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# Predictors of Survival in Severe, Early Onset COPD\*

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**Study objectives:** Multiple risk factors for mortality in patients with COPD have been described, but most studies have involved older, primarily male subjects. The purpose of this study was to determine the mortality rate and predictors of survival in subjects with severe, early onset COPD. **Design, setting, and participants:** The cohort of 139 probands in the Boston Early-Onset COPD Study was recruited from lung transplant and general pulmonary clinics between September 1994 and July 2002. Subjects were < 53 years old, had an FEV<sub>1</sub> of < 40% of predicted, did not have severe  $\alpha_1$ -antitrypsin deficiency, and had not undergone lung transplantation. The initial evaluation included a standardized respiratory questionnaire, spirometry, and a blood sample. A follow-up telephone interview was conducted between May and December 2002.

**Measurements and results:** Subjects were young (mean age at enrollment, 47.9 years) and had severe airflow obstruction (mean baseline FEV<sub>1</sub>, 19.4% predicted). A total of 72.7% of the subjects were women (p < 0.0001 [comparison to equal gender distribution]). The median estimated survival time was 7.0 years from the time of study enrollment, determined by the Kaplan-Meier method. The majority of deaths were due to cardiorespiratory illness. In a multivariable Cox proportional hazards model, adjusting for age, gender, and baseline FEV<sub>1</sub>, lifetime cigarette consumption (hazard ratio [HR], 1.20 [per 10 pack-years]; 95% confidence interval [CI], 1.02 to 1.40) and recent smoking status (HR, 2.50; 95% CI, 1.03 to 6.05) were both significant predictors of mortality.

**Conclusion:** In this cohort, recent smoking status predicted increased mortality independent of the effects of lifetime smoking intensity. Smoking cessation may confer a survival benefit even among patients with very severe COPD. (CHEST 2004; 126:1443-1451)

**Key words:** COPD; pulmonary emphysema; smoking; survival analysis

**Abbreviations:** ATS = American Thoracic Society; BMI = body mass index; CI = confidence interval; HR = hazard ratio; LVRS = lung volume reduction surgery

COPD is the fourth-leading cause of death in the United States, and the mortality rate from COPD has increased over the past 2 decades, while mortality rates from cardiovascular disease and can-

cer have decreased.<sup>1,2</sup> Starting in the 1960s, numerous studies<sup>3-11</sup> have examined the prognosis of subjects with COPD. Multiple risk factors for mortality from COPD have been identified, including age, measures of pulmonary function (including bronchodilator and bronchoconstrictor responsiveness), arterial blood gas values, pulmonary hypertension, functional status, and comorbid illness. These factors were detailed in a review by Gerardi and ZuWalla-ck.<sup>12</sup> More recent studies<sup>13-15</sup> have examined the effects on mortality of surgical treatments for COPD, including lung transplantation and lung volume reduction surgery (LVRS).

In the Boston Early-Onset COPD Study, an ongoing study to identify the genetic determinants of COPD, we have assembled a cohort of probands with severe, early onset COPD who were recruited primarily from lung transplant and LVRS programs in New England, and their families. Previous work

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from this study has shown that genetic factors may be involved in the susceptibility to develop COPD in response to cigarette smoking, as evidenced by an increased risk of reduced FEV<sub>1</sub>, chronic bronchitis, and bronchodilator responsiveness among currently smoking and ex-smoking first-degree relatives of the study probands, compared to currently smoking and ex-smoking control subjects.<sup>16,17</sup> Further analysis revealed that female first-degree relatives might be particularly susceptible to these effects.<sup>18</sup> Linkage analyses for both quantitative and qualitative phenotypes in the early onset COPD study have been published.<sup>19–21</sup>

To provide insight into the natural history of severe, early onset COPD unrelated to severe  $\alpha_1$ -antitrypsin deficiency, a follow-up questionnaire was administered to early onset COPD patients or their proxy respondents, at a mean of 3.54 years following study enrollment. This report outlines the baseline characteristics of the first 139 probands enrolled in the study, details the events recorded during the follow-up period, and presents a survival analysis of the cohort of subjects with severe, early onset COPD.

