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Predictive 5-Year Survivorship Model of Cystic Fibrosis

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Abstract

The objective of this study was to create a 5-year survivorship model to identify key clinical features of cystic fibrosis. Such a model could help researchers and clinicians to evaluate therapies, improve the design of prospective studies, monitor practice patterns, counsel individual patients, and determine the best candidates for lung transplantation. The authors used information from the Cystic Fibrosis Foundation Patient Registry (CFFPR), which has collected longitudinal data on approximately 90% of cystic fibrosis patients diagnosed in the United States since 1986. They developed multivariate logistic regression models by using data on 5,820 patients randomly selected from 11,630 in the CFFPR in 1993. Models were tested for goodness of fit and were validated for the remaining 5,810 patients for 1993. The validated 5-year survivorship model included age, forced expiratory volume in 1 second as a percentage of predicted normal, gender, weight-for-age *z* score, pancreatic sufficiency, diabetes mellitus, *Staphylococcus aureus* infection, *Burkholderia cepacia* infection, and annual number of acute pulmonary exacerbations. The model provides insights into the complex nature of cystic fibrosis and supplies a rigorous tool for clinical practice and research.

Keywords

cystic fibrosis; logistic models; models, theoretical; multivariate analysis; proportional hazards models; survival analysis

Cystic fibrosis is an autosomal recessive, multisystem disease leading to significant morbidity and early death. Since the disease was described in 1938 (1,2), treatments for its pancreatic and pulmonary manifestations have improved median survival in the United States from less than 6 months to about 32 years in 1998 (3). Severe pulmonary disease is the primary cause of cystic-fibrosis-related mortality, constituting 76.4 percent of such deaths in 1998 (3). Chronic inflammation and infection of the airways characterize cystic-fibrosis-related

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pulmonary disease. *Staphylococcus aureus* and *Haemophilus influenzae* infections, commonly found early in the course of the disease, are often supplanted by *Pseudomonas aeruginosa* infection as the disease progresses (3). Infection with *Burkholderia cepacia* is associated with accelerated pulmonary disease (4,5). Malnutrition, in part due to pancreatic insufficiency, was the major feature of the disease according to early reports, and it continues to be a substantial problem (1-3). With improved survival, additional manifestations such as diabetes mellitus have been recognized (6,7).

Many studies have considered the survival effect of a variety of clinical and physiologic features of cystic fibrosis such as forced expiratory volume in 1 second as a percentage of predicted normal (FEV₁%), gender, age, pregnancy, or particular therapies (4-26). We developed a single survivorship model that integrated many characteristics of cystic fibrosis and quantified the relative contribution of each.

The current most commonly used survival model of cystic fibrosis was developed in 1992 and is based on FEV₁% alone or on age, gender, and FEV₁% (15). Clinicians often use this model to select patients to refer for lung transplantation. The model is relatively simple to use for estimating cystic fibrosis survival, but it has not been validated and does not incorporate clinical features of cystic fibrosis now recognized as important predictors of mortality (4-7,9,12,14, 15,18,22-26). We examined the validity of the previous simple models and compared their accuracy with that of our new model.

MATERIALS AND METHODS

Cystic Fibrosis Foundation Patient Registry data

We used information from the Cystic Fibrosis Foundation Patient Registry (CFFPR; 1986–1997), which contains longitudinal data on 27,849 patients at 115 cystic fibrosis care centers, representing approximately 90 percent of all cystic fibrosis patients in the United States (3). Reports for each patient, containing a wide range of clinical data, are submitted annually to the CFFPR. CFFPR methods are described elsewhere (27). In accordance with the Cystic Fibrosis Foundation data access policy, we applied for and received access to a 1986–1996 longitudinal database, which was later updated with the complete 1997 database and 1998 mortality data.

Patient selection

Cystic fibrosis patients who were alive on January 1, 1993, and for whom follow-up data were available through December 31, 1997, were included in our study. Data on patients with odd identification numbers were used to develop survival models; those from patients with even identification numbers were used for the validation set. Patients were excluded from the study if they had undergone solid organ transplantation of any type or lacked pulmonary function testing information, a key clinical parameter of cystic fibrosis.

