Lung transplantation for pulmonary sarcoidosis. Twenty-five years of experience in the USA

ABSTRACT

Objective Lung transplantation is the ultimate treatment for end-stage pulmonary sarcoidosis. Post-transplant survival outcomes remain unclear.

Methods Survival models were used to assess survival and graft outcomes in patients with sarcoid among 20 896 lung transplants performed in the USA.

Results 695 lung recipients were transplanted for pulmonary sarcoidosis. Sarcoid lung recipients had similar median survival rate (69.7 months (IQR 60.2–79.3)) compared with the non-sarcoid lung recipients (63.1 months (IQR 61.4–64.8), p=0.88). In multivariate Cox regression, sarcoidosis was not independently associated with worse mortality (HR 0.96 (95% CI 0.85 to 1.08), p=0.51). Among the sarcoid lung recipients, double lung transplantation (HR 0.76 (0.58 to 0.99), p=0.04) and lung allocation score era (HR 0.74 (0.56 to 0.97), p=0.03) were associated with improved survival.

Conclusions Recipients of lung transplants for pulmonary sarcoidosis had similar outcomes compared with non-sarcoid lung recipients.

INTRODUCTION

Sarcoidosis is a systemic multiorgan disorder characterised by CD4 T-lymphocytes response and non-caseating granulomata. Approximately 95% of patients with sarcoidosis develop pulmonary disease during their lifetime. A small minority progress to develop end-stage fibrocystic disease.[1] Lung transplantation is often performed in irreversible advanced cases who have failed medical therapy.[2] However, post-transplant survival and graft outcomes remain unclear, primarily due to the recurring nature of the disease,[3] extrapulmonary involvement and chronic lung infections.[4] Given the paucity of data reporting outcomes of transplantation for sarcoidosis,[5–7] the objective of this study was to examine the outcomes associated with lung transplantation for pulmonary sarcoidosis in a large multicentre registry-based cohort.

PATIENTS AND METHODS

The Organ Procurement and Transplantation Network database was queried for all lung-only first-time transplants between 1987 and 2012. Patients diagnosed with sarcoidosis were compared with all other transplanted cases. The primary outcome was median survival rate. The secondary outcomes were allograft dysfunction rates.

STATISTICAL ANALYSIS

The method of Kaplan–Meier with log-rank tests were used to compare unadjusted survival rates between sarcoidosis and control groups. Multivariate Cox regression models were performed to assess the independent contribution of clinical variables on all-cause mortality in the total cohort and in the sarcoid cohorts (see online supplementary table S1).

RESULTS

Since 1987, 20 896 patients received a lung transplant, with a median follow-up of 33.5 months (range 0–268). Of those, 695 lung recipients (3.3%) were transplanted for pulmonary sarcoidosis. Compared with the non-sarcoid lung recipients, sarcoid lung recipients were of similar age (p=0.55); however, they included more female (p<0.001), fewer Caucasian (p<0.001) and more double lung transplant recipients (p<0.001). The sarcoid lung recipients had similar median survival rate (69.7 months (IQR 60.2–79.3)) compared with the non-sarcoid lung recipients (63.1 months (IQR 61.4–64.8), log-rank p=0.88) (figure 1). The two groups had similar rates of bronchioalveolitis obliterans syndrome (BOS) (p=0.42), and new O_2 requirements (p=0.9). Fewer sarcoid lung recipients underwent retransplantation (p=0.03) (table 1). Multivariate Cox regression analysis demonstrated that sarcoidosis was not independently associated with worse all-cause mortality (HR 0.96 (95% CI 0.85 to 1.08), p=0.51) (see online supplementary table S1). Among sarcoid lung recipients, only double lung transplantation (0.76 (0.58 to 0.99), p=0.04) and lung allocation score (LAS) era (0.74 (0.56 to 0.97), p=0.03) emerged as protective factors (see online supplementary tables S1–S3).

DISCUSSION

Transplantation for sarcoidosis remains uncommon, with rates ranging from 3% to 5%. Prior smaller-scale studies have reported similar survival rates to our findings, with 5-year survival rate of approximately 50%, similar to non-sarcoid lung transplants.[5 8] Additionally, sarcoid diagnosis was not associated with worse hazard of survival (HR 0.94 (0.33 to 2.67)) in one study.[8] Conversely, data remain limited on graft outcomes. In our study, similar rates of BOS, new O_2 requirements and lower rates of retransplantation supported equivalent outcomes to non-sarcoid lung recipients, in spite of the known risks of disease recurrence and its systemic nature.

