Original Investigation

Single- vs Double-Lung Transplantation in Patients With Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis Since the Implementation of Lung Allocation Based on Medical Need

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IMPORTANCE Outcomes of single- and double-lung transplantation have not been rigorously assessed since the allocation of donor lungs according to medical need as quantified by the Lung Allocation Score, which began in 2005.

OBJECTIVE To compare outcomes in single- and double-lung transplant recipients since the Lung Allocation Score was implemented.

DESIGN, SETTING, AND PARTICIPANTS In this exploratory analysis, adults with idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease (COPD) who underwent lung transplantation in the United States between May 4, 2005, and December 31, 2012, were identified in the United Network for Organ Sharing thoracic registry, with follow-up to December 31, 2012. Posttransplantation graft survival was assessed with Kaplan-Meier analysis. Propensity scores were used to control for treatment selection bias. A multivariable flexible parametric prognostic model was used to characterize the time-varying hazard associated with single- vs double-lung transplantation.

EXPOSURE Single- or double-lung transplantation.

MAIN OUTCOMES AND MEASURES Composite of posttransplant death and graft failure (retransplantation).

RESULTS Patients with IPF (n = 4134, of whom 2010 underwent single-lung and 2124 underwent double-lung transplantation) or COPD (n = 3174, of whom 1299 underwent single-lung and 1875 underwent double-lung transplantation) were identified as having undergone lung transplantation since May 2005. Median follow-up was 23.5 months. Of the patients with IPF, 1380 (33.4%) died and 115 (2.8%) underwent retransplantation; of the patients with COPD, 1138 (34.0%) died and 59 (1.9%) underwent retransplantation. After confounders were controlled for with propensity score analysis, double-lung transplants were associated with better graft survival in patients with IPF (adjusted median survival, 65.2 months [interquartile range {IQR}, 21.4-91.3 months] vs 50.4 months [IQR, 17.0-87.5 months]; $P < .001$) but not in patients with COPD (adjusted median survival, 67.7 months [IQR, 25.2-89.6 months] vs 64.0 months [IQR, 25.2-88.7 months]; $P = .23$). The interaction between diagnosis type (COPD or IPF) and graft failure was significant ($P = .049$). Double-lung transplants had a time-varying association with graft survival; a decreased instantaneous late hazard for death or graft failure among patients with IPF was noted at 1 year and persisted at 5 years postoperatively (instantaneous hazard at 5 years, hazard ratio, 0.67 [95% CI, 0.52-0.84] in patients with IPF and 0.89 [95% CI, 0.71-1.13] in patients with COPD).

CONCLUSIONS AND RELEVANCE In an exploratory analysis of registry data since implementation of a medical need–based lung allocation system, double-lung transplantation was associated with better graft survival than single-lung transplantation in patients with IPF. In patients with COPD, there was no survival difference between single- and double-lung transplant recipients at 5 years.

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Before 2005, lung transplant allocation in the United States was based on accumulated time on the lung transplant waiting list after matching for ABO blood type.[1] In response to increasing wait times, the US Department of Health and Human Services issued a Final Rule mandating the development of an allocation system based on medical need instead of waiting time. The resulting system—the Lung Allocation Score (LAS) organ allocation algorithm—was implemented on May 4, 2005.[2] A patient's LAS is based on risk factors associated with either wait list or posttransplantation mortality.[3] Analyses of early post-lung transplantation survival have suggested equivalent outcomes before and after the LAS was implemented, despite the increase in patient comorbidities noted in lung transplant recipients after implementation.[4,5] Because this implementation occurred only recently, moderate- and long-term outcomes in patients who have undergone lung transplantation since then have been unavailable for study.

Single- and double-lung transplantation represent therapeutic options in patients with advanced lung disease refractory to medical management.[6] Analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry has shown that survival is better in double-lung than single-lung transplant recipients (median survival, 6.7 vs 4.6 years; $P < .001$), although this association is confounded by the large differences between these populations, particularly with respect to patients' underlying conditions.[7] More focused analyses of the ISHLT and United Network for Organ Sharing (UNOS) registries have shown improved 10-year survival with double-lung transplantation in patients with chronic obstructive pulmonary disease (COPD) but equivalent 5-year outcomes between single- and double-lung transplantation in patients with idiopathic pulmonary fibrosis (IPF), after adjustment for patient comorbidities.[8,9] However, the data used in these analyses were largely collected before the LAS was implemented. The use of the LAS has brought with it a change in the demographics of single- and double-lung transplant recipients; what effect this may have on posttransplantation outcomes has not been assessed.[5] In this study, we reviewed UNOS data to summarize the contemporary demographics and outcomes of IPF and patients with COPD who underwent single- or double-lung transplantation since the LAS was implemented.

CMV *cytomegalovirus*
HLA *human leukocyte antigen*
LAS *Lung Allocation Score*
pTLC *predicted total lung capacity*
PRA *panel reactive antibody*

Methods

Study Population and Primary End Point

We retrospectively reviewed data from UNOS and the Organ Procurement and Transplantation Network. The institutional review boards at both Baylor St Luke's Medical Center, Houston, Texas, and Stanford Hospital and Clinics, Stanford, California, granted the study an exemption because the data analyzed were deidentified. Demographic and clinical characteristics at the time of transplantation were compared between single- and double-lung transplant recipients with a diagnosis of IPF or COPD. The study's primary end point was graft survival, a composite of posttransplantation mortality and graft failure (ie, retransplantation). Patients were censored at the time of last known follow-up. Analyses were conducted with Stata software, version 13 (StataCorp).

Statistical Analyses

The standardized differences approach (as opposed to 2-sample *t* test and χ^2 or Fisher exact test) was used to compare covariates between single- and double-lung transplant recipients to facilitate comparison with subsequent weighted analyses.[10] Means are presented with standard deviations, and hazard ratios (HRs) are presented with 95% confidence intervals. All testing was 2-sided, and $P \leq .05$ was considered significant; because of the exploratory nature of this study, no adjustments were made for multiple comparisons.[11] Posttransplantation survival distributions were estimated with the nonparametric Kaplan-Meier method.[12] The log-rank test was used to compare differences between survival distributions in the unadjusted analyses, whereas adjusted survival curves were generated by using the approach of Cole and Hernan, and both the stratified log-rank test and Cox regression–based test for equality of survival curves were used to compare adjusted curves.[13-15]

Center Volume and Center-Specific Variation

Because both center volume and center-specific variation are independently associated with posttransplantation outcomes,[16] we included these variables in our analysis. A transplant center was considered high volume if it performed at least 388 lung transplantations during the 93-month study period (≥50 transplantations/year) and moderate volume if it performed 194 to 377 lung transplantations (25-49 transplantations/year). Cut points were chosen by using a restricted cubic spline analysis; these cut points have been used in previous studies.[17] The annual transplantation volume of centers varied minimally during the study period. Center-specific variation in posttransplantation graft survival was modeled as a random effect in a multivariable Cox model with random effects that included all variables listed in **Table 1** and **Table 2**.[19] Given that random-effects models have yet to be extended to flexible parametric analysis (our analysis of choice for prognostic model building), the random association between center and outcomes was calculated for all 72 transplant centers, and a dichotomous variable representing centers in the top third of graft survival performance was generated to account for center-specific variation in subsequent analyses.

