Survival Effect of Lung Transplantation Among Patients With Cystic Fibrosis

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Context Patients with cystic fibrosis (CF) are the second largest group of lung transplant recipients in the United States. The survival effect of transplantation on a general CF population has not previously been measured.

Objective To determine the impact of bilateral lung transplantation on survival in patients with CF.

Design, Setting, and Patients Retrospective observational cohort study of 11 630 CF patients who did not undergo lung transplantation (controls) and 468 transplant recipients with CF from 115 CF centers in the United States, 1992-1998. Patients were stratified into 5 groups based on a 5-year survival prediction model (survival group 1: <30%; survival group 2: 30 to <50%; survival groups 3-5: 50 to <100%.)

Main Outcome Measure Five-year survival from date of transplantation in 1992-1997 in the transplant group and from January 1, 1993, in the control group.

Results Lung transplantation increased 5-year survival of CF patients in survival group 1. Survival group 2 had equivocal survival effects, and groups 3-5 had negative survival effects from transplantation. From 1994-1997, there was a mean annual prevalence of 238 patients in survival group 1 and mean annual incidence of 154 patients entering the group, approximately 1.5 times the number of lung transplantations performed each year in CF patients (mean, 104). Use of the criterion of forced expiratory volume in 1 second of less than 30% resulted in an equivocal survival benefit and identified 1458 potential candidates for transplantation in 1993.

Conclusions Cystic fibrosis patients in group 1 have improved 5-year survival after lung transplantation. The majority of patients with CF have equivocal or negative survival effects from the procedure. Selection of patients with CF for transplantation based on group 1 survival predictions maximizes survival benefits to individuals and may reduce the demand for scarce donor organs.

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CYSTIC FIBROSIS (CF) IS AN AUTOSOMAL recessive, multisystem disease leading to significant morbidities and early death. Treatments for pancreatic and pulmonary manifestations have improved median survival in the United States from less than 6 months to about 32 years in 1998.[1] Severe pulmonary disease is the primary cause of mortality in CF, underlying 76.4% of deaths in 1998.[1]

Multiple medical therapies specifically treat CF-related pulmonary disease. However, lung transplantation is the most aggressive therapy available for CF patients with severe pulmonary disease.[2-4] Bilateral lung transplantation, introduced in 1988, is now the most widely used technique.[2] Cystic fibrosis is the second most common indication for lung transplantation,[5] and lung transplantation–related deaths are the second most common cause of death in CF patients.[1] The current demand for donated lungs exceeds the available supply.[6] Approximately 11% of all patients awaiting lung transplantation in 1998 died prior to receiving an organ.[5]

Despite the high costs, high risks of morbidity, and unmeasured survival benefit, a rigorous, prospective clinical trial of lung transplantation has not been and probably will not ever be performed. A recent estimate of the survival effect of lung transplantation comparing survival among CF patients posttransplantation with survival of those on the waiting list is limited in generalizability because it studied highly selected CF patients.[7] Deaths of patients on the wait list may have created a survivor bias for patients who actually received transplants. Which patients should be referred, when referrals should be made, and what survival effect results from transplantation are questions that remain unanswered.

Since 1992, patient selection for transplantation has been heavily influenced by a survival model based on percent predicted forced expiratory volume in 1 second (FEV_1%).[8] That model suggested that the 2-year mortality rate

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Table 1. Predictive 5-Year Survivorship Model of Cystic Fibrosis*

Covariate (β_0-β_{10})	Coefficient (x_0-x_{10})	FEV_1% Equivalence
Y-intercept	1.93	. . .
Age (per year)	−0.028	−0.7
Sex (male = 0, female = 1)	−0.23	−6
FEV_1% (per %)	0.038	1
Weight-for-age *z* score	0.40	10
Pancreatic sufficiency (0 or 1)	0.45	12
Diabetes mellitus (0 or 1)	−0.49	−13
Staphylococcus aureus infection (0 or 1)	0.21	6
Burkholderia cepacia infection (0 or 1)	−1.82	−48
No. of acute exacerbations (0-5)	−0.46	−12
No. of acute exacerbations x *B cepacia*	0.40	10