Data handling and statistical modeling tools

We used S-PLUS software (version 3.4, release 1 for Sun SPARC, SunOS 5.3: 1996 (Mathsoft, Inc., Cambridge, Massachusetts)) to perform statistical analyses (28). S-PLUS is hosted by the Sun UltraSPARC 2170/2200 cluster (Sun Microsystems, Inc., Palo Alto, California) of the University of Utah Department of Mathematics.

Prediction equations for FEV₁% and forced vital capacity

Raw spirometry values, forced expiratory volume in 1 second (FEV₁), and forced vital capacity were normalized to FEV₁% and percentage of predicted forced vital capacity. We used regression formulae from the Third National Health and Nutrition Examination Survey (29).

Calculation of weight-for-age z scores

Weight-for-age z scores were calculated by using National Center for Health Statistics (Hyattsville, Maryland) weight-for-age growth tables for males and females. Gender and age were used to determine the appropriate median weight for age for each patient in the 1993 CFFPR. Because the distribution of weight for age was not normal, the z score was calculated by using the approximation method of Lai et al. and Dibley et al. (13,30).

Rate of decline in FEV₁%

To estimate the slopes of the rates of decline in FEV₁%, linear and mixed-effects linear models were generated for each patient who was alive on January 1, 1993, and for whom there was more than one measurement (23). We used all 1986–1992 pulmonary function test data (two to five measurements).

Statistical models for survival analysis

To predict 5-year survivorship for cystic fibrosis patients, we used a binary variable, alive or deceased within a 5-year time period, as the outcome variable. All potential explanatory covariates were incorporated into a logistic regression model. Forward stepwise procedures and log-likelihood ratio tests were used to select variables for the model. Parallel analysis with Cox proportional hazards regression was performed.

Selection of variables for survival analysis

Data on 317 variables were collected by the CFFPR in 1993. We excluded variables that related directly to ongoing research protocols, for which data were sparse, or that recorded clinically uncommon or rare characteristics (table 1). However, our analysis included infection with *B. cepacia* (2.8 percent of the population affected) because of prior reports of its effects on mortality (4,5,24,31) and infection with *Stenotrophomonas maltophilia* (1.7 percent of the population affected) because of its increasing prevalence (3). The pertinent variables, including weight-for-age z scores and FEV₁% slopes, were tested by using univariate logistic regression for an effect on 5-year survivorship. Potentially interacting variables were identified by using stratified regression analysis (31).

Modeling of 5-year survivorship

Variables that demonstrated an association with 5-year survivorship at an absolute *t*-test value of more than two were considered for multivariate logistic regression analysis. Twenty-one variables were included in the final multivariate analysis. The model was subjected to stepwise analysis of variance to derive an intermediate model (32). By using these variables, along with patient age, we constructed models that included all possible interactions and excluded statistically nonsignificant terms by using stepwise analysis of variance prior to validation. All possible interaction terms were considered, including those identified by stratified analysis, and terms that lacked statistical significance were excluded (31). For comparison, we developed simpler models by using only the covariates identified by Kerem et al. (15).

Assessing models for goodness of fit and validation

Models developed by using information from odd-numbered patients were validated by using 1993 patients who had even identification numbers. We used the Hosmer-Lemeshow test to eliminate models that fit poorly; the remaining models were compared with standard χ^2 likelihood ratio statistics (31).

RESULTS

The CFFPR contains 1993 data on 19,156 patients. Of these, we excluded 730 patients because they were recipients of solid organ transplantation and 5,686 because they lacked FEV₁% measurements. Of these latter patients, 4,190 were excluded because they were younger than age 5.5 years, a group for whom FEV₁% cannot be measured using standard techniques, or were members of ethnic or racial groups for whom FEV₁% standards do not exist (54 patients). Microbiology, pancreatic sufficiency, diabetes, or acute exacerbation information was missing for 1,056 patients. Of the 12,686 patients remaining after exclusions, we included information on 11,630 (92 percent) of them in developing and validating the model.

