Sarcoidosis lung transplantation waitlist mortality, a national registry database study

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Shareable abstract (@ERSpublications)
Lung transplant candidates with advanced pulmonary sarcoidosis have a disproportionately high waitlist mortality, and the grouping of these patients in the Lung Allocation Score and Composite Allocation System should be revised @dcfleitassosa https://bit.ly/3BDOgvq

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Abstract

Background The Lung Allocation Score (LAS) prioritises lung transplantation candidates, balancing waitlist mortality and post-transplant survival. The score groups sarcoidosis candidates based on mean pulmonary artery pressure: those with ⩽30 mmHg (sarcoidosis A) are grouped with COPD and those with >30 mmHg (sarcoidosis D) with idiopathic pulmonary fibrosis (IPF). We hypothesise that sarcoidosis candidates have a higher waitlist mortality than other candidates within their LAS grouping.

Methods This is a retrospective cohort study of consecutive lung transplantation candidates from the Scientific Registry of Transplant Recipients database from May 2005 to May 2019. We included candidates aged ⩾18 years diagnosed with sarcoidosis, COPD or IPF. Univariate, multivariate and survival estimate analyses were performed.

Results We identified 385 sarcoidosis A, 642 sarcoidosis D, 7081 COPD and 10 639 IPF lung transplantation candidates. 17.3% of sarcoidosis D, 14.8% of IPF, 14.3% of sarcoidosis A and 9.8% of COPD candidates died awaiting transplant. Sarcoidosis A was an independent risk factor for waitlist mortality. Sarcoidosis A had a lower waitlist survival probability compared to COPD. Sarcoidosis D had the highest waitlist mortality. IPF candidates had lower waitlist survival probability than sarcoidosis D in the first 60 days after listing.

Conclusion Based on our results, the grouping of candidates with sarcoidosis in allocation systems should be revised to mitigate waitlist mortality disparity.

Introduction

Introduced in May 2005 in the United States, the Lung Allocation Score (LAS) system uses diagnosis, functional status, exercise capacity, lung function, haemodynamic data and supplemental oxygen needs to prioritise patients with the highest urgency of lung transplantation while considering the chances of survival post-transplant [1]. The implementation of the LAS system in May 2005 immediately shortened the time to transplantation and decreased waitlist mortality for the most commonly transplanted lung diseases: idiopathic pulmonary fibrosis (IPF), COPD and cystic fibrosis [2, 3]. Patients with IPF benefited most from the LAS [4]. It is less clear how the LAS affected lung transplantation waitlist outcomes in patients with less commonly transplanted lung diseases, such as advanced pulmonary sarcoidosis (APS) [5].

Sarcoidosis is a multisystem inflammatory disease characterised by noncaseating granulomas, with >90% of patients having lung involvement. Most patients with pulmonary sarcoidosis have a relatively benign

disease course [6–11]. However, despite optimal medical management, a small percentage of sarcoidosis patients progresses to APS, a group for whom lung transplantation is often required for improvement in quality of life and survival [6, 12]. In the United States, APS is a relatively uncommon indication for lung transplantation candidacy [13]. In contrast, COPD and IPF are the most common indications for lung transplantation candidacy [13]. Despite this disparity, post-transplant survival seems to be similar between APS and other indications [14–16]. However, less is known about APS candidacy survival and transplant efficiency.

Under the LAS and the Composite Allocation System (CAS), sarcoidosis patients with a mean pulmonary artery pressure (mPAP) ⩽30 mmHg are assigned to group A with obstructive lung disease. APS patients with mPAP >30 mmHg are grouped in group D with fibrotic lung disease [1, 9, 12, 17, 18]. Our prior single-centre experience found higher waitlist mortality in sarcoidosis compared to COPD and IPF [19]. We hypothesise that at a national level, sarcoidosis patients have a higher transplant waitlist mortality than patients in the same grouping diagnosis. As a secondary objective, we aim to determine whether sarcoidosis is an independent risk factor for waitlist mortality and identify other factors that impact waitlist mortality.

Materials and methods

Study population

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, United States Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the United States government. We are including lung transplant candidate data of the SRTR database since the implementation of the LAS in May 2005 to May 2019.

We restricted our analysis to adult lung transplant candidates (aged ⩾18 years) with the primary diagnosis of APS, COPD, IPF as defined in the OPTN database. Our research proposal was reviewed, and the use of data was approved by the SRTR.