## MATERIALS AND METHODS

### Study Participants

The recruitment of participants with severe, early onset COPD was performed in three phases. Details of the 44 probands in phase 1 (September 1994 to October 1996) and the 40 probands in phase 2 (January 1998 to June 1999) have been reported previously.<sup>16,18</sup> Fifty-five additional probands were recruited in phase 3 (June 1999 to July 2002). In all three phases, participants with severe, early onset COPD were enrolled primarily from the lung transplant and LVRS programs at Brigham and Women's Hospital and Massachusetts General Hospital, as well as from pulmonary clinics at these hospitals and at the Brockton/West Roxbury Veterans Affairs Hospital. Eligibility criteria included an FEV<sub>1</sub> of < 40% of the predicted value, age < 53 years, and absence of severe  $\alpha_1$ -antitrypsin deficiency (*eg*, PI Z or PI null-null). Participants were excluded from the study if they had previously undergone lung transplantation.

After giving written informed consent, participants completed a protocol that included a questionnaire, spirometry (before and after bronchodilator use), and a blood sample. The protocol was approved by the Human Research Committees of Partners Health Care (Brigham and Women's Hospital and Massachusetts General Hospital) and of the Brockton/West Roxbury Veterans Affairs Hospital.

### Baseline Evaluation

Each participant completed a modified version of the 1978 American Thoracic Society (ATS)-Division of Lung Diseases epidemiology questionnaire.<sup>16,18,22</sup> Smoking status was defined by the responses to this questionnaire. Number of pack-years of cigarette smoking as of study enrollment were computed as the product of the duration of smoking (in years) and the average

number of cigarettes smoked per day, which was divided by 20 to convert the results to the number of packs. The diagnosis of chronic bronchitis was determined from responses to questions for chronic cough and chronic phlegm production for at least 3 months per year for at least 2 years. Body mass index (BMI) was calculated by dividing the self-reported weight (in kilograms) by the square of the measured height (in meters). Underweight was defined as a BMI of < 18.5, according to published standards.<sup>23</sup>

Spirometry was performed (Survey Tach Spirometer; Warren E. Collins; Braintree, MA) in accordance with ATS specifications.<sup>24</sup> Pulmonary function test results are expressed as a percentage of the predicted value, using prediction equations from Crapo and coworkers<sup>25</sup> for adult white participants and from Hankinson and coworkers<sup>26</sup> for African-American participants. Spirometry was repeated after the inhalation of 180  $\mu$ g (2 puffs) albuterol through a spacer device. Bronchodilator responsiveness was calculated as the absolute change in FEV<sub>1</sub> divided by the predicted value for FEV<sub>1</sub> and was expressed as a percentage.

For the subjects who had undergone LVRS prior to study enrollment, preoperative spirometry results were used in the analysis. For four additional subjects, outside spirometric values were used, because of geographic distance, previous major lung surgery, or illness, precluding performance of the test.

### Follow-up Study

Surviving subjects and the next-of-kin of nonsurvivors were contacted for a telephone interview between May and November 2002. Respondents were questioned regarding treatment history, including lung transplantation and LVRS, hospitalizations, including ICU admissions and requirement for mechanical ventilation, comorbid diagnoses, cigarette smoking, and cause of death of the deceased subjects. Because data were collected from proxy respondents for a substantial number of participants, cigarette smoking since study enrollment was defined only as the presence or absence of any smoking during that period.

The Social Security Death Index was searched to ascertain the vital status of all subjects as of November 1, 2002, and to determine the dates of death of the decedents. When available, hospital records were accessed to determine the history of lung transplantation and LVRS of the participants who did not complete the telephone interview. The follow-up study was approved by the Human Research Committee of Partners Health Care.