Missing Data

Variables with missing values were imputed to avoid case deletion in our propensity score and multivariable analyses.[20] Multiple imputation involving all nonredundant variables was performed by using a regression switching (chained equations) approach with predictive mean matching for continuous and semicontinuous variables, logistic regression for binary variables, and ordered logistic regression for ordinal variables; the model included the event indicator and the

Table 1. Characteristics at the Time of Single-Lung or Double-Lung Transplant in IPF and COPD Subgroups for Nonimputed Data Set

	IPF						COPD					
	Unadjusted			Weighted			Unadjusted			Weighted		
	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]
Total No. of patients in study population	2010	2124					1299	1875				
Baseline characteristics												
Age, y												
Mean (SD)	62.8 (7.3)	57.5 (9.0)	0.646	59.0	59.9	0.112	61.6 (5.5)	59.4 (6.4)	0.364	60.3	60.3	0.000
>60	1387 (69.0)	919 (43.3)	0.537	54.4	54.3	−0.002	815 (62.7)	879 (46.9)	0.323	54.6	53.0	0.033
Male	1484 (73.8)	1498 (70.5)	0.074	71.0	71.4	0.009	611 (47.0)	1023 (54.6)	0.151	50.7	51.0	0.006
Race												
White	1706 (84.9)	1691 (79.6)	0.138	82.5	81.5	0.026	1206 (92.8)	1708 (91.1)	0.064	92.5	92.0	0.019
African American	90 (4.5)	168 (7.9)	0.143	6.2	6.2	0.002	70 (5.4)	132 (7.0)	0.068	5.7	6.2	0.019
Hispanic	155 (7.7)	201 (9.5)	0.063	8.4	9.6	0.045	14 (1.1)	19 (1.0)	0.006	1.2	1.0	0.024
College education	1179 (64.7)	1081 (58.3)	0.131	61.6	61.0	0.012	522 (45.3)	710 (42.3)	0.061	44.3	44.1	0.003
Private insurance	1061 (52.9)	1430 (67.4)	0.299	60.2	59.7	0.010	553 (42.7)	913 (48.8)	0.121	47.2	46.4	0.018
Body mass index[d]												
Mean (SD)	27.6 (3.8)	27.3 (4.1)	0.076	27.2	27.4	0.041	24.7 (4.1)	24.5 (4.2)	0.048	24.5	24.6	0.040
≤18 or ≥35	54 (2.7)	68 (3.2)	0.030	3.1	3.0	0.007	56 (4.3)	96 (5.1)	0.038	4.8	4.6	0.005
Illness severity/ functional status												
Lung Allocation Score, mean (SD)[e]	48.7 (15.3)	55.6 (18.8)	0.405	52.9	52.3	0.034	34.2 (4.4)	35.9 (8.2)	0.252	35.6	35.2	0.059
NYHA class												
IV	194 (9.7)	370 (17.4)	0.228	15.8	13.7	0.060	78 (6.0)	179 (9.6)	0.133	8.2	8.3	0.001
III or IV	1780 (88.6)	1952 (91.9)	0.113	90.5	90.6	0.004	1144 (88.1)	1711 (91.3)	0.105	90.1	90.6	0.017
6-min walk												
Distance, mean (SD), ft	817 (462)	750 (474)	0.144	768	779	0.023	715 (334)	752 (372)	0.104	732	741	0.024
<500 ft	1480 (73.7)	1441 (68.1)	0.124	68.9	70.2	0.027	319 (24.7)	452 (24.2)	0.011	23.9	24.4	0.013
Life support												
Ventilator	40 (2.0)	154 (7.3)	0.253	5.3	4.2	0.056	18 (1.4)	44 (2.4)	0.071	1.5	2.0	0.034
Extracorporeal membrane oxygenation	11 (0.6)	47 (2.2)	0.143	0.8	1.3	0.044	0	10 (0.5)	0.104	0	0.4	0.088
Ventilation/oxygenation												
Forced vital capacity, mean (SD), %	47.5 (15.3)	46.3 (17.3)	0.074	46.4	46.7	0.018	51.8 (16.7)	51.4 (17.2)	0.025	51.2	51.7	0.032
Oxygen requirement at rest	1843 (91.7)	2037 (96.0)	0.177	95.3	93.6	0.028	1196 (92.2)	1744 (93.2)	0.038	93.1	92.8	0.013
Hemodynamics												
Cardiac index, mean (SD), L/min/m^2	2.82 (0.68)	2.83 (0.71)	0.013	2.83	2.84	0.008	2.86 (0.70)	2.92 (0.72)	0.078	2.88	2.89	0.004
Pulmonary artery pressure, mm Hg												
Mean (SD)	23.2 (7.5)	27.9 (11.2)	0.495	25.3	25.5	0.020	25.1 (6.7)	26.4 (8.1)	0.167	25.8	25.8	0.013
≥30, mean (SD)	338 (16.9)	780 (37.0)	0.463	26.1	27.0	0.021	306 (23.6)	497 (26.6)	0.068	26.8	24.2	0.061
PCWP, mean (SD), mm Hg	9.5 (4.0)	10.0 (5.5)	0.099	9.75	9.74	0.003	11.9 (5.0)	12.4 (5.2)	0.094	12.1	12.1	0.002

(continued)

Table 1. Characteristics at the Time of Single-Lung or Double-Lung Transplant in IPF and COPD Subgroups for Nonimputed Data Set (continued)

	IPF						COPD					
	Unadjusted			Weighted			Unadjusted			Weighted		
	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]
Renal function												
Creatinine clearance, mL/min												
Mean (SD)	98.3 (27.6)	107.0 (31.0)	0.297	106.3	103.3	0.100	91.2 (26.2)	96.3 (28.1)	0.102	94.0	93.9	0.004
<50 or dialysis	27 (1.3)	25 (1.2)	0.015	1.0	1.1	0.010	41 (3.2)	32 (1.7)	0.094	2.2	2.4	0.011
Diabetes	408 (20.3)	452 (21.3)	0.024	21.4	21.4	0.001	142 (10.9)	203 (10.9)	0.003	11.3	11.3	0.000
Lung preference at transplantation												
Double only	44 (2.2)	1354 (63.8)	1.732	3.6	59.6	1.576	31 (2.4)	1276 (68.1)	1.892	3.0	65.7	1.808
Single only	1381 (68.7)	32 (1.5)	1.982	61.3	2.1	1.746	830 (63.9)	38 (2.0)	1.747	57.1	2.5	1.543
Single or double	585 (29.1)	738 (34.8)	0.121	35.1	38.3	0.069	438 (33.7)	561 (29.9)	0.082	39.9	31.8	0.174
Transplant center characteristics												
High-performing transplant center[f]	765 (38.1)	744 (35.0)	0.063	37.6	36.2	0.030	455 (35.0)	793 (42.3)	0.150	41.8	39.7	0.043
Moderate- or high-volume institution[g]	1501 (74.7)	1602 (75.4)	0.017	73.2	74.4	0.026	837 (64.4)	1345 (71.7)	0.157	67.7	67.6	0.002
High-volume institution[h]	790 (39.3)	857 (40.4)	0.021	38.0	38.8	0.017	334 (25.7)	792 (42.4)	0.358	36.6	35.5	0.018

Abbreviations: COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.