Statistical analysis and end-points

Our analysis focused on comparing APS with mPAP ⩽30 mmHg (sarcoidosis A) to COPD and APS with mPAP >30 mmHg (sarcoidosis D) to IPF. Our primary outcome, waitlist mortality, was the composite of candidates who died on the waitlist and those who were removed due to clinical deterioration (*i.e.* were too sick to receive a transplant or unsuitable). Other reason for removal from waitlist were reported as "other" and included refused transplant, removed after transfer to another centre, candidate removed in error, unable to contact candidate and other reasons.

We analysed variables that are incorporated in the LAS calculator formula and additional clinically relevant variables. We included baseline characteristics, ABO blood type, race, height, maximum donor height, body mass index (BMI) and surgical preference for single *versus* double lung for transplantation, as well as clinical variables such as oxygen requirement, steroid use >5 mg·day^{-1}, pulmonary function testing, 6-min walk distance (6MWD), pulmonary haemodynamics from right heart catheterisation including mPAP and cardiac output and functional status at time of listing. Transplant candidacy waitlist outcome variables included time on waitlist and reason for removal from candidacy waitlist. We looked at the overall waitlist mortality, and more specifically at the waitlist mortality up to 1 year after listing.

All continuous variables are presented as mean±SD or median (interquartile range) unless otherwise stated. Categorical variables are compared using the Pearson Chi-squared test, ANOVA one-way or Fisher exact test where applicable. Continuous variables are compared between groups using the Mann–Whitney U-test when they did not show normality. All statistical tests are two-tailed, and p-values <0.05 were considered to indicate statistical significance. Statistical analyses were performed with the use of STATA (v14; StataCorp, College Station, TX, USA). Waitlist survival probability was determined *via* Kaplan–Meier curve. Multivariate Cox regression was used to determine whether the diagnosis of sarcoidosis was an independent risk factor for waitlist mortality.

Results

We identified 385 sarcoidosis A, 642 sarcoidosis D, 7081 COPD and 10 639 IPF candidates listed for lung transplantation. Overall, 13% died of these listed candidates died on the waitlist. Baseline characteristics

are described in table 1. Sex was similarly distributed by diagnosis for COPD and sarcoidosis, but only 29.2% of patients with IPF were female. In general, sarcoidosis candidates were younger, more often black and less likely to have a smoking history. In contrast, IPF and COPD candidates were >90% white. Latino ethnicity candidates represented 9.3% of IPF, 3.9% of sarcoidosis A, 1.6% of sarcoidosis D and 1.2% of COPD patients. Blood type O was the most frequent blood type. History of cigarette use was reported more frequently in COPD (96.2%). Height and BMI values between groups were overall numerically similar, although statistically different (table 1).

Oral corticosteroid use was more frequent in sarcoidosis. Diabetes mellitus was more frequent in sarcoidosis A when compared to COPD ($p<0.0001$), but similar between IPF and sarcoidosis D ($p=0.14$) (table 1).

Surgical preference for double lung transplantation was more frequent in sarcoidosis group A and D, as compared to COPD and IPF, respectively ($p<0.0001$). Clinical characteristics and LAS variables are compared by group in table 2. Based upon the LAS functional status assessment, 28.3% of sarcoidosis A and sarcoidosis D patients required no assistance *versus* 35.1% of COPD patients and 31% of IPF patients ($p<0.0001$). Sarcoidosis candidates required higher supplemental oxygen than their LAS group counterparts. All groups were similar regarding their need of life support. Cardiac output was similar between COPD and sarcoidosis A. Group D sarcoidosis candidates had higher mPAP than IPF patients (table 2).

Overall, 81.1% of all candidates underwent lung transplantation, 13% died and 4.9% were removed from the list for other reasons. Waitlist mortality was highest among sarcoidosis D candidates (17.3%), followed by IPF (14.8%) and sarcoidosis A (14.3%). COPD had the lowest waitlist mortality (9.8%). 80.5% of candidates with COPD, 75% of sarcoidosis A, 82.2% with IPF and 69% of candidates with sarcoidosis D were transplanted. Univariate analysis showed statistically significant higher waitlist mortality among sarcoidosis A candidates than COPD ($p=0.013$) and higher waitlist mortality among sarcoidosis D candidates than IPF patients ($p<0.0001$). A table with detailed reasons for waitlist removal is provided in the supplementary material.

