Risk Factors for Death of Patients with Cystic Fibrosis Awaiting Lung Transplantation

Richard A. Belkin, Noreen R. Henig, Lianne G. Singer, Cecilia Chaparro, Ronald C. Rubenstein, Sharon X. Xie, Justin Y. Yee, Robert M. Kotloff, David A. Lipson, and Greta R. Bunin

Divisions of Pulmonary, Allergy, and Critical Care, and Biostatistics, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Medical Center; Divisions of Pulmonary Medicine and Oncology, Children's Hospital of Philadelphia; Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Division of Pulmonary and Critical Care Medicine, Stanford University Medical Center, Stanford, California; and Division of Respiriology, University Health Network and University of Toronto, Toronto, Ontario, Canada

Rationale: The optimal timing for listing of cystic fibrosis patients for lung transplantation is controversial.

Objectives: We conducted a retrospective cohort study of 343 patients listed for lung transplantation at four academic medical centers to identify risk factors for death while awaiting transplantation.

Methods: Data on possible risk factors were abstracted from medical records.

Measurements: Time to death, patient demographic characteristics, and risk factors for death while awaiting transplantation were assessed. Univariate and multivariate survival analyses were performed using Cox regression.

Results: By univariate analyses, $FEV_1 \leq 30\%$ predicted (HR, 3.8; 95% CI, 2.0–7.5), $Pa_{CO_2} \geq 50$ mm Hg (HR, 1.85; 95% CI, 1.1–3.0), and shorter height (HR, 1.8; 95% CI, 1.1–3.0) were associated with a higher risk of death. Referral from an accredited cystic fibrosis center was associated with a lower risk (HR, 0.53; 95% CI, 0.30–0.92). The final multivariate model included referral from an accredited cystic fibrosis center (HR, 0.5; 95% CI, 0.3–1.0) and listing year after 1996 (HR, 0.4; 95% CI, 0.2–0.7); both were associated with a lower risk of death. $FEV_1 \leq 30\%$ predicted (HR, 6.8; 95% CI, 2.4–19.3), $Pa_{CO_2} \geq 50$ mm Hg (HR, 6.9; 95% CI, 1.5–32.1), and use of a nutritional intervention (HR, 2.3; 95% CI, 1.3–4.1) were associated with increased risk. Patients with $FEV_1 > 30\%$ predicted had a higher risk of death only when their Pa_{CO_2} was ≥ 50 mm Hg (HR, 7.0; 95% CI, 1.5–32), while the increased risk of death with $FEV_1 \leq 30\%$ was not further influenced by the presence of hypercapnia.

Conclusions: We identified risk factors for waiting list mortality that could impact on transplant listing and allocation guidelines.

Keywords: cystic fibrosis; lung transplantation; survival

Cystic fibrosis (CF) is a multisystem autosomal recessive disease with a median survival of 33 yr. Lung transplantation is offered to patients with advanced CF lung disease as a potential life-extending and life-improving treatment (1). Because about 90% of patients with CF die from end-stage obstructive lung disease, CF is now the third leading indication for lung transplantation (2).

For each patient with CF there is a “transplant window” that opens when the risks of delay in referral for lung transplant outweigh those of the transplant procedure and closes when the

patient is too ill, or too high an operative risk, to be an acceptable candidate for transplant. In general, patients must be sufficiently ill to require transplantation, but not so sick that they cannot tolerate the procedure. Commonly used guidelines for referring a patient for lung transplant include (1) FEV_1 less than 30% predicted or rapidly progressive respiratory deterioration with an FEV_1 greater than 30% predicted, (2) Pa_{CO_2} greater than 50 mm Hg, (3) Pa_{O_2} less than 55 mm Hg on room air, and/or (4) female sex and age less than 18 yr with FEV_1 greater than 30% predicted, and deteriorating rapidly. These guidelines are largely based on data published in 1992 from the University of Toronto (Toronto, ON, Canada) (3–5). However, by using these criteria up to 30% of listed patients with CF die before transplantation (6). These high waiting list mortality data may reflect the inaccuracy of identifying the transplant window, or may highlight the limitations of waiting time–based donor allocation. We therefore conducted a 10-yr retrospective multicenter study to better identify predictors in a population “selected” by their physicians for lung transplantation, with the aim of obtaining a better understanding of the factors related to mortality while awaiting transplant. Recognition of these factors may lead to better lung allocation algorithms that maximize the survival benefit of transplantation.

Two groups have published models of predicted mortality based on retrospective analysis of the Cystic Fibrosis Foundation (Bethesda, MD) Patient Registry. The model of Liou and coworkers (7) predicts 5-yr survival on the basis of 10 characteristics. In a study employing this model, Liou and coworkers (8) demonstrated that only those adult patients with CF with a predicted 5-yr survival of less than 50% and who do not have *Burkholderia cepacia* colonization or CF-related arthropathy at the time of transplant derive a survival advantage from transplantation.

Mayer-Hamblett and coworkers (9) developed a multiple logistic regression model for predicting 2-yr mortality in patients 6 yr of age or more, based on 1996 U.S. Cystic Fibrosis Foundation Patient Registry data. This model included five variables in addition to mean FEV_1 . Unfortunately, this model had no better predictive accuracy for 2-yr mortality than FEV_1 of less than 30% predicted alone. Both percent predicted FEV_1 and the model presented had low positive predictive values. This study reaffirms the need to identify better predictors of short-term outcome in an attempt to improve mortality on the waiting list.

