Annals of Internal Medicine | ARTICLE

Survival After Bilateral Versus Single-Lung Transplantation for Idiopathic Pulmonary Fibrosis

Gabriel Thabut, MD, PhD; Jason D. Christie, MD, MS; Philippe Ravaud, MD, PhD; Yves Castier, MD, PhD; Gaëlle Dauriat, MD; Gilles Jebrak, MD; Michel Fournier, MD, PhD; Guy Lesèche, MD, PhD; Raphaël Porcher, PhD; and Hervé Mal, MD

Background: Patients with end-stage idiopathic pulmonary fibrosis (IPF) are increasingly having bilateral rather than single-lung transplantation.

Objective: To compare survival after single and bilateral lung transplantation in patients with IPF.

Design: Analysis of data from the United Network of Organ Sharing registry.

Setting: Transplantation centers in the United States.

Patients: 3327 patients with IPF who had single (2146 patients [64.5%]) or bilateral (1181 patients [35.5%]) lung transplantation between 1987 and 2009.

Measurements: Survival times and causes of death after lung transplantation. Selection bias was accounted for by multivariate risk adjustment, propensity score risk adjustment, and propensity-based matching.

Results: Median survival time was longer after bilateral lung transplantation than single-lung transplantation (5.2 years [CI, 4.3 to 6.7 years] vs. 3.8 years [CI, 3.6 to 4.1 years]; $P < 0.001$). However, survival times for the 2 procedures did not differ after adjustment for baseline differences, with adjusted hazard ratios (HRs) for mortality with bilateral transplantation ranging from 0.89 (95% CI, 0.79 to 1.02) to 0.96 (CI, 0.77 to 1.20) in different analyses. Bilateral lung transplantation seemed to result in harm within the first year (HR, 1.18 [CI, 0.98 to 1.42]) but survival benefit thereafter (HR, 0.72 [CI, 0.59 to 0.87]). Primary graft failure was a more common cause of death among patients who had bilateral rather than single-lung transplantation (3.7% vs. 1.9%; $P = 0.002$). Cancer was a more common cause of death among patients who had single rather than bilateral lung transplantation (unadjusted HR for death among single vs. bilateral transplant recipients, 3.60 [CI, 2.16 to 6.05]; $P < 0.001$).

Limitation: Causes of death were ascertained without an adjudication committee and must be interpreted cautiously.

Conclusion: Survival did not differ between patients who had single and bilateral lung transplantation. Single-lung transplantation confers short-term survival benefit but long-term harm, whereas bilateral transplantation confers short-term harm but long-term survival benefit.

Primary Funding Source: None.

Ann Intern Med. 2009;151:767-774. www.annals.org

For author affiliations, see end of text.

Idiopathic pulmonary fibrosis (IPF) often progresses to end-stage lung disease and is the second most common reason for lung transplantation (1, 2), accounting for more than 25% of lung transplantation procedures (2). The procedure can involve single or bilateral lung transplantation (1–3). Single-lung transplantation was considered the procedure of choice after the first report of successful transplantation for patients with IPF by the Toronto Group (4, 5). However, patients with IPF are having bilateral lung transplantation with greater frequency, and the procedure now accounts for almost 50% of all lung transplantations in patients with IPF (2). The reason for this progressive shift toward bilateral transplantation is unclear. Because no randomized, controlled studies have addressed this issue, current evidence comes from observational studies and yields conflicting results (6–9).

Using data from the United Network for Organ Sharing (UNOS), we aimed to compare survival rates after single and bilateral lung transplantation for patients with IPF by using multivariate model risk adjustment, propensity score risk adjustment, and propensity-based matching techniques to account for confounding factors.

METHODS

Patients

The UNOS supplied all data as a standard analysis and research file, based on Organ Procurement and Transplantation Network data as of February 2009, and included coded transplant-center identifiers. The registry contains data on all patients who had lung transplantation in the United States since the registry's inception in 1987. Before May 2005, recipients were allocated organs on the basis of wait-list times. Since May 2005, priority on the waiting list has been determined by the Lung Allocation Score, which ranks patients according to the difference between survival benefit and survival on the waiting list (10). All adult patients were eligible for the study if they had cadaveric single or bilateral lung transplantation for IPF (code 1604 of the UNOS data set) and the date of transplantation, date of last follow-up, and vital status at last follow-up were known.

See also:

Print
Editors' Notes 768

Web-Only
Appendix
Appendix Table
Appendix Figures
Conversion of graphics into slides

Context

Patients with end-stage lung disease caused by idiopathic pulmonary fibrosis often have bilateral lung transplantation, but the benefits of this procedure over single-lung transplantation are unclear.

Contribution

In this comparison of outcomes for patients who received 1 or 2 lungs, overall survival did not differ but causes of death did. Bilateral transplantation seemed to increase mortality in the first year and decrease mortality thereafter.

Caution

Unmeasured variables associated with transplantation might have contributed to the study's findings.

Implication

Single and bilateral lung transplantation carry different short- and long-term benefits and harms for patients with idiopathic pulmonary fibrosis.

—The Editors

We collected data on donor, surgery, and recipient characteristics at the time of transplantation from the UNOS registry. We excluded variables for which data were sparse or those that described clinically uncommon or rare characteristics, and we calculated several variables from those that were available (such as donor and recipient body mass indexes and mismatches of sex and blood type). The **Appendix Table** (available at www.annals.org) lists the variables we included in the analyses.

Outcomes

The primary outcome was recipient survival. We assessed cause of death of the lung recipient as a secondary end point.

Statistical Analysis

We adjusted for confounding factors by using multivariate model risk adjustment, propensity-score risk adjustment, and matching on the propensity score.

Multivariate model risk adjustment is a conventional modeling approach that incorporates all known confounders, including interactions, into a regression model. Controlling for these confounders produces a risk-adjusted treatment effect and removes overt bias due to these factors. We used Cox proportional hazards regression models to compare mortality rates between the single and bilateral lung transplantation groups, adjusted for covariates. We used purposeful selection of covariates, as described by Hosmer and Lemeshow (11), to select the multivariate model. The first step was the inclusion of all variables significant at the 20% level in the bivariate analysis, as well as all variables known to be clinically relevant (12). The second step was to remove, one by one, variables that did not significantly contribute to the multivariate model on the basis of the Wald test P value and the change in the coefficient of the remaining variables. We assessed the scale of the continuous covariates by using residual analysis (13). We only considered first-order interactions with surgical procedure. We took transplant center effects into account by including centers in the multivariate analyses as a random effect with a Gaussian distribution. Residual plots supported a linear relation between all continuous covariates and the log hazard for death. No significant interaction was retained in the final model; interactions between age at transplantation and procedure and between systolic pulmonary artery pressure and procedure were not significant. The final model included recipient variables (age, body mass index, functional status, and mean pulmonary artery pressure), donor variables (body mass index and cytomegalovirus status), and procedure-related variables (transplantation year, surgical procedure, lung transplantation center, and lung transplantation center volume).

