Determinants of the Survival Benefit of Lung Transplantation in Patients with Chronic Obstructive Pulmonary Disease

Gabriel Thabut[1,2], Philippe Ravaud[2,3], Jason D. Christie[4], Yves Castier[5], Michel Fournier[1], Hervé Mal[1], Guy Lesèche[5], and Raphaël Porcher[6,7]

[1]Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat et Université Paris 7, Paris, France; [2]INSERM U738, Paris, France; [3]Département d'Epidémiologie, de Biostatistiques et de Recherche Clinique, Hôpital Bichat et Université Paris 7, Paris, France; [4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania; [5]Service de Chirurgie Thoracique et Vasculaire, Hôpital Bichat et Université Paris 7, Paris, France; [6]INSERM U717, Paris, France; and [7]Département de Biostatistique et Informatique Médicale, Hôpital Saint-Louis et Université Paris 7, Paris, France

Rationale: **Although chronic obstructive pulmonary disease is the first indication for lung transplantation, the benefit of the procedure in terms of survival remains debated.**

Objectives: **To estimate the determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease.**

Methods: **Using information from the United Network for Organ Sharing database on 8,182 patients, we developed an approach based on numerical simulations to estimate the survival effect of lung transplantation.**

Measurements and Main Results: **The main outcome measure was the difference between median survival with transplantation and that without transplantation measured from time of transplant list registration. Survival benefit was greater with double than with single lung transplantation (mean difference, 307 d [95% confidence interval, 217–523]). With double lung transplantation, 44.6% of patients would gain 1 year or more, 29.4% would gain or lose less than 1 year, and 26% would lose 1 year or more. Major determinants of the survival effect of transplantation were systolic pulmonary artery pressure, FEV_1, body mass index, exercise capacity, functional status, and the need for continuous mechanical ventilation or oxygen. For instance, 79% of patients with an FEV_1 less than 16% of the predicted value would gain 1 year or more with double lung transplantation as compared with only 11% of patients with an FEV_1 of more than 25%.**

Conclusions: **We identified several factors associated with the survival benefit of lung transplantation. External validation of our models is required before translating these results into clinical practice.**

Keywords: lung transplantation; chronic obstructive pulmonary disease; prognosis

Chronic obstructive pulmonary disease (COPD) is a major public health problem and the fourth leading cause of chronic morbidity and mortality in the United States (1, 2). Lung transplantation (LT) is the ultimate therapy available for severely disabled patients with COPD (3, 4). According to the 2006 report of the United Network for Organ Sharing (UNOS) registry (www.unos.org), almost one-half of LTs performed worldwide involve COPD cases (5). As outlined in the international guidelines for the selection of LT candidates, transplantation should be performed when life expectancy after transplantation exceeds life expectancy without the procedure (6, 7). Despite recent improvements in long-term survival, survival after LT lags far behind survival with other solid-organ transplantations, with a median survival time of approximately 5 years for patients with COPD (5).

Although COPD is debilitating, mortality from this disorder may not be as high as that from other forms of end-stage lung disease (8). Consequently, the survival benefit of LT in patients with COPD is unclear. A survival benefit of LT for these patients has been shown in some studies (9, 10), whereas other studies failed to detect obvious survival benefit (7, 11). However, these studies had several shortcomings. First, assessment of survival benefit with LT raises complex statistical issues, and usual survival models are not well suited for this purpose. Second, most studies assessed the survival benefit of LT for the whole cohort of patients with COPD, but some subgroups may have actually benefited. The identification of patients with COPD most likely to benefit from LT is of critical importance to better determine which patients to consider for the procedure.

We aimed to analyze data from the UNOS registry to (*1*) determine the survival effect of LT in patients with COPD, (*2*) determine the patients with COPD most likely to benefit from LT, and (*3*) create an instrument for caregivers to compute the expected survival effect of LT for a given patient. Such an instrument might help clinicians and patients determine the survival benefit of the procedure. We developed an approach based on numerical simulations to address these issues.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The survival benefit of lung transplantation for patients with chronic obstructive pulmonary disease remains debated.

What This Study Adds to the Field

This study identifies the characteristics of patients who would most likely benefit from lung transplantation in terms of survival.

METHODS

Study Design

We compared the survival of patients with and without LT according to different baseline values of covariates. For this purpose, we built two

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Correspondence and requests for reprints should be addressed to Gabriel Thabut, M.D., Service de Pneumologie B et Transplantation Pulmonaire, Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris, France. E-mail: gabriel.thabut@bch.aphp.fr

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multivariable parametric models to describe the survival of patients while on the waiting list and that after LT. Such models allowed us to predict the expected survival time distribution for a given set of covariates. Simulations were used to determine the median survival from the time of placement on the waiting list for cohorts of patients according to whether or not they underwent LT.

