Respiratory Medicine 157 (2019) 69–76

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Mortality for sarcoidosis patients on the transplant wait list in the Lung Allocation Score era: Experience from a high volume center

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ARTICLE INFO

Keywords:
Sarcoidosis
Lung transplantation
Wait list outcomes

ABSTRACT

Rationale: Sarcoidosis progresses to end stage fibrotic lung disease in 10% of patients and may necessitate lung transplantation. Organ allocation is currently determined by the Lung Allocation Score (LAS), but its performance in a sarcoidosis population has not been evaluated.

Objectives: To determine sarcoidosis-specific wait list mortality and identify predictive factors of death on the transplantation wait list.

Methods: This was a single-center retrospective study of all sarcoidosis patients listed for lung transplant from March 2012 to February 2019. We compared patients who were transplanted to those who died awaiting organs. We collected baseline listing characteristics, physiologic testing, and outcomes data. Statistical analysis was performed by 2-tailed Student's t-test, Mann-Whitney *U* test, and Chi-Square analysis (where appropriate). Receiver-operating characteristic curves were constructed for variables reaching statistical significance.

Results: Twenty eight sarcoidosis patients were included in analysis. Mortality among wait listed patients was 18%, which exceeded the mortality of COPD and IPF. LAS scores did not differ at initial listing (41 vs. 46, $p = 0.35$) or at transplant/death (41 vs. 41, $p = 0.91$); wait list times also did not statistically differ (307 days vs. 177 days, $p = 0.19$). We identified bilirubin (AUC = 0.92), DLCO (AUC = 0.84), FEV1/FVC at transplant/death (AUC = 0.85), and composite physiologic index (AUC = 0.86) as predictors of death on the transplant list. Pulmonary hypertension was not associated with death.

Conclusion: Unexpected sudden death was common in our cohort and was associated with markers of advanced fibrotic disease, not pulmonary hypertension.

1. Introduction

Sarcoidosis is a multisystem disease characterized by noncaseating granulomatous infiltration with > 90% of cases having pulmonary involvement [1]. Despite its highly prevalent lung involvement, over 80% of patients have stability or improvement in symptoms, radiographic changes, and physiologic severity [2]. Death from respiratory failure only occurs in < 10% of sarcoidosis patients [3] with a five-year mortality that approaches 10% [4]. Advanced pulmonary sarcoidosis represents 2.5–3.5% of referrals for lung transplant evaluation [5–7]. Sarcoidosis patients are evaluated and listed under the category of interstitial lung disease (which also includes idiopathic and connective tissue-disease related fibrotic lung disease) by the International Society for Heart and Lung Transplantation (ISHLT) [8].

Compared to an overall transplant wait list overall mortality of 17.2 death per 100-waitlist years, mortality for fibrotic lung disease patients exceeds 25 deaths per 100-wait list years according to the most recent Scientific Registry of Transplant Recipients (SRTR) annual report [9]. However, the mortality for sarcoidosis subpopulation has thus far only been examined in the pre-Lung Allocation Score (LAS) era [5,10,11]. The LAS was implemented in May 2005 by Organ Procurement Transplantation Network (OPTN) in an effort to prioritize organ

Abbreviations: AUC, Area Under the Curve; CPI, Composite Physiologic Index; DLCO, Diffusion Capacity of the Lungs for Carbon Monoxide; ISHLT, International Society for Heart and Lung Transplantation; IPF, Idiopathic Pulmonary Fibrosis; LAS, Lung Allocation Score; mPAP, Mean Pulmonary Arterial Pressure; OPTN, Organ Procurement Transplantation Network; ROC, Receiver Operating Characteristic; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing; 6MWT, 6-min walk test

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https://doi.org/10.1016/j.rmed.2019.09.001
Received 2 April 2019; Received in revised form 18 June 2019; Accepted 3 September 2019
Available online 07 September 2019
0954-6111/

allocation for pulmonary deterioration as opposed to time on the wait list [12,13]. Nevertheless, despite acceptable mortality post-transplantation comparable to that of other indications for lung transplantation [6] there remains the question of how LAS prioritization has affected the survival of sarcoidosis patients on the waiting list. During the initial development of the LAS, sarcoidosis data was too sparse to develop disease-specific prognostic factors and therefore was grouped with COPD (termed Group A) or idiopathic pulmonary fibrosis (IPF) (termed Group D) depending on the patient's mean pulmonary artery pressure (mPAP) as pulmonary hypertension accelerates clinical decline [13]. A query of outcomes early after the LAS′ introduction demonstrated that sarcoidosis patients listed for double lung transplantation had lower LAS scores and longer waiting times (nearly 200 days longer) compared to IPF [14]. However, our literature search failed to reveal a more in-depth characterization of prognostic factors and outcomes on the waiting list. We wish to determine how the LAS predicts decline in functional status and mortality risk in a sarcoidosis population.