These data suggest that criteria by which to best identify patients with CF appropriate for lung transplant can still be improved. Because Liou and coworkers (8) and Mayer-Hamblett and coworkers (9) used Cystic Fibrosis Foundation Patient Registry data, there may be misclassification bias present (e.g., lack of validated diagnostic criteria for risk factors such as CF-related diabetes mellitus). Our study used careful review of charts from each center and standardization of criteria for categorization of risk factors. Clinical risk factors potentially associated with higher risk of death in patients with CF in previous studies are

(Received in original form October 13, 2004; accepted in final form December 16, 2005)

Supported by a Third Year Clinical Research Award, the Cystic Fibrosis Foundation, and NIH/NHLBI (F32 HL74534-01).

Correspondence and requests for reprints should be addressed to Richard A. Belkin, M.D., Department of Pulmonary and Critical Care Medicine, Sansum-Santa Barbara Medical Foundation Clinic, 215 Pesetas Lane, Santa Barbara, CA 93110. E-mail: rbelkin@sansumclinic.org

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 173, pp 659–666, 2006

Originally Published in Press as DOI: 10.1164/rccm.200410-1369OC on January 19, 2006
Internet address: www.atsjournals.org

listed in Table 1. The purpose of this study was to identify other important risk factors for death specifically in patients with CF awaiting lung transplantation. Our current criteria for listing are quite poor at predicting who will survive to transplantation and who will die. Thus, a 10-yr retrospective, multicenter study was done to identify predictors in a population "selected" by their physicians. This may allow modification of who is listed as well as timing of listing to attempt to improve survival on the waiting list.

Some of the results of our study have been previously reported in the form of abstracts (10, 11).

METHODS

Study Population

The study population consisted of 343 adult and pediatric patients with CF listed for lung, heart–lung, or heart–lung–liver transplantation at the University of Pennsylvania Medical Center (Philadelphia, PA), Stanford University Medical Center (Stanford, CA), Children's Hospital of Philadelphia (Philadelphia, PA), Toronto General Hospital (Toronto, ON, Canada) and the Hospital for Sick Children in Toronto (Toronto, ON, Canada) from January 1990 to December 2002. Heart–lung transplant candidates were included in this study because this procedure was routinely performed at Stanford University Medical Center in the early 1990s. Institutional review board approval was obtained at each institution. Data were collected by chart review, using standardized procedures (see the online supplement for the detailed manual). A 10% sample of charts was reabstracted. Three patients were excluded because either the listing date or removal date was unknown.

Definition of Risk Factors

We collected demographic, body measurement, pulmonary function, and hemodynamic data at the time of listing and data on microbiology, nutritional status, CF-related diabetes mellitus, osteoporosis, and use of preventive therapies before or at the time of listing. See Table E3 of the online supplement for a complete list of data items collected. A description of reference equations for percent predicted FEV₁ is also presented in the online supplement.

Death while listed for transplant was the primary endpoint for all analyses. Patients who underwent lung transplantation were censored on the date of their operation, and those alive and waiting for transplantation were censored at the end of the study on December 31, 2002. Patients removed from the transplant waiting list for other reasons

(voluntary removal, transfer to another center, "too well," or "too sick") were censored at the time of removal.

Statistical Analysis

Statistical analysis was performed with Stata 7.0 (StataCorp, College Station, TX). All statistical tests were two-sided.

Comparisons of categorical variables between survivors and nonsurvivors were performed by χ^2 or Fisher's exact test. Continuous variables were summarized as mean $\pm$ SD and 95% confidence interval (95% CI), or as median, range, and interquartile range (25–75%). Comparisons between survivors and nonsurvivors were performed by *t* test for normally distributed variables and by Wilcoxon rank-sum test for other variables.

Each potential risk factor was first analyzed separately by the Kaplan-Meier method to estimate survival, by univariate Cox regression to estimate the hazard ratios, and by log rank test to test survival differences between groups. Hazard ratios are presented for a 10% decrease in percent predicted FEV₁ and FVC and for a 10-mm Hg increase in PaO₂ and PaCO₂.

We used Cox regression for multivariate analyses to determine hazard ratios, and the Wald χ^2 test to calculate *p* values. The final model was generated by a backward model selection procedure from variables with *p* < 0.20 from the univariate Cox regression analyses, significant confounders, and biologically plausible effect modifiers. Variables were eliminated from highest to lowest *p* value, but remained in the model if the *p* value was less than 0.05. Variables believed to be highly clinically significant or found to be independent predictors of death in prior studies were included in these analyses irrespective of their *p* value. Minus log–minus log plots were used to confirm that the proportional hazards assumption was met.

To assess the impact of potential informative censoring, a sensitivity analysis was performed to determine the effect of two extreme cases (12). The impact of missing data was also assessed by comparing characteristics of patients included in the final multivariate model with those removed because of missing data. Analyses were also performed for each center separately to assess intercenter variability.

RESULTS

A total of 346 patients were identified; three patients were excluded because either their listing date or removal date was unknown. A total of 343 patients were analyzed (University of Pennsylvania Medical Center, *n* = 85; Stanford University Medical Center, *n* = 94; Children's Hospital of Philadelphia, *n* = 26; and Toronto General Hospital and the Hospital for

TABLE 1. CLINICAL RISK FACTORS POTENTIALLY ASSOCIATED WITH HIGHER RISK OF DEATH AMONG PATIENTS WITH CYSTIC FIBROSIS

Factors Associated with Higher Risk of Death in General CF Population		Factors Associated with Higher Risk of Death in CF Population on Lung Transplant List	
Factor	Reference(s)	Factor	Reference(s)
1. Pulmonary function and exercise capacity	3, 7, 9, 14, 18–29	1. Yearly rate of decline in percent predicted FEV ₁	19
2. Microbiology (i.e., <i>Burkholderia cepacia</i> , <i>Pseudomonas aeruginosa</i>)	30–35	2. Shorter 6-min walk distance	14
3. Nutritional status (weight)	36, 37	3. Presence of pulmonary hypertension	14
4. Age	18, 19, 23, 24, 28, 38	4. Presence of diabetes mellitus	14, 26
5. Female sex	13, 32, 33, 37	5. Shorter height	26, 44
6. Pancreatic insufficiency	35, 39		
7. CFRDM	13, 29, 35		
8. Lower socioeconomic status	40		
9. Pulmonary hypertension	14, 41		
10. Number of acute exacerbations	13		
11. Geographic location	42		
12. Care in CF center	32, 43		

Definition of abbreviations: CF = cystic fibrosis; CFRDM = cystic fibrosis–related diabetes mellitus.