In our analyses of cause of death, we used the cumulative incidence estimator and the proportional subdistribution hazard model described by Fine and Gray (14) to account for competing causes.

Propensity scores estimate the probability that a patient with specific pretreatment characteristics will receive a treatment, in this case bilateral rather than single-lung transplantation (15, 16). Within propensity score strata, covariates in both groups tend to be similarly distributed. We computed propensity scores by using logistic regression, in which surgical procedure was the dependent variable and the variables listed in the **Appendix Table** (available at www.annals.org) were independent variables. We judged the success of the propensity score modeling by assessing balance on baseline characteristics within deciles of propensity score or after matching propensity scores for patients in the single and bilateral lung transplantation groups, and found balanced distribution of variables within deciles.

We used Cox proportional hazards regression to estimate the effect of bilateral lung transplantation on survival, adjusting for the propensity score (on the linear predictor scale) and surgical procedure. In another analysis, we took only data with propensity score overlap into account and adjusted the estimates on the deciles of the propensity score. We used a 1:1 matching algorithm without replacement to match patients, with calipers defined to have a maximum width of 0.25 SD of the logit of the estimated propensity score. We used marginal Cox models, accounting for correlation within matched pairs, to compare the single and bilateral lung transplantation groups in terms of adjusted survival (17).

We used several statistical methods to assess whether the effect of surgical procedure was constant over time (proportional hazards assumption), including residual plots (as described by Grambsch and Therneau [18]) and fitting of additive regression models (as described by Aalen [19]).

For variables involved in the multivariate model risk adjustment and propensity score analysis, we imputed missing data by using the multiple imputations by chained equation method (20), which resulted in 20 imputed data sets. We independently analyzed each of the 20 data sets. We averaged estimates of the variables to give a single mean estimate and adjusted SEs according to the Rubin rules (20–22). The **Appendix** (available at www.annals.org) lists the steps of the imputation procedure.

All analyses were performed by using R, version 2.5 (R Foundation for Statistical Computing, Vienna, Austria), and Stata, version 10.2 (StataCorp, College Station, Texas), for Windows XP. Propensity-score matching was done by using the "Matching" package for R.

Role of the Funding Source

This study received no funding. The authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

The UNOS database included data for 33 252 patients registered on a waiting list for lung transplantation in the United States during the study period; 18 333 (55.1%) had lung transplantation. Of these, 3411 (18.6%) had received a diagnosis of IPF at the time of transplantation. We excluded 11 patients who received grafts from non–heart-beating donors, 25 patients who were younger than 18 years at the time of transplantation, and 48 patients whose survival time was unknown. The final analysis included the remaining 3327 patients who had lung transplantation in 88 U.S. centers (median, 120 lung transplantations per center [25th to 75th percentile, 22 to 323 transplantations per center]).

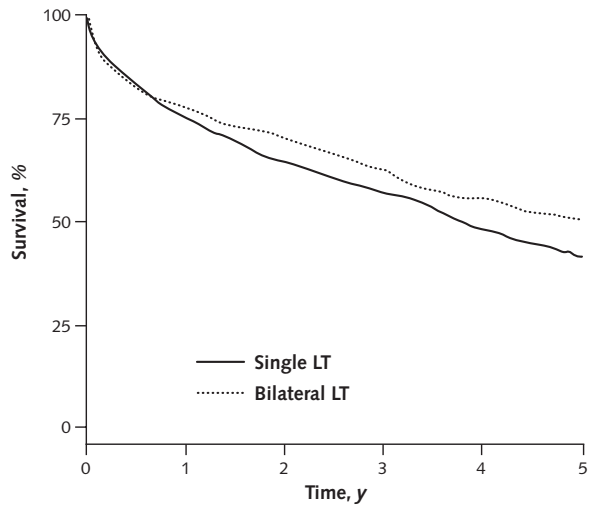
The number of patients who had lung transplantation for IPF increased over time, from 59 in 1992 to 409 in 2008; 2146 (64.5%) had single-lung transplantation and 1181 (35.5%) had bilateral lung transplantation. The proportion of patients who had bilateral lung transplantation

Table 1. **Main Baseline Patient Characteristics, by Type of Lung Transplantation**

Characteristic	Nonmissing Data, *n (%)*	Single-Lung Transplantation (*n* = 2146)	Bilateral Lung Transplantation (*n* = 1181)	Standardized Difference, %*
Recipient				
Mean age (SD), *y*	3327 (100)	57.1 (9.0)	54.0 (10.0)	32.1
Age distribution, *n (%)*	3327 (100)			
≤50 y		424 (19.8)	362 (30.7)	25.3
51–55 y		324 (15.1)	188 (15.9)	2.3
56–60 y		552 (25.7)	279 (23.6)	4.9
>60 y		846 (39.4)	352 (29.8)	20.3
Women, *n (%)*	3327 (100)	705 (32.9)	358 (30.3)	5.5
Functional status, *n (%)*†	2852 (85.7)			
Class I		464 (26.0)	213 (19.9)	14.6
Class II		928 (52.1)	483 (45.1)	13.9
Class III		390 (21.9)	374 (35.0)	29.3
Diabetes, *n (%)*	3044 (91.5)	279 (14.7)	186 (16.2)	4.1
Oxygen required at rest, *n (%)*	2498 (75.1)	1318 (76.1)	642 (83.8)	19.4
Mean FVC (SD), *% predicted*	3082 (92.6)	49.0 (16.0)	47.4 (17.9)	9.3
Mean pulmonary capillary wedge pressure (SD), *mm Hg*	2842 (85.4)	8.8 (5.9)	10.1 (6.1)	22.8
Mean pulmonary artery pressure (SD), *mm Hg*	2474 (74.4)	23.4 (8.8)	28.4 (11.5)	49.2
Mean body mass index (SD), kg/m^2	3193 (96.0)	27.2 (4.5)	26.8 (4.3)	11.0
Donor				
Mean age (SD), *y*	3327 (100)	32.2 (13.6)	33.0 (14.9)	5.3
Female, *n (%)*	3327 (100)	775 (36.1)	532 (45.0)	18.3
Mean body mass index (SD), kg/m^2	3146 (94.6)	24.8 (5.1)	25.0 (5.1)	3.2
Diabetes, *n (%)*	3060 (91.9)	76 (4.0)	46 (4.0)	0
Cause of death, *n (%)*	3149 (94.6)			
Anoxia		136 (6.8)	98 (8.5)	6.3
Stroke		740 (37.1)	445 (38.6)	3.0
Head trauma		1105 (55.4)	599 (51.9)	7.0
CNS tumor		14 (0.7)	12 (1.0)	3.6
Donor-to-recipient				
Cytomegalovirus status mismatches, *n (%)*	2361 (71.0)	610 (44.3)	434 (44.2)	0.2
Sex mismatches, *n (%)*	3327 (100)	616 (28.7)	418 (35.4)	14.4
Blood group mismatches, *n (%)*	3327 (100)	221 (10.3)	101 (8.6)	6.0
HLA mismatches, *n (%)*	2735 (82.2)	4.6 (1.1)	4.7 (1.1)	7.6

