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RESEARCH LETTER

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Predictors of hospitalization for respiratory failure among patients with sarcoidosis-associated pulmonary hypertension

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Abstract

Pulmonary hypertension leads to significant morbidity and mortality in patients with sarcoidosis. In this study, we examined clinical factors associated with the risk of respiratory failure-related hospitalization in 58 patients with sarcoidosis-associated pulmonary hypertension. Pulmonary vasodilator therapy and spirometry were associated with reduced risk of hospitalization in this cohort.

KEYWORDS

pulmonary hypertension, pulmonary vasodilator therapy, respiratory failure, sarcoidosis

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease, with the majority of patients experiencing respiratory involvement.[1] Anywhere from 5.7% to 28.3% of patients with sarcoidosis develop sarcoidosis-associated pulmonary hypertension (SAPH).[2] SAPH occurs more so within fibrotic sarcoidosis, but it can occur even in the absence of significant lung disease. Pulmonary hypertension (PH) confers increased morbidity and mortality among patients with sarcoidosis.[2] Almost 74% of patients with sarcoidosis referred for lung transplantation have SAPH.[3]

The risk factors for mortality within patients with SAPH have been studied. Certain cut-off values for mean pulmonary artery pressure (mPAP), cardiac index, and right atrial pressure (RAP) were found to be risk factors for mortality in patients with sarcoidosis listed for lung transplant.[4] Decline in functional vital capacity (FVC), a diffusing capacity of the lung for carbon monoxide (DLCO) <35% predicted, and a six-min walk distance (6MWD) <300 m were associated with decreased survival in patients with SAPH.[5–7] However, to our knowledge, there are no studies specifically examining risk factors for morbidity, specifically hospitalizations for respiratory failure, among patients with SAPH. We aimed to determine clinical factors associated with risk of respiratory-failure-related hospitalization among patients with SAPH undergoing lung transplant evaluation.

METHODS

Study design and definitions

This was a retrospective cohort study of patients with SAPH undergoing lung transplantation evaluation at our institution from 2008 to 2021. SAPH was defined as mPAP > 25 mmHg on right heart catheterization (RHC) in patients with biopsy-proven sarcoidosis, as this was the definition of PH during the majority of the time period. Patient characteristics, comorbidities, anti-inflammatory treatment, and RHC values at the time of PH diagnosis were collected. Spirometry, 6MWD, and oxygen requirement were collected at the time of PH

diagnosis and at 12 months after initial PH diagnosis; as part of the lung transplant evaluation at our institution, patients undergoing evaluation perform routine spirometry and 6-min walk testing every 4–8 weeks. If patients were deceased or underwent lung transplantation before 12 months after PH diagnosis, values at last follow-up before death or transplant were collected. Hospitalizations for respiratory failure and the time to hospitalizations (primary outcome) were collected. Hospitalization for respiratory failure was defined as increase in dyspnea and/or oxygen requirement requiring hospitalization stay. Our study met approval for waiver of informed consent by the Western Institutional Review Board (Protocol #29957).

Statistical analysis

Mean values are presented as mean ± SD where applicable. Univariate analysis to determine associations of variables with the primary outcome was performed using univariate Cox regression. Variables that had a p value < 0.1 in the univariate analysis were included in the multivariable Cox regression analysis to determine significant and independent predictors of the outcome of risk of respiratory failure-related hospitalizations ($p < 0.05$). All data collected and statistical analyses included the entire cohort.

RESULTS

We identified 58 patients with SAPH who underwent lung transplant evaluation at our institution between 2008 and 2021. The average age was 56.9 ± 8.5 years. The average body mass index (BMI) was 27.6 ± 3.1 kg/m^2. Fifty-three percent of patients were female, and 79.3% of patients were black. Among the cohort, 24% had extrapulmonary sarcoidosis, 22% had diabetes, 40% had concomitant chronic obstructive pulmonary disease, 53% had chronic kidney disease, 11% had liver disease attributed to hepatic sarcoidosis, and 81.0% had heart disease. In total, 31.0% of patients had hypertension, 8.6% had systolic heart failure, 27.6% had diastolic heart failure, and 27.6% had coronary artery disease.