Listed are potential risk factors for death, in the general CF population (*left*) and among patients with CF listed for lung transplantation (*right*), that have been previously studied.

Sick Children in Toronto, $n = 138$). Seventy-eight patients died (nonsurvivors group; $n = 78$). Two hundred and fifteen patients received a transplant, with patients receiving a bilateral lung transplant ($n = 205$), heart–lung transplant ($n = 7$), lung–liver transplant ($n = 2$), or heart–lung–liver transplant ($n = 1$). Thirty-four were still waiting at the end of the study and 16 were removed for other reasons (survivors group; $n = 265$).

Demographic and clinical profiles of the survivors and non-survivors are shown in Table 2. One notable difference between the groups was percent-predicted FEV₁. There was a significant difference in the mean percent-predicted FEV₁ and proportion of patients with an FEV₁ of less than 30% predicted between survivors and nonsurvivors ($p < 0.01$; Table 2). Nonsurvivors had a greater 6-min walk distance, were more likely to have multidrug-resistant *Pseudomonas* (defined as resistant to three or more different antibiotics), and were more likely to use inhaled recombinant human DNase. Height was similar between the groups ($p = 0.3$). Survival rates for the entire cohort were 80% at 1 yr, 64% at 2 yr, and 50% at 3 yr. Mean time to death

among the nonsurvivors was 347 ± 314 d, which was similar to the average time to transplantation among the survivors (368 ± 351 d). Median time to death in the nonsurvivors group was 267 d (interquartile range, 92–489 d), whereas the median time to transplant in the survivors group was 251 d (interquartile range, 100–510 d). These results are further detailed in Table 2. The mean waiting time for those still waiting at the end of the study was 551 ± 483 d.

Univariate Analysis

Table 3 depicts the results of the univariate analyses. An FEV₁ of less than 30% predicted was associated with a higher risk of death (*see also* Figure 1), as was a 10% decrease in FEV₁ and FVC. Hypercapnia was also associated with a higher risk of death; a 10-mm Hg rise in PaCO₂ was associated with a hazard ratio (HR) of 1.3 and a 95% CI of 1.1 to 1.7, whereas PaCO₂ of 50 mm Hg or greater (compared with PaCO₂ < 50 mm Hg) had an HR of 1.8 and a 95% CI of 1.1 to 3.0. Referral from an accredited CF center was associated with a lower risk of death

TABLE 2. PROFILE OF PATIENTS AT TIME OF REFERRAL FOR TRANSPLANTATION

General Characteristics	Nonsurvivors		Survivors		p Value
	Value	No.	Value	No.	
Age, yr: mean $\pm$ SD	27 $\pm$ 9	76	26.9 $\pm$ 8	262	0.90
Sex, female: no. (%)	40 (51)	78	122 (46)	265	0.44
Height, cm: mean $\pm$ SD	163 $\pm$ 13	78	164 $\pm$ 14	259	0.30
Race, white: no. (%)	76 (100)	76	253 (77)	264	0.47
BMI, mean $\pm$ SD	19.4 $\pm$ 3	78	19.3 $\pm$ 3	258	0.93
Pulmonary function					
FEV ₁ % predicted, mean $\pm$ SD	24 $\pm$ 7	75	27 $\pm$ 8	257	< 0.01
FEV ₁ $\leq$ 30% predicted, no. (%)	65 (87)	75	171 (67)	257	< 0.01
FVC% predicted, mean $\pm$ SD	42 $\pm$ 11	75	44 $\pm$ 14	222	0.13
Gas exchange, mean $\pm$ SD					
PaO ₂ , mm Hg	64 $\pm$ 12	70	64 $\pm$ 10	195	0.46
PaCO ₂ , mm Hg	47 $\pm$ 9	71	46 $\pm$ 9	224	0.22
SIXMW, ft	1,021 $\pm$ 451	63	900 $\pm$ 520	214	0.06
Microbiology, no. (%)					
<i>Burkholderia cepacia</i>	14 (19)	75	57 (22)	257	0.63
<i>Stenotrophomonas maltophilia</i>	1 (1)	76	24 (9)	257	0.02
<i>Achromobacter xylosoxidans</i>	2 (3)	76	8 (3)	257	0.99
MDR <i>Pseudomonas</i>	19 (25)	76	50 (20)	257	0.33
MRSA	1 (1)	76	16 (6)	257	0.13
<i>Aspergillus</i> spp.	7 (9)	76	49 (19)	256	0.05
CMV (IgG)	21 (31)	68	102 (39)	261	0.26
Hemodynamics, no. (%)					
Pulmonary hypertension	6 (21)	29	29 (29)	100	0.48
RV dysfunction	7 (21)	33	76 (51)	150	< 0.01
Presence of, no. (%)					
Osteoporosis	5 (23)	21	25 (23)	108	0.99
Chronic sinusitis	47 (65)	72	154 (63)	245	0.78
Nutritional intervention	25 (33)	75	55 (27)	201	0.37
Liver disease	5 (7)	75	28 (11)	259	0.38
CF-related diabetes mellitus	16 (21)	76	65 (25)	260	0.54
Use of					
Inhaled TOBI, no. (%)	43 (57)	75	161 (65)	247	0.22
Inhaled rhDNase, no. (%)	45 (60)	75	114 (46)	247	0.05
Waiting time, d					
Mean	347	78	369	265	0.87
Median	251 (100–510)*	78	267 (92–489)*	265	

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; CMV = cytomegalovirus; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; rhDNase = recombinant human DNase; RV = right ventricular; SIXMW = 6-min walk; TOBI = tobramycin solution for inhalation.