We developed the survivorship model by using data on 5,820 patients with odd identification numbers, and we validated the model externally by using data on 5,810 patients with even identification numbers. Baseline characteristics of the development and validation patient populations were similar (table 2). There were 1,419 deaths spread evenly between the development and validation groups.

Univariate logistic regression analyses identified 21 variables with a significant predictive value for 5-year survivorship. Clinically relevant variables that did not add predictive information to the model were eliminated (table 1). In our investigation of interactions among the remaining variables using stratified analysis, we found five potential interaction terms for multivariate analysis.

The best multiple logistic regression model included nine variables with one interaction (table 3). Higher FEV₁%, higher weight-for-age *z* score, pancreatic sufficiency, and *S. aureus* infection predicted increased survivorship. Increasing age, female gender, diabetes mellitus, *B. cepacia* infection, and a higher number of acute pulmonary exacerbations predicted decreased survivorship. After stepwise analysis, only one of the five potential interaction terms (*B. cepacia* infection $\times$ number of acute pulmonary exacerbations) was statistically significant. The single interaction term showed that each acute exacerbation had a markedly reduced, although persistent, negative effect when *B. cepacia* infection was present.

We normalized the effect of each variable in terms of the equivalent loss or gain in FEV₁% to show the relative effect of each variable in a clinically meaningful way (table 3). For example, *B. cepacia* infection was a major negative predictor of survival, as expected on the basis of previous reports (4,5,24). The survival effect was the same as a 48 percent drop in FEV₁% in a patient without *B. cepacia* infection. Four acute exacerbations in a single year had the same negative effect on survival as infection with *B. cepacia*.

Parallel analysis in which we used Cox proportional hazards regression generated a model with identical covariates and similar coefficients (table 4). Because the logistic regression model is potentially simpler to use and interpret in a clinical setting, we focused our analysis on the results of logistic regression modeling (33,34).

Simpler models using age, gender, and FEV₁% or FEV₁% alone, the covariates identified by Kerem et al. (15), produced much lower log-likelihood scores than the new model (table 5) did. The simpler models failed the Hosmer-Lemeshow test for goodness of fit on the validation set of data (31) and failed to identify the patients with the lowest 5-year conditional probability of survival (figure 1).

DISCUSSION

We developed and validated a 5-year survivorship model of cystic fibrosis that identified eight characteristics of the disease, in addition to FEV₁%, that together accurately predict survival.

The model provides insight into the relative effect of each characteristic and underscores the importance of considering multiple clinical factors when assessing the likelihood of 5-year survival. It is generalizable to cystic fibrosis patients who have undergone pulmonary function testing. In addition, it may provide a method of estimating the impact of therapies that have not been studied in a randomized and controlled fashion. Five-year survivorship of cystic fibrosis patients may be changing because of changes in practice patterns, and our model provides a way to gauge this survival effect. For individual patients, the model enables prognosis to be estimated.

Previous modeling of cystic fibrosis survivorship concentrated on FEV₁% as the main predictor of 2-year survival (15). However, this simple model and models based on FEV₁%, gender, and age do not pass validation tests and fail to identify those patients at the highest risk of death, because they ignore other critical covariates that influence mortality (4-7,9,12,14,15,18, 22-26).

The new, validated model that we developed identified the additional covariates needed for a predictive survivorship model of cystic fibrosis. Some of these covariates were not surprising (14,15,25). Nutritional status, as indicated by weight-for-age *z* score, substantially affects long-term outcome. Our model confirms that female gender is associated with a worse long-term outcome (14). The underlying reason remains unexplained, but we found that pregnancy was not the cause (9,11,35). *S. aureus* infection was associated with improved 5-year survival. We also found the survival effect independent of age, but the specific underlying cause is unknown. Each acute pulmonary exacerbation within the year had an unexpectedly large, negative impact on 5-year survival equal to subtracting 12 percent from the measured FEV₁% value.

Infection with *B. cepacia* had the largest effect of any model variable for predicting 5-year survivorship. Cystic fibrosis patients infected with *B. cepacia* tend to have the poorest predicted 5-year survival and often are deemed ineligible for lung transplantation because of reports of poorer post-transplantation outcomes (22,36).

