Risk of Death in Cystic Fibrosis Patients With Severely Compromised Lung Function*

Carlos E. Milla, MD; and Warren J. Warwick, MD

Background: Lung disease accounts for most of the mortality in patients with cystic fibrosis (CF). Lung transplantation is an option for patients severely impaired, being recommended when life expectancy is estimated to be <2 years. Our objectives were to evaluate in our patient population the validity of currently accepted criteria for low life expectancy and to identify other potentially useful criteria.

Methods: Data were retrieved from CF patients followed up at our center who reached and kept an FEV₁ <30% predicted. A life table was created and stratified according to characteristics believed to be of importance. In addition, the rate of decline in percent predicted FEV₁ was analyzed. These characteristics were evaluated as predictors of risk of death.

Results: The median survival was 3.9 years (95% confidence interval, 2.88 to 4.12 years), with no significant differences according to gender, nutritional status, presence of diabetes, or decade in which the patient was cared for. Only by age was there a significant difference in the median survival (p<0.05). By proportional hazards regression, only the rate of decline in percent predicted FEV₁ was a significant predictor of the risk of death, with a borderline effect from younger age (p=0.06).

Conclusion: In our patient population, a cutoff value of FEV₁ of <30% predicted is not a reliable predictor of high risk of death within 2 years. The yearly rate of decline of percent predicted FEV₁ is a better parameter to identify those patients at high risk for death.

(CHEST 1998; 113:1230-34)

Key words: cystic fibrosis; lung transplantation; pulmonary function; survival

Abbreviations: CF=cystic fibrosis; CI=confidence interval

Cystic fibrosis (CF) is the most common inherited life shortening disease in whites, affecting close to 30,000 individuals in the United States alone. Better understanding of the disease pathophysiology, as well as advances in medical therapies and the recognition of the importance of centralized care, led to a continuous improvement in the survival and quality of life of affected individuals, with the current median survival in the United States being 30 years of age. However, there is much variability from patient to patient in terms of the severity of the disease manifestations, as well as the pattern of disease manifestations, even between affected siblings. Also, female subjects tend to have more severe pulmonary disease than male subjects and shortened survival rates.

Much of the morbidity and mortality of CF is related to the pulmonary manifestations of the disease. A chronic, progressive, and irreversible obstructive pattern, similar to that seen in COPD, is characteristic of the pulmonary function test results of CF patients. The only definitive treatment available for severe advanced pulmonary disease in CF patients is lung transplantation. Severe lung disease with a life expectancy of <2 years is widely accepted as the best criterion for transplantation in CF patients. This criterion is extrapolated from the experience with lung transplantation for other chronic lung diseases.

Kerem et al showed, in the Toronto CF patient population, that patients with an FEV₁ <30% of the normal predicted value for height and sex (percent predicted) had a 2-year mortality rate >50%. This parameter was already being used by some centers as the criterion to identify CF patients who need a
transplant, and is now recommended as the level of lung function impairment at which this treatment option should be presented.9

A “2-year life expectancy” criterion is a very reasonable indication for lung transplantation, taking into account the current prolonged waiting period for a lung transplant. However, for the individual CF patient, this can be hard to predict. There is a wide patient-to-patient variability in the progression of the lung disease, as well as a wide variability in the therapeutic approach from center to center, which makes comparisons between centers difficult.10 Thus, we were interested in more precisely defining characteristics that would identify CF patients at high risk of death.

Our objectives were to first evaluate the level of pulmonary function in CF patients followed up at the University of Minnesota CF center who died from pulmonary complications of the disease. Secondly, based on this experience, we aimed to evaluate the validity of the FEV1 <30% predicted criterion, and also look for other parameters that would be helpful as predictors of death in CF patients with advanced lung disease.

**Materials and Methods**

Spirometry results, microbiological results, and demographic data from all the patients with CF followed up at our center since 1975 (which is the earliest data in the database) were obtained from the Minnesota Cystic Fibrosis Database.11 Spirometry is routinely performed at our center on all patients at every clinic visit and during hospitalizations. Spirometry is performed following previously described procedures12 and standardized to the predicted norm for sex and height.13 Only patients on whom at least 3 years of follow-up data were available were included in the study.