2. Methods

2.1. Participants

This was a retrospective chart review of patients that have been listed for lung transplantation at Temple University Hospital (Philadelphia, PA) from March 2012 to February 2019. We are a quaternary care center that has performed > 550 lung transplants during the study period. All patients listed for lung transplantation during the study period with a primary or secondary listing diagnosis of sarcoidosis were included in analysis. We did not include patients listed for en-bloc heart-lung transplantation to minimize confounding by significant cardiac involvement (n = 1). We had also planned to exclude patients listed for re-transplantation but this did not apply to any patient with a sarcoidosis diagnosis during the study period. 2012 was selected as the starting date for data collection as our current cardiothoracic surgical group joined the institution during this period and we wished to minimize confounding by changes in listing practice. Our study met approval for waiver of informed consent by the Western Institutional Review Board (Protocol #1251040).

2.2. Data collection

Patient data was extracted from the Epic Electronic Health Record (Epic Systems Corporation, Madison WI) collected in routine clinical care. The “primary event” was defined as transplantation or death. Baseline patient characteristics and physiologic parameters were collected at earliest time point prior to their initial activation on the transplant list.

Baseline patient characteristics were derived from transplant candidate evaluation testing. Pathology reports from explanted lungs and other biopsies were reviewed to confirm the diagnosis of sarcoidosis. For patients who died while awaiting transplantation, the cause of death was identified, if available. Demographic and comorbidity data included age, gender, race, height and weight, BMI, medication use including steroid and immunosuppression usage, smoking history, previous history of aspergillosis, and exacerbation frequency. Physiologic testing data included pulmonary function tests (spirometry, plethysmography, diffusion capacity of the lungs for carbon monoxide (DLCO)), 6-min walk test (6MWT) distance and supplemental oxygen requirements, echocardiographic findings, and heart catheterization findings. Laboratory data included cell counts, serum chemistries, and room air arterial blood gases. The Composite Physiologic Index (CPI) was calculated as previously described, with higher scores signifying worse prognosis [15].

Transplant waitlist outcomes were derived from both our internal transplant database as well as the publicly available United Network for Organ Sharing (UNOS)/OTPN database (https://optn.transplant.hrsa.gov/data).

2.3. Statistical analysis

Our specific aims were to calculate overall wait list mortality and identify predictive factors for death among sarcoidosis patients listed for lung transplantation. Categorical data was compared using Chi-square analysis. Continuous variables were compared using 2-tailed Student's t-test or Mann-Whitney *U* test (where appropriate for non-parametric data). Significance level was set at $p = 0.05$. For those variables reaching significance on univariate testing and those deemed to have predictive value based on clinical experience and previous literature, receiver-operating characteristic (ROC) curves were constructed for their power predict death on the transplant list with area under the curve (AUC) reported. Statistical analyses were performed using SPSS Statistical Software 24 (IBM, Armonk NY).

3. Results

Thirty three sarcoidosis patients were listed for lung transplantation by our transplant program during the study period. Of those, 5 remain actively listed and are not included in the current analysis. 22 patients survived to transplant (3.9% of all lung transplants at our center), while 6 died on the wait list (6.2% of all transplant wait list deaths at our center) leading to an 18.2% mortality among sarcoidosis patients listed for lung transplant. A patient selection diagram is presented in Fig. 1. In comparison, there was a 12.3% mortality among listed IPF patients and an 8.7% mortality among listed COPD at our institution during the study period.

Of the 6 patients who died, cause of death was documented in the medical chart for 3 of them: patient #1 died of clear progressive respiratory failure, patient #2 died in the setting of respiratory distress at home (but etiology not determined), and patient #3 died of witnessed ventricular arrhythmia. The remaining patients (#4–6) died at home with no autopsy performed. Characteristics and parameters of the patients who died are presented in Table 1. None of the patients who died had a prior history of atrial fibrillation, ventricular arrhythmia, or pacemaker requirement. Out of the entire study population, advanced cardiac imaging with cardiac MRI was performed to evaluate for granulomatous involvement in 8 cases (6 in the transplanted cohort and 2 in the deceased cohort). In both cohorts, positive findings were seen in 50%.

All patients had a primary listing diagnosis of sarcoidosis, with 11

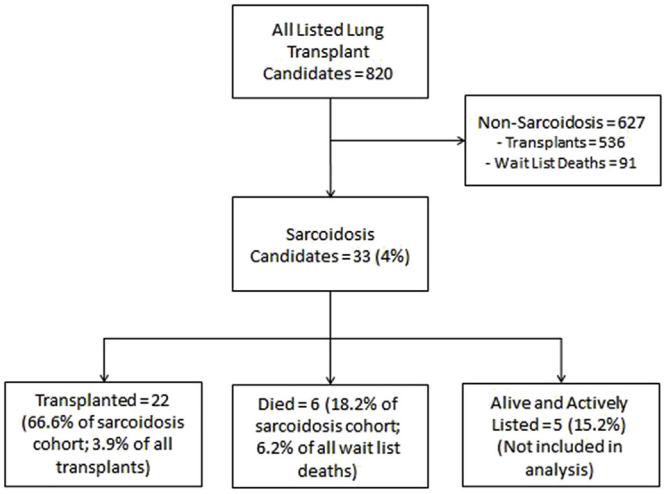

Fig. 1. Patient Selection Diagram. This represents all patients listed for lung transplantation from 2012–February 2019 at Temple University Hospital (Philadelphia, PA).

