Use of Lung Transplantation Survival Models to Refine Patient Selection in Cystic Fibrosis

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Lung transplantation in cystic fibrosis may improve survival for patients with low 5-year predicted survival. Identifying characteristics that affect post-transplantation survival may improve patient selection and survival benefit. Using Cystic Fibrosis Foundation Patient Registry and United Network for Organ Sharing data, we identified 845 lung transplant recipients from 1991–2001, and 12,826 control patients from 1997. We used Cox proportional hazards models to identify variables that influence post-transplantation survival. To estimate the survival benefit of transplantation for patients affected by identified variables, we compared Kaplan-Meier survival curves of transplanted and control patients stratified by 5-year predicted survival. Post-transplantation survival improved annually. Youth, *Burkholderia cepacia,* and cystic fibrosis–related arthropathy increased the post-transplantation hazard of death. Compared with control subjects, transplanted adults with a 5-year predicted survival of less than 50% without *B. cepacia* or arthropathy have improved survival. Transplanted adults with *B. cepacia,* arthropathy, or a 5-year predicted survival of greater than 50% have decreased survival. Transplantation never improves survivorship for pediatric patients. Patients with arthropathy, *B. cepacia* infection, or younger age derive no aggregate survival benefit and must appraise carefully the high risk of decreased post-transplantation survival. Adult patients with low 5-year predicted survival without *B. cepacia* infection should receive priority for lung transplantation.

Keywords: age; arthropathy; *Burkholderia cepacia*; Cox proportional hazards model; organ allocation

Cystic fibrosis (CF) is the most common genetically determined disease in the United States. It causes multisystem disease primarily involving the gastrointestinal tract and the respiratory system. Approximately 80% of patients die of progressive respiratory disease (1). Lung transplantation, as heart-lung, cadaveric bilateral single lung, and living-donor procedures, remains the most aggressive treatment of end-stage lung disease since its introduction (2–4). However, complications of lung transplantation are the second most frequent cause of death for patients afflicted with CF, accounting for approximately 12% of deaths in 2002 (1).

Because of the high risks associated with lung transplantation, we recently analyzed its effect on survival in patients with CF stratified by 5-year predicted survival. We used the logistic regression survival model of CF that we previously validated to determine 5-year predicted survival (5). This model includes nine variables and one interaction to make accurate predictions of 5-year survival: age, sex, FEV_1, weight-for-age *z* score, pancreatic sufficiency status, diabetes status, *Staphylococcus aureus* infection status, *Burkholderia cepacia* infection status, and number of acute exacerbations of CF in 1 year, and an interaction term between *B. cepacia* and number of acute exacerbations.

Using this model, we demonstrated that only patients with a less than 30% chance of living 5 years had a clear survival benefit from lung transplantation (6). Lung transplantation decreased survival for patients with a 5-year predicted survival greater than 50%. Patients with a 30 to 50% chance of 5-year survival had essentially no survival effect of lung transplantation in 5 years of follow-up. Physicians wishing to apply this model to individual patients can use worksheets that we have provided to manually calculate a 5-year predicted survival (aje.oupjournals.org/cgi/content/full/153/4/345/DC1) (or contact the authors).

In our earlier analysis, patients stratified before transplantation into different 5-year predicted survivorship groups all had the same post-transplant survivorship (6, 7). However, if different factors determine pre- and post-transplant survivorship, patients with similar predicted 5-year nontransplanted survival may have significant differences in post-transplantation survival. Identification of specific pretransplantation variables that predict post-transplantation survivorship may improve patient selection for the procedure.

Patients infected with *B. cepacia* have poor post-transplantation survivorship compared with other transplanted patients (8, 9). Nine different *B. cepacia* genomovars appear to alter survivorship to different degrees (10, 11). However, because *B. cepacia* markedly reduces nontransplanted survival, there may still be a survival benefit from transplantation despite the reduced post-transplantation survival. There have been no comparisons of survival between transplanted and nontransplanted patients with *B. cepacia* stratified by expected survival.