[a] Data are expressed as No. (%) of patients unless otherwise indicated.

[b] The standardized differences approach was used to compare means and prevalences of baseline characteristics for assessment of variable balance in nonweighted and inverse probability weighted samples.

[c] Data are expressed as weighted percentage unless otherwise indicated.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] The Lung Allocation Score (range, 0-100) is based on risk factors associated with either wait list or posttransplantation mortality.[3] A higher score implies a higher-acuity patient who would benefit from lung transplantation, and patients with higher scores are given preference for organs.

[f] In the top third of graft survival performance among all 72 transplant centers.

[g] Performed more than 194 lung transplants during the 93-month study period (>25 transplants/year).

[h] Performed at least 388 lung transplants during the 93-month study period (≥50 transplants/year).

Nelson-Aalen estimator of the hazard of death.[21,22] Twenty imputations were performed in light of our large sample size and small amount of missing data (<10%).[23]

Propensity Score Analysis

Observed preoperative differences between single- and double-lung transplant recipients were controlled for with propensity score analysis.[24] Separate propensity scores were generated for the IPF and COPD patient cohorts by using a doubly robust augmented inverse probability of treatment weighting (IPTW) estimator that included all available variables except for lung preference and organ ischemic time (2 variables directly affected by whether a patient received single- or double-lung transplant).[25] Balance between covariates was assessed between the weighted groups by using the standardized differences approach and by comparing the distribution of propensity scores and covariates in our unadjusted and IPTW-adjusted analyses.[10,26]

Flexible Parametric Analysis

An extensive sensitivity analysis was undertaken to corroborate the findings from our propensity score analysis. We initially used Cox proportional hazards regression modeling to assess the association of demographic, clinical, transplant center, operative, and donor characteristics with graft survival after lung transplantation in both the COPD and IPF patient cohorts.[27] A test for interaction between diagnosis (COPD and IPF) and treatment type (single- or double-lung transplantation) was performed. When the proportional hazards assumption was tested with the Grambsch-Therneau method[28] of plotting scaled Schoenfeld residuals, we noted that the variable of interest (single- vs double-lung transplant) had a time-varying association with survival. We therefore used a flexible parametric analysis that used restricted cubic splines with varying spline knots as described by Royston and Parmar[29] (RP model) to facilitate fitting the nonproportional effect of single- vs double-lung transplant. The proportional hazards scale was used in our RP models to facilitate the comparison of HRs obtained in our study with those obtained from Cox models in other studies. Purposeful selection of covariates was used to create the models; variables hypothesized or previously shown to be of clinical significance in lung transplant recipients were included, along with novel variables that were plausibly significant ($P \leq .20$) on bivariable analysis.[30] Variables that were not statistically significant ($P > .05$) by the Wald test in our multivariable models but that were plausibly associated with graft

Table 2. Operative Characteristics, Donor Characteristics, and Donor-Recipient Matching at the Time of Single-Lung or Double-Lung Transplantation in IPF and COPD Subgroups for Nonimputed Data Set

	IPF						COPD					
	Unadjusted			Weighted			Unadjusted			Weighted		
	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]
Total No. of patients in study population	2010	2124					1299	1875				
Operative characteristics												
Double-lung transplant	0	2124 (100)	NA	0	100	NA	0	1875 (100)	NA	0	100	NA
Right single-lung transplant	886 (44.2)	NA	NA	46.8	NA	NA	668 (51.4)	NA	NA	50.8	100	NA
Year of wait list or transplantation, median (IQR)	2009 (2007-2011)	2009 (2007-2011)	0.129	2009	2009	0.024	2008 (2006-2010)	2009 (2007-2011)	0.253	2009	2009	0.042
Organ ischemic time, mean (SD), h	4.36 (1.37)	5.62 (1.62)	0.840	4.39	5.64	0.834	3.90 (1.34)	5.52 (1.60)	1.094	3.94	5.46	1.027
Distance organ transported, median (IQR), mile	176 (26-361)	163 (26-351)	0.046	148	166	0.017	104 (12-307)	103 (13-308)	0.009	97	105	0.006
Local organ (nonregional, nonnational)	891 (44.3)	1010 (47.6)	0.065	47.5	46.6	0.019	743 (57.2)	1101 (58.7)	0.031	58.6	58.5	0.001
Donor characteristics												
Age, y												
Mean (SD)	34.5 (14.4)	34.4 (14.6)	0.008	34.3	34.4	0.006	34.0 (14.2)	35.4 (14.3)	0.097	34.6	34.8	0.007
>50	354 (17.6)	384 (18.1)	0.012	16.3	18.0	0.043	224 (17.2)	357 (19.0)	0.047	18.4	18.0	0.009
Po_2:FIo_2 ratio												
Mean (SD)	437 (116)	442 (104)	0.042	439	440	0.010	433 (109)	435 (112)	0.018	433	433	0.002
<250	107 (5.4)	82 (3.9)	0.070	5.0	4.1	0.044	75 (5.8)	112 (6.0)	0.008	5.4	6.4	0.041
Smoking history >20 pack-years	245 (12.3)	200 (9.5)	0.093	11.1	10.5	0.019	153 (11.9)	255 (13.8)	0.056	12.4	12.7	0.007
CDC high-risk donor[d]	133 (6.6)	153 (7.2)	0.023	6.6	6.5	0.006	79 (6.1)	182 (9.7)	0.135	7.9	8.1	0.009
Hypertension	478 (23.9)	471 (22.3)	0.039	24.3	23.5	0.019	298 (23.1)	439 (23.5)	0.011	22.2	22.9	0.017
Diabetes	138 (6.9)	136 (6.4)	0.019	6.8	7.0	0.005	90 (6.9)	137 (7.4)	0.016	6.9	7.3	0.016

(continued)

survival were included in our final models; covariate selection was also guided by optimizing the Akaike information criterion, as was the selection of the number of internal spline knots in the RP model (4) and spline knots for time-dependent effects (2).[31,32] Univariate and multivariable HRs were generated by using both Cox regression and a flexible parametric RP model; results from the 2 approaches were compared (eTables 1 and 2 in the Supplement).

Covariates used in both the COPD and IPF models included age, sex, insurance status, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), New York Heart Association (NYHA) functional status, 6-minute walk test performance, a life support (ventilator or extracorporeal membrane oxygenation) requirement, pulmonary hypertension, dialysis dependence or a creatinine clearance less than 50 mL/min, transplant center performance, transplant center volume, donor age, a donor diagnosis of diabetes, a donor-recipient race match, a donor-recipient human leukocyte antigen (HLA) mismatch, an elevated panel reactive antibody (PRA) level, and the variable of interest: whether the patient underwent single- or double-lung transplantation (modeled as having a time-dependent effect). Variables specific to the COPD model included diabetes status and an oversized donor lung (donor/recipient predicted total lung capacity [pTLC] ratio ≥1.1). Variables specific to the IPF model included race, whether the organ was procured regionally, a donor smoking history of more than 20 pack-years, and a close size match between donor and recipient (ie, a donor/recipient pTLC ratio of 0.8-1.2).

