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Lung transplantation for high-risk patients with idiopathic pulmonary fibrosis

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Abstract. *Background:* Survival for patients with idiopathic pulmonary fibrosis (IPF) and high lung allocation score (LAS) values may be significantly reduced in comparison to those with lower LAS values. *Objectives:* To evaluate outcomes for high-risk IPF patients as defined by LAS values ≥46 (N=42) versus recipients with LAS values <46 (N=89). *Methods:* We retrospectively reviewed records of 131 consecutive patients with IPF who received lung transplants at our institution between 1999 and 2013. *Results:* The mean LAS was significantly higher (59.5, interquartile range 43.9-75.9 vs. 39.3, interquartile range 37.7-44.3; p<0.01) for the high-risk cohort. The higher LAS cohort had significantly lower percent predicted forced vital capacity (FVC) versus recipients with LAS <46 (41.3±14.1% vs. 53.2±16.2%; p<0.01) and required more supplemental oxygen (7±5 vs. 4±2 L/min, p<0.01) prior to transplant versus recipients with LAS <46. Although the incidence of early post-LTX pulmonary complications was increased for the higher LAS group versus recipients with LAS <46, 30-day mortality and actuarial survival did not differ between the two cohorts. *Conclusions:* Although lung transplantation in patients with IPF and high LAS values is associated with increased risk of early post-transplant complications, long-term post-transplant survival for our high-LAS cohort was equivalent to that for the lower LAS recipients. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 235-241)*

Key words: lung transplantation, idiopathic pulmonary fibrosis, lung allocation score

Abbreviations:

CLAD = Chronic Lung Allograft Dysfunction
ECMO = Extracorporeal Membrane Oxygenation
ICU = Intensive Care Unit
IPF = Idiopathic Pulmonary Fibrosis
LAS = Lung Allocation Score
LTX = Lung Transplantation
NO = Nitric Oxide
OPTN = Organ Procurement and Transplantation Network
UNOS = United Network for Organ Sharing

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of interstitial lung disease (ILD) that is associated with poor survival, especially for patients with advanced and progressive disease (1-4). Although newly available anti-fibrotic drugs (pirfenidone and nintedanib) may significantly slow disease progression for patients who respond to these therapies (5,6), the majority of patients with IPF are still likely to suffer progres-

sive respiratory failure and death (3,7). Additionally, a significant number of patients may develop an acute exacerbation of their disease that rapidly leads to their demise and responds poorly to therapeutic interventions (8,9). Lung transplantation (LTX) is the only therapy that can lead to improved quality of life and prolonged survival, but only a subset of patients with IPF meet criteria for being placed on lung transplant waitlists (4,10).

Due to the relative shortage of organs, the growing number of patients on the waiting list, and the increasing number of deaths during the wait for organs, the lung allocation score (LAS) was implemented in 2005 by the Organ Procurement and Transplantation Network (OPTN) for lung transplants performed in the United States. Goals of LAS implementation were to reduce the number of deaths on the lung transplant waiting list, increase the transplant benefit for lung recipients, and ensure the efficient and equitable allocation of lungs to active lung transplant candidates (11). The LAS significantly changed lung allocation from the previous system that was based solely on accrued time on the waitlist to the new algorithm based on survival probability while on the waitlist combined with the probability of survival to one year following transplantation. Since 2007, IPF has surpassed chronic obstructive pulmonary disease (COPD) as the leading indication for LTX (10), and patients with IPF usually receive higher LAS values than patients with other disease indications for lung transplant (11).

Although higher scores reflect increased urgency due to risk of death over time without a transplant, higher scores may also be associated with poorer survival following LTX. When compared to patients with LAS values <50, recipients with LAS values ≥75 have been shown to have significantly higher morbidity, increased resource utilization, and lower survival rates following LTX (12). Additionally, Weiss et al. (13) have reported that patients with LAS >52 had significantly increased 90-day and 1-year mortality compared to those with lower scores when OPTN data for May 2005 to December 2007 were analyzed. Liu et al. (14) also observed an inverse relationship between LAS values and survival and noted that recipients with IPF with LAS values ≥60 had an increased risk of death versus recipients with lower LAS values.