### Statistical Analysis

Differences in baseline characteristics and in treatments were compared using the Wilcoxon rank sum test, the Fisher exact test, or the  $\chi^2$  test, where appropriate. Univariate analysis of survival time from the date of study entry was performed using the Kaplan-Meier method, the log rank test, and Cox proportional hazards regression.<sup>27–29</sup> Tests were performed using a statistical software package (SAS, version 8.2; SAS Institute; Cary, NC) on a personal computer. Lung transplantation and LVRS that occurred during the follow-up period were treated as time-varying explanatory variables, and survival time was dependent on the current value of the variable, as opposed to its value at study entry.<sup>30</sup>

To assess the effects of the baseline and follow-up variables on mortality, a multivariable Cox proportional hazards model was constructed using the subjects with complete data on all pertinent variables. Because of the clinical relevance, adjustment for age and gender was included. Other risk factors with a significance level of  $p < 0.2$  on univariate analysis were included in the

final model. To check the assumption of proportional hazards for a given covariate, the product of that covariate with (censored) survival time was added to each model as an interaction term. The proportional hazards assumption was violated only for the time-dependent covariate for lung transplantation, and the interaction term was retained in models that included lung transplantation as a predictor.

The model then was repeated excluding the eight subjects who had already undergone LVRS at the time of study enrollment, as well as one other subject who had previously undergone bilateral apical bullectomy.

## RESULTS

### Baseline Characteristics of Early Onset COPD Subjects

A total of 139 probands were enrolled in the three phases of the study (Table 1). Details of the demographics and spirometry of the first 84 probands (phases 1 and 2) have been previously reported.<sup>16,18</sup> The female predominance noted through the first two phases (71.4% women) persisted in the third phase (74.6% women), and both of these values are significantly different than the predicted equal sex distribution ( $p < 0.0001$  [phases 1 and 2];  $p = 0.0003$  [phase 3]). Overall, women make up 72.7% of the probands enrolled during all three phases, which also constitutes a highly significant excess ( $p < 0.0001$ ).

There were no differences between the women and men in terms of age at enrollment, baseline FEV<sub>1</sub> as a percentage of predicted values, bronchodilator responsiveness, or diagnosis of chronic bron-

chitis. Men tended to have smoked more pack-years at baseline, but the difference was not significant ( $p = 0.11$ ). Men were more likely to smoke during the follow-up period (men who reported smoking, 41.4%; women who reported smoking, 20.5%;  $p = 0.029$ ). There was no difference in age, baseline FEV<sub>1</sub>, or number of pack-years smoked between those who did and did not report smoking during the follow-up.

The subjects had profound airflow obstruction (mean baseline FEV<sub>1</sub>, 19.4% predicted), and 41.7% met the ATS criteria for the definition of chronic bronchitis.<sup>31</sup> A history of cigarette smoking was nearly universal. Only three subjects were lifetime nonsmokers. The mean ( $\pm$  SD) lifetime cigarette consumption was  $38.9 \pm 21.6$  pack-years prior to study enrollment. The cohort was predominantly white, with only four African-American subjects. The mean response to an inhaled bronchodilator was an increase of 3.0% of the predicted FEV<sub>1</sub> value, and only 17 subjects had an absolute increase in FEV<sub>1</sub> of  $\geq 200$  mL.

### Follow-up Study

Subjects were followed up for a mean period of 3.54 years (range, 2 months to 8.1 years). Over that period, there were 37 deaths among the 139 subjects (Table 2). The majority of the deaths were due to cardiorespiratory illness. Lung cancer had been diagnosed in five participants since study enrollment. Questionnaires were completed for 108 of the 139 subjects (77.7%). Most follow-up questionnaires were completed by the probands themselves (78.7%), and the remainder were obtained from interviews with proxy respondents.

Of those subjects for whom complete follow-up data were available, almost 90% had used home oxygen, and more than two thirds had completed pulmonary rehabilitation therapy. Twenty-six percent reported any cigarette smoking since study enrollment.

Twenty-one subjects had undergone single-lung or double-lung transplantation since the time of study enrollment. The mean baseline FEV<sub>1</sub> was significantly lower in the group of patients who had received lung transplants, compared to those who did not (15.3% vs 20.1% predicted, respectively;  $p = 0.0039$ ). There were no differences in age, gender, or number of pack-years of smoking between the transplanted and nontransplanted groups.