*Patients were stratified after application of this model to calculate their conditional probability of 5-year survival using the coefficients listed. The FEV_1% (% predicted forced expiratory volume in 1 second) equivalence column shows the survival effect of each variable expressed as the effective equivalent change in FEV_1%. For example, a diagnosis of diabetes mellitus has the same survival effect as subtracting 13% from the actual measured FEV_1%. To assist clinicians making 5-year survival predictions for individual patients, a worksheet is available at: http://www.jhsph.edu/Publications/JEPI/liou.htm, or from the authors. Reproduced with permission.[13]

approaches or exceeds 50% for CF patients with an FEV_1 less than 30%, and that these patients should be considered for lung transplantation. However, while this model continues to influence patient selection for transplantation,[9,10] it fails to identify the high-mortality population originally intended.[8,11,12]

Recent consensus statements suggest the use of FEV_1% along with a number of other clinical factors such as PCO_2 and PO_2 values, female sex, increasing numbers of hospitalizations, rate of decline of FEV_1%, and increasing cachexia.[9,10] Other clinical factors, especially the number of acute exacerbations and poor nutrition, have been shown to be correlated with survival, but only when combined with multiple other variables.[13]

We recently developed and validated a multivariable logistic regression survivorship model for CF.[13] The model includes multiple clinical features of CF and is generalizable to the majority of CF patients. It includes most of the consensus criteria for lung transplantation and quantitatively shows the relative impact of each variable on survival. Application of the model allows measurement of the impact of lung transplantation performed in the United States from 1992 through 1997 on CF survival.

METHODS

Patients

We used data from the CF Foundation Patient Registry (CFFPR), which contains longitudinal data on 27 849 patients at 115 CF care centers, representing approximately 90% of all CF patients in the United States.[1] Reports for each patient, containing a wide range of clinical data, are submitted annually to the CFFPR. Over 300 pieces of clinical and socioeconomic data, including survival status and death dates, are recorded annually. Our application to use registry data was reviewed and approved by the data access committee at the CF Foundation. Our study was also reviewed by the institutional review board of the University of Utah. We received access to a longitudinal database for the years 1986 through 1997 which was later updated with 1998 mortality data.

Patients in the CFFPR who were alive on January 1, 1993, were eligible for inclusion in the control group if they had survival data through December 31, 1997 and had pulmonary function data. Patients were excluded if they lacked data needed to calculate a 5-year survival prediction or if they received any type of solid organ transplant prior to December 31, 1997.

Patients in the CFFPR who received bilateral lung transplantation from January 1, 1992 through December 31, 1997 without other solid organ transplantation were eligible for inclusion in the transplant group if they had survival data through December 31, 1997 or for 5 years following transplantation and had pretransplantation pulmonary function data. We chose 1992 because it was the first year in which substantial numbers of bilateral lung transplants were done in the United States. We included patients through 1997 because overall posttransplantation survival rates have not changed.[5] Including patients from 1992 through 1997 provided a large enough population for sufficient statistical power. Patients were excluded if they lacked the additional pretransplantation data needed for 5-year survival predictions. To ascertain transplantation dates, we requested data from the United Network for Organ Sharing (UNOS) Web site (http://www.unos.org) for all patients who received any type of lung transplantation for CF through 1997.

Predictions of 5-Year Survival

To predict 5-year survival for CF patients, we used a multivariable logistic regression model, fully described elsewhere.[13] This model estimates the likelihood of survival for 5 years from the day of calculation based on 9 clinically relevant and commonly assessed variables (TABLE 1). The model was developed using data derived from 5810 patients in the 1993 CFFPR with survival data through 1997 and was validated using data from an additional 5820 patients from 1993. Approximately 92% of patients older than 5.5 years were included in the development and validation of the model. Thus the model is generalizable to CF patients older than 5.5 years who have undergone pulmonary function testing. Other models derived from small cohorts or highly selected cohorts may not be so generalizable and may not allow an evaluation of the survival effect of transplantation on a general population of CF patients.[7,8,14,15] The new model makes predictions that are more accurate than predictions made by models that include FEV_1% or age, sex, and FEV_1%,[8] and it is easier and more

precise to use than older models that include large, subjective components.[16,17]

Survival predictions for patients who received lung transplantation were based on data collected within the 24 months prior to transplantation. The CFFPR does not include a transplant wait-listing date; however, once listed, patients wait approximately 2 years for the procedure.[5] Many transplant candidates have little data reported to the CFFPR in the last year prior to transplantation.

Survival predictions for control patients were based on data from 1993. Additional predictions among nontransplanted patients for 1994 through 1997 were based on data gathered during each of those years.

