

## Supplementary Appendix

### Procedure Preference and “Intention-to-treat” Outcomes after Listing for Lung Transplantation among U.S. Adults: A Cohort Study

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**Figure E6:** Kaplan Meier survival curves for the primary “intention-to-treat” composite outcome (time from listing until death before or after transplantation, removal from the waiting list due to clinical deterioration, or re-transplantation) among candidates with ILD stratified by use of mechanical support (mechanical ventilation or extracorporeal membrane oxygenation).

**Figure E7:** Cumulative incidence curves for transplantation and death or removal from the waiting list among candidates with (A) COPD and (B) ILD.

**Figure E8:** Kaplan-Meier curves for time to graft survival (death or re-transplantation) after lung transplantation among candidates with (A) COPD and (B) ILD.

**Table E1:** Characteristics of 9,424 transplant recipients and donors at the time of transplantation

Characteristic	Chronic Obstructive Pulmonary Disease			Interstitial Lung Disease		
	Restricted (n = 1,987)	Unrestricted (n = 1,634)	P value	Restricted (n = 2,663)	Unrestricted (n = 3,140)	P value
<b>Recipient Characteristics</b>						
Bilateral Transplantation performed	1875 (94%)	756 (37%)		2508 (94%)	1375 (33%)	
Age, years	58 (53-63)	61 (57-65)	<.001	57 (49-62)	62 (57-66)	<.001
Male	1,060 (53%)	792 (48%)	.004	1,703 (64%)	2,142 (68%)	<.001
Race/Ethnicity						
White	1,737 (87%)	1,475 (90%)	.004	1866 (70%)	2,571 (82%)	<.001
Black	179 (9%)	130 (8%)		444 (17%)	213 (7%)	
Hispanic	44 (2%)	15 (1%)		257 (10%)	260 (8%)	
Other	27 (1%)	14 (1%)		96 (4%)	96 (3%)	
BMI	24.1 (21.2-27.5)	24.4 (21.4-27.6)	.30	27.3 (24.2-30.1)	27.8 (24.8-30.1)	.002
Height, cm	170.2 (162.6-177.8)	167.6 (160.0-175.3)	.002	171.0 (165.0-177.8)	172.7 (165.1-177.8)	.12
ABO						
A	782 (39%)	679 (42%)	.14	1,006 (38%)	1,237 (39%)	.43
AB	102 (5%)	74 (5%)		87 (3%)	104 (3%)	
B	249 (13%)	169 (10%)		313 (12%)	333 (11%)	
O	854 (43%)	712 (44%)		1,257 (47%)	1,466 (47%)	
Lung allocation score	34.1 (32.7-36.4)	33.5 (32.4-35.3)	<.001	48.7 (41.0-66.4)	45.6 (39.2-39.6)	<.001
< 35	1239 (62%)	1,188 (73%)		113 (4%)	226 (7%)	
35-45	700 (35%)	430 (26%)		1446 (54%)	1828 (58%)	
45-55	125 (6%)	48 (3%)		1,022 (38%)	1,115 (36%)	
>55	100 (5%)	29 (2%)		996 (37%)	937 (30%)	
Use of mechanical support	24 (1%)	13 (1%)	.22	88 (3%)	82 (3%)	.12
Pulmonary Hypertension						
None	896 (45%)	817 (50%)	<.001	955 (36%)	1,818 (58%)	.001
Mild	531 (27%)	451 (28%)		442 (17%)	665 (21%)	
Moderate	297 (15%)	246 (15%)		396 (15%)	326 (10%)	

Severe	263 (13%)	120 (7%)		870 (33%)	331 (11%)	
<b>Donor Characteristics</b>						
Age, years	32 (22-47)	32 (22-47)	.97	32 (22-47)	33 (22-47)	.13
Male	1,396 (70%)	1,163 (71%)	.53	1,387 (52%)	1,738 (55%)	.01
BMI	25.3 (22.6-28.7)	24.8 (22.2-28.5)	.02	25.2 (22.3-29.0)	25.2 (22.3-28.5)	.22
Height, cm	175.3 (167.6-182.9)	175.3 (167.6-182.9)	.09	170.0 (162.6-177.0)	170.2 (163.0-177.8)	.04
Heavy alcohol use	300 (15%)	242 (15%)	.91	330 (12%)	394 (13%)	.89
Cigarette Use	221 (11%)	164 (10%)	.30	240 (9%)	314 (10%)	.42
Pulmonary Infection	1,022 (51%)	848 (52%)	.77	1,338 (50%)	1,691 (54%)	.01
Diabetes	141 (7%)	117 (7%)	.33	184 (7%)	212 (7%)	.97
<b>Donor Cause of Death</b>						
Anoxia	3332 (17%)	232 (14%)	.17	391 (15%)	587 (16%)	.19
Cerebrovascular Event	660 (33%)	527 (32%)		1,025 (39%)	1,118 (36%)	
Head Trauma	937 (47%)	828 (51%)		1,168 (44%)	1,424 (45%)	
Central Nervous System Tumor	9 (1%)	9 (1%)		19 (1%)	24 (1%)	
Other	45 (2%)	34 (2%)		59 (2%)	85 (3%)	
Donor PaO <sub>2</sub> on 100% FiO <sub>2</sub>	416 (272-488)	407 (218-489)	.08	416 (238-487)	420 (258-491)	.29

Values are presented as number (%) or median(IQR).

Definition of abbreviations: BMI: body mass index, PaO<sub>2</sub>: partial pressure of oxygen in arterial blood; FiO<sub>2</sub> indicates fraction of inspired oxygen

P values represents levels of significance for test statistics from t tests or chi-square tests.

