables showed PVR ≥ 5 WU (HR 2.07, 95% CI 1.06–4.05, $p = 0.03$) and 6MWD < 300 m (HR 1.79, 95% CI 1.04–3.07, $p = 0.04$) to be independently and significantly associated with increased risk of death or lung transplantation, while duration of SAPH diagnosis before registry enrollment (HR 0.98, 95% CI 0.97–0.99, $p = 0.002$) was associated with decreased risk of death or lung transplantation (Table 3). Additional univariate cox regression analysis was also performed for the prior defined cut-offs of severe PH (mPAP ≥ 35 mmHg, mPAP ≥ 25 mmHg with CI ≤ 2 L/min/m^2) and association with the outcome of death or lung transplantation. Neither mPAP ≥ 35 mmHg (HR 1.4, 95% CI 0.87–2.39, $p = 0.16$) nor mPAP ≥ 25 mmHg with CI ≤ 2 L/min/m^2 (HR 0.79, 95% CI 0.40–1.58, $p = 0.51$) were significantly associated with this outcome.

DISCUSSION

Among patients with precapillary SAPH, those with mPAP ≥ 40 mmHg had significantly worse 1-year, 5-year, and overall transplant-free survival as compared to those with mPAP < 40 mmHg. Those

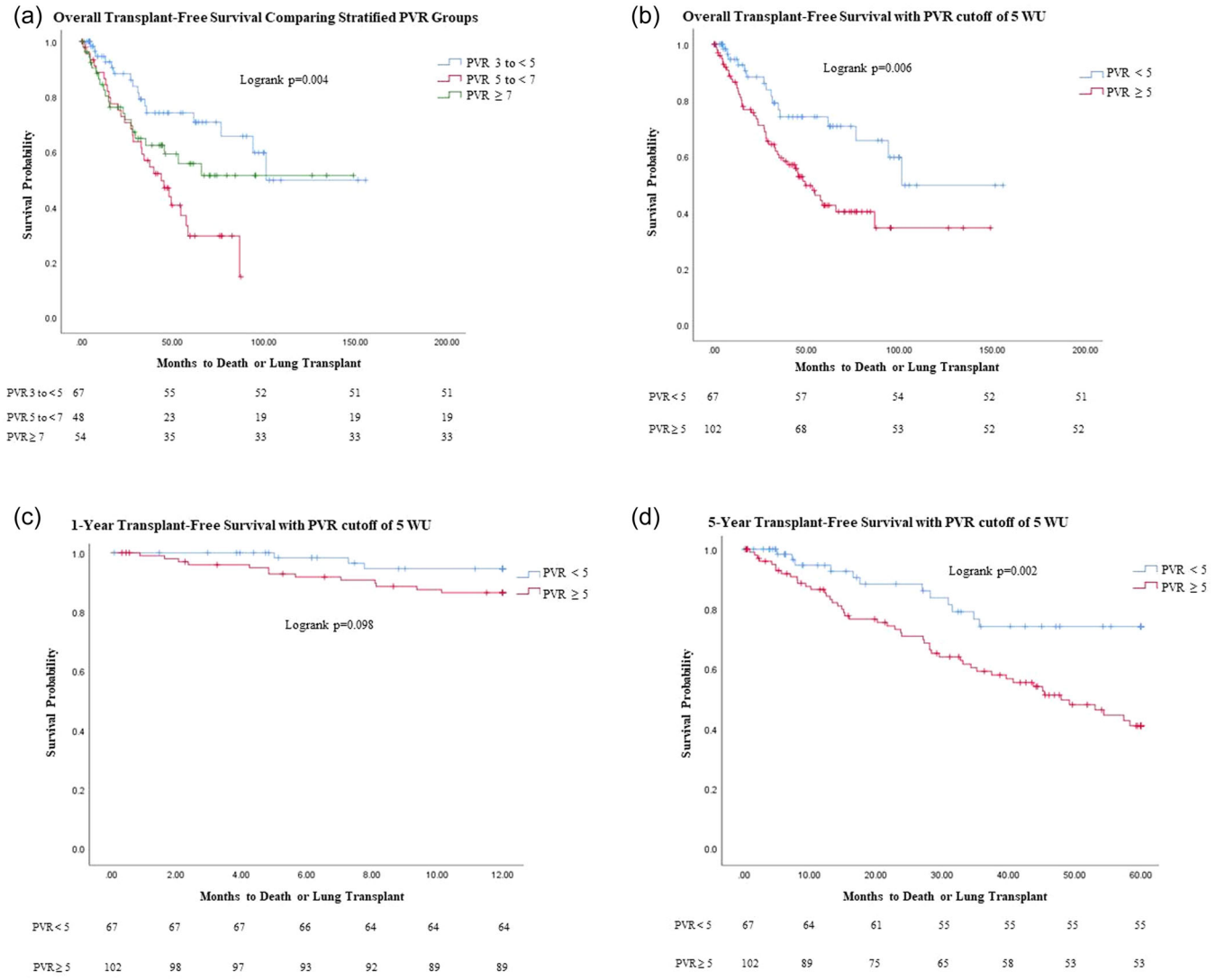

FIGURE 2 Kaplan–Meier survival analysis of pulmonary vascular resistance. Kaplan–Meier analysis was performed to identify PVR cut-off where transplant-free survival worsened. Number at risk displayed at bottom of each graph, with change in curves due to death or lung transplantation. (a) Comparison of overall transplant-free survival between PVR ≥ 3 WU to <4 WU, PVR ≥ 4 WU to <5 WU, PVR ≥ 5 WU to <6 WU, PVR ≥ 6 WU to <7 WU, PVR ≥ 7 WU to <8 WU, and PVR ≥ 8 