In terms of pulmonary function/spirometry data at the time of PH diagnosis, mean forced expiratory volume in 1 s (FEV1) was 1.26 ± 0.52 L, mean percent-predicted FEV1 was 47.1 ± 16.5%, mean FVC was 1.82 ± 0.68 L, mean percent-predicted FVC was 53.5 ± 15.4%, and mean percent-predicted DLCO was 27.9 ± 12.2%. In all, 43.1% of patients had a reduced FEV1/FVC ratio (<0.70). All patients had Scadding Stage 4 chest radiographs. The mean initial 6MWD was 239.3 ± 86.5 m.

In terms of RHC values, average values were as follows: RAP 7.9 ± 3.9 mmHg, mPAP 34.6 ± 8.1 mmHg, pulmonary capillary wedge pressure (PCWP) 9.9 ± 5.1 mmHg, cardiac index 2.7 ± 0.7 L/min/m^2, and pulmonary vascular resistance (PVR) 5.6 ± 3.0 Woods units. The average prednisone dose prescribed was 10.4 ± 7.8 mg daily, and 43% of patients were on additional anti-inflammatory therapy. Thirty-eight patients (65.5%) were prescribed pulmonary vasodilator therapy for PH. The average oxygen requirement at the time of PH diagnosis was 3.1 ± 2.8 L/min.

Twenty-nine patients (50.0%) were New York Heart Association (NYHA) functional class III, 28 patients (48.3%) were NYHA functional class IV, and 1 patient (1.7%) was NYHA functional class II. Thirty-eight patients (65.5%) received pulmonary vasodilator therapy. Twenty-three received phosphodiesterase-5 inhibitors, 26 received endothelin-receptor antagonists, 3 received inhaled prostacyclin, and 3 received subcutaneous prostacyclin. Twenty-two patients received single-agent therapy, 15 patients received dual-agent therapy, and 1 patient received triple-agent therapy.

With regard to outcomes, 39 patients (67.2%) were hospitalized for respiratory failure from the time of PH diagnosis before lung transplantation or mortality. The average time to first hospitalization was 14.5 months. At the end of 12 months (or sooner if death or transplant occurred before 12 months), FEV1 decreased by 79.7 ± 22.4 mL, FVC decreased by 87.8 ± 33.3 mL, and 6MWD decreased by 27.2 ± 71.5 m in the entire cohort.

Univariate Cox regression for the outcome of respiratory-failure-related hospitalization (Table 1) showed treatment with pulmonary vasodilators was significantly associated with decreased risk of hospitalization (hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.26–0.96, $p = 0.036$). Additionally, percent-predicted DLCO at the time of PH diagnosis, history of extrapulmonary sarcoidosis, B-type natriuretic peptide (BNP), and percent-predicted FEV1 at the time of PH diagnosis showed a trend towards association with the risk of hospitalization (Table 1). As these five variables had a p-value < 0.1 in univariate Cox regression, they were utilized in subsequent multivariable Cox regression for the outcome of respiratory-failure-related hospitalization (Table 1). Multivariable Cox regression found treatment with pulmonary vasodilator therapy (HR: 0.23, 95% CI 0.08–064, $p = 0.005$) and percent-predicted FEV1 at the time of PH diagnosis (HR: 0.96, 95% CI: 0.93–0.99, $p = 0.018$) to be independently and significantly associated with reduced risk of respiratory failure-related hospitalization. Pulmonary vasodilator therapy was associated with a 77% reduction in risk of hospitalization. For every 1% increase in percent-predicted FEV1, the risk of hospitalization decreased by 4%.

TABLE 1 Analysis of predictors of respiratory failure-related hospitalizations in patients with sarcoidosis-associated pulmonary hypertension.

