Effect of Including Important Clinical Variables on Accuracy of the Lung Allocation Score for Cystic Fibrosis and Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Clinical variables associated with shortened survival in patients with advanced-stage cystic fibrosis (CF) are not included in the lung allocation score (LAS).

Objectives: To identify variables associated with wait-list and post-transplant mortality for CF lung transplant candidates using a novel database and to analyze the impact of including new CF-specific variables in the LAS system.

Methods: A deterministic matching algorithm identified patients from the Scientific Registry of Transplant Recipients and the Cystic Fibrosis Foundation Patient Registry. LAS wait-list and post-transplant survival models were recalculated using CF-specific variables. This multicenter, retrospective, population-based study of all lung transplant wait-list candidates aged 12 years or older from January 1, 2011, to December 31, 2014, included 9,043 patients on the lung transplant waiting list and 6,110 lung transplant recipients between 2011 and 2014, comprising 1,020 and 677 with CF, respectively.

Measurements and Main Results: Measured outcomes were changes in LAS and lung allocation rank. For CF candidates, any *Burkholderia* sp. (hazard ratio [HR], 2.8; 95% confidence interval [CI], 1.2–6.6), 29–42 days hospitalized (HR 2.8; CI 1.3–5.9), massive hemoptysis (HR 2.1; CI 1.1–3.9), and relative drop in FEV_1 $\geq$30% over 12 months (HR 1.7; CI 1.0–2.8) increased wait-list mortality risk; pulmonary exacerbation time 15–28 days (1.8; 1.1–2.9) increased post-transplant mortality risk. A relative drop in FEV_1 $\geq$10% in chronic obstructive pulmonary disease (COPD) candidates was associated with increased wait-list mortality risk (HR 2.6; CI 1.2–5.4). Variability in LAS score and rank increased in patients with CF. Priority for transplant increased for COPD candidates. Access did not change for other diagnosis groups.

Conclusions: Adding CF-specific variables improved discrimination among wait-listed CF candidates and benefited COPD candidates.

Keywords: cystic fibrosis; lung allocation; lung transplant

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At a Glance Commentary

Scientific Knowledge on the Subject: The lung allocation score (LAS) system was implemented in 2005 to help prioritize allocation of donor lungs to candidates in the United States. Variables used to create this score were derived from the Scientific Registry of Transplant Recipients (SRTR), which collects data on all U.S. transplant candidates and recipients. For patients with cystic fibrosis (CF), unique clinical factors that affect their survival are not currently collected by SRTR.

What This Study Adds to the Field: Using a merged database comprising the Cystic Fibrosis Foundation Patient Registry and the SRTR, this study identified important clinical variables that were unavailable when the LAS was created. Clinical variables previously shown to affect morbidity and mortality in the CF population were evaluated to determine whether they improved the predictive accuracy of the LAS. Addition of these variables allowed for improved identification of CF and of some candidates with chronic obstructive pulmonary disease at risk of mortality on the waiting list. Including these variables did not change transplant access for candidates with other diagnoses. These findings demonstrate the importance of comprehensive disease registries and updated patient cohorts in improving the predictive accuracy of lung allocation models to appropriately prioritize candidates, reducing wait-list mortality and optimizing post-transplant survival.

Cystic fibrosis (CF) is the most common lethal autosomal recessive disease among white people, affecting more than 30,000 individuals in the United States (1). Over 1,800 mutations have been found in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene, leading to heterogeneous phenotypes and survival patterns (1, 2). In 2016, the median age of death for people with CF was 29.6 years (1, 2). Because almost all individuals with CF die of respiratory failure, lung

Table 1. Characteristics of Lung Transplant Candidates and Recipients in Lung Allocation Score Remodel Cohort, 2011–2014