Nine variables were included in the model (Table 1). Raw spirometry measurements of FEV_1 were normalized to FEV_1% using regression formulae from the third National Health and Nutrition Evaluation Survey.[18] The sex, weight, and age of each patient were used to determine the appropriate median weight-for-age,[19] and z score was calculated using approximation methods.[20,21] Binary variables were assigned a value of 1 if present and 0 if absent pretransplant in the transplant group in 1993 for the control group, or in another year of interest for nontransplanted patients. The number of acute pulmonary exacerbations were counted up to a maximum of 5 per year. Additional exacerbations do not further decrease predicted survival.[13] For patients receiving transplants, we used the number of acute exacerbations during the calendar year prior to the year of transplantation. S-plus version 3.4 (Mathsoft Inc, Cambridge, Mass) was used for all analyses.

Determination of the Survival Benefit of Lung Transplantation

Our model produces survival predictions for the day of calculation.[13] We calculated the 5-year conditional probability of survival for each control patient on January 1, 1993 and for each transplant recipient on the day of transplantation. We stratified patients into 5 groups according to 5-year predicted survival: group 1, <30%; group 2, 30% to <50%; group 3, 50% to <70%; group 4, 70% to <90%; and group 5, 90% to <100%. Within each survival stratum, we used Kaplan-Meier survival analysis to examine the effect of lung transplantation during the 5-year follow-up period (log-rank test).

Because current practice in the selection of lung transplantation candidates is influenced by FEV_1%,[8-10] we performed a parallel analysis of the survival benefit of lung transplantation using that parameter alone. We stratified the patients into 2 groups ($FEV_1 \leq 30\%$ and $FEV_1 > 30\%$) and used Kaplan-Meier survival analysis to examine the effect of lung transplantation during 5 years of follow-up.

Evaluation for Systematic Bias

We assessed our methods for potential bias. Data for transplanted patients were gathered within 24 months prior to transplantation rather than during 12 months as for controls. We compared 5-year survival predictions made on the basis of data gathered less than 12 months prior to transplant to predictions made based on older data. To assess survival effect due to such bias, we repeated Kaplan-Meier survival analysis using only transplant patients with data within the final pretransplant year.

We estimated bias from including wait list deaths but not wait list survival in the analysis of control patients. Kaplan-Meier analysis was repeated to elucidate any change in survival effect of lung transplantation.

Finally, there was a subtle bias introduced because development and validation of the predictive model excluded patients who received solid organ transplantation.[13] Patients chosen for transplantation who survive the wait list period and receive a transplant prove themselves to be more likely to survive than patients who die while on the wait list. This bias might increase the apparent survival benefit of lung transplantation.

Selection of Potential Candidates for Lung Transplantation

We compared the effect of using the FEV_1% criterion vs the validated model for selecting candidates for lung transplantation from the 1993 CFFPR. We calculated 5-year predicted survival for all nontransplanted patients for each year from 1994 through 1997 to discover how many patients might be chosen for lung transplantation after stratification into survival groups using the validated survival model.

RESULTS

Patients

The CFFPR contains 1993 data for 19 156 patients. Of these, 6470 were ineligible for inclusion in the control group: 730 patients received solid organ transplantation of some type before the end of 1997, 54 belonged to racial or ethnic groups for whom FEV_1% standards do not exist, and 5686 lacked FEV_1 measurements. Of the latter, 4190 were younger than 5.5 years, a group for whom FEV_1 cannot be measured by standard techniques. Out of 12 686 patients eligible, we excluded 1056 who lacked data for microbiology, pancreatic sufficiency, diabetes, or acute exacerbation. The remaining 11 630 patients were the control group for this study (TABLE 2).

In the CFFPR, 692 patients received bilateral lung transplantation without other organ transplantation from 1992 through 1997. We excluded 145 patients for lack of pulmonary function data at any time before lung transplantation and an additional 15 without pulmonary function data within 2 years prior to transplantation. One patient was excluded for lack of standards to calculate FEV_1% for the patient's ethnicity and race. We excluded 12 patients for lack of acute exacerbation data and an additional 49 patients for lack of microbiology reports, pancreatic sufficiency status, or weight information. Two patients were excluded for lack of a transplantation date. The remaining 468 patients were included in the transplantation group. Characteristics of control and transplant patients within each survival stratum were well matched (Table 2).