Patient variable	Univariate analysis	Multivariable analysis
Age	HR: 0.98, 95% CI: 0.95–1.02, $p = 0.35$	
BMI	HR: 0.98, 95% CI: 0.96–1.05, $p = 0.13$	
Female gender	HR: 0.73, 95% CI 0.39–1.37, $p = 0.33$	
Race (Black)	HR: 2.22, 95% CI: 0.53–9.25, $p = 0.27$	
Oxygen requirement	HR: 0.96, 95% CI: 0.85–1.08, $p = 0.51$	
History of extrapulmonary sarcoidosis	HR: 1.88, 95% CI: 0.93–3.81, $p = 0.079$[a]	HR: 1.82, 95% CI: 0.65–5.14, $p = 0.26$
History of diastolic heart failure	HR: 1.17, 95% CI: 0.59–2.30, $p = 0.66$	
History of systolic heart failure	HR: 1.36, 95% CI: 0.48–3.89, $p = 0.57$	
History of coronary artery disease	HR: 0.71, 95% CI: 0.34–1.50, $p = 0.37$	
History of hypertension	HR: 1.67, 95% CI: 0.86–3.23, $p = 0.13$	
History of diabetes	HR: 1.06, 95% CI: 0.50–2.23, $p = 0.89$	
History of additional lung disease (COPD)	HR: 1.37, 95% CI: 0.72–2.63, $p = 0.34$	
NYHA functional class	Class III: HR: 1.39, 95% CI: 0.12–2.72, $p = 0.90$	
	Class IV: HR: 1.74, 95% CI: 0.31–2.86, $p = 0.91$	
6MWD at PH diagnosis	HR: 1.00, 95% CI: 0.99–1.03, $p = 0.77$	
FEV1 at PH diagnosis	HR: 0.72, 95% CI: 0.37–1.41, $p = 0.34$	
Percent-predicted FEV1 at PH diagnosis	HR: 0.98, 95% CI: 0.96–1.03, $p = 0.084$[a]	HR: 0.96, 95% CI: 0.93–0.99, $p = 0.018$[b]
FVC at PH diagnosis	HR: 0.86, 95% CI: 0.52–1.41, $p = 0.54$	
Percent-predicted FVC at PH diagnosis	HR: 0.98, 95% CI: 0.96–1.01, $p = 0.12$	
FEV1/FVC at PH diagnosis	FEV1/FVC < 0.70: HR: 0.94, 95% CI: 0.49–1.79, $p = 0.86$	
Percent-predicted DLCO at PH diagnosis	HR: 1.03, 95% CI: 0.99–1.06, $p = 0.098$[a]	HR: 1.03, 95% CI: 0.99–1.06, $p = 0.12$
BNP	HR: 1.01, 95% CI: 1.00–1.02, $p = 0.097$[a]	HR: 1.01, 95% CI: 1.00–1.02, $p = 0.085$
mPAP	HR: 0.99, 95% CI: 0.96–1.03, $p = 0.75$	
PVR	HR: 0.95, 95% CI: 0.85–1.06, $p = 0.35$	
Cardiac index	HR: 1.27, 95% CI: 0.81–1.98, $p = 0.30$	
Prednisone dose	HR: 1.03, 95% CI: 0.99–1.07, $p = 0.12$	
Additional anti-inflammatory treatment	HR: 0.99, 95% CI: 0.53–1.89, $p = 0.99$	
Treatment with pulmonary vasodilator therapy	HR: 0.50, 95% CI: 0.26–0.96, $p = 0.036$[a]	HR: 0.23, 95% CI: 0.08–0.64, $p = 0.005$[b]
Change in FEV1 over 12 months	HR: 0.74, 95% CI: 0.52–1.10, $p = 0.13$	
Change in FVC over 12 months	HR: 0.53, 95% CI: 0.19–1.46, $p = 0.22$	
Change in 6MWD over 12 months	HR: 1.00, 95% CI: 0.99–1.01, $p = 0.95$	

Abbreviations: 6MWD, 6 min walk distance; BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HR, hazard ratio; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

[a]Variable had p value < 0.1 in univariate Cox regression and utilized in multivariable Cox regression.