Because we have transplanted patients with IPF and very high LAS values at our institution over the past decade, we examined our outcomes data to see if higher LAS values (defined as LAS ≥46) were associated with worse outcomes for our recipients who underwent LTX for end-stage lung disease due to IPF when compared to recipients with lower LAS values (LAS <46).

Methods

A retrospective review of the charts and transplant data for 131 consecutive IPF patients who met criteria for the diagnosis of IPF (2) and underwent LTX at our institution between 1999 and 2013 was performed. LAS values were calculated for recipients who received transplants prior to implementation of the LAS system using the appropriate variables that were available close to the time of LTX to allow this group to be pooled with recipients who received transplants under the LAS system from 2005 onward. We chose a LAS value of 46 as a threshold for lower versus higher risk of compromised outcomes due to a high LAS score as has been done by others (14), and patients with LAS≥46 (high-LAS, n=42) were compared to patients with LAS<46 (low-LAS, n=89). This investigation was approved by the University of Wisconsin Human Subjects Committee (approval number M-2009-1308).

Donor and recipient characteristics

Between 1999 and 2013, a total of 474 lung transplants from deceased donors were performed at the University of Wisconsin Hospital and Clinics (UWHC). Among these patients, 131 (27.6%) consecutive patients with IPF underwent LTX. The high-risk IPF patients with LAS ≥46 (high-LAS, n=42) were compared to the patients with LAS <46 (low-LAS, n=89). Patient demographics, donor characteristic, graft function, post-transplant complications, and graft survival rates were assessed.

Organ procurement, preservation, and implantation

After median sternotomy, 30,000 units of heparin and 10 mg of phentolamine were given intravenously to prevent vasospasm and to facilitate subsequent organ flushing. Four liters of preservative solution was infused in situ via the main pulmo-

nary artery, and 2L of retrograde flush was instilled through the pulmonary veins. Most donor organs were perfused with UW solution prior to 2007, but Perfadex® (Vitrolife, Göteborg, Sweden) was used as the preservation solution from 2007 onward. The donor lungs were then stored in preservation solution at 4°C and returned to our center for implantation. Patients were routinely listed for either single (SLT) or bilateral lung transplantation (BLT), and choice of procedure was generally made on the basis of organ availability and donor-recipient matching.

Post-transplant surveillance

All recipients underwent periodic surveillance including spirometry, chest imaging, and bronchoscopy to detect infection, allograft rejection, and/or persistent decline in lung function that met criteria for chronic lung allograft dysfunction (CLAD) (15).

Data acquisition and follow-up

The Institutional Review Board of our institution approved this study. Data were collected prospectively and analyzed retrospectively. The lung transplant database was reviewed for demographic, operative, perioperative, and outcomes data. Follow-up data were obtained through chart review.

Statistical analysis

Categorical data were summarized with frequency distributions and percentages. The mean ± standard deviation values were calculated for variables that were normally distributed, and the medians with interquartile range (IQR) values were presented for those that were skewed. Continuous variables were compared by the unpaired t-test or nonparametric Mann-Whitney U-test, whereas nominal variables were compared by means of Chi-Square or the Fisher exact test, as appropriate. The Kaplan-Meier method was used to assess lung graft survival. Log-rank tests were used to assess statistical significance in survival differences between the pre-LAS and LAS groups. A p value <0.05 (two-sided) was considered to be statistically significant. Survival data were analyzed via the Cox proportional hazards method with LAS as a continuous variable to determine if there was a specific LAS value above which patient outcomes may be compromised. All analyses were performed using the SPSS statistical software program (SPSS for Windows version 19.0, SPSS Inc.; Chicago, Ill.).

Results

High-risk IPF patients had more severe pulmonary dysfunction (%FVC predicted = 41% [higher LAS] vs. 53% [lower LAS] and %FEV1 predicted = 41% vs. 57%; p<0.01 for both variables) and required more supplemental oxygen prior to transplant (7 vs. 4 L/min, p<0.01) (Table 1). The mean LAS value was significantly higher (59.9 [range, 43.9-75.9] vs. 39.3 [37.7-44.3], p<0.01), and the waiting time trended towards being shorter (128 vs. 215 days, p=0.08) in the high LAS group. The higher LAS recipients had a lower body mass index (BMI) when compared to the lower LAS group (26.8 vs 28.4, p = 0.02). The rate of a BLT procedure was significantly higher in the higher LAS group (21% vs 9%, p = 0.05), although there was no significant difference in rates of cardiopulmonary bypass (CPB) usage or duration of cold ischemic time.