Table 1
Clinical Characteristics of Patients who Died on the Transplant Wait List. Abbreviations: LAS = Lung Allocation Score; SupplO2 = Supplemental Oxygen; LPM = Liters per Minute; CPI = Composite Physiologic Index; RAP = Right Atrial Pressure; mPAP = mean Pulmonary Artery Pressure; PAWP = Pulmonary Arterial Wedge Pressure; CO = Cardiac Output; CI = Cardiac Index.

Patient ID	Age (Years) Gender	Initial LAS LAS at Death	Time on Wait List (days)	Cause of Death (if recorded)	Height (meters) BMI (kg/m2)	Blood Type	Pack Years Smoking	6-Minute Walk Test Distance (meters)	SupplO2 at Rest SupplO2 With Exercise	FVC% FEV1/FVC % DLCO% CPI	Mean RAP (mmHg) mPAP (mmHg) PAWP (mmHg) CO (L/min) and CI (L/min/m2)	Comments
1	64 Female	52.15 76.99	86 days	Progressive Respiratory Failure	1.52m 20.2kg/m^2	B	0	254m	3LPM 8LPM	18% 91% 10% 82.3	1mmHg 26mmHg 5mmHg 4.51 and 2.92	
2	59 Female	34.49 37.28	265 days	PEA Arrest	1.70m 19.9kg/m^2	O	6.5	300m	10LPM 10LPM	46% 64% 18% 68.2	11mmHg 28mmHg 4mmHg 4.43 and 2.68	Etiology of PEA not determined, no evidence of pneumothorax
3	62 Female	32.97 35.47	273 days	Vtach/Vfib	1.63m 26.8kg/m^2	O	0	260m	Room air 6LPM	66% 84% 18% 68.8	1mmHg 34mmHg 7mmHg 7.62 and 4.28	
4	50 Female	53.86 53.86	19 days	Unknown	1.63m 23.9kg/m^2	O	0	0	8LPM Not performed	37% 75% 10% 76.8	1mmHg 30mmHg 5mmHg 3.36 and 1.99	No enhancement on Cardiac MRI; highest PCO2 of cohort (72mmHg)
5	47 Male	39.47 38.62	319 days	Unknown	1.68m 30kg/m^2	O	26	210m	Room air 5LPM	50% 87% 19% 71.1	4mmHg 28mmHg 6mmHg 5.04 and 2.50	Positive for enhancement on Cardiac MRI
6	63 Female	61.51 42.59	101 days	Unknown	1.65m 35.3kg/m^2	O	0	180m	NRB Mask NRB Mask	38% 75% 17% 72.8	11mmHg 61mmHg 19mmHg 6.84 and 3.42	

Table 2
Demographics Comparison between Transplanted Cohort and Deceased Cohort at Time of Initial Listing Candidacy Evaluation. Values are presented as mean ± standard deviation or as median (range) for continuous variables, or as absolute numbers (where indicated). 'Final LAS' refers to LAS at time of primary event (transplantation or death on the wait list).

	Transplanted n = 22	Wait List Deaths n = 6	p-value
Age, years	59.7 ± 6.2	57.5 ± 7.2	NS
Gender, M/F	12/10	1/5	NS
Black versus White or Hispanic	18/4	4/2	NS
Height, meters	1.69 (1.5–2.0)	1.64 (1.5–1.7)	NS[a]
BMI, kg/m^2	27.46 ± 5.1	26.0 ± 6.0	NS
Respiratory hospitalizations per year	0.67 (0–14.5)	1.0 (0–6.8)	NS[a]
PRA, %	10 (0–97)	10 (0–46)	NS[a]
Blood Type, B/A or O	8/14	1/5	NS
Former Smoker, %	11/11	2/4	NS
Pack Years	0.63 (0–40)	0 (0–26)	NS[a]
Hemoglobin, g/dL	12.6 ± 1.7	12.3 ± 2.3	NS
Bilirubin, mg/dL	0.5 (0.2–1)	0.3 (0.1–0.3)	0.003[a]
Steroid Dose, mg	17.2 ± 23.0	7.1 ± 7.5	NS
Pulmonary Hypertension Therapy, Y/N	10/12 patients PDE5-I: 4 ERA: 9 Prostaglandin: 1	2/4 patients PDE5-I: 2 ERA: 0 Prostaglandin: 0	NS
Immunosuppressant Use, Y/N	4/18 patients Methotrexate: 2 Leflunomide: 1 Mycophenolate: 1	1/5 patients Hydroxychloroquine: 1	NS
Previous PCI, Y/N	18/4	6/0	NS
Atrial Fibrillation, Y/N	20/2	6/0	NS
Pacemaker, Y/N	21/1	6/0	NS
HFpEF, Y/N	11/11	4/2	NS
Hypertension, Y/N	10/12	1/5	NS
Diabetes, Y/N	15/7	5/1	NS
Creatinine Clearance < 60 mL/min/1.73m^2, Y/N	18/4	6/0	NS
Initial LAS	40.9 ± 10.9	45.7 ± 11.7	NS
Final LAS	41.1 (34.1–79)	40.6 (35.5–77.0)	NS[a]
LAS Change/Year	1.5	1.7	NS[a]
Wait List Time, days	307.3 ± 308.6	177.2 ± 123.4	NS

Abbreviations: NS = Non-significant; BMI = Body Mass Index; PRA = Panel Reactive Antibodies; PDE5-I= Phosphodiesterase Type 5 Inhibitor Therapy; ERA = Endothelin Receptor Antagonist; PCI = Percutaneous Coronary Intervention; HFpEF = Heart Failure with Preserved Ejection Fraction; LAS = Lung Allocation Score.