Other than *B. cepacia,* no pretransplantation variables have been shown to affect post-transplantation survival (12, 13). We used the U.S. CF Foundation Patient Registry (CFFPR) and the United Network for Organ Sharing (UNOS) database to analyze post-transplantation survivorship to discover additional variables that may help predict success or failure with lung transplantation for patients with end-stage lung disease from CF. The CFFPR contains data for 33,415 unique patients with CF followed at 117 certified CF care centers across the United States (1). An estimated 90% of all patients with CF in the United States are included in the CFFPR (1). Some of the results of this study have been previously reported in abstract form at the North American CF Conference, 2004, in St. Louis, MO (14).

METHODS

We used the 1988–2001 CFFPR and the 1988–2002 UNOS data set to identify patients for study. The CF Foundation, UNOS, and the University of Utah Investigational Review Board each reviewed and approved our project. Written consent was waived.

Patients in the transplantation group were matched between the CFFPR and the UNOS data set using exact birth date, sex, and year of transplantation to ascertain exact transplantation dates. We calculated

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survival from the day of transplantation to December 31, 2001, including death or loss to follow-up. Patients were considered lost to follow-up from January 1 of the year after the last recorded data for that patient in the CFFPR.

Patients included as controls had not received solid organ transplantation before 1997. To compare transplant survival with the latest available 5-year period for control subjects, survival was calculated from January 1, 1997, to December 31, 2001, death, lung transplantation, or loss to follow-up. Survival was censored on transplantation.

We used our logistic regression model of 5-year survivorship to predict survival for each control and transplant recipient (5). Data required for the calculation included birth date, sex, weight-for-age z score, FEV_1 normalized to percent predicted (FEV_1%), diabetes status, *S. aureus* and *B. cepacia* status, and number of acute exacerbations in 1997 for control subjects or in the year before transplantation for transplant recipients (5). We used Splus (Insightful Corp., Seattle, WA) (15) to calculate FEV_1% and weight-for-age z score and to apply our logistic regression model to calculate 5-year predicted survival, as previously described (5, 16).

To detect variables that plausibly alter the hazard of post-transplantation death, we used variables from the CFFPR, excluding those pertaining to clinical investigations or with sparse data. Using forward and backward stepwise selection procedures, we developed a final candidate multivariate Cox proportional hazards model of death after lung transplantation for CF (17).

We created univariate Cox proportional hazards models using each variable. Variables with an absolute z statistic of less than 1 were rejected from further consideration. Remaining variables were candidates for the forward model construction procedure. After creating a multivariate Cox proportional hazards model by the standard forward model construction procedure (17), we applied a backward selection procedure with a criterion of a p value of less than 0.05 to retain only variables that had a significant effect in the multivariate Cox model (17).

For the backward stepwise selection procedure, we included all variables with sufficient data and plausible biological effect on survival in a multivariate Cox model. We sequentially removed variables with a p value of greater than 0.05 to arrive at a final candidate multivariate Cox model. We examined remaining variables for two-way interactions, eliminating interactions involving small numbers of patients or interactions with year of transplantation because there can be no impact on patient selection (17).

We evaluated the survival effect of variables included in the final multivariate Cox proportional hazards model. For each covariate in the Cox model, we selected a control group of patients and a transplant group of recipients. After selection, we stratified the patients by 5-year predicted survival of less than 50%, between 50 and 90%, and greater than 90%. Within strata, we used Cox proportional hazards models to test whether transplantation affected survival.

RESULTS

Patients

The 1991–2001 CFFPR contains 30,930 patients. From 1991 through 2001, 1,379 patients in the CFFPR underwent lung transplantation. We excluded 209 patients who also underwent heart, liver, or other solid organ transplantation, 126 patients missing pulmonary function data, 38 missing microbiology data, and 2 missing weights. Of 1,004 patients for whom we were able to calculate a 5-year predicted survival, we ascertained a transplantation date for 845, the final number of patients included in this study.

The 1997 cohort of nontransplanted patients numbered 20,650 patients. We excluded 5,604 patients missing pulmonary function information (3,338 were too young for testing, 2,266 were simply missing), 268 patients of ethnic or racial backgrounds for whom we lack equations to normalize FEV_1%, 1,133 patients missing acute exacerbations data, 799 patients missing microbiology data, 13 patients missing pancreatic sufficiency data, and 7 patients missing weight information. This left 12,826 patients for whom we were able to calculate a 5-year predicted survival.

