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Increasing Lung Allocation Scores predict worsened survival among lung transplant recipients

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Abstract

Implemented in 2005, the Lung Allocation Score (LAS) aims to distribute donor organs based on overall survival benefits for all potential recipients, rather than on waiting list time accrued. While prior work has shown that patients with scores greater than 46 are at increased risk of death, it is not known whether that risk is equivalent among such patients when stratified by LAS score and diagnosis. We retrospectively evaluated 5,331 adult lung transplant recipients from May 2005 to February 2009 to determine the association of LAS (groups based on scores of ≤46, 47–59, 60–79, ≥80) and post-transplant survival. When compared with patients with LAS ≤ 46, only those with LAS ≥ 60 had an increased risk of death (LAS 60–79: hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.21–1.90; LAS ≥ 80: HR, 2.03; CI, 1.61–2.55; p<0.001) despite shorter median waiting list times. This risk persisted after adjusting for age, diagnosis, transplant center volume, and donor characteristics. By specific diagnosis, an increased hazard was observed in patients with COPD with LAS ≥ 80, as well as those with IPF with LAS ≥ 60.

Introduction

Lung transplantation can improve survival and quality of life for patients suffering from end-stage lung disease(1). However, access to this therapy is severely limited by organ availability(2). Prior to 2005, donor organs were distributed to those with the longest accrued time on the lung transplant waiting list. Such a system, however, was thought to disfavor diagnoses often associated with rapid declines in lung function and high waiting list mortality, most notably idiopathic pulmonary fibrosis (IPF)(3,4). The Lung Allocation Score (LAS), implemented in May 2005 by the Organ Procurement and Transplant Network (OPTN), was created in part as a response to these perceived imbalances. By design, it aims to maximize overall survival benefits among patients on the waiting list as well as those who undergo transplantation(5).

In the LAS system, patients registered on the lung transplant waiting list are assigned a score that aims to balance waitlist mortality and post-transplant survival. The scoring algorithm utilizes clinical data that includes diagnosis, respiratory function, health status, and hemodynamic data(5). When donor organs are offered, priority is given to patients with the highest scores within local and regional Organ Procurement Organizations. Several studies have evaluated the early impact of the LAS on waiting list time, diagnostic indications for transplant, and overall mortality(6–10). Recent work also demonstrates that those with

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scores greater than 46 are at increased risk of death following transplant(11). However, it does not address whether that risk is equivalent for all patients, categorized either by score or diagnosis, within this group—a topic of interest to patients, practitioners, and policy makers.

We evaluated lung transplant recipients as a function of stratified LAS since May 2005. Using data available through the United Network of Organ Sharing (UNOS), our aim was to describe associations between Lung Allocation Scores and post-transplant survival.

Methods

We performed a retrospective cohort study of all adults (≥ 18 years) who underwent lung transplantation after implementation of the LAS on May 5, 2005 until February 19, 2009 (5,331subjects). Patients who did not have any follow-up data (157 subjects) were excluded from survival analysis. The median follow-up time for all subjects was 365 days (range 0–1266). Subject data were collected at U.S. transplant centers using standard UNOS worksheets. The data were made available through a Standard Transplant Analysis and Research file based on OPTN data as of May 22, 2009.

Subjects were divided according to their LAS at the time of transplant. Cut-off points were selected based on previous work demonstrating worse survival for lung transplant recipients with LAS scores greater than 46 as well as clinical judgment and center experience(11). Patients with scores less than or equal to 46 comprised LAS group 1. Those with scores above 46 were divided into LAS groups 2, 3, and 4, and had scores of 47–59, 60–79, and 80–100, respectively. Median follow-up time was 371, 338, 302, and 185 days for LAS groups 1 through 4, respectively. Diagnosis groups were classified according to LAS algorithm guidelines(5). Where specified, individual diagnoses were evaluated independently. Transplant center volume was categorized by the number of transplants performed at each center since the introduction of the LAS; cut-off points were <80, 80–159, 160–239, and ≥240 transplants performed. Data on age, diagnosis group, and transplant center volume was available in all patients. Donor age, graft ischemic time, and donor PaO_2/FiO_2 (P/F) ratio were used as continuous variables in the final ‘donor’ model. Patients in whom donor ischemic time or P/F ratio data was not available (724 patients) were excluded only from analyses that specifically utilized donor data. Dates of transplantation, length of follow-up, and patient outcomes were obtained from the UNOS dataset. Patients who did not die during follow-up were censored as alive on the last date of follow-up reported to UNOS.

