Impact of the Lung Allocation Score on Lung Transplantation for Pulmonary Arterial Hypertension

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Rationale: In 2005, lung allocation for transplantation in the United States changed from a system based on waiting time to a system based on the Lung Allocation Score (LAS).

Objectives: To study the effect of the LAS on lung transplantation for idiopathic pulmonary arterial hypertension (IPAH) compared with other major diagnoses.

Methods: We studied 7,952 adults listed for lung transplantation between 2002 and 2008. Analyses were restricted to patients with IPAH, idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). Transplantation, waiting list mortality, and post-transplant mortality were compared between diagnoses for patients listed before and after implementation of the LAS.

Measurements and Main Results: The likelihood of transplantation from the waiting list increased for all diagnoses after implementation of the LAS. Waiting list mortality decreased for every diagnosis, except for IPAH, which remained unchanged. Implementation of the LAS was not associated with changes in post-transplant mortality for any diagnosis. Under the LAS system, patients with IPAH were less likely to be transplanted than patients with IPF (hazard ratio [HR], 0.53; $P < 0.001$) or CF (HR, 0.49; $P < 0.001$) and at greater risk of death on the waiting list than patients with COPD (HR, 3.09; $P < 0.001$) or CF (HR, 1.83; $P = 0.025$) after adjustment for demographics and transplant type. Post-transplant mortality for IPAH was not statistically different from that of other diagnoses.

Conclusions: Implementation of the LAS has improved the likelihood of lung transplantation for listed patients with IPAH, but mortality on the waiting list remains high compared with other major diagnoses.

Keywords: lung transplantation; pulmonary arterial hypertension; lung allocation score

Idiopathic pulmonary arterial hypertension (IPAH) has been historically associated with an estimated median survival of less than 3 years (1). With the approval of pulmonary-specific vasodilator therapy, survival has begun to improve over the past decade. Although treatment appears to delay disease progression, many patients continue to deteriorate in spite of maximal medical therapy. Survival among patients requiring treatment with intravenous prostacyclin is approximately 63% at 3 years (2,

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The Lung Allocation Score (LAS) was developed to prioritize patients most in need of transplant and most likely to benefit. The effect of the LAS on patients with pulmonary arterial hypertension has not been studied.

What This Study Adds to the Field

Implementation of the LAS system has improved the likelihood of transplantation for listed patients with pulmonary arterial hypertension, but mortality on the waiting list remains high.

3). Lung transplantation therefore remains an important treatment option for patients with advanced IPAH.

In the United States, donor lung allocation is overseen by the Organ Procurement and Transplantation Network (OPTN), which is operated by the United Network for Organ Sharing (UNOS). Until a few years ago, time on the waiting list had been used to determine priority for lung transplantation. Under this previous system, diagnoses associated with a more rapid decline in lung function, such as idiopathic pulmonary fibrosis (IPF), were believed to be at a disadvantage due to difficulty accruing sufficient time on the waiting list to be transplanted (4). In an attempt to address this problem, a modification was introduced in 1995 granting all patients with IPF an additional 90 days of waiting time. Although this modification increased priority for patients with IPF, it did not address similar discrepancies among other diagnoses (5).

In May of 2005, the OPTN introduced an entirely new allocation system for lung transplantation. Under the new system, each patient is now assigned a Lung Allocation Score (LAS) designed to estimate their survival benefit from a lung transplant (6). The LAS is calculated on the basis of clinical data collected for each patient, including information such as functional status, exercise capacity, lung function, hemodynamic data, and the need for oxygen or ventilatory support (7). Transplant benefit, and thus priority, is determined by predictive models that weigh medical urgency (risk of death while on waiting list) against expected outcome (post-transplant survival at 1 yr). The main objectives guiding development of the LAS were to minimize waiting list mortality, maximize transplant benefit, and ensure the efficient and equitable allocation of donor lungs (7).

Little is known about how the LAS has affected transplantation for patients with IPAH. Studies of the effect of the LAS have focused predominantly on patients with IPF, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) (8–11). Because IPAH accounts for only a minority of the total lung transplants performed each year, studies published to date

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contain little to no information on these patients. The data that do exist indicate that the proportion of patients transplanted for IPAH has decreased relative to other diagnoses but provide little information as to why (9, 10).

