Association between Initial Disease Presentation, Lung Disease Outcomes, and Survival in Patients with Cystic Fibrosis

HuiChuan J. Lai1,2, Yu Cheng2, Hyungjun Cho2, Michael R. Kosorok2,3, and Philip M. Farrell3

1 Department of Nutritional Sciences, University of Wisconsin College of Agriculture and Life Sciences, Madison, WI.
2 Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine, Madison, WI.
3 Department of Pediatrics, University of Wisconsin School of Medicine, Madison, WI.

Received for publication May 19, 2003; accepted for publication October 16, 2003.

This US study was conducted to determine whether mode of diagnosis and initial disease presentation influence lung disease and survival in patients with cystic fibrosis. The study population included 27,703 patients reported to the 1986–2000 Cystic Fibrosis Foundation Registry. Patients were segregated into four diagnostic categories: meconium ileus (MI), prenatal/neonatal screening (SCREEN), positive family history (FH), and symptoms other than meconium ileus (SYMPTOM). When compared with patients in the SCREEN group, those in the MI or SYMPTOM group were found to have significantly greater risks of shortened survival, Pseudomonas aeruginosa acquisition, and forced expiratory volume in 1 second (FEV1) below 70% of predicted. In the SYMPTOM group, the greatest risks of shortened survival, P. aeruginosa acquisition, and FEV1 <70% occurred for patients presenting with combined respiratory and gastrointestinal symptoms, followed by respiratory or gastrointestinal symptoms alone; the best outcomes were in patients with other presenting features. Additionally, patients with presumably “severe” genotypes (∆F508 plus other class I, II, III mutations in both alleles) had greater risks of shortened survival and P. aeruginosa acquisition compared with patients with presumably “mild” genotypes (class IV or V mutations in one or both alleles).

cystic fibrosis; diagnosis; genotype; lung diseases; registries; signs and symptoms; signs and symptoms, respiratory; survival

Abbreviations: CFTR, cystic fibrosis transmembrane regulator gene; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FH, group of patients with a positive family history without symptoms; GI, group of patients with gastrointestinal symptoms; MI, group of patients with meconium ileus; OR, odds ratio; OTHER, group of patients with other symptoms; RESP, group of patients with respiratory symptoms; SCREEN, group of patients without meconium ileus and identified via prenatal/neonatal screening; SYMPTOM, group of patients with symptoms other than meconium ileus.

Cystic fibrosis is an inherited disorder characterized by high electrolyte levels in sweat, pancreatic insufficiency, meconium ileus, malnutrition, and progressive lung disease (1). The degree of disease severity manifested in individual patients with newly diagnosed cystic fibrosis is determined by multiple, interrelated factors. These factors include not only cystic fibrosis–specific characteristics, such as genetic abnormalities (e.g., specific mutations of the cystic fibrosis transmembrane regulator gene, abbreviated CFTR) and phenotypic presentations (e.g., meconium ileus and pancreatic insufficiency), but also demographic characteristics (e.g., the well-described gender gap in cystic fibrosis) and mode of diagnosis (e.g., neonatal screening or conventional diagnosis). The intuitive associations among genotype, phenotype, and prognosis are best evidenced by findings from observational studies showing that, in general, patients with homozygous ∆F508 mutations, pancreatic insufficiency, or Pseudomonas aeruginosa colonization experience.

Reprint requests to Dr. HuiChuan Lai, Department of Nutritional Sciences, University of Wisconsin College of Agriculture and Life Sciences, 1415 Linden Drive, Madison, WI 53706-1562 (e-mail: lai@nutrisci.wisc.edu).
greater morbidity and mortality than those with less severe CFTR mutations or pancreatic sufficiency or without P. aeruginosa colonization (1–7). A significant gender association regarding cystic fibrosis survival has been repeatedly reported, with females experiencing a higher mortality rate than males (5, 8–11). The potential association between mode of diagnosis and prognosis is evidenced by the findings that delayed diagnosis leads to severe malnutrition (12, 13), potentially accelerated respiratory problems (14), and possibly greater mortality risk (15–19).