Continuous variables were described as mean ± standard deviation and compared using Students *t* test or ANOVA. Non-parametric data were described by median and interquartile range (IQR) and compared by Kruskal-Wallis equality-of-populations rank test. Categorical variables were summarized using frequency and percentage and compared with χ^2 test. Time-to-event analysis and survival estimates were performed using Kaplan-Meier survival analysis; differences between groups were assessed using log-rank testing. Cox proportional hazards regression analysis was used to estimate hazard ratios. Proportional hazards assumptions were tested by scaled Schoenfeld residuals. Diagnosis group did not meet proportional hazards assumptions and was used to stratify multivariate Cox regression. Statistical analyses were performed using Stata/IC 10.1 for Macintosh (Stata Corporation, College Station, TX).

Results

Baseline characteristics of the lung transplant recipients are displayed in Table 1. The mean LAS score for all recipients was 43.4 ± 14.5. The majority of patients were in LAS group 1

(n=3,991, 74.9%); their mean LAS was 36.6 ± 4.1 (Table 1). While subjects with LAS of 60 or greater accounted for fewer than 1 in 8 transplants during the overall study period (n=626, 11.7%), this proportion increased over time. Subjects with LAS of 60 or greater accounted for 8.5% versus 15.1% of transplants in 2006 versus 2008, respectively. At the time of transplant, subjects with high LAS scores had higher rates of hospitalization, intensive care unit admission, and need for mechanical ventilation. They also required the longest post-transplant hospitalizations (22 ± 26 versus 38 ± 36 days for LAS groups 1 and 4, respectively, *p*-value <0.0001). Median time on the waiting list considerably shortened with increasing LAS scores (Table 1, 98 [IQR, 30–301] versus 20 [6–75] days for LAS groups 1 and 4, respectively, *p*-value <0.0001).

Between LAS groups, recipient organs were received from donors who did not differ significantly by age or P/F ratio. Donor organ graft ischemic time was shorter in LAS group 1 but not different between LAS groups 2, 3, and 4 (Table 1). Notable differences in diagnosis groups were present between LAS cohorts (Figure 1). Chronic obstructive pulmonary disease (COPD) was the most frequent diagnosis in LAS group 1 and accounted for nearly 37% of transplants. In contrast, IPF accounted for over half of transplants performed in LAS groups 2, 3, and 4. In these groups, COPD accounted for about fewer than 5% of transplants. Graft failure of any cause leading to re-transplantation accounted for only 3% of transplants in LAS group 1 while in group 4 it accounted for nearly 13% of transplants. Idiopathic pulmonary hypertension accounted for fewer than 6 transplants (0.4%) in LAS groups 2, 3, and 4.

There were 1,135 deaths during the study. Patients in the higher LAS strata had progressively worsening post-transplant survival (Figure 2, $p < 0.0001$ between groups). Compared to subjects in LAS group 1, those in higher LAS groups were at an increased risk of death (Table 2). Subjects carrying the highest risk had LAS scores of 80 or greater (Table 2, LAS group 4 hazard ratio [HR], 2.03; 95% confidence interval [CI], 1.61–2.55; p<0.001). Those with LAS scores of 60 to 79 also had an increased risk compared to those in LAS group 1 (HR, 1.52; CI, 1.21–1.90; p<0.001). The increased risk of death persisted after adjustment for age, diagnosis, and transplant center volume (group 4 HR, 2.05; CI, 1.62–2.61; group 3 HR, 1.50; CI, 1.19–1.89; p<0.001 for both), as well as donor characteristics (group 4 HR, 1.97; CI, 1.52–2.56; group 3 HR, 1.59; CI: 1.24–2.03; p<0.001 for both). After adjusting for mechanical ventilation, the hazard ratio point estimates were reduced but patients in LAS groups 3 and 4 remained at an increased risk of death (group 4 HR, 1.49; CI, 1.13–1.96; p=0.004; group 3 HR, 1.33; CI, 1.05–1.69; p=0.02). Patients with LAS scores of 47 to 59 did not demonstrate an increased risk of death in any model (unadjusted HR, 1.08; CI, 0.91–1.30; p=.37) compared to those in LAS group 1. Both 30-day and 1-year survival progressively declined with increased LAS scores. Survival at 30 days was 96.2% (CI: 95.5–96.7), 95.6% (93.7–96.9), 94.3% (91.1–96.4), and 92.3% (88.4–95.0) for LAS groups 1, 2, 3, and 4, respectively. One-year survival was 83.7% (82.4–85.0), 81.5% (77.9–84.5), 75.1% (69.3–80.0), and 68.7% (61.9–74.6), respectively.