In this study, we used national data from UNOS to describe waiting list and post-transplant outcomes for patients with IPAH listed before and after implementation of the LAS. We compared outcomes for patients with IPAH to patients with IPF, COPD, and CF. We hypothesize that by taking medical urgency into account, the current LAS system has increased the prioritization of patients with IPAH and decreased their mortality on the waiting list. Preliminary results of this study have been previously reported in the form of an abstract (12).

METHODS

Study Population

For this analysis, we obtained OPTN data from UNOS for all lung transplantation registrants in the United States listed from May 4, 2002 to May 3, 2008 (Standard Transplant Analysis and Research file #012009-9). We restricted our analyses to 7,952 adult lung transplant candidates (age 18 or older) with one of four primary diagnoses defined in the OPTN database: "Primary Pulmonary Hypertension," "Idiopathic Pulmonary Fibrosis," "COPD/Emphysema," and "Cystic Fibrosis." In adherence with the revised nomenclature and classification of pulmonary hypertension (13), we refer to "Primary Pulmonary Hypertension" as IPAH. Patients classified as "Secondary Pulmonary Hypertension" were excluded, because the proportion of these patients with true pulmonary arterial hypertension could not be reliably ascertained from the database. Listings for combined heart-lung transplantation were excluded to avoid any potential bias resulting from patients with congenital heart disease that may have been misclassified as IPAH. This study was reviewed by the Committee on Human Research at the University of California, San Francisco, and was determined to meet criteria for exempt certification.

Data Analysis

To study the effect of the LAS on donor lung allocation, patients were divided into a "pre-LAS" cohort and a "post-LAS" cohort based on their initial date of registration for lung transplant. The pre-LAS time frame was defined as the 3-year period before implementation of the LAS (May 4, 2002 to May 3, 2005). The post-LAS time frame was defined as the 3-year period after implementation of the LAS (May 4, 2005 to May 3, 2008). Comparison of patient characteristics were performed using *t* tests for continuous variables and χ^2 tests for

categorical variables. Comparison of nonnormally distributed variables, specifically the LAS, were performed using Wilcoxon rank-sum tests. For pairwise comparisons between IPAH and the other three diagnoses, a *P* value less than 0.016 ($= 0.05/3$) was used to determine statistical significance.

Waiting-list outcomes were studied using a survival analysis technique known as "competing risks." Competing risks exist when one type of event prevents another event of interest from occurring. In the case of this analysis, death on the waiting list precludes transplantation, and vice versa. To account for competing risks, we modeled outcomes as a three-state Markov chain consisting of one initial state (alive on the waiting list) and two mutually exclusive absorbing states (transplantation and death on the waiting list) (14). All patients were followed from the time of their initial listing to the time of their removal from the list, including any time during which patients were listed as Status 7 ("temporarily inactive"). Patients removed from the list, for reasons other than transplant or death, represented only a minority of cases and were right-censored at the date of removal. Patients not removed from the list during the defined observation period were treated as alive on the waiting list.

Cumulative incidences of transplantation and death on the waiting list between the pre-LAS and post-LAS periods were compared using Gray's test (15) for each diagnosis group. Gray's test is a nonparametric log-rank type test that compares the equality of cumulative incidence functions of a competing risk and does not require proportionality of hazards. Comparisons of waiting-list outcomes between diagnoses within each LAS period were performed using a method developed by Fine and Gray (16). This approach uses the partial likelihood principle and weighting techniques to define a proportional hazards model for the subdistribution (marginal probability function) of each competing risk. To assess proportionality of hazards between diagnoses, we plotted residuals returned for each competing risk (analogous to Schoenfeld residuals) with respect to time. No major violations of the proportionality assumption were found. In addition, we tested for departures from proportionality directly in our models by using time-varying covariates based on duration of follow-up. Interactions between diagnosis and these covariates were not statistically significant, and therefore were not included in our final models.