As median survival continues to increase, diabetes mellitus becomes a greater clinical concern. This disease is found in a minority of children with cystic fibrosis, but its prevalence rises to approximately 50 percent by age 30 years and to 70 percent by age 40 years (10). For cystic fibrosis patients, diabetes is associated with reduced pulmonary function (26), increased effort to breathe, and increased energy expenditure (37). Untreated diabetes may predispose patients to additional infections (26). The survival effect of diabetes mellitus in cystic fibrosis patients has been controversial (38), but our model demonstrated a large negative effect of diabetes on 5-year survival, independent of other covariates.

Predictive models of disease, similar to ours, are used in multiple ways as research and clinical tools. One example that continues to be enormously useful more than 15 years after it was developed is the multivariate logistic regression model of the acute physiology and chronic health evaluation (APACHE) II score (39). These scores are used to correct for differences in expected mortality between control and experimental groups (40), to weight cost analyses of critical illness (41), to assess the impact of changes in the health delivery system (42), and to estimate individual patient prognosis (43).

To facilitate practical and efficient use of the new model in clinical settings, we developed two worksheets that enable the weight-for-age *z* score and the conditional probability of 5-year survival to be calculated rapidly. These worksheets (available on the *Journal* website at www.jhsph.edu/Publications/JEPI/liou.htm) reduce the chance of arithmetic errors during calculation. Because they eliminate the need to calculate the exponential term inherent in a logistic regression model, these worksheets can be used when the only tools available are paper and pencil.

Our survivorship model of cystic fibrosis may have similar widespread applications. It may help to improve study design by providing a way to select patients with equivalent survival predictions for control and experimental arms of prospective studies. The model also may be useful in evaluating whether survival has changed in response to changing practice patterns. As a research tool, it has the potential for use in investigating the effect of therapies that have not been evaluated randomly, such as lung transplantation. Our analyses suggest that many patients who undergo transplantation have no survival benefit from the procedure. (T. G. Liou et al., University of Utah, unpublished manuscript). Our model will be an objective aid to individual cystic fibrosis patients and their physicians contemplating difficult therapeutic choices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Anderson DH. Cystic fibrosis of the pancreas and its relation to celiac disease. A clinical and pathologic study. *Am J Dis Child* 1938;56:344–95.
2. Farber S. Some organic digestive disturbances in early life. *J Michigan Med Sci* 1945;44:587–94.
3. Cystic Fibrosis Foundation Patient Registry annual data report, 1998. Bethesda, MD; Cystic Fibrosis Foundation: 1999.
4. Isles A, Maclusky I, Corey M, et al. *Pseudomonas cepacia* infection in cystic fibrosis: an emerging problem. *J Pediatr* 1984;104:206–10. [PubMed: 6420530]
5. Thomassen MJ, Demko CA, Klinger JD, et al. *Pseudomonas cepacia* colonization among patients with cystic fibrosis. *Am Rev Respir Dis* 1985;131:791–6. [PubMed: 3923882]
6. Rodman HM, Doershuk CF, Roland JM. The interaction of 2 diseases: diabetes mellitus and cystic fibrosis. *Medicine* 1986;65:389–97. [PubMed: 3097455]
7. Reisman J, Corey M, Canny G, et al. Diabetes mellitus in patients with cystic fibrosis: effect on survival. *Pediatrics* 1990;86:374–7. [PubMed: 2388786]
8. Bedrossian CWM, Greenberg SP, Singer DB, et al. The lung in cystic fibrosis. A quantitative study including prevalence of pathologic findings among different age groups. *Hum Pathol* 1976;7:195–204. [PubMed: 1262016]
9. Cohen LF, di Sant' Agnese PA, Friedlander J. Cystic fibrosis and pregnancy: a national survey. *Lancet* 1980;2:842–4. [PubMed: 6107509]
10. Lanng S, Thorsteinsson B, Lund-Andersen C, et al. Diabetes mellitus in Danish cystic fibrosis patients: prevalence and late diabetic complications. *Acta Paediatr* 1994;83:72–7. [PubMed: 8193478]
11. FitzSimmons SC, Fitzpatrick S, Thompson B, et al. A longitudinal study of the effects of pregnancy on 325 women with cystic fibrosis. *Pediatr Pulmonol* 1996;(suppl 13):99–101.
12. Davis PB, Byard PJ, Konstan MW. Identifying treatments that halt progression of pulmonary disease in cystic fibrosis. *Pediatr Res* 1997;41:161–5. [PubMed: 9029632]
13. Lai HC, Kosorok MR, Sondel SA, et al. Growth status in children with cystic fibrosis based on the National Cystic Fibrosis Patient Registry data: evaluation of various criteria used to identify malnutrition. *J Pediatr* 1998;132:478–85. [PubMed: 9544905]