\*Thirteen subjects were missing type of procedure performed (bilateral vs. single), 11 subjects were missing donor age, 11 subjects were missing donor gender, 19 subjects were missing donor body mass index, 11 subjects were missing donor height, 11 subjects were missing donor blood type, 13 subjects were missing donor alcohol use, 11 subjects were missing donor cigarette use, 11 subjects were missing donor diabetes, 11 subjects were missing donor pulmonary infection, 11 subjects were missing donor cause of death, and 74 subjects were missing donor P<sub>a</sub>O<sub>2</sub>.

**Table E2:** Associations between lung preference and the primary outcome among lung transplant recipients with adjustment for time-varying covariates

<b>Condition</b>	<b>N</b>	<b>Hazard Ratio (95% CI)</b>	<b>p value</b>
COPD	3,621	0.95 (0.86 to 1.05)	.29
ILD	5,803	1.01 (0.94 to 1.09)	.77

Analyses adjusted for participant characteristics reported at the time of listing (ABO blood group, height age, gender, race) and characteristics at the time of listing and transplantation as time-varying covariates (lung allocation score, body mass index, use of mechanical support and mean pulmonary arterial pressure)

**Table E3:** Association between lung preference and overall survival in fully adjusted models including time-dependent covariate for waiting list time

	<b>N</b>	<b>Hazard Ratio (95% CI)</b>
COPD		
Waitlist Time <1,000 days	4,217	0.95 (0.86 to 1.05)
Waitlist Time >1,000 days	461	1.75 (1.07 to 2.85)
ILD		
Waitlist Time <1,850 days	7,432	1.03 (0.96 to 1.11)
Waitlist Time >1,850 days	45	0.53 (0.15 to 1.90)

Analyses adjusted for lung allocation score at listing, ABO blood group, height, age, gender, race, use of mechanical ventilation or extracorporeal membrane oxygenation at listing, body mass index, and mean pulmonary arterial pressure. Listing center included as random effect

**Table E4:** Multivariable-adjusted associations between lung preference and the primary outcome by pre-specified stratification variables (also depicted in Figure 3)

	<u>Chronic Obstructive Pulmonary Disease</u>				<u>Interstitial Lung Disease</u>			
	N	Hazard Ratio (95% CI)	P value	P for interaction	N	Hazard Ratio (95% CI)	P value	P for interaction
Mechanical Support				.28				.21
No Mechanical Support	4633	0.97 (0.88 to 1.07)	.57		7160	1.02 (0.95 to 1.10)	.59	
Mechanical Support	45	0.52 (0.15 to 1.76)	.29		317	1.05 (0.75 to 1.45)	.79	
Age at Listing				.68				.10
Age < 65	3752	0.91 (0.82 to 1.01)	.09		5635	1.01 (0.93 to 1.10)	.83	
Age ≥ 65	926	1.01 (0.82 to 1.24)	.93		1842	1.10 (0.95 to 1.27)	.19	
Lung Allocation Score				.73				.30
LAS < 40	4481	0.97 (0.88 to 1.07)	.59		3075	1.03 (0.91 to 1.16)	.65	
LAS 40-45	106	1.44 (0.65 to 3.18)	.36		1467	1.20 (1.02 to 1.40)	.03	
LAS 45-50*	24				833	0.90 (0.73 to 1.11)	.32	
LAS > 50	67	0.73 (0.34 to 1.58)	.43		2102	1.01 (0.88 to 1.14)	.93	
Pulmonary Hypertension				.53				.24
No PH	2796	0.91 (0.80 to 1.05)	.21		4061	1.01 (0.90 to 1.12)	.90	
Mild PH	1006	0.99 (0.82 to 1.19)	.91		1231	1.00 (0.85 to 1.17)	.98	
Moderate PH	490	1.06 (0.84 to 1.33)	.65		809	0.90 (0.74 to 1.09)	.28	
Severe PH	386	1.04 (0.79 to 1.37)	.77		1376	1.17 (0.99 to 1.39)	.07	
Overall	4678	0.97 (0.89 to 1.07)	.60		7477	1.01 (0.94 to 1.08)	.77	

Mechanical support =mechanical ventilation or extracorporeal membrane oxygenation at time of listing; LAS= lung allocation score, PH=pulmonary hypertension.

\*Small number of waiting list events among COPD subjects with LAS between 45 and 50, thus no analysis performed.

**Table E5:** Multivariable adjusted associations between baseline characteristics and a restricted preference

Characteristic	COPD		ILD	
	Prevalence Ratio (95% CI)	<i>P</i> value	Prevalence Ratio (95% CI)	<i>P</i> value
Age, per 5 year increment	0.90 (0.89 to 0.92)	<.001	0.91 (0.90 to 0.92)	<.001
Male	1.02 (0.95 to 1.10)	.52	0.96 (0.91 to 1.02)	.19
Race/ethnicity				
White	1 (Ref)		1 (Ref)	
Black	1.02 (0.94 to 1.10)	.69	1.11 (1.05 to 1.17)	<.001
Hispanic	1.07 (0.93 to 1.23)	.34	1.04 (0.97 to 1.11)	.32
Other	1.16 (0.97 to 1.38)	.11	1.02 (0.91 to 1.13)	.78
BMI, per 5 kg/m <sup>2</sup> increment	1.00 (0.98 to 1.03)	.79	0.97 (0.95 to 0.996)	.02
Height, per 5 cm increment	1.02 (1.00 to 1.04)	.02	1.00 (0.99 to 1.02)	.67
ABO blood group				
A	1 (Ref)		1 (Ref)	
AB	1.04 (0.92 to 1.17)	.53	0.94 (0.84 to 1.06)	.33
B	1.07 (0.99 to 1.16)	.10	1.01 (0.95 to 1.08)	.71
O	1.01 (0.96 to 1.07)	.64	1.01 (0.97 to 1.06)	.55
Mechanical Support	0.92 (0.73 to 1.16)	.48	0.96 (0.87 to 1.05)	.37
Lung allocation score				
< 40	1 (Ref)		1 (Ref)	
40-45	1.22 (1.08 to 1.38)	.002	0.99 (0.94 to 1.05)	.84
45-50	1.18 (0.91 to 1.53)	.22	0.98 (0.91 to 1.06)	.63
LAS > 50	1.16 (0.98 to 1.38)	.08	1.04 (0.98 to 1.09)	.19
Mean pulmonary artery pressure				
None	1 (Ref)		1 (Ref)	
Mild	1.02 (0.96 to 1.08)	.58	1.14 (1.07 to 1.22)	<.001
Moderate	1.01 (0.94 to 1.09)	.82	1.38 (1.29 to 1.47)	<.001
Severe	1.16 (1.08 to 1.25)	<.001	1.76 (1.67 to 1.86)	<.001

Prevalence ratios are from binomial regression models with restricted preference as the dependent variable. All of the variables listed in the table were included as independent variables.