Using unadjusted models, we first estimated the hazard ratio (HR) and 95% confidence interval (CI) for IPAH versus each of the other three diagnosis groups for transplantation and death within each LAS period. We then fitted adjusted models that included covariates for age, sex, race, height, weight, blood type, and cytomegalovirus (CMV) status. To account for the influence of lung transplant type, indicator variables for right, left, and bilateral lung requests were added. Alternatively, subgroup analyses including only bilateral lung requests were also performed. Adjusted hazard ratios for the fully adjusted model, including covariates for transplant type, were reported sepa-

TABLE 1. CHARACTERISTICS OF 7,952 PATIENTS LISTED FOR LUNG TRANSPLANTATION

	Pre-LAS (May 2002–May 2005)				Post-LAS (May 2005–May 2008)			
	IPAH	IPF	COPD	CF	IPAH	IPF	COPD	CF
N (%)	278 (6.8)	1,418 (34)	1,717 (42)	706 (17)	141 (3.7)	1,563 (41)	1,537 (40)	592 (15)
Age, years $\pm$ SD	40 $\pm$ 11	55 $\pm$ 9*	57 $\pm$ 6*	29 $\pm$ 9*	43 $\pm$ 13†	58 $\pm$ 9*	58 $\pm$ 6*	30 $\pm$ 9*
Sex								
Female	205 (74)	523 (37)*	944 (55)*	364 (52)*	111 (79)	506 (32)*	802 (52)*	302 (51)*
Race								
White	207 (74)	1,110 (78)	1,585 (92)*	673 (95)*	109 (77)	1,231 (79)	1,410 (92)*	560 (95)*
Black	22 (8)	146 (10)	90 (5)	8 (1)*	11 (8)	129 (8)	97 (6)	10 (2)*
Other	49 (18)	162 (11)*	42 (2)*	25 (4)*	21 (15)	203 (13)	30 (2)*	22 (4)*
Lung request‡								
Right	38 (14)	907 (64)*	1,218 (71)*	12 (2)*	11 (8)	758 (49)*	830 (54)*	15 (3)*
Left	23 (8)	974 (69)*	1,152 (67)*	12 (2)*	10 (7)	865 (55)*	732 (48)*	15 (3)*
Bilateral	267 (96)	683 (48)*	755 (44)*	702 (99)*	137 (97)	945 (60)*	976 (64)*	583 (98)
LAS at listing	NA	NA	NA	NA	33.3 (31.8–35.3)	40.9* (36.0–48.3)	32.6* (31.6–34.0)	36.2* (34.2–39.4)

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score; NA = not applicable.

Values are n (%), mean $\pm$ SD, or median (interquartile range), unless otherwise specified.

* *P* < 0.01 compared to IPAH.

† *P* = 0.05 compared to pre-LAS (for IPAH only).

‡ Lung-request categories are not mutually exclusive.

Figure 1. Cumulative incidence curves comparing transplantation and death on the waiting list before and after implementation of the Lung Allocation Score (LAS) for idiopathic pulmonary arterial hypertension, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and cystic fibrosis combined. Dashed line = pre-LAS; solid line = post-LAS.

rately for each LAS period. To determine whether hazard ratios differed significantly between periods, we used a comprehensive model (including pre- and post-LAS data) to test for interactions between diagnosis and LAS period. For patients listed post-LAS, we fitted additional models that included the log transformation of the LAS at listing as a single continuous covariate and tested for mediation by assessing the magnitude of its effect on the unadjusted estimates. Other variables used to calculate the LAS were excluded from these models to avoid potential collinearity.

In addition to the models just described, we also performed sensitivity analyses that accounted for events that may have occurred after patients were removed from the list. Specifically, we used dates of death from the Social Security Death Master File to identify patients who died after removal from the list and then retested our models treating those patients as alive on the waiting list until their recorded date of death. We also considered alternative models in which removal from the list was treated as death or as a separate competing risk.

Post-transplant mortality among patients who received a lung transplant was evaluated using standard Kaplan-Meier methods. Due to limited follow-up time among transplant recipients listed in the post-

LAS period, we restricted our analyses to events occurring during the first year post-transplant. Log-rank tests were used to compare mortality between the pre- and post-LAS periods and between diagnosis groups within each LAS period. Proportional hazard models were considered but were not used due to nonproportionality detected during the early postoperative period. Competing risk analyses were performed using the *cmprsk* package in R 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria). Standard survival analyses were performed using Stata/IC 10.0 (StataCorp, College Station, TX).

RESULTS

Of 10,539 adults listed for lung transplantation between May 2002 and May 2008, 7,952 (75%) had a primary diagnosis of either IPAH, IPF, COPD, or CF. Among the four major diagnoses, 4,119 (52%) were listed before implementation of the LAS and 3,833 (48%) were listed after implementation of the LAS. Patients with IPAH consisted of 6.8% who were listed in the pre-LAS period and 3.7% of those listed in the post-LAS period ($P < 0.001$).