Variables	Candidates		Recipients	
	n	%	*n*	%
All patients	9,043	100.00	6,110	100.00
Age				
12–17 yr	138	1.53	95	1.55
18–34 yr	999	11.05	619	10.13
35–49 yr	1,151	12.73	689	11.28
50–64 yr	4,411	48.78	2,940	48.12
⩾65 yr	2,344	25.92	1,767	28.92
Sex				
F	3,859	42.67	2,196	35.94
M	5,184	57.33	3,914	64.06
Race				
White	7,414	81.99	5,072	83.01
Black	799	8.84	502	8.22
Hispanic	605	6.69	394	6.45
Other	225	2.49	142	2.32
Diagnosis group*				
A	2,435	26.93	1,437	23.52
B	325	3.59	181	2.96
C	1,020	11.28	677	11.08
D	5,263	58.20	3,815	62.44
BMI				
<18.5 kg/m^2	812	8.98	538	8.81
18.5 to <25 kg/m^2	3,369	37.26	2,259	36.97
25 to <30 kg/m^2	3,340	36.93	2,299	37.63
30 to <35 kg/m^2	1,444	15.97	961	15.73
⩾35 kg/m^2	78	0.86	53	0.87
Functional status				
No assistance	834	9.22	475	7.77
Some assistance	7,464	82.54	5,186	84.88
Total assistance	743	8.22	448	7.33
Unknown	2	0.02	1	0.02
LAS				
<30	113	1.25	4	0.07
30 to <35	2,750	30.41	1,206	19.74
35 to <40	2,147	23.74	1,190	19.48
40 to <50	1,974	21.83	1,540	25.20
50 to <60	658	7.28	709	11.60
⩾60	1,401	15.49	1,461	23.91
Supplemental oxygen				
Yes	7,400	81.83	5,172	84.65
No	1,643	18.17	938	15.35
Diabetes				
Yes	2,094	23.16	1,474	24.12
No	6,949	76.84	4,636	75.88
Mechanical ventilation				
Yes	583	6.45	323	5.29
No	8,460	93.55	5,787	94.71
Died within 1 yr				
No	8,044	88.95	—	—
Yes	999	11.05	—	—
Transplant within 1 yr				
No	2,933	32.43	—	—
Yes	6,110	67.57	—	—
CF-specific variables				
Any *Staphylococcus* species				
Yes	437	42.84	280	41.36
No	136	13.33	87	12.85
Missing	447	43.82	310	45.79
Any *Burkholderia* species				
Yes	34	3.33	21	3.10
No	713	69.90	443	65.44
Missing	273	26.76	213	31.46

(Continued)

Table 1. (*Continued*)

Variables	Candidates		Recipients	
	n	%	*n*	%
Any *Pseudomonas* species				
Yes	635	62.25	396	58.49
No	249	24.41	194	28.66
Missing	136	13.33	87	12.85
Any *Haemophilus* species				
Yes	24	2.35	9	1.33
No	860	84.31	581	85.82
Missing	136	13.33	87	12.85
Massive hemoptysis				
Yes	56	5.49	30	4.43
No	699	68.53	439	64.84
Missing	265	25.98	208	30.72
Pulmonary exacerbation days				
None	48	4.71	33	4.87
1–28	621	60.88	411	60.71
29–42	70	6.86	48	7.09
⩾43	77	7.55	51	7.53
Missing	204	20.00	134	19.79
Intravenous antibiotic days				
None	648	63.53	432	63.81
1–28	331	32.45	219	32.35
⩾29	41	4.02	26	3.84
Hospitalization days				
None	313	30.69	205	30.28
1–28	616	60.39	408	60.27
29–42	36	3.53	25	3.69
⩾43	55	5.39	39	5.76

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; LAS = lung allocation score. Demographic data, diagnosis, and markers of illness severity for lung transplant candidates and recipients from 2011 to 2014 are shown. CF-specific variables are included with the proportion of total recipients with that variable. Patients with CF comprised 11.3% of total wait-list candidates and 11.1% of total lung transplant recipients.
*Group A = obstructive lung disease; group B = pulmonary vascular disease; group C = cystic fibrosis and immunodeficiency disorders; group D = restrictive lung disease.

transplant is an important therapeutic option for patients with advanced lung disease (1). Lungs are prioritized for allocation to U.S. transplant candidates using the lung allocation score (LAS), a composite score derived primarily by calculating the risk of wait-list mortality and incorporating post-transplant survival (3). The variables used for LAS calculation were derived from the Scientific Registry of Transplant Recipients (SRTR). However, patients with CF have unique clinical characteristics known to predict death that are not collected in Organ Procurement and Transplantation Network (OPTN) data, which populate the SRTR, and are therefore not considered in the LAS calculation (4–6).

We merged the most comprehensive U.S. CF and transplant registries, the CF Foundation Patient Registry (CFFPR) and the SRTR, to include CF-specific variables in the LAS calculation. The impetus for creating this database was to improve the LAS's risk discrimination in the heterogeneous CF population awaiting lung transplant to more accurately identify candidates likely to attain the greatest transplant benefit (7–10). We hypothesized that adding CFFPR variables would improve the LAS calculation to better differentiate CF candidates with the highest risk of mortality on the transplant waiting list and the best chance of survival after transplant (2). Some of the results of these studies have been reported previously in the form of an abstract (11).