Development of Survival Models

Patients. We used information from the UNOS registry as of June 7, 2004. Mortality data were from the U.S. Social Security Death Master File. All patients on the waiting list for LT between 1987 and 2004 were eligible for the study, provided they fulfilled the following criteria: (*1*) diagnosis of COPD or emphysema, including COPD related to α_1-antitrypsin deficiency (1); (*2*) LT planned as single or double; (*3*) known date of placement on the waiting list; (*4*) known date of follow-up; and (*5*) known status at the last follow-up. A total of 9,211 patients fulfilling the inclusion criteria were retrieved from the UNOS database. Of these patients, 1,519 had a diagnosis of α_1-antitrypsin deficiency–related emphysema and 7,692 had COPD (no α_1-antitrypsin deficiency). Of these, 1,029 (11.1%) were removed from the waiting list and were not included, which left 8,182 patients for analysis. During the study, 5,942 (72.6%) underwent LT, 1,074 (13.1%) were still waiting for LT, and 1,166 (14.3%) died while on the waiting list.

Model building. We used fully parametric proportional hazards models (12–14). Unlike the Cox model, these models give a complete probability specification for the data, allowing the simulation of survival times. A Weibull model was used for survival while on the waiting list. For model estimation, we considered that LT was noninformative censoring for survival of patients on the waiting list. This assumption is supported by the organ allocation policy for LT in the pre-2005 UNOS database, which took into account only waiting time on the list. Sensitivity analyses showed that our results are fairly robust to small departures from this assumption (data not shown) (15). Usual parametric models were not well suited for investigating survival after LT, because the baseline hazard function follows a “bathtub” shape, decreasing sharply after LT and increasing slowly thereafter, a shape previously found with renal transplantation (14). We thus decided to use a modified Weibull model; the formula is given in the online supplement.

The model development steps are as follows:

1. *Covariate selection*: Variables listed in Table 1 were tested for association with survival by univariate analysis. Only variables with $P < 0.2$ were considered for inclusion in the multivariate model.
2. *Missing data*: For variables considered for multivariate analysis, missing data were imputed by use of the multiple imputation by chained equation (16), which resulted in five imputed datasets. The steps of the imputation procedure are given in the online supplement.
3. *Linearity assumptions and transformation of continuous covariates*: This step involved a graphical analysis of martingale residuals (17, 18).
4. *Final model*: Model development involved the following steps repeated for each of the five imputed datasets: (*1*) 1,000 bootstrap samples were drawn; (*2*) stepwise selection algorithm with backward elimination of predictors from a full model using a stooping rule based on the Akaike’s information criterion was performed (this procedure was performed on each bootstrap sample, including prespecified first-order interactions); and (*3*) the model most frequently selected among the 5,000 bootstrap samples was kept as the final model (19).
5. *Fitting of the final model*: The final model was fitted to the five imputed datasets, and results were combined. A shrinkage factor was determined by bootstrap resampling and applied to the coefficients (20, 21).
6. *Test of the proportional hazards assumption*: This step involved a graphical analysis of the scaled Schoenfeld residuals (22).
7. *Calibration of the final model*: We compared predicted versus observed survival for four groups of patients stratified according to the values of the prognostic index (20, 21).
8. The discrimination of the model was assessed by the Harell-c index (23).

TABLE 1. MAIN CHARACTERISTICS OF PATIENTS IN THE UNITED NETWORK FOR ORGAN SHARING REGISTRY MEASURED AT REGISTRATION AND AT TRANSPLANTATION

	Registration (*n* = 8,182)		Transplantation (*n* = 5,873)	
Variables	Value	Missing (%)	Value	Missing (%)
Age, yr	53.5 (7.2)	0	56.0 (7.1)	0
Female sex, %	52.8	0	51.8	0
Period of listing, %				
1987–1995	28.6	0	27.1	0
1995–1998	23.1		20.2	
1999–2001	30.1		24.4	
2002–2004	18.3		28.2	
α_1-Antitrypsin deficiency, %	16.7	0	17.9	0
Functional status class*, %		18.7		22.9
I, II	37.0		30.1	
III	59.6		62.9	
IV	3.4		7.0	
Diabetes, %	3.2	17.9	2.6	21.5
Oxygen required at rest, %	72.7	13.9	70.5	12.8
Six-minute-walk distance < 150 ft, %	7.9	7.9	7.8	8.4
Continuous mechanical ventilation, %	0.23	0	0.9	0
FEV_1, % predicted	21.4 (9.1)	18.2	23.3 (14.5)	14.7
FVC, % predicted	52.9 (17.4)	18.4	51.5 (17.1)	15.9
PCWP, mm Hg	10.2 (6.4)	20.8	12.0 (5.5)	36.4
PAPs, mm Hg	36.2 (10.2)	29.3	36.1 (10.2)	33.2
Body mass index†	23.8 (5.0)	2.0	23.6 (4.6)	6.6
Single lung transplantation, %	—	—	72.2	0

Definition of abbreviations: PAPs = systolic pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

Values are mean (SD) unless otherwise indicated.