Shown are profiles of patients at the time of listing for transplantation. Six-minute walk is defined as the distance walked (in feet) as performed at the respective transplant centers. Categorical variables were summarized as frequencies, and comparisons were performed by χ^2 or Fisher's exact test. Continuous variables were summarized as mean $\pm$ SD and 95% confidence interval, or as median, range, and 95% confidence interval. Comparisons were performed by two-tailed *t* test if the data were normally distributed or by Wilcoxon rank-sum test if the data were not normally distributed.

* Median values with interquartile ranges.

TABLE 3. UNIVARIATE ANALYSIS

Variable	No. (343 total)	Hazard Ratio (95% CI)	p Value
Pulmonary function			
FEV ₁ % predicted (10% ‡*)	332	2.1 (1.5–3.0)	< 0.01
FVC% predicted (10% ‡)	297	1.3 (1.1–1.6)	0.01
FEV ₁ ≤ 30% predicted	332	3.8 (2.0–7.5)	< 0.01
Ventilation/oxygenation			
PaCO ₂ mm Hg (10 mm Hg ‡*)	295	1.3 (1.1–1.7)	0.02
PaCO ₂ ≥ 50 mm Hg	295	1.8 (1.1–3.0)	0.02
PaO ₂ mm Hg (10 mm Hg ‡)	265	1.2 (0.9–1.4)	0.19
Stature			
Shortest height quartile†	343	1.4 (0.9–2.4)	0.18
Age less than 18 yr	338	0.9 (0.5–1.7)	0.76
BMI	336	1.0 (0.9–1.1)	0.91
Microbiology			
<i>Stenotrophomonas maltophilia</i>	333	0.2 (0.02–1.2)	0.07
<i>Burkholderia cepacia</i>	332	1.1 (0.6–1.9)	0.83
<i>Achromobacter xylosoxidans</i>	333	0.9 (0.2–3.6)	0.86
MDR <i>Pseudomonas</i>	333	1.1 (0.7–1.9)	0.64
MRSA	333	0.3 (0.04–12.3)	0.26
<i>Aspergillus</i> spp.	332	0.6 (0.3–1.3)	0.19
CMV	329	0.8 (0.5–1.4)	0.50
Hemodynamics			
Pulmonary hypertension	129	2.7 (0.8–9.4)	0.11
RV dysfunction	183	0.4 (0.2–1.0)	0.06
Others			
Accredited CF center	334	0.5 (0.3–0.9)	0.03
Six-minute walk, ft	277	1.0 (0.99–1.0)	0.19
Presence of osteoporosis	129	1.1 (0.40–3.0)	0.88
Nutritional intervention	276	1.4 (0.90–2.2)	0.19
Use of TOBI	322	0.8 (0.50–1.30)	0.40
Use of rhDNase	322	1.0 (0.63–1.6)	0.98
Presence of CFRDM	336	1.1 (0.60–1.9)	0.50
Presence of liver disease	334	0.8 (0.3–2.0)	0.67
Listing year (continuous variable)	321	0.9 (0.8–0.9)	< 0.01
Listing year ≥ 1996	321	0.4 (0.3–0.7)	< 0.01

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; CFRDM = cystic fibrosis-related diabetes mellitus; CI = confidence interval; CMV = cytomegalovirus; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; rhDNase = recombinant human DNase; RV = right ventricular; TOBI = tobramycin solution for inhalation.

Potential significant factors identified by univariate analyses are presented.

* ↓ = decrease; ‡ = increase.

† Adjusted for age.

(HR, 0.5; 95% CI, 0.3–0.9). Listing year during or after 1996 was associated with a lower risk of death (HR, 0.4; 95% CI, 0.3–0.7). Also, the use of a nutritional intervention was potentially associated with a higher risk of death (HR, 1.4; 95% CI, 0.9–2.2). The presence of *Stenotrophomonas maltophilia* (HR, 0.2; 95% CI, 0.02–1.2) and *Aspergillus* (HR, 0.6; 95% CI, 0.3–1.3) may be associated with a lower risk of death. The presence of *B. cepacia* colonization was not associated with a higher risk of death (HR, 1.1; 95% CI, 0.6–1.9). The univariate results did not appreciably change when only the 230 patients with complete data on all variables included in the final multivariate model were used (see Tables E2 and E3).

Multivariate Analysis

The results of the multivariate analysis are shown in Table 4. Of the original cohort of 343 patients, 230 had complete data for all variables and were included in the final model. An FEV₁ of less than 30% predicted is an independent predictor of death (HR, 6.8; 95% CI, 2.4–19.3). However, there was a significant interaction between PaCO₂ and FEV₁. Patients with FEV₁ > 30% predicted had a significantly higher risk of death when their PaCO₂ was 50 mm Hg or greater versus those patients with PaCO₂ of less than 50 mm Hg (HR, 7.0; 95% CI, 1.5–32.0). Conversely, there was no significant difference in the risk of death between those patients with PaCO₂ of 50 mm Hg or greater and those with

PaCO₂ of less than 50 mm Hg when their percent predicted FEV₁ was less than 30 (HR, 1.4; 95% CI, 0.4–5.0).