Methods

Study Population

This study used SRTR data. The SRTR data system includes data on all donors, transplant candidates, and transplant recipients in the United States, submitted by the members of OPTN. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors. This study was approved by the institutional review boards of the Cleveland Clinic, Cleveland, Ohio (protocol number 17-979), and Seattle Children's Hospital, Seattle, Washington, acting on behalf of the Cystic Fibrosis Foundation (protocol number 15489). Patients in the CFFPR (or guardians for minors) provide informed consent for data to be used for research purposes. We created a database that matched patients found in both the SRTR and CFFPR databases (8, 10). The CFFPR is estimated to include approximately 81–84% of people with CF in the United States and included 29,497 individuals in 2016 (1, 9). Prior validation of the CFFPR, performed in 2012, has demonstrated congruence with the medical record for 82.6–99.9% of recorded variables. The area with the greatest inaccuracy was medications (1.3–17.4%); medical factors had a higher degree of accuracy (95.2–99.9%) (9). The SRTR database includes 100% of U.S. listed lung transplant candidates and recipients. The study cohort included all wait-list candidates aged 12 years or older, the most recent 3-year period in the matched dataset, spanning from January 1, 2011, to December 31, 2,014.

Database Linkage

Database linkage was performed using a deterministic matching algorithm including name, birth date, death date, sex, race, state of residence, and zip code that matched 94% of patients. A second probabilistic linkage was performed for CFFPR patients identified as having undergone transplant in CFFPR data but not identified in the original linkage. The online supplement provides further details of the linkage.

Variable Selection

The study goal was to identify variables from CFFPR data beyond those currently available from SRTR data to improve risk prediction in the models underlying the LAS. We chose CFFPR variables that were reported risk factors for morbidity and mortality in the CF population (1–9). Dichotomous variables were considered positive if noted at any point in the 12 months preceding listing/transplant.

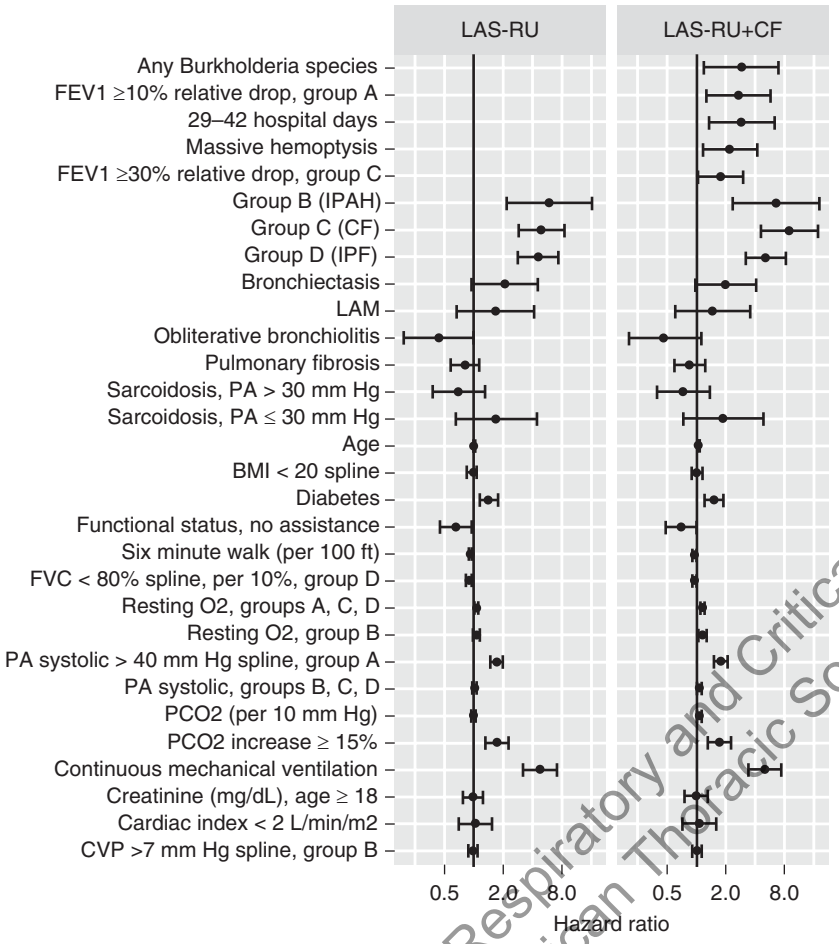

Figure 1. Hazard ratios by variable in the model predicting 1-year wait-list mortality for the updated revised lung allocation score (LAS-RU; left panel) and the updated revised LAS with cystic fibrosis (CF) variables (LAS-RU + CF; right panel). Diagnosis group hazard ratios are based on group A (chronic obstructive pulmonary disease) as a reference group. An increased hazard ratio (>1) indicates an increased risk of wait-list mortality, which increases the LAS. Significant variables, those that increased the hazard ratio for wait-list mortality, were included in addition to the other variables present in the current LAS. The variables any *Burkholderia* species, 29–42 hospitalization days, and massive hemoptysis are present only for group C (CF) candidates. BMI = body mass index; CVP = central venous pressure; IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; PA = pulmonary artery pressure.