TABLE 1 Baseline characteristics by listing diagnosis

	COPD	Sarcoidosis A	p-value	IPF	Sarcoidosis D	p-value
Patients	7081	385		10 639	642	
Female	3613 (51.0)	209 (54.3)	0.21	3107 (29.2)	340 (53.0)	<0.0001
Age at listing years	60.5±6.4	54.1±9.2	<0.0001	61.0±8.7	53.0±8.0	<0.0001
Race (SRTR)			<0.0001			<0.0001
Asian	25 (0.4)	8 (2.1)		290 (2.7)	6 (0.9)	
Black	537 (7.6)	208 (54.0)		658 (6.2)	466 (72.6)	
Other	37 (0.5)	4 (1.1)		77 (0.7)	6 (0.9)	
White	6482 (91.5)	165 (42.9)		9614 (90.4)	164 (25.5)	
Latino ethnicity	85 (1.2)	15 (3.9)	<0.0001	993 (9.3)	10 (1.6)	<0.0001
Height cm	168.2±10.0	168.6±10.1	0.50	171.4±10.3	169.1±9.5	<0.0001
BMI kg·m^{-2}	24.6±4.5	25.9±4.4	<0.0001	27.8±38.7	26.6±4.5	0.004
Minimum acceptable donor height cm	145.9±17.4	143.4±16.8	0.005	146.1±16.7	144.5±16.7	0.015
Maximum acceptable donor height cm	195.7±16.9	192.8±18.9	0.004	194.9±18.4	192.7±18.8	0.003
Blood type			<0.0001			<0.0001
A	2909 (41.1)	123 (31.9)		4078 (38.3)	183 (28.5)	
AB	288 (4.1)	13 (3.4)		383 (3.6)	32 (5.0)	
B	753 (10.6)	63 (16.4)		1128 (10.6)	120 (18.7)	
O	3080 (43.5)	186 (48.3)		4988 (46.9)	304 (47.4)	
Other blood type	51 (0.7)	0 (0.0)		62 (0.6)	3 (0.5)	
Diabetes	645 (9.1)	78 (20.3)	<0.0001	2058 (19.3)	113 (17.6)	0.14
Steroids (>5 mg·day^{-1})	1295 (30.2)	118 (57.6)	<0.0001	2537 (43.6)	216 (60.2)	<0.0001
Preference double lung	3269 (46.2)	264 (68.6)	<0.0001	4151 (39.0)	542 (84.4)	<0.0001
History of cigarette use	6807 (96.2)	170 (44.2)	<0.0001	6473 (60.9)	328 (51.6)	<0.0001
Initial listing LAS	33.2±6.2	38.3±9.4	<0.0001	48.1±17.6	43.6±14.5	<0.0001
LAS average	33.3±6.4	39.7±11.1	<0.0001	50.8±17.8	45.5±16.0	<0.0001

Data are presented as n, n (%) or mean±SD, unless otherwise stated. IPF: idiopathic pulmonary fibrosis; SRTR: Scientific Registry of Transplant Recipients; BMI: body mass index; LAS: Lung Allocation Score.

TABLE 2 Clinical variables by listing diagnosis

	COPD	Sarcoidosis A	p-value	IPF	Sarcoidosis D	p-value
Patients	7081	385		10 639	642	
Functional status			<0.0001			<0.001
No assistance needed	2526 (35.7)	109 (28.3)		3297 (31.0)	182 (28.3)	
Some assistance needed	4328 (61.1)	247 (64.2)		5755 (54.1)	383 (59.7)	
Total assistance needed	160 (2.3)	28 (7.3)		1491 (14.0)	63 (9.8)	
Unknown	67 (0.9)	1 (0.3)		96 (0.9)	14 (2.2)	
FVC % pred	54.6±16.5	45.3±14.8	<0.001	48.4±16.5	48.6±16.4	0.78
mPAP mmHg	25.7±7.3	23.9±4.7	<0.001	25.7±9.7	43.4±10.4	<0.001
Cardiac output L·min^{-1}	5.2±1.4	5.3±1.3	0.16	5.4±1.4	5.1±1.6	<0.001
Oxygen requirement at rest L·min^{-1}	3.0±2.1	3.7±3.1	0.0006	5.2±5.1	4.7±4.1	0.042
6MWD ft	730.3±367.7	830.9±418.1	0.0006	768.1±495.1	723.3±409.1	0.044
Patient on life support	122 (1.7)	8 (2.1)	0.61	579 (5.4)	26 (4.1)	0.14
Mechanical ventilation	59 (0.8)	4 (1.0)	0.67	396 (3.7)	8 (1.2)	0.001
P_{CO_2} mmHg	49.6±11.8	45.4±9.8	<0.0001	42.4±9.2	44.3±11.2	0.005

Data are presented as n, n (%) or mean±SD, unless otherwise stated. IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; mPAP: mean pulmonary artery pressure; 6MWD: 6-min walk distance; P_{CO_2}: carbon dioxide tension.