In view of these findings, we hypothesized that patients presenting with milder cystic fibrosis, compared with those presenting with more severe disease, have a better prognosis. This hypothesis led us to formalize an innovative concept of “baseline risk,” which reflects the inherently variable degree of disease severity associated with individual cystic fibrosis patients, and to further incorporate this “baseline risk” component for developing cystic fibrosis survival models. In this study, we designed a series of analyses to investigate the potential contribution of baseline risk factors to survival and lung disease outcomes in cystic fibrosis. Data from the Cystic Fibrosis Foundation Patient Registry reported during the period 1986–2000 were used.

MATERIALS AND METHODS

Study population

The Cystic Fibrosis Foundation Registry documents the diagnosis and annual follow-up evaluations of cystic fibrosis patients who are seen at accredited centers in the United States, as described in detail elsewhere (20). In the present study, Registry data reported during 1986 through 2000 were used. Among the 32,229 patients documented during this period, 2,192 were reported once (908 newly diagnosed in 2000, 452 deceased, 832 lost to follow-up); hence, their data could not be used in time-to-event analysis. For another 2,334 patients, information on “reasons leading to diagnosis,” described separately under the subheading “Classification of presentation of meconium ileus” was missing, and these patients could not be classified according to their timing and conditions at the time of cystic fibrosis diagnosis. The remaining 27,703 patients were included in the present study.

Study design

We performed a sequence of analyses to examine the hypothesis that survival and lung disease vary among patients with inherently different degrees of baseline risk, which can be reflected by their age at diagnosis and their initial disease profile at the time of cystic fibrosis diagnosis. With this concept in mind, and considering the common clinical practices that lead to identification of cystic fibrosis, we segregated patients into four groups reflective of their age and mode of diagnosis. These four categories of diagnostic groups were constructed according to the following sequence: patients identified at birth because of the presence of intestinal obstruction known as meconium ileus (MI), patients identified shortly after birth via prenatal/neonatal screening (SCREEN), patients identified at variable ages because of a positive family history without symptoms (FH), and patients identified at variable ages because of symptoms other than meconium ileus (SYMPTOM). The sequence of constructing these categories is important because patients may have meconium ileus and were diagnosed via screening. In this case, they were assigned to the MI group because the presentation of meconium ileus, which is manifested at birth, was what prompted the diagnosis of cystic fibrosis.

Our first analysis examined whether survival and lung disease differed among these four diagnostic groups. Subsequently, the associations of gender and CFTR genotype with baseline risk were evaluated. The method we used to classify CFTR genotype is described separately under the subheading “Classification of CFTR mutations.”

The second analysis was performed to further examine cystic fibrosis patients in the SYMPTOM subgroup to determine whether survival and lung disease were influenced by the timing and type of initial presenting symptoms. The timing of diagnosis was defined by using age at diagnosis. The type of presenting symptoms was defined by using data on “reasons leading to diagnosis,” described separately under the subheading “Classification of presenting symptoms.”

Classification of CFTR mutations

The Cystic Fibrosis Foundation Patient Registry records whether the patient has been genotyped and provides the specific CFTR allele for the 25 most frequently found mutations. These 25 mutations were divided into five classes according to the scheme developed by Welsh and Smith (21), listed in the last footnote of table 1. Second, in view of the observation that class I, II, and III mutations are generally associated with a more “severe” phenotype (21), whereas class IV and V mutations are generally associated with a milder phenotype (21), the following six genotype groupings were created: 1) ΔF508/ΔF508; 2) ΔF508/non-ΔF508-I, II, III; 3) ΔF508/IV, V; 4) non-ΔF508-I, II, III/non-ΔF508-I, II, III; 5) non-ΔF508-I, II, III/IV, V; and 6) IV, V/IV, V. Third, the three genotype groups with class IV or V mutations in at least one allele were combined and were referred to as “mild genotype,” whereas the ΔF508/non-ΔF508-I, II, III and the non-ΔF508-I, II, III/non-ΔF508-I, II, III groups were combined and were referred to as “severe genotype other than homozygous ΔF508.” These two groups were compared with “homozygous ΔF508.”