Survival Benefit of Lung Transplantation

Comparison of the Kaplan-Meier survivorship curves of 468 CF patients who

underwent lung transplantation from 1992 through 1997 to survivorship curves of control patients demonstrated that survival effects of lung transplantation were specific for each survival group (FIGURE).[22] For group 1 patients, lung transplantation was associated with slightly decreased survivorship during the first 6 months after the procedure, but a survival advantage for transplanted patients was evident by 2 years and increased with time (Figure, A). Patients in group 2 had an equivocal survival effect 5 years after transplantation but a survival disadvantage for the first 3 posttransplantation years (Figure, B). Patients in groups 3 through 5 had a statistically significant decrease in 5-year survival due to lung transplantation (Figure, C-E).

Kaplan-Meier analysis of survival for patients chosen using FEV_1% as the only criterion for lung transplantation showed that the FEV_1 less than 30% transplant group had a disadvantage for 3 years following transplantation and equivocal benefit in the fourth and fifth years following transplantation (Figure, F).

Systematic Biases

We made approximately half of the survival predictions for lung transplantation recipients based on data collected before the 12 months prior to transplantation. This could create a bias that decreases positive survival effects of transplantation if patients move into lower survival groups while on the waiting list. Comparison of predictions made based on data collected before and after this 1-year mark demonstrated no decrease in predicted survival (P=.17 by Kolmogorov-Smirnov test[23]).

Table 2. Characteristics of Control and Transplant Groups From the United States Cystic Fibrosis Foundation Registry, 1992-1998*

Variable	Survival Group (Predicted Survival)				
	1 (0% to <30%)	2 (30% to <50%)	3 (50% to <70%)	4 (70% to <90%)	5 (90% to <100%)
No.					
Control patients	292	530	898	2086	7824
Transplant recipients	95	138	128	89	18
Age, median					
Control patients	25.6	23.6	21.9	20.8	12.7
Transplant recipients	27.2	23.8	24.4	23.1	22.6
Women, %					
Control patients	51	50	47	50	45
Transplant recipients	56	46	43	41	39
FEV_1%, mean†					
Control patients	21.26	27.66	33.31	44.01	82.12
Transplant recipients	24.45	28.09	31.79	34.71	77.81
Weight-for-age *z* score, mean‡					
Control patients	−2.36	−1.87	−1.59	−1.22	−0.53
Transplant recipients	−1.98	−1.69	−1.41	−1.20	−1.22
Pancreatic sufficiency, %					
Control patients	1	1	1	3	7
Transplant recipients	0	2	2	5	9
Diabetes mellitus, %					
Control patients	39	18	14	9	2.4
Transplant recipients	57	21	26	16	17
Straphylococcus aureus infection, %					
Control patients	12	19	21	22	36
Transplant recipients	14	18	26	18	17
Burkholderia cepacia infection, %					
Control patients	16	15	11	6	1
Transplant recipients	10	3	4	2	9
No. of acute exacerbations, mean§					
Control patients	4.3	3.6	2.6	1.6	0.46
Transplant recipients	4.7	4.0	2.8	1.4	1.6
Percent 5-year survival prediction, mean‖					
Control patients	22	41	61	82	97
Transplant recipients	22	39	60	79	94

*Control data do not include data from transplant patients prior to transplantation. With increasing predicted survival, each variable included within the survival model has a trend toward improvement as expected.[13] FEV_1% indicates % predicted forced expiratory volume in 1 second.
†SD for mean FEV_1% is approximately 25%-30% of the mean for each group of patients.
‡SD for weight-for-age *z* score is approximately 0.94 for each group.
§Mean is calculated from the number of acute exacerbations adjusted by assigning 5 exacerbations to each patient with 5 or more exacerbations per year.[13] The SD for acute exacerbations ranged from 0.6 to 1.7.
‖SD for 5-year survival predictions was 5% to 6% for groups 1-4; for group 5, SD = 2% to 3%. Survival predictions for groups 4 and 5 are significantly different between control patients and transplant recipients. We randomly selected 100 subsets of each control group that were matched for 5-year survival prediction with each respective transplanted group (.1 <P value <.9, by Kolmogorov-Smirnov test[23]). One hundred repetitions of the Kaplan-Meier survival analysis for each transplant group using the selected control subsets produced results identical to Figure, D and E (log-rank P values <.001 for all 200 comparisons).

Kaplan-Meier survival analysis using only the transplant patients with data collected within the 12 months before transplantation showed the same results as our main analysis.