Monthly COPD waitlist mortality remained similarly distributed up to 12 months after listing (figure 1). Sarcoidosis A and D showed a bimodal peak; in months 1 and 4 an increase in death on the waitlist was seen. Most IPF waitlist mortality occurred within the first 2 months of listing.

Within group A there was no difference in wait time to transplant. Sarcoidosis A waitlist deaths occurred earlier than COPD waitlist deaths. However, in group D, sarcoidosis D patients waited significantly longer than IPF patients. IPF waitlist deaths occurred earlier than sarcoidosis D deaths (table 3).

The Kaplan–Meier waitlist survival estimate shows a lower candidate survival probability for sarcoidosis A than COPD, with an early and clear separation of the curves (log-rank p<0.001) (figure 2).

Multivariate Cox regression analysis of sarcoidosis A and COPD showed that the diagnosis of sarcoidosis was associated with increased waitlist mortality (hazard ratio (HR) 1.91, 95% CI 1.25–3.60) independent of other risk factors (age, race, BMI, diagnosis of diabetes, functional status, 6MWD, forced vital capacity (FVC), oxygen requirement, life support, creatinine, cardiac output, mPAP, height, maximum donor height, blood type or preference for double lung at listing) (table 4). Moreover, our model showed that requiring ⩾3 L·min^{-1} of oxygen, total assistance and higher mPAP constituted independent risk factors for candidate waitlist mortality. At the same time, having a carbon dioxide tension >40 mmHg, 6MWD ⩾150 ft, and age <65 years decreased the chances of waitlist death and behaved as protective factors (figure 3).

The survival analysis for patients with IPF and sarcoidosis D (figure 4) showed significantly lower candidate waitlist survival probability among IPF patients (log-rank p=0.0075). Subsequent analysis, available in the supplementary material, showed that the difference is probably derived by IPF candidate's waitlist death in the first 60 days (supplementary figures S1 and S2). After 60 days, both groups showed a similar survival probability.

Multivariate Cox regression analysis of sarcoidosis D and IPF showed that IPF was associated with increased waitlist mortality (HR 1.807, 95% CI 1.423–2.295), probably due to the higher mortality seen in the first 60 days. Oxygen requirement (HR 1.75, 95% CI 1.457–2.103) and mPAP >30 mmHg (HR 1.329, 95% CI 1.176–1.503) were also associated with increased transplant waitlist mortality. The IPF *versus* sarcoidosis D model was also adjusted for age, race, BMI, diagnosis of diabetes, functional status, 6MWD, FVC, oxygen requirement, life support, creatinine, cardiac output, mPAP, height, maximum donor height, blood type and preference for double lung at listing (supplementary table S1).

Discussion

This large retrospective analysis based on the SRTR database constitutes the first attempt to evaluate the assumptions made about APS during the development of the LAS and sheds light on its impact on waitlist mortality. We showed that candidates with sarcoidosis A had a disproportionately high waitlist mortality (14.2%) when compared to COPD (9.8%).