Classification of presenting symptoms

Data on “reasons leading to diagnosis” were reclassified into five mutually exclusive categories: 1) “respiratory (RESP)”: patients presenting with “acute or persistent respiratory symptoms” but without other symptoms; 2) “gastrointestinal (GI)”: patients presenting with “failure to thrive/malnutrition” and/or “steatorrhea/abnormal stools/malabsorption” but without other symptoms; 3) “RESP + GI”: patients presenting with both respiratory and gastrointestinal symptoms; 4) “OTHER + RESP/GI”: patients presenting with other less common symptoms including electrolyte imbalance, nasal polyps/sinus disease, rectal prolapse, liver problems, and other unspecified symptoms in combination with respiratory and/or gastrointestinal
Survival and lung disease outcomes

Information on vital status was available for all 27,703 patients. With regard to lung disease outcomes, we used the two most common indices of lung disease—P. aeruginosa acquisition as an index of lung infection, and forced expiratory volume in 1 second (FEV1) as an index of airway obstruction and lung function.

In terms of P. aeruginosa acquisition, only those patients who were diagnosed after 1986 and were negative for P. aeruginosa at their first documented visits were included in the analysis (n = 10,632). Onset of P. aeruginosa acquisition was defined by time to the first reported positive P. aeruginosa culture. Patients positive for P. aeruginosa at their first documented visits were excluded from the analyses because these data combine the characteristics of left truncation and double censoring, which require complex statistical methods not readily available in common statistical analysis software. By excluding patients positive for P. aeruginosa at their first documented visits, we could then analyze the data by using survival methods adjusted for left truncation and right censoring, described in the “Statistical analysis” section below.

With regard to FEV1, included in the analysis were only those patients who were diagnosed after 1986, were older than 6 years of age at their first documented visits, and had experienced their first FEV1 above 70 percent of predicted (n = 6,249). Similar to the method used for P. aeruginosa outcome, patients whose FEV1 was below 70 percent of predicted at their first documented visits were left censored; thus, they were excluded from the analyses. Poor lung function was defined by time to first FEV1 below 70 percent of predicted. The percent predicted values for FEV1 were calculated by using the Dockery equations (22, 23).

Statistical analysis

Data processing and descriptive analyses were performed by using SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina, 2001). Nonparametric analysis of variance was used to compare medians, and chi-square tests were used to compare frequency distributions.

Survival curves were generated in R (downloaded from the following Internet site: http://www.r-project.org) according to Kaplan-Meier computations adjusted for left-
truncated and right-censored data (24). These computations were performed by using the SURV and SURVFIT functions available in the survival package (downloaded from the following Internet site: http://cran.us.r-project.org). Adjustment for left truncation avoided the bias introduced by assuming that all patients were followed from birth. Age at entry was defined as age at the first documented visit listed in the Cystic Fibrosis Foundation Registry. The Cox proportional hazards model for left-truncated and right-censored data was used to assess the effect of various baseline risk factors on survival and other time-to-event outcomes. Where appropriate, the time-to-event models were stratified by calendar years of diagnosis. All time-to-event analyses were performed by using PROC PHREG in SAS or COXPH in R.

RESULTS

Characteristics of the study population

Table 1 shows the baseline characteristics of the study population. The majority of patients (72 percent) were identified because of symptoms other than meconium ileus. No significant gender difference was observed in the relative percentage of patients in the four diagnostic groups ($p = 0.93$). The median age at diagnosis was the youngest in the MI and SCREEN groups, with 56 percent of patients diagnosed during the neonatal period.