* Functional status classes range from I to IV, with IV indicating that the patient experiences symptoms even at rest.

† The body mass index is the weight in kilograms divided by the square of the height in meters.

Simulation Study

We tested 68,000 combinations of prognostic factors. For each combination, one virtual cohort of 100,000 patients was simulated. All patients belonging to the same virtual cohort were assigned the same value of prognostic factors.

Each simulated patient was assigned three event times: (*1*) a spontaneous survival time (without transplantation), randomly chosen from the distribution of survival times according to the first model, fed with the value of the prognostic factors under test, assessed at time of being placed on the waiting list for transplantation; (*2*) a waiting time for LT chosen from a log-normal distribution with parameters that mimic the waiting time distribution in the UNOS database (mean, 6.3; SD, 0.4; median waiting time, 18 mo); and (*3*) a post-transplant survival time, randomly chosen from the distribution of survival times according to the second model. This model was fed with the value of the prognostic factors under test, except for age, which was updated by adding the waiting time to the age at entry.

When the spontaneous survival was shorter than the waiting time, the patient was considered as having died on the list, with a survival time equal to the spontaneous survival. When the spontaneous survival was longer than the waiting time, the survival time, computed from inscription on the list was calculated by adding the waiting time to the post-transplant survival time. We were thus able to calculate the median survival of each virtual cohort of 100,000 patients together with the rate of death on the waiting list, and to compare this survival with the spontaneous survival of patients. These steps are summarized in Figure E4 of the online supplement. All simulations of post-transplant survival were for patients who would undergo LT in the 2001–2004 period.

Primary Endpoint

The primary endpoint was the difference between the median survival with transplantation and that without transplantation, both measured from the time of placement on the waiting list—the survival effect of transplantation.

Statistical Analysis

Continuous variables are described by means and standard deviations. Categorical variables are described by frequencies and percentages. All tests were two-sided, with $P < 0.05$ indicating statistical significance. Tests were not corrected for multiple testing. All the analyses involved use of the software R (24).

RESULTS

Waiting List Analysis

The main characteristics of the 8,182 patients at the time of registration for the waiting list are summarized in Table 1. The maximum follow-up was 14.8 years. Median survival time while on the waiting list was 73.8 months (95% confidence interval [CI], 67.5–81.1). The median waiting time for transplantation was 18.6 months (95% CI, 17.8–19.5). Parameters associated with survival while on the waiting list are summarized in Table 2. Multivariate analysis retained the following determinants measured at registration (without their interaction): age, α_1-antitrypsin deficiency, functional status, oxygen requirement, six-minute-walk distance, continuous mechanical ventilation, FEV_1, systolic pulmonary artery pressure, and body mass index. This model was selected in 62.4% of the bootstrap samples. The assumptions of linearity of continuous covariates and of proportional hazards were supported by graphical inspection of Martingale residuals (Figure E1) and scaled Schoenfeld residuals, respectively. The shrinkage factor was 0.97. Calibration of the model was good as indicated by the good agreement between observed and expected survival (Figure E3). Discrimination as assessed by the c-statistic was 0.74 (95% CI, 0.73–0.75).

Post-transplantation Analysis

Of the 5,942 patients who underwent LT, survival times were not available for 69, who were thus excluded from the analysis. Main characteristics of the remaining patients are shown in Table 1. The maximum follow-up was 14.9 years. Median survival after LT was 55.7 months (95% CI, 53.9–59.1). Parameters associated with survival after LT are summarized in Table 2. Multivariate analysis retained the following variables measured at transplantation (without interaction): age, year when the transplantation took place, continuous mechanical ventilation, functional status, presence of diabetes, and surgical procedure (single/double LT). This model was selected in 70.9% of the bootstrap samples. The assumptions of linearity of continuous covariates and of proportional hazards were supported by graphical inspection of martingale residuals (Figure E2) and scaled Schoenfeld residuals, respectively. The shrinkage factor was 0.94. Calibration of the model was good as indicated by the good agreement between observed and expected survival (Figure E3). Discrimination as assessed by the c-statistic was 0.68 (95% CI, 0.64–0.70).

Simulation Studies

Parameters used for simulation are given in Table 3. The survival effect of single or double LT for the 8,182 patients on the waiting list is shown in Figure 1. An estimated 50.1% of patients undergoing single and 63.7% undergoing double LT would benefit from LT (median survival with LT exceeding that without LT). For patients who underwent single LT, 22.3% would gain 1 year or more, 43% would gain or lose less than 1 year, and 34.7% would lose 1 year or more. For patients who underwent double LT, 44.6% would gain 1 year or more, 29.4% would gain or lose less than 1 year, and 26% would lose 1 year or more. Survival benefit was greater with double than with single lung transplantation (mean difference, 307 d [95% CI, 217–523]).