Model Development

We started with a total of 24 variables with plausible biological effects for analysis (Table 1). Other than variables included in the 5-year predicted survival model (5), no variables were significant predictors of survival by univariate logistic regression in the control group of patients. The 5-year predicted survival itself was not a predictor of post-transplantation survival using univariate logistic regression. Transplant recipients had lower weight and pulmonary function, and more diabetes, pancreatic insufficiency, infections, and acute exacerbations of disease (Table 2). The incidence of each condition among the transplant recipients was sufficient to test the variables for effects on post-transplantation survival.

Univariate Cox proportional hazards models identified 10 variables as potentially significant predictors of survival with a p value of 0.2 or less: age ($p = 0.0004$), acute exacerbations ($p = 0.02$), arthropathy ($p = 0.01$), *B. cepacia* ($p = 0.0004$), FEV_1% ($p = 0.2$), liver disease ($p = 0.15$), mucoid *Pseudomonas aeruginosa* ($p = 0.065$), nonmucoid *P. aeruginosa* ($p = 0.18$), weight-for-age z score ($p = 0.16$), and year of transplantation ($p = 0.008$).

Forward and backward selection procedures both identified a four-variable candidate model of the hazard of death after lung transplantation for CF, which includes year of transplantation, age at transplantation, infection with *B. cepacia,* and arthropathy (Table 3). We additionally considered the effect of *B. cepacia* genomovar but found that there is insufficient information in the CFFPR to analyze the effects after transplantation.

The interaction between age at transplantation and *B. cepacia* was significant and was included in the final Cox proportional hazards model (Table 3). The coefficient for age (-0.0252; Table 3) shows that the hazard of death decreases with age. The significant interaction with *B. cepacia* infection implies that the age effect on the hazard of death is altered by the status of *B. cepacia* infection. With *B. cepacia* infection, each additional year of age is associated with a 6% increase in the hazard of death. Of the nine variables and one interaction in our 5-year predicted survival model of nontransplanted patients with CF, only the

TABLE 1. VARIABLES TESTED FOR SURVIVAL EFFECT

Age,yr*
Acute exacerbations, no./yr*
Alcaligenes (Achromobacter) xylosoxidans
Allergic bronchopulmonary aspergillosis
Arthropathy*
Aspergillus species
Atypical mycobacteria
*Burkholderia cepacia**
Diabetes status
FEV_1%
Height
Sex, male/female
Liver disease, three variables*
Methicillin-resistant *Staphylococcus aureus*
Mucoid *Pseudomonas aeruginosa**
Nonmucoid *Pseudomonas aeruginosa**
Pancreatic sufficiency status
Staphylococcus aureus
Stenotrophomonas maltophilia
Weight-for-age z score*
Year of transplantation*
5-Year predicted survival

* Univariate Cox proportional hazards models found 10 variables were potentially significant predictors of survival ($p < 0.2$; *see* RESULTS). Stepwise selection procedures eliminate all but age, arthropathy, *B. cepacia*, and year of transplantation from the multivariate Cox proportional hazards model.

TABLE 2. PATIENT CHARACTERISTICS AND THE EFFECT OF STRATIFICATION BY 5-YEAR PREDICTED SURVIVAL

			Patients Stratified by 5-Year Predicted Survival			
	All Study Patients		Control Patients		Transplant Recipients	
Variable (except as noted, % affected)	Control	Transplant	< 50%	50–90%	< 50%	50–90%
No. patients	12,826	845	579	2,539	347	471
Deaths	9.3	36.0	55.4	24.1	41.8	36.1
Age, yr, mean ± SD	25.1 ± 9.1	25.1 ± 9.0	25.3 ± 9.1	23.6 ± 9.7	25.7 ± 8.2	24.8 ± 9.6
Acute exacerbations, mean no./yr ± SD	0.90 ± 1.44	2.75 ± 1.74	4.05 ± 1.40	2.15 ± 1.61	4.02 ± 1.22	1.93 ± 1.50
Arthropathy	1.42	1.78	2.9	3.2	2.6	1.3
Burkholderia cepacia	4.26	7.57	19.5	11.9	12.4	4.4
Diabetes	6.55	16.6	25.7	14.4	26.8	9.5
FEV_1%, % ± SD	76.0 ± 28.8	28.6 ± 11.8	28.8 ± 9.4	45.1 ± 15.1	24.8 ± 7.3	29.7 ± 10.6
Sex, % male	47.2	47.1	52.8	50.7	53.9	43.3
Pancreatic sufficiency	6.4	2.72	1.9	3.4	1.7	3.0
Staphylococcus aureus	42.3	23.4	20.9	30.8	18.2	25.7
Weight for age *z* score, ± SD	−0.71 ± 1.05	−1.46 ± 1.00	−1.96 ± 0.87	−1.28 ± 0.95	−1.82 ± 0.90	−1.22 ± 0.96