Results

We identified 12 330 usable records of patients with a documented LAS who underwent lung transplant between May 4, 2005, and December 31, 2012. We excluded 11 patients identified as having received transplants since the LAS was implemented but without an identifiable LAS, 57 patients who underwent multiorgan transplantation, and 370 patients who were younger than 18 years, resulting in a cohort of 11 892 adults who underwent single-lung (n = 4136) or double-lung (n = 7756)

Table 2. Operative Characteristics, Donor Characteristics, and Donor-Recipient Matching at the Time of Single-Lung or Double-Lung Transplantation in IPF and COPD Subgroups for Nonimputed Data Set (continued)

	IPF						COPD					
	Unadjusted			Weighted			Unadjusted			Weighted		
	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]	Single Lung[a]	Double Lung[a]	Standardized Difference[b]	Single Lung[c]	Double Lung[c]	Standardized Difference[b]
Donor-recipient matching												
Sex match, No. (%)	1398 (69.6)	1371 (64.6)	0.107	68.5	66.6	0.042	877 (67.5)	1343 (71.6)	0.089	68.6	69.2	0.012
Race match, No. (%)	1128 (56.1)	1156 (54.4)	0.034	54.9	54.9	0.000	789 (60.7)	1222 (65.2)	0.092	60.8	62.9	0.042
Donor positive for CMV, recipient negative	527 (26.2)	561 (26.4)	0.004	26.2	25.7	0.014	293 (22.6)	477 (25.4)	0.68	23.4	24.8	0.033
Donor/recipient pTLC ratio												
Mean (SD)[e]	0.97 (0.16)	0.95 (0.17)	0.126	0.96	0.97	0.013	1.15 (0.20)	1.11 (0.19)	0.213	1.13	1.13	0.035
≥1.1	311 (15.5)	305 (14.4)	0.031	14.5	15.9	0.040	674 (52.1)	820 (43.9)	0.164	49.2	47.6	0.031
0.8-1.2	1565 (78.0)	1555 (73.3)	0.108	77.3	74.8	0.059	851 (65.7)	1350 (72.2)	0.141	66.9	69.0	0.046
Nonidentical ABO blood group match (only compatible)	165 (8.2)	126 (5.9)	0.091	8.3	7.1	0.050	132 (10.2)	206 (11.0)	0.027	11.0	10.8	0.007
Total HLA mismatches (maximum, 6), mean (SD)	4.7 (1.1)	4.6 (1.1)	0.028	4.6	4.6	0.000	4.6 (1.1)	4.6 (1.1)	0.004	4.59	4.60	0.012
Complete HLA mismatch (all 6 alleles mismatched)	402 (22.7)	434 (22.5)	0.004	22.4	23.4	0.025	228 (21.9)	360 (21.4)	0.011	22.7	21.9	0.006
Panel reactive antibody, %												
Mean (SD)	4.8 (12.9)	5.7 (14.8)	0.065	5.6	5.6	0.003	5.6 (16.5)	5.1 (14.7)	0.035	5.50	5.35	0.009
≥20	152 (8.2)	207 (10.4)	0.078	9.4	10.1	0.025	106 (9.0)	145 (8.3)	0.027	9.0	8.6	0.012
≥10	244 (13.1)	299 (15.1)	0.056	14.0	14.9	0.025	149 (12.7)	218 (12.4)	0.008	13.5	13.2	0.011

Abbreviations: CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; HLA, human leukocyte antigen; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; NA, not applicable; pTLC, predicted total lung capacity.

[a] Data are expressed as No. (%) of patients unless otherwise indicated.

[b] The standardized differences approach was used to compare means and prevalences of baseline characteristics for assessment of variable balance in nonweighted and inverse probability weighted samples.

[c] Data are expressed as weighted percentage unless otherwise indicated.

[d] A donor who is thought to be at high risk of human immunodeficiency virus, hepatitis B/C virus, or sexually transmitted infection according to Centers for Disease Control and Prevention (CDC) criteria.[18]

[e] Ratio of pTLC of the donor over pTLC of the recipient. The pTLC is calculated for men as 7.99×(height in meters)−7.08 and for women as 6.60×(height in meters)−5.79.

transplantation. The median duration of follow-up was 23.5 months (interquartile range [IQR], 8.3-46.3 months).

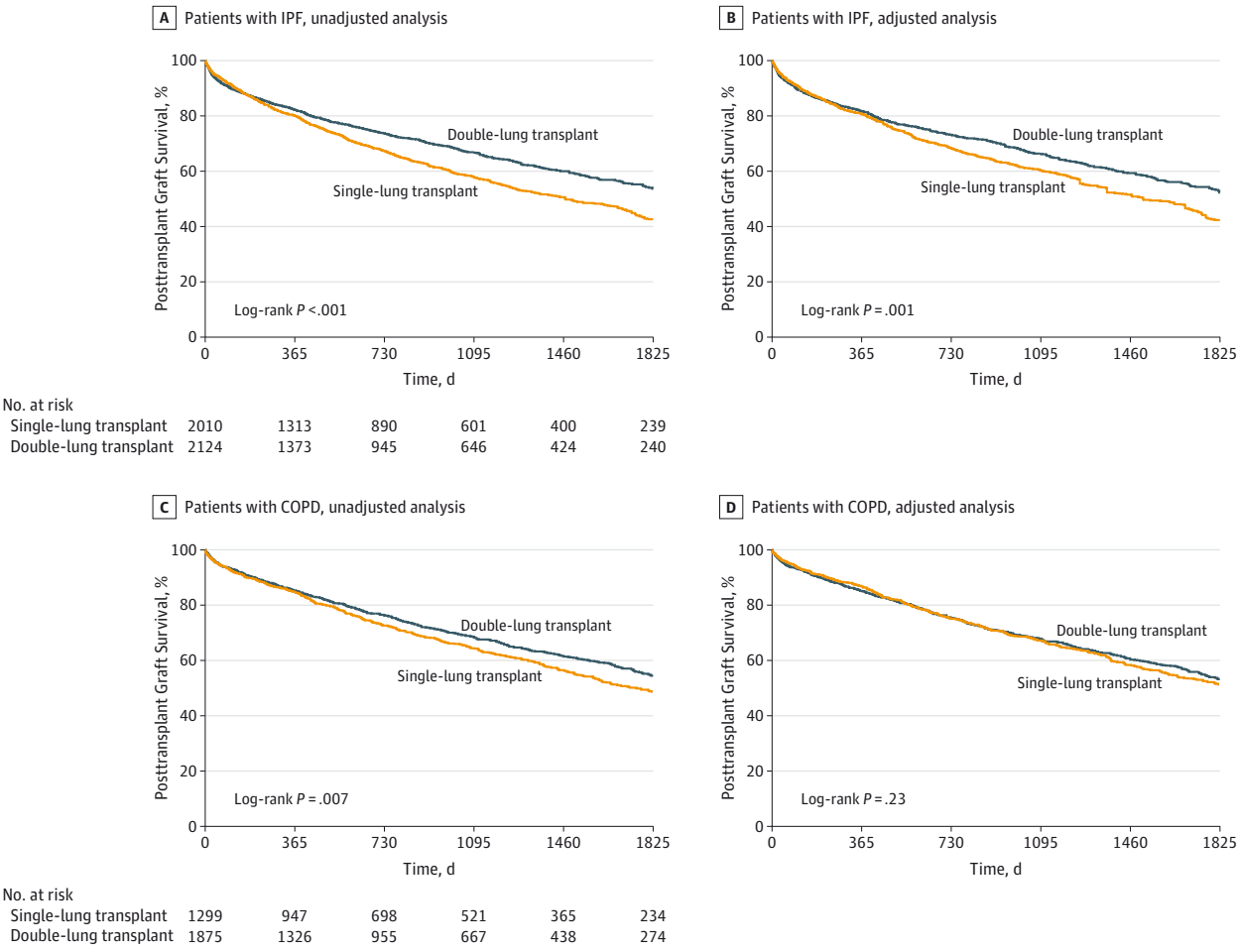
Of the 11 892 patients, 1322 were initially listed for transplant before LAS implementation and were relisted afterward with an identifiable LAS score. More than 80% of single-lung transplantations were performed among patients with either COPD or IPF, and we limited our study to 2 separate analyses of patients with IPF (n = 4134) and COPD (n = 3174) to avoid confounding by underlying condition. A significant interaction (P = .049) was observed between diagnosis (COPD or IPF) and treatment type (single- or double-lung transplantation), substantiating the decision to analyze COPD and IPF patients separately (eTable 3 in the Supplement).