Continuous variables were calculated in the 12 months preceding listing/transplant. Variables considered for inclusion in univariate analysis included FEV_1 decline in the year before listing/transplant; massive hemoptysis (defined as acute bleeding ⩾240 ml in a 24-h period or recurrent bleeding >100 ml over several days); pathogens including any *Burkholderia* species, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*; hospital days in the year before listing/transplant; days receiving intravenous antibiotics; number of pulmonary exacerbations; gastroesophageal reflux; pneumothorax; and allergic bronchopulmonary aspergillosis. Variables that predicted outcomes in univariate analysis were included in a multivariable model that included current LAS variables.

We reexamined the data including FEV_1 decline for all diagnosis groups. FEV_1 was studied for inclusion in the original LAS; FEV_1 and FEV_1 decline over a 12-month period were considered for the 2015 revision, but they were not retained by prediction models. We believed that the magnitude of FEV_1 decline in the year preceding listing, rather than during the wait-list period as previously studied, might differentiate wait-list mortality risk among patients with CF. Moreover, FEV_1 is known to be a risk factor for death among non-CF lung transplant patient populations (12, 13). Therefore, we included FEV_1 before listing for patients with CF and after listing for all patients. From the CFFPR data, we computed change in FEV_1 as the relative difference between the value at listing and every value known in the year before listing, and then we computed variables indicating relative FEV_1 decline of ⩾10%, 20%, 30%, 40%, 50%, and 60%. Among all wait-list candidates, we computed a similar variable using SRTR data, indicating a relative change of ⩾10%, 20%, and 30% during any 6-month interval on the list.

Analysis

The original LAS went into effect in 2005, and the first major revision was implemented in 2015 (revised LAS). The cohort used to build the revised LAS comprised a wait-list cohort, spanning from September 1, 2006, to September 30, 2008; and a post-transplant cohort, spanning from May 5, 2005, to September 30, 2008. We updated the revised LAS with a more recent cohort, spanning 2011–2014, to reflect more current SRTR data available for building two new models. First, parameters defining the revised LAS wait-list and post-transplant survival models were refit using candidates and recipients from the updated 2011–2014 cohort, using Cox proportional hazards survival methods to produce updated LAS model coefficients for an updated revised LAS (LAS-RU). Next, each selected CFFPR variable was added in isolation to the updated LAS wait-list and post-transplant survival models. CFFPR variables that improved prediction when added alone were then included in multivariate models, and those retained at the $P < 0.05$ level were kept in the final updated revised LAS with CF model (LAS-RU + CF). LAS and LAS rank were calculated for each of the two models (LAS-RU and LAS-RU + CF).

The LAS is a composite score based on two prediction models: risk of dying on the waiting list within 1 year and probability of surviving 1 year after transplant, normalized on a 0–100 scale. Risk of death on the waiting list is given twice the weight of expected post-transplant survival (3). The lung allocation system uses LAS values to rank candidates from the highest to lowest score, with a lower rank indicating increased access to transplant.