By diagnosis, IPF patients in LAS groups 3 and 4 were at significantly elevated risk of death when compared with those in LAS group 1 (Table 2; group 3 HR, 1.87; CI, 1.35–2.59; p<0.001; group 4 HR, 1.87; CI, 1.32–2.63; p=0.001). Patients with COPD in LAS group 4 had the most pronounced risk of death post-transplant (HR, 12.19; CI, 6.17–24.08, p<0.001). There was a trend towards an increased risk of death among cystic fibrosis patients and those with graft failure undergoing re-transplant in higher LAS groups, however, this finding did not reach statistical significance (Table 2). When groups were stratified by transplant center volume since LAS implementation, all patients in LAS group 4 remained at an increased risk of post-transplant death (Table 2).

Discussion

We found that increasing Lung Allocation Scores at the time of transplant predicted worsened post-transplant survival for patients with LAS scores of 60 or greater. The risk of death for those with LAS scores of 60–79 and 80 or greater, compared to subjects with LAS less than 47, was 1.5- to 2-fold higher. These findings were present after adjusting for age, diagnosis, transplant center volume, mechanical ventilation, and donor characteristics. In subgroup analysis, an increased hazard was observed for patients with COPD requiring transplantation in LAS group 4, as well as IPF patients in groups 3 and 4. Despite shorter waitlist times, patients with LAS ≥ 60 had worse 1-year survival when compared with patients in LAS group 1.

We also confirmed reported differences in diagnoses among LAS cohorts. IPF represented over half of transplants performed in LAS groups 2, 3, and 4, while COPD accounted for less than 5% of transplants in the same groups. This inverse distribution suggests that the LAS system effectively accounts for the worse waitlist survival of IPF patients (7–9,11). It might appear that the increasing hazard for IPF patients present in LAS groups 3 and 4 accounts for the increased risk seen among all transplant recipients. Notably, however, even after removing IPF patients from multivariate Cox regression, the hazard for the remaining patients in LAS group 4 remained more than 2-fold higher when compared with those in LAS group 1 (HR, 2.48; CI, 1.81–3.40; $p<0.001$, data not shown).

Interestingly, COPD patients in LAS group 4 also had a significant increase in their risk of death when compared with those in LAS group 1. While half of the 12 COPD patients in this group were hospitalized, other baseline characteristics did not provide a clear explanation for this finding. Given this small sample size, however, this finding should be interpreted with caution. Among cystic fibrosis patients and patients undergoing re-transplantation, there was a trend towards modestly increased risk across the LAS groups; however, this result did not reach statistical significance. The observed variability in hazard ratios suggests that the association between LAS scores and post-transplant survival is not uniform across individual diagnoses. Thus, for example, the risk of post-transplant death for a patient with a LAS score of 80 may differ based on whether the indication for transplant is COPD versus cystic fibrosis. Such a finding is not surprising since the LAS scoring algorithm weights clinical variables differently based on a patient's underlying disease.

We also found that donor age and P/F ratio did not differ between groups; mean graft ischemic time was shorter for organ recipients in LAS group 1 than those in groups 2, 3, and 4. Adjusting for donor characteristics, however, did not significantly alter our findings suggesting that the increased risk of death does not result from substantial differences in donor organ selection and quality. Adjusting for transplant center volume, known to be associated with post-transplant outcomes(12,13), also did not alter our findings. When patients were stratified by both LAS group and transplant center volume, those in LAS group 4 had worsened survival regardless of center volume.

Previous work by Merlo et al reported similar findings regarding increased risk for those with LAS scores greater than 46(11). However, since their groups were determined by LAS quintile, they did not report on risk stratification among those with scores in this highest quintile(11). While the aggregate risk of death is elevated for patients with LAS scores greater than 46, our study demonstrates that the risk is primarily carried by those with LAS scores ≥ 60. Thus, we propose that a LAS score of 60, rather than 46, provides enhanced discrimination for assessing the risk of death following transplant.

By design, the goals of the LAS adhere closely to the Final Rule on organ allocation(5,14) and are to: reduce deaths on the waitlist, increase survival benefit for transplant recipients,

and ensure efficient and equitable organ allocation(5). Recent studies have suggested that the LAS system has decreased overall waiting times for lung transplant while maintaining post-transplant survival(6–11,15).