**Table E6:** Multivariable-adjusted associations between lung preference and the rate of transplantation by pre-specified stratification variables

	<u>Chronic Obstructive Pulmonary Disease</u>				<u>Interstitial Lung Disease</u>			
	N	Sub-hazard Ratio (95% CI)	P value	P for interaction	N	Sub-hazard Ratio (95% CI)	P value	P for interaction
Mechanical Support				.85				.51
No Mechanical Support	4633	1.11 (1.03 to 1.19)	.004		7160	1.08 (1.02 to 1.14)	.01	
Mechanical Support	45	1.09 (0.44 to 2.67)	.89		317	1.22 (0.9 to 1.66)	.20	
Age at Listing				.65				.09
Age < 65	3752	1.16 (1.08 to 1.26)	<.001		5635	1.10 (1.04 to 1.17)	.002	
Age ≥ 65	926	1.01 (0.87 to 1.17)	.89		1842	1.21 (1.08 to 1.37)	.001	
Lung Allocation Score				.57				.38
LAS < 40	4481	1.09 (1.02 to 1.17)	.01		3075	1.14 (1.04 to 1.24)	.004	
LAS 40-45	106	1.36 (0.77 to 2.39)	.29		1467	1.17 (1.04 to 1.32)	.01	
LAS 45-50	24	0.59 (0.19 to 1.85)	.36		833	1.16 (0.99 to 1.35)	.07	
LAS > 50	67	1.29 (0.61 to 2.7)	.50		2102	1.01 (0.91 to 1.13)	.79	
Pulmonary Hypertension				.09				.38
No PH	2213	1.15 (1.04 to 1.27)	.007		3526	1.07 (0.98 to 1.16)	.13	
Mild PH	1281	1.12 (0.98 to 1.28)	.09		1407	1.09 (0.96 to 1.25)	.17	
Moderate PH	669	1.02 (0.86 to 1.22)	.79		929	0.99 (0.85 to 1.15)	.89	
Severe PH	515	0.96 (0.77 to 1.20)	.73		1615	1.20 (1.05 to 1.37)	.008	

**Definitions of abbreviations:** MS = mechanical support (mechanical ventilation or extracorporeal membrane oxygenation); LAS= lung allocation score, PH=pulmonary hypertension, HR = hazard ratio

Models are adjusted for lung allocation score at listing, ABO blood group, height, age, gender, race, body mass index (stratification variable excluded from its own analysis).

**Table E7:** Multivariable-adjusted associations between lung preference and risk of death or removal by pre-specified stratification variables

	<u>Chronic Obstructive Pulmonary Disease</u>				<u>Interstitial Lung Disease</u>			
	N	Sub-hazard Ratio (95% CI)	P value	P for interaction	N	Sub-hazard Ratio (95% CI)	P value	P for interaction
Mechanical Support				.54				.90
No Mechanical Support	4633	0.70 (0.58 to 0.84)	<.001		7160	0.86 (0.76 to 0.97)	.02	
Mechanical Support*	45	0.10 (0.01 to 1.61)	.10		317	0.81 (0.56 to 1.18)	.28	
Age at Listing				.68				.69
Age < 65	3752	0.71 (0.58 to 0.88)	.001		5635	0.84 (0.74 to 0.95)	.006	
Age ≥ 65	926	0.71 (0.45 to 1.10)	.12		1842	0.69 (0.53 to 0.88)	.004	
Lung Allocation Score				.33				.94
LAS < 40	4481	0.70 (0.58 to 0.85)	<.001		3075	0.78 (0.63 to 0.96)	.02	
LAS 40-45	106	0.14 (0.01 to 1.80)	.13		1467	0.76 (0.58 to 1.01)	.06	
LAS 45-50*	24				833	0.82 (0.58 to 1.17)	.28	
LAS > 50	67	1.13 (0.36 to 3.56)	.83		2102	0.99 (0.83 to 1.18)	.94	
Pulmonary Hypertension				.24				.90
No PH	2213	0.70 (0.53 to 0.94)	.02		3526	0.87 (0.72 to 1.04)	.12	
Mild PH	1281	0.58 (0.40 to 0.85)	.005		1407	0.81 (0.62 to 1.07)	.13	
Moderate PH	669	1.00 (0.60 to 1.67)	.99		929	1.21 (0.87 to 1.68)	.26	
Severe PH	515	0.90 (0.55 to 1.47)	.67		1615	0.71 (0.53 to 0.93)	.01	

**Definitions of abbreviations:** MS = mechanical support (mechanical ventilation or extracorporeal membrane oxygenation); LAS= lung allocation score, PH=pulmonary hypertension, HR = hazard ratio

Values are displayed as hazard ratios (95% confidence intervals).

All analyses adjusted for lung allocation score at listing, ABO blood group, height, age, gender, race, body mass index (stratification variable excluded from its own analysis)

\*There were only 5 events among COPD subjects using mechanical support, thus no analysis performed.

