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Defining and identifying early-onset lung disease in cystic fibrosis with cumulative clinical characteristics

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Abstract

Background: Because of the heterogeneity in cystic fibrosis (CF) lung disease among young children, a clinical method to identify early-onset lung disease is needed.

Objective: To develop a CF early-onset lung disease (CFELD) scoring system by utilizing prospectively collected longitudinal data on manifestations in the first 3 years of life.

Design: We studied 145 infants born during 2012–2017, diagnosed through newborn screening by age 3 months, and followed to 36 months of age. Cough severity, pulmonary exacerbations (PEx), respiratory cultures, and hospitalizations were collected at each CF center visit (every 1–2 months in infancy and quarterly thereafter). These data were used to construct the CFELD system

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

and to classify lung disease into five categories: asymptomatic, minimal, mild, moderate, and severe.

Results: The most frequent manifestation of CF early lung disease was MD-reported PEx episodes, PEx hospitalizations, and positive *Pseudomonas aeruginosa* cultures. Parent-reported cough severity was correlated with the number of respiratory hospitalizations ($r = 0.48$, $p < 0.0001$). The distribution of CFELD categories was 10% asymptomatic, 17% minimal, 29% mild, 33% moderate, and 12% severe. The moderate and severe categories occurred threefold higher in pancreatic insufficient (PI, 49%) versus sufficient subjects (16%), $p < 0.0001$. In addition to PI, gastrointestinal and nutrition-related hospitalizations, plasma cytokines interleukin (IL)-6 and IL-10, duration of CFTR modulator therapy, and type of health insurance were significant predictors of CFELD scores.

Conclusion: The CFELD scoring system is novel, allows systematic evaluation of lung disease prognosis early, and may aid in therapeutic decision-making particularly in the initiation of CFTR modulator therapy.

Keywords

cough; cystic fibrosis; hospitalization; lung disease; *Pseudomonas aeruginosa* ; pulmonary exacerbation; *Staphylococcus aureus*

1 | INTRODUCTION

Cystic fibrosis (CF), the most frequent life-threatening autosomal recessive disease of Caucasians, is now commonly diagnosed through newborn screening (NBS).[1] Routine diagnosis during the neonatal period by detecting pathogenic variants in the CF transmembrane conductance regulator (*CFTR*) gene has allowed identification of the earliest CF manifestations of infants beyond the 15–20% who present with meconium ileus (MI) at birth.[2] Early measurement of fecal elastase concentration[3] in conjunction with clinical signs of intestinal malabsorption allows more objective detection of pancreatic insufficiency (PI) that causes malnutrition. Widespread implementation of NBS for CF also generated new data consistent with clinical impression that respiratory infections and cough were the characteristic features of early CF lung disease.[4] These observations have added significantly to the invaluable autopsy studies on young infants revealing that although the CF lung appears normal at birth, irreversible pathology, particularly bronchiectasis, develops within 2–4 months.[5–7] A variety of clinical studies with very sensitive assessment capability like chest computed tomography (CT) have also revealed that lung disease can be evident as early as 10 weeks of age.[8,9] In fact, chest CT observations in the AREST CF intensive surveillance program showed that nearly one-third of patients had bronchiectasis at 3 months of age.[10] These findings are in keeping with observations in the Wisconsin RCT of NBS that led to discovery of surprisingly early respiratory symptoms, particularly quantifiable cough in many infants[10] and high impact infections with *Pseudomonas aeruginosa* (PA) leading to hospitalizations.[11,12] More recent evaluation of 6654 children with CF diagnosed through NBS from 2010 to 2018 in the United States revealed that about one-third were hospitalized before 1 year of age, most hospitalizations were for pulmonary exacerbations (PEx), some required repeated admissions, and the proportion hospitalized did not change over time.[4]

Thus, even though the CF lung appears normal at birth,[5,7] the detrimental impact of the CFTR ion channel defect on the respiratory system can develop early in life and be severe enough to cause frequent hospitalizations and irreversible pathology.[4,7–9] In addition, early development of lung disease correlates with its progression in children.[13,14]