A total of 33 subjects had undergone either unilateral or bilateral LVRS, with 14 having undergone LVRS prior to study enrollment, and 19 having undergone surgery during the follow-up period. In addition, two subjects had volume reduction surgery

**Table 1—Baseline Characteristics of Early Onset COPD Subjects\***

Variable	Value
Age, yr	47.9 $\pm$ 4.8
Sex	
Female	101 (72.7)
Male	38 (27.3)
Race	
White	135 (97.1)
African-American	4 (2.9)
FEV <sub>1</sub> , % predicted	19.4 $\pm$ 7.4
FEV <sub>1</sub> /FVC, % predicted	39.1 $\pm$ 12.8
Bronchodilator responsiveness, % of predicted FEV <sub>1</sub> †	3.0 $\pm$ 2.8
Ever-smoker	136 (97.8)
Smoking,‡ pack-yr	38.9 $\pm$ 21.6
Chronic bronchitis	58 (41.7)
Underweight§	16 (13.2)

\*Values given as mean  $\pm$  SD or No. (%); n = 139.

†Postbronchodilator spirometry was not available in 11 subjects.

‡Includes three lifelong nonsmokers.

§Defined as BMI < 18.5. Weight at enrollment was not available for the 18 subjects who had either undergone LVRS pre-enrollment or lived at a great geographic distance.

**Table 2—Follow-up Survey of Early Onset COPD Subjects\***

Variable	Value
Duration of follow-up, yr	3.54 ± 2.29
Person completing questionnaire (n = 108)	
Proband	85 (78.7)
Spouse	11 (10.2)
Sibling	4 (3.7)
Child	3 (2.8)
Other	5 (4.6)
Deaths	37 (26.6)
Cause of death, No.†	
Respiratory	19
Cardiac	2
Other	7
Diagnosed with lung cancer (n = 108)	5 (4.7)
Lung transplant	21 (15.1)
LVRS‡	33 (23.7)
Prior to study enrollment	14
Following study enrollment	19
Smoking since study enrollment (n = 107)§	28 (26.2)
Ever used home oxygen (n = 108)	97 (89.8)
Attended pulmonary rehabilitation (n = 104)§	71 (68.3)

\*Values given as mean ± SD or No. (%) unless otherwise indicated.

A total of 139 subjects were included, except where indicated.

†Twenty-three subjects had cause of death available. More than one cause may have been listed.

‡Does not include two subjects who underwent LVRS on the contralateral lung following single-lung transplantation.

§A total of < 108 are listed due to missing responses on the follow-up questionnaire.

performed on the native lung subsequent to a single-lung transplant. For the purpose of this study, this was not considered to be LVRS.

A significantly greater proportion of the female participants underwent LVRS during the study period compared to male participants (19.6% vs 3.1%, respectively;  $p = 0.025$ ). However, the 19 subjects who underwent LVRS during the study period were not different from those who did not in terms of baseline FEV<sub>1</sub>, age, or number of pack-years of smoking.

Among the 40 subjects who received surgical therapy for COPD during the study period, the mean baseline FEV<sub>1</sub> was significantly lower in those who underwent lung transplantation compared to LVRS (15.3% vs 19.2% predicted, respectively;  $p = 0.019$ ). Women tended to be treated with LVRS more commonly than with transplantation, although this did not reach statistical significance ( $p = 0.095$ ). There were no differences in age or smoking history (in pack-years) comparing those subjects who had undergone transplantation with those who had undergone LVRS.

#### *Survival Analysis of Early Onset COPD Subjects*

Starting at the point of study entry, the 3-year survival rate was 85% and the 5-year survival rate was

72%. The median survival time since enrollment for the cohort was 7.0 years, which was estimated by the Kaplan-Meier method. The stratified Kaplan-Meier survival estimates are shown in Figure 1. Survival was not different between women and men ( $p = 0.16$  [log rank test]). Baseline FEV<sub>1</sub> analyzed by quartile ( $p = 0.0058$ ) and smoking since study enrollment ( $p = 0.0070$ ) were both significant predictors of mortality. The intensity of cigarette smoking, defined by quartiles of pack-years, showed a trend toward significance ( $p = 0.098$ ).