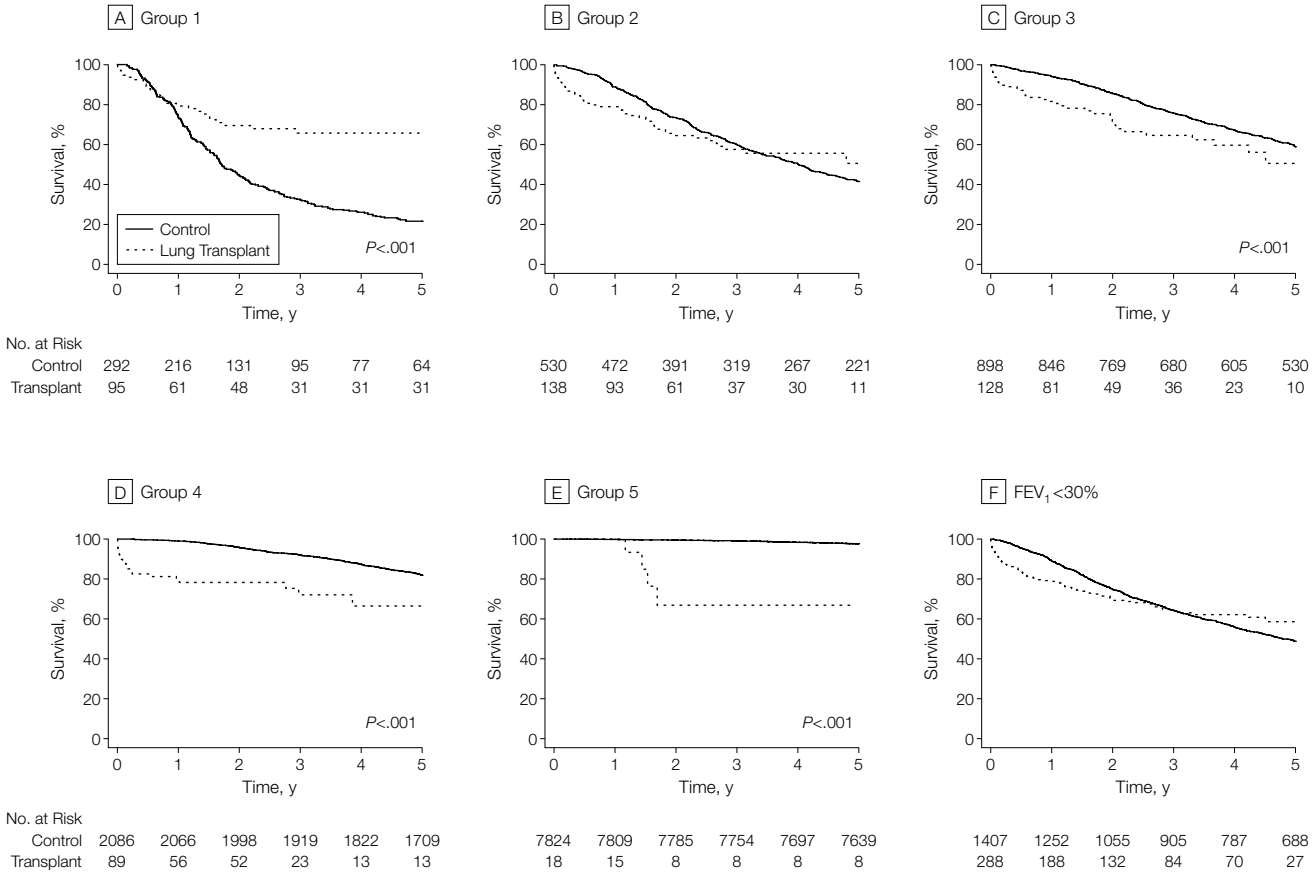
Patients selected for transplantation who die while on the waiting list are not identified in the CFFPR. These deaths would be counted in the control group while years of life on the waiting list by eventual transplant recipients were excluded. This could create a bias that increases the apparent survival benefit of transplantation by artifactually decreasing the survival of control group patients. We stratified 316 patients in the 1993 CFFPR transplanted after January 1, 1993, with the never-transplanted control patients and censored them at the time of transplantation. At transplant, these patients were placed in the appropriate transplant survival groups. Comparison of Kaplan-Meier analysis of these groups of patients to our primary analysis showed that this bias results in a maximum 4% underestimate of survival among the control groups for groups 1 and 2, less than 2% for group 3, and less than 1% for groups 4 and 5 (data not shown). No change in benefit or harm from lung transplantation resulted from this bias. For patients in group 2, the length of time of survival disadvantage was extended by 3 or 4 months, which reinforces the result that lung transplantation had equivocal survival effects for this group.