Survival effect by covariates measured at registration for the waiting list. Figure 2 shows the survival effect of single and double LT according to the identified prognostic factors. For instance, 79% of patients with an FEV_1 less than 16% of the predicted value would gain 1 year or more with double LT as compared with only 11% of patients with an FEV_1 more than 25%. More patients

TABLE 2. HAZARD RATIO FOR DEATH WHILE ON THE WAITING LIST AND THAT AFTER LUNG TRANSPLANTATION FOR UNITED NETWORK FOR ORGAN SHARING REGISTRY PATIENTS

	Registration (*n* = *8,182*)		Transplantation (*n* = *5,873*)	
Variables	Hazard Ratio (*95% CI*)	*P* Value	Hazard Ratio (*95% CI*)	*P* Value
Age (per 10-yr increase)	1.29 (1.19–1.40)	<0.001	1.15 (1.09–1.21)	<0.001
Female sex	1.08 (0.96–1.21)	0.21	1.02 (0.95–1.09)	0.65
Period of listing		<0.001		<0.001
1987–1995	1		1	
1996–1998	1.03 (0.89–1.19)		0.91 (0.83–0.99)	
1999–2001	0.79 (0.68–0.91)		0.80 (0.73–0.89)	
2002–2004	0.64 (0.50–0.81)		0.62 (0.54–0.71)	
α_1-Antitrypsin deficiency	0.58 (0.49–0.70)	<0.001	1.03 (0.96–1.13)	0.57
Functional status class*		<0.001		0.003
I, II	1		1	
III	1.43 (1.24–1.64)		1.02 (0.92–1.12)	
IV	2.47 (1.78–2.43)		1.36 (1.14–1.62)	
Diabetes	1.18 (0.85–1.65)	0.33	1.41 (1.08–1.83)	0.02
Oxygen required at rest	2.68 (2.20–3.27)	<0.001	0.91 (0.84–0.99)	0.02
Six-minute-walk distance < 150 ft	1.79 (1.46–2.20)	<0.001	1.07 (0.93–1.23)	0.35
Continuous mechanical ventilation	7.30 (3.61–14.60)	<0.001	2.04 (1.44–2.89)	<0.001
FEV_1 (per 10% of predicted)	0.62 (0.57–0.68)	<0.001	1.0 (0.97–1.03)	0.95
FVC (per 10% of predicted)	0.77 (0.74–0.80)	<0.001	1.0 (0.98–1.03)	0.81
PAPs (per 10-mm Hg increase)	1.18 (1.12–1.24)	<0.001	1.02 (0.98–1.07)	0.36
PCWP (per 10-mmHg increase)	1.30 (1.16–1.45)	<0.001	1.0 (0.92–1.09)	0.95
Body mass index† (per 5-point increase)	0.80 (0.75–0.85)	<0.001	1.01 (0.97–1.05)	0.56
Single lung transplantation	—	—	1.30 (1.19–1.43)	<0.001

Definition of abbreviations: PAPs = systolic pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure.

* Functional status classes range from I to IV, with IV indicating that the patient experiences symptoms even at rest.

† The body mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 3. PARAMETERS USED FOR SIMULATIONS

	Survival while on the Waiting List		Survival after Lung Transplantation	
Parameters	β (*log HR*)	SD	β (*log HR*)	SD
Age (per 10-yr increase)	0.29	0.048	0.23	0.05
Era of listing				
1987–1995			0	—
1996–1998			−0.02	0.05
1999–2001			−0.14	0.08
2002–2004			−0.34	0.10
No α_1-antitrypsin deficiency	0.31	0.09		
Functional status class*				
I, II	0	—	0	—
III	0.12	0.06	0	—
IV	0.43	0.15	0.09	0.04
Oxygen required at rest	0.38	0.08		
Six-minute-walk < 150 ft	0.32	0.10		
Continuous mechanical ventilation	1.58	0.32	0.72	0.36
FEV_1 (per 10% predicted)	0.29	0.03		
PAPs (per 10-mm Hg predicted)	0.013	0.002		
Body mass index (per 5-pt increase)†	0.37	0.06		
Diabetes			0.37	0.17
Double lung transplantation			−0.17	0.07
Model parameters	Weibull		Modified Weibull	
λ	1.036		0.535	
γ	1.10		0.544	
α	—		1.55	

Definition of abbreviations: HR = hazard ratio; PAPs = systolic pulmonary artery pressure.

* Scores on the functional status class can range from 1 to 4, with a score of 4 indicating that the patient experiences symptoms even at rest.

† Body mass index is the weight in kilograms divided by the square of the height in meters.

in functional status class III would gain 1 year or more compared with patients in functional status class IV. At the individual level, the survival benefit is higher for patients with functional status class IV than for those with class III; however, because the number of patients who undergo LT is low because of high mortality on the waiting list, the survival benefit for the whole cohort of patients is lower.