The LAS system was implemented in the USA in 2005, and prioritised candidacy by expected post-transplant survival and predicted waiting list urgency in attempt to decrease the waitlist mortality rate and waiting time.[9] Our data showed that LAS was associated with improved survival

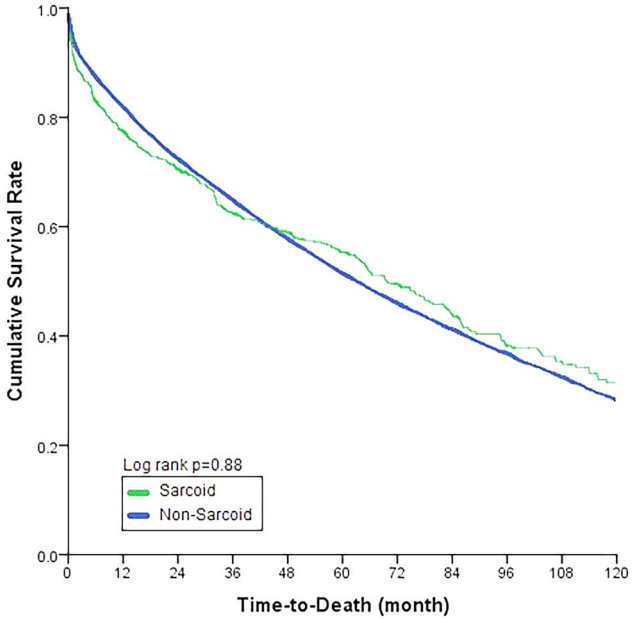

Figure 1 Unadjusted Kaplan–Meier survival curve comparing sarcoid versus non-sarcoid transplant recipients.

Table 1 Baseline characteristics and transplantation outcomes

Variable	Total (n=20 971)	Sarcoid (n=695, 3.3%)	Non-sarcoid (n=20 201, 96.7%)	p Value
Pretransplant				
Age, year, mean±SD	50.2±15.0	49.9±8.7	50.2±15.1	0.55
Males, n (%)	11 165 (53.2)	300 (43.0)	10 865 (53.6)	<0.001
Caucasian, n (%)	18 309 (87.3)	227 (32.6)	18 082 (89.2)	<0.001
Waiting time, month, median (range)	5.3 (0–195)	5.9 (0–97)	5.3 (0–195)	0.24
Life support, n (%)				
Inhaled NO	18 (0.1)	0 (0)	18 (0.1)	0.43
Prostacyclin	63 (0.3)	4 (0.5)	59 (0.3)	0.41
ECMO-bridge	43 (0.2)	0 (0)	43 (0.2)	0.22
Mechanical ventilation	312 (1.5)	5 (0.7)	307 (1.5)	0.10
Transplant				
Graft ischemic time, hour, mean±SD	4.8±1.7	5.1±1.8	4.8±1.7	<0.001
Double lung transplant, n (%)	12 011 (57.3)	480 (68.9)	11 531 (56.9)	<0.001
Donor				
Age, year, mean±SD	31.9±14.2	33.7±13.7	31.8±14.1	<0.001
Male, n (%)	12 861 (61.3)	369 (52.9)	12 492 (61.6)	<0.001
Caucasian, n (%)	14 285 (68.1)	432 (62)	13 853 (68.3)	<0.001
LAS era, post, n (%)	10 245 (49.0)	381 (54.8)	9864 (48.8)	0.002
Post-transplant				
Survival				
Median (IQR), months	63.4 (61.7–65.0)	69.7 (60.2–79.3)	63.1 (61.4–64.8)	0.88
1 year (%)	72	71	73	
5 years (%)	47	50	46	
10 years (%)	26	28	26	
Allograft dysfunction				
Retransplanted, n (%)	787 (3.8)	15 (2.2)	772 (3.8)	0.03
BOS, n (%)	7283 (35.6)	222 (31.9)	7061 (35.7)	0.42
New O_2 requirement, n (%)	1065 (27.8)	129 (27.5)	3936 (27.8)	0.9

Prostacyclin in the intravenous or inhaled formulations.
BOS, post-transplant bronchioalveolitis obliterans syndrome; ECMO, extracorporeal membrane oxygenation; LAS, lung allocation score; NO, inhaled nitric oxide.

benefit in sarcoid lung transplants up until 7 years of follow-up, after which that survival benefit started to decline. This finding suggests a potential negative long-term effect, and an unintentional consequence of emphasis on the 1-year survival. Nonetheless, implementation of the LAS system has decreased the list waiting times, which may have resulted in the improved graft outcomes identified in our study.