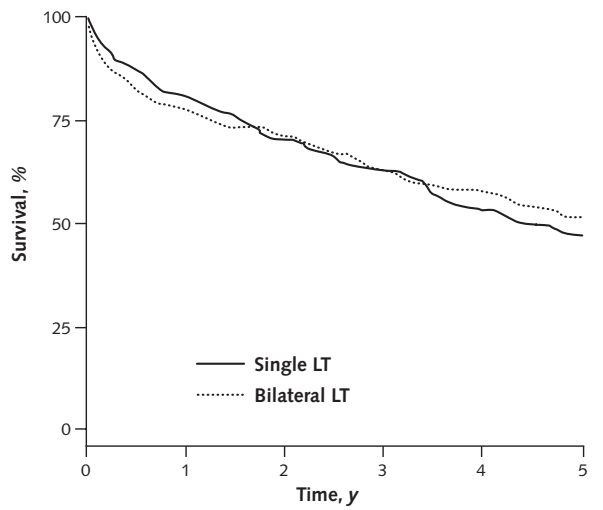
CNS = central nervous system.
* Mean difference divided by the pooled SD, expressed as a percentage.
† Ranges from class I to III, indicating that the patient performs activities of daily living with no, some, or total assistance, respectively.

Figure 1. **Kaplan–Meier estimates for survival after lung transplantation.**



At risk, *n*

Single LT	2146	1378	1003	765	551	404
Bilateral LT	1181	648	435	284	199	129
Total	3327	2026	1438	1049	750	533



At risk, *n*

Single LT	795	499	333	235	153	112
Bilateral LT	795	456	325	225	164	105
Total	1590	955	658	460	317	217

LT = lung transplantation. **Top.** For 3327 patients with idiopathic pulmonary fibrosis. **Bottom.** For 795 pairs of patients who were matched by propensity score.

also increased over time, from 6 of 59 total procedures (10.2%) in 1992 to 223 of 409 procedures (54.5%) in 2008 (**Appendix Figure 1**, available at www.annals.org). **Appendix Figure 2** (available at www.annals.org) shows the proportion of bilateral lung transplantation by transplantation center volumes for IPF and all indications and suggests that high-volume centers were more likely than low-volume centers to perform bilateral lung transplantation.

Recipient Characteristics, by Procedure

Table 1 details characteristics of recipients and donors by recipient procedure. We found large, standardized between-group differences in recipient age, functional status, pulmonary artery pressures, and transplantation date (**Appendix Figure 1**, available at www.annals.org). Except for a small imbalance in sex, donor characteristics in general did not differ between recipients of single-lung and bilateral lung transplantation, either overall or by recipient pulmonary artery pressure (data not shown).

Patients who had bilateral lung transplantation had a significantly longer total graft ischemic time than those who had single-lung transplantation (5.5 hours [SD, 1.7] vs. 4.0 hours [SD, 1.4]); $P < 0.001$) and a longer median hospital stay (14 days [25th to 75th percentile, 9 to 24 days] vs. 17 days [25th to 75th percentile, 11 to 31 days]; $P < 0.001$).

Survival

Median follow-up time was 1.6 years (range, 0 to 17.0 years). During follow-up, 1556 patients (46.8%) died, 52 (1.6%) were lost to follow-up, 94 (2.8%) had retransplantation, and 1625 (48.8%) were alive at last follow-up. Median survival after transplantation was 4.0 years (95% CI, 3.8 to 4.3 years). Survival rates were 76.1% (CI, 74.6% to 77.6%) at 1 year, 58.6% (CI, 56.7% to 60.6%) at 3 years, and 43.9% (CI, 41.7% to 46.2%) at 5 years. Survival improved in more recent years (median before 2002, 3.2 years [CI, 2.9 to 3.6 years] [1149 patients]; from 2002 onward, 4.7 years [CI, 4.3 to 5.3 years] [2178 patients]; $P < 0.001$).

Median survival was significantly longer after bilateral lung transplantation than single-lung transplantation (5.2 years [CI, 4.3 to 6.7 years] vs. 3.8 years [CI, 3.6 to 4.1 years]; $P < 0.001$) (**Figure 1**, *top*), but the difference was not evident in an analysis restricted to patients who had lung transplantation from 2002 onward (5.0 years [CI, 4.2 to ∞] [960 patients] vs. 4.6 years [CI, 4.2 to 5.1 years] [1218 patients]; $P = 0.29$). Retransplantation was less common among patients who had bilateral transplantation than those who had single-lung transplantation (20 patients [1.7%] vs. 74 patients [3.4 %]; $P = 0.03$).