Computation of the survival effect of LT for a given patient. To determine the survival effect of LT for a given patient, we simulated 68,000 possible combinations of prognostic factors and illustrated the results for three patients chosen from the UNOS registry. The characteristics of these patients, their expected survival effect with single and double LT, and their expected rate of death on the waiting list are displayed in Figure 3, which highlights the great variability in survival effect of LT depending on baseline characteristics of patients. Patient 1 would experience reduced survival regardless of undergoing single or double LT, patient 2 would have a small improvement in survival with double LT and a small reduction in survival with single LT, and patient 3 would have improved survival regardless of undergoing single or double LT.

Our website (http://www.copdtransplant.fr/) gives an estimate of the following parameters for a patient considering LT, given 68,000 possible combinations of prognostic factors: survival estimate on the waiting list, rate of death while on the waiting list, survival estimate after LT, and survival effect of LT (difference between the expected median survival with LT and that without LT).

Sensitivity analyses. To test the impact of excluding patients who were removed from the waiting list, the same analyses were performed taking into account all patients placed on the list: median survival of the whole cohort was 75.1 months (95% CI, 71.5–85.1), the model building process selected the same multivariable model, and simulations results were very close to those reported above (data not shown).

To test the impact of the waiting time on survival effect of LT, we also computed the survival benefit of LT for the three patients described above according to four different waiting time distributions (Table E2). At a median waiting time of 1 month to 2 years, the survival benefit of double LT ranged from −496 to −706 days for patient 1, +187 to +152 days for patient 2, and +544 to +1,130 days for patient 3.

DISCUSSION

This study highlights the following: (*1*) many patients with COPD eventually benefit from LT; (*2*) the survival benefit of LT is greater with double than with single LT; (*3*) systolic pulmonary

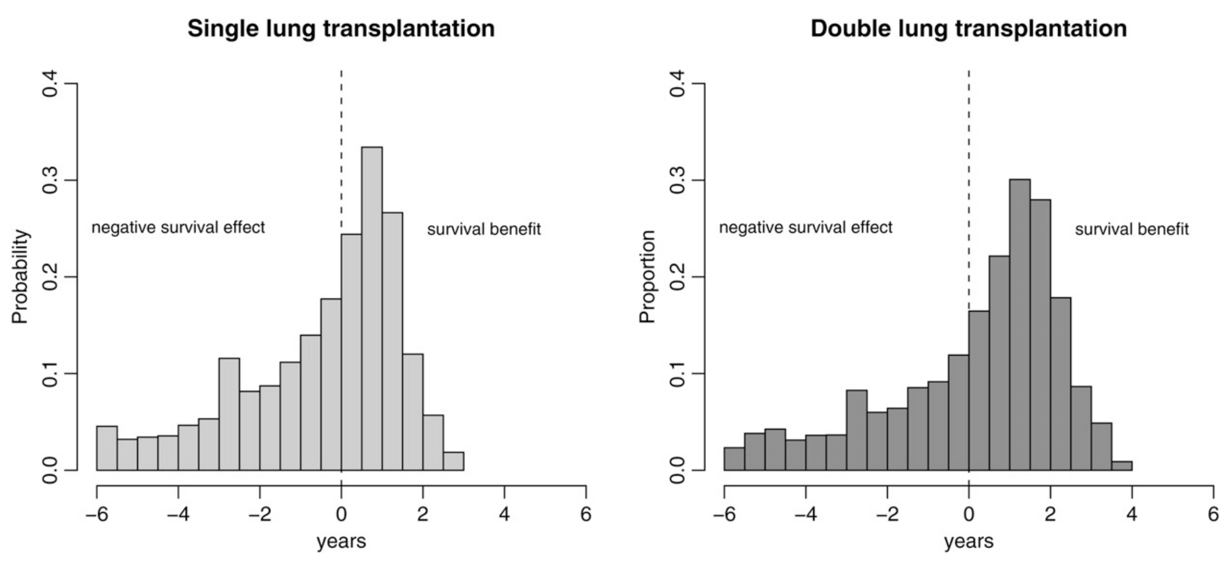

Figure 1. Survival effect of lung transplantation for the 8,182 UNOS (United Network for Organ Sharing) patients according to surgical procedure: single or double transplantation. The survival effect of lung transplantation is defined as the difference between the expected median survival with lung transplantation and that without lung transplantation.