In univariate Cox proportional hazards models, the baseline FEV<sub>1</sub> percentage of predicted, the number of pack-years of cigarette smoking, and smoking status since study enrollment were significantly associated with survival time (Table 3). A higher FEV<sub>1</sub> percentage of predicted was linearly associated with an increased survival time. Over the range of values observed, a 1% increase in baseline FEV<sub>1</sub> percentage of predicted led to an 8% decrease in the risk of dying (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.86 to 0.97). Greater smoking intensity was associated with decreased survival, and the risk increased by 20% for each 10 pack-years of smoking (HR, 1.19; 95% CI, 1.05 to 1.35). Subjects who smoked during the study period had a risk of mortality that was almost three times that of abstainers (HR, 2.83; 95% CI, 1.29 to 6.21).

Age, gender, symptoms of chronic bronchitis, bronchodilator responsiveness, underweight, use of home oxygen, and completion of pulmonary rehabilitation were not significant predictors of survival. Treatment with LVRS did not predict survival in this cohort. In the univariate analysis, there was a trend toward a significant effect of lung transplantation ( $p = 0.065$ ). The time interaction term was significant, indicating nonproportionality of the hazards; therefore, the risk of mortality varied with time following the surgery. Early after transplantation, the trend was toward a survival benefit, but this effect was attenuated over time.

In the multivariable Cox proportional hazards model, including the 107 subjects with complete data on all relevant predictors, the two variables measuring cigarette smoking (lifetime pack-years of smoking and smoking since study enrollment) were significantly associated with survival time, when adjusted for age, sex, baseline FEV<sub>1</sub> percentage of predicted, and transplant status (Table 4). For each 10 pack-years of smoking, the risk of dying increased by 20% (HR, 1.20; 95% CI, 1.02 to 1.40), as in the unadjusted model. The risk of dying in those who smoked following enrollment remained increased, and the HR of 2.50 (95% CI, 1.03 to 6.05) was similar to that seen in the unadjusted analysis. In the