A total of 72 US transplant centers were identified that performed 2 to 855 lung transplantations (median, 274; IQR, 168-457) since LAS implementation. Center-specific variation was modeled as a random effect in a multivariable mixed-effects Cox model and was found to be significant (likelihood ratio test of $\theta = 0$, 30.51; $P < .001$).

Patient Characteristics in Unadjusted and Weighted Comparisons

In both patients with IPF and patients with COPD, single- and double-lung transplant recipients differed with respect to the majority of demographic, clinical, transplant center, operative, and donor characteristics measured (Table 1 and Table 2). Separate propensity scores were generated for patients with COPD and those with IPF (eFigure 1 in the Supplement); scores closer to 0 indicate characteristics more like those of a single-lung transplant recipient, whereas scores closer to 1 indicate characteristics more like those of a double-lung transplant recipient. The distributions of propensity scores in the unadjusted cohort (eFigure 1, A and C) support the evidence from Table 1 and Table 2 that single- and double-lung transplant re-

Figure 1. Kaplan-Meier Analysis of Posttransplantation Graft Survival in Single- and Double-Lung Transplant Recipients in the Years Since the Lung Allocation Score Was Implemented



Data were adjusted by the inverse probability of treatment weights (IPTW). The number of patients at risk (ie, those who were still alive and not censored) during each year of follow-up are not applicable in the adjusted IPTW analysis. COPD indicates chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

cipients differed with respect to the majority of measured covariates. However, after IPTW adjustment of all variables (except those directly affected by the treatment of interest: lung preference and organ ischemic time), the distribution of propensity scores (eFigure 1, B and D) and patient characteristics was similar (Table 1 and Table 2).

Posttransplantation Graft Survival

Of the 4134 patients with IPF (34.8% of cohort, 2010 [48.6%] of whom underwent single-lung transplantation), 1380 (33.4%) died and 115 (2.8%) required a retransplantation procedure. Of the 3174 patients with COPD (26.7% of cohort, 1299 [40.9%] of whom underwent single-lung transplantation), 1138 (34.0%) died and 59 (1.9%) required a retransplantation procedure. Kaplan-Meier estimates of survival (**Figure 1**) in patients with IPF showed that median graft survival was longer after double-lung transplantation in both the unadjusted group (70.7 months [IQR, 22.2-91.3 months] vs 48.9 months [IQR, 16.3-87.5 months]; $P < .001$ by log-rank test) and the IPTW-adjusted group (65.2 months [IQR, 21.4-91.3 months] vs 50.4 months [IQR, 17.0-87.5 months]; $P = .001$ by stratified log-rank test). In patients with COPD, the survival advantage associated with double-lung transplantation was less pronounced in the unadjusted analysis (median survival, 69.3 months [IQR, 26.1-74.6 months] vs 58.6 months [IQR, 24.4-88.7 months]; $P = .007$ by log-rank test) and was not statistically significant in the IPTW-adjusted comparison (67.7 months [IQR, 25.2-89.6 months] vs 64.0 months [IQR, 25.2-88.7 months]; $P = .23$ by stratified log-rank test).

Flexible Parametric Analysis of Variables Associated With Graft Survival

In patients with IPF, 26 of the 54 variables analyzed were associated with survival on univariate flexible parametric analysis (eTable 1 in the Supplement). The time-fixed univariate analysis associated double-lung transplant with improved survival (HR, 0.76; 95% CI, 0.68-0.84; $P < .001$), an association confirmed by the time-varying model (eFigure 2A in the Supplement). The prognostic multivariable RP model found that of the 21 variables included, 6 were significantly associated with

graft failure: age, an excessively high or low BMI (≤18 or ≥35), worse functional status (ie, higher NYHA class), poor 6-minute walk test performance, donor age, and a complete HLA mismatch (**Table 3**). Five other variables were significantly associated with longer graft survival: undergoing transplantation at a high-performing transplant center, undergoing transplantation at a moderate- or high-volume transplant center, receiving a locally allocated organ, a donor/recipient race match, and receiving a double-lung transplant. The time-varying effect of double-lung transplantation in the prognostic RP model of patients with IPF is shown in **Figure 2**A; this finding supports those of the IPTW-adjusted analysis, indicating that double-lung transplantation was associated with improved graft survival in patients with IPF.

In patients with COPD, 24 of the 54 variables analyzed were associated with survival on univariate flexible parametric analysis (eTable 2 in the Supplement). The time-fixed univariate analysis associated double-lung transplant with improved survival (HR, 0.85; 95% CI, 0.75-0.96; P = .007), although this association was less pronounced in the time-varying model (eFigure 2B in the Supplement). The prognostic multivariable RP model found that of the 19 variables included, 7 were significantly associated with graft failure: age, worse functional status (NYHA class), poor 6-minute walk test performance, pulmonary hypertension, low creatinine clearance or dialysis dependence, a complete HLA mismatch, and an elevated PRA level (Table 3). Three other variables were significantly associated with longer graft survival: undergoing transplantation at a high-performing transplant center, undergoing transplantation at a moderate- or high-volume transplant center, and an oversized graft (donor/recipient pTLC ratio ≥1.1). The time-varying effect of receiving a double-lung transplant in the prognostic RP model in patients with COPD is shown in Figure 2B; the 95% CI includes an HR of 1 and confirms the finding of the IPTW-adjusted analysis that double-lung transplantation was not associated with improved graft survival in patients with COPD at 5 years.