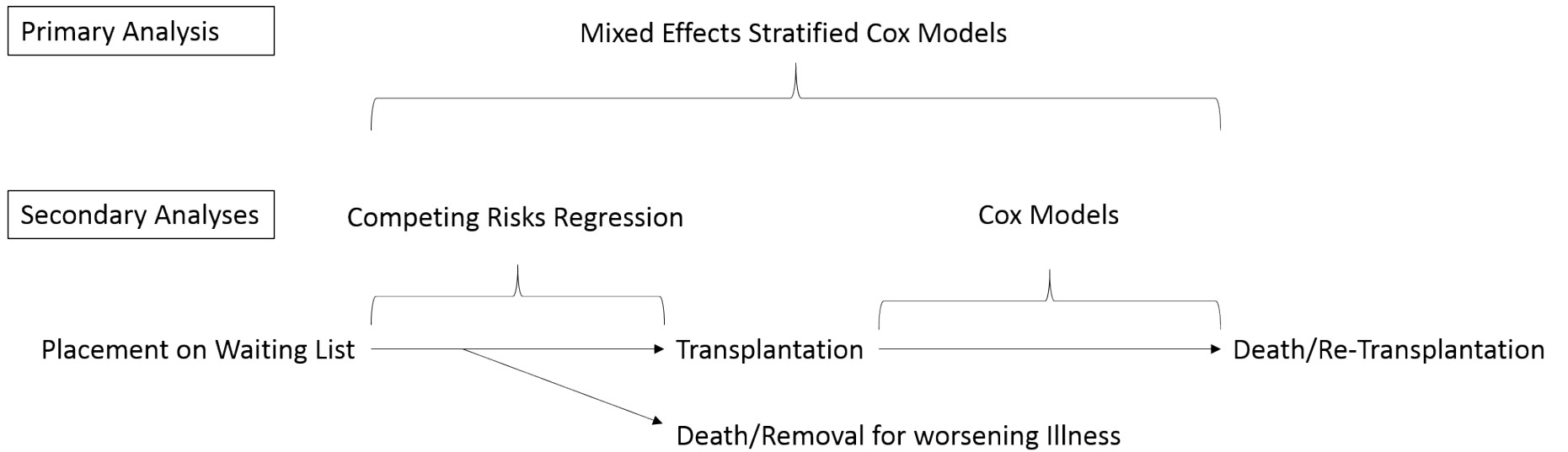
**Table E8:** Association between type of transplant procedure and 1- and 5- year survival after transplantation among 9,424 transplant recipients

Outcome	Chronic Obstructive Pulmonary Disease			Interstitial Lung Disease		
	Bilateral	Single	P value	Bilateral	Single	P value
<b>Graft failure at 1 year</b>						
Number of events	318	129		609	325	
Event rate (95% CI)*	13.7 (12.3 to 15.3)	13.9 (11.7 to 16.5)		18.0 (16.6 to 19.4)	18.7 (16.8 to 20.8)	
Unadjusted hazard ratio	1	0.97 (0.78 to 1.2)	.77	1	1.03 (0.9 to 1.19)	.64
Fully adjusted hazard ratio <sup>§</sup>	1	0.99 (0.79 to 1.25)	.96	1	1.01 (0.87 to 1.18)	.86
<b>Graft failure at 5 years</b>						
Number of events	866	420		1,399	809	
Event rate (95% CI)*	11.3 (10.6 to 12.1)	14.0 (12.7 to 15.4)		13.1 (12.4 to 13.8)	15.5 (14.4 to 16.6)	
Unadjusted hazard ratio	1	1.24 (1.09 to 1.40)	.001	1	1.19 (1.08 to 1.30)	<.001
Fully adjusted hazard ratio <sup>§</sup>	1	1.19 (1.09 to 1.42)	.001	1	1.15 (1.04 to 1.27)	.008

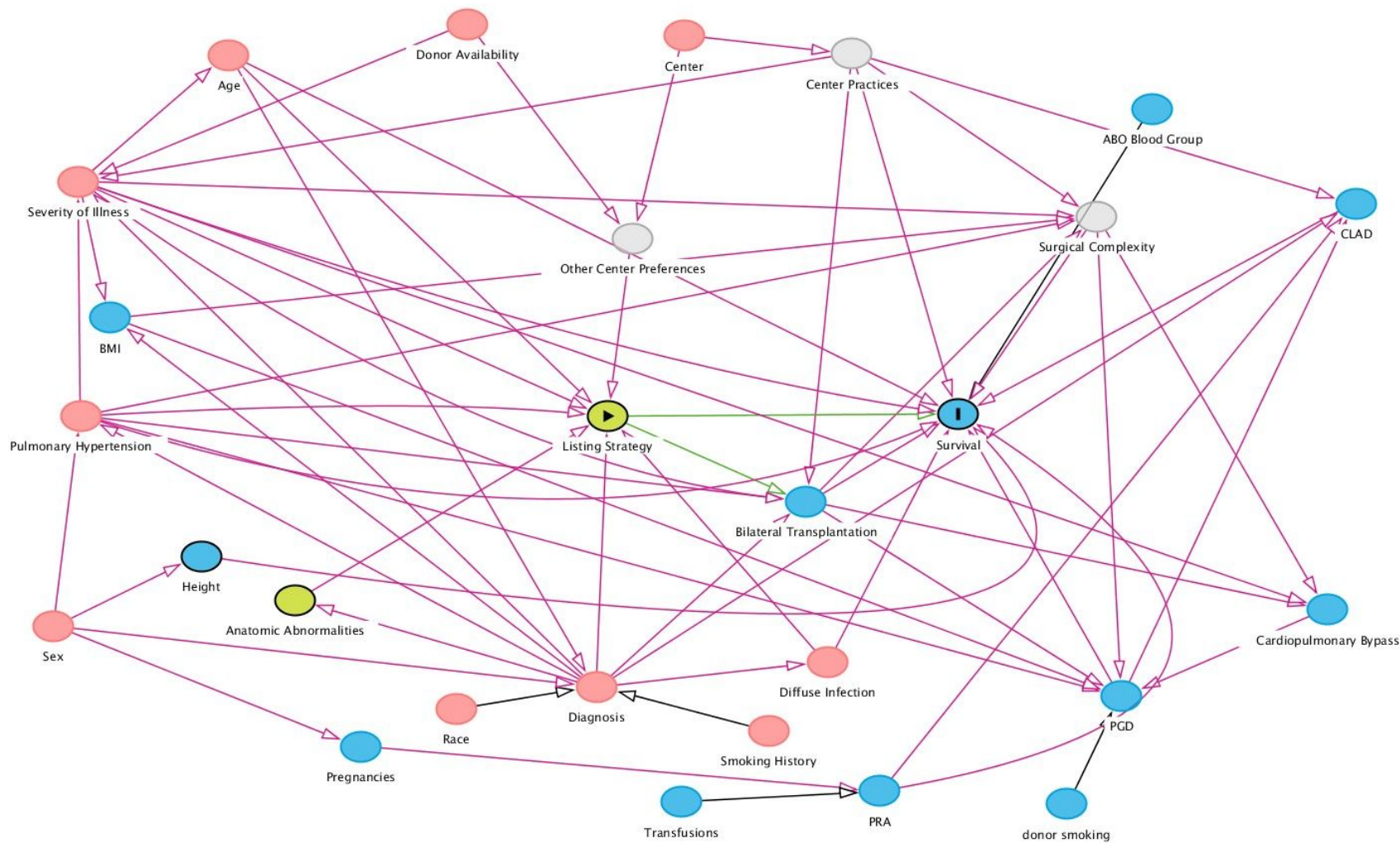
\* Expressed as rate per 100-person years