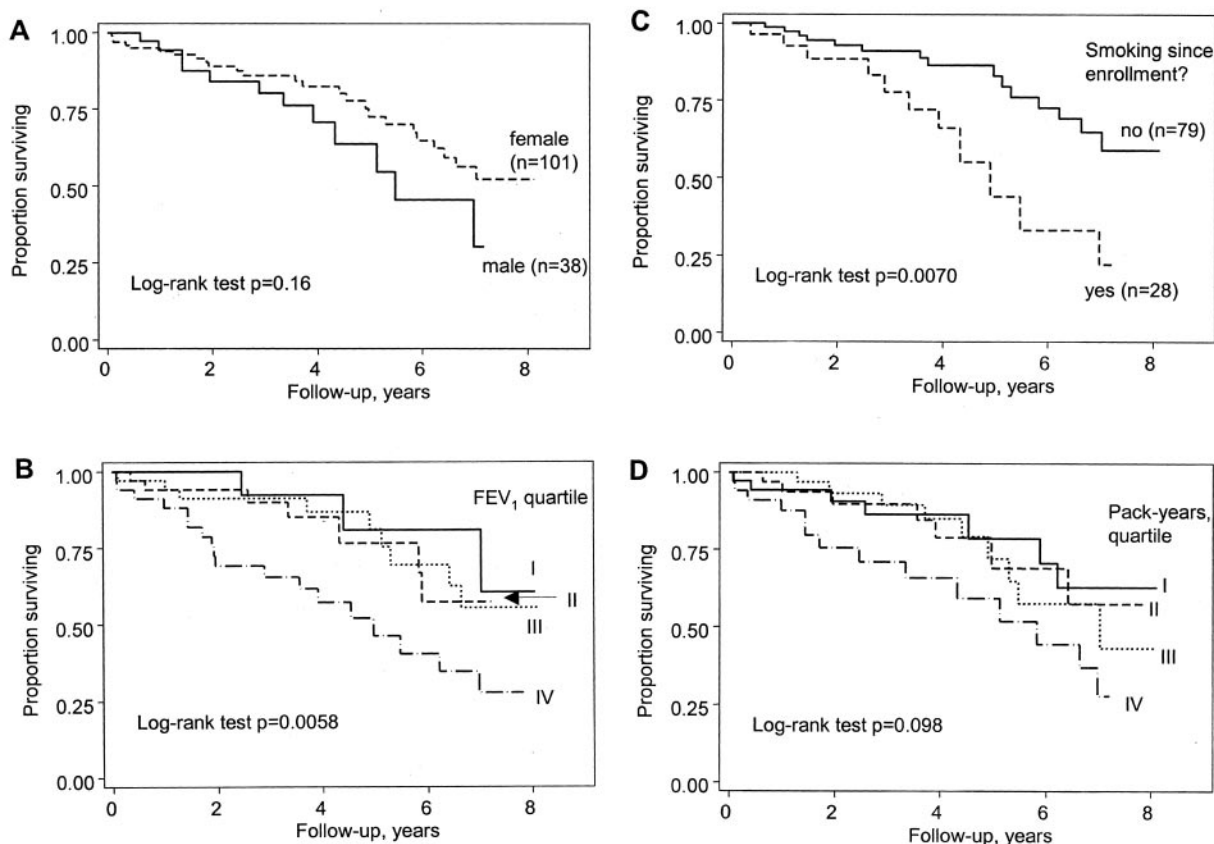


FIGURE 1. Kaplan-Meier survival curves for severe, early onset COPD subjects. *Top left, A:* stratified by sex (139 subjects). *Bottom left, B:* stratified by quartile of baseline FEV<sub>1</sub> percentage of predicted (139 subjects). The mean FEV<sub>1</sub> percentage of predicted values for each quartile were as follows: I, 29.5% predicted; II, 21.3% predicted; III, 15.6% predicted; IV, 10.9% predicted. *Top right, C:* stratified by smoking status since study enrollment (107 subjects). *Bottom right, D:* stratified by the quartile of the number of pack-years of cigarette smoking (n = 139). The mean numbers of pack-years for each quartile were as follows: I, 14.7; II, 30.9; III, 44.1; and IV, 67.1.

adjusted model, baseline FEV<sub>1</sub> was no longer a significant predictor of mortality in this cohort.

As in the unadjusted analysis, lung transplantation showed a trend toward significance in the multivariable model ( $p = 0.067$ ). The trend continued to be toward early benefit, with a decrease in benefit over time, compared to those who did not undergo transplantation. In the multivariable model, the time interaction term was borderline significant, but it was retained in the model based on its significance in the unadjusted analysis.

## DISCUSSION

Since the 1960s, multiple studies have investigated the risk factors that influence mortality in a variety of populations of COPD patients. In the current report, we examined the survival of a unique cohort of subjects with severe early onset COPD. The most striking finding was that two separate measures of

cigarette smoking had the strongest effect on outcome. The number of pack-years smoked prior to study enrollment as well as smoking during the follow-up period were both independent predictors of mortality.

In the univariate analysis, a higher baseline FEV<sub>1</sub> predicted a lower mortality rate during the follow-up period, but this effect did not persist in the multivariable model, when adjusted for age, sex, lung transplantation, and the two measures of cigarette smoking. This is in contrast to the results of the majority of the prior studies. Previous studies have found inconsistent effects of smoking on survival in subjects with COPD; however, many studies, especially the earlier reports, did not measure or account for smoking-related variables. The unique features of this cohort (*ie*, relatively young age, severely reduced FEV<sub>1</sub>, and female predominance) may explain the differences in the predictors of mortality in this cohort compared to those in other published studies.

**Table 3—Univariate Cox Regression Models for Survival in Early Onset COPD Subjects\***

Variable	HR	95% CI
Continuous		
Age by year	1.00	0.94–1.07
FEV <sub>1</sub> % predicted	0.92	0.86–0.97
Bronchodilator responsiveness as a % of predicted FEV <sub>1</sub> †	0.97	0.89–1.10
Smoking intensity by 10 pack-yr	1.19	1.05–1.35
Age started smoking	0.96	0.83–1.10
Categorical		
Female sex	0.61	0.31–1.23
Chronic bronchitis	1.07	0.55–2.07
Underweight†‡	1.26	0.49–3.25
Smoking since study enrollment†	2.83	1.29–6.21
Home oxygen use ever†	1.20	0.16–9.13
Attended pulmonary rehabilitation†	0.61	0.26–1.44
LVRS‡	0.77	0.36–1.65
Lung transplantation§	0.022	0.00–1.17

\*n = 139.

†n < 139 due to missing data.

‡Defined as BMI < 18.5.