Discussion

We examined posttransplantation graft survival among patients who underwent single- and double-lung transplantation since the LAS was implemented, finding that they differed substantially in their demographic, clinical, transplant center, operative, and donor characteristics. In unadjusted analysis, there was an association between double-lung transplantation and improved median graft survival whether patients had IPF or COPD, but in a weighted analysis, this association was significant only for patients with IPF. The interaction between diagnosis (COPD or IPF) and treatment type (single- and double-lung transplantation) was significant, supporting the finding that the benefit of double-lung transplantation may differ by diagnosis. Likewise, prognostic models designed to account for the time-varying effect of double-lung transplantation (compared with single-lung transplantation) showed that double-lung transplantation was significantly associated with graft survival among patients with IPF but not among patients with COPD. Other variables associated with graft failure included age, excessively high or low BMI, worse functional status, poor 6-minute walk test performance, pulmonary hypertension (in patients with COPD), low creatinine clearance or dialysis dependence, donor age, complete HLA mismatch, and elevated PRA. Variables associated with graft survival included undergoing transplantation at a high-performing center, undergoing transplantation at a moderate- or high-volume transplant center, receiving a locally allocated organ, donor-recipient race match (in patients with IPF), and donor-recipient graft oversizing (in patients with COPD).

Posttransplantation Survival in Single- and Double-Lung Recipients

Annual analyses of the ISHLT and UNOS registries have demonstrated an association between double-lung transplantation and longer survival than single-lung transplantation but are prone to treatment selection bias.[7,33] The IPTW-adjusted analysis findings support the survival benefit of double-lung transplantation in patients with IPF but not in patients with COPD at 5 years. Controversy exists whether the benefit of double-lung transplantation is attributable to increased functional capacity or to avoidance of the complications associated with leaving a diseased contralateral lung in situ, such as infection, lung cancer, hyperinflation, pneumothorax, and progression of pulmonary hypertension.[34-36] Whether the contralateral diseased lung is more viable or less prone to complications in patients with COPD than in patients with IPF, thereby making single-lung transplantation a more feasible option in patients with COPD, is unknown.

Prior studies were largely limited to patients treated before LAS implementation, and the demographics of lung transplant recipients have changed during the past decade, particularly after the LAS algorithm was implemented.[3,7,33] Compared with patients with IPF or COPD in previous analyses, those in the current study appear to have been older, had worse functional status, more commonly required oxygen at rest, and had a higher prevalence of diabetes. These differences reflect the changing demographics of lung transplant recipients and may also partly explain the difference in findings between our study and those performed before LAS implementation.

In 2 studies, Thabut et al[8,9] found that patients with COPD, but not patients with IPF, derived significant survival benefit from double-lung transplantation. Although the unadjusted survival analysis by Thabut et al showed better survival in IPF double-lung vs single-lung transplant recipients, this was not supported in their propensity-matched analysis. It is possible that the propensity-score IPF analysis was underpowered, given that their propensity-matching algorithm was unable to match nearly half of the patients studied. Another reason Thabut et al may have found no benefit from double-lung transplantation in patients with IPF was the significant early hazard associated with double-lung transplantation, a finding supported by other studies of

Table 3. Variables Associated With Mortality for Single-Lung and Double-Lung Transplant Recipients With an Underlying Diagnosis of IPF or COPD

	IPF				COPD			
	Multivariable HR (95% CI)[a]	*P* Value[b]	Univariate HR (95% CI)[a]	*P* Value[c]	Multivariable HR (95% CI)[a]	*P* Value[d]	Univariate HR (95% CI)[a]	*P* Value[e]
Baseline characteristics								
Age	1.014 (1.007-1.022)	<.001	1.019 (1.012-1.025)	<.001	1.027 (1.017-1.038)	<.001	1.028 (1.018-1.039)	<.001
>60 y			1.27 (1.14-1.41)	<.001			1.33 (1.18-1.49)	<.001
Male	1.07 (0.95-1.20)	.30	1.05 (0.94-1.18)	.39	1.00 (0.87-1.14)	.98	1.06 (0.95-1.19)	.31
Race								
White			1.11 (0.97-1.28)	.12			0.96 (0.77-1.19)	.72
African American	0.90 (0.71-1.13)	.36	0.83 (0.67-1.04)	.10			1.04 (0.82-1.33)	.75
Hispanic			0.96 (0.80-1.16)	.70			1.03 (0.57-1.86)	.93
College education			1.10 (0.98-1.23)	.10			1.01 (0.89-1.14)	.91
Private insurance	0.92 (0.83-1.03)	.14	0.84 (0.75-0.93)	.001	0.96 (0.85-1.08)	.53	0.90 (0.80-1.01)	.08
Body mass index[f]			0.995 (0.982-1.008)	.41	1.014 (0.999-1.029)	.07	1.019 (1.005-1.33)	.008
≤18 or ≥35	1.49 (1.14-1.93)	.003	1.44 (1.11-1.86)	.006			0.98 (0.75-1.28)	.87
Illness severity/ functional status								
Lung Allocation Score[g]			1.006 (1.003-1.009)	<.001			1.012 (1.004-1.020)	.003
NYHA class								
IV (symptoms at rest, usually bedbound)	1.38 (1.20-1.58)	<.001	1.44 (1.26-1.64)	<.001	1.25 (1.03-1.51)	.02	1.25 (1.04-1.50)	.02
III or IV (marked limitation in activities)			1.24 (1.05-1.47)	.01			1.15 (0.96-1.38)	.12
6-min walk			0.99983 (0.99972-0.99994)	.003			0.9995 (0.9994-0.9997)	<.001
<500 ft	1.21 (1.08-1.36)	.001	1.19 (1.06-1.32)	.002	1.25 (1.09-1.43)	.001	1.34 (1.18-1.53)	<.001
Any life support (ventilator or extracorporeal membrane oxygenation)	1.16 (0.90-1.50)	.24	1.31 (1.03-1.65)	.03	1.09 (0.72-1.63)	.69	1.33 (0.90-1.98)	.15
Ventilation/oxygenation								
Forced vital capacity			0.999 (0.996-1.002)	.64			0.999 (0.996-1.003)	.90
Oxygen requirement at rest			1.21 (0.96-1.51)	.10			1.03 (0.83-1.29)	.77
Hemodynamics								
Cardiac index			0.97 (0.90-1.05)	.44			0.98 (0.90-1.07)	.67
Mean pulmonary artery pressure			0.996 (0.991-1.001)	.14			1.011 (1.003-1.019)	.005
≥30 mm Hg	0.96 (0.85-1.09)	.53	0.94 (0.84-1.06)	.32	1.14 (1.00-1.31)	.05	1.24 (1.09-1.41)	.001
Pulmonary capillary wedge pressure			0.993 (0.984-1.003)	.17			1.005 (0.994-1.017)	.37
Renal function								
Creatinine clearance			0.997 (0.995-0.998)	<.001			0.999 (0.996-1.001)	.29
<50 mL/min or dialysis	1.46 (0.98-2.18)	.07	1.58 (1.07-2.35)	.02	1.51 (1.07-2.13)	.02	1.41 (1.01-1.98)	.05
Diabetes			0.98 (0.86-1.11)	.76	1.19 (0.99-1.42)	.06	1.29 (1.08-1.53)	.005
Lung preference at transplant								
Bilateral only			0.85 (0.76-0.95)	.004			0.92 (0.81-1.04)	.18
Single only			1.26 (1.14-1.40)	<.001			1.18 (1.04-1.33)	.008
Single or bilateral			0.91 (0.81-1.02)	.10			0.92 (0.81-1.05)	.21
Transplant center								
High-performing institution[h]	0.74 (0.66-0.82)	<.001	0.79 (0.71-0.88)	<.001	0.80 (0.70-0.90)	<.001	0.85 (0.75-0.96)	.009
Moderate- or high-volume institution[i]	0.82 (0.73-0.92)	.001	0.84 (0.75-0.94)	.003	0.78 (0.69-0.88)	<.001	0.74 (0.66-0.84)	<.001
High-volume institution[j]			1.003 (0.90-1.11)	.95			0.87 (0.77-0.99)	.03
Operative characteristics								
Double-lung transplant[k]			0.76 (0.68-0.84)	<.001			0.85 (0.76-0.96)	.007
Organ ischemic time			1.00 (0.97-1.03)	.98			0.97 (0.94-1.01)	.14
Distance organ transported, per mile			1.0002 (1.0000-1.0004)	.04			0.9998 (0.9996-1.0001)	.20
Local organ (nonregional, nonnational)	0.88 (0.79-0.98)	.02	0.86 (0.78-0.95)	.004			1.08 (0.96-1.22)	.20