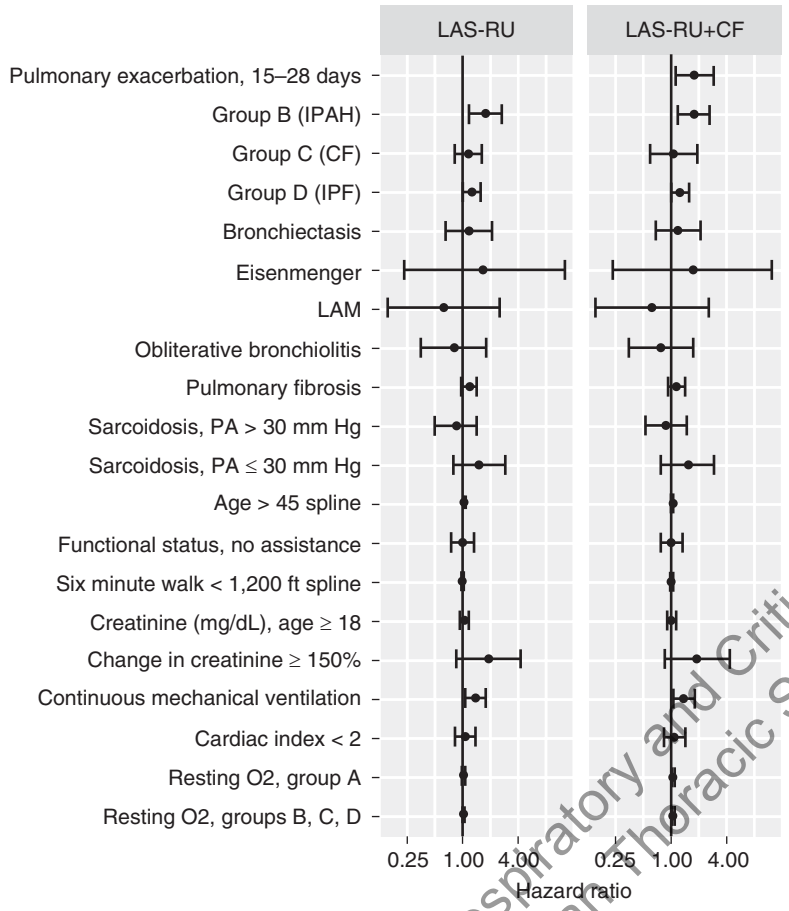

Figure 2. Hazard ratios by variable for the model predicting death within 1 year of transplant for the updated revised lung allocation score (LAS-RU; left panel) and the updated revised LAS with cystic fibrosis (CF) variables (LAS-RU + CF; right panel). An increased hazard ratio (>1) indicates an increased risk of post-transplant mortality, which decreases the LAS. IPAH = idiopathic pulmonary arterial hypertension; IPF = idiopathic pulmonary fibrosis; LAM = lymphangioleiomyomatosis; PA = pulmonary artery pressure.

The analysis was performed using SAS 9.4 and R 3.4.1 software (14, 15).

Results

Baseline Characteristics

The study population comprised 9,043 lung transplant candidates between 2011 and 2014, of whom 6,110 were lung transplant recipients. This cohort included candidates and recipients across four diagnosis groups as designated by the LAS system: group A (obstructive lung disease; e.g., chronic obstructive pulmonary disease [COPD]), group B (pulmonary vascular disease; e.g., idiopathic pulmonary arterial hypertension), group C (CF and immunodeficiency disorders), and group D (restrictive lung disease; e.g., idiopathic pulmonary fibrosis). Candidates with CF (group C) made up 11.3% of the waiting list and 11.1% of the transplant population.

Table 1 shows baseline characteristics of the wait-list and post-transplant cohorts used to remodel the LAS. CF-specific variables are included in Table 1 to demonstrate the characteristics of the CF population. Prevalence of infections among CF candidates included 42.8% with positive cultures for *S. aureus*, 3.3% with any *Burkholderia* species, 62.3% with *P. aeruginosa*, and 2.4% with *H. influenzae*. Of CF candidates, 5.5% had massive hemoptysis, 14.4% had 29 or more days of exacerbation in the previous 12 months, 4% required 29 or more days of intravenous antibiotic use in the previous 12 months, and 8.9% spent 29 or more days in the hospital in the previous 12 months; and 67.6% underwent transplant, and 11.1% died within 1 year. By diagnosis, 59.0%, 55.7%, 66.4%, and 72.5% of candidates in groups A, B, C, and D, respectively, underwent transplant within 1 year of listing; 4.2%, 15.4%, 11.2%, and 13.9%, respectively, died within 1 year while awaiting transplant.

Comparison between LAS-RU and LAS-RU + CF Models

The addition of CF-specific variables improved the predictive accuracy of the LAS wait-list mortality model for CF lung transplant candidates. Variables that increased the risk of death on the waiting list included a relative decline in $FEV_1 \geqslant 30\%$ in the 12 months preceding listing/transplant, presence of any *Burkholderia* species, 29–42 days in the hospital in the 12 months preceding listing/transplant, and massive hemoptysis. Figure 1 shows hazard ratios (HRs) for death on the waiting list derived from the LAS-RU and LAS-RU + CF wait-list mortality models. Presence of any *Burkholderia* species was significant in the model (HR, 2.8; 95% confidence interval [CI], 1.2–6.6; $P = 0.02$). Massive hemoptysis increased the wait-list risk of death (HR, 2.1; 95% CI, 1.1–3.9; $P = 0.02$), as did 29–42 days in the hospital in the 12 months preceding listing (HR, 2.8; 95% CI, 1.3–5.9; $P = 0.01$). A relative 30% FEV_1 decline in the year preceding listing trended toward statistical significance (HR, 1.7; 95% CI, 1.0–2.8; $P = 0.05$). The addition of relative change in FEV_1 on the waiting list also affected COPD candidates, but it did not affect other disease groups. A relative decline of 10% in FEV_1 on the waiting list for group A was associated with increased risk of death (HR, 2.6; 95% CI, 1.2–5.4; $P = 0.01$).