Patient characteristics for each diagnosis group, pre-LAS and post-LAS, are shown in Table 1. Characteristics of patients with IPAH were similar between the pre-LAS and post-LAS periods except for a small difference in age ($P = 0.05$). In general, patients with IPAH were younger than those with IPF ($P < 0.001$) or COPD ($P < 0.001$) but were older than patients with CF ($P < 0.001$). Patients with IPAH were more likely to be female compared with any of the other three diagnoses ($P < 0.001$ for all pairwise comparisons) and more likely to be non-white compared with patients with COPD ($P < 0.001$) and CF ($P < 0.001$). The proportion of patients requesting bilateral lungs was higher for patients with IPAH than for IPF ($P < 0.001$) or COPD ($P < 0.001$). Among patients listed in the post-LAS period, the median LAS for IPAH was lower than that of IPF ($P < 0.001$) or CF ($P < 0.001$) but was slightly higher than that of COPD ($P = 0.002$).

Waiting-List Outcomes

Cumulative incidence curves for transplantation and death for all four diagnoses combined, before and after implementation of the LAS, are shown in Figure 1. Implementation of the LAS was associated with an overall increased likelihood of transplantation ($P < 0.001$) and an overall decreased risk for death on the waiting list ($P < 0.001$). Cumulative incidence estimates at 6 and 12 months by diagnosis are shown in Table 2. Likelihood of transplantation increased significantly from the pre-LAS to post-LAS period for all four diagnoses ($P < 0.001$ in all

TABLE 2. WAITING LIST OUTCOMES BY DIAGNOSIS BEFORE AND AFTER LAS IMPLEMENTATION

Outcome	Pre-LAS		Post-LAS		P value†
	6 mo*	12 mo*	6 mo*	12 mo*	
Transplantation, %†					
IPAH	10 (6–13)	17 (12–21)	29 (21–36)	37 (29–46)	<0.001
IPF	26 (23–28)	38 (36–41)	68 (65–70)	77 (74–79)	<0.001
COPD	25 (23–27)	39 (37–42)	51 (48–54)	64 (62–67)	<0.001
CF	20 (17–23)	31 (27–34)	54 (49–58)	64 (60–68)	<0.001
Death while on waiting list, %†					
IPAH	8 (5–12)	14 (10–19)	14 (8–20)	20 (12–27)	0.193
IPF	15 (13–17)	21 (19–23)	9 (8–11)	11 (10–13)	<0.001
COPD	3 (2–3)	5 (4–6)	2 (1–3)	3 (2–5)	0.002
CF	10 (8–12)	15 (12–18)	9 (6–11)	10 (7–13)	<0.001

Definition of abbreviations: CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score.

Values are cumulative incidence (95% confidence interval) expressed as percentage.

* Time from initial listing for transplant.

† Gray's test of equality between pre-LAS and post-LAS cumulative incidence functions.

Figure 2. Cumulative incidence curves comparing transplantation and death on the waiting list between diagnoses before and after implementation of the Lung Allocation Score (LAS). Idiopathic pulmonary arterial hypertension (solid line). Idiopathic pulmonary fibrosis (dashed line). Chronic obstructive pulmonary disease (gray line). Cystic fibrosis (dotted line).

cases). Risk of death on the waiting list decreased significantly for every diagnosis, except for IPAH, which showed no significant change ($P = 0.193$).
Diagnosis-specific cumulative incidence curves for each outcome, before and after implementation of the LAS, are shown

in Figure 2. Results of competing risk models used to compare IPAH to each of the other three diagnoses are shown in Table 3. Before implementation of the LAS, likelihood of transplant was highest for COPD and lowest for IPAH (Figure 2, upper left panel). After adjusting for age, sex, race, height, weight, blood