However, our findings raise concerns that over time the LAS system may increase the fraction of transplant recipients with the poorest survival by prioritizing patients with the greatest waitlist urgency as determined by allocation scores. Even though patients in LAS groups 3 and 4 spent only a median of 33 days on the waiting list before undergoing transplant, their post-transplant survival was worse at 1-year than those in LAS group 1 whose median waiting time was 98 days. This finding demonstrates that prioritizing high-risk patients to undergo more rapid transplant does not equalize or 'reset' their risk of post-transplant mortality to the level of those with the lowest scores. Instead, such a system facilitates transplantation for patients demonstrated to have the poorest outcomes in our study. Patients in group 4 also had the shortest median follow-up time, which could result from their increasing frequency over time as well as their worsened survival. It should be noted, however, that our analysis only examined post-transplant survival and did not attempt to characterize waiting list mortality in the various subgroups. Thus, it is possible that under the current LAS system, increased emphasis on preventing waitlist deaths will come at the expense of diminished survival benefit for transplant recipients.

The LAS system has made transplantation available to the sickest patients by successfully reducing their waiting times; it has also improved waiting list mortality in the high LAS groups. However, since implementation, its prognostic implications on post-transplant survival have not been fully evaluated. As a result, only minor improvements to the scoring algorithm have been enacted and have affected a relatively small number of patients. However, by identifying groups with significantly worse outcomes following lung transplantation, our data strongly suggests that the current allocation system can be improved by re-calibrating the risk between waiting list mortality and one-year post-transplant survival. Observed differences in median

Although the data regarding outcomes are clear, the observed differences in post-transplant survival among LAS cohorts should be noted with caution because they could influence practices among transplant programs. Since post-transplant survival is used to judge performance, programs might avoid listing patients in the highest LAS cohorts out of concern that such recipients would negatively impact their program's overall survival. Such practice would place higher weight on post-transplant outcomes perhaps to the detriment of waiting list, or even unlisted, end-stage lung disease patients and might represent an unintended consequence of LAS implementation. Taken further, our data might lead some to conclude that LAS "cut-offs"—scores above which transplantation should not be performed because of futility or inappropriate resource utilization—should be considered. However, it should be noted that the increased risk noted in our study is of similar magnitude to that associated with other clinical characteristics, such as older age or idiopathic pulmonary hypertension, that are not currently considered contraindications to transplant(1).

In conclusion, we have shown that higher LAS scores predict worse post-transplant survival. This difference is present for patients with LAS scores of 60 or greater—a group that comprises an increasing fraction of all transplant recipients. Despite decreased median wait times, patients in LAS groups 3 and 4 have a 1.5- to 2-fold higher risk of death after transplant, compared to those in LAS group 1, and significantly worse 1-year survival. The magnitude of their risk also varies based on their underlying diagnosis. As the lung transplant community strives to improve its outcomes, additional studies aimed at characterizing the impact of the LAS system for all potential recipients and waitlist patients

are needed. Our results advocate for ongoing refinements to the current LAS algorithms to calibrate the projected survival estimates to observed outcomes.

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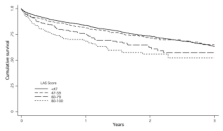

Figure 1.
Kaplan-Meier survival curves based on Lung Allocation Score (LAS). Log-rank test p-value < 0.0001

Table 1

Baseline characteristics of lung transplant recipients by Lung Allocation Score group.