As a group, transplant recipients have lower FEV_1% and weight-for-age *z* score, and more acute exacerbations, pancreatic insufficiency, diabetes, and infections (except *S. aureus*) than control patients. After stratification by 5-year predicted survival, significant differences were minimized between control and transplant patients. For example, our 5-year predicted survival model adjusts for significant differences in prevalence of *B. cepacia* infection between low predicted survival control and transplant patients.

interaction of age and *B. cepacia* infection status appeared in the final Cox model for post-transplantation survival.

Two variables included in consensus guidelines for patient selection for lung transplantation (19, 20), sex and weight, were eliminated from the final Cox model. We examined weight-for-age *z* score distribution among control subjects and transplant recipients to see if there was a selection bias that might have compromised our ability to find a significant influence on post-transplantation survival. We found no evidence of such a bias (Kolmogorov-Smirnov test [18], $p = 0.08$).

We illustrate two selected features of our post-transplantation Cox model with Kaplan-Meier survival curves. The progressive improvement in lung transplantation over time is shown by comparing survival for patients transplanted 1991–1997 and 1998–2001 (Figure 1). There were 473 patients who underwent transplantation during 1991–1997 and 372 patients during 1998–2001.

CF-related arthropathy affected 15 patients who underwent lung transplantation. It was not reported in the other 830 patients in our transplant group. Arthropathy had the largest hazard ratio in our Cox model (Table 3). The arthropathy-affected transplant recipients had a much worse post-transplantation survival compared with other transplant recipients (Figure 2). Ten of the patients died during the initial 5 years of follow-up; half of the deaths occurred during the first 6 months post-procedure.

Impact on Patient Selection for Lung Transplantation

We estimated the survival effect of arthropathy, *B. cepacia* infection, and age on transplanted patients compared with control subjects stratified by 5-year predicted survival. First, we considered the effect of age on transplant recipients uninfected by *B. cepacia.* Even those children with 5-year predicted survival of less than 50% had no survival benefit from lung transplantation (Figure 3A). Adults with a less than 50% 5-year predicted survival had a slight survival disadvantage related to transplantation, which persisted for a year after the procedure, but the survival curves crossed at 1 year and resulted in a net survival benefit of lung transplantation for these patients after 5 years of follow-up (Figure 3C). As expected (6), both children (Figure 3B) and adults (Figure 3D) with 5-year predicted survival between 50 and 90% had a significant decrease in survival related to lung transplantation.

Second, we considered the effects of age for transplant recipients infected with *B. cepacia*. Children (< 18 years) infected with *B. cepacia* had no survival effect related to lung transplantation whether they had a 5-year predicted survival of less than 50% (Figure 4A) or 50 to 90% (Figure 4B), although it should be noted that there were only nine patients and two deaths in the latter group. Adults with *B. cepacia* infection with a 5-year predicted survival of less than 50% (Figure 4C) suffered decreased survival after transplantation. Adults with *B. cepacia* infection and 5-year predicted survival of 50 to 90% (Figure 4D) had no survival benefit. Finally, patients with arthropathy and either low or high 5-year predicted survival did poorly with transplantation, primarily because of early postoperative deaths compared with other transplant recipients (Figure 2), and had no

TABLE 3. MULTIVARIATE COX PROPORTIONAL HAZARDS MODEL OF THE HAZARD OF DEATH AFTER LUNG TRANSPLANTATION

Variable	Coefficient	SE	Hazard Ratio	95% Confidence Interval	p Value
Age	−0.0252	0.0067	0.975	0.96–0.99	< 0.001
Arthropathy	0.802	0.32	2.23	1.19–4.18	0.013
B. cepacia	−0.723	0.62	0.485	0.144–1.636	0.24
Year of Transplant	−0.0618	0.022	0.94	0.90–0.98	0.006
Age × *B. cepacia*	0.0587	0.024	1.060	1.01–1.12	0.013

The model includes four variables and a single interaction term. *B. cepacia* as a single variable does not reach statistical significance but is included because of the strong and significant interaction term with age. The model demonstrates that the hazard of death after lung transplantation for cystic fibrosis has improved by approximately 6%/year between 1991 and 2001. *See* text for other discussion and Figure 1.