TABLE 3. WAITING LIST OUTCOMES FOR IPAH VERSUS OTHER MAJOR DIAGNOSES

Outcome	IPAH vs. IPF		IPAH vs. COPD		IPAH vs. CF	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Transplantation						
Pre-LAS						
Unadjusted	0.43 (0.33–0.56)	<0.001	0.36 (0.27–0.46)	<0.001	0.51 (0.38–0.67)	<0.001
Adjusted*	0.66 (0.50–0.86)	0.002	0.79 (0.61–1.04)	0.093	0.60 (0.45–0.81)	0.001
Post-LAS						
Unadjusted	0.29 (0.22–0.39)	<0.001	0.43 (0.32–0.58)	<0.001	0.41 (0.31–0.56)	<0.001
Adjusted*	0.53 (0.40–0.71)	<0.001	0.85 (0.64–1.14)	0.280	0.49 (0.36–0.67)	<0.001
Death while on waiting list						
Pre-LAS						
Unadjusted	0.65 (0.48–0.89)	0.008	2.68 (1.90–3.79)	<0.001	0.90 (0.64–1.26)	0.529
Adjusted*	0.43 (0.30–0.62)	<0.001	1.74 (1.18–2.57)	0.005	0.75 (0.52–1.09)	0.131
Post-LAS						
Unadjusted	1.87 (1.26–2.78)	0.002	6.05 (3.87–9.46)	<0.001	2.09 (1.34–3.25)	0.001
Adjusted*	0.91 (0.58–1.42)	0.668	3.09 (1.90–5.05)	<0.001	1.83 (1.08–3.12)	0.025

Definition of abbreviations: CF = cystic fibrosis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LAS = lung allocation score.
* Adjusted for age, sex, race, height, weight, blood type, cytomegalovirus status, type of transplant.

Figure 3. Cumulative incidence curves comparing post-transplant mortality before and after implementation of the Lung Allocation Score (LAS) for idiopathic pulmonary arterial hypertension, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and cystic fibrosis combined. Dashed line = pre-LAS; solid line = post-LAS.

type, CMV status, and type of transplant, patients with IPAH were less likely to receive transplants than patients with IPF (HR, 0.66; 95% CI, 0.50–0.86) and CF (HR, 0.60; 95% CI, 0.45–0.81). After implementation of the LAS, likelihood of transplant was highest for IPF and lowest for IPAH (Figure 2, *upper right panel*). After adjusting for patient demographics and transplant type, patients with IPAH were less likely to receive transplants than patients with IPF (HR, 0.53; 95% CI, 0.40–0.71) and CF (HR, 0.49; 95% CI, 0.36–0.67). Models testing the interaction between diagnosis and LAS period demonstrated that the relative likelihood of transplant decreased significantly between the pre-LAS and post-LAS periods for IPAH versus IPF ($P = 0.02$), but not for comparisons with COPD ($P = 0.622$) and CF ($P = 0.215$).

Before implementation of the LAS, the risk of death while on the waiting list was highest for IPF and lowest for COPD (Figure 2, *lower left panel*). After adjusting for age, sex, race, height, weight, blood type, CMV status, and type of transplant, patients with IPAH were at lower risk of death on the waiting list than patients with IPF (HR, 0.43; 95% CI, 0.30–0.62), but they were at greater risk of death than COPD (HR, 1.74; 95% CI, 1.18–2.57). After implementation of the LAS, risk of death on the waiting list was highest for IPAH and lowest for COPD

(Figure 2, *lower right panel*). After adjusting for patient demographics and transplant type, patients with IPAH were at greater risk of death than patients with COPD (HR, 3.09; 95% CI, 1.90–5.05) and CF (HR, 1.83; 95% CI, 1.08–3.12). Models testing the interaction between diagnosis and LAS period demonstrated that the relative risk of death while on the waiting list for IPAH increased significantly between the pre-LAS and post-LAS periods relative to other major diagnoses ($P < 0.01$ in all cases).

Subgroup analyses that included only patients listed for bilateral lung transplant yielded similar results to our main analyses, which we adjusted for lung transplant type. Sensitivity analyses performed to take into account those deaths that occurred after removal from the waiting list did not substantially affect the significance of our findings. Alternative models in which we treated nontransplant/nondeath removals from the waiting list as a separate competing risk also did not substantially affect our findings (see Table E1 in the online supplement).