WU. (b) Comparison of overall transplant-free survival between PVR < 5 WU and PVR ≥ 5 WU. (c) Comparison of 1-year transplant-free survival between PVR < 5 WU and PVR ≥ 5 WU. (d) Comparison of 5-year transplant-free survival between PVR < 5 WU and PVR ≥ 5 WU. PVR, pulmonary vascular resistance; WU, woods units.

with PVR ≥ 5 WU had significantly worse 5-year and overall transplant-free survival as compared to those with PVR < 5 WU. Given these findings of worsened transplant-free survival, mPAP ≥ 40 mmHg and/or PVR ≥ 5 WU could better define severity in patients with pre-capillary SAPH.

While prior studies have shown mPAP cut-offs associated with worsened survival in patients with SAPH, to our knowledge, this is the first large study to demonstrate worsened transplant-free survival among SAPH patients with mPAP ≥ 40 mmHg specifically as compared to SAPH patients with mPAP < 40 mmHg. Notably, to our knowledge, this is also the first study at all to demonstrate a PVR cut-off with decreased transplant-free survival among patients with SAPH. Severe PH in chronic lung disease has previously been defined as mPAP ≥ 35 mmHg or mPAP ≥ 25 with CI ≤ 2 L/min/m^2.[6] However, there is limited evidence to define severity in patients specifically with SAPH, with definitions often adopted from other, more common lung diseases.[4,6] We did not find either of these criteria for severe PH to be associated with death or lung transplantation among precapillary SAPH patients.

TABLE 3 Cox regression analysis of death or lung transplantation.