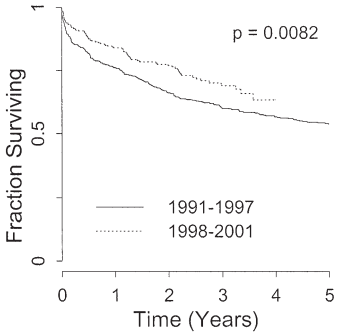

Figure 1. Survival post-transplantation for patients with CF has improved with time as shown by survival in two transplantation eras. Post-transplantation survival for 473 patients (217 deaths) with CF transplantation from 1991 through 1997 is compared to survival for 372 patients (87 deaths) transplanted from 1998 through 2001. The hazard ratio of death in each year is 94% of the hazard in the previous year ($p = 0.006$, *from* Table 3). Thus, for example, the hazard for patients transplanted in 1996 is 0.73 compared with patients transplanted in 1991.

improvement in survival when compared with nontransplanted patients with arthropathy (not shown).

DISCUSSION

The intention of lung transplantation is to improve outcomes for patients with CF. Clinicians focus on post-transplantation survival as the easiest measure of efficacy. However, post-transplantation survival must be compared with nontransplanted survival to obtain a complete picture of the survival effect of transplantation. Factors present pretransplantation that affect post-transplantation survival may help identify individuals who will have improved post-transplantation survivorship.

A transplantation selection factor, such as age, that predicts longer post-transplantation survival is an indication for transplantation only if it also predicts an increase in survival compared with nontransplantation. A factor that predicts decreased survival in a transplant recipient relative to other transplant recipients might still result in survival benefit when comparing post-transplantation survival to nontransplanted survival within a 5-year predicted survival stratum. In the case of patients with *B. cepacia*, infection decreases survival post-transplantation but also decreases nontransplanted survival. Potentially, the negative survival impact of *B. cepacia* infection might be lessened in transplanted patients compared with nontransplanted control subjects, resulting in a survival benefit from the procedure.

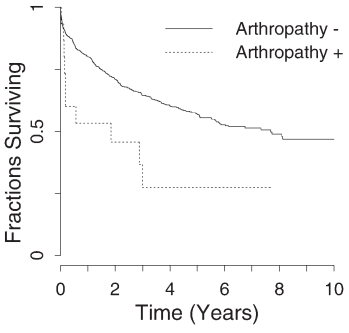

Figure 2. Substantial effect of arthropathy on post-transplantation survival is shown. Patients with CF and with arthropathy were rare as reflected in the small number of transplant recipients with arthropathy (15). Survival was compared with 830 transplant recipients not affected by arthropathy. Despite small numbers, the effect of arthropathy on post-transplantation survival was profound (hazard ratio, 2.23; $p = 0.013$; *from* Table 3) and persisted beyond 5 years of follow-up. There were 10 deaths among the 15 transplant recipients with arthropathy compared with 320 deaths among the 830 recipients without arthropathy.