For patients listed after implementation of the LAS, we assessed the degree to which the LAS mediated relationships between diagnosis and waiting-list outcomes. LAS at listing was significantly associated with diagnoses (Table 1), and was a strong predictor of both transplantation (HR [per unit change on log scale], 9.66; 95% CI, 6.83–13.67) and death on the waiting list (HR [per unit change on log scale], 2.27; 95% CI, 1.86–2.78). Evidence of partial mediation by the LAS was detected in our models as manifested by a modest reduction in the observed effect size. Specifically, the lower likelihood of transplantation for IPAH relative to IPF and CF, and the increased risk of death for IPAH relative to COPD, were attenuated by differences in LAS at listing. Despite evidence of partial mediation, all observed relationships remained significant after adjustment for the LAS (see Table E2 in the online supplement).

Post-Transplant Mortality

Cumulative incidence of death over the first year post-transplant for all four diagnoses combined, before and after implementation of the LAS, is shown in Figure 3. Implementation of the LAS was not associated with a significant change in overall post-transplant mortality at 1 year ($P = 0.902$). Post-transplant mortality at 6 and 12 months by diagnosis are shown in Table 4. No significant changes in post-transplant mortality were found for any of the four diagnoses between the pre- and post-LAS periods.

Diagnosis-specific cumulative incidence curves for post-transplant mortality, before and after implementation of the LAS, are shown in Figure 4. Before implementation of the LAS, post-transplant mortality for IPAH was higher than for COPD ($P = 0.008$) and CF ($P = 0.037$), but not statistically

TABLE 4. POST-TRANSPLANT MORTALITY BY DIAGNOSIS BEFORE AND AFTER LAS IMPLEMENTATION

Outcome	Pre-LAS		Post-LAS		P value†
	6 mo*	12 mo*	6 mo*	12 mo*	
Death post-transplant, %					
IPAH	20 (12–33)	26 (16–39)	18 (9–32)	18 (9–32)	0.316
IPF	14 (11–17)	21 (18–25)	14 (12–16)	20 (17–22)	0.494
COPD	8 (6–10)	13 (11–16)	10 (8–12)	14 (12–16)	0.054
CF	8 (5–13)	13 (9–18)	6 (4–9)	10 (7–14)	0.981

See Table 2 for definition of abbreviations.

Values are cumulative incidence (95% confidence interval) expressed as percentage.

* Time from transplantation.

† Log-rank test of equality between pre-LAS and post-LAS survivor functions.

Figure 4. Cumulative incidence curves comparing post-transplant mortality between diagnoses before and after implementation of the Lung Allocation Score (LAS). Idiopathic pulmonary arterial hypertension (solid line). Idiopathic pulmonary fibrosis (dashed line). Chronic obstructive pulmonary disease (gray line). Cystic fibrosis (dotted line).

different from IPF ($P = 0.165$). After implementation of the LAS, post-transplant mortality for IPAH was not statistically different from IPF ($P = 0.885$), COPD ($P = 0.446$), or CF ($P = 0.182$).

DISCUSSION

Before May 2005, the allocation of lungs for transplantation in the United States was based on waiting time, which resulted in early listing of patients, long waiting times, and high mortality among patients with an immediate life-threatening illness. The LAS was developed to address these issues by prioritizing patients on the basis of medical urgency and expected outcome. Using national transplant data from UNOS, we found that the LAS has been successful in improving the likelihood of transplantation and decreasing the risk of death for the majority of patients on the waiting list without negatively affecting 1-year post-transplant mortality. Our data indicate, however, that the relative impact of these changes varied substantially between diagnoses. Compared with other diagnoses, transplantation for IPAH remains low, whereas mortality on the waiting list for IPAH is equal or higher.

The fact that the LAS has improved the time to transplantation for all diagnoses is not particularly surprising. Under the previous wait-based system, patients were listed early in the course of their disease, thereby inflating the waiting list with patients for whom transplant was not an immediate consideration. By removing waiting time from the equation, the LAS has drastically reduced the number of patients on the waiting list, effectively shortening time to transplantation for all diagnoses (17). Earlier studies that have attempted to evaluate the impact of the LAS are limited in size, but they suggest that under the new system transplant priority has increased for patients with IPF and decreased for patients with COPD (8, 10). Our results support these findings in that we observed a significant increase in transplantation for IPF, relative to other diagnoses, accompanied by a significant decrease in death on the waiting list. A similar pattern of benefit was observed among patients with CF.