Lung transplantation is unique in that donor organ can be used for one recipient for a double transplant; or split to potentially benefit two patients, each with a single lung transplant. Similar to our sarcoidosis cohort, long-term outcomes also favoured double lung transplantation in patients with idiopathic pulmonary fibrosis.[10] Disease recurrence[3 5] and progression of disease despite ongoing immune suppression could potentially explain the need for double transplantation.

In conclusion, the diagnosis of sarcoidosis did not appear to be associated with worse lung transplantation survival or allograft dysfunction.

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Contributors All authors had a significant role in the study. ZT formulated the hypothesis, performed the statistical analysis and wrote the manuscript. MIH formulated the hypothesis and wrote the manuscript. SS wrote the manuscript. MP formulated the hypothesis and wrote the manuscript.

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Lung Transplantation for Pulmonary Sarcoidosis. 25 Years of Experience in the United States

Supplement Material

Methods

Data and design

This study used data from the Standard Transplant Analysis and Research (STAR) files collected by the Organ Procurement and Transplantation Network (OPTN). The STAR files report a longitudinal de-identified patient database including data on all organ donor and transplant recipients in the United States (US). The Health Resources and Services Administration of the US Department of Health and Human Services provides oversight of the activities of the OPTN. The present work was exempt from the University of Minnesota School of Medicine Institutional Review Board.

We performed a retrospective analysis of all patients undergoing lung transplantation between October 1, 1987 and December 31, 2012. Our inclusion criteria included all lung-only first-time transplants. Exclusion criteria included multiple organ transplantation. We identified patients diagnosed with sarcoidosis, and compared that group to all other transplanted cases. The control group included patients diagnosed with idiopathic pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, primary pulmonary arterial hypertension, and “other” diagnoses.

Outcomes and definitions

The primary outcome was median survival rate. The secondary outcomes were allograft dysfunction rates, namely; the incidence of bronchiolitis obliterans syndrome (BOS), re-

transplantation, or new requirement for supplemental oxygen (O2) at rest post-transplant. Data for recipient survival rates were censored at 10 years.

Statistical analysis

Continuous data were reported as mean ± standard deviation, and compared using t-test. Categorical variables were compared using chi-square (χ^2) test. The method of Kaplan Meier (KM) with log-rank testing was used to assess and compare unadjusted survival rates between sarcoidosis and control groups, in a time to death fashion. Cox proportional hazards regression analysis was used to determine the variables predictive of mortality. The outcome of interest was all-cause mortality. All other outcomes, including re-transplantation, alive or lost to follow up were censored in the model. Variables that were associated with death (vs survivors) with $p < 0.05$ in univariate analysis were eligible to be included in the multivariate model. The covariates examined include sarcoidosis, recipient sex, age, race, need for mechanical ventilation, double-lung transplantation, graft ischemic time, lung allocation score (LAS) era, and donor age, sex and race on survival in lung transplantation. Results were reported as hazard ratio (HR) with 95% confidence interval (95% CI). The Levene and Kolmogorov–Smirnov tests were used to assess for the distribution of data across the subgroups, and the proportional hazard assumptions over time were met. All data variables in the registry that reported values for less than 2/3 of the entire patient cohort were excluded from the study; these included pre-transplant hemodynamics, post-transplant forced vital capacity, forced expiratory volume, and pre-transplant oxygen requirements. All tests were two-tailed, and a p-value <0.05 was considered statistically significant. Analyses were performed using SAS version 9.0 (SAS Institute, Cary NC).