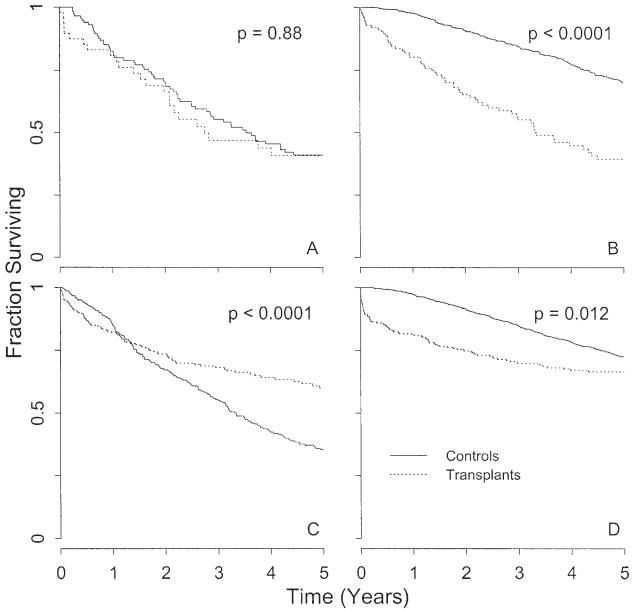

Figure 3. Age affects survival following lung transplantation for CF. Patients infected with *B. cepacia* are excluded from this analysis. Year of transplantation had no correlation with either age at transplantation or 5-year predicted survival. Patients with arthropathy are included in this analysis but were too few to have any effect on results. (*A*) Children with a 5-year predicted survival of less than 50% had no survival benefit from lung transplantation. Survival for 57 transplant recipients younger than 18 years (28 deaths) and 139 control subjects (73 deaths) is shown. (*B*) Children with a 5-year predicted survival between 50 and 90% had decreased survivorship from lung transplantation. Survival for 127 transplant recipients (61 deaths) and 720 control patients (181 deaths) is shown. (*C*) Adults with a 5-year predicted survival of less than 50% had a survival advantage from transplantation. Survival for 362 control patients (198 deaths) and 258 transplant recipients (with 85 deaths) is shown. (*D*) Adults with a 5-year predicted survival between 50 and 90% did poorly with lung transplantation. Survival for 330 transplant recipients (96 deaths) and 1,532 control patients (354 deaths) is shown.

We examined 24 clinical variables, including 5-year predicted survival (Table 1), to discover whether any had a significant effect on survival after lung transplantation. The 5-year predicted survival itself and variables incorporated into the 5-year predicted survival prediction other than age or *B. cepacia* infection had no effect on post-transplantation survival (Table 3) (6, 7).

Body weight is used by 79% of lung transplantation centers in the United States to select patients for the procedure (21). Our analysis found that there was no effect of body weight or of other nutritional factors on post-transplantation survival (Table 1). Patient selection procedures that use body weight already in place at transplant centers might have biased our analysis, but we found that there was no difference in weight-for-age *z* score distribution between transplanted and nontransplanted patients with 5-year predicted survival less than 50%. This suggests that body weight may not be rigorously used as a selection criterion for transplantation, but our analysis suggests that there may be no need for this criterion.

A sex-based selection preference for lung transplantation has been suggested (19, 20) because of the decreased survival of females with CF compared with males (5, 22). Our method of patient selection for transplantation (6) incorporates sex into the calculations of weight-for-age *z* score, FEV_1%, and 5-year predicted survival. Our new finding that sex caused no direct

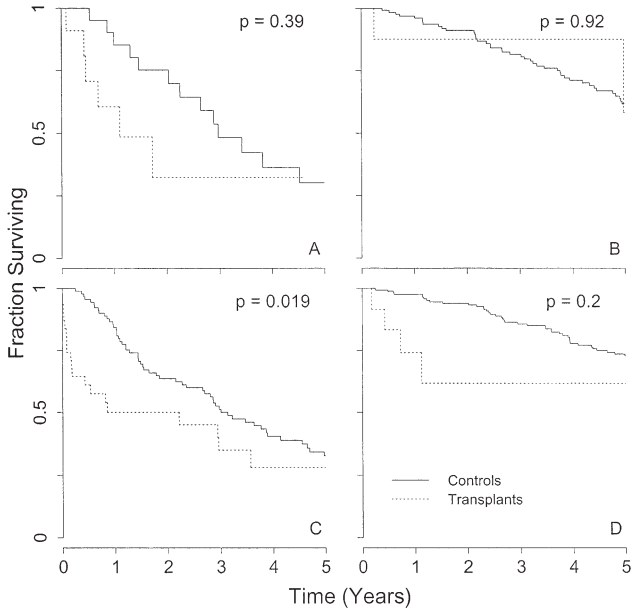

Figure 4. The survival effect of *B. cepacia* infection for lung transplant recipients by age and predicted survival status is shown. For children infected with *B. cepacia,* survival is unchanged by lung transplantation whether 5-year predicted survival is (*A*) less than 50% or (*B*) between 50 and 90%. *A* shows survival of 22 control patients younger than 18 years (13 deaths) and 12 transplant recipients younger than 18 years (6 deaths). *B* shows survival of 127 control patients younger than 18 years (42 deaths) and 9 transplant patients younger than 18 years (2 deaths). (*C*) Adults with *B. cepacia* infection suffered a survival decrease with lung transplantation even though nontransplanted 5-year predicted survival was already poor. Survival of 91 control patients (55 deaths) and 31 transplant recipients (19 deaths) is shown. (*D*) Adults with *B. cepacia* infection with a pretransplantation 5-year predicted survival between 50 and 90% had no survival benefit with lung transplantation. Survival of 174 control patients (42 deaths) and 12 transplant recipients (4 deaths) is shown.

post-transplantation survival effect demonstrates that it need not be separately considered as a criterion for lung transplantation.