Our results build upon existing data by providing additional insight into those patients with IPAH, a significantly under-

studied population in lung transplantation. We found that the proportion of patients listed for IPAH dropped significantly compared with IPF, COPD, and CF. Despite this, the likelihood of transplantation for IPAH improved from the pre-LAS to post-LAS period. Although this may seem counterintuitive, it reflects an overall reduction in waiting time and a decrease in the total number of patients on the waiting list after implementation of the LAS. In our analysis, we considered likelihood of transplant, given that a patient was listed, and found that transplantation for IPAH did not improve relative to other diagnoses (as was observed in the case of IPF). Furthermore, implementation of the LAS did not reduce mortality on the waiting list for patients with IPAH, despite reductions in mortality observed for IPF, COPD, and CF.

One potential explanation may be that patients with IPAH are less likely to receive transplants because of differences in the available donor pool. For example, patients with IPAH are typically listed for bilateral lung transplant whereas patients with IPF and COPD commonly compete for both single and bilateral lungs. To address this, we controlled for lung transplant type in our analyses. In addition, we also controlled for demographic differences including age, sex, race, height, weight, blood type, and CMV status. Despite taking these factors into account, we still found that patients with IPAH were less likely to receive transplants than patients with IPF and CF, and more likely to die while on the waiting list than patients with COPD and CF. We obtained similar results when we restricted our analyses to the subgroup of patients listed for bilateral lung transplant only.

Another potential explanation for our findings may be differences in LAS at listing. Among those listed in the post-LAS period, we found that patients with IPAH had lower scores than patients with IPF and CF, which explains in part the lower likelihood of transplantation. Despite having lower LAS at listing, patients with IPAH demonstrated higher mortality on the waiting list when taking the lower likelihood of transplantation into account as a competing risk. Emerging data from other studies have led to speculation that the LAS may underestimate the risk of death in patients with IPAH (18). The LAS relies on diagnosis-specific estimating equations for IPF, COPD, CF, and IPAH developed using historical data collected

by UNOS (7). Clinical data most relevant to patients with IPAH (i.e., measures of right ventricular function) were not systematically collected at the time and therefore do not inform the LAS. Hemodynamic variables currently included in the LAS, such as pulmonary capillary wedge pressure, provide little predictive information for patients with IPAH. In contrast, mean right atrial pressure and cardiac index, which are known to be strong predictors of mortality in the pulmonary hypertension (1), are not utilized by the estimating equations for IPAH. Serum biomarkers, such as BNP, that correlate well with right ventricular function (19, 20), may also be important but are not taken into account.

Notably, we found that the observed differences in transplantation and waiting list mortality for IPAH were only partly mediated by differences in LAS itself. Such results suggest that factors other than the LAS at listing are also likely to be involved. In fact, factors determined at the time of organ matching often have a larger impact on determining who ultimately receives a lung transplant. For example, organ size matching, immunologic compatibility, and geographic proximity to the donor hospital are all factors that frequently play an important role. It remains possible there may be something inherent about the lower likelihood of transplantation in IPAH that was not captured in the data used for our analyses.

Other limitations must also be taken into consideration. As previously mentioned, it should be recognized that the changes in listing practices and referral patterns could have contributed to our findings. Because UNOS data contains only information for those on the waiting list, no conclusions can be drawn about patients who may not have been listed as a result of the change in allocation system. Furthermore, secular trends, such as advances in surgical techniques, perioperative management, and immunosuppressive therapy, may have influenced our results. In the case of IPAH, recent advances in pulmonary hypertension therapy could explain, in part, the lower likelihood of transplantation (if newer treatments reduce medical urgency), but does not account for the higher mortality of IPAH while on the waiting list. A more likely explanation may be that, with the accrued waiting time out of the equation and new therapies available, patients with IPAH are listed later in the course of their disease only after medical therapy has already failed. Such patients have often entered into a rapid phase of deterioration, thereby inflating their risk of death while on the waiting list relative to other diagnoses.

In conclusion, our results indicate that although the LAS has been successful in improving the efficiency of lung allocation for the majority of patients, lung allocation remains an ongoing challenge especially for underrepresented diagnoses such as IPAH. Further research is needed to understand why patients with IPAH continue to be at a high risk of death while on the waiting list despite the recently implemented LAS. How data currently collected by UNOS will be used to revise the original predictive models used by the LAS remains to be seen. Modifications of the LAS that include additional information, such as measures of right ventricular function, may help to improve transplant priority for patients with IPAH.

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