	Univariate Cox regression	Multivariable Cox regression
Age (years)	HR 1.02, 95% CI 0.99–1.05, $p = 0.10$	N/A
Race	Black: HR 0.92, 95% CI 0.55–1.55, $p = 0.75$ Other: HR 1.87, 95% CI 0.92–4.38, $p = 0.10$	N/A
Scadding stage	Stage I: HR 1.01, 95% CI 0.55–1.85, $p = 0.85$ Stage II: HR 1.37, 95% CI 0.69–2.69, $p = 0.78$ Stage III: HR 1.73, 95% CI 0.51–5.92, $p = 0.38$ Stage IV: HR 0.75, 95% CI 0.26–2.15, $p = 0.59$	N/A
mPAP ≥ 40 mmHg	HR 1.80, 95% CI 1.11–2.92, $p = 0.018$[a]	HR 1.54, 95% CI 0.88–2.69, $p = 0.13$
PVR ≥ 5 WU	HR 2.18, 95% CI 1.24–3.85, $p = 0.007$[a]	HR 2.07, 95% CI 1.06–4.05, $p = 0.03$[b]
FEV1 (L)	HR 0.78, 95% CI 0.47–1.30, $p = 0.34$	N/A
FVC (L)	HR 0.91, 95% CI 0.66–1.24, $p = 0.54$	N/A
FEV1/FVC > 0.70	HR 1.07, 95% CI 0.65–1.75, $p = 0.02$[a]	HR 0.81, 95% CI 0.45–1.44, $p = 0.47$
DL_{CO} < 40% predicted	HR 2.19, 95% CI 1.11–4.30, $p = 0.02$[a]	HR 1.29, 95% CI 0.65–2.56, $p = 0.46$
6MWD < 300 m	HR 3.57, 95% CI 1.95–6.54, $p < 0.001$[a]	HR 1.79, 95% CI 1.04–3.07, $p = 0.04$[b]
Duration of SAPH diagnosis before enrollment in registry (months)	HR 0.98, 95% CI 0.97–0.99, $p = 0.001$[a]	HR 0.98, 95% CI 0.97–0.99, $p = 0.002$[b]
Cardiac Sarcoidosis	HR 0.51, 95% CI 0.23–1.13, $p = 0.10$	N/A
Pulmonary vasodilator therapy	HR 0.49, 95% CI 0.21–1.16, $p = 0.10$	N/A
Exertional desaturation	HR 1.18, 95% CI 0.72–1.93, $p = 0.52$	N/A

Note: Exertional desaturation defined as decrease in pulse oximetry by >5% with exertion during a 6 min walk test.

Abbreviations: 6MWD, 6 min walk distance; DLCO, Diffusing capacity for carbon monoxide; FEV1, Forced expiratory volume in 1 s; FVC, forced vital capacity; mPAP: mean pulmonary artery pressure; PVR, pulmonary vascular resistance; WU, woods units.

[a]variable significantly associated with risk of death or lung transplantation in univariate cox regression and utilized in subsequent multivariable cox regression;

[b]variable significantly associated with risk of death or lung transplantation in multivariable cox regression.

An earlier study by Arcasoy et al. of patients with sarcoidosis listed for lung transplantation found that mPAP ≥ 35 mmHg, CI ≤ 2 L/min/m^2, and RAP ≥ 15 mmHg were risk factors for mortality, with mortality most closely linked to RAP ≥ 15 mmHg. Patients with these pulmonary hemodynamic parameters had significantly worse 1- and 2-year survival than those who did not (mPAP < 35 mmHg, CI > 2 L/min/m^2, and RAP < 15 mmHg).[14] However, in a more recent analysis of the ReSAPH database, Shlobin et al. demonstrated that neither severe PH, defined as mPAP ≥ 35 mmHg, nor PVR ≥ 4.4 WU (median value in the cohort at the time of analysis) were predictive of transplant-free survival.[7] This was reflected in the current analysis, as we did not find previously defined classifications of severe PH to be associated with death or lung transplantation among this pre-capillary SAPH cohort.

It is important to note that Arcasoy et al. found a lower survival rate in their cohort; 1-year survival was 66% and 3-year survival was only 31% as compared to 89.2% and 71.7% in Shlobin et al.'s ReSAPH database analysis.[7,14] The transplant-free survival rates in this current ReSAPH analysis were higher as well. The sarcoidosis patients studied by Arcasoy et al. were all undergoing lung transplant evaluation, which could indicate a greater severity of underlying parenchymal lung disease that, in addition to PH, may have contributed to mortality. Indeed, the extent of fibrosis on computed tomography (CT) has been identified as an independent predictor of mortality in APS.[15,16]