§Both LVRS and transplant status were treated as time-varying covariates, survival time was dependent on the current value of the variable.

||Includes a significant time interaction term (p = 0.025) to account for the nonproportionality of hazards. HR for interaction term, 1.002 (95% CI, 1.000 to 1.005), indicating a decrease in benefit over time.

Beginning with the earliest studies, multiple authors<sup>3–5,7</sup> have shown the importance of measures of pulmonary function, usually expressed as FEV<sub>1</sub>, as predictors of mortality in patients with COPD, including those with severe disease. More recent studies<sup>9,11,32–34</sup> have confirmed the findings of these earlier studies. As in our cohort, the majority of the subjects in all of these studies had a history of cigarette smoking. Yet, many authors did not control for smoking, which is likely to confound the relationship between FEV<sub>1</sub> and survival.

Throughout the literature, the reported effects of

**Table 4—Multivariable Cox Regression Model for Survival in Early Onset COPD Subjects\***

Variable	HR	95% CI
Age by year	1.03	0.90–1.17
Female sex	0.80	0.28–2.26
FEV <sub>1</sub> % predicted	0.94	0.86–1.02
Smoking intensity by 10 pack-yr	1.20	1.02–1.40
Smoking since study enrollment	2.50	1.03–6.05
Lung transplantation†	0.008	0.00–1.39

\*n = 107 subjects with complete data on included predictors.

†Time-varying covariate. Survival time is dependent on the current value of the variable. Includes a time interaction term (p = 0.052) to account for the nonproportionality of hazards. HR for interaction term, 1.003 (95% CI, 1.000 to 1.005), indicating a decrease in benefit over time.

cigarette smoking on mortality in COPD patients have been inconsistent. This may be due to the use of different measures of cigarette smoking. Authors quantifying smoking intensity (in pack-years or in the number of cigarettes smoked per day) have found this measure to be a consistent predictor of mortality.<sup>6,34,35</sup> However, studies<sup>6,7,11,35,36</sup> using dichotomous measures of smoking (*ie*, either ever-smoking vs never-smoking or current smoking vs ex-smoking [and never-smoking]) have not always found an association with mortality.

In the present population, the confounding effect of cigarette smoking, especially pack-year history of smoking, likely explains why FEV<sub>1</sub> was a significant predictor of mortality in the univariate analysis, but not in the multivariable model. In addition, the fact that all the subjects had severe airflow obstruction limits the ability to discern an effect of pulmonary function on survival across the narrow range of values of FEV<sub>1</sub> that were seen in this cohort. A similar result was found in a Dutch study<sup>8</sup> of patients with severe COPD.

The majority of the previous studies<sup>4,5,8,11,32,34</sup> has shown an effect of age on mortality in COPD patients, yet the present study did not confirm these results. However, there was an upper limit of age for study enrollment, leading to a younger cohort than in any of the previous studies. The mean age in the probands was 48 years, compared to means ranging between 54 and 69 years in the studies noted above. As with FEV<sub>1</sub>, our cohort had a narrow range of ages, limiting the power to detect any effect of age on mortality.

The female predominance is a unique feature of the Boston Early-Onset COPD Study cohort, and previous work<sup>18</sup> in this cohort has suggested that women may have a higher risk of the development of severe COPD. The persistence of a female predominance in the 55 previously unreported severe, early onset COPD probands provides further evidence for increased susceptibility to COPD in women. Despite the significant excess of female subjects, gender was not a significant predictor of outcome in the multivariable Cox regression model. Survival was not different between male and female subjects, so reduced survival among male patients with severe early onset COPD is unlikely to explain the observed female predominance in the Boston Early-Onset COPD Study.

Previous studies<sup>4</sup> have reported that women with COPD may have decreased mortality compared to men. In a Japanese study of patients using long-term oxygen therapy, and in studies in Barcelona and Finland of emergency department and hospital patients, the survival rate of women with COPD was significantly better than that of men.<sup>10,37,38</sup> However,

none of these studies controlled for cigarette smoking. Higher rates of cigarette smoking in men, especially in Western Europe and Asia, may be sufficient to explain the gender-related survival differences seen in these studies.<sup>39</sup> In one study<sup>34</sup> that did control for smoking intensity, no effect of gender on survival in COPD patients was found.