(continued)

Table 3. Variables Associated With Mortality for Single-Lung and Double-Lung Transplant Recipients With an Underlying Diagnosis of IPF or COPD (continued)

	IPF				COPD			
	Multivariable HR (95% CI)[a]	*P* Value[b]	Univariate HR (95% CI)[a]	*P* Value[c]	Multivariable HR (95% CI)[a]	*P* Value[d]	Univariate HR (95% CI)[a]	*P* Value[e]
Donor characteristics								
Age								
Mean	1.005 (1.001-1.009)	.01	1.006 (1.002-1.009)	.001	1.000 (0.996-1.005)	.86	1.000 (0.996-1.004)	.96
>50 y			1.30 (1.14-1.47)	<.001			1.04 (0.89-1.20)	.63
Po_2:Fio_2 ratio[l]			1.0000 (0.9996-1.0005)	.84			0.9999 (0.9994-1.0005)	.82
<250			1.01 (0.80-1.29)	.92			1.12 (0.88-1.42)	.35
Smoking, >20 pack-years	1.12 (0.96-1.30)	.16	1.13 (0.97-1.31)	.11			1.02 (0.87-1.20)	.80
CDC high-risk donor[m]			1.05 (0.86-1.27)	.64			0.91 (0.72-1.14)	.41
Hypertension			1.17 (1.04-1.32)	.008			1.08 (0.95-1.24)	.25
Diabetes	1.17 (0.96-1.43)	.12	1.24 (1.02-1.51)	.03	1.15 (0.91-1.45)	.24	1.22 (0.98-1.51)	.08
Donor-recipient matching								
Sex match			0.98 (0.88-1.09)	.70			0.99 (0.87-1.13)	.90
Race match	0.87 (0.78-0.97)	.009	0.89 (0.80-0.98)	.02	0.96 (0.85-1.08)	.50	0.88 (0.78-0.99)	.03
Donor positive for cytomegalovirus, recipient negative	1.28 (1.13-1.43)	<.001	1.25 (1.12-1.40)	<.001	1.18 (1.03-1.36)	.02	1.12 (0.98-1.29)	.09
Donor/recipient pTLC ratio[n]			0.78 (0.57-1.07)	.12			0.70 (0.51-0.96)	.03
≥1.1			0.99 (0.86-1.14)	.92	0.85 (0.75-0.97)	.02	0.86 (0.77-0.97)	.01
0.8-1.2	0.91 (0.81-1.02)	.11	0.92 (0.82-1.04)	.17			1.00 (0.88-1.14)	.98
Nonidentical ABO blood group match (only compatible)			1.04 (0.86-1.26)	.70			1.07 (0.89-1.28)	.45
Total HLA mismatches (maximum, 6)[o]			1.05 (1.00-1.10)	.05			1.08 (1.02-1.15)	.01
Complete HLA mismatch (all 6 alleles mismatched)	1.13 (1.00-1.27)	.05	1.13 (1.00-1.28)	.05	1.22 (1.05-1.42)	.008	1.24 (1.07-1.43)	.004
Panel reactive antibody[p]			1.002 (0.998-1.006)	.32			1.007 (1.004-1.011)	<.001
≥20%	1.18 (0.97-1.44)	.10	1.16 (0.96-1.41)	.12			1.40 (1.14-1.73)	.001
≥10%			1.13 (0.96-1.33)	.13	1.34 (1.11-1.61)	.003	1.32 (1.11-1.59)	.002

Abbreviations: COPD, chronic obstructive pulmonary disease; HLA, human leukocyte antigen; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; NYHA, New York Heart Association; pTLC, predicted total lung capacity.

[a] Reference increment for continuous variables are units of measurement (eg, age, per year; forced vital capacity, per percentage point) unless otherwise noted.

[b] *P* value obtained from multivariable Royston-Parmar flexible parametric model of variables associated with post–lung transplant outcomes in patients with IPF, with the variable double-lung transplant vs single-lung transplant modeled as having a time-dependent effect (see Methods).

[c] *P* value obtained from univariate Royston-Parmar flexible parametric proportional hazards regression model of variables associated with post–lung transplant outcomes in patients with IPF (see Methods).

[d] *P* value obtained from multivariable Royston-Parmar flexible parametric model of variables associated with post–lung transplant outcomes in patients with COPD, with the variable double-lung transplant vs single-lung transplant modeled as having a time-dependent effect (see Methods).

[e] *P* value obtained from univariate Royston-Parmar flexible parametric model of variables associated with post–lung transplant outcomes in patients with COPD (see Methods).

[f] Calculated as weight in kilograms divided by height in meters squared.

[g] The Lung Allocation Score (range, 0-100) is based on risk factors associated with either wait list or posttransplantation mortality.[3] A higher score implies a higher-acuity patient who would benefit from lung transplantation, and patients with higher scores are given preference for organs.

[h] In the top third of graft survival performance among all 72 transplant centers.

[i] Performed more than 194 lung transplants during the 93-month study period (>25 transplants/year).

[j] Performed at least 388 lung transplants during the 93-month study period (≥50 transplants/year).

[k] For multivariable analysis, modeled as time-varying covariate; see eFigure 2 in the Supplement.

[l] The reference increment for Po_2:Fio_2 ratio is each 1-unit increase.