Limitations

Our study had several limitations. The retrospective nature of our study required us to assume integrity of data received from the referring transplant centers. Therefore, we were constrained by the type and form of data collected. However, given the rarity and low number of sarcoid transplants, utilization of registry data allowed for more robust analysis and facilitated hypothesis formulation. Since patient management in terms of post-transplant care is center-dependent, we cannot discount that center-specific factors may had affected our findings. Finally, we did not have any sufficient data about disease recurrence post-transplant, pulmonary function testing and the specific immunosuppressive regimens used. The universal definition of BOS, as a chronic decline in FEV1 due to the development of BOS post-transplant, represented the major criteria of diagnosis since the 1980s. However, as a consequence of new insights into the pathophysiology of BOS and the evolution of treatment strategies, the first statement on BOS diagnostic criteria was published in 1993[1], updated in 2002[2], with a likely new term use (chronic lung allograft dysfunction) in the near future[3]. Thus, we were constrained by the varying definitions used by the OPTN since 1987.

Table 1S. Multivariate predictors of all-cause mortality, in the total cohort and the sarcoid cohort.

	Total cohort		**Sarcoid cohort**	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sarcoidosis	0.96(0.85-1.08)	0.51	--	--
Age	1.003(1.002-1.005)	<0.001	1.00(0.99-1.01)	0.90
Male	1.03(0.99-1.08)	0.17	0.90(0.69-1.18)	0.45
Caucasian	0.95(0.89-1.02)	0.14	0.84(0.65-1.10)	0.21
Mechanical ventilation	1.42(1.19-1.70)	<0.001	0.99(0.24-4.03)	0.98
Double lung transplant	0.80(0.76-0.84)	<0.001	0.76(0.58-0.99)	0.04
Graft ischemic time	0.99(0.98-1.00)	0.06	1.06(0.99-1.13)	0.11
Donor-Caucasian	0.88(0.85-0.92)	<0.001	1.00(0.79-1.28)	0.99
Donor-male	1.00(0.96-1.05)	0.87	1.31(1.00-1.72)	0.05
Donor-age	1.003(1.001-1.004)	0.001	1.01(1.00-1.01)	0.21
LAS era	0.90(0.86-0.95)	<0.001	0.74(0.56-0.97)	0.03

LAS: lung allocation score.

Table 2S. Single versus double lung transplantation in the sarcoid cohort

Variable	Sarcoid (n=695)	Single-lung (n=216, 31.1%)	Double-lung (n=479, 68.9%)	p-value
Pre-transplant				
Age, year	49.9±8.7	50±8.9	49.8±8.6	0.58
Males, n(%)	300(43.0)	81(37.5)	217(45.3)	0.05
Caucasian, n(%)	227(32.6)	91(42.1)	135(28.2)	<0.001
Waiting time, month	5.9(0-97)	7.5(0-60)	5.1(0-97)	0.18
Transplant				
Life support, n(%)				
Inhaled NO	0(0)	0(0)	0(0)	1.0
Prostacyclin	4(0.5)	4(0.8)	0(0)	0.24
ECMO-bridge	0(0)	0(0)	0(0)	1.0
Mechanical ventilation	5(0.7)	5(1.0)	0(0)	0.13
Graft ischemic time, hour	5.1±1.8	4.1±1.5	5.6±1.8	<0.001
Post-LAS, n(%)	380(54.7)	66(30.6)	314(65.6)	<0.001
Donor				
Age, year	33.7±13.7	32.5±13.2	34.2±13.9	0.12
Male, n(%)	369(52.9)	127(58.8)	241(50.3)	0.04
Caucasian, n(%)	432(62)	144(66.7)	287(59.9)	0.09
Post-transplant				
Survival				
Median (IQR), month	69.7(60.2-79.3)	61.5(41.8-81.1)	82.2(64.5-100.0)	0.01
1-year (%)	71	67	72	
5-year (%)	50	43	54	
10-year (%)	28	23	32	
Allograft dysfunction				
Re-transplanted, n(%)	15(2.2)	6(2.8)	9(1.9)	0.46
BOS, n(%)	222(31.9)	83(38.4)	139(29.0)	0.01
New O_2 requirement, n(%)	129(27.5)	63(39.9)	66(21.2)	<0.001

BOS: post-transplant bronchioalveolitis syndrome. IQR: interquartile range. NO: inhaled nitric oxide, ECMO: extracorporeal membrane oxygenation. Prostacyclin in the intravenous or inhaled formulations.