[a] Mann-Whitney *U* Test performed for non-parametric data.

patients (39%) having a secondary listing diagnosis of pulmonary hypertension. Median follow up time at our center prior to listing was 1.9 years (range 0.2–8 years). All were preferentially listed for double lung transplant. In the transplanted cohort, pathology reports were available from explants or other previous biopsies confirming granulomatous involvement consistent with sarcoidosis in 17 patients (77%). The remaining explant pathology showed end stage fibrosis but no other findings suggestive of alternative diagnoses. Only 1 patient in the deceased cohort had a positive biopsy result for granulomas. The remaining patients were diagnosed by historical report but confirmatory pathology was unavailable in our EHR.

Table 2 presents demographic data, including LAS at the time of initial listing and at the primary event. Importantly, there was no significant difference in LAS between those who survived to transplant and those who died on the waiting list at either initial listing or primary event. Mean time on the wait list was 307 days in the transplanted cohort versus 177 days for those who died on the wait list, but did not reach statistical significance. In regards to baseline laboratory data during initial candidate evaluation process, only bilirubin showed a significant difference between the groups, with patients surviving to transplant having higher valves (0.51 mg/dL vs. 0.24 mg/dL, p = 0.003). No differences were seen between prednisone doses, immunosuppressant use, or pulmonary vasodilator use; individual changes in prednisone doses are presented in Fig. 2.

Pulmonary function testing, 6MWT data, ABG data, and right heart catheterization data are presented in Tables 3 and 4. DLCO and CPI were significantly higher in the transplanted population compared to those who died (26% vs. 15%, p = 0.01 and 61 vs. 73, p = 0.02, respectively). Final FEV1/FVC ratio at the time of primary event was significantly higher in the patients who died while awaiting transplant (61% vs. 80%, p = 0.03); this was likely driven by a non-significant decrease in FVC% (58% vs. 49%, p = 0.24). None of the right heart catheterization parameters met statistical significance including mean pulmonary artery pressure and right atrial pressure. There was no evidence of obstructive coronary artery disease on left heart catheterization at the time of evaluation for any patient listed. In terms of echocardiogram data, ejection fraction showed a trend towards significance in favor of those patients who survived to transplantation, although this was not felt to be a clinically relevant difference (60% vs. 54%, p = 0.057). Tricuspid annular plane systolic excursion comparisons could not be performed given multiple missing data points.

ROC curves for delisting bilirubin, FEV1/FVC, DLCO, and CPI are presented in Fig. 3. Lower bilirubin values had the highest predictive of death on the transplant list with an AUC of 0.92. A cutoff value of 0.35 mg/dL or less had both high sensitivity (100%) and specificity (81%). The DLCO was highly predictive of death on the transplant list with an AUC of 0.84. A DLCO of ≤21% had 100% sensitivity for predicting death on the transplant list with moderate specificity (67%). CPI also had very good predictive value (AUC = 0.86) with 100% sensitivity and 77% specificity at a score ≥67.7. An FEV1/FVC ratio of 64.5% or higher had 100% sensitivity but was very poor specificity (46%).

ROC curves were also constructed for initial and delisting LAS, wait list times, left ventricular systolic ejection fraction, FVC, DLCO/VA, 6MWT distance and supplemental oxygen requirements, mean right atrial pressure, and mPAP given their clinical implications as well as