<sup>§</sup> Adjusted for lung allocation score at transplant, ABO blood group, height, age, gender, race, use of mechanical ventilation or extracorporeal membrane oxygenation at transplant, body mass index at transplant, mean pulmonary arterial pressure at listing, donor gender, donor body mass index, donor height, donor alcohol use, donor cigarette use, donor pulmonary infection, donor diabetes, donor PaO<sub>2</sub>, donor cause of death and listing center  
Transplant procedure missing on 3 subjects with COPD and 16 subjects with ILD.

**Figure E1:** Summary of analyses by time period.

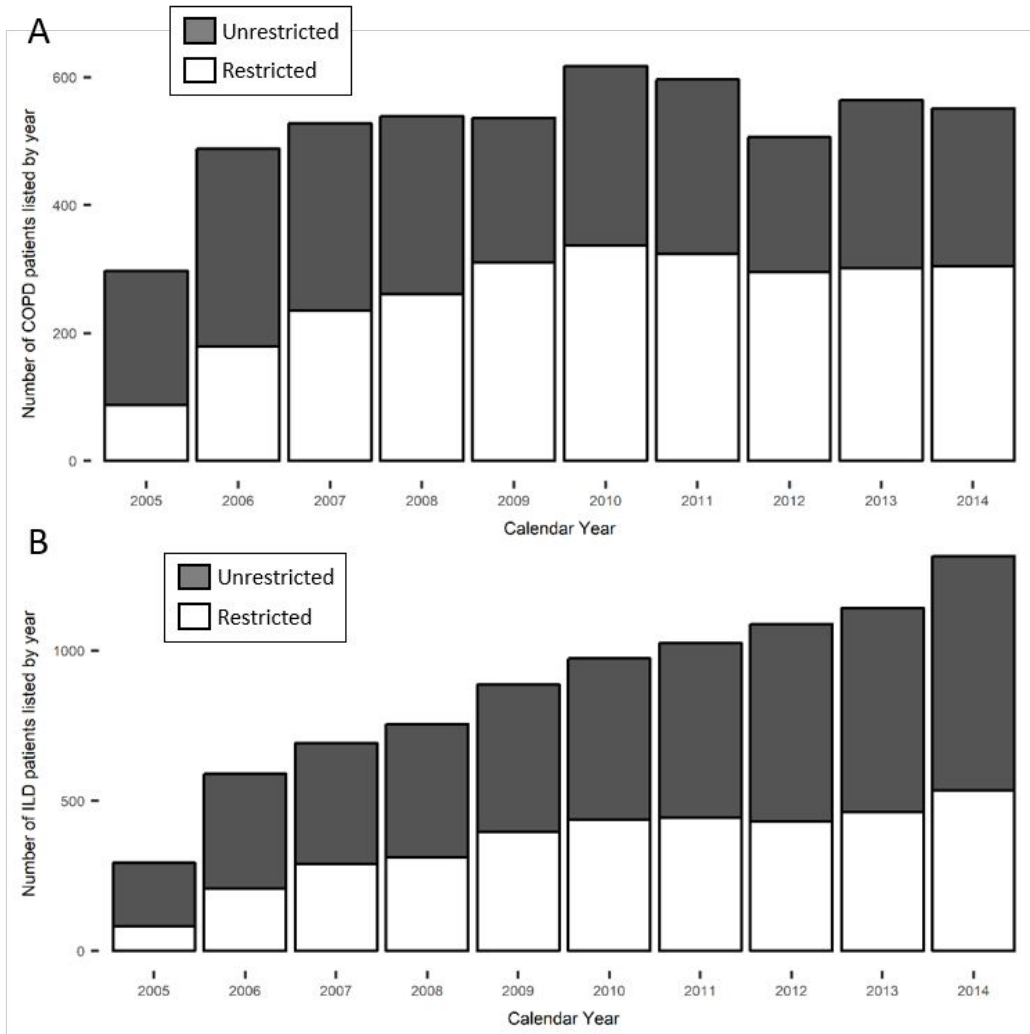


**Figure E2:** Directed acyclic graph for the primary analysis. All back-door paths close with control of: age, sex, race, body mass index, height, ABO blood group and lung allocation score.