The presence of *S. maltophilia* colonization in the respiratory tract, shorter 6-min walk distance, and the presence of hypoxemia were all removed from the multivariate model as their p value increased to more than 0.05 during the backward selection procedure. Because *B. cepacia* has been associated with a higher risk of death in prior studies (9, 13), the presence of *B. cepacia* was forced into the multivariate model. CF-related diabetes mellitus was a significant risk factor for death in the one study (14) and thus was also forced into the model. Although the presence of pulmonary hypertension was found to be an independent predictor in the same study, we had too many missing data to include it in our final model. The presence of either *B. cepacia* and/or CF-related diabetes mellitus still did not significantly alter the other covariates when forced into the final multivariate model, and therefore these parameters were ultimately excluded from the model. Also, age, both as a continuous variable and as a dichotomous variable (using 18 yr as the cutoff) was forced into the model (age < 18 yr: HR, 1.8; 95% CI, 0.8–3.9; p = 0.13). Although there was a trend toward a higher risk of death for patients whose age was less than 18 yr, when removed from the model the hazard ratios of the other variables did not appreciably change and thus it was excluded from the model.

Figure 1. Kaplan-Meier survival plot of the proportion of patients with cystic fibrosis awaiting lung transplantation, based on a cutoff in FEV₁ of 30% predicted. The p value from the log-rank test is less than 0.01. Solid line, FEV₁ > 30% predicted; dashed line, FEV₁ ≤ 30% predicted.

N=	96	45	25	7	3	1
(FEV ₁ >30% pred.)						
N=	236	81	25	8	2	0
(FEV ₁ ≤30% pred.)						

In the final model, year of listing (1996 and beyond compared with before 1996) was associated with a lower risk of death on the transplant waiting list (HR, 0.4; 95% CI, 0.2–0.7). Also, the use of a nutritional intervention was associated with a higher risk of death (HR, 2.3; 95% CI, 1.3–4.1). The final model is shown in Table 4.

We assessed whether transplant candidates from accredited CF centers differ from candidates not from accredited CF centers in markers of more severe disease (Table 5). Patients referred from an accredited CF center had a higher percent-predicted FEV₁ (27 ± 8) than did those that were not referred from an accredited CF center (25 ± 8).

The sensitivity analysis tested the effect on the hazard ratios of two extreme situations concerning the patients removed from the transplant list for reasons other than death or transplant, such as transfer to another center and voluntary removal. In one case we assumed all patients in the “other” category experienced the event (death) after the longest survival time of any individual in the data set, that is, the censoring time is replaced by the longest survival time (1,783 d). In the second case, we

assumed the “other” patients died on the day of censoring. In both situations, the hazard ratios for patients with FEV₁ of less than 30% predicted with PaCO₂ of more than 50 mm Hg decreased compared with the original analysis but were still significantly greater than 1.0. For the other variables, there was no substantial change in the hazard ratios. These data suggest that informative censoring did not influence our model (results shown in Tables E2A and E2B).

Because of the possibility of confounding by center, we performed the univariate analyses on the data from each center with sufficient numbers of patients (all centers other than Children’s Hospital of Philadelphia). There were no substantial differences between centers in the HR for death using FEV₁ of 30% predicted or less and PaCO₂ of 50 mm Hg or greater. At one site (Stanford), referral from an accredited CF center showed a trend toward an increased risk of death (HR, 1.4; 95% CI, 0.2–11). However, only eight patients were not referred from a CF center, so the estimate is imprecise (see Table E4).

Also, the effect of missing data was assessed. The main difference between those patients excluded from the final model

TABLE 4. MULTIVARIATE ANALYSIS

Variable	Hazard Ratio for Death (95% CI)	p Value
FEV ₁ ≤ 30% predicted	6.8 (2.4–19.3)	< 0.01
PaCO ₂ ≥ 50 mm Hg	6.9 (1.5–32.1)	0.01
FEV ₁ ≤ 30% predicted × PaCO ₂ ≥ 50 mm Hg*	0.2 (0.04–1.0)	0.05
In patients with FEV ₁ > 30% predicted, PaCO ₂ ≥ 50 mm Hg (n = 5) versus PaCO ₂ < 50 mm Hg (n = 62)	7.0 (1.5–32)	0.01
In patients with FEV ₁ ≤ 30% predicted, PaCO ₂ ≥ 50 mm Hg (n = 52) versus PaCO ₂ < 50 mm Hg (n = 111)	1.4 (0.4–5.0)	0.7
Listing year ≥ 1996	0.4 (0.2–0.7)	< 0.01
Nutritional intervention	2.3 (1.3–4.1)	< 0.01
Accredited CF center	0.5 (0.3–1.0)	0.06

Definition of abbreviations: CF = cystic fibrosis; CI = confidence interval.

Results of multivariate analyses are shown. Hazard ratios of FEV₁ ≤ 30% predicted and PaCO₂ ≥ 50 mm Hg alone are not reported because of the significant interaction between the two. The number of patients in each subgroup is listed. Of the 343 patients included in the study, 230 were entered into the final Cox proportional hazards model because of missing data.

* Interaction between FEV₁ and PaCO₂.

TABLE 5. COMPARISON OF MARKERS OF SEVERE DISEASE IN PATIENTS REFERRED FROM ACCREDITED CYSTIC FIBROSIS CENTERS AND PATIENTS NOT REFERRED FROM ACCREDITED CYSTIC FIBROSIS CENTERS

Variable	Referred from Accredited CF Center (n = 277)	Not Referred from Accredited CF Center (n = 57)	p Value
FEV ₁ % predicted, mean ± SD	27 ± 8	25 ± 8	0.02
PaCO ₂ (mm Hg), mean ± SD	46 ± 9	48 ± 11	0.3
Listing year ≥ 1996, %	30	37	0.3
Nutritional intervention, %	31	22	0.3

Definition of abbreviation: CF = cystic fibrosis.