Sixty-six percent of all patients had been genotyped, and 75 percent of those genotyped had $CFTR$ mutations specified as one of the 25 mutations in both alleles. The MI group had the highest percentage of patients (99.0 percent of those specified) with “severe” genotypes compared with 93.3 percent, 92.1 percent, and 94.3 percent in the SCREEN, FH, and SYMPTOM groups, respectively ($p < 0.001$). Baseline characteristics of the subgroups of patients included in the analyses of lung disease outcomes did not differ significantly when compared with those of the entire study population.

Survival and lung disease by diagnostic groups

Figure 1 compares survival and lung disease patterns among the four diagnostic groups. The MI group showed a 1.80-fold higher risk of shortened survival (95 percent confidence interval [CI]: 1.27, 2.56; $p = 0.001$) compared with the SCREEN group. The SYMPTOM group also showed a 1.76-fold higher risk of shortened survival (95 percent CI: 1.08, 1.39; $p = 0.001$) and 1.14-fold higher in the SYMPTOM group (95 percent CI: 1.01, 1.28; $p = 0.03$) when compared with the SCREEN group. Consistently, the risk of FEV$_1$ below 70 percent was significantly associated with survival. For each year increase in age at diagnosis, the risk of shortened survival (95 percent CI: 0.93, 0.97; $p < 0.001$) compared with the SCREEN group ($p = 0.001$), FH ($p = 0.048$), or SYMPTOM ($p = 0.001$) group relative to the SCREEN group remained unchanged. A parallel analysis was performed on the subgroup of 13,687 patients diagnosed after 1986. In this subgroup analysis, $p$ values became greater, although they remained significant between the MI and SCREEN groups ($p = 0.014$).

With regard to lung disease (figure 1), our analyses showed that the risks of acquiring $P.$ aeruginosa were 1.23-fold higher in the MI group (95 percent CI: 1.08, 1.39; $p = 0.001$) and 1.14-fold higher in the SYMPTOM group (95 percent CI: 1.01, 1.28; $p = 0.03$) when compared with the SCREEN group. Consistently, the risk of FEV$_1$ <70 percent decreased by 3 percent (95 percent CI: 0.32, 0.65; $p = 0.001$) compared with the SCREEN group. The FH group showed a slightly higher risk of shortened survival when compared with the SCREEN group ($p = 0.046$).

In view of significant advances in the treatment of cystic fibrosis over the last two decades, we examined the potential cohort effect on survival patterns for the four diagnostic groups. As expected, survival was the best among patients diagnosed after 1990 followed by those diagnosed after 1980, and it was the worst for those diagnosed after 1970 (figure 2). Because proportionately more patients in the SCREEN group were diagnosed in a more recent cohort (i.e., 90 percent were diagnosed after 1980 compared with 75 percent, 55 percent, and 67 percent in the MI, FH, and SYMPTOM groups, respectively), which may explain their better survival pattern, we adjusted this cohort effect by including calendar year of diagnosis as a covariate in the analysis. The survival disadvantage associated with the MI ($p = 0.001$), FH ($p = 0.048$), or SYMPTOM ($p = 0.001$) group relative to the SCREEN group remained unchanged. A parallel analysis was performed on the subgroup of 13,687 patients diagnosed after 1986. In this subgroup analysis, $p$ values became greater, although they remained significant between the MI and SCREEN groups ($p = 0.014$).

With regard to lung disease (figure 1), our analyses showed that the risks of acquiring $P.$ aeruginosa were 1.23-fold higher in the MI group (95 percent CI: 1.08, 1.39; $p = 0.001$) and 1.14-fold higher in the SYMPTOM group (95 percent CI: 1.01, 1.28; $p = 0.03$) when compared with the SCREEN group. Consistently, the risk of FEV$_1$ below 70 percent of predicted tended to be higher in the MI (odds ratio [OR] = 1.39, $p = 0.07$) and the SYMPTOM (OR = 1.32, $p = 0.11$) groups, but the statistical significances were borderline.