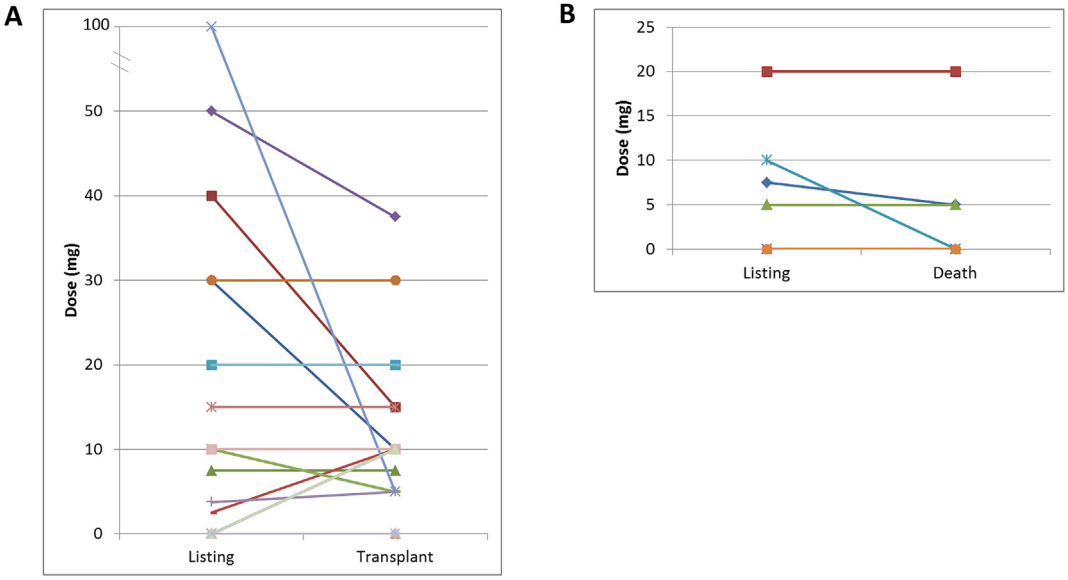

Fig. 2. Prednisone Doses for Cohort. Changes from baseline to delisting prednisone dosages for patients surviving to transplant (A) versus deceased cohort (B). No significant differences were seen between baseline dose ($p = 0.27$), final dose before primary event (transplantation or death) ($p = 0.06$), or absolute change in dose ($p = 0.62$).

previous associations with higher mortality among sarcoidosis patients listed for lung transplantation. However, all had poor predictive value, with an AUC < 0.7 (not shown).

4. Discussion

Advanced pulmonary sarcoidosis is relatively uncommon but leads to significant morbidity and mortality [3,4,14,16]. Lung transplantation serves as a therapeutic option in advanced pulmonary sarcoidosis. Sarcoidosis patients experience a median post-transplant survival rate of 70 months, similar to that of other indications [6]. Among patients listed in the UNOS database from 1995 to 2000, mortality among the sarcoidosis patient was comparable to IPF on the wait list (28%); however sarcoidosis patients were less likely to undergo transplantation (30.8% vs. 37.3%) with significantly longer wait times under the older system [10]. Wait list times were significantly longer than those reported in the most recent SRTR annual report, which reported median wait times for Groups A and D patients (of which sarcoidosis can be included) of 1.9–4 months [9]. Predictors identified in earlier sarcoidosis pre-transplant studies included African American race, higher supplemental O2 usage, and higher mean pulmonary artery pressure (41 mmHg vs. 32 mmHg) without a significant increase in PAWP. While race conferred the highest contributor to mortality risk in the prediction model, pulmonary artery pressures displayed a nonlinear relationship [11].

The LAS system can contribute to improved survival in listed sarcoidosis patients post-transplant [6]. While this is reassuring for post-transplant outcomes, it still leaves uncertainty how the LAS predicts survival among candidates with sarcoidosis. This exploratory study attempted to identify predictive factors for death on the transplant wait. Despite our small sample size, we made several interesting observations that should be further investigated with larger cohorts. We observed higher mortality among sarcoidosis patients as compared to other common listing indications such as COPD and IPF. We observed no difference in LAS at listing and before primary event or wait list times between sarcoidosis patients who were successfully transplanted and those who died on the wait list. A wide range of wait list times was observed, which may be due to our smaller sample size and individual patient characteristics that affect their organ selection. Physiologic markers of advanced fibrotic disease including reduced DLCO, "normal" FEV/FVC, and an elevated CPI were significant predictors of death on the transplant list, consistent with previous research.

While higher FEV1/FVC during follow up predicted death on the list, the main driver for this observation seemed to be a nonsignificant drop in FVC. A severely reduced FEV1 or FVC < 50% of predicted is only found in < 4% of the overall sarcoidosis population [1], and while changes in spirometry tend to be concordant, they do not consistently follow progression of symptoms, radiographic staging over time, or outcomes [2,4]. FVC did not significantly predict mortality for wait list patients in pre-LAS literature [11] or in a recent retrospective analysis of a general sarcoidosis population [3]. Advanced fibrotic disease nevertheless has been identified as a significant risk factor for 5-year mortality, regardless of the presence or absence of high risk complications such as chronic pulmonary aspergillosis [3,16]. Incorporating FEV1, FVC, and DLCO into the CPI score better captures advanced fibrotic lung disease rather than a single spirometric value; a score > 40 has good predictive value for mortality among patients with sarcoidosis (regardless of extensive radiographic fibrosis) [17] and other fibrotic lung diseases [15]. The CPI values observed in our transplant candidate population far exceeded those previously reported in a general population [3,17], with extremely good predictive value at a level > 67 (AUC for ROC = 0.86).

DLCO had no significant predictive value for wait list mortality in single-center, pre-LAS literature and was actually higher in patients who died while awaiting transplant [5]. In a larger pre-transplant UNOS population, DLCO was not reported data and therefore limits confirmation of these findings [10,11]. A DLCO ≤21% (AUC = 0.84) captured all deaths in our study population. While this value is well below the recommended DLCO referral criteria by the ISHLT (DLCO < 40% of predicted) [13], these were all values obtained at initial listing. This may suggest a global delay in referral for transplant evaluation that is reflected by our single-center experience; however, our study was not designed to assess this. The CPI, which integrates DLCO with other spirometry values, has good prognostic value in a sarcoidosis population [17].