An unadjusted multivariate analysis suggested lower mortality with bilateral than with single-lung transplantation (unadjusted hazard ratio, 0.80 [CI, 0.71 to 0.89]), but the effect was attenuated and no longer statistically significant when we adjusted for recipient, donor, and procedure-related variables (adjusted hazard ratio, 0.92 [CI, 0.81 to 1.06]; adjusted hazard ratio in a complete-case analysis, 0.96 [CI, 0.81 to 1.15]). We observed similar results when we restricted the analysis to the 2178 patients who had lung transplantation from 2002 onward (adjusted hazard ratio, 1.0 [CI, 0.84 to 1.21]). Recipient age and transplantation year seemed to be the strongest confounders (data not shown); the effects of bilateral transplantation did not differ by pulmonary artery pressure at

the time of transplantation (**Appendix Figure 3**, available at www.annals.org).

We obtained similar results from a multivariate analysis that adjusted for propensity score only (adjusted hazard ratio, 0.89 [CI, 0.79 to 1.02]) and for propensity score with the other recipient, donor, and procedure-related variables (adjusted hazard ratio, 0.90 [CI, 0.78 to 1.03]) and from analyses restricted to patients with propensity score overlap (adjusted hazard ratio, 0.90 [CI, 0.78 to 1.03]).

In addition, we successfully matched 795 patients who had single-lung transplantation with 795 patients who had bilateral lung transplantation on the basis of propensity score. **Table 2** gives the main characteristics of these patients by procedure and shows that we had a good balance of baseline characteristics between the 2 groups, with all standardized mean differences less than 10%. In a Cox model that accounted for correlation within matched pairs, the hazard ratio for mortality was 0.96 (CI, 0.77 to 1.20). **Figure 1**, *bottom*, shows survival of the patients matched on propensity score, by transplantation procedure.

Despite our generally consistent findings of no adjusted differences in mortality between procedures, tests of the analyses' proportional hazards assumptions with residual plots and additive models suggest an increased relative risk for death with bilateral lung transplantation in the early postoperative period, followed by a decreased relative risk for death (**Figure 2**). We confirmed these findings with a separate analysis of hazard ratio according to 2 postoperative periods (within the first postoperative year and after 1 year following lung transplantation) for both the full data set and the propensity score–matched data set (**Table 3**).

Causes of Death

Among the 1556 patients who died during follow-up, the cause of death was available for 1391 (89.4%). **Table 4** lists the main causes of death. Among patients who had bilateral lung transplantation, 44 of 1181 (3.7%) died of primary graft failure, compared with 40 of 2146 (1.9%) of those who had single-lung transplantation ($P = 0.002$). Conversely, the single-lung transplantation group had a higher incidence of death due to cancer than the bilateral lung transplantation group (**Appendix Figure 4**, available at www.annals.org). The hazard ratio for death due to cancer between single and bilateral lung transplantation was 3.60 (CI, 2.16 to 6.05; $P < 0.001$) in univariate analysis (Fine and Gray model) and 2.67 (CI, 1.59 to 4.48; $P < 0.001$) after we adjusted for recipient age and transplantation year.

DISCUSSION

In our observational study of mortality among patients with IPF who had single or bilateral lung transplantation between 1987 and 2009, we detected no statistically significant differences in survival between the 2 interventions in several analyses that accounted for potential confounding factors. Unilateral transplantation seems to have short-term survival benefit but long-term harm, whereas bilateral transplantation seems to have short-term harm but long-term survival benefit.

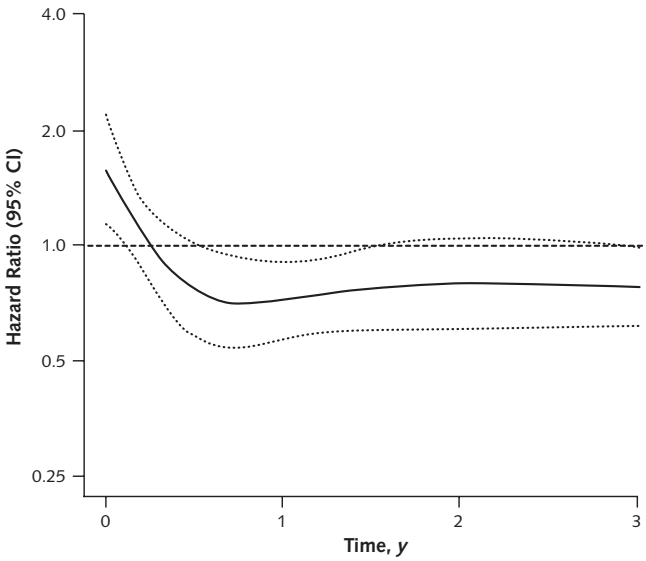
Successful single-lung transplantation was first reported in 1986 in 3 patients with IPF (4); in 1990, the same group detailed the functional results in 20 patients with fibrotic lung diseases (5). After these reports, single-lung transplantation was considered the procedure of

Table 2. **Main Baseline Characteristics of Patients Matched by Propensity Score, by Type of Lung Transplantation**

Characteristic	Single-Lung Transplantation ($n = 795$)	Bilateral Lung Transplantation ($n = 795$)	Standardized Difference, %*
Recipient			
Mean age (SD), *y*	56.0 (8.4)	55.9 (8.4)	0.7
Age distribution, *n (%)*			
≤50 y	172 (21.6)	180 (22.6)	2.4
51–55 y	134 (16.9)	126 (15.8)	2.7
56–60 y	218 (27.4)	214 (26.9)	1.1
>60 y	271 (34.1)	275 (34.6)	1.1
Women, *n (%)*	244 (30.7)	229 (28.8)	4.2
Functional status, *n (%)*†			
Class I	179 (22.5)	173 (21.8)	1.8
Class II	369 (46.4)	376 (47.3)	1.8
Class III	247 (31.1)	246 (30.9)	0.3
Diabetes, *n (%)*	143 (18.0)	125 (15.7)	6.0
Oxygen required at rest, *n (%)*	674 (84.8)	672 (84.5)	0.7
Mean FVC (SD), *% predicted*	48.9 (16.6)	48.5 (17.4)	2.4
Mean PCWP (SD), *mm Hg*	9.7 (6.0)	9.5 (5.6)	4.5
Mean pulmonary artery pressure (SD), *mm Hg*	24.8 (8.6)	24.7 (8.7)	0.3
Body mass index (SD), kg/m^2	27.2 (4.4)	26.9 (4.2)	5.8
Donor			
Mean age (SD), *y*	32.9 (13.8)	33.3 (15.0)	2.5
Female, *n (%)*	334 (42.0)	329 (41.4)	1.3
Mean body mass index (SD), kg/m^2	25.0 (5.2)	25.0 (5.1)	0.2
Diabetes, *n (%)*	31 (3.9)	36 (4.5)	2.0
Cause of death, *n (%)*			
Anoxia	64 (8.1)	68 (8.6)	1.8
Stroke	297 (37.4)	305 (38.4)	2.1
Head trauma	425 (53.5)	412 (51.8)	3.3
CNS tumor	9 (1.1)	10 (1.3)	1.2
Donor-to-recipient			
Cytomegalovirus status mismatches, *n (%)*	363 (45.7)	354 (44.5)	2.3
Sex mismatches, *n (%)*	248 (31.2)	248 (31.2)	0
Blood group mismatches, *n (%)*	75 (9.4)	74 (9.3)	0.4
HLA mismatches, *n (%)*	4.6 (1.0)	4.6 (1.1)	3.4