[b]Variable has significant, independent association with risk of respiratory failure-related hospitalization in multivariable Cox regression.

DISCUSSION

Among patients with SAPH undergoing lung transplant evaluation, over two-thirds of patients were hospitalized at least once for respiratory failure before lung transplantation or death, suggesting a high degree of morbidity among this patient population. Treatment with pulmonary vasodilator therapy for PH and a higher baseline percent-predicted FEV1 were independently and significantly associated with decreased risk of hospitalization. Pulmonary vasodilator therapy had the strongest association, with an associated decrease in risk of hospitalization for respiratory failure by almost 80%. These findings highlight both the difficulty in predicting hospitalization risk for patients with SAPH with clinical factors, as well as a potential benefit to pulmonary vasodilator therapy in this patient population.

PH is known to increase morbidity in patients with sarcoidosis.[2] A recent study identified older age, female gender, lower income, corticosteroid prescription, and methotrexate prescription to be associated with increased risk of hospitalization among patients with sarcoidosis.[8] Prior studies have additionally found hospitalization rates among sarcoidosis patients to be higher among black patients and associated with comorbid conditions.[9] Despite being established risk factors for hospitalization, we did not find female gender, anti-inflammatory treatment, race, or comorbid conditions to be associated with respiratory failure-related hospitalization among our SAPH cohort. It is important to note that these previously identified risk factors for hospitalization were for patients with sarcoidosis in general, as opposed to patients with SAPH specifically.

Given this, it may be possible that hospitalization risk among those with SAPH is driven by PH risk factors. N-terminal pro-brain natriuretic peptide, anemia, and renal dysfunction have been identified as independent predictors of 2-year hospitalization in patients with Group 1 pulmonary arterial hypertension (PAH).[10] Therapy with certain vasodilators has been found to improve morbidity in patients with PAH, including reducing hospitalizations.[11,12] While we did not find renal dysfunction or BNP to be associated with hospitalization risk among our SAPH cohort, we did find that pulmonary vasodilator treatment was associated with reduced risk of hospitalization, similar to the effect of certain pulmonary vasodilators in PAH.

While there are studies establishing risk factors for hospitalization and morbidity among patients with sarcoidosis and patients with PH separately, to our knowledge this is the first study to examine predictors of hospitalization among patients with SAPH. Many of the risk factors that were found for both sarcoidosis and PH were not predictive of hospitalization risk among our SAPH cohort. This suggests difficulty exists in prognosticating morbidity among patients with SAPH, specifically those with severe disease warranting transplantation evaluation. However, we demonstrate that pulmonary vasodilator therapy is associated with significantly reduced risk of hospitalization among those with SAPH. This is an important finding that could help guide decision-making in terms of treating PH in those with SAPH, for which guidelines and recommendations are uncertain.

Limitations of our study include its retrospective nature, as well as emphasis on a specific subset of patients with SAPH. Given that this study focused on patients with SAPH undergoing lung transplantation evaluation, these findings may not be generalizable to those with less severe lung disease or those who may not be candidates for lung transplantation evaluation, such as older patients with significant comorbid conditions. Additionally, the clinical significance of the association between percent-predicted FEV1 and risk of hospitalization is unclear. While this may suggest that those with better lung function are at decreased risk of hospitalization for respiratory failure, we would expect a similar association with FVC. However, it is encouraging that we find a potential benefit to pulmonary vasodilator therapy in a group of patients with such severe lung and pulmonary vascular disease. Further prospective studies are required to fully elucidate risk factors for hospitalization among patients with SAPH and the benefit of pulmonary vasodilator therapy in these patients.