Adding CF-specific variables affected the LAS post-transplant survival model less than the wait-list model. Figure 2 shows HRs resulting from the LAS-RU and LAS-RU + CF post-transplant survival mortality models. In the post-transplant model, adding CFFPR variables did not change the statistical significance of any variables in the model for the updated cohort (Figure 2). The only CFFPR variable that enhanced predictive accuracy of the post-transplant survival model was number of pulmonary exacerbation days. Pulmonary exacerbation time of 15–28 days in the year preceding transplant increased the risk of post-transplant death (HR, 1.8; 95% CI, 1.1–2.9; $P = 0.02$). These findings

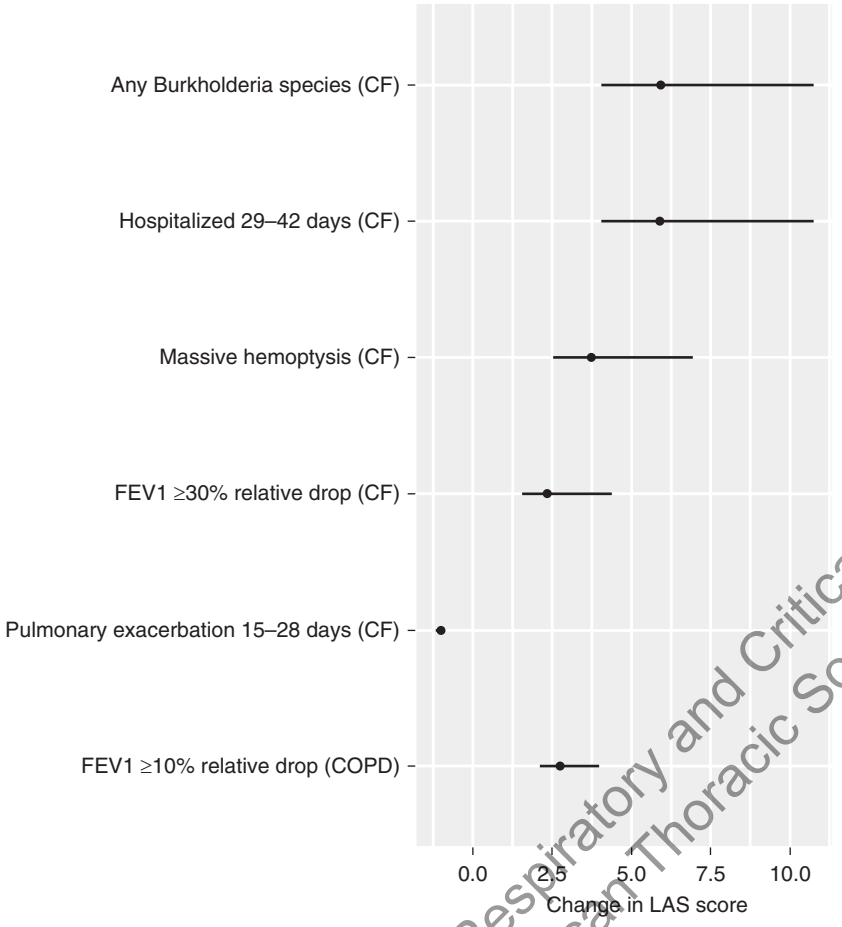

Figure 3. Change in lung allocation score (LAS) for an individual patient using new variables in the updated revised LAS with cystic fibrosis (CF) variables model. Estimated ranges of changes in LAS for an individual patient with CF or chronic obstructive pulmonary disease (COPD) are shown. Pulmonary exacerbations of 15–28 days' duration increased the risk of post-transplant mortality and thus decreased the LAS. Other variables increased the risk of wait-list mortality and thus increased the LAS.

indicate that CF-specific variables are more important to predicting mortality on the waiting list than survival in the first year after transplant. A decline in the FEV_1 in the year before transplant did not affect post-transplant survival for any diagnosis group. Figure 3 shows the estimated range of change in LAS value for a wait-list candidate based on the presence of CF-specific variables. To assess model performance, the C-statistic, Brier score, and Akaike information criterion (AIC) were used. The C-statistic and Brier score were similar and the AIC decreased when we compared the LAS-RU with the LAS-RU + CF model. The changes in AIC indicate improvement in model fit, particularly in the wait-list model, but the similar C-statistic and Brier score may be due to the added variables affecting only some candidates.

Changes in LAS and Transplant Rank between Models

Adding CFFPR variables minimally affected LAS for candidates from diagnosis groups B and D, as expected. Among patients with CF, adding CFFPR variables lowered the median LAS but increased the variability of LAS values. Importantly, a greater number of candidates who died had an increased LAS value, which may have increased their access to transplant. Among CF candidates who died while on the waiting list, 36.8% would have had an LAS increase of at least 5 points with the addition of CFFPR variables. Some recipients in group A, particularly those with LAS values less than 40, had increases in their LAS scores, which correlates with increased access to transplant (Figure 4). Figure E1 in the online supplement demonstrates the change in LAS rank, which follows the LAS trend in Figure 4. A higher LAS value corresponds to a lower numerical rank, meaning a candidate has a higher priority for receiving an organ. Figure E2 shows LAS value by diagnosis group for the LAS-RU and LAS-RU + CF models.