14. Rosenfeld M, Davis R, FitzSimmons S, et al. Gender gap in cystic fibrosis mortality. *Am J Epidemiol* 1997;145:794–803. [PubMed: 9143209]
15. Kerem E, Reisman J, Corey J, et al. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;326:1187–91. [PubMed: 1285737]
16. Fuchs HJ, Borowitz DS, Christiansen DH, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med* 1994;331:637–42. [PubMed: 7503821]
17. Eigen H, Rosenstein BJ, FitzSimmons S, et al. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group. *J Pediatr* 1995;126:515–23. [PubMed: 7699528]
18. Frederiksen B, Lanng S, Koch C, et al. Improved survival in the Danish center-treated cystic fibrosis patients: results of aggressive treatment. *Pediatr Pulmonol* 1996;21:153–8. [PubMed: 8860069]
19. Mortensen J, Falk M, Groth S, et al. The effects of postural drainage and positive expiratory pressure physiotherapy on tra-cheobronchial clearance in cystic fibrosis. *Chest* 1991;100:1350–7. [PubMed: 1935294]
20. Desmond KJ, Schwenk WF, Thomas E, et al. Immediate and long-term effects of chest physiotherapy in patients with cystic fibrosis. *J Pediatr* 1983;103:538–42. [PubMed: 6620013]
21. Massard G, Shennib H, Metras D, et al. Double-lung transplantation in mechanically ventilated patients with cystic fibrosis. *Ann Thorac Surg* 1993;55:1087–92. [PubMed: 8494415]
22. Aris RM, Gilligan PH, Neuringer IP, et al. The effects of pan-resistant bacteria in cystic fibrosis patients on lung transplant outcome. *Am J Respir Crit Care Med* 1997;155:1699–704. [PubMed: 9154879]
23. Corey M, Edwards L, Levison H, et al. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr* 1997;131:809–14. [PubMed: 9427882]
24. Whiteford ML, Wilkinson JD, McColl JH, et al. Outcome of *Burkholderia (Pseudomonas) cepacia* colonisation in children with cystic fibrosis following a hospital outbreak. *Thorax* 1995;50:1194–8. [PubMed: 8553277]
25. Chase HP, Long MA, Lavin MH. Medical progress: cystic fibrosis and malnutrition. *J Pediatr* 1979;95:337–47. [PubMed: 381615]
26. Lanng S, Thorsteinsson B, Nerup J, et al. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr Scand* 1994;83:849–53.
27. FitzSimmons SC. The changing epidemiology of cystic fibrosis. *J Pediatr* 1993;122:1–9. [PubMed: 8419592]
28. Becker, RA.; Chambers, JM.; Wilks, AR. The new S language. Rev ed.. Boca Raton, FL: CRC Press; 1988.
29. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;159:179–87. [PubMed: 9872837]
30. Dibley MJ, Goldsby JB, Staehling NW, et al. Development of normalized curves for the international growth reference: historical and technical considerations. *Am J Clin Nutr* 1987;46:736–48. [PubMed: 3314468]
31. Hosmer, DW.; Lemeshow, S. Applied logistic regression. New York, NY: John Wiley & Sons, Inc; 1989. p. 63-8.p. 115-18.p. 140-5.
32. Venables, WN.; Ripley, BD. Modern applied statistics with S-Plus. 2. New York, NY: Springer-Verlag; 1997.
33. Green MS, Symons MJ. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. *J Chronic Dis* 1983;36:715–24. [PubMed: 6630407]
34. Abbott RD. Logistic regression in survival analysis. *Am J Epidemiol* 1985;121:465–71. [PubMed: 4014135]
35. Jankelson D, Robinson M, Parsons S, et al. Cystic fibrosis and pregnancy. *Aust N Z J Obstet Gynaecol* 1998;38:180–4. [PubMed: 9653856]
36. Snell GI, de Hoyos A, Krajden M, et al. *Pseudomonas cepacia* in lung transplant recipients with cystic fibrosis. *Chest* 1993;103:466–71. [PubMed: 7679347]