CNS = central nervous system; PCWP = pulmonary capillary wedge pressure.
* Mean difference divided by the pooled SD, expressed as a percentage.
† Ranges from class I to III, indicating that the patient performs activities of daily living with no, some, or total assistance, respectively.

Figure 2. **Estimate of the hazard ratio for death associated with bilateral lung transplantation as a function of time after lung transplantation.**



This plot is a smoothing of the scaled Schoenfeld residuals as described in reference 18.

choice for patients with IPF. Despite the availability of bilateral lung transplantation by the end of the 1980s, most lung transplantation centers preferred single-lung transplantation, with the procedure accounting for up to 80% of lung transplantations performed in patients with IPF in the 1990s. From 2000 onward, the proportion of bilateral lung transplantations performed in patients with IPF increased sharply; these now account for almost 50% of all lung transplantation procedures in the International Society for Heart and Lung Transplantation (ISHLT) registry (2). We cannot explain this trend.

Several retrospective studies compared outcomes after either procedure; they yielded conflicting results (6–9). The first study (8) describes 45 patients with IPF but reveals no difference between single (32 patients) and bilateral lung transplantation (13 patients) in terms of survival, hospital stay, or occurrence of bronchiolitis obliterans. Another study (7), based on data from the UNOS Registry, focused on 821 patients who had lung transplantation (636 single and 185 bilateral) for IPF over more than 6 years in the United States. Comparing survival by procedure within 3 age groups, the authors found that in patients younger than 60 years, survival was higher after single-lung transplantation than bilateral lung transplantation. Similarly, for 830 patients with IPF in the ISHLT Registry who had bilateral or single-lung transplantation, bilateral lung transplantation (as well as increasing pulmonary artery pressure) was identified as an independent risk factor for 90-day mortality (9). In contrast, a more recent study (6) that compared the results of both procedures in 82 patients with IPF in a single center concluded that single-lung transplantation was associated with worse survival than bilateral transplantation. Finally, for the first time, unadjusted analyses in the latest report from the ISHLT Registry (2) indicate a survival advantage with bilateral lung transplantation in more than 3300 patients with IPF who had single or bilateral lung transplantation. Methodological considerations, including how confounding factors were dealt with, could explain these conflicting results.

We investigated cause of death as a secondary end point. Primary graft failure was more frequently reported as a cause of death after bilateral transplantation than after single-lung transplantation and could explain the increased early mortality that we and previous investigators observed after bilateral lung transplantation. We also found a higher incidence of cancer after single-lung transplantation than after bilateral lung transplantation, which persisted even after we adjusted for recipient age. In cases of single-lung transplantation, complications involving the remaining lung could account for this observation.

Our study has several strengths. First, we included patients who had lung transplantation up to 2009. Because survival with lung transplantation has changed over time, the results for patients who had lung transplantation 5 years ago may no longer apply. Second, we included many prognostic factors in our models that have never been taken into account in previous studies. For instance, the year of transplantation is linked to survival and to the likelihood of having bilateral lung transplantation (**Appendix Figure 1**, available at www.annals.org) and may thus be an important confounding factor. Including such a large number of patients gave us the opportunity to adjust for this confounding factor (and many others), whereas previous studies could not. Third, we applied several methods of adjustment to take potential selection biases into account, and we attempted to address the potential limitations of this study by performing sensitivity analyses. The fact that all these methods yielded similar conclusions further strengthens the soundness of our results. Previous

Table 3. **Multivariate Cox Regression Analysis for Association Between Bilateral Lung Transplantation and Death, by Postoperative Period***

Postoperative Period	Hazard Ratio (95% CI)	
	Complete Data Set (n = 3327)	Matched Data Set (n = 1590)
<1 y	1.18 (0.98–1.42)	1.30 (1.03–1.64)
≥1 y	0.72 (0.59–0.87)	0.68 (0.53–0.86)

* Adjusted for recipient variables (age, body mass index, functional status, and mean pulmonary artery pressure), donor variables (body mass index and cytomegalovirus status), and procedure-related variables (transplantation year, lung transplantation center, and lung transplantation center volume).

studies were either not powerful enough to adjust for confounding factors or involved only conventional modeling approaches.

Conventional modeling approaches can produce biased estimates if background characteristics are extremely unbalanced or the effect of a surgical procedure is not constant across values of background characteristics. To circumvent this limitation, we used propensity scores, which have been shown to reduce bias considerably (15–17, 23). The propensity score is the probability of a person being treated (that is, of having bilateral lung transplantation), on the basis of that person's covariate values. Covariates in both groups are similarly distributed within propensity score strata, and the score can be incorporated in the analysis by stratification or by matching each treated patient with 1 control patient within a preset amount (or caliper) of the treated patient's propensity score. In our study, we found 795 pairs of patients who shared close propensity scores. This approach was successful in creating pairs of patients with similar background covariates, as shown in **Table 2**. None of these statistical methods can be viewed as the gold standard for removing bias, and all have drawbacks. However, all methods yielded similar results in our study, which supports the robustness of our findings.