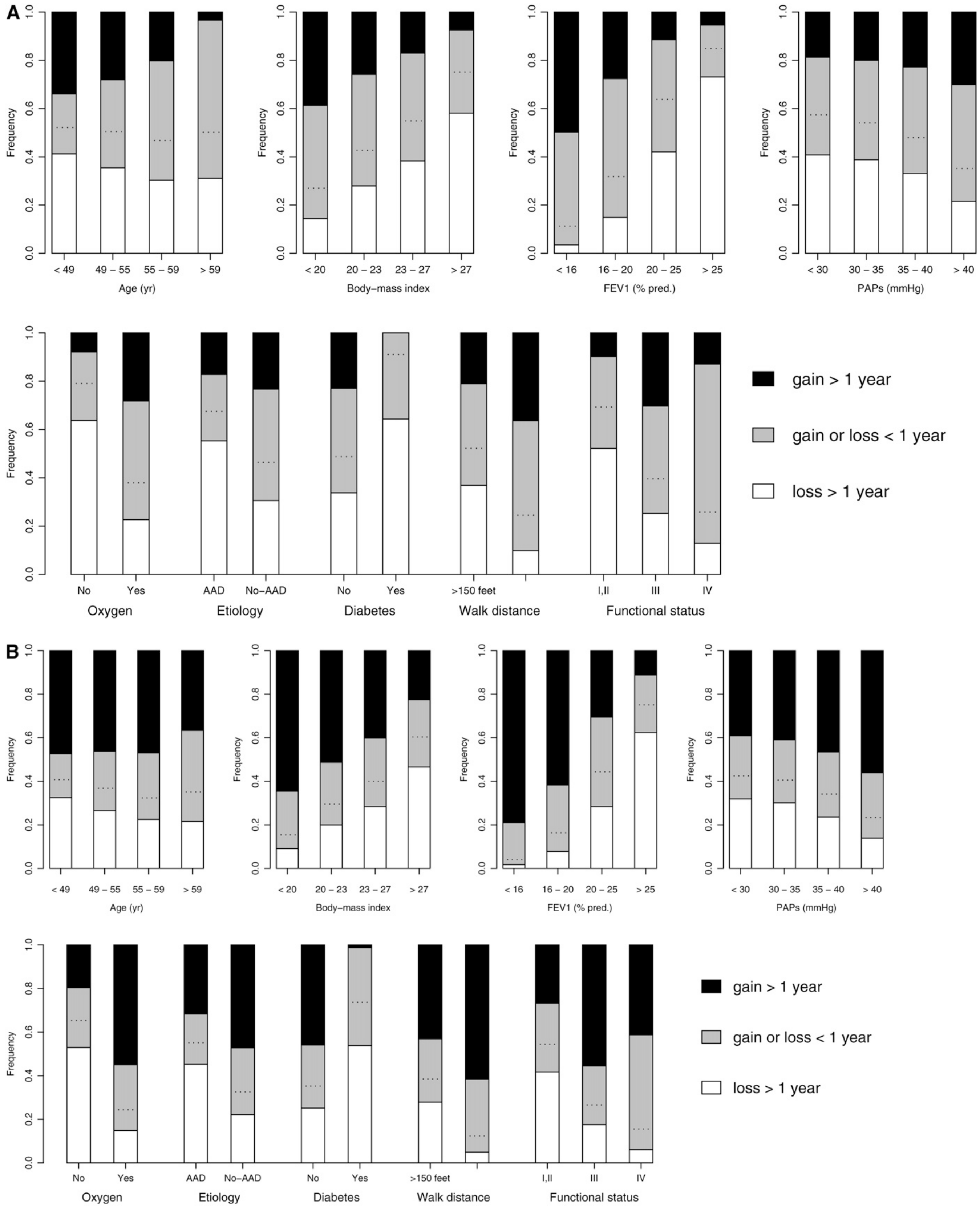

Figure 2. Survival effect of single (*A*) and double (*B*) lung transplantation according to values of prognostic variables. The survival effect of lung transplantation is defined as the difference between the expected median survival with lung transplantation and that without lung transplantation. The survival benefit is divided into loss of 1 year or more, gain of 1 year or more, and loss or gain less than 1 year. The *dashed line* separates between gain and loss of survival. For continuous variables (*top row* in *A* and *B*), four classes are defined according to the quartiles of the variable. AAD = α_1-antitrypsin deficiency; PAPs = systolic pulmonary artery pressure.