To more specifically look at those patients with an FEV1 <30% predicted, we selected patients who had an FEV1 <30% predicted in more than three subsequent measures within a year, and who did not have a subsequent value >30% predicted on more than one occasion. The date at which the patients who met these criteria had, for the first time, an FEV1 <30% predicted was defined as their “entry date” to create a life table for the group.

If a patient had already died at the time of the analysis, his or her date of death was defined as the “event date.” The difference between this date and the “entry date” determined his or her “survival time.” If a patient was still alive at the time of the analysis, he or she was considered a “date censored observation” and his or her survival time was determined by the difference between the date of the analysis and his or her “entry date.” Similarly, those patients who had received a lung transplant before the date of the analysis were considered as “date censored observations.”

The FEV1 and FVC results observed since acquiring an FEV1 <30% predicted for each individual patient were retrieved and the rate of change in FEV1 was determined through mixed linear modeling. This method was chosen due to the characteristics of the data, repeated measures along time on multiple subjects.14 Additionally, the rate of change in FEV1 was determined for each individual by linear regression.

The patients were stratified according to characteristics believed to be of prognostic significance and differences in survival between strata were calculated with the log rank test. Cox proportional hazards regression was used to test the rate of change in FEV1 as a risk factor for death in this group, along with other factors believed to be potential predictors of risk of death.

All statistical analyses were performed using a statistical package (SAS; SAS Institute, Cary, NC). A significance level of 0.05 was used for all analyses.

**Results**

From 1975, we have followed up at our center 635 patients who were able to perform valid spirometry testing and on whom consistent follow-up data were available to the time of their death, lung transplantation, or the time of this analysis. Of this group, 57 patients had died from pulmonary complications of the disease at the time of the analysis.

In this group of 57 deceased patients, and close to the time of their death, 49 (86%) had an FEV1 <30% predicted.

For the 49 patients who had an FEV1 <30% predicted close to the time of their death, only 17 (33%) had reached that level within 2 years of their death; the remainder of the group lived with an FEV1 <30% predicted for a period ranging from 2 to 14 years.

At the time of the analysis, we had data on 61 patients who consistently had had an FEV1 <30% predicted, as defined above. There were 12 patients with this characteristic who were alive at the time of the analysis. An analysis of survival of all these patients was performed, including both deceased patients (n=49) and those who were still alive at the time of the analysis (n=12), and who were considered as censored observations for the purposes of the analysis.

The survival plot for the group as a whole is presented in Figure 1. The median survival for the group was 45.5 months (3.9 years) with a 95% confidence interval (CI) of 31.1 to 49.4 months. The range of the survival time with an FEV1 <30% predicted in this patient population was 0.3 to 172.6 months.

Age, sex, nutritional status, and presence of insulin-dependent diabetes are generally regarded as important prognostic indicators in CF patients with advanced pulmonary disease. These characteristics were used for stratification, and a stratified survival analysis was performed with each to assess differences in survival (Table 1). Only for age were significant differences in the median survival found, with younger patients (age <18 years) having a shorter median survival than older patients.
(p<0.05). No significant differences in overall survival were seen with any of the variables by log-rank test.

The results of respiratory secretions cultures, from the time of acquisition of an FEV\textsubscript{1} <30% predicted, were also retrieved. Forty-five individuals had positive cultures for nonmucoid Pseudomonas, 49 for mucoid Pseudomonas, and 7 for Burkholderia cepacia. No significant differences in survival were apparent when the patients were classified according to their microbiological results; however, the individuals with positive cultures for B cepacia had a shorter survival than the rest of the group (1.87 years; p=0.06).