Gender and genotype as baseline risk factors

Our subsequent analysis incorporated gender and genotype in the previously established model that included the four diagnostic groups. Compared with males, females with cystic fibrosis were at higher risk of shortened survival and $P.$ aeruginosa acquisition (table 2). Compared with the “homozygous ∆F508” group, “severe genotype other than homozygous ∆F508” was associated with a significantly lower risk of shortened survival, whereas the “mild genotype” group had lower risks of shortened survival and $P.$ aeruginosa acquisition (table 2). No differences in the risk of having poor lung function were found among all genotype groups.

Survival and lung disease outcomes by type of initial presenting symptoms

Table 3 shows the baseline characteristics, and figure 3 compares survival and lung disease patterns, by type of initial presenting symptoms. Compared with the RESP + GI group, the OTHER group had a 54 percent risk of shortened survival (95 percent CI: 0.37, 0.71; $p < 0.001$), a 66 percent risk of acquiring $P.$ aeruginosa (95 percent CI: 0.54, 0.79; $p < 0.001$), and a 46 percent risk of poor lung function (95 percent CI: 0.32, 0.65; $p < 0.001$). The OTHER + RESP/GI group was also found to have lower risks of shortened survival ($p < 0.001$) and poor lung function ($p < 0.001$) but not $P.$ aeruginosa acquisition ($p = 0.15$) when compared with the RESP + GI group. These trends remain unchanged when the analyses were restricted to patients diagnosed after 1986.

Age at diagnosis was found to be significantly associated with survival. For each year increase in age at diagnosis, the risks of shortened survival, acquisition of $P.$ aeruginosa, and FEV$_1$ <70 percent decreased by 3 percent (95 percent CI: 0.96, 0.98; $p < 0.001$), 5 percent (95 percent CI: 0.93, 0.97; $p < 0.001$), and 3 percent (95 percent CI: 0.95, 0.99; $p < 0.001$), respectively. When we included gender and genotype in these analyses, the better survival and lung function
outcome observed in the OTHER group (OR = 0.49, 95 percent CI: 0.27, 0.90; \( p = 0.02 \) for survival and OR = 0.45, 95 percent CI: 0.25, 0.79; \( p = 0.005 \) for lung function) and in the OTHER + RESP/GI group (OR = 0.69, 95 percent CI: 0.56, 0.86; \( p = 0.001 \) for survival and OR = 0.66, 95 percent CI: 0.51, 0.86; \( p = 0.002 \) for lung function) relative to the RESP + GI group remained statistically significant.

**DISCUSSION**

In the present study, we used a new approach to incorporate the concept of “baseline risk” into the development of innovative models to assess survival and lung disease outcomes in the cystic fibrosis population. To our knowledge, our strategy for constructing the major baseline risk variable, that is, segregating patients into four diagnostic...
groups according to the timing and condition leading to identification of cystic fibrosis, is novel. For example, a common approach used by previous studies (6, 25, 26) to examine whether the timing of diagnosis influences survival has been to include age at diagnosis as a predictor in the statistical model. This strategy is flawed because age at diagnosis is confounded by mode of diagnosis. An early age at diagnosis could be a result of meconium ileus, a “severe” cystic fibrosis phenotype that may lead to shortened survival. Alternatively, an early age at diagnosis could be a result of positive prenatal/neonatal screening, which generally identifies cystic fibrosis infants at presymptomatic stages, and thus could lead to improved survival. Second, a late age at diagnosis could be a result of an unsatisfactory health care delivery system, which might result in substantial progression of disease because of inadequate treatment, creating a negative association between age at diagnosis and survival. Alternatively, a late age at diagnosis could be attributable to a late presentation of symptoms, which may indicate mild cystic fibrosis; this possibility could create a positive associ-
Disease Presentation and Survival in Cystic Fibrosis

Our findings that patients presenting with meconium ileus had the worst survival and lung disease outcomes, whereas patients identified via prenatal/neonatal screening had the best survival and lung disease outcomes, provide strong evidence of the confounding effects between age at diagnosis and mode of diagnosis on cystic fibrosis prognosis.