Because the present cohort was younger and had more severe airflow obstruction than did subjects in the previous studies, the overall mortality rates between studies may not be directly comparable. Differences in standards of care, especially the use of home oxygen therapy, make comparisons to the earliest studies difficult. Two of the more recent studies<sup>33,34</sup> reported survival rates that are similar to those seen in the present cohort. However, patients in both of these studies had less severe airflow obstruction than our patients, but were older.

Since we have hypothesized that early onset COPD is likely to have stronger genetic influences than late-onset disease, perhaps a more valid comparison group would be subjects with emphysema due to severe  $\alpha_1$ -antitrypsin deficiency. Among 1,129 enrollees in the National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of  $\alpha_1$ -Antitrypsin, the 5-year survival rate was 81%.<sup>40</sup> The mean age among registry patients (46 years) was similar to that of our cohort, but the severity of airflow obstruction was not as great, with a mean FEV<sub>1</sub> of 47% predicted. Gender was not associated with survival in the  $\alpha_1$ -Antitrypsin Deficiency Registry patients, but age and baseline FEV<sub>1</sub> were significant predictors. Initial smoking status was not related to survival. Approximately 10% of the registry patients underwent lung transplantation, and this was associated with an increase in the risk of mortality.

The data from the United Network for Organ Sharing and the International Society for Heart and Lung Transplantation Registry have suggested that lung transplantation does not confer a survival benefit in recipients with COPD.<sup>13</sup> However, one study<sup>41</sup> from a single transplant center revealed a significant survival benefit. In the present analysis, there was a suggestion of improved short-term survival following lung transplantation, with a decrease in benefit over time. However, these findings should be interpreted with caution. Our study was not designed to address this specific question, as the overall number of transplants was low and the results did not reach statistical significance.

In the early onset COPD cohort, LVRS was not found to have an effect on survival. This finding is even more difficult to interpret, for reasons similar to the limitations regarding transplantation, as well as the presence of 14 subjects who underwent LVRS

prior to study enrollment. However, the multivariable survival model did not change appreciably when these subjects were excluded. In our population, we did not have the data that would be necessary to define the subgroups of patients with the greatest chance of benefit or the highest risk of harm from LVRS, based on the results of the National Emphysema Treatment Trial.<sup>14,15</sup>

There are additional limitations to the present analysis. The vital status could be accurately recorded for all 139 probands. However, the follow-up questionnaire was completed for only 108 subjects, so information on smoking during the study period was limited to these respondents. For deceased subjects, proxy respondents were interviewed, which may lead to recall bias. However, one would still expect proxies to know whether the subjects had been actively smoking following study enrollment, even though a detailed smoking history may not be available. Therefore, smoking since study enrollment could be analyzed only as a yes/no response. For participants without follow-up questionnaire data, history of lung transplantation was assessed by a review of medical records from the two adult lung transplant centers in New England. It is possible, but unlikely, that subjects could have undergone lung transplantation elsewhere.

The survival analysis was performed using all-cause mortality as the outcome. Due to incomplete data on the causes of death, the analysis could not be limited to respiratory deaths only. For the 23 subjects for whom cause of death was listed by proxy respondents, 19 (83%) listed a respiratory diagnosis as one of the causes of death. The two subjects who had cardiac causes of death listed also had respiratory causes reported. These events likely reflect the presence of sequelae of end-stage lung disease. Because of the predominance of cardiorespiratory causes of death listed for the deceased subjects, we contend that the use of all-cause mortality as an end point of the study was appropriate.

Current smokers are ineligible for lung transplantation or LVRS, so the effects of these surgical procedures may be seen as confounders of the effects of recent smoking status. However, this bias is unlikely to explain the observed association, since we found that LVRS was not associated with improved survival, and the marginal benefit of lung transplantation was controlled for by including this variable in the final model.

In a cohort of patients with severe early onset COPD, we have found that a greater cumulative history of cigarette smoking and recent smoking are both strong, independent predictors of increased mortality. This suggests a benefit of smoking cessation on survival even among patients with very severe



airflow obstruction. Physicians should encourage smoking cessation in all patients with COPD, regardless of the severity of their disease.

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