Our study also has limitations. First, we used observational data to study the effect of surgical procedure on long-term survival. Although we used several statistical approaches to take a large number of confounders into account, residual confounding is possible. Only a randomized, controlled trial would definitely answer this question. To take an expected 5% difference in 5-year survival into account, such a trial should enroll and follow more than 3000 patients for 5 years. Such a large-scale trial seems unlikely to be performed in lung transplantation. However, in certain respects, our approach produced results that could be more useful than those from a randomized, controlled trial, especially in terms of external validity. Most randomized, controlled trials recruit only a small proportion of the patients with the disease of interest, and those recruited are likely to systematically differ from those not recruited. Second, the choice of the procedure is driven by several additional variables, such as computed tomography results, exercise capacity, exertional desaturation, or diagnostic methods that are not available in the UNOS data set. We could not account for right ventricular function, a clinically and physiologically important variable. Third, we ascertained causes of recipient death without using an adjudication committee and our findings must be interpreted cautiously. As others have shown (24), cause of death is difficult to assess reliably without the use of an adjudication committee. Finally, although we considered only patients who received a diagnosis of IPF both at the time of inclusion on the wait list and time of transplantation, misdiagnosis may have occurred for some patients.

Table 4. **Main Causes of Death, by Type of Lung Transplantation**

Cause of Death	Single-Lung Transplantation (n = 1150), n (%)	Bilateral Lung Transplantation (n = 406), n (%)
Infection*	278 (24.2)	89 (21.9)
Primary graft failure	40 (3.5)	44 (10.8)
Cancer†	142 (12.3)	16 (3.9)
Chronic rejection	99 (8.6)	32 (7.9)
Respiratory failure	136 (11.8)	46 (11.3)
Other	338 (29.4)	131 (32.3)
Missing data	117 (10.2)	48 (11.8)

* Includes fungal, bacterial, and viral infection regardless of graft involvement.
† Includes neoplastic diseases (solid or not) regardless of lung involvement and metastatic diseases.

The question of the optimal transplantation procedure for IPF is not insignificant. Idiopathic pulmonary fibrosis is the second most frequent disease for which lung transplantation is performed, and according to the latest report of the ISHLT registry (2), the frequency of lung transplantation for IPF has increased markedly since 2000 (from 15% to 26%). Because the decision to favor bilateral rather than single-lung transplantation has important consequences in terms of absolute number of lung transplantations performed worldwide, the decision should be supported by sound data. Because we did not demonstrate the superiority of bilateral over single-lung transplantation for patients with IPF, it seems reasonable to favor single-lung transplantation for IPF in a setting where donor organs remain in short supply. Alternatively, in patients who are deemed to have low operative risk or in the rare setting where donor organs are less scarce, the lower long-term complications rate of bilateral transplantation may favor that procedure. Our data also do not discount the common clinical understanding that bilateral lung transplantation might be a better option for some subsets of patients, such as those with high pulmonary pressure, pretransplantation *Aspergillus* colonization, large cystic cavities in the honeycombing areas, marked traction bronchiectasis with recurrent bacterial exacerbations, or daily bronchorrhea (25). We adjusted for level of pulmonary artery pressure, but lack of data prevented us from investigating outcomes for the other patient subsets.

In conclusion, our study does not support the routine use of bilateral lung transplantation for patients with IPF for perceived survival benefit. In a setting where lung donors are scarce, single-lung transplantation may be the procedure of choice to allow for better utilization of organs, provided that suitable recipients are available. Furthermore, because we found shorter-term survival benefits and longer-term harms with single-lung transplantation and shorter-term harms and longer-term survival benefits with bilateral lung transplantation, the optimal procedure may be considered in the context of the patient's risk profile.

From Hôpital Bichat, APHP et Université Paris-Diderot Paris-7, INSERM U738, INSERM U717, and Hôpital Saint-Louis, Paris, France, and the University of Pennsylvania, Philadelphia, Pennsylvania.

Disclaimer: The data reported here have been supplied by UNOS as the contractor for the Organ Procurement and Transplantation Network. The interpretation and reporting of these data are the responsibility of the authors and should in no way be seen as an official policy of or interpretation by the Organ Procurement and Transplantation Network or the U.S. government.

Potential Conflicts of Interest: None disclosed.

Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Thabut (gabriel.thabut@bch.aphp.fr). *Data set:* Available on request from UNOS (www.unos.org).

Requests for Single Reprints: Gabriel Thabut, MD, PhD, Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France; e-mail, gabriel.thabut@bch.aphp.fr.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Arcasoy SM, Kotloff RM.** Lung transplantation. N Engl J Med. 1999;340:1081-91. [PMID: 10194239]
2. **Christie JD, Edwards LB, Aurora P, Dobbels F, Kirk R, Rahmel AO, et al.** Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report—2008. J Heart Lung Transplant. 2008;27:957-69. [PMID: 18765187]
3. **Trulock EP.** Lung transplantation. Am J Respir Crit Care Med. 1997;155:789-818. [PMID: 9117010]
4. **Toronto Lung Transplant Group.** Unilateral lung transplantation for pulmonary fibrosis. N Engl J Med. 1986;314:1140-5. [PMID: 3515192]
5. **Grossman RF, Frost A, Zamel N, Patterson GA, Cooper JD, Myron PR, et al.** Results of single-lung transplantation for bilateral pulmonary fibrosis. The Toronto Lung Transplant Group. N Engl J Med. 1990;322:727-33. [PMID: 2308601]
6. **Mason DP, Brizzio ME, Alster JM, McNeill AM, Murthy SC, Budev MM, et al.** Lung transplantation for idiopathic pulmonary fibrosis. Ann Thorac Surg. 2007;84:1121-8. [PMID: 17888957]
7. **Meyer DM, Edwards LB, Torres F, Jessen ME, Novick RJ.** Impact of recipient age and procedure type on survival after lung transplantation for pulmonary fibrosis. Ann Thorac Surg. 2005;79:950-7; discussion 957-8. [PMID: 15734411]
8. **Meyers BF, Lynch JP, Trulock EP, Guthrie T, Cooper JD, Patterson GA.** Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis: a ten-year institutional experience. J Thorac Cardiovasc Surg. 2000;120:99-107. [PMID: 10884661]
9. **Whelan TP, Dunitz JM, Kelly RF, Edwards LB, Herrington CS, Hertz MI, et al.** Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis. J Heart Lung Transplant. 2005;24:1269-74. [PMID: 16143244]
10. **Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al.** Development of the new lung allocation system in the United States. Am J Transplant. 2006;6:1212-27. [PMID: 16613597]
11. **Hosmer D, Lemeshow S.** Applied Survival Analysis: Regression Modeling of Time to Event Data. Vol. 1. New York: J Wiley; 1999.
12. **Mickey RM, Greenland S.** The impact of confounder selection criteria on effect estimation. Am J Epidemiol. 1989;129:125-37. [PMID: 2910056]
13. **Grambsch PM, Therneau TM, Fleming TR.** Diagnostic plots to reveal functional form for covariates in multiplicative intensity models. Biometrics. 1995;51:1469-82. [PMID: 8589234]
14. **Fine JP, Gray RJ.** A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496-509.
15. **D'Agostino RB Jr.** Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998;17:2265-81. [PMID: 9802183]
16. **D'Agostino RB Jr, D'Agostino RB Sr.** Estimating treatment effects using observational data [Editorial]. JAMA. 2007;297:314-6. [PMID: 17227985]
17. **Austin PC, Grootendorst P, Normand SL, Anderson GM.** Conditioning on the propensity score can result in biased estimation of common measures of treatment effect: a Monte Carlo study. Stat Med. 2007;26:754-68. [PMID: 16783757]
18. **Grambsch P, Therneau T.** Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515-526.
19. **Aalen OO.** A linear regression model for the analysis of life times. Stat Med. 1989;8:907-25. [PMID: 2678347]
20. **Little RJ, Rubin DB.** Statistical Analysis with Missing Data. New York: J Wiley; 1987.
21. **Raghunathan TE, Lepkowski JM, van Hoewyk J, Solenberger P.** A multivariate technique for multiply imputing missing values using a sequence of regression models. Surv Methodol. 2001;27:85-95.
22. **Rubin DB, Schenker N.** Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991;10:585-98. [PMID: 2057657]
23. **Austin PC, Grootendorst P, Anderson GM.** A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med. 2007;26:734-53. [PMID: 16708349]
24. **Mant J, Wilson S, Parry J, Bridge P, Wilson R, Murdoch W, et al.** Clinicians didn't reliably distinguish between different causes of cardiac death using case histories. J Clin Epidemiol. 2006;59:862-7. [PMID: 16828682]
25. **Williams TJ, Wilson JW.** Challenges in pulmonary fibrosis: 7—Novel therapies and lung transplantation. Thorax. 2008;63:277-84. [PMID: 18308963]