Somewhat unexpectedly, we found a significant reduction in hazard of death post-transplantation for patients who underwent transplantation later during the study period (Table 3). Careful inspection of the Kaplan-Meier survival plot comparing the 1998–2001 cohort of transplanted patients with the 1991–1997 cohort revealed that the gain appears to be because of improved survival during the first 6 months post-transplantation (Figure 1).

Three patient-specific factors available before transplantation appear to significantly alter post-transplantation survival: CF-related arthropathy, *B. cepacia* infection, and younger age. CF-related arthropathy is a variable, ill-defined condition with no clear etiology, diagnostic algorithm, or uniformly effective treatment (23). Patients frequently have joint pain but lack history of injury, clear association with other characteristic findings of CF, evidence of articular erosions or positive markers, such as rheumatoid factor, or autoimmune-related arthritis. In our prior study of survival in CF (5), arthropathy had no impact on survival. However, in recipients of lung transplantation, arthropathy appeared to have a profound independent negative effect on post-transplantation survival, especially within 2 months of transplantation (Figure 2).

Our results, although significant (Table 3), depend on the outcomes of only 15 transplanted patients with CF-related arthropathy compared with 830 transplant recipients without arthropathy. Arthropathy is likely to be greatly underreported. Up to one-third of patients with CF have some type of arthropathy or arthritis (23). However, only 1.5% of patients in our control group were recorded to have arthropathy. These results suggest that clinicians should take arthropathy into account when considering lung transplantation. But arthropathy should not be considered a contraindication until there is a better disease definition, better reporting, more information about pathophysiology, and more long-term post-transplantation survivorship data.

The hazard of death decreased with increasing age at transplantation. One quarter of transplanted patients were younger than 18 years. Comparison of survival between young transplanted and control patients without *B. cepacia* infection showed that younger patients did not derive survival benefit from lung transplantation, even with low 5-year predicted survival (Figure 3A). The survival benefit of lung transplantation among patients with low 5-year predicted survival seen in our earlier study came entirely from adult transplant recipients (Figure 3C) (6).

Using CFFPR and UNOS data, we can only speculate about possible causes for the increased hazard of death after transplantation in pediatric patients with CF. We found a nonsignificantly higher hazard of death among patients aged 14 to 17 years compared with even younger transplant recipients (data not shown). Rapid growth, physical and emotional maturation, and large social changes occur in this age range. These factors may contribute to poorer transplantation outcomes. For example, young transplant recipients likely benefit from constant parental reminders to take transplantation medications but, as a consequence, may not internalize understanding of the need for treatment. This may predispose to decreased compliance with post-transplantation management in adolescence, a period when conflicts between children and parents often arise in the CF as well as in the general population.

Our results may suggest a rigid cutoff age of 18 for lung transplantation. Comparison between pediatric recipients and the next quartile of transplant recipients, aged 18 to 24 years, showed a sharp and significant improvement in survival benefit when transplanted survival was compared with nontransplanted survival (data not shown). Young patients, their families, and physicians contemplating lung transplantation must consider that increased survival is relatively unlikely, especially if the patient is younger than 18 years with a 5-year predicted survival greater than 50%.

Immediate or rapid transplantation in the pediatric age group should be considered only if there are compelling reasons for transplantation other than improved survival. Those pediatric patients weighing the risks and benefits of transplantation during adolescence may wish to consider maximizing other therapies for CF and delaying transplantation until after reaching age 18. Besides moving into a more favorable transplant group (Figure 3), the passage of time may allow significant improvements in the procedure itself (Figure 1).