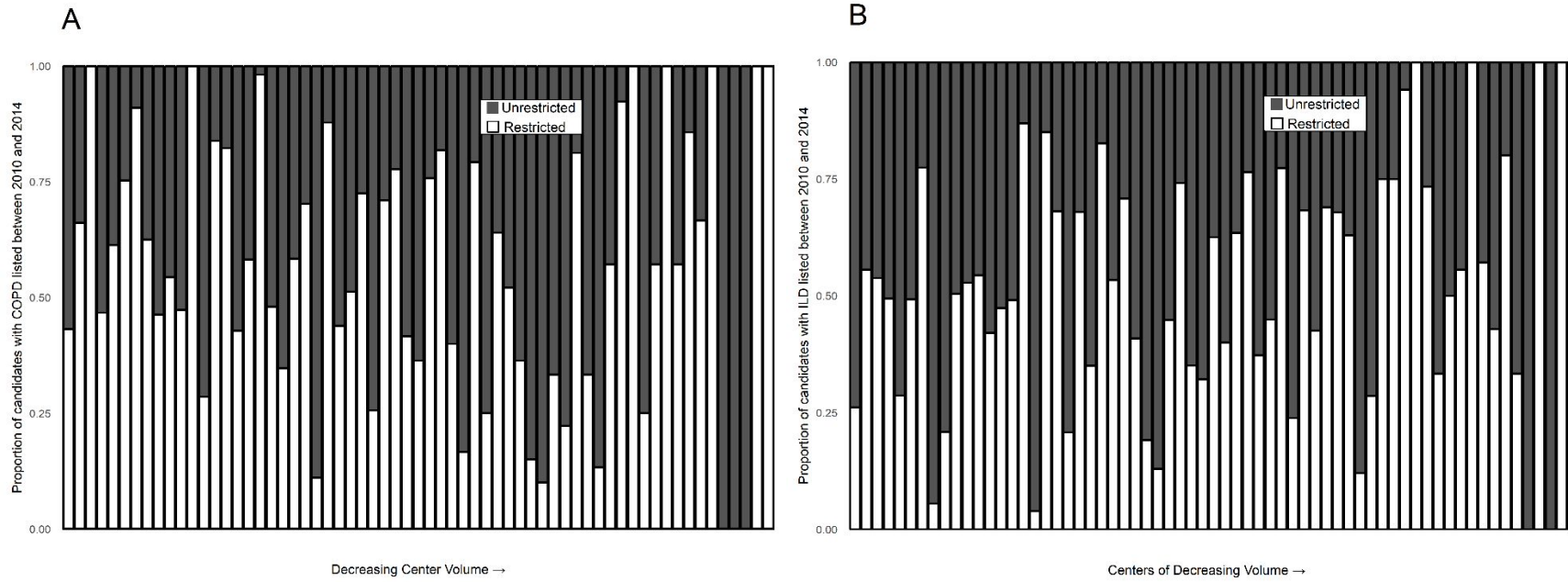


**Figure E3:** Number of candidates listed with restricted and unrestricted listing preferences by calendar year

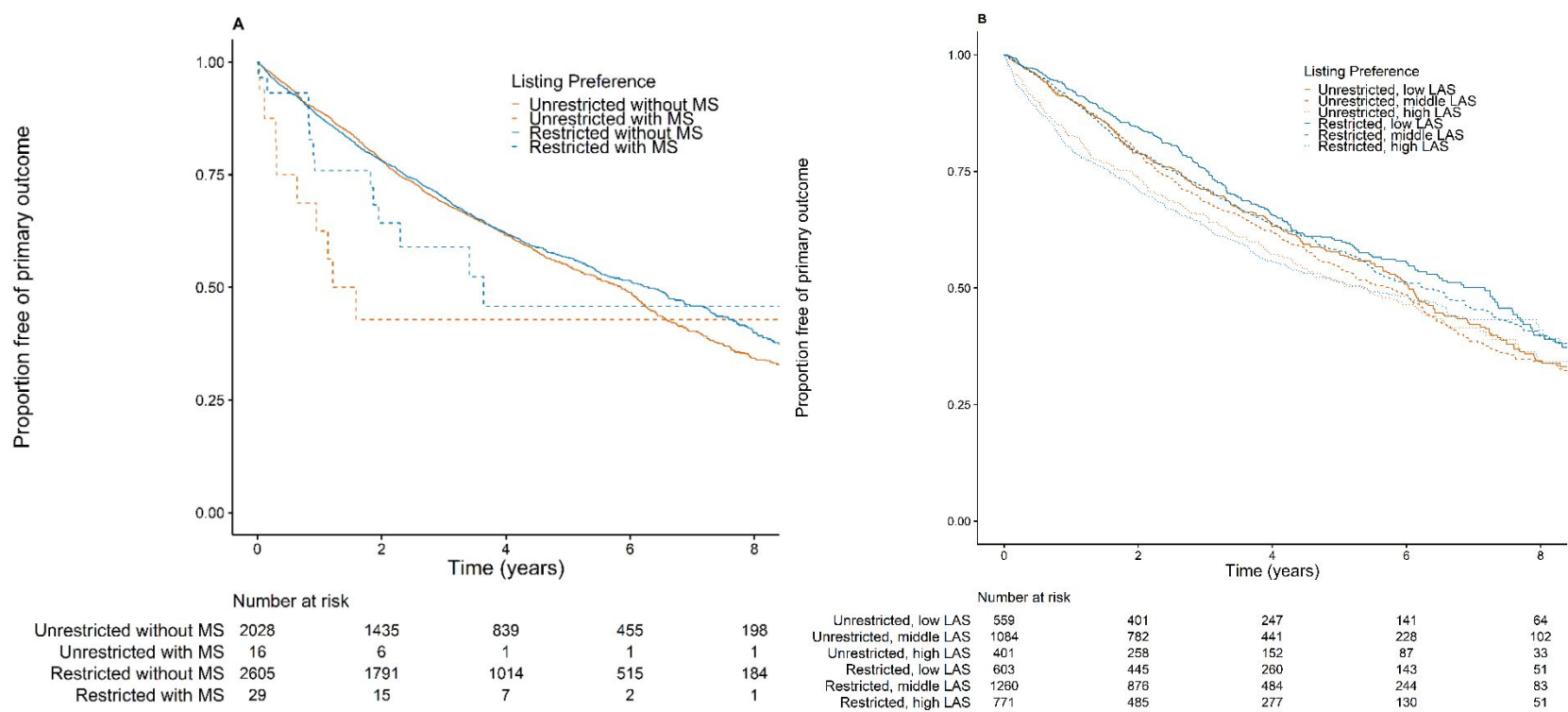
\*The year 2005 represents only those listed for transplant between May 5 2005 and December 31, 2005