A comparison of some markers of more severe disease in patients referred from an accredited CF center versus those patients not referred from an accredited CF center. Categorical variables are summarized as frequencies, and comparisons were performed by χ^2 or Fisher's exact test. Continuous variables are summarized as means ± SD and 95% confidence intervals. Comparisons were performed by two-tailed *t* test if the data were normally distributed or by Wilcoxon rank-sum test if the data were not normally distributed.

because of missing data and those included with complete data was a shorter waiting time (see Table E5).

DISCUSSION

Accurate prediction of the appropriate time for listing a patient with CF with end-stage lung disease is of paramount importance to minimize mortality on the transplant waiting list and to maximize the survival benefit after transplantation. An FEV₁ of less than 30% predicted has been the guidepost for referral for lung transplantation, based on the landmark study published by Kerem and coworkers (3). Despite this practice, mortality while on the waiting list remains high. Subsequent studies by Liou and coworkers (7) and Mayer-Hamblett and coworkers (9) may allow better prediction of mortality among patients with CF, using multiple variables. Although the model by Liou and coworkers seems useful it deals with transplantation as an on-demand treatment, and does not consider the issues of a waiting list. The model developed by Mayer-Hamblett and coworkers (9) is more targeted at the usual time of waiting for transplantation once listed, but unfortunately is no better at predicting 2-yr mortality compared with FEV₁ of less than 30% predicted alone. The goal of this study was to further identify who on the waiting list should be prioritized for transplantation.

By inclusion of data not collected by the Cystic Fibrosis Foundation Patient Registry, this multicenter study identifies some new clinical risk factors while confirming other clinical risk factors for waiting list mortality. Consistent with the findings of Kerem and coworkers (3), we observed that FEV₁ of less than 30% predicted was a highly significant risk factor for death among patients with CF awaiting lung transplantation, even though the multivariate results for FEV₁ of less than 30% predicted are misleading without the interaction terms. Also, to our knowledge prior studies such as that of Kerem and coworkers did not look extensively for interactions (the only potential interactions tested were between sex and percent predicted FEV₁ and between sex and age), so it is not known whether additional interactions were present. We observed that hypercapnia may be an independent risk factor for death among patients with CF with better lung function. Hypercapnia was one of the main factors identified by Kerem and coworkers and that criterion was included in the International Society for Heart and Lung Transplantation guidelines (15, 16). In patients with severely impaired lung function as indicated by an FEV₁ of less than 30% predicted, and thus advanced obstructive lung disease, hypercapnia seems not as important a marker for higher risk of death, and may be in fact caused by poor airflow obstruction. These

data suggest a hypothesis that hypercapnia in the face of better airflow may have a fundamentally different physiologic basis.

Referral from an accredited CF center to one of the transplant centers included in this study was associated with a lower risk of death in both the univariate and multivariate analyses (although not strictly significant in the latter). These observations may reflect earlier recognition or aggressive management of advanced disease in patients referred from accredited CF centers. There are 117 accredited specialized CF care centers in the United States and 38 in Canada that offer comprehensive care to patients with CF and their families. To our knowledge, no studies have shown that outcomes of patients cared for at these centers are better than those of patients cared for by physicians without specialized training in the care of patients with CF and without access to the team approach offered at the accredited CF centers. The previous models for predicting survival also may have excluded subjects who were not cared for in CF care centers, as data from these patients may not have been included in the U.S. Cystic Fibrosis Foundation Registry that served as the source data for these models (9, 13). We also assessed whether patients not referred from CF centers may have markers of more severe disease (Table 5). Patients who are referred from nonaccredited CF centers do have lower percent predicted FEV₁ values. This may reflect later recognition of more severe disease by physicians not as familiar with CF.

Our observation that nutritional intervention, defined as use of an appetite stimulant (i.e., megestrol acetate [Megace]), placement of a gastrojejunostomy tube, or use of parenteral nutrition, is associated with a higher risk of death while awaiting lung transplantation is, at first glance, somewhat surprising. Interestingly, use of these interventions does not correlate with body mass index (which was not found to be associated with a higher risk of death) in this study as well as in another (9). One hypothetical explanation of these data is that requirement for additional nutritional support is a marker of a more ill patient. Such a situation may occur if a patient has increased nutritional demand due to, for example, a higher level of ongoing inflammation from lung disease. However, we observed no differences in markers of more severe disease in patients who received a nutritional intervention and those who did not with respect to markers of more severe disease (see Table E6).

Year of listing was also an important factor for survival on the waiting list, with listing during or after 1996 reducing the risk of death. There are a number of potential explanations for this observation. It may be a function of improved survival over the last 10 yr in general for patients with CF. Alternatively, it may merely reflect physician practice to list patients for transplant

earlier (when they are presumably less ill) with recognition of increased waiting time for suitable donor organs. The study by Liou and coworkers (8) showed improved posttransplant survival in more recent years as well.

It was surprising that none of the microbiological data were predictive of survival (i.e., presence of *B. cepacia* or methicillin-resistant *Staphylococcus aureus*). This may have to do with listing practices at the U.S. centers (in more recent years no one with *B. cepacia* on sputum culture is listed for transplant) whereas in Toronto, where *B. cepacia* patients are eligible for transplant listing, the overall waiting list mortality is low (15%).