Increased variability occurred in the LAS values of CF candidates on the waiting list with the addition of CF-specific variables to the LAS models. The difference in LAS and LAS rank order by diagnosis group for the LAS-RU and LAS-RU + CF models is shown in Figures 4 and E1, respectively. The addition of the "drop in FEV_1" variable to the models also resulted in improved discrimination of the LAS for transplant candidates with COPD.

Discussion

Principal Findings

Including variables from the CFFPR with SRTR data improved the predictive accuracy of the LAS models for transplant candidates with CF, allowing better identification of those with the highest risk of mortality while on the waiting list and best chance of survival after transplant. The "drop in FEV_1" variable increased the risk for wait-list mortality in candidates with CF and COPD. Adding these variables to the LAS calculation did not adversely affect access to transplant for other diagnosis groups.

LAS and CF

We showed that risk of wait-list mortality was highest for CF candidates with any *Burkholderia* species, massive hemoptysis, and 29–42 days in the hospital over a 12-month period. Including these variables in the LAS calculation resulted in higher scores, increasing access as measured by a higher LAS (lower rank) in this at-risk population. In addition, a relative FEV_1 decline of $\geqslant$30% in the year preceding listing increased risk of death on the waiting list, a trend that referring physicians should consider in identifying high-risk patients for transplant. Another indicator of worsening pulmonary status, 15–28 pulmonary exacerbation days, increased risk of post-transplant death in the first year, indicating that patients sicker before transplant may experience worse survival after transplant.

Perhaps the most well-known variable predicting risk of death in patients with CF

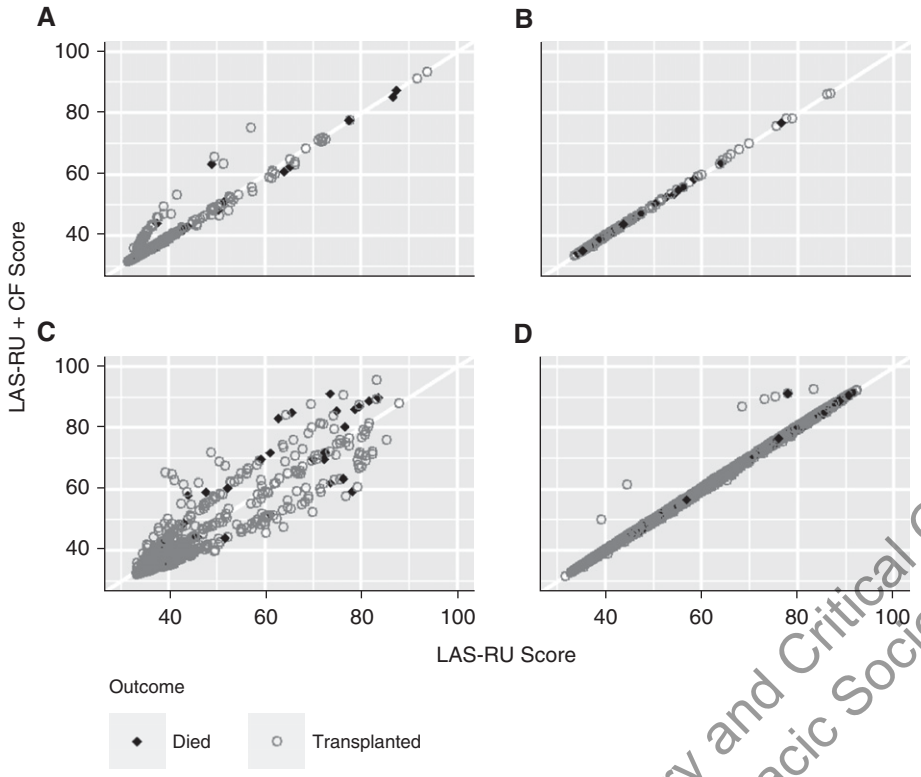

Figure 4. Lung allocation score (LAS) by diagnosis group, updated revised LAS (LAS-RU) versus updated revised LAS with cystic fibrosis (CF) variables (LAS-RU + CF). Gray open circles indicate a single wait-list candidate who underwent transplant, and black closed diamonds indicate a candidate who died while on the waiting list. Candidates who were still waiting for transplant are not represented in the figure. Points above the 45-degree line indicate increased access, and points below the 45-degree line indicate decreased access. (*A*) Obstructive lung disease (group A). (*B*) Pulmonary vascular disease (group B). (*C*) Cystic fibrosis and immunodeficiency disorders (group C). (*D*) Restrictive lung disease (group D).