The incidence of post-LTX pulmonary complications (Table 2) was higher for the high LAS group. Most notably, rates of severe PGD (grade 2 or 3) were significantly higher in the higher LAS group (45% vs 21%, p = 0.03), and inhaled NO usage (81% vs 63%, p = 0.04) and mechanical ventilatory support duration >48 hrs (48% vs 20%; p<0.01) were also higher in the higher LAS cohort (Table 2). However, there was no statistically significant increase in the rate of extracorporeal membrane oxygenation (ECMO) support, average duration of mechanical ventilation, or requirement for prolonged NO administration, although these all trended toward a significant increase for the higher LAS cohort. Other complications such as re-intubation, tracheostomy, dialysis, stroke, and arrhythmia were no different between the two groups. The length of intensive care unit (ICU) stay (7.1 vs. 4.5 days; p=0.12) and 30-day mortality (5% vs. 6%; p=0.77 did not differ between the groups. However, there was a trend towards longer total hospital stay in the higher LAS group that nearly reached significance (30.5 vs 18.3 days, p = 0.06).

There was no significant difference in long-term actuarial patient survival between the two cohorts,

Table 1. Patient demographics

Parameter	Low-LAS (n = 89)	High-LAS (n = 42)	p-value
Age (y)	58.0 ± 6.6	57.6 ± 8.5	0.79
Gender (female)	15 (17%)	9 (21%)	0.66
Race (Caucasian)	83 (93%)	38 (91%)	0.39
BMI (kg/m2)	28.4 ± 3.6	26.8 ± 3.8	0.02
FVC (% of predicted)	53.2 ± 16.2	41.3 ± 14.1	<0.01
FEV1 (% of predicted)	57.1 ± 15.5	41.3 ± 14.1	<0.01
Required Oxygen (L/min)	4 ± 2	7 ± 5	<0.01
Assisted ventilation	10 (11%)	8 (19%)	0.23
Systolic PAP (mmHg)	40 ± 13	46 ± 16	0.03
Mean PAP (mmHg)	26 ± 8	29 ± 11	0.03
PCWP (mmHg)	11 ± 5	14 ± 8	0.01
Cardiac index (L/min/m2)	2.7± 0.5	2.8 ± 0.8	0.97
Serum creatinine (mg/dl)	1.0 ± 0.2	0.9 ± 0.2	0.02
History of diabetes	30 (34%)	15 (36%)	0.82
History of smoking	58 (65%)	28 (67%)	0.79
Time on waiting list (days)	215	128	0.08
LAS	39.3 (IQR, 37.7-44.3)	59.9 (IQR, 43.9-75.9)	<0.01
Bilateral lung transplant procedure	8 (9%)	9 (21%)	0.05
Cardiopulmonary bypass	29 (33%)	19 (45%)	0.16
Cold ischemic time (min)	299 ± 111	290 ± 87	0.65
Donor age (y)	34.0 ± 14.3	36.0 ± 15.7	0.47
Donor gender (female)	29 (33%)	12 (29%)	0.46

Abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV1 = forced expiratory volume in one second; LAS = lung allocation score; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure

Table 2. Post-operative outcomes

Parameter	Low-LAS (n = 89)	High-LAS (n = 42)	p-value
PGD (Grade 0 or 1)	70 (79%)	23 (55%)	0.03
PGD (Grade 2 or 3)	19 (21%)	19 (45%)	
Required ECMO support	1 (1%)	1 (2%)	0.29
Inhalation of nitric oxide	56 (63%)	34 (81%)	0.04
≥ 48 hrs of inhalation	13 (15%)	11 (26%)	0.09
Mechanical ventilated period (d)	2.2 (IQR, 1.7-2.7)	4.9 (IQR, 3.2-6.6)	0.14
≥ 48 hrs of ventilator support	18 (20%)	20 (48%)	<0.01
Re-intubation	13 (15%)	9 (21%)	0.27
Tracheostomy	6 (7%)	7 (17%)	0.10
Dialysis	0	3 (7.1%)	0.09
Stroke	0	0	--
Arrhythmia (atrial)	27 (30%)	14 (33%)	0.81
Length of ICU stay (d)	4.5	7.1	0.12
Length of hospital stay (d)	18.3 (IQR, 18-20)	30.5 (IQR, 24-37)	0.06
30-day mortality	5 (6%)	2 (5%)	0.77