Figure 1S. Unadjusted Kaplan-Meier survival curve comparing double lung transplant group to single lung transplant group in the sarcoid cohort.

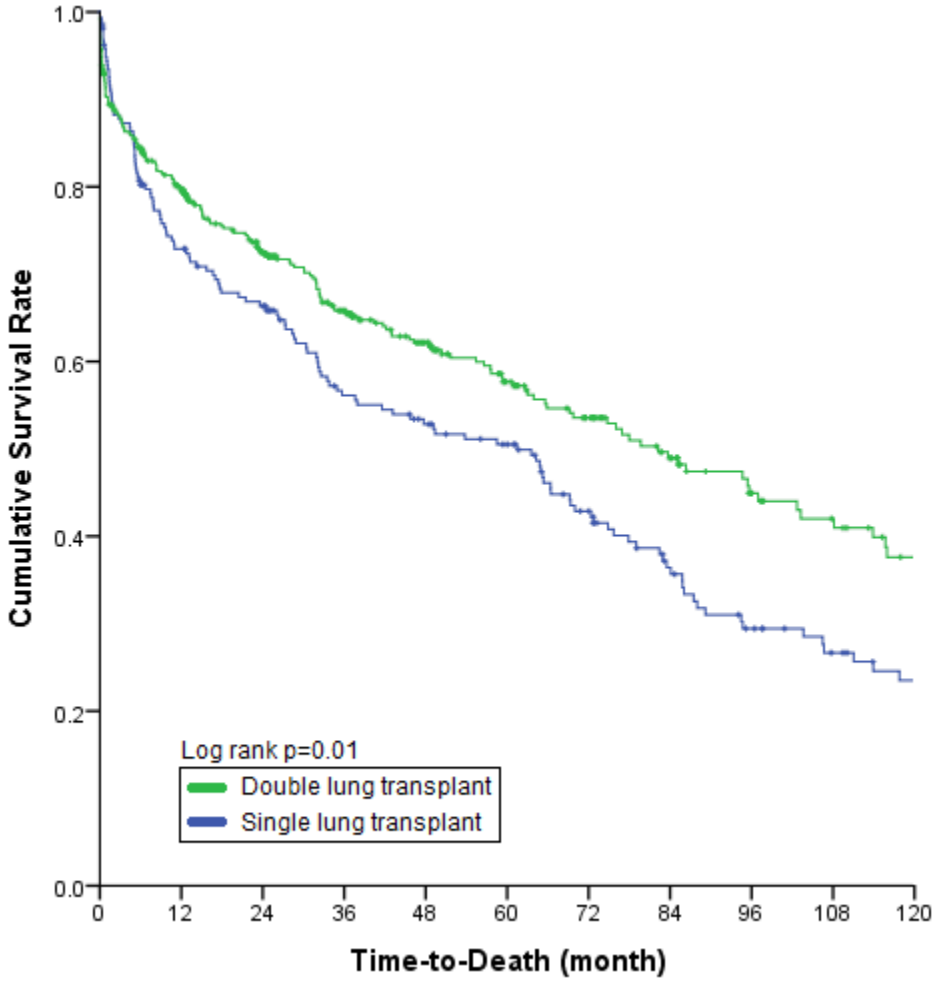
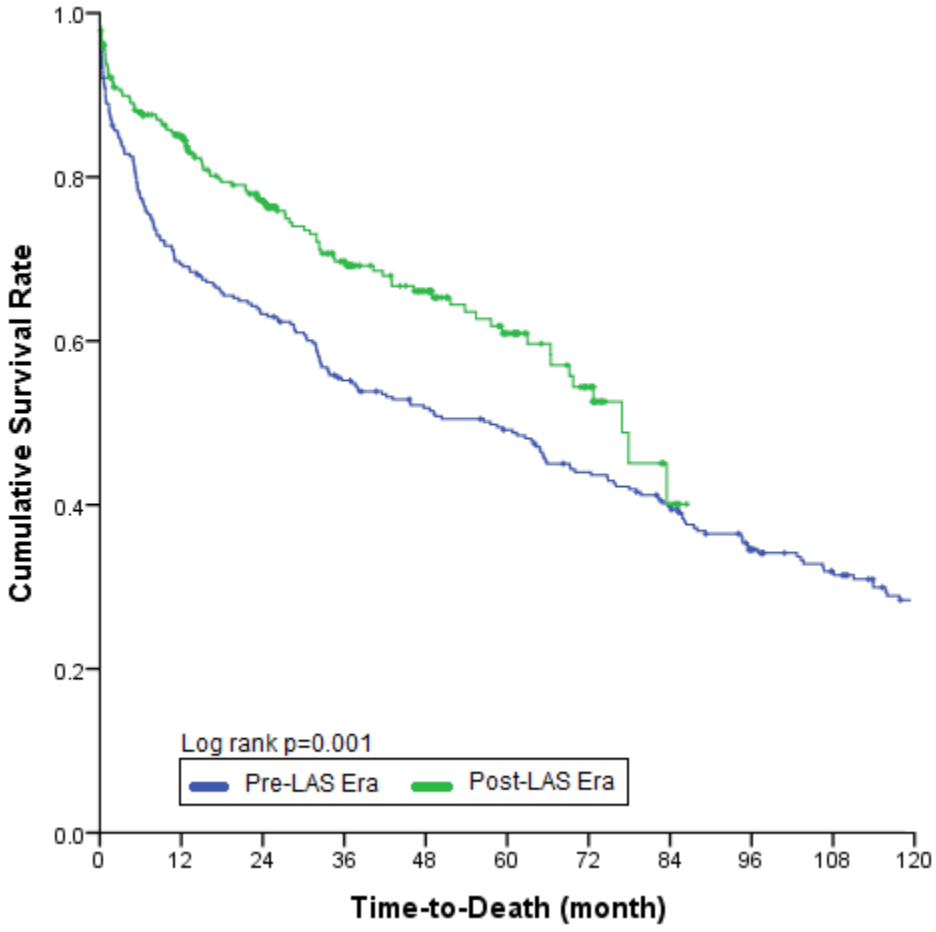