Pulmonary hypertension has previously been associated with worsened outcomes in sarcoidosis, particularly in end-stage fibrosis [3–5,10,11]. A single center retrospective study of 43 patients referred for transplantation identified 53% mortality while on the transplant list. Right atrial pressure > 15 mmHg strongly predicted mortality by

Table 3
Pulmonary Physiologic Data Comparison between Transplanted Cohort and Deceased Cohort At Time of Initial Listing Candidacy Evaluation. Values are presented as mean ± standard deviation or as median (range) for continuous variables, or as absolute numbers (where indicated). 'Final' spirometry values refer to spirometry at time of primary event (transplantation or death on the wait list).

	Transplanted n = 22	Wait List Deaths n = 6	p-value
6MWT Distance, meters	260 (150–377)	232 (0–300)	NS[a]
Supplemental O2 Requirements (Rest), Y/N[b]	16/5 patients Room air: 5 1 – 2LPM: 3 3LPM – 6LPM: 11 7LPM – 15LPM: 1 Nonrebreather: 1	4/2 patients Room air: 2 1 – 2LPM: 0 3LPM – 6LPM: 1 7LPM – 15LPM: 2 Nonrebreather: 1	NS
Supplemental O2 Requirements (Exercise), Y/N[c]	21/0 patients Room air: 0 1 – 2LPM: 2 3LPM – 6LPM: 8 7LPM – 15LPM: 8 Nonrebreather: 3	5/0 patients Room air: 0 1 – 2LPM: 0 3LPM – 6LPM: 2 7LPM – 15LPM: 2 Nonrebreather: 1	NS
Listing FEV1, %	45.5 (23–92)	37.5 (21–70)	NS[a]
Listing FVC, %	54.5 (23–90)	42.0 (18–66)	0.08[a]
Listing FEV1/FVC, %	66.9 ± 16.2	79.3 ± 9.9	0.09
Final FEV1, %[d]	44.9 ± 13.0	47.8 ± 22.8	NS
Final FVC, %[d]	57.5 ± 11.3	48.8 ± 19.3	NS
Final FEV1/FVC, %[d]	61.5 ± 15.3	80.0 ± 10.6	0.03
CPI	60.8 ± 11.4	72.9 ± 5.5	0.02
TLC, %	63.0 ± 19.8	47.0 ± 13.8	0.08
RV, %	80.7 ± 42.6	50.3 ± 21.8	NS
DLCO, %	25.0 (13–47)	17.5 (10–19)	0.01[a]
DLCO/VA, %	47.0 (31–80)	43.0 (30–50)	NS[a]
pH	7.29 ± 0.67	7.42 ± 0.04	NS
PaCO2, mmHg	46.5 (30–76)	48.5 (37–72)	NS[a]
PaO2, mmHg	59.5 (32–148)	62.5 (29–76)	NS[a]

Abbreviations: NS = Non-significant; 6MWT = 6-min Walk Test; LPM = Liters per Minute; CPI = Composite Physiologic Index; DLCO/VA = DLCO corrected for alveolar volume.

[a] Mann-Whitney *U* Test performed for non-parametric data.

[b] Data unavailable from 1 patient in the transplanted cohort as formal 6MWT not performed during inpatient transplant evaluation.

[c] Data unavailable from 1 patient in each cohort. In transplanted cohort, formal 6MWT not performed during inpatient transplant evaluation. In deceased cohort, patient was too hypoxic to perform exercise portion.

[d] Data unavailable for 9 patients in the transplanted cohort and 1 patient in the deceased cohort.

multivariate analysis. In addition, pulmonary hypertension was common among patients who died with 83% of patients had mean pulmonary artery pressures > 35 mm Hg and > 50% having either a reduced cardiac index of ≤2 L/min/m^2 or hypoxemia (PaO2 < 60 mmHg); these did not remain significant predictors of mortality on multivariate testing [5]. As compared to IPF transplant candidates, sarcoidosis patients have significantly elevated mPAP (34 mmHg vs. 26 mmHg) [10]. Interestingly, our study found no significant association between mPAP and outcomes. A disproportionately low DLCO can be associated with underlying pulmonary vascular disease but pulmonary hemodynamics in our study was not suggestive that this was the main driver. This may be more reflective of advanced fibrotic disease in our patients who died while awaiting transplant in conjunction with our other findings of "normal" FEV1/FVC and reduced CPI. The small sample size and limited statistical power could explain this observation.

There was only 1 patient in our study who died of witnessed ventricular arrhythmia; sudden cardiac death could not be excluded in most of the remaining patients. Despite only 5% of sarcoidosis patients having clinically evident cardiac involvement, autopsy studies have demonstrated nearly 25% incidence of granulomatous involvement; when clinically significant, its contribution to mortality risk can be

Table 4
Right Heart Catheterization Hemodynamics at Time of Initial Listing Candidacy Evaluation. Values are presented as mean ± standard deviation or as median (range).