In the newly implemented United Network for Organ Sharing (UNOS; Richmond, VA) allocation model (http://www.unos.org/SharedContentDocuments/Calculation_Guide.pdf), candidates for lung transplantation are assigned priority for transplant based on a lung allocation score (17). The factors used to predict the risk of death on the lung transplant waiting list included FVC, pulmonary artery systolic pressure, O_2 required at rest, age, body mass index, insulin-dependent diabetes, functional status (New York Heart Association class), 6-min walk distance, and ventilator use. The actual Cox proportional hazard model used to determine these risk factors has not been published. The risk factors used in their model are not specific to CF but are used more broadly for all disease populations. Also, the UNOS allocation model is based on a retrospective evaluation of variables collected by UNOS for the purpose of listing patients and has not been prospectively validated. Surprisingly, FEV₁, traditionally the benchmark for prediction of death among patients with CF being considered for transplant, is not included in this allocation model. Hypoxemia, body mass index, presence of CF-related diabetes mellitus, and 6-min walk distance were all evaluated in this study and not found to be predictors of increased risk of death. Pulmonary artery systolic pressure in our study had too many missing values to lead to a meaningful conclusion, while functional status and ventilator use were not assessed in this study. Thus, we cannot compare our data with the UNOS model.

The main limitation of our study is missing data. Table E2 shows a comparison of patients with missing data and not included in the final multivariate model and those with complete data and included in the final model. Because of missing data we could not include some potential risk factors for death, such as the presence of pulmonary artery hypertension and reduced right ventricular ejection fraction. This study evaluated a selected population: those listed for transplantation. The rationale was to identify the factors that led to death before transplantation as a way to identify patients with CF who might require a higher priority for lung allocation. Differences in listing criteria for lung transplant between the centers were carefully considered. For instance, Toronto has a large population of patients with *B. cepacia* and lists and transplants patients with this organism, whereas most U.S. transplant centers, including the ones in this study, do not list patients with *B. cepacia*. Also, Toronto has an allocation system that is partially based on medical urgency and with generally shorter waiting times (median, < 6 mo). It is, therefore, possible that patients listed at Toronto have different risk factors for waiting list mortality compared with the other centers in the study. However, no differences were found among the listed patients at the four sites. We therefore repeated a Cox proportional hazards model including only patients from Toronto, and found that *B. cepacia* was not a significant risk factor for death in this population.

The results of our study do not agree with the results of a single-center study by Vizza and coworkers (14), in which a Cox proportional hazards model identified short 6-min walk distance, higher pulmonary artery systolic pressure, and diabetes mellitus as significant risk factors for death while waiting for lung trans-

plantation. These differences may have occurred for a few reasons. First, we had a significant number of missing echocardiograms and thus pulmonary hypertension could not be included in our model. Second, our definition of diabetes mellitus included patients who were taking insulin or oral hypoglycemic medications at any point in time before listing and not taking concomitant corticosteroids, so our classification of patients with CF-related diabetes mellitus is different. Third, in our study short 6-min walk distance showed no significant association with a higher risk of death (HR, 0.98; 95% CI, 0.96–1.0) in either our univariate or multivariate analyses. It is possible this may be related to differences in rehabilitation practice at the centers included in our study.

As mentioned above, the possibility of informative censoring exists, where the reason for removal from the list is not independent of the outcome (in this case, death). The results of our sensitivity analysis are reassuring in that informative censoring in the group of patients removed from the list for “other” reasons does not occur.

Another possible limitation is the inclusion of patients with heart–lung, lung–liver, or heart–lung–liver transplants. To assess the possible impact on our results from including such patients, the multivariate modeling was performed only with patients who had lung transplantation only (excluding heart–lung and heart–lung–liver transplants). There was no significant difference in the hazard ratios for any of the variables in the final model.

Under the previous time-based allocation system employed in the United States, patients waited up to 2 to 3 yr from listing to transplantation. The system has changed and now allocation of lungs is based on severity of disease (priority-based system) rather than waiting time. Thus, improved prediction models are critical in determining anticipated mortality among patients with CF being considered for lung transplantation. On the basis of these data, the presence of hypercapnia in the setting of better lung function and the requirement for nutritional interventions are additional factors that should be considered in developing future models to be used in allocating organs to the CF population.

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

References

- Charman SC, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. *J Heart Lung Transplant* 2002;21:226–232.
- Zuckerman JB, Kotloff RM. Lung transplantation for cystic fibrosis [review]. *Clin Chest Med* 1998;19:535–554, vii.
- Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187–1191.
- Arcasoy SM, Kotloff RM. Lung transplantation. *N Engl J Med* 1999;340:1081–1091.
- Geller DE, Kaplowitz H, Light MJ, Colin AA; Scientific Advisory Group, Investigators, and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Allergic bronchopulmonary aspergillosis in cystic fibrosis: reported prevalence, regional distribution, and patient characteristics. *Chest* 1999;116:639–646.
- Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet* 1998;351:24–27.
- Liou TG, Adler FR, Cahill BC, FitzSimmons SC, Huang D, Hibbs JR, Marshall BC. Survival effect of lung transplantation among patients with cystic fibrosis. *JAMA* 2001;286:2683–2689.
- Liou TG, Adler FR, Huang D. Use of lung transplantation survival models to refine patient selection in cystic fibrosis. *Am J Respir Crit Care Med* 2005;171:1053–1059.
- Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss CH, Aitken ML. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. *Am J Respir Crit Care Med* 2002;166:1550–1555.