Current Author Addresses: Drs. Thabut, Dauriat, Jebrak, Fournier, and Mal: Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France.
Dr. Christie: Division of Pulmonary and Critical Care Medicine, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, 8th Floor, Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104.
Dr. Ravaud: Département d'Épidémiologie, de Biostatistiques, et de Recherche Clinique, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France.
Drs. Castier and Lesèche: Service de Chirurgie Thoracique et Vasculaire, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France.
Dr. Porcher: Département de Biostatistique et Informatique Médicale, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris, France.

Author Contributions: Conception and design: G. Thabut, J.D. Christie, P. Ravaud, M. Fournier, G. Lesèche, H. Mal.
Analysis and interpretation of the data: G. Thabut, J.D. Christie, P. Ravaud, Y. Castier, M. Fournier, G. Lesèche, R. Porcher, H. Mal, G. Dauriat.
Drafting of the article: G. Thabut, J.D. Christie, Y. Castier, H. Mal.
Critical revision of the article for important intellectual content: J.D. Christie, P. Ravaud, Y. Castier, M. Fournier, G. Lesèche, R. Porcher, H. Mal, G. Dauriat.
Final approval of the article: J.D. Christie, P. Ravaud, Y. Castier, M. Fournier, R. Porcher, H. Mal, G. Dauriat.
Provision of study materials or patients: J.D. Christie, G. Jebrak, G. Lesèche.
Statistical expertise: G. Thabut, J.D. Christie, R. Porcher.
Administrative, technical, or logistic support: P. Ravaud, G. Jebrak, M. Fournier, G. Dauriat.
Collection and assembly of data: G. Jebrak.

Appendix: Multiple Imputation Method Used to Handle Missing Data

Like most large registries, the UNOS registry contains missing values. Most data analysts exclude observations with any missing variable values from the analysis—the standard complete-case analysis. This approach ignores the information contained in incomplete cases and the possible systematic differences between the complete and the incomplete cases. Several procedures have been developed to deal with missing values. We used the multiple imputation by chained equation method to handle missing data (20). Multiple imputation is a Monte Carlo technique in which the missing values are replaced by m (in this study, 20) simulated versions. The missing values are drawn from an appropriate distribution that characterizes the conditional relation of the imputed variables to other variables. Because the missing values are drawn from a distribution, a range of values is imputed for each missing value, with this variation reflecting the uncertainty about the missing value.

We implemented our multiple imputation on the basis of the procedure described by Raghunatan and colleagues (21) by using the MICE package for R, version 2.5.

In brief, the multiple-imputation-by-chained equation proceeds as follows:

1. For each variable in turn, missing values are filled in with randomly chosen observed values.

2. Filled-in values in the first variable are discarded, leaving the original missing values. These missing values are then imputed by regression imputation on all other variables.

3. The filled-in values in the second variable are discarded. These missing values are then imputed by using proper regression imputation on all other variables.

4. This process is repeated for each variable in turn. A cycle is completed when each variable has been imputed by the regression method. The process continues for 10 cycles.

After imputation, each of the m completed data sets is analyzed separately, and the results are combined by using the following formulas (20, 22).

Within-imputation variance is calculated as follows:

$$\bar{v}_{within} = \frac{1}{m}\sum_{i=1}^{m}\hat{v}_i$$

Between-imputation variance is calculated as follows:

$$\bar{v}_{between} = \frac{1}{m-1}\sum_{i=1}^{m}(\hat{\beta}_i - \bar{\beta})^2$$

Total variance is calculated as follows:

$$\bar{v}_{total} = \bar{v}_{within} + \left(1 + \frac{1}{m}\right)\bar{v}_{between}$$

where m = the number of sets imputed and analyzed; $\hat{\beta}_i$ = point estimate from analyzing the ith set; $\hat{v}_i$ = variance estimate from analyzing the ith set; $\bar{\beta}$ = combined estimate of β; and $\bar{v}$ = combined estimate of v.

$$\bar{\beta} = \frac{1}{m}\sum_{i=1}^{m}\hat{\beta}_i$$

The between-imputation variance reflects the uncertainty related to missing observations.