	Transplanted n = 22	Wait List Deaths n = 6	p-value
Mean RAP, mmHg	4.6 ± 3.7	4.8 ± 4.9	NS
RVSP, mmHg	52.7 ± 19.4	51.5 ± 23.5	NS
RVEDP, mmHg	6.0 (-3–24)	3.0 (1–16)	0.13[a]
PASP, mmHg	53.9 ± 19.5	54.0 ± 20.1	NS
PADP, mmHg	20.1 ± 9.1	20.5 ± 9.2	NS
mPAP, mmHg	28.5 (14–55)	29.0 (26–61)	NS[a]
PAWP, mmHg	9.4 ± 4.0	7.7 ± 5.7	NS
Cardiac Output, L/min	4.9 ± 1.1	5.3 ± 1.6	NS
Cardiac Index, L/min/m^2	2.9 ± 1.4	3.0 ± 0.8	NS
PVR, Wood Units	5.1 ± 2.9	5.7 ± 1.1	NS

Abbreviations: NS = Non-significant; TAPSE = Tricuspid Annular Plane Systolic Excursion; LVSEF = Left Ventricular Systolic Ejection Fraction; RAP = Right Atrial Pressure; RVSP = Right Ventricular Systolic Pressure; RVEDP = Right Ventricular End Diastolic Pressure; PASP = Pulmonary Artery Systolic Pressure; PADP = Pulmonary Artery Diastolic Pressure; mPAP = mean Pulmonary Artery Pressure; PAWP = Pulmonary Arterial Wedge Pressure; CO = Cardiac Output; CI = Cardiac Index; PVR = Pulmonary Vascular Resistance.

[a] Mann-Whitney *U* Test performed for non-parametric data.

substantial [7,20]. In a large Finish retrospective study, atrioventricular conduction blocks and ventricular arrhythmias represented nearly 80% of reported cardiac manifestations, with sudden cardiac death being responsible for most deaths in this study population. Nevertheless overall cardiac survival (including transplant-free survival) approached 90% at 1 year and 70% at 10 years, with extra-cardiac involvement having some protective association. Many of these patients underwent more advanced cardiac imaging (MR or PET) and invasive endomyocardial biopsy, perhaps reflecting the selected population [21]. Hu et al. [20] reported that among 35 autopsies performed for sarcoidosis patients, 7 deaths were directly attributable to sarcoidosis; 6 were from cardiac involvement. Furthermore, 4 of these deaths were due to sudden cardiac death from arrhythmia and even more alarming many were undiagnosed [20]. In the sarcoidosis transplant candidate population specifically, angina as a comorbidity has been previously associated with death on the wait list [11]. Our findings, in addition to earlier data, may point towards a possibility of missed life-threatening cardiac sarcoidosis or a greater propensity of sudden arrhythmias in patients with advanced pulmonary sarcoidosis. Standard of care informed by expert opinion for myocardial evaluation in sarcoidosis patients is to perform advanced testing when the patient has symptoms or abnormal basic cardiac testing, and this was our local practice in conjunction with cardiology consultation. There were several additional barriers to advanced myocardial evaluation such as insurance denials in the absence of abnormal echocardiography or EKG. We recognize this is a limitation of our findings as other centers may adopt more widespread testing. While less than 30% of our population had advanced cardiac imaging as part of their listing evaluation, this did not seem to alter outcomes based on positive testing. Caution should be made in interpreting this as a lack of efficacy of cardiac involvement evaluation during the transplant evaluation process given the low numbers in our study and low percentage of patients with overt cardiac sarcoidosis. Our findings may suggest a need for universal advanced cardiac imaging as part of transplant candidacy evaluation and early referral to electrophysiology consultants.

The observed relationship between elevated bilirubin and survival is less clear. Incidence of liver involvement in sarcoidosis ranges from 6 to 24% [1–3,18,19]. Most individuals are asymptomatic, having only abnormal biochemical testing as the presenting feature. Cholestatic injury pattern is typically evident but usually marked by an elevated alkaline phosphatase or gamma-glutamyl transferase and frequently improves