The findings of various investigators achieving early diagnosis of patients without meconium ileus, particularly those using newborn screening (12–14, 17–19), have led to an

TABLE 2. Associations of baseline risk factors with survival and lung disease outcomes in US patients reported to the 1986–2000 Cystic Fibrosis Foundation Patient Registry

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>Survival (n = 13,690)</th>
<th>FEV1 &lt;70% (n = 3,320)</th>
<th>Pseudomonas aeruginosa acquisition (n = 5,290)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR† 95% CI†</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Diagnostic group (compared with SCREEN†)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI†</td>
<td>2.59** 1.28, 5.25</td>
<td>1.18 0.78, 1.80</td>
<td>1.18* 1.01, 1.36</td>
</tr>
<tr>
<td>FH†</td>
<td>2.21* 1.06, 4.61</td>
<td>0.99 0.57, 1.73</td>
<td>1.25* 1.01, 1.56</td>
</tr>
<tr>
<td>SYMPTOM†</td>
<td>2.63** 1.31, 5.29</td>
<td>1.15 0.77, 1.71</td>
<td>1.13 0.98, 1.30</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.27*** 1.14, 1.41</td>
<td>1.11 0.95, 1.28</td>
<td>1.10** 1.02, 1.17</td>
</tr>
</tbody>
</table>

Genotype (compared with ∆F508/∆F508)

Severe genotype other than ∆F508/∆F508‡: 0.76*** 0.67, 0.86; 0.88 0.74, 1.05; 1.03 0.95, 1.11

Mild genotype§: 0.51*** 0.37, 0.70; 1.16 0.55, 1.33; 0.65* 0.42, 1.00

* p ≤ 0.05; ** p ≤ 0.01; *** p ≤ 0.001.
† FEV1, forced expiratory volume in 1 second; OR, odds ratio; CI, confidence interval; SCREEN, group of patients without meconium ileus and identified via prenatal/neonatal screening; MI, group of patients with meconium ileus; FH, group of patients with a positive family history without symptoms; SYMPTOM, group of patients with symptoms other than meconium ileus.
‡ Includes ∆F508/non-∆F508-I, II, III and non-∆F508-I, II, III, non-∆F508-I, II, III; refer to table 1 for specific mutations categorized to classes I–V.
§ Includes ∆F508/IV, V; non-∆F508-I, II, III/IV, V; and IV, V/IV, V. See table 1 for specific mutations categorized to classes I–V.

atation between age at diagnosis and survival. Our findings that patients presenting with meconium ileus had the worst survival and lung disease outcomes, whereas patients identified via prenatal/neonatal screening had the best survival and lung disease outcomes, provide strong evidence of the

TABLE 3. Demographic and genotypic characteristics, by type of initial presenting symptoms, of 19,956 US patients identified because of symptoms other than meconium ileus, 1986–2000