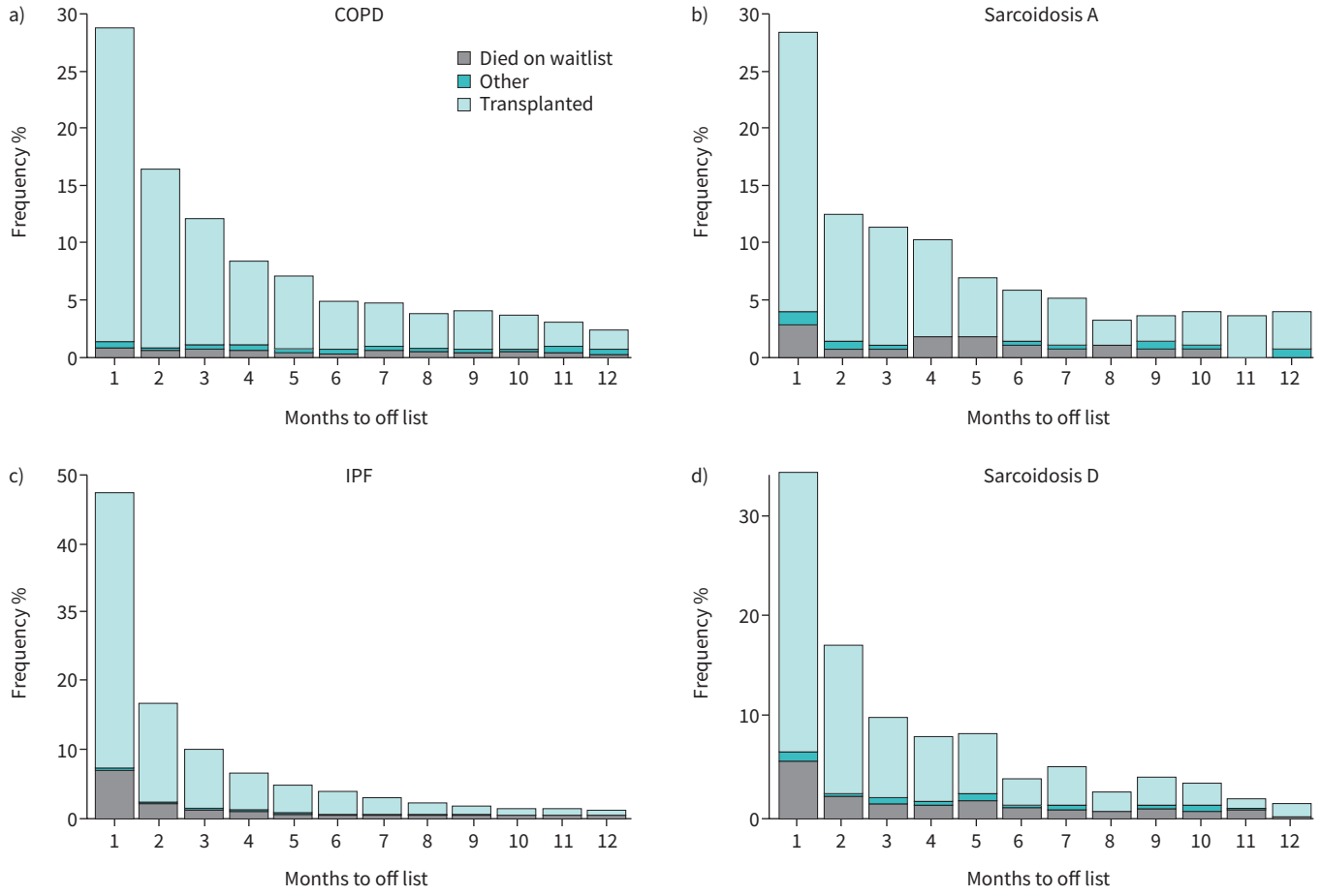

FIGURE 1 Waitlist removal reasons by diagnosis per month in the first year after listing, expressed as percentages. a) COPD; b) sarcoidosis A; c) idiopathic pulmonary fibrosis (IPF); and d) sarcoidosis D.

Sarcoidosis A candidates died earlier and had a lower survival probability at 1 year after listing. Furthermore, in our multivariate analysis the diagnosis of sarcoidosis A was an independent risk factor for waitlist death and patients had a 94.1% higher chance of dying on the waitlist when compared to COPD. We would like to emphasise that the risk conferred by the diagnosis of sarcoidosis A is independent of other clinical factors that affect urgency, including factors that significantly affect organ allocation such as height, surgical preference and ABO blood type.

We acknowledge the immediate and well documented positive impact that the LAS had on waitlist survival compared with the previous seniority-based system in the United States and how this was replicated by Germany and the Netherlands after the adoption of the LAS [20, 21]. The waitlist survival benefit is seen across the common indications for lung transplantation.

TABLE 3 Time on the transplant list by reasons for removal and listing diagnosis

	COPD	Sarcoidosis A	p-value	IPF	Sarcoidosis D	p-value
Transplant days	92.0 (30.0–266.0)	106.0 (35.0–307.0)	0.37	38.0 (12.0–109.0)	71.0 (22.0–203.0)	<0.0001
Death days	375.0 (145.0–766.0)	189.0 (103.0–461.5)	0.003	42.0 (11.0–162.0)	128.0 (27.0–332.0)	<0.0001
Other reasons days	567.5 (273.5–1000.5)	569.0 (273.0–1505.0)	0.41	330.0 (94.0–639.0)	430.0 (172.5–924.5)	0.020
Overall days to off list	128.0 (38.0–378.0)	141.5 (47.0–375.0)	0.57	41.0 (12.0–123.0)	97.0 (25.0–273.0)	<0.0001

Data are presented as median (interquartile range), unless otherwise stated. IPF: idiopathic pulmonary fibrosis.