AUTHOR CONTRIBUTIONS

Shameek Gayen contributed to the study design, data collection, data analysis, and manuscript writing/editing. Albert J. Mamary formulated the study design and reviewed and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was performed in accordance with the ethical standards of the Western 111 IRB and the Helsinki Declaration of 1975.

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REFERENCES

1. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, Abston E, Bernstein RC, Blankstein R, Chen ES, Culver DA, Drake W, Drent M, Gerke AK, Ghobrial M, Govender P, Hamzeh N, James WE, Judson MA, Kellermeyer L, Knight S, Koth LL, Poletti V, Raman SV, Tukey MH, Westney GE, Baughman RP. Diagnosis and detection of sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;201(8):e26–51. https://doi.org/10.1164/rccm.202002-0251ST
2. Duong HT, Bonham CA. Sarcoidosis-associated pulmonary hypertension: pathophysiology, diagnosis, and treatment. Clin Pulm Med. 2018;25(2):52–60. https://doi.org/10.1097/CPM.0000000000000252
3. Shorr AF, Helman DL, Davies DB, Nathan SD. Pulmonary hypertension in advanced sarcoidosis: epidemiology and clinical characteristics. Eur Respir J. 2005;25(5):783–8. https://doi.org/10.1183/09031936.05.00083404
4. Arcasoy SM, Christie JD, Pochettino A, Rosengard BR, Blumenthal NP, Bavaria JE, Kotloff RM. Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest. 2001;120(3):873–80. https://doi.org/10.1378/chest.120.3.873
5. Tanizawa K, Handa T, Nagai S, Ikezoe K, Kubo T, Yokomatsu T, Ueda S, Fushimi Y, Ogino S, Watanabe K, Nakatsuka Y, Hirai T, Izumi T. Lung function decline in sarcoidosis. Respir Investig. 2022;60(4):551–61. https://doi.org/10.1016/j.resinv.2022.02.009
6. Shlobin OA, Kouranos V, Barnett SD, Alhamad EH, Culver DA, Barney J, Cordova FC, Carmona EM, Scholand MB, Wijsenbeek M, Ganesh S, Lower EE, Engel PJ, Wort J, Price L, Wells AU, Nathan SD, Baughman RP. Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: results from an international registry. Eur Respir J. 2020;55(5):1901747. https://doi.org/10.1183/13993003.01747-2019
7. Gupta R, Baughman RP, Nathan SD, Wells AU, Kouranos V, Alhamad EH, Culver DA, Barney J, Carmona EM, Cordova FC, Huitema M, Scholand MB, Wijsenbeek M, Ganesh S, Birring SS, Price LC, Wort SJ, Shlobin OA. The six-minute walk test in sarcoidosis associated pulmonary hypertension: results from an international registry. Respir Med. 2022;196:106801. https://doi.org/10.1016/j.rmed.2022.106801
8. Fidler LM, Gershon A, Fisher JH, Stanbrook MB, To T, Balter M. Hospitalizations in sarcoidosis: a cohort study of a universal healthcare population. Ann Am Thorac Soc. 2021;18(11):1786–94. https://doi.org/10.1513/AnnalsATS.202009-1134OC
9. Foreman MG, Mannino DM, Kamugisha L, Westney GE. Hospitalization for patients with sarcoidosis: 1979–2000. Sarcoidosis Vasc Diffuse Lung Dis. 2006;23(2):124–9. https://www.ncbi.nlm.nih.gov/pubmed/17937108
10. Sargento L, Longo S, Lousada N, dos Reis RP. Nt-ProBNP, anaemia and renal function are independent predictors of hospitalization in outpatients with pulmonary artery hypertension. Rev Port Pneumol. 2015;21(1):46–7. https://doi.org/10.1016/j.rppnen.2014.09.004
11. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522–33. https://doi.org/10.1056/NEJMoa1503184
12. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BKS, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809–18. https://doi.org/10.1056/NEJMoa1213917

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