<table>
<thead>
<tr>
<th>Type of initial presenting symptoms (category)</th>
<th>RESP* + GI*</th>
<th>RESP</th>
<th>GI</th>
<th>OTHER + RESP/GI</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Patients</td>
<td>7,391 37.0</td>
<td>4,575 22.9</td>
<td>4,746 23.8</td>
<td>2,623 13.1</td>
<td>621 3.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3,952 53.5</td>
<td>2,400 52.5</td>
<td>2,583 54.4</td>
<td>1,367 52.1</td>
<td>346 55.7</td>
</tr>
<tr>
<td>Female</td>
<td>3,439 46.5</td>
<td>2,175 47.5</td>
<td>2,163 45.6</td>
<td>1,256 47.9</td>
<td>275 44.3</td>
</tr>
<tr>
<td>Age at diagnosis (months) Median</td>
<td>8.4</td>
<td>25.8</td>
<td>6.0</td>
<td>16.2</td>
<td>29.0</td>
</tr>
<tr>
<td>Mean (standard deviation)</td>
<td>31.1 (59.6)</td>
<td>84.7  (124.3)</td>
<td>20.8 (41.1)</td>
<td>57.2 (100.9)</td>
<td>72.2 (107.3)</td>
</tr>
<tr>
<td>Genotyped</td>
<td>4,690 63.5</td>
<td>2,871 62.8</td>
<td>2,948 62.1</td>
<td>1,927 73.5</td>
<td>436 70.2</td>
</tr>
<tr>
<td>CFTR mutations specified</td>
<td>3,568 48.3</td>
<td>1,822 39.8</td>
<td>2,290 48.3</td>
<td>1,409 53.7</td>
<td>276 44.4</td>
</tr>
<tr>
<td>Genotypes among those with CFTR specified†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆F508/∆F508</td>
<td>2,545 71.3</td>
<td>1,046 57.4</td>
<td>1,675 73.1</td>
<td>928 65.9</td>
<td>174 63.0</td>
</tr>
<tr>
<td>∆F508/non-∆F508-I, II, III</td>
<td>790 22.1</td>
<td>461 25.3</td>
<td>509 22.2</td>
<td>344 24.4</td>
<td>60 21.7</td>
</tr>
<tr>
<td>∆F508/IV, V</td>
<td>93 2.6</td>
<td>180 9.9</td>
<td>25 1.0</td>
<td>74 5.3</td>
<td>23 8.3</td>
</tr>
<tr>
<td>Non-∆F508-I, II, III, non-∆F508-I, II, III</td>
<td>108 3.0</td>
<td>74 4.1</td>
<td>72 3.1</td>
<td>42 2.5</td>
<td>10 3.6</td>
</tr>
<tr>
<td>Non-∆F508-I, II, III/IV, V</td>
<td>20 0.56</td>
<td>40 2.2</td>
<td>8 0.35</td>
<td>20 1.4</td>
<td>9 3.3</td>
</tr>
<tr>
<td>IV, V/IV, V</td>
<td>12 0.34</td>
<td>21 1.15</td>
<td>1 0.04</td>
<td>1 0.07</td>
<td>0</td>
</tr>
</tbody>
</table>

* RESP, group of patients with respiratory symptoms; GI, group of patients with gastrointestinal symptoms.
† Refer to table 1 for specific mutations categorized to classes I–V.

Am J Epidemiol 2004;159:537–546
expectation that better survival might result from presymptomatic identification and early treatment of children with cystic fibrosis. This expectation is supported by an early observational study by Shwachman and Kulczycki (15) and more recent, regional-based studies by Merelle et al. (17) and Assael et al. (19), all of which demonstrated the trends toward better survival in favor of neonatal screening. However, these trends failed to reach statistical significance because of small numbers of deaths in the study populations, and each assessment was potentially confounded by ascertainment and screening biases. One trial (18) with randomly generated, concurrently managed patients demonstrated 5 percent mortality in the nonscreened group compared with no deaths with early diagnosis during the first 5 years of life.
In the present study, we used the large database from the Cystic Fibrosis Foundation Registry and demonstrated significant associations between initial disease presentation and prognosis. Nevertheless, convincing evidence on the potential survival benefit of neonatal screening will depend on results from longitudinal controlled clinical trials such as the Wisconsin Cystic Fibrosis Neonatal Screening Project (12, 13).

In addition to mode of diagnosis, we observed that type and severity of the initial presenting symptom are also significantly associated with lung disease outcomes and survival. It has long been suspected that the condition of patients at the time of diagnosis has a strong influence on their prognosis. For instance, Shwachman et al. (27) reported on the condition of 130 infants diagnosed presymptomatically with either mild or severe symptoms requiring hospitalization and found that those with predominantly lung disease had relatively reduced survival. Hudson and Phelan (6) reported similar results. These investigators postulated that both age and condition at diagnosis were important factors in contributing to morbidity and mortality. Nevertheless, generalization of the findings from these studies (6, 27) is limited because of their small study populations. By using the large Cystic Fibrosis Foundation Registry and excluding patients identified because of meconium ileus or prenatal/ neonatal screening, we demonstrated that initial presentation involving the combination of respiratory and gastrointestinal manifestations was associated with the greatest risk, whereas initial presentation involving only the less common features of cystic fibrosis was associated with the lowest risk, of shortened survival and poor lung disease outcomes.