The potential underestimate of survival for patients who survive the waiting list and receive lung transplantation is smaller than the biases just discussed. No change in benefit or harm results for recipients of lung transplantation.

Identification of Potential Lung Transplantation Recipients

Use of the FEV_1 less than 30% criterion identified 1458 CF patients in 1993 as potential transplant recipients. For these patients, 5-year predicted survival ranged from 6% to 94%. Patients with an FEV_1 greater than 30% had survival predictions ranging from 13% to greater than

Figure. Kaplan-Meier Analysis of Survival Effect of Lung Transplantation for Patients With Cystic Fibrosis, 1992-1997



Patients were grouped according to their predicted 5-year survival. A, The survival advantage with lung transplantation begins to be evident at approximately 18 months posttransplantation. B, Transplanted patients had a survival benefit that is equivocal. C, Transplanted patients had a decreased survival in the early postoperative period and never improved relative to the control group. D, Transplant recipients had a significantly lower 5-year survival than control patients. E, Transplant recipients in the highest predicted survival group were few in number but had the largest decrease in survival due to lung transplantation. F, Survival was superior for nontransplanted control patients during the first 2.5 years of follow-up. Survival benefit due to transplantation was not seen for 4 years.

99%. FEV_1 ranged below and above 30% for patients in all survival groups (TABLE 3).

Survival benefit from transplantation occurred only in survival group 1. We identified 309 patients in the 1993 CFFPR in this group. There were 17 784 nontransplanted patients in the 1994 through 1997 CFFPR. After calculation of 5-year survival predictions, we found that the mean number of patients entering group 1 status each year was 154, approximately 1.5 times the number of lung transplants performed each year for CF (TABLE 4).

COMMENT

We used a validated multivariable logistic regression model to quantify the survivorship benefits of lung transplantation for CF. Our analysis indicates that CF patients most likely to benefit from transplantation had a predicted 5-year survival of less than 30%. For this group, transplantation markedly improved 5-year survival. There was equivocal survival benefit for patients with 30% to 50% predicted survival. For the patients with predicted survival of 50% or more, transplantation reduced survival.

Current practice considers patients for referral for lung transplantation using a number of criteria, including FEV_1 less than 30%.[8-10] However, our survival curves demonstrated that the survival benefit is equivocal when patients are selected by the FEV_1 less than 30% criterion. This criterion was originally proposed because it seemed to select patients with a less than 50% 2-year survival.[8] It was hypothesized that patients with low predicted survival have the greatest potential survival benefit from lung transplantation. Using a validated survival model of CF, we have demonstrated the truth of that original hypothesis.

Unfortunately, the survival model based on FEV_1% may not apply to CF populations outside of the original center where it was developed,[11,12] and it does not validate in the large CFFPR.[13] The FEV_1% criterion fails to select the originally intended group of patients. In our study, use of FEV_1% alone selected a group of patients for lung transplantation that had a wide range of 5-year survival predictions. This variability resulted from the exclusion of other clinically relevant factors and makes estimates of the true survival benefit of transplantation difficult. Our analysis suggested that use of the FEV_1% criterion leads to an equivocal survival benefit for this heterogeneous group.

Using FEV_1% as the primary criterion for lung transplantation is fraught with potential difficulties. Requiring an FEV_1 less than 30% for lung transplantation might have excluded many patients in group 1 who had improved posttransplant survival. Conversely, a majority of transplanted patients in groups 2 through 4 who had equivocal or negative survival effects due to transplantation had an FEV_1 less than 30%. These patients had few of the negative factors identified in our model[13] that determined 5-year survival.

When applied to patients in the 1993 CFFPR, the FEV_1 less than 30% criterion identified 1458 patients as potential transplant recipients. Such an approach virtually guarantees that the waiting list for organs will continue to grow. Patients in group 1 who have an FEV_1 greater than 30% would die without qualifying for transplantation. Many other patients in group 1 would likely die while on the waiting list for lung transplantation. Some have proposed that deaths on the waiting list would be reduced by referring patients with higher FEV_1% for transplantation (FEV_1 <50%).[24] This strategy would lengthen the waiting list by identifying several thousand additional candidates with CF for lung transplantation (data not shown) and lead to increased risk to patients with low predicted survivorship.