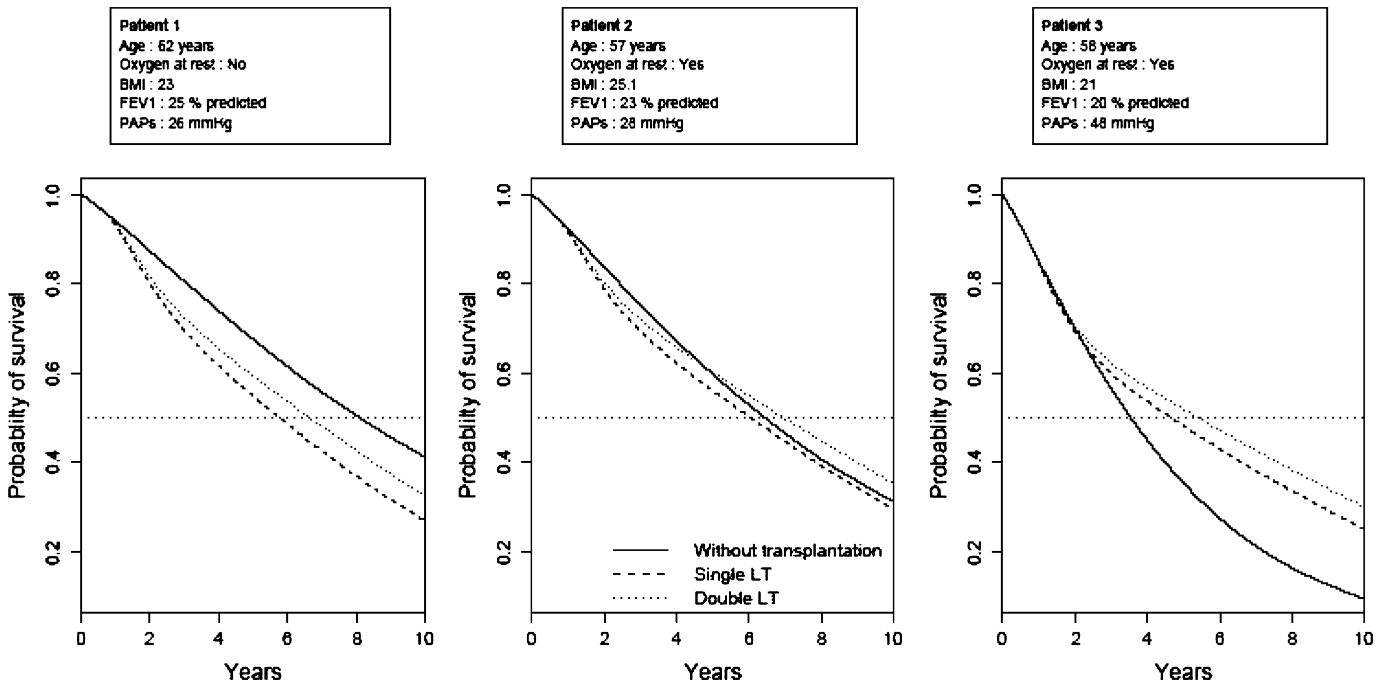

Figure 3. Estimation of survival with and without lung transplantation for three patients chosen from the UNOS registry. The three patients exhibited no α_1-antitrypsin deficiency or diabetes, a six-minute-walk distance of more than 150 ft, and functional status class III. Survival was computed from time of placement on the waiting list. For patient 1, the survival effect is a loss of 509 days (95% confidence interval [CI], 461–569) with double lung transplantation and 805 days (95% CI, 749–855) with single lung transplantation. The death rate estimate while on the waiting list is 9.9% (95% CI, 8.9–10.9). For patient 2, the survival effect is a gain of 188 days (95% CI, 117–238) for double lung transplantation and a loss of 137 days (95% CI, 84–183) with single lung transplantation. The death rate estimate while on the waiting list is 12.7% (95% CI, 11.7–13.6). For patient 3, the survival effect is a gain of 668 days (95% CI, 584–751) with double lung transplantation and 425 days (95% CI, 362–489) with single lung transplantation. The death rate estimate while on the waiting list is 23.8% (95% CI, 23.1–24.6). BMI = body mass index; PAPs = systolic pulmonary artery pressure.

arterial pressure, FEV_1, body mass index, exercise capacity as measured by the six-minute-walk test, functional status, and the need for continuous mechanical ventilation or oxygen affect the survival benefit of LT; and (*4*) many patients have a net loss in survival from the procedure.

Assessment of the survival benefit of transplantation is not straightforward (11, 25–27). A way to study the survival benefit of LT is to create a survival model accounting for prognostic factors of patients that includes LT as a time-varying covariate. Proportional and nonproportional hazards models for this purpose have been reported in the literature (11, 25, 28). Although these models correct for baseline differences between patients who will and will not undergo LT, they make stringent assumptions about the relation between the instantaneous risk of death (hazard) while on the waiting list and that after LT. The baseline hazard shapes found in the present study clearly violated these assumptions.

We developed a method based on simulations to address this issue, a method previously used by the Scientific Registry of Transplant Recipients, which developed thoracic simulation allocation models to compare various organ allocation policies (29). From our two models, describing survival while on a waiting list and survival after LT, we can simulate the survival times of cohorts of patients with given values of prognostic factors. Because the distribution of time to transplantation is known, the course of simulated cohorts of patients can be re-created and the expected survival with and without transplantation compared.