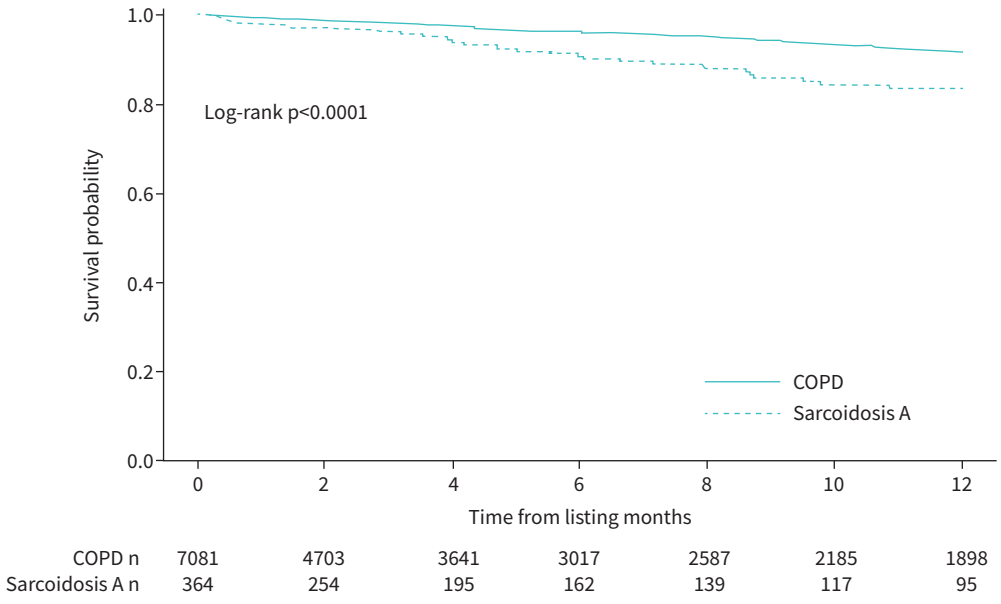

FIGURE 2 Comparison of the survival probability in the first year after listing of sarcoidosis A and COPD.

The adequacy of grouping of patients in the LAS system and assessing survival before transplant is less certain. However, for less common indications of lung transplantation there appears to be a need to revisit some assumptions that were necessary during the development of the LAS. Chen *et al.* [5] analysed the impact of the LAS on PAH, and while the chances of transplantation improved, there was an unacceptably high risk of dying on the waitlist. Comparably, our research shows that further consideration needs to be given to how we classify patients with sarcoidosis and how we calculate their risk of dying on the waitlist.

TABLE 4 Multivariate analysis sarcoidosis A *versus* COPD

	HR (95% confidence limit)	p-value
Sarcoidosis	1.941 (1.261–2.986)	0.0152
Age <65 years	0.712 (0.541–0.937)	0.2571
Race black	1.224 (0.863–1.735)	0.2915
BMI <30 kg·m^{-2}	1.201 (0.854–1.689)	0.5062
Diabetes	0.872 (0.583–1.305)	0.3901
Some assistance needed	1.123 (0.862–1.464)	<.0001
Total assistance needed	9.653 (6.080–15.323)	0.2249
FVC ⩾70% pred	0.768 (0.501–1.177)	0.0470
Oxygen requirement at rest ⩾3 L·min^{-1}	1.370 (1.004–1.870)	<.0001
6MWD ⩾150 ft	0.427 (0.280–0.651)	0.1294
Life support on a ventilator	0.389 (0.115–1.318)	0.0136
P_{CO2} >40 mmHg	0.627 (0.433–0.908)	<.0001
mPAP mmHg	1.057 (1.045–1.070)	0.1731
Cardiac output ⩾4 L·min^{-1}	0.809 (0.596–1.097)	0.6979
Creatinine ⩾2 mg·dL^{-1}	1.490 (0.199–11.147)	0.0551
Blood type AB	1.850 (0.987–3.469)	0.3345
Blood type B	1.227 (0.810–1.860)	0.1171
Blood type O	1.232 (0.949–1.600)	0.1516
Blood type other/A	2.095 (0.762–5.756)	0.7887
Height cm	1.002 (0.988–1.016)	0.0610
Lung preference double lung	1.264 (0.989–1.616)	0.8405
Candidate maximum height	0.999 (0.992–1.007)	0.8405

HR: hazard ratio; BMI: body mass index; FVC: forced vital capacity; 6MWD: 6-min walk distance; P_{CO_2}: carbon dioxide tension; mPAP: mean pulmonary artery pressure.