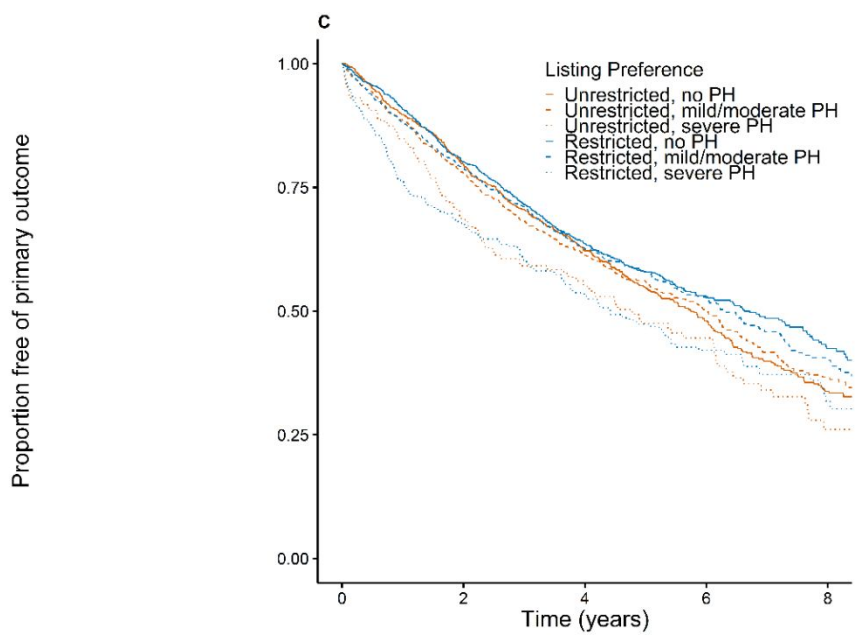
**Figure E4:** Relative distribution of listing preferences among U.S. waiting list candidates listed between 2010 and 2015 with (A) COPD and (B) ILD ranked by center volume. Each column is one transplant center.



**Figure E5:** Kaplan Meier survival curves for the primary “intention-to-treat” composite outcome (time from listing until death before or after transplantation, removal from the waiting list due to clinical deterioration, or re-transplantation) among candidates with COPD stratified by (A) use of mechanical support (mechanical ventilation or extracorporeal membrane oxygenation), (B) lung allocation score, and (C) severity of pulmonary hypertension. Numbers below each panel are the number of subjects at risk at each time point. LAS = lung allocation score; PH = pulmonary hypertension; mild PH = mean pulmonary artery pressure greater than or equal to 25 but less than 30; moderate PH = mean pulmonary artery pressure greater than or equal to 30 but less than 35; severe PH = mean pulmonary artery pressure greater than or equal to 35.