There is great heterogeneity in the severity of CF, particularly in both the onset and the progression of lung disease.[14–18] Even among patients homozygous for the F508del variant or siblings with the same *CFTR* genotype and home environment, the severity of lung disease is variable.[19] This heterogeneity appears during the first few years of life[4,11] but is challenging to recognize or predict definitively with current care practices. Although high sensitivity assessment methods like chest CT and lung clearance index (LCI) by the multiple breath washout technique are promising,[20,21] they apply best to research studies rather than routine practice.[22] The lack of a standardized clinical method of evaluating the severity and progression of CF lung disease in preschool children limits both research and individualized therapeutic decision-making in this evolving era of precision personalized medicine. Yet it is reasonable to assume and hypothesize that the most characteristic features of CF lung disease are clear enough that they should be recognizable by systematic, prospective clinical evaluations. These include cough, PA-positive cultures, and PEx episodes that are all potentially recurrent and quantifiable. Proceeding under this assumption, we were afforded an ideal opportunity to address this gap in knowledge in a multicenter prospective longitudinal project known as FIRST (Feeding Infants Right…from the STart) that disclosed heterogeneity in clinical outcomes during early childhood in a relatively large cohort.[23] The primary aim of this study was to establish a novel scoring system using the longitudinal pulmonary data gathered through the FIRST project to characterize early-onset lung disease in young children with CF. The secondary aim was to identify the risk factors associated with an early-onset phenotype.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The FIRST cohort consists of 183 infants who were born during 2012–2017, enrolled after NBS, and are being followed at six CF Centers (Madison and Milwaukee, WI; Boston, MA; Indianapolis, IN; Salt Lake City, UT and Chicago, IL) until all children reach age 6 years in 2023. Study visits are conducted in conjunction with routine clinical care at these CF centers according to clinical practice guidelines for treatment and regular follow up evaluations,[3,22] i.e., monthly after diagnosis until age 6 months, bi-monthly from 6 to 12 months, and every 3 months thereafter. The FIRST project was approved by the Institutional Review Boards at all participating institutions. Informed written consent was obtained from the parents/guardians of all participating infants.

The entire FIRST cohort reached 3 years of age by 12/31/2020: 172 (94%), 160 (87%) and 145 children (79%) completed follow-up to ages 12, 24, and 36 months, respectively.[23] We recognized that the subgroup of 145 infants (79% of enrollees) afforded us an unprecedented opportunity to evaluate in detail the evolving characteristics of lung disease, if any, during early childhood. Table 1 provides demographic, socioeconomic (SES), and CF characteristics on these children. In the present study, we report quantitated clinical

features of CF lung disease in the first year of life, cumulative over 1–2 years, and cumulative over 1–3 years using a novel scoring system we developed and refer to as CFELD for CF early-onset lung disease. The methods used in the development process were based on our previous experience creating an infant lung disease index applicable to bronchopulmonary dysplasia[24] and the Wisconsin Cystic Fibrosis Chest Radiograph Scoring System[25]—both of which relied on applying multiattribute utility theory[26] with contributions from a group of four pediatric pulmonologists. After an initial assessment of the FIRST database observations and organization of the lung disease indicators, the panel of pulmonology experts, with a total of over 100 years' experience taking care of CF infants and children, considered and recommended options for aggregating the data into an early lung disease scoring system that could be validated with the same data as done previously[24,25] in keeping with the multiattribute methodology.[26,27]

2.2 | Characterizing clinical manifestations of CF lung disease

At each FIRST study visit, a pulmonary interval history questionnaire is administered by trained research coordinators to collect data on respiratory symptoms, PEx, respiratory infections, and hospitalizations during the interval since the last clinic visit. A total of 2469 pulmonary interval history questionnaires were prospectively collected in the first 3 years of life and used to assess cough and respiratory infections described below.

Respiratory symptoms included parent-reported cough and wheezing scored as 0 (none), 1 (occasional), 2 (frequent) and 3 (constant), as well as MD-reported cough during physical exam at the time of clinic visit, with a score of 0 (none), 1 (occasional), 2 (mild dry cough), 3 (mild productive cough) or 4 (severe productive cough). The raw cough scores at each visit were used to calculate a cumulative cough score (running average of all previous visits' scores) at age 1 year, cumulative over 1–2 years, and cumulative over 1–3 years, respectively. Our intent was to utilize the cumulative cough scores to define a "chronic cough" phenotype as we assume that (1) chronic cough is the first symptom of CF lung disease in most children, and (2) parents are sensitive observers in detecting and rating cough of their infants in their first years of life. The severity of chronic cough was defined by a cumulative cough score indicating greater than occasional cough for <50% of the time (score of <1.5), 50–74% of the time (score of 1.5–1.74), or more than 75% of the time (score of ≥1.75).

Respiratory infections were also documented in each pulmonary interval history questionnaire; these data include the number of infections since the last clinic visit, and whether each infection was a PEx (MD-reported PEx) as judged by clinicians who were guided by the pulmonary interval history form to record the symptoms of PEx, namely, increased cough, runny/stuffy nose, sputum production, fever of >100 degrees Fahrenheit, shortness of breath, decreased appetite and activity, as well as treatment with antibiotics.

Microbial infections were assessed by respiratory microbiology using oropharyngeal cultures at each study site during the subject's routine CF center visits. Culture results were entered to the FIRST study database as normal flora, or positive for the following microorganisms commonly detected in young children with CF[28]: *Staphylococcus aureus* (SA), PA, Methicillin-resistant SA (MRSA), *Haemophilus influenzae, Stenotrophomonas*

maltophilia, Achromobacter xylosoxidans, and Burkholderia cepacia complex. A total of 2190 respiratory culture reports were evaluated to determine the age and number of PA and SA infections in the first 3 years of life.

Hospitalizations since the last clinic visit were retrieved from discharge