37. Ward SA, Tomezsko JL, Holschaw DS, et al. Energy expenditure and substrate utilization in adults with cystic fibrosis and diabetes mellitus. *Am J Clin Nutr* 1999;69:913–19. [PubMed: 10232630]
38. Finkelstein SM, Wielinski CL, Elliott GR, et al. Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 1988;112:373–7. [PubMed: 3346774]
39. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13:818–29. [PubMed: 3928249]
40. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995;152:1835–46. [PubMed: 8520744]
41. Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care: methods and human and capital inputs. *Crit Care Med* 1996;24:1168–72. [PubMed: 8674330]
42. Carson S, Stocking C, Podsadecki T, et al. Effects of organizational change in the medical intensive care unit of a teaching hospital. *JAMA* 1996;276:322–8. [PubMed: 8656546]
43. Pittet D, Thievent B, Wenzel RP, et al. Bedside prediction of mortality from bacteremic sepsis. *Am J Respir Crit Care Med* 1996;153:684–93. [PubMed: 8564118]
44. Friedman, JH. A variable span smoother. Stanford, CA: Department of Statistics, Stanford University; 1984. Technical report LCS5
45. Mathsoft. S-Plus 2000 guide to statistics. 1. Seattle, WA: MathSoft, Data Analysis Products Division; 2000.

Abbreviations

CFFPR

Cystic Fibrosis Foundation Patient Registry

FEV₁

forced expiratory volume in 1 second

FEV₁%

forced expiratory volume in 1 second as a percentage of predicted normal

FIGURE 1.

Graphic representation of application of the Hosmer-Lemeshow test (31) to validate a 5-year logistic regression model of cystic fibrosis, United States, 1993. The difference in predictive ability between the two models shown was statistically significant ($p < 0.0001$). A. Comparison of actual and predicted 5-year survival for patients in the validation set (table 2). The percentage of patients predicted to survive was calculated directly by using the new model (table 3). A “perfect” fit of predictions to actual outcomes would produce the dashed line shown, with slope 1 and intercept 0. The smoothed-curve fit of our model (44,45) closely approximated this ideal. B. Comparison of actual and predicted percentage of survival using a 5-year logistic regression model based on age, gender, and forced expiratory volume in 1 second as a percentage of

predicted normal (15). This model did not identify any patients with the lowest chances of survival, so the curve abruptly ends when the percentage predicted to survive drops below approximately 30%. The model was inaccurate when the percentage predicted to survive 5 years within the group was less than 60%, as shown by the large deviation of the model curve from ideal (dashed line).

TABLE 1

Covariates excluded from the survivorship model used to identify key clinical features of cystic fibrosis, Cystic Fibrosis Foundation Patient Registry, United States, 1993

Not statistically significant [*]	Insufficient data [†]
Height (raw value and percentile)	Other <i>Pseudomonas</i>
$\Delta F508^{\ddagger}$	Mucoid <i>Pseudomonas</i>
<i>Pseudomonas aeruginosa</i>	<i>Alcaligenes xylosoxidans</i>
<i>Stenotrophomonas maltophilia</i>	<i>Aspergillus fumigatus</i>
<i>Haemophilus influenzae</i>	Methicillin-resistant <i>Staphylococcus aureus</i>
Pregnancy	Birth complications
Sweat chloride test value at diagnosis	Employment
Education	Insurance status
FEV ₁ % [§] slope by linear regression	Marital status
FEV ₁ % slope by mixed-effects modeling	

* $p > 0.05$.