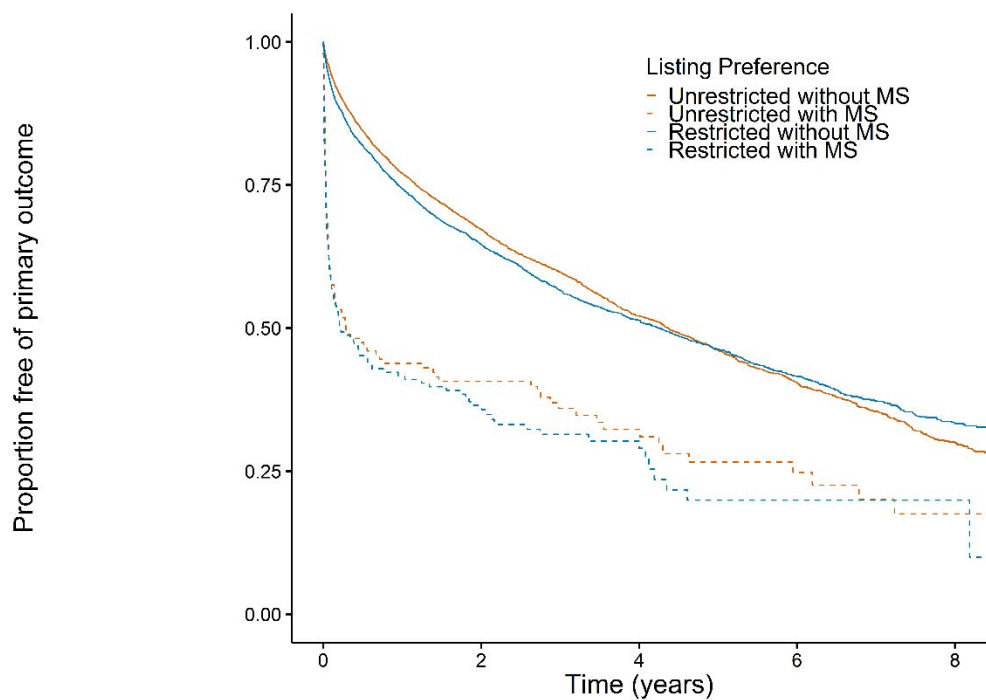






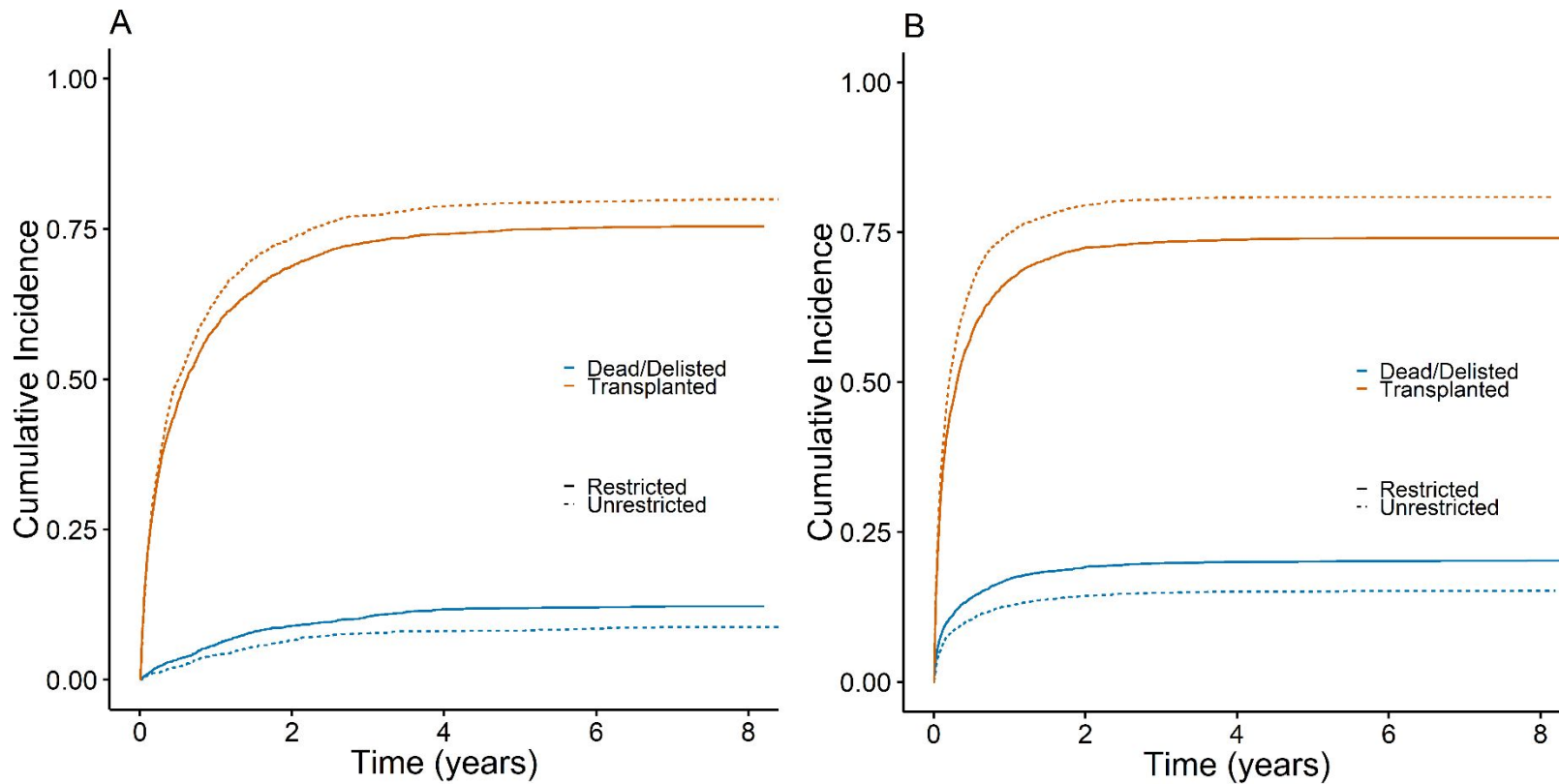
	Number at risk				
Unrestricted, no PH	1019	731	419	226	107
Unrestricted, mild/moderate PH	866	613	351	189	78
Unrestricted, severe PH	159	97	70	41	14
Restricted, no PH	1194	828	468	234	92
Restricted, mild/moderate PH	1084	767	424	220	72
Restricted, severe PH	356	211	129	63	21

**Figure E6:** Kaplan Meier survival curves for the primary “intention-to-treat” composite outcome (time from listing until death before or after transplantation, removal from the waiting list due to clinical deterioration, or re-transplantation) among candidates with ILD by use of mechanical support (mechanical ventilation or extracorporeal membrane oxygenation). Numbers below each panel are the number of subjects at risk at each time point. MS = mechanical support.



	Number at risk				
	0	2	4	6	8
Unrestricted without MS	3742	2183	1096	522	202
Unrestricted with MS	139	49	25	12	5
Restricted without MS	3418	1905	1068	531	188
Restricted with MS	178	51	24	6	2

**Figure E7:** (A) Cumulative incidence curves for transplantation (orange,  $P < 0.001$ ) and death or removal from the waiting list (blue,  $P < 0.001$ ) among COPD candidates. (B) Cumulative incidence curves for transplantation (orange,  $P < 0.001$ ) and death or removal from the waiting list (blue,  $P < 0.001$ ). P values are for the association between lung preference and the outcome of interest using unadjusted competing risks models.



**Figure E8:** Kaplan-Meier curves for time to graft survival (death or re-transplantation) after lung transplantation among candidates with (A) COPD and (B) ILD. Numbers below each panel are the number of subjects at risk at each time point. \*Missing post-transplant survival time on 11 people with COPD (6 restricted, 5 unrestricted) and 4 people with ILD (1 restricted, 3 unrestricted)