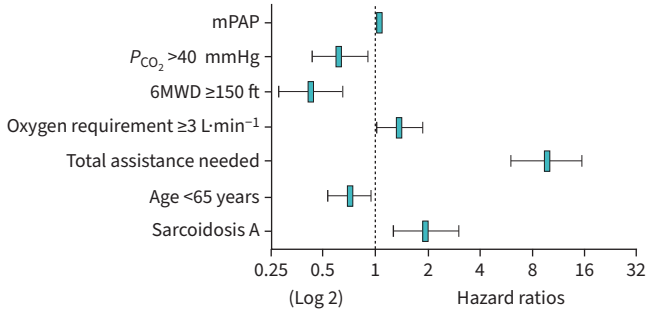

FIGURE 3 Hazard ratios (95% confidence limits) of statistically significant variables of the multivariable analysis comparing sarcoidosis A and COPD. Statistically nonsignificant variables considered in the multivariable analysis were race, body mass index, diabetes, functional status, cardiac output, lung preference, height and creatinine. mPAP: mean pulmonary artery pressure; P_{CO_2}: carbon dioxide tension; 6MWD: 6-min walk distance.

EGAN *et al.* [1] describe how, in the development of the LAS, "Diagnoses that did not have enough statistical information upon which to base a grouping decision were assigned to one of the four groups entirely on clinical grounds". They explain that sarcoidosis mortality on their analysis was different to their grouping diagnosis and the solution given for this problem was the stratification of sarcoidosis by mPAP with a cut-off of 30 mmHg. It was assumed that sarcoidosis A had a similar mortality to COPD on the waitlist and sarcoidosis D behaved more like IPF. However, contrary to this assumption, our analysis indicates that this assumption is not true for sarcoidosis A. We theorise that additional pathophysiological risk factors related to sarcoidosis, which may include comorbid conditions not accounted for or considered in the LAS calculation, contribute to high waitlist mortality independent of the presence or absence of pulmonary hypertension, and thus the current medical urgency is underestimated.

Sarcoidosis A candidates are at higher risk of dying while they are waitlisted for transplant in comparison to COPD, as is evident in the univariate, multivariate and the Kaplan–Meier analyses presented in this study. A revision of how the LAS groups sarcoidosis should be strongly considered to correct this disparity of waitlist survival. These results are especially relevant as we transition to the continuous organ distribution system that will use a composite allocation score (CAS) that maintains some of the LAS

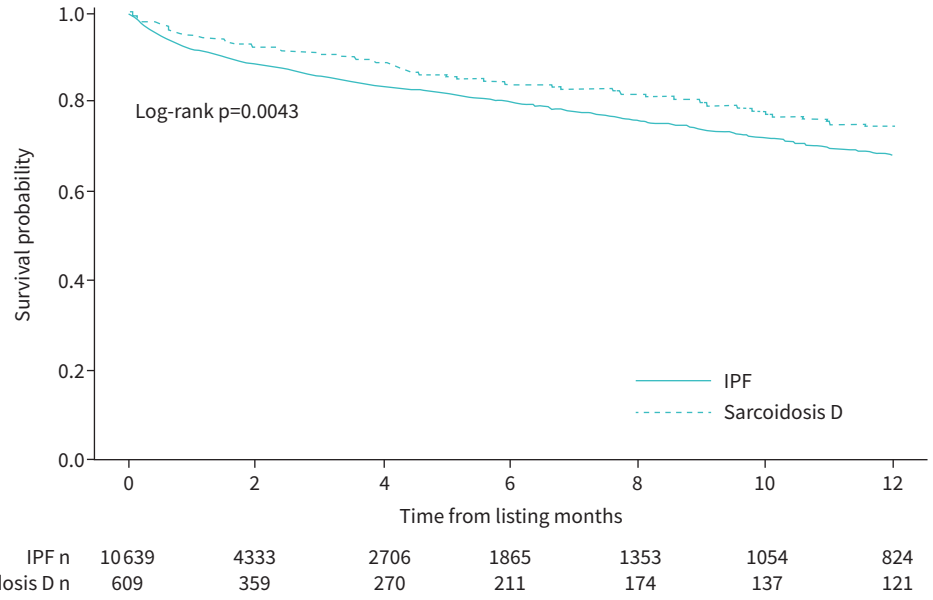

FIGURE 4 Comparison of the survival probability in the first year after listing of sarcoidosis D and idiopathic pulmonary fibrosis (IPF).

assumptions when calculating medical urgency, including the current grouping of patients with sarcoidosis [18]. In the CAS, medical urgency has the same weight as post-transplant survival, highlighting the relevance of revisiting how we consider sarcoidosis risk of waitlist death or medical urgency.