Our approach has several advantages. First, no assumption is made about the relation between instantaneous risk of death while on the waiting list and that after LT. Second, we can assess survival of cohorts of patients on the waiting list since their placement on the list. Indeed, to undergo LT and to benefit (if at all) from the procedure, a patient must be able to wait until LT occurs. If mortality while on a waiting list is very high, only a few patients benefit from LT. Consequently, the benefit of LT must be viewed in terms of the whole cohort of patients on a waiting list, not just patients who eventually undergo LT. Finally, our approach better mimics real life, because the physician decides whether or not to register a patient for a waiting list, not whether to perform LT.

Our simulations allow for determining the survival effect of LT according to many possible combinations of prognostic factors measured at registration for a waiting list. It should help clinicians and patients with COPD to decide the survival benefit of LT because they can calculate, for given values of prognostic variables, the expected survival with and without LT, together with the probability of death while on the waiting list. For a patient whose characteristics would indicate a negative expected survival effect of LT, placement on the waiting list could be postponed until the evolution of functional parameters indicates a clear survival benefit with the procedure. The results of this study may prompt clinicians not to propose LT for some patients who are unlikely to benefit at any time.

Our results support double LT for patients with COPD. In all simulations, double LT was associated with increased survival as compared with single LT, with the difference in survival being, on average, 1 year. However, we must be cautious in interpreting these results because residual confounding could bias this finding.

The results of our study need to be interpreted in the light of the Lung Allocation Score (LAS) in use in the United States since

May 2005 (30). This score ranks patients on a waiting list for transplant based on the difference between survival benefit and waiting list survival but does not inform about expected survival with or without LT. The multivariable models underlying this score predict both the expected number of days lived without transplant during an additional year on the waiting list and the expected number of days lived during the first year after transplant. Transplant benefit was defined as the number of expected additional days of life over the next year if the candidate received the transplant rather than remained on the waiting list. From our analysis of the UNOS registry, we find that the LAS incorporates, for the most part, the same variables as in our models but not surgical procedure (single or double LT), which is a clear determinant of survival benefit. Moreover, the LAS does not capture the whole benefit of LT because its estimation of survival benefit is limited to the first year after placement on the waiting list. However, our simulations revealed many situations of the benefit of LT several years after the procedure. In other words, a patient who has no expected 1-year benefit according to the LAS may actually show a survival benefit beyond 1 year. How the inclusion of the LAS in the organ allocation policy would modify our results remains to be determined, but it might slightly modify our calculation of expected benefit of LT. The implementation of the LAS might have detrimental effects on the ranking of patients with COPD, likely increasing the waiting time for these patients (31). Our sensitivity analyses demonstrated that a waiting time of 2 years instead of 18 months would only slightly modify the expected benefit of LT. As expected, patients with a high rate of death on the waiting list would benefit most from a shorter wait (patient 3). However, most patients with COPD have low LAS scores and are thus unlikely to undergo LT soon after placement on the waiting list.

This study has some limitations. First, the external validation of our models has not been completed. External validation is a mandatory step before translating these results into clinical practice. The online calculator is given to facilitate the validation of this score and should not be used in clinical practice. In this study, we used bootstrap methods both for model selection and model validation, as previously described (19–21, 32, 33). Bootstrapping provides nearly unbiased estimates of predictive accuracy that are of relatively low variance, and has an additional advantage in that the entire dataset is used for model development. However, such validation is only an internal validation technique, and our model must be confirmed by different authors (external validation). Second, some assumptions underlying our prognostic models could be not verified, leading to biased results. Of importance is the assumption of noninformative censoring for survival of patients on the waiting list. Although this assumption is supported by the lung allocation policy in use in the United States before 2005, we cannot exclude that some informative censoring has occurred in the dataset. There is unfortunately no method to rule out informative censoring (15, 34). Third, we decided to exclude patients who were removed from the list for reasons other than transplantation or death. Although this decision may be a source of bias, we performed sensitivity analyses demonstrating largely unchanged results when these patients were included. Fourth, the population on which we based our simulations is from a population of patients put on the waiting list and cannot be viewed as a random sample of all patients with end-stage COPD. Thus, our results apply only to patients with end-stage COPD who can be placed on an LT waiting list according to current selection criteria. Fifth, the UNOS dataset is a self reported dataset with a considerable amount of missing data, and as in any observational study, residual or unmeasured confounding may still lead to biased estimates of covariate effects. Sixth, survival benefit does not encompass the whole benefit of LT. Several studies have shown substantial improvement in quality-of-life indices for patients undergoing LT, including those with a preoperative diagnosis of emphysema (35, 36). Some patients may prefer to achieve 5 years of quality life with transplantation rather than 5 years of misery without it, even with no benefit in absolute number of days lived.

In conclusion, our study demonstrates that LT improves the survival of some patients with COPD. We developed an approach to determine the patients most likely to benefit from LT. As soon as external validation is completed, this tool will help physicians select patients who would benefit from the procedure.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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