Appendix Table. **Variables Tested for Association With Survival After Lung Transplantation**

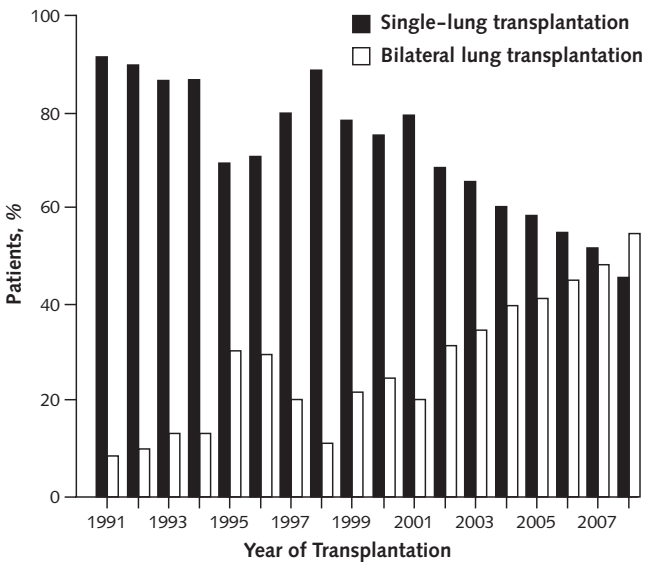
Donor-related characteristics: age, sex, height, weight, cause of death, history of diabetes, blood group, cytomegalovirus status, HLA typing, and gas exchange

Surgery-related characteristics: surgical procedure (single or bilateral transplantation), graft ischemic time, transplantation year, transplantation volume, and transplantation center

Recipient characteristics: age; sex; height; weight; history of diabetes; blood group; cytomegalovirus status; HLA typing; previous cancer; ventilatory support; hospitalization within 90 d before transplantation; functional status; oxygen requirement; FEV_1; FVC; systolic, mean, and diastolic pulmonary artery pressure; pulmonary capillary wedge pressure; cardiac output; 6-min walking distance; and Pco_2

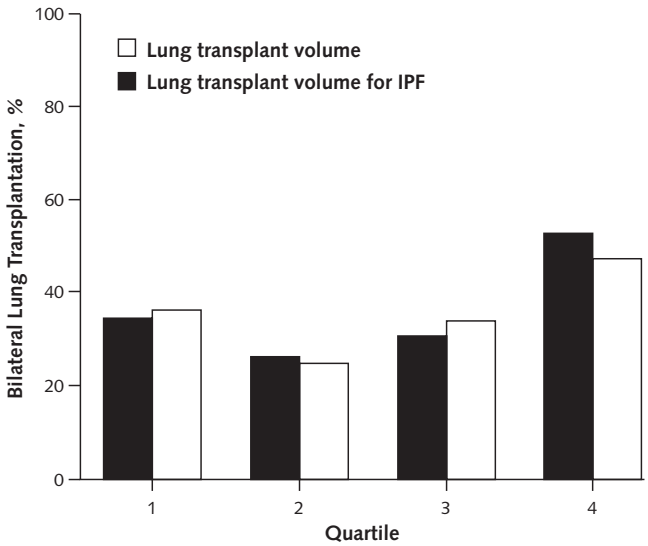
Calculated variables: blood group mismatch, cytomegalovirus status mismatch, number of HLA mismatches, sex mismatch, and donor and recipient body mass index

Appendix Figure 1. **Rates of single and bilateral lung transplantation over time in patients with idiopathic pulmonary fibrosis.**



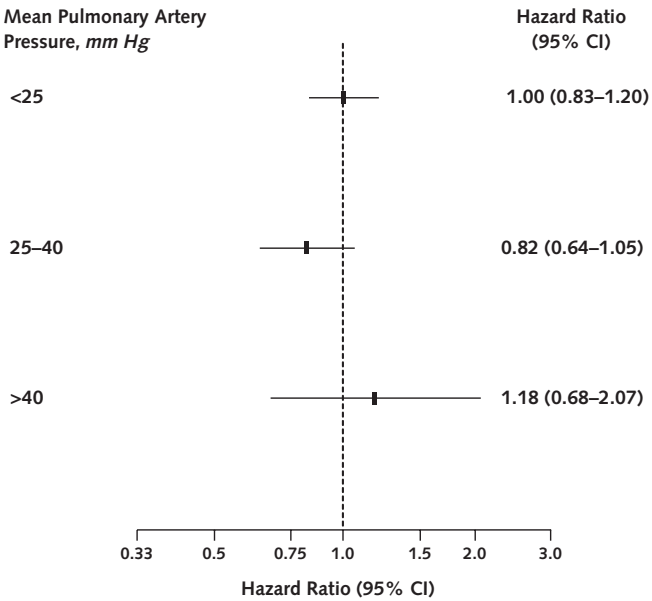
Data are from the United Network for Organ Sharing registry.

Appendix Figure 2. **Proportion of bilateral lung transplantations, by center volume.**



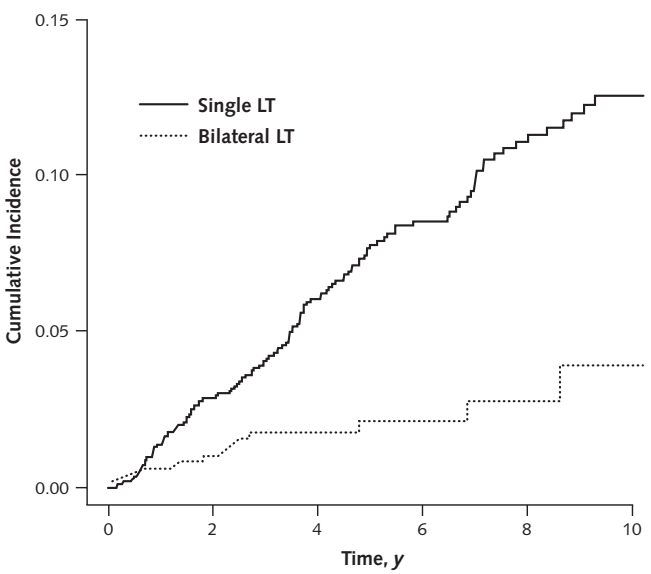
IPF = idiopathic pulmonary fibrosis.

Appendix Figure 3. **Hazard ratios for death associated with bilateral lung transplantation, by recipient mean pulmonary artery pressure at transplantation.**



We adjusted the ratios for recipient age, body mass index, functional status, and mean pulmonary pressure; donor body mass index and cytomegalovirus status; transplantation year; and lung transplantation center and center volume.

Appendix Figure 4. **Cumulative incidence of cancer, by type of lung transplantation.**



LT = lung transplantation.