Abbreviations: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile ratio; LAS = lung allocation score; PGD = primary graft dysfunction

Table 3. Multivariate Cox regression analysis of risk factors for death

Variable	HR (95% CI)	p-value
Age	1.08 (1.025-1.134)	0.03
Bilateral lung transplant	0.91 (0.36-2.34)	0.85
Lung allocation score	1.01 (0.99-1.03)	0.54

Abbreviations: HR = hazard ratio

nor was there a significant difference for the incidence of CLAD. For the lower LAS group, actuarial survival rates at 1, 3 and 5 years were 78.6%, 67.2%, and 58.3%, respectively. For the higher LAS group, actuarial survival rates at 1, 3, and 5 years were 78.6%, 62.0%, and 57.2%. There was no statistical difference in the survival between the groups (Log-rank test, p

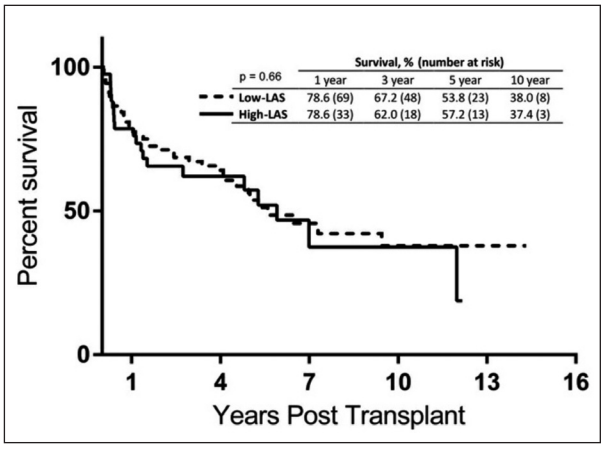

Fig. 1. Post-transplant survival by Kaplan-Meier analysis

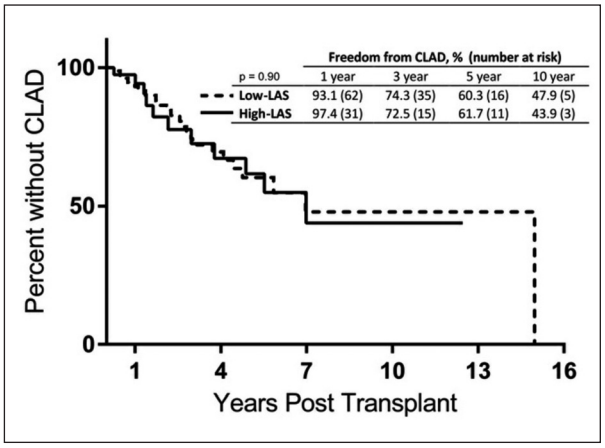

Fig. 2. Post-transplant freedom from chronic lung allograft dysfunction (CLAD) by Kaplan-Meier analysis

= 0.66, Figure 1). When LAS was used as a continuous variable in a Cox multivariate regression analysis while controlling for age and BLT procedure, there was no association with increased mortality (HR 1.01, p = 0.54). However, higher recipient age was a risk factor for increased risk of mortality.

Discussion

Prior to the adoption of the LAS, lung allocation was primarily based upon time accrued on the waiting list by eligible candidates (16). However, it eventually became clear that accrued time on the list was not a good surrogate for disease severity and risk of death without a transplant, and patients in dire need of a lung transplant would often die without having the opportunity to undergo LTX. The LAS was adopted to maximize transplant benefit while minimizing waitlist mortality, thereby avoiding the tendency of providers to list less ill patients due to the perception that the sickest patients with the poorest prognosis and greatest urgency had little chance of surviving while waiting for a donor organ to become available. However, a concern with the LAS, which places somewhat greater weight on expected waitlist survival than post-transplant survival, has been that such a system may preferentially allocate donor lungs to more critically ill patients and, thus, compromise post-transplant outcomes (17).