	Lung Allocation Score Group (*LAS*)				
	Overall	**1**	**2**	**3**	**4**
Variable		***≤ 46***	***47 – 59***	***60 – 79***	***> 80***
Number, n (%)	5,331	3,991 (74.9)	714 (13.4)	345 (6.5)	281 (5.3)
Age*	53 ± 13	53 ± 13	53 ± 13	53 ± 13	52 ± 14
Female*	2,216 (41.6)	1,698 (42.6)	284 (39.8)	139 (40.3)	95 (33.8)
LAS score*	43.4 ± 14.5	36.6 ± 4.1	51.3 ± 3.9	68.9 ± 5.6	88.4 ± 3.9
Time on waiting list*, days median (IQR)	81 (24–261)	98 (30–301)	55 (20–177)	44 (12–165)	20 (6–75)
Diagnosis*					
COPD	1,553 (29.1)	1,494 (37.4)	27 (3.8)	20 (5.8)	12 (4.3)
iPH	85 (1.6)	79 (2.0)	3 (0.4)	2 (0.6)	1 (0.4)
Cystic fibrosis	662 (12.4)	512 (12.8)	85 (11.9)	39 (11.3)	26 (9.3)
IPF	1,681 (31.5)	963 (24.1)	389 (54.5)	172 (49.9)	157 (55.9)
Graft failure	211 (4.0)	111 (2.8)	44 (6.2)	20 (5.8)	36 (12.8)
Sarcoidosis	180 (3.4)	141 (3.5)	21 (2.9)	13 (3.8)	5 (0.2)
other	959 (18.0)	691 (17.3)	145 (20.3)	79 (22.9)	44 (15.7)
Hospitalized, in ICU*	404 (7.6)	139 (3.6)	53 (7.7)	69 (20.0)	143 (50.9)
On mechanical ventilation*	274 (5.1)	88 (2.2)	30 (4.2)	45 (13.0)	111 (39.5)
Length of stay post-transplant*, days	24 ± 28	22 ± 26	26 ± 38	32 ± 38	38 ± 36
Donor organ variables					
Donor age	33 ± 14	33 ± 14	34 ± 14	33 ± 14	34 ± 15
Graft ischemia, hrs*	5.0 ± 1.7	5.0 ± 1.7	5.2 ± 1.6	5.3 ± 1.8	5.3 ± 1.7
Donor P/F ratio	384 ± 150	384 ± 150	378 ± 153	383 ± 152	404 ± 139

* p-value for comparisons between LAS groups < 0.05. Percentages do not add up to 100% because of rounding estimates. Reported values are either mean ± standard deviation or number (%) unless otherwise specified.

IQR: interquartile range; COPD: chronic obstructive pulmonary disease; iPH: idiopathic pulmonary hypertension; IPF: idiopathic pulmonary fibrosis; ICU: intensive care unit.

Table 2

Univariate and multivariate hazard ratios of risk of death based on Lung Allocation Score, diagnosis, and transplant center volume.

	Hazard Ratio (95% CI)			
	Lung Allocation Score group			
Model	**1 (≤46)**	**2 (47–59)**	**3 (60–79)**	**4 (80–100)**
All recipients				
Unadjusted	1.00 [reference]	1.08 (0.91 – 1.30)	1.52 (1.21 – 1.90)	2.03 (1.61 – 2.55)
Age-adjusted	1.00 [reference]	1.08 (0.90 – 1.30)	1.52 (1.22 – 1.91)	2.01 (1.63 – 2.58)
Multivariate*	1.00 [reference]	1.05 (0.87 – 1.27)	1.50 (1.19 – 1.89)	2.05 (1.62 – 2.61)
Multivariate + donor†	1.00 [reference]	1.01 (0.82 – 1.24)	1.59 (1.24 – 2.03)	1.97 (1.52 – 2.56)
By selected diagnoses‡				
IPF	1.00 [reference]	1.12 (0.86 – 1.48)	1.87 (1.35 – 2.59)	1.87 (1.32 – 2.63)
COPD	1.00 [reference]	1.06 (0.47 – 2.39)	1.84 (0.76 – 4.48)	12.19 (6.17 – 24.08)
Cystic fibrosis	1.00 [reference]	1.39 (0.80 – 2.41)	1.43 (0.72 – 2.84)	1.56 (0.57 – 4.28)
Graft failure, all cause	1.00 [reference]	0.90 (0.46 – 1.77)	1.07 (0.41 – 2.77)	1.83 (0.94 – 3.56)
By center volume (transplants since LAS)*				
< 80	1.00 [reference]	1.11 (0.70 – 1.77)	1.17 (0.62 – 2.20)	2.36 (1.17 – 4.76)
80–159	1.00 [reference]	1.07 (0.81 – 1.41)	1.57 (1.12 – 2.21)	2.18 (1.55 – 3.09)
160–239	1.00 [reference]	0.74 (0.45 – 1.22)	1.43 (0.89 – 2.30)	1.63 (1.00 – 2.66)
≥ 240	1.00 [reference]	1.33 (0.86 – 2.06)	1.72 (0.96 – 3.09)	2.14 (1.19 – 3.87)

*adjusted for age, diagnosis group, ventilator use, and transplant center volume.

†Multivariate and donor age, graft ischemic time, and donor PaO_2/FiO_2 ratio

‡adjusted for age and transplant center volume.

*adjusted for age and diagnosis group

LAS groups defined as 1 (LAS ≤46), 2 (LAS 47–59), 3 (LAS 60–79), 4 (LAS >80). IPF: idiopathic pulmonary fibrosis; COPD: chronic obstructive pulmonary disease