The comparison of sarcoidosis D and IPF waitlist mortality is more nuanced and complex. We see the highest absolute percentage of waitlist death in sarcoidosis D (17.3%), followed by IPF (14.8%), but the multivariate and Kaplan–Meier analyses identified IPF as having higher predicted risk of 1-year waitlist death.

Our analysis suggests that IPF waitlist death occurred disproportionately in the first 60 days after listing. There is a need for IPF patients to be diagnosed and referred early for lung transplantation evaluation, considering the predictable downward clinical course of advanced IPF [22]. It is interesting to note the further analysis showing that after surviving 60 waitlist days, IPF and sarcoidosis D have similar chances of waitlist survival. These results confirm the appropriate assumptions of the LAS for sarcoidosis D grouping, which identified the higher medical need of these patients.

Our study contributes to the understanding of waitlist mortality risk factors for APS. The last evaluation of factors analysing waitlist mortality for APS was undertaken by Shorr *et al.* [23, 24] using the United Network for Organ Sharing (UNOS) database and including patients from 1995 to 2000. They concluded that race, pulmonary hypertension and oxygen requirement played a role in waitlist mortality. Our study includes all sarcoidosis lung transplant candidates and their waitlist outcomes since the LAS implementation in May 2005. Our multivariate analysis for sarcoidosis A *versus* COPD identified the following independent risk factors for waitlist candidate mortality: diagnosis of sarcoidosis A, use of $\geqslant 3\ L \cdot min^{-1}$ of oxygen, requiring total physical assistance and higher mPAP. In the comparison of IPF and sarcoidosis D, mPAP and use of $\geqslant 3\ L \cdot min^{-1}$ of oxygen were also independent waitlist mortality risk factors. Contrary to the findings of Shorr *et al.* [24], race was not a significant contributor in both multivariate analyses.

Other clinically relevant variables such as mechanical ventilation or extracorporeal membrane oxygenation support, height and BMI did not independently impact waitlist death in our group comparison. It is important to note that the variables that affect organ matching and procurement such as patient height, maximum candidate donor height, blood type and surgical preference for double lungs did not have a statistically significant impact on risk of waitlist mortality. This differs notably from prior studies, which have shown that shorter stature and O blood type are predictive of worse transplant waitlist outcomes, including waitlist mortality [25–28].

The limitations of the present study include all those associated with observational retrospective studies, including susceptibility to selection bias, confounding variables and missing data, present in the UNOS database. We attempted to address these limitations by utilising multivariable analysis to account for confounding variables. In addition, not every clinical predictor or variable that describes disease severity or risk of waitlist death was available in the UNOS database, and certainly additional confounding variables that are not accounted for in our model could exist. For example, we did not have access to panel of reactive antibodies data by candidate or their LAS scores over time. As strengths of the study, our data include all patients listed for transplant since the implementation of the LAS system in the United States and is a description of their real-life outcomes.

Conclusion

This study describes the waitlist mortality of APS lung transplant candidates. We demonstrate that sarcoidosis candidates with mPAP $\leqslant 30$ mmHg have a significantly higher waitlist mortality when compared to COPD and this is independent of other risk factors. Other factors identified as independent predictors of waitlist mortality for sarcoidosis A and COPD are mPAP, oxygen requirement $\geqslant 3\ L \cdot min^{-1}$ and requiring total assistance. Oxygen requirement $\geqslant 3\ L \cdot min^{-1}$ was an independent risk factor for waitlist death in sarcoidosis D and IPF as well. Sarcoidosis patients with mPAP >30 mmHg had greater waitlist mortality than COPD and sarcoidosis with mPAP $\leqslant 30$ mmHg, but similar to IPF. IPF waitlist mortality was predictably higher in the first 60 days after listing, but similar to sarcoidosis with mPAP >30 mmHg thereafter. APS lung transplant candidates have unacceptably high waitlist mortality and therefore the allocation systems for lung transplantation (LAS and CAS) should be modified by placing APS in a distinct group which reflects their substantial risk of waitlist mortality and unique pathophysiology.

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