There might be additional factors aside from progressive fibrosis and pulmonary hemodynamics that contribute to survival among patients with sarcoidosis. A 24-month decline in FVC ≥ 10% and in DL_{CO} of ≥15% have been found to be risk factors for mortality in patients with sarcoidosis in general.[17] We found that in addition to our identified hemodynamic cutoffs, severely reduced DL_{CO}, 6MWD < 300 m, and normal FEV1/FVC ratio were associated with increased risk of death or lung transplantation. We also found that as the duration from SAPH diagnosis to registry enrollment increased, the risk of death or lung transplantation significantly decreased. Multivariate cox regression incorporating these variables showed that only decreased 6MWD, duration of SAPH diagnosis to registry enrollment, and PVR ≥ 5 WU had independent and significant associations with the risk of death or lung transplantation. The significance of duration from SAPH diagnosis to registry enrollment is in line with prior ReSAPH analysis, which found that prevalent SAPH patients (diagnosed with SAPH > 1 year before ReSAPH enrollment) had longer transplant-free survival than incident SAPH patients (diagnosed with SAPH < 1 year before ReSAPH enrollment). This was felt to be due to survival bias in the prevalent patients due to enrichment with less severe cases and lead-time bias as the prevalent patients were further along the disease course.[7] Our findings of the significance of decreased 6MWD suggests that 6MWD could serve as a potential cut-off for both a predictor of mortality and therapeutic end-point in future clinical trials in patients with SAPH. Prior ReSAPH analysis found that 6MWD correlates inversely with mPAP, while DL_{CO} inversely correlates with both mPAP and PVR.[10,13] Awareness of the correlation between pulmonary hemodynamic variables and pulmonary function parameters, including 6MWD, is important, as this data is more readily obtainable and might provide "clues" to the presence and severity of PH.

Of the pulmonary hemodynamic parameters, we found only mPAP and PVR to be associated with the outcome of death or lung transplantation, prompting in-depth survival analysis to identify cut-offs. This led to the identification of mPAP ≥ 40 mmHg and PVR ≥ 5 WU as cut-offs associated with decreased transplant-free survival, with PVR ≥ 5 WU having an independent and significant association when accounting for other pertinent variables. Given that we did not find patients with mPAP ≥ 35 mmHg or mPAP ≥ 25 mmHg with CI ≤ 2 L/min/m^2 to have increased risk of death or lung transplantation, our identified cut-off values of mPAP ≥ 40 mmHg and in particular PVR ≥ 5 WU could signify a new severity category for PH among patients with sarcoidosis.

It is important to note that our findings appear to contrast with those of Shlobin et al.'s ReSAPH analysis, which did not find pulmonary hemodynamics to be predictive of transplant-free survival among patients with SAPH.[7] However, that analysis used a previously determined mPAP cut-off of 35 mmHg that was defined in a cohort unique from the ReSAPH cohort, while we found new mPAP and PVR cut-offs specific to the larger ReSAPH cohort. Additionally, as the ReSAPH database is ongoing, we analyzed more patients with a longer follow-up period as compared to Shlobin et al.'s ReSAPH analysis. As such, our study may be better powered to detect the association of mPAP and PVR cutoffs on transplant-free survival. Also, the mean PVR in this study is higher (6.4 WU) than in Shlobin et al.'s study (5.9 WU).[7] This indicates that this current analysis is focusing on a SAPH population with more hemodynamically significant PH. These could all explain the apparent discrepancy between our analysis and the 2020 ReSAPH analysis with regard to the significance of pulmonary hemodynamics.

Our findings of PVR as a marker of SAPH severity are in line with the most recent definition of severe PH in chronic lung disease discussed in the 2022 ESC/ERS Guidelines for the diagnosis and treatment of PH.[18] These guidelines shift away from mPAP and CI parameters towards a PVR cut-off for severe (PVR > 5 WU) and nonsevere (PVR ≤ 5 WU) PH in chronic lung disease.[18] This recommendation was based on two studies which showed that elevated PVR > 5 WU predicted mortality in PH associated with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD).[19,20] Our results suggest that a PVR cut-off of 5 WU to define severe PH can be applicable to patients with SAPH as well. These findings can guide decision-making in the treatment of patients with pre-capillary SAPH. Given the significance of PVR ≥ 5 WU and mPAP ≥ 40 mmHg with regard to transplant-free survival, patients with pulmonary hemodynamics approaching these cut-offs may benefit from earlier lung transplantation referral and evaluation. Given that the majority of patients in the registry have pulmonary fibrosis as evidenced by Scadding scores, it is likely that the mPAP and PVR elevation is mostly due to precapillary disease in the setting of parenchymal disease. However, there is minimal CT information to discern the influence of mediastinal inflammation and lymph node calcification on mPAP and PVR elevation.