Since changing medical practices over the years may have influenced the survival seen in these patients, we classified the individuals according to the decade in which they reached an FEV\textsubscript{1} <30% predicted, to see whether there were differences in survival between the decades. We divided the group into those whose acquisition date was between 1975 and 1984 and those who had an acquisition date between 1985 and 1994. For the 1975 to 1984 group (n=36), the median survival was 44.4 months (95% CI, 24.9 to 77.3 months) and for the 1985 to 1994 group (n=25), the median survival was 48.7 months (95% CI, 24.8 to 49.5 months). There was no significant difference in survival between the two groups (χ\textsuperscript{2}=0.1; p=0.75).

The survival times for the individuals who survived beyond the median for the group had a wider range than that of those surviving below the median (45.5 to 172.6 months vs 0.3 to 45.5 months). We then defined these two groups: one comprised of those dying before reaching the median survival observed for the group as a whole and the second comprised by those dying past the median survival for the group as a whole. Data on FVC and FEV\textsubscript{1} from the date of acquisition of an FEV\textsubscript{1} <30% predicted and until the time of death, or the date of this analysis for those still living, were obtained for each individual. These data were used to calculate the rate of change in FVC and FEV\textsubscript{1} experienced by the subjects during the time they had an FEV\textsubscript{1} <30% predicted. There were no significant differences in the FVC, FEV\textsubscript{1}, or age at the time of death between the groups.

For FVC, a rate of change of −2.06% predicted per year (SE=0.16) was found for the group who died before reaching the median survival and an average rate of change of −1.67% predicted per year (SE=0.15) was found for the group who died past the median. There was no significant difference between these rates (p=0.1).

For FEV\textsubscript{1}, an average rate of change of −1.80% predicted per year (SE=0.18) was found for the group dying before reaching the median survival and an average rate of change of −0.73% predicted per year (SE=0.03) was found for the group who survived past the median, with a significant difference between these rates (p=0.0001). Furthermore, the yearly rate of change in percent predicted FEV\textsubscript{1} for the last 5 years of life for those patients who died before reaching the median was very similar (−1.67% predicted per year; SE=0.2), suggesting

![Figure 1. Survival plot for the group of patients with an FEV\textsubscript{1} <30% predicted. The median survival (50%) is 3.9 years, with a wider range in the survival times for those who lived past the median for the group.](image)

**Table 1—Results of Stratified Survival Analysis for Patients With an FEV\textsubscript{1} <30% Predicted**

<table>
<thead>
<tr>
<th>Variable and Strata</th>
<th>Median Survival, mo (Difference in Median in Overall Survival)</th>
<th>p Value\textsuperscript{1}</th>
<th>p Value\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>23.6 (&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18</td>
<td>48.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>36.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition (50% of ideal weight cutoff)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well nourished</td>
<td>48.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Malnourished</td>
<td>45.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>49.2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Present</td>
<td>46.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decade of acquisition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975-1984</td>
<td>44.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>1985-1994</td>
<td>48.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{1}FEV\textsubscript{1} <30% predicted in more than three subsequent measures within a year and without a subsequent value >30% predicted on more than one occasion.

\textsuperscript{2}NS=not significant.
that these patients were experiencing a faster rate of decline before reaching a poor level of lung function, as defined by an FEV$_1$ <30% predicted.

The rate of change in FEV$_1$ seen for each individual patient before censoring or death was entered into a Cox proportional hazards model that also included all of the variables used in the stratified analysis. Only the rate of decline in FEV$_1$ was a significant predictor of death (p=0.0001), with an increase in the risk of death of 1.3 for every unit of increase in the magnitude of the rate of decline (in percent predicted per year). Age had an effect of borderline significance (p=0.06), with younger individuals having a higher risk. To test the proportional hazards assumption of a constant hazard rate across time, a model that included rate of decline and a time interaction variable was created. This model was not significant, providing evidence that the hazard rate ratio was constant at all times.

**DISCUSSION**

Prediction of prognosis and survival in patients with chronic obstructive lung disease, as CF is, has often proved to be difficult because of the variable course of the disease in the individual patient. Many studies have agreed in that physiologic variables such as FEV$_1$ can be important predictors of the risk of death and are strongly related to survival.$^{15-19}$ However, specific cutoff points of excess risk found in a population study do not necessarily apply to the individual patient.