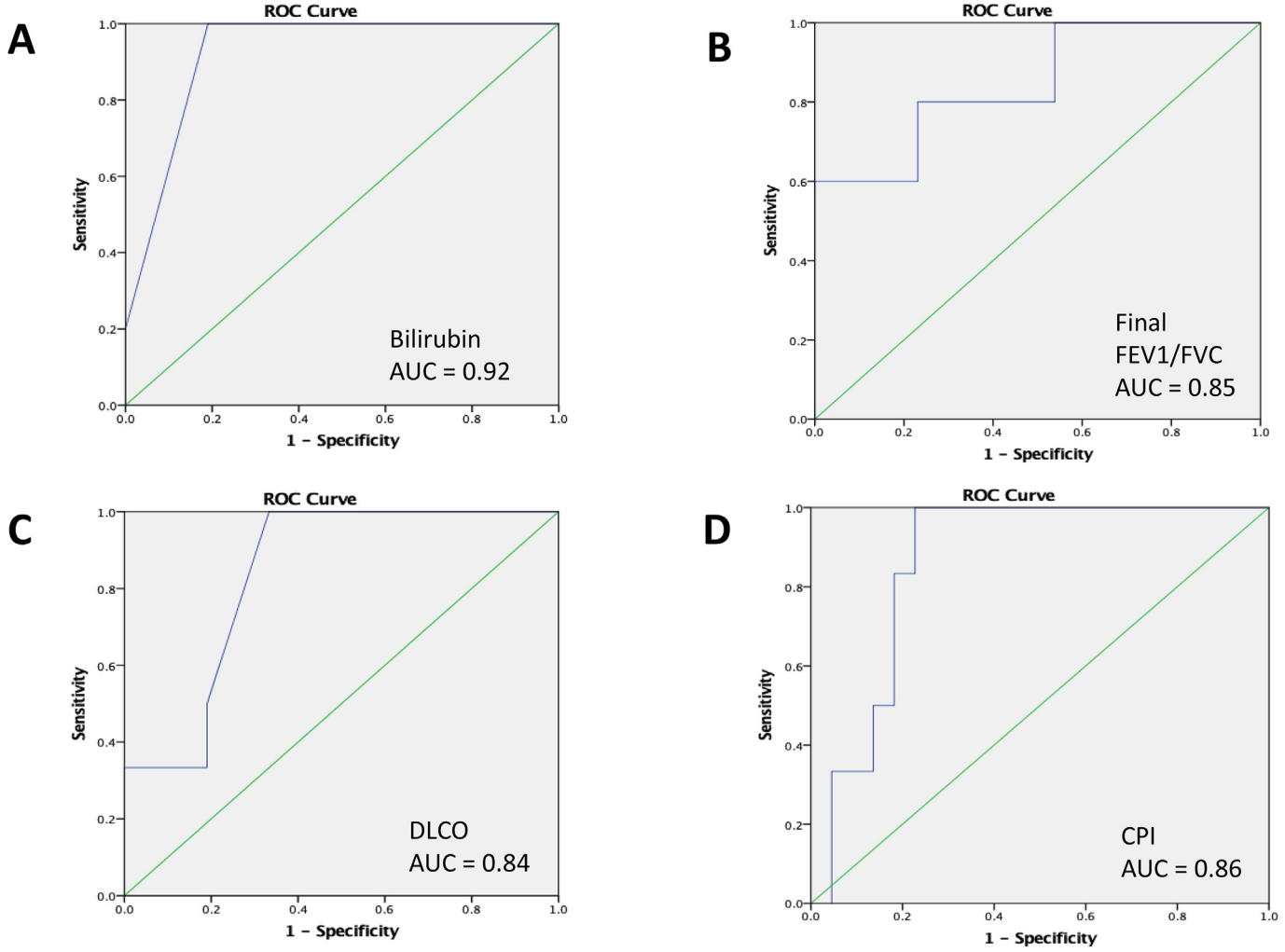

Fig. 3. ROC Curves for Physiologic Predictors of Lung Transplant Wait List Deaths. Low bilirubin (A), higher FEV1/FVC before death (B), lower DLCO (C), and higher CPI (D) all had high predictive value for death on the transplant list among sarcoidosis patients.

during follow up [18,19]; hyperbilirubinemia was relatively uncommon in a small population-based study [18]. Progression to cirrhosis or death from hepatic failure is uncommon [18,20]. Nevertheless, the difference in biochemical testing was minimal and may be more a factor of small sample size in our study. To attribute the elevation due to passive congestion also does not completely fit given the lack of difference between our subgroups in pulmonary hypertension severity.

Strengths of our study include pathologic confirmation of granulomatous involvement in this population, confirming a homogeneous population. Our study population was well-characterized in regards to pulmonary function testing and pulmonary vascular disease during the initial listing process. Limitations include our retrospective, single center design and inability to control for non-standardized data collection at later time points closer to the primary event. Nevertheless, our analysis suggests severe interstitial disease at baseline predicts mortality in this population and is not necessarily captured by the LAS system. This further supports previous literature showing advanced fibrosis to be a poor prognostic factor. Another limitation of our study is the small overall number of patients in our study. However, advanced pulmonary sarcoidosis is relatively uncommon and very few proceed to lung transplantation consideration. We are a high-volume center and the proportion of patients transplanted for advanced pulmonary sarcoidosis mirrors national trends.

5. Conclusion

Sarcoidosis patients on the lung transplant wait list experience a high mortality, even exceeding mortality for IPF patients at our center. The listing LAS and change in LAS did not predict death on the wait list and may point to a limitation in the LAS' applicability to this group. Pulmonary hypertension at time of listing likewise did not predict death. We found that markers of advanced fibrotic disease burden such as low DLCO and high CPI were statistical predictors of death, as has been previously observed in non-transplant population. At listing the severity of disease was out of proportion to the degree that is recommended for consideration for transplant referral by the ISHLT. Furthermore, we also observed a large number of patients experienced sudden out of hospital death. Whether this may suggest that unidentified cardiac disease requiring more comprehensive evaluation is a significant cause of mortality requires further study in a larger cohort. Reconsideration of current referral and transplant candidacy listing recommendations for advanced pulmonary sarcoidosis may be warranted.

Prior presentation

Portions of this research were presented in abstract format at the American Thoracic Society 2019 annual meeting [22].

Financial Support

None.

Financial conflicts of interest

None relevant to the present study.

Contributions

AJG was responsible for project planning, data collection and analysis, and preparation of the manuscript. CM, MZ, MBL participated in data collection. FC, NM, and GJC provided oversight during manuscript preparation and data interpretation. RG and AJM were responsible for project planning, data interpretation, and manuscript preparation.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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