[m] A donor who is thought to be at high risk of human immunodeficiency virus, hepatitis B/C virus, or sexually transmitted infection according to Centers for Disease Control and Prevention (CDC) criteria.[18]

[n] Ratio of pTLC of the donor over pTLC of the recipient. The pTLC is calculated for men as 7.99×(height in meters)−7.08 and for women as 6.60×(height in meters)−5.79.

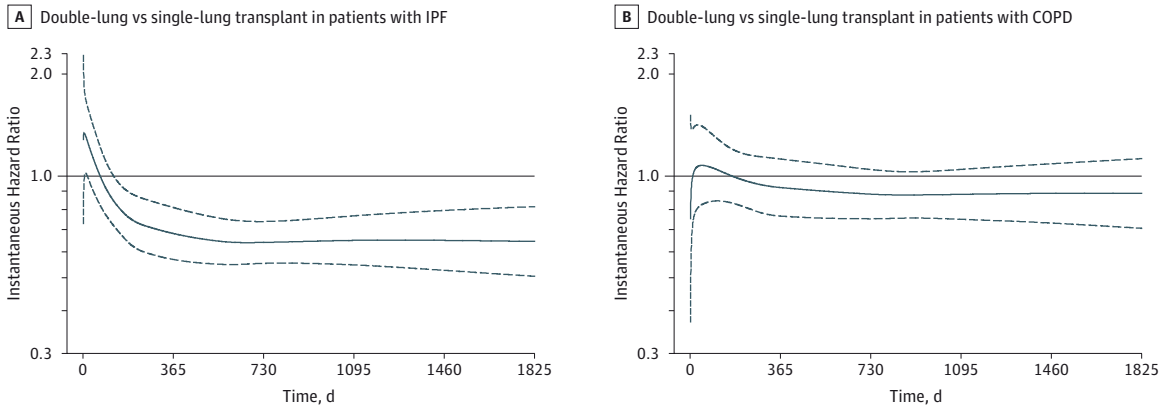
[o] The reference increment for total HLA mismatches is each 1-unit increase.

[p] The reference increment for panel reactive antibody is each 1% increase.

double-lung transplantation in patients with IPF in the era before LAS implementation.[37,38] In contrast, the early hazard we found for double-lung transplantation (Figure 2A) was more modest, possibly reflecting improvements in the operative and postoperative care of double-lung transplant recipients since the LAS was implemented.

Similar to the current study, the unadjusted survival analysis by Thabut et al found an association between double-lung transplantation and better survival in patients with COPD, although our study had more limited follow-up (510 patients at risk at 5 years compared with 461 at risk at 10 years).[8] We hypothesize that the analysis of COPD out-

Figure 2. Estimates of the Time-Varying Hazard of Posttransplantation Graft Survival With Double- vs Single-Lung Transplantation in Patients Who Received Lung Transplants Since the Lung Allocation Score Was Implemented



Hazard ratio is expressed as a function of time using a Royston-Parmar flexible parametric analysis model with 4 internal spline knots (5 degrees of freedom) for non–time-varying parameters and 2 internal spline knots (3 degrees of freedom) to model the time-varying effect of double- vs single-lung transplantation. Dashed lines indicate 95% CIs. COPD indicates chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

comes by Thabut et al might have shown equivalent outcomes in single- and double-lung transplant recipients had the analysis been limited to 5-year outcomes instead of 10-year outcomes (as our analysis was). We suspect that although the difference in 5-year survival was minimal between single- and double-lung transplant recipients with COPD in our adjusted analysis, it may become both statistically and clinically significant at 10 years (as was shown by Thabut et al before the LAS was implemented). Meyer et al[39] arrived at a similar conclusion; they recommended single-lung transplantation for older patients with COPD who have poorer expected post-lung transplantation survival and double-lung transplantation for younger patients with COPD who have above average expected post-lung transplantation survival.

Variables Associated With Outcomes at Time of Transplantation

The multivariable flexible parametric analysis showed that double-lung transplant was significantly associated with graft survival among patients with IPF but not among patients with COPD, substantiating the findings of the weighted survival analyses. This multivariable analysis also demonstrated an association of lower posttransplantation survival with multiple variables—including age, worse functional status, poor performance on the 6-minute walk test, elevated pulmonary artery pressures, worse renal function, and increased donor age—which helps to substantiate current assumptions regarding variables associated with post-lung transplantation mortality. The multivariable analysis also supports the finding of Thabut et al that both institutional volume and center variability were independently associated with graft survival.[16] Also, our finding that an excessively high or low BMI was associated with worse outcomes is partly validated by previous evidence that obesity is independently associated with primary graft dysfunction.[40]

Variables related to donor-recipient matching (including race, pTLC, cytomegalovirus [CMV]-positive donor/CMV-negative recipient, HLA levels, and PRA levels) had significant associations with long-term survival in patients with IPF or COPD. Race matching between donor and recipient was associated with graft survival in recipients with IPF but not those with COPD. Race matching has been associated with improved lung transplant outcomes; however, it has been suggested that race is confounded by donor-recipient size matching, and assessments stratified by diagnosis (specifically with respect to COPD and IPF) remain lacking.[41,42] An oversized graft (indicated by a donor/recipient pTLC ratio ≥1.1) was significantly associated with graft survival in patients with COPD, whereas a reasonable size match (donor/recipient pTLC of 0.8-1.2) approached significance as a variable associated with better outcomes in patients with IPF. An oversized allograft has been associated with better outcomes in patients from the general lung transplant population, as well as in a subgroup of patients with idiopathic pulmonary artery hypertension, but not to our knowledge in a group of only patients with COPD.[42,43] Implanting lungs from a CMV-positive donor to a CMV-negative recipient has previously been found to be associated with worse survival, and we confirm this finding in both patients with COPD and patients with IPF.[7] We found that in both types of patients, complete donor-recipient HLA mismatch was common (>20%) and was associated with worse graft survival. Finally, an elevated PRA was associated with worse graft survival; this association was significant in patients with COPD and nearly so in patients with IPF.

Limitations

Our study was limited by its retrospective design, susceptibility to selection bias, and the limited availability of complete data sets in the UNOS database. We attempted to address these limitations by using multiple imputation to account for missing data, IPTW adjustment to account for

treatment selection bias, and a separate sensitivity multivariable flexible parametric analysis to account for confounding (and the time-varying effect of) variables. Nevertheless, unmeasured variables and the observational design of this study are potential sources of residual bias that may confound our results. Also, given the size of the UNOS registry, it is impossible to entirely validate data entered into it, and some amount of inaccuracy should be expected, although random misclassification of data would not be expected to alter our findings.

Conclusions

In an exploratory analysis of registry data collected since the implementation of a medical need–based lung allocation system, double-lung transplantation was associated with better survival than single-lung transplantation in patients with IPF. In patients with COPD, there was no survival difference between single- and double-lung transplantation at 5 years.

ARTICLE INFORMATION

Author Contributions: Dr Schaffer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schaffer, Singh, Zamanian, Mallidi.
Acquisition, analysis, or interpretation of data: Schaffer, Singh, Reitz, Mallidi.
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