is FEV_1, which is currently not included in LAS models. An FEV_1 predicted value of ⩽30% has been shown to be an important risk factor for death in patients with CF, and its value in predicting mortality has been replicated across multiple studies (16–18). In addition to the absolute FEV_1 value, decline in FEV_1 in the year before listing has been shown to increase wait-list mortality but not to adversely affect post-transplant survival (6). Our study corroborated the predictive value of a relative decline in FEV_1 of ⩾30%, which was associated with increased risk of death on the waiting list but did not affect post-transplant survival. Massive hemoptysis is also known to be associated with significant morbidity and mortality for patients with CF with end-stage lung disease and has not historically been included in transplant registries (19, 20). In our study, presence of massive hemoptysis in the previous year doubled the odds of death on the waiting list.

Recurrent pulmonary exacerbations are known to increase the risk of death in patients with CF, and increased frequency of exacerbations leads to decremental changes in FEV_1 (2, 19–21). This was also demonstrated for transplant candidates in our study, because the variables "hospitalization days" and "pulmonary exacerbation days" served as significant predictors of wait-list and post-transplant mortality, respectively, though a clear dose–response relationship was not observed. This is likely due to increasing collinearity among variables as candidates with CF clinically worsen. The impact of *Burkholderia cepacia* complex has been studied extensively, with genomovars including *B. cenocepacia* and *B. gladioli* identified as significant risk factors for mortality and postoperative complications (22–26). In our study, presence of any *Burkholderia* species in wait-list CF candidates was a significant risk factor for wait-list death but not post-transplant survival. Genomovar *B. cenocepacia* is known to negatively affect post-transplant survival and is often considered a contraindication to transplant. We were unable to analyze its effect on survival, owing to a small number of patients ($n = 4$) with documented infection or colonization (28, 29).

LAS and COPD

Adding new variables, in this case decline in FEV_1, provided better discrimination of wait-list mortality among transplant candidates with CF and COPD. Transplant candidates with COPD had a higher risk of wait-list death based on an even smaller FEV_1 decline of 10%. Candidates with COPD make up 32% of the U.S. lung transplant waiting list, and lack of the FEV_1 variable has long been a criticism of the LAS (30). Prior research identified FEV_1 as an important predictor of mortality in COPD, and it is included in the BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity), a commonly used tool to predict mortality in patients with COPD (13, 29–34).

In prior iterations of the LAS, both absolute value and change in FEV_1 and FVC were analyzed, but only the absolute FVC value remained in the final LAS model. FEV_1 is a more appropriate physiologic measure of COPD severity, whereas FVC is more applicable in restrictive lung diseases. Our study confirms the importance of FEV_1 in predicting wait-list mortality for lung transplant candidates with COPD. This incongruence with prior iterations of the LAS may reflect our use of a more modern cohort.

Limitations

The CFFPR includes specific data for patients with CF, but these variables, such as FEV_1, infection data, number of hospital days, intravenous antibiotic duration, or exacerbation days, can potentially predict risk of death for candidates from other diagnosis groups. Further investigation of these associations in other patient populations should be considered. An important limitation is lack of longitudinal databases for diseases such as COPD or idiopathic pulmonary fibrosis, which limits the ability to draw conclusions from prelisting clinical status. We compared multiple models—the original LAS, revised LAS, LAS-RU, and LAS-RU + CF—and found that limitations in data collection

existed. Some new data elements, particularly bilirubin values, were added to the OPTN data collection forms when the revised LAS was implemented in 2015, and these were not available for our 2011–2014 cohort. Thus, our models might underestimate the revised LAS in group B (pulmonary vascular disease) patients. Genomovar *B. cenocepacia* data were analyzed because *B. cenocepacia* is commonly considered a contraindication to transplant, but owing to small numbers, we were unable to reach conclusions regarding its effect on risk of death.

Conclusions

The LAS was developed with the goal of allocating organs to candidates at the greatest risk of death and most likely to experience a survival benefit with transplant (3). This goal was not achieved for CF candidates, owing to lack of a comprehensive registry including CF-specific variables. We have shown that including CFFPR variables in the LAS calculation allows for better discrimination of disease severity among CF candidates, providing improved access to transplant for those at the highest risk of death. At the same time, access improved for COPD candidates because of the addition of change in FEV_1. This change for COPD candidates likely reflects use of an updated cohort, arguing for more frequent updates to the cohorts used for LAS calculations. This study demonstrates that using comprehensive disease registries and updated patient cohorts improves prediction of the LAS, allowing lung transplant candidates to receive appropriate prioritization for transplant to reduce wait-list mortality and optimize post-transplant survival. ■

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