[†] Information on some of these covariates was available from less than 5 percent of the population. If information was available, covariates were excluded if less than 5 percent of the cystic fibrosis population was affected; most of these excluded variables affected fewer than 10 patients.

[‡] A specific test of whether the presence of no, one, or two $\Delta F508$ alleles had a survival effect.

[§] FEV₁%, forced expiratory volume in 1 second as a percentage of predicted normal.

TABLE 2

Characteristics of model development and validation patients, Cystic Fibrosis Foundation Patient Registry, United States, 1993

Characteristic	Patients	
	Development	Validation
No. of patients	5,820	5,810
Mean age (years) (SD *)	17.58 (9.25)	17.64 (9.36)
Median age (years) (range)	15.52 (5.5–62.44)	15.32 (5.5–71.05)
Mean FEV ₁ %* (SD)	67.7 (29.2)	67.4 (29.3)
Female gender (%)	2,729 (47)	2,692 (46)
Mean weight-for-age z score (SD)	−0.85 (1.07)	−0.84 (1.05)
Pancreatic sufficiency (%)	311 (5.3)	308 (5.3)
With diabetes mellitus (%)	357 (6.1)	367 (6.3)
With <i>Staphylococcus aureus</i> (%)	1,780 (30.6)	1,802 (31.0)
With <i>Burkholderia cepacia</i> (%)	186 (3.2)	231 (4.0)
Mean no. of acute exacerbations (range)	1.1 (0–18)	1.2 (0–19)

* SD, standard deviation; FEV₁%, forced expiratory volume in 1 second as a percentage of predicted normal.

TABLE 3

Validated 5-year logistic regression survivorship model for cystic fibrosis,* Cystic Fibrosis Foundation Patient Registry, United States, 1993

Covariate [†] (x ₀₋₁₀)	Coefficient		Odds ratio	FEV ₁ % [‡] equivalence [§]
	β ₀₋₁₀	SE [‡]		
(Intercept)	1.93	0.27	6.88	50
Age (per year)	-0.028	0.0060	0.97	-0.7
Gender (male = 0, female = 1)	-0.23	0.10	0.79	-6
FEV ₁ % (per %) [¶]	0.038	0.0028	1.04	1
Weight-for-age z score	0.40	0.053	1.50	10
Pancreatic sufficiency (0 or 1) [¶]	0.45	0.31	1.58	12
Diabetes mellitus (0 or 1) [¶]	-0.49	0.15	0.61	-13
<i>Staphylococcus aureus</i> (0 or 1) [¶]	0.21	0.12	1.24	6
<i>Burkholderia cepacia</i> (0 or 1) [¶]	-1.82	0.30	0.16	-48
No. of acute exacerbations (0-5) [¶]	-0.46	0.031	0.63	-12
No. of acute exacerbations × <i>B. cepacia</i>	0.40	0.12	1.49	10

* Hosmer-Lemeshow *p* value = 0.54; no significant difference between predicted and actual survivorship of the validation group of patients (31).

[†] The conditional probability of 5-year survival by logistic regression analysis is $\pi = \exp(x)/(1 + \exp(x))$, where the logit *x* is:

$$x = \beta_0 + \beta_1 \times \text{Age} + \beta_2 \times \text{Gender} + \beta_3 \times \text{FEV}_1 \% + \beta_4 \times \text{z score} +$$

$$\beta_5 \times \text{PancreaticSufficiency} + \beta_6 \times \text{diabetes} +$$

$$\beta_7 \times \text{S. aureus} + \beta_8 \times \text{B. cepacia} + \beta_9 \times \text{Exacerbations} +$$

$$\beta_{10} \times (\text{Exacerbations} \times \text{B. cepacia})$$

For a covariate *x_i* and its coefficient β_{*i*}, the term exp(β_{*i*} × *x_i*) gives the incremental odds ratio for that covariate. Coefficients for each covariate are unitless unless specified.