In our patient population, a value of FEV$_1$ <30% predicted, representing poor lung function and advanced disease, was commonly observed at the time of death (86% of those patients who died). However, that level of lung function was reached, on average, 3.8 years before death, and half of the patients were able to survive for longer periods. This contrasts with the results of Kerem et al.$^7$ in which an FEV$_1$ <30% predicted was associated with a 50% chance of death within 2 years. However, it must be kept in mind that differences in the populations in which these analyses were performed, as well as differences in therapeutic approach and diagnostic procedures, among other known and unknown factors, are possibly involved.

For patients with an FEV$_1$ <30% predicted, by stratified analysis we found that among several patient characteristics believed to be of important prognostic value, only by age was there a borderline difference in survival. The Toronto study has also shown that younger individuals with poorly preserved pulmonary function are at a higher risk for death.$^7$ This suggests that young individuals are less able to tolerate the severe obstructive process that an FEV$_1$ <30% predicted represents, and which in patients with CF not uncommonly goes along with chronic infection and malnutrition. In addition, no significant difference in the survival seen during the 1975 to 1984 decade and the 1985 to 1994 decade was found, which suggests that recent advances in medical therapy did not alter the course of individuals with this level of poor lung function.

An important finding in our analysis was that the level of lung function at the start of the observation period and the yearly rate of change of the percent predicted FEV$_1$ were the only variables associated with risk of death. For those patients with an FEV$_1$ <30% predicted, the yearly rate of change in percent predicted FEV$_1$ was much increased in those who died within a relatively shorter period of time (−1.80% predicted per year) compared with those who died after a longer period of time (−0.73% predicted). This higher rate was present before reaching an FEV$_1$ <30% predicted. In our current CF patient population, an average rate of change of −0.8% predicted per year is seen in those patients who have an abnormal FEV$_1$ (defined as <85% predicted). Thus, the rate of decline found for those who died past the median was comparable to that seen in CF patients with better preserved lung function, whereas the rate found in those who died before reaching the median was more than two times higher (p<0.0001).

The fact that there were no differences in FVC is an interesting one. This may possibly reflect that the progressive obstructive process implied is a marker of rapidly deteriorating lung health.

Our data define the yearly rate of change of FEV$_1$ as an important predictor of death for patients with severely compromised lung function, defined as an FEV$_1$ <30% predicted. Since this high rate of decline is present before reaching that level of pulmonary function, patients at a higher risk of death within a short period are potentially identifiable earlier than if a single cutoff value of FEV$_1$ is used. We believe this high-risk group ought to be identified early and be placed on a more aggressive regimen. Perhaps this is also the time to present to them the possibility of lung transplantation. This will increase their chances of surviving to the procedure.

Frequent pulmonary function testing is of great importance for CF patients,$^{30}$ especially those with advanced disease, to monitor the rate of change along time. This will enable medical caregivers to detect high-risk patients at the start of their deterioration, so that their therapeutic regimen can be intensified.

In a patient with moderate to severely compromised lung function, frequent monitoring also per-
mits the evaluation of the response to a more aggressive regimen. If this fails to revert the fast rate of decline detected, lung transplantation should be considered, even if the FEV₁ <30% predicted. This will also help the patient in the decision process, for there is generally a long lag time between the presentation of the lung transplant option to a patient and the decision making by the patient.21

In conclusion, in the University of Minnesota CF center patient population, the cutoff value of FEV₁ <30% predicted is not a reliable predictor of high risk of dying within 2 years. The determination of the rate of decline of FEV₁ can be used to identify those patients at high risk for death. In addition, younger individuals seem to be at higher risk, although this effect was not significant in our analysis. Sex, respiratory secretions microbiology, insulin-dependent diabetes, and nutritional status were not associated with important differences in survival.

REFERENCES
1 FitzSimmons SC. The changing epidemiology of cystic fibrosis. J Pediatr 1993; 122:1-9
3 Cystic Fibrosis Foundation Patient Registry. 1995 annual data report. Bethesda, Md, September 1996