A number of investigations have subsequently demonstrated that adoption of the LAS has not had adverse effects on waitlist time, waitlist mortality, or overall post-transplant mortality despite increasing LAS scores and recipient acuity (18-20). Interestingly, lung transplant candidates with higher LAS scores (≥50) have been suggested to derive the greatest survival benefit from lung transplantation when UNOS data for patients ≥12 years of age who were listed between May 2005 and May 2009 were analyzed (20). However, some investigators have reported that high LAS scores have been associated with increased risk of death upon analytical review of cumulative Organ Procurement and Transplantation Network (OPTN) data (11-13) or examination of single-center experience (21). Weiss et al. (13) retrospectively analyzed OPTN data and found that recipients with pulmonary fibrosis in the highest LAS quartile (LAS ≥52) had a significantly increased risk of death at 90 days and at 1 year post-transplant with a 50% increase risk in mortality at 1 year post-transplant. Russo et al. (22) examined UNOS data and found that high LAS scores were associated with diminished post-transplant survival, increased morbidity, and longer length of hospital stay, and individuals with pulmonary fibrosis and LAS ≥75 had significantly worsened post-transplant survival. Finally, Liu et al. (14) performed a retrospective cohort study of UNOS data and reported that patients with IPF had a significantly increased risk of death if their LAS score was ≥60.

Limitations of our investigation include its single-center, retrospective nature and cohort size. However, recipients in the high LAS group had

scores that ranged up to 94.2, and they were significantly more ill from their disease as reflected by their considerably lower FVC and their greater need for supplemental oxygen. Some patients were intubated prior to transplant, and a number of others required very high supplemental oxygen concentrations and were on the verge of requiring intubation. As expected, their time on the waitlist was significantly shorter than the low LAS group. They tended to have more post-transplant complications with a requirement for more prolonged ventilatory support, and a trend toward increased need for prolonged inhaled NO, an increased incidence of re-intubation, and tracheostomy placement were also observed. Additionally, length of stay in the hospital post-transplant was prolonged versus the lower LAS group, although this did not quite reach significance. However, hospital mortality, 30-day mortality, and overall post-transplant survival did not differ between the two cohorts.

In summary, lung transplantation in high-risk IPF patients as defined by high LAS values was associated with increased post-transplant pulmonary complications versus the IPF cohort with lower LAS values. Although very high LAS scores correlate with increased risk of death while on the lung transplant waitlist (23) and have also been associated with increased risk for poor outcome post-transplant (11-13,22), we did not find a significant difference for longer term post-transplant survival for our patients with higher LAS versus those with lower LAS scores, and Cox multivariate regression analysis did not reveal the LAS value as a risk factor for death following LTX. However, we found that increased age was a risk factor for diminished survival, and this observation raises concern for survival outcomes for elderly patients with IPF who may increasingly be listed for LTX with extension of the lung transplant candidacy age range up to age 75 years per the recent update of International Society for Lung Transplantation guidelines (24). We also note that the gradual trend toward transplanting patients with higher LAS values since implementation of the LAS system has been recently found to be associated with significantly increased resource utilization when candidates with high LAS values are hospitalized for lung transplantation (25), and the impact of this trend on optimal donor organ utilization needs further evaluation. Lastly, because management of high-risk IPF patients is quite challenging both before and after LTX, and we suggest that shrewd judgment should be exercised when selecting candidates with IPF who are more ill and would have very high LAS scores at the time the decision is made to place them on the lung transplant waitlist. Indeed, various factors including degree of frailty should be considered (26), especially when elderly candidates are considered for LTX, to optimize use of a limited supply of donor lungs and avoid post-transplant complications that can significantly reduce survival and consume an inordinate quantity of medical resources.

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Author contributions:
Drs. De Oliveira and Dr. Meyer take full responsibility for the integrity of the work as a whole, from inception to published article.
Dr. De Oliveira: contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.
Dr. Julliard contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.
Dr. Osaki: contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.
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Dr. Cornwell: contributed to the study data collection, data interpretation, and manuscript composition.

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Dr. Meyer : contributed to the study design, data collection, statistical analysis, data interpretation, and manuscript composition.

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