Strengths of our study include its large, international, multicenter nature, as well as its long-term data on patients with SAPH. Additionally, our cut-off findings are in line with the latest ESC/ERS guideline definitions for severe PH in chronic lung disease. Limitations to our study

are namely those inherent to multicenter registry data, such as missing data and potential variability in clinical care and testing among centers. However, all patients with precapillary SAPH available to be analyzed had RHC data with mPAP and PVR available, likely minimizing the impact of missing pulmonary hemodynamic data in this study. The patients in this ReSAPH registry do not reflect the most recent ESC/ERS definitions of pre-capillary PH, defined as mPAP > 20 mmHg, PCWP ≤ 15 mmHg, and PVR > 2 WU.[18] As such, our analysis may not capture the wider spectrum of mPAP and PVR values, but this likely does not diminish the significance of our findings of mPAP ≥ 40 mmHg and PVR ≥ 5 WU among patients with precapillary SAPH. Additionally, we were unable to account for the differences in treatment with pulmonary vasodilators and anti-inflammatory therapy across countries and institutions involved in the ReSAPH database. The registry also did not have consistent data on the change in FVC, and as such this could not be tested for correlation with pulmonary hemodynamics. A further limitation is that of our endpoint itself. The "lumping" of transplant as an equivalent event has inherent issues. First, not all patients within the ReSAPH were lung transplant candidates and therefore eligible to meet this endpoint. Lung transplant itself can be a somewhat arbitrary event with multiple factors determining this. Additionally, the lung allocation score system prioritizes patients with sarcoidosis and elevated pulmonary artery pressures, which is certainly supported by our study. However, our study is unique in that we identified different hemodynamic cut-offs, in particular PVR ≥ 5 WU, that hold predictive value in this specific cohort of patients with SAPH; notably, the lung allocation score does not take into account PVR in its calculation.[21] Regardless, transplantation as an outcome is clinically significant for the care of this high-risk phenotype of APS.

CONCLUSION

Prior definitions of severe PH in patients with sarcoidosis are not well defined due to lack of strong evidence with different cut-offs and have not been able to consistently predict transplant-free survival among patients with SAPH. This analysis of patients with pre-capillary SAPH demonstrated that patients with the prior definitions of severe PH did not have decreased transplant-free survival. Rather, those with mPAP ≥ 40 mmHg and PVR ≥ 5 WU had decreased transplant-free survival. This is the first study to demonstrate a PVR cut-off with decreased transplant-free survival among patients with SAPH, in line with the new ESC/ERS definitions of severe PH in chronic lung disease. These findings may help guide decision-making in the treatment of patients with pre-capillary SAPH, in particular with regard to lung transplantation evaluation.

AUTHOR CONTRIBUTIONS

Author Shameek K. Gayen contributed to study design, data analysis, statistical analysis, and manuscript writing/editing. Authors Rohit Gupta, BHL, Oksana A. Shlobin, and Robert P. Baughman contributed to study design and revised and reviewed the manuscript. Authors Steven D. Nathan, Athol U. Wells, Vasilis Kouranos, Esam H. Alhamad, Daniel A. Culver, Joseph Barney, Eva M. Carmoma, Francis C. Cordova, Marloes Huitema, Mary Beth Scholand, Marlies Wijsenbeek, Sivagini Ganesh, Surinder S. Birring, Laura C. Price, and Stephen J. Wort revised and reviewed the manuscript.

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Shameek Gayen is the guarantor of the content of the manuscript, including the data and analysis.

CONFLICTS OF INTEREST STATEMENT

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: S. J. W. has received honoraria for lectures and advisory boards from Janssen (previously known as Actelion), Bayer, MSD and GSK. He has received travel grants from Janssen and GSK. He has received research grants from Bayer and Janssen. RPB has grant support from Gilead, Bayer, Actelion, Genentech, aTyr, Novartis, and Bellephron for studies in sarcoidosis. O. A. S. consults for and is a speaker for Bayer, United Therapeutics, and Janssen & Janssen. She also consults for Altavant. L. C. P. declares personal fees from Janssen Pharmaceuticals, outside the submitted work. SB has received consultancy fees from aTy and Kinevant. S. D. N. is a consultant for Boehringer-Ingelheim, Roche, United Therapeutics, Bellerophon, Third Pole, and Merck. He is on the speakers bureau for Boehringer-Ingelheim and United Therapeutics. R. G. has received consultancy fees from Mallinckrodt. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The remaining author declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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