The additional criteria proposed in recent consensus statements about lung transplantation in CF are not quantified.[9,10] The lack of specific guidelines makes application of these criteria dif-

Table 3. FEV_1% and Survival Group*

	Transplant Recipients, 1992-1997		Control Patients, 1993	
Survival Group	FEV_1 ≤30%	FEV_1 >30%	FEV_1 ≤30%	FEV_1 >30%
1	82	13	265	27
2	89	49	340	190
3	70	58	405	493
4	46	43	381	1705
5	1	17	16	7808
Total	**288**	**180**	**1407**	**10223**

*Patients with cystic fibrosis who received lung transplantation during 1992-1997 and the 1993 never-transplanted control patients are divided according to survival group and FEV_1% (% predicted forced expiratory volume in 1 second). While higher FEV_1% is correlated with better 5-year survival, FEV_1% alone cannot be used to predict 5-year survival[13] as underscored by the large number of patients in survival group 4 with an FEV_1 less than 30%. The FEV_1% criterion would have excluded 27 patients from 1993 control group 1 from being considered for lung transplantation.

Table 4. Numbers of Group 1 Patients and Lung Transplants for CF, 1994-1997*

	Survival Group 1		
Year	Prevalent Cases	Incident Cases	CF Transplants
1994	248	164	76
1995	210	158	113
1996	265	161	103
1997	229	134	122
Yearly average	238	154	104

*We calculated 5-year survival predictions for all nontransplanted patients in the Cystic Fibrosis Foundation Patient Registry (CFFPR) in 1994-1997 and stratified the patients into survival groups 1-5 (see "Methods" section). There were 23 542 patients in the CFFPR for this period. A total of 52 260 predictions were made for 17 784 patients. There were 5501 patients excluded for lack of pulmonary function test results (4313 were too young to perform the test) and 257 for lack of microbiology reports, diabetes, pancreatic sufficiency, or acute exacerbation data. Of the included patients, 17 077 never entered group 1 survival status, and 707 were in group 1 at least once during the period. There were of 414 lung transplants for patients in the CFFPR undergoing the procedure for the first time during the period.

ficult, and rigorous assessment of impact on survival impossible.

In contrast, we show that use of our model[13] to determine group 1 status and identify transplantation candidates conferred greatly improved 5-year survival for recipients of the procedure. All other patients had an equivocal or negative survival effect from transplantation. This conclusion is unaffected after considering several biases that might have changed our results.

Furthermore, the number of patients entering group 1 survival status from 1994 to 1997 was approximately 1.5 times the number of transplants done per year in patients followed by the CFFPR. Use of group 1 status as a transplantation selection criterion may reduce the lung transplant waiting list among CF patients.

There are several limitations of this study. Retrospective studies may be as powerful as prospective studies if biases are adequately addressed.[25,26] We have identified and accounted for a number of likely biases,[26,27] but we are unable to completely exclude bias in patient selection for transplantation that may have an effect on survival outcome. Such unknown biases may or may not favor transplantation. A major source of bias in our study is the average 2-year interval between the decision to perform transplantation and actual transplantation. We have shown that these biases tend to decrease the apparent survival of nontransplanted controls and might increase the apparent survival benefit of lung transplantation. Although these biases exist, they do not change the results of our analysis. Should a rigorous randomized controlled study of transplantation be done, the waiting period between randomization and actual transplantation could introduce the opposite bias.[28] The survival benefit of lung transplantation might be minimized or eliminated because of the waiting list period.

Finally, a study of survival does not directly address health-related quality of life. Standardized methods to evaluate quality of life in patients with CF have not existed until recently, and validation is incomplete.[29] We observed, however, that patients with CF in groups 4 or 5 had few of the health limitations that decrease quality of life, whereas patients in groups 1 or 2 had most if not all of the clinical features of CF that physically make life more difficult. By better defining survival effects, our work may provide an objective background for patients and their physicians to assess the quality of life surrounding transplantation.[30]

Our study demonstrates that lung transplantation improved survival only for the minority of CF patients who had a 5-year predicted survival of less than 30%. In light of our analyses, we urge a revision of lung transplantation selection criteria to maximize survival among the most severely ill CF patients.

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