Combining results from our present and previous (28) studies, we demonstrated that patients with meconium ileus experience more severe malnutrition, greater risks of acquiring P. aeruginosa and having poor lung function, and a greater mortality risk compared with patients identified at similar ages via prenatal/neonatal screening. Although several studies in the past decade (29–32) reported that meconium ileus patients no longer had poorer survival or clinical progression compared with patients without meconium ileus, these studies examined small numbers of patients, and the analyses did not account for the difference in timing of diagnosis and treatment. Therefore, our findings provide strong evidence to support the hypothesis proposed by other investigators that meconium ileus represents a distinct cystic fibrosis phenotype (6, 33).

The potential associations between genotype and phenotype have been studied since the CFTR gene was discovered in 1989 (34). A strong link between the homozygous ΔF508 genotype and pancreatic insufficiency has been reported consistently, and several class IV or V mutations have been reported to be associated with pancreatic sufficiency (2, 35). However, the associations between genotype and lung disease remain unclear. Some studies reported poorer lung function and a higher P. aeruginosa colonization rate among patients with homozygous ΔF508 relative to heterozygous ΔF508 and non-ΔF508 mutations (3, 35); others reported no significant correlations (7, 36–38). Very few studies have examined the association between genotype and survival. In a recent study by Liou et al. (9), who analyzed the 1993–1997 Cystic Fibrosis Foundation Registry, risk of shortened survival was found not to differ significantly with respect to the ΔF508 genotype. However, this study (9) did not control for differences in timing and initial disease presentation, and it excluded young patients who did not yet have FEV₁ values. We found that patients with the homozygous ΔF508 genotype had a significantly greater risk of shortened survival and earlier P. aeruginosa acquisition but not poor lung function when compared with patients with presumably “mild” genotypes (those containing class IV or V mutations in one or both alleles).

Despite these findings, several limitations of the present study should be noted. First, the differential survival and lung disease outcomes associated with initial presentations may not be solely attributable to these presentations because insufficient data on the timing, adequacy, and appropriateness of treatment are available from the Cystic Fibrosis Foundation Registry to enable treatment effects to be removed. Additional prospective studies with long-term follow-up are needed to examine the relative contributions of baseline risk factors versus treatment influences. Second, interpretations of our results rely on the assumption that patients who were reported to the Cystic Fibrosis Foundation Registry had experiences similar to those who were not observed. Third, results on lung disease outcomes are limited by statistical techniques not yet routinely available to analyze P. aeruginosa colonization and FEV₁ data with left-truncation and double-censoring characteristics and because only one parameter (i.e., FEV₁ <70 percent predicted) was used to indicate lung function status.

In conclusion, results from the present study support our concept that baseline risk, determined by age and condition at the time of diagnosis, significantly influences lung disease and survival in cystic fibrosis patients. Early diagnosis of presymptomatic patients through newborn screening may lower the morbidity of chronic lung disease and increase survival. On the other hand, patients presenting with meconium ileus, although typically diagnosed and treated early in life, have greater risks of shortened survival and poor lung disease outcomes.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants K01-DK02891, DK34108, and M01 RR03186.

The authors thank Dr. Preston W. Campbell of the Cystic Fibrosis Foundation for providing the Registry data. They also thank Dr. Virginie Scotet of the Universite de Bretagne Occidentale Medical School, Brest, France, for providing assistance with classification of the CFTR mutations.

REFERENCES


21. Sokol RJ, Pegelow CH, Raff RH, et al. Genetic determination of...