Our Cox model confirms past reports of decreased post-transplantation survival for patients infected with *B. cepacia* compared with post-transplantation survival of patients without *B. cepacia* infection (8, 10, 11). Our sample of *B. cepacia*–infected transplant recipients is larger than any prior report, allowing our model to detect a strong interaction between *B. cepacia* infection and age (Table 3) and allowing us to analyze survival effect stratified by age and 5-year predicted survival.

Because of the interaction, pediatric transplant recipients with *B. cepacia* infection did not suffer decreased post-transplantation survival relative to uninfected pediatric recipients of transplantation. In contrast, adult transplant recipients had a marked decrease in survival related to *B. cepacia* infection. Comparison of post-

transplantation survival to nontransplanted survival in patients stratified by 5-year predicted survival showed no survival benefit of lung transplantation regardless of 5-year predicted survival for young patients (Figures 4A and 4B) and adult patients with high predicted survival (Figure 4D), and actual harm for adult patients with low predicted survival (Figure 4C).

Our study has some limitations. It is retrospective, and selection of patients for lung transplantation may have changed during the period of study. We have limited ability to detect biases in selection for transplantation, and the use of our 5-year survival prediction model to stratify patients for analysis may not have fully controlled for subtle biases. Using the 5-year predicted survival excluded a few patients who were too ill to perform pulmonary function testing. However, we were able to include 84% of transplanted patients and 87% of control patients older than 5.5 years. Although our results apply only to patients with complete data for calculating a 5-year predicted survival, the high percentage of inclusion suggests broad generalizability.

We could not consider other variables, not tracked by the CFFPR, that may have a significant impact on survival in CF and lung transplantation. For example, our model did not consider hypercapnia, which may independently identify gravely ill patients (24). Patients so desperately ill as to require mechanical ventilation have been shown to have survival benefit from lung transplantation if suitable organs could be found in time (25, 26). In practice, however, the challenge of finding suitable organs in time for such patients is often insurmountable.

Furthermore, this retrospective study cannot address all questions about the survival effect of *B. cepacia* on lung transplantation. We cannot account for the possibility of improving treatments for *B. cepacia* infection with and without transplantation that might have improved outcomes (8). Because there is insufficient information in the CFFPR, we were unable to distinguish differing survival patterns among patients infected with different genomovars of *B. cepacia*. Although patients with *B. cepacia* infection did poorly with transplantation and did not have a survival benefit from the procedure, we cannot tell if there might be a subset of patients with *B. cepacia* who would do better. Although collection of additional genomovar information is desirable, we are uncertain if it will be helpful. New information suggests that infections even by a single genomovar of *B. cepacia* may have greatly differing severity depending on the patient or geographic region (27).

Finally, our study, by the nature of the data, cannot give direct guidance to those patients seeking improved quality of life even at the expense of shortened survival. As we have previously conjectured, poor quality of life may correlate with low 5-year predicted survival (6, 7, 28). Thus, the greatest improvement in quality of life may accompany the greatest survival benefit of lung transplantation. Data do not exist that would allow a test of this hypothesis. We are hopeful, however, that new methods for measuring quality of life will facilitate such a test (29).

Clinicians should seek lung transplantation for patients only if there is an increase in survival relative to nontransplanted survival. They should avoid transplantation for patients who will suffer harm, even if post-transplantation survival appears favorable compared with other transplant recipients. Focusing only on post-transplantation survival without considering survival benefit relative to nontransplantation risks maximizing graft survival at the expense of decreased patient survival. For patients likely to have survival benefit, the amount of benefit and the length of post-transplantation survival may help decide how best to allocate scarce donor organs.

Our validated 5-year predictive model made it possible to stratify transplanted and control patients by survivorship. Our study confirms that patients with 5-year predicted survival greater than 50% should not be transplanted in order to avoid reducing survival. Moreover, we found no survival benefit of lung transplantation for children or for patients of any age infected with *B. cepacia*. For patients with 5-year predicted survival of less than 50%, we recommend that patients and physicians temper their expectations of survival benefit from lung transplantation when patients are young or infected with *B. cepacia*. CF-related arthropathy should be a concern for possible transplant recipients but not a contraindication. Because there is an ongoing shortage of suitable organs for transplantation, those patients seeking improved quality of life despite a likely reduction in survival should be deferred in favor of patients likely to have survival benefit from transplantation in addition to any possible improvement in quality of life because of better lung function.

Conflict of Interest Statement: T.G.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; F.R.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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