Table 3S. Lung allocation score in the sarcoid cohort

Variable	Sarcoid (n=695)	Pre-LAS (n=315, 45.3%)	Post-LAS (n=380, 54.7%)	p-value
Pre-transplant				
Age, year	49.9±8.7	47.8±8.7	51.7±8.2	<0.001
Males, n(%)	300(43.0)	112(35.6)	186(48.9)	<0.001
Caucasian, n(%)	227(32.6)	108(34.3)	118(31.1)	0.37
Waiting time, month	5.9(0-97)	9.3(0-65)	3.75(0-97)	<0.001
Transplant				
Life support, n(%)				
Inhaled NO	0(0)	0(0)	0(0)	1.0
Prostacyclin	4(0.5)	0(0)	4(1.1)	0.11
ECMO-bridge	0(0)	0(0)	0(0)	1.0
Mechanical ventilation	5(0.7)	1(0.3)	4(1.1)	0.25
Graft ischemic time, hour	5.1±1.8	4.8±1.8	5.4±1.8	<0.001
Double lung transplant, n(%)	480(68.9)	165(52.4)	314(82.6)	<0.001
Donor				
Age, year	33.7±13.7	32.5±13.7	34.7±13.7	0.04
Male, n(%)	369(52.9)	181(57.5)	187(49.2)	0.03
Caucasian, n(%)	432(62)	211(67.0)	220(57.9)	0.01
Post-transplant				
Survival				
Median (IQR), month	69.7(60.2-79.3)	57.5(39.7-75.4)	76.9(67.2-86.6)	0.001
1-year (%)	71	63	77	
5-year (%)	50	44	56	
10-year (%)	28	13	--	
Allograft dysfunction				
Re-transplanted, n(%)	15(2.2)	9(2.9)	6(1.6)	0.26
BOS, n(%)	222(31.9)	123(39.0)	99(26.1)	<0.001
New O_2 requirement, n(%)	129(27.5)	70(31.8)	59(23.7)	0.049

BOS: post-transplant bronchioalveolitis syndrome. IQR: interquartile range. NO: inhaled nitric oxide. ECMO: extracorporeal membrane oxygenation. Prostacyclin in the intravenous or inhaled formulations.

Figure 2S. Unadjusted Kaplan Meier Curve comparing post-LAS sarcoid lung transplant group to pre-LAS sarcoid lung transplant group in the sarcoid cohort.



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