[‡] FEV₁%, forced expiratory volume in 1 second as a percentage of predicted normal; SE, standard error.

[§] FEV₁% equivalence was calculated as β_{*i*}/βFEV₁%. Except for age, values are rounded to the nearest integer. For age, weight-for-age z score, and acute exacerbations, the equivalences are per year, per z score point, and per exacerbation, respectively.

[¶] FEV₁% was calculated by using raw FEV₁ results reported to the Cystic Fibrosis Foundation Patient Registry in 1993 for patients who did not undergo transplantation. Pancreatic sufficiency was defined as not using pancreatic enzyme supplementation. Diabetes was defined as the need for insulin during or before 1993. Values for *S. aureus* and *B. cepacia* infections are from reported microbiologic data. Number of acute exacerbations is the number of episodes of acute pulmonary exacerbations of cystic fibrosis requiring treatment in 1993, up to a maximum of five.

TABLE 4

Cox proportional hazards model of cystic fibrosis developed from Cystic Fibrosis Foundation Patient Registry data, United States, 1993

Covariate* (x_{0-10})	Coefficient		Odds ratio
	β_{0-10}	SE [†]	
Age (per year)	0.011	0.0049	1.011
Gender (male = 0, female = 1)	0.15	0.074	1.16
FEV ₁ % [†] (per %)	-0.042	0.0025	0.96
Weight-for-age z score	-0.28	0.041	0.75
Pancreatic sufficiency (0 or 1)	-0.14	0.23	0.87
Diabetes mellitus (0 or 1)	0.44	0.098	1.55
<i>Staphylococcus aureus</i> (0 or 1)	-0.25	0.09	0.78
<i>Burkholderia cepacia</i> (0 or 1)	1.41	0.19	4.12
No. of acute exacerbations (0–5)	0.35	0.024	1.42
No. of acute exacerbations $\times$ <i>B. cepacia</i>	-0.28	0.06	0.75

* Covariates developed for this model are identical to those for the logistic regression model (table 3). Values of the covariates are similar but opposite in sign because the Cox model predicts mortality, whereas the logistic regression model (table 3) predicts survival. Data used to develop this model are identical to those for the development data set for the logistic regression model. Unless specified, coefficients for each covariate are unitless.

[†] SE, standard error; FEV₁%, forced expiratory volume in 1 second as a percentage of predicted normal.

TABLE 5

Statistical tests of 5-year logistic regression survivorship models of cystic fibrosis developed from Cystic Fibrosis Foundation Patient Registry data, United States, 1993

	Test of validation	
	χ^2 likelihood ratio	Hosmer-Lemeshow p value [*]
Best model [†]	-1,460	0.54
Best model with no interaction terms [‡]	-1,462	0.99
Model with interaction terms [§]	-1,472	0.79
Age, gender, FEV ₁ % [¶]	-1,636	0.007
FEV ₁ % only [#]	-1,635	0.014

^{*} The Hosmer-Lemeshow p value calculation (31) measures how well the predictions of a model fit actual outcomes. A p value of >0.05 shows that model predictions cannot be distinguished from actual outcomes and demonstrates successful external validation of a logistic regression model. These values are calculated independently of the χ^2 likelihood ratio.

[†] 5-year conditional probability of survival as a function of the coefficients listed in table 3.

[‡] 5-year conditional probability of survival as a function of age, gender, FEV₁%, weight-for-age z score, pancreatic sufficiency, diabetes mellitus, *Staphylococcus aureus*, *Burkholderia cepacia*, and number of acute exacerbations (coefficients not shown).

[§] 5-year conditional probability of survival as a function of 22 terms, including interaction terms in addition to the terms listed in table 3. Stepwise procedures eliminate all but one interaction term to produce the best model reported in table 3 (and evaluated in the top row of this table).

[¶] 5-year conditional probability of survival as a function of age, gender, and forced expiratory volume in 1 second as a percentage of predicted normal (FEV₁%). The model is based on variables identified by Kerem et al. (15).

[#] Refer to reference 15.