10. Belkin RA, Singer LG, Henig NR. Height, *Aspergillus* and MRSA: potential predictors of death in CF patients on the lung transplant waiting list [abstract]. *Pediatr Pulmonol* 2001;32:317.
11. Belkin RAB, Singer LG, Rubenstein RC, Xie SX, Kotloff RM, Lipson DA, Henig NR. Elevated PaCO₂ as a risk factor for death in CF patients awaiting lung transplantation [abstract]. *Pediatr Pulmonol* 2004; 38(Suppl. 27):317.
12. Collett D. Informative censoring. In: Collett D, editor. *Modelling survival data in medical research*. London: Chapman & Hall; 2003. p. 319.
13. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol* 2001;153:345–352.
14. Vizza CD, Yusef RD, Lynch JP, Fedele F, Alexander Patterson G, Trulock EP. Outcome of patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med* 2000;162:819–825.
15. Yankaskas JR, Mallory GB Jr. Lung transplantation in cystic fibrosis: consensus conference statement. *Chest* 1998;113:217–226.
16. Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR; International Society for Heart and Lung Transplantation, American Thoracic Society, American Society of Transplant Physicians, European Respiratory Society. International guidelines for the selection of lung transplant candidates. *J Heart Lung Transplant* 1998;17: 703–709.
17. United Network for Organ Sharing. Organ distribution. Richmond, VA: United Network for Organ Sharing; 2004. Policies 3.5–3.9. Available from: <http://www.unos.org/policiesandbylaws/policies.asp?resources=true> (accessed January 6, 2006).
18. Kotloff RM, Zuckerman JB. Lung transplantation for cystic fibrosis: special considerations. *Chest* 1996;109:787–798.
19. Milla CE, Warwick WJ. Risk of death in cystic fibrosis patients with severely compromised lung function. *Chest* 1998;113:1230–1234.
20. Doershuk CF, Stern RC. Timing of referral for lung transplantation for cystic fibrosis: overemphasis on FEV₁ may adversely affect overall survival. *Chest* 1999;115:782–787.
21. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117.
22. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant* 1997;16: 313–319.
23. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med* 1992;327:1785–1788.
24. Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, Hodson ME, Anker SD, Henein MY. Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax* 2001;56:746–750.
25. McAllister TA, Mocan H, Murphy AV, Beattie TJ. Antibiotic susceptibility of staphylococci from CAPD peritonitis in children. *J Antimicrob Chemother* 1987;19:95–100.
26. Egan TM, Bennett LE, Garrity ER, Grover FL, Ring WS, Robbins RC, Trulock E, Wood DE. Predictors of death on the UNOS lung transplant waiting list: results of a multivariate analysis. *J Heart Lung Transplant* 2001;20:242.
27. Hayllar KM, Williams SG, Wise AE, Pouria S, Lombard M, Hodson ME, Westaby D. A prognostic model for the prediction of survival in cystic fibrosis. *Thorax* 1997;52:313–317.
28. Augarten A, Akons H, Aviram M, Bentur L, Blau H, Picard E, Rivlin J, Miller MS, Katznelson D, Szeinberg A, et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. *Pediatr Transplant* 2001;5:339–342.
29. Rosenecker J, Hofler R, Steinkamp G, Eichler I, Smaczny C, Ballmann M, Posselt HG, Bargon J, von der Hardt H. Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. *Eur J Med Res* 2001;6:345–350.
30. Ledson MJ, Gallagher MJ, Jackson M, Hart CA, Walshaw MJ. Outcome of *Burkholderia cepacia* colonisation in an adult cystic fibrosis centre. *Thorax* 2002;57:142–145.
31. Frangolias DD, Mahenthiralingam E, Rae S, Raboud JM, Davidson AG, Wittmann R, Wilcox PG. *Burkholderia cepacia* in cystic fibrosis: variable disease course. *Am J Respir Crit Care Med* 1999;160:1572–1577.
32. Davis PB. Clinical pathophysiology and manifestations of lung disease. In: Yankaskas JR, Knowles MR, editors. *Cystic fibrosis in adults*. Philadelphia, PA: Lippincott-Raven; 1999. pp. 45–67.
33. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: *Pseudomonas aeruginosa* infection. *J Clin Epidemiol* 1995;48:1041–1049.
34. Goss CH, Otto K, Aitken ML, Rubenfeld GD. Detecting *Stenotrophomonas maltophilia* does not reduce survival of patients with cystic fibrosis. *Am J Respir Crit Care Med* 2002;166:356–361.
35. Schaedel C, de Monestrol I, Hjelte L, Johannesson M, Kornfalt R, Lindblad A, Strandvik B, Wahlgren L, Holmberg L. Predictors of deterioration of lung function in cystic fibrosis. *Pediatr Pulmonol* 2002;33:483–491.
36. Huang NN, Schidlow DV, Szatrowski TH, Palmer J, Laraya-Cuasay LR, Yeung W, Hardy K, Quitell L, Fiel S. Clinical features, survival rate, and prognostic factors in young adults with cystic fibrosis. *Am J Med* 1987;82:871–879.
37. Rosenfeld M, Davis R, FitzSimmons S, Pepe M, Ramsey B. Gender gap in cystic fibrosis mortality. *Am J Epidemiol* 1997;145:794–803.
38. Lewis P. CF epidemiology: population perspective and impact [Symposium Session Summaries]. Annual North American Cystic Fibrosis Conference, 2000.
39. Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr* 1982;100:857–862.
40. Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med* 2001;163:1331–1337.
41. Fraser KL, Tullis DE, Sasson Z, Hyland RH, Thornley KS, Hanly PJ. Pulmonary hypertension and cardiac function in adult cystic fibrosis: role of hypoxemia. *Chest* 1999;115:1321–1328.
42. Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;41:583–591.
43. Walters S, Britton J, Hodson ME. Hospital care for adults with cystic fibrosis: an overview and comparison between special cystic fibrosis clinics and general clinics using a patient questionnaire. *Thorax* 1994;49:300–306.
44. Beker LT, Russek-Cohen E, Fink RJ. Stature as a prognostic factor in cystic fibrosis survival. *J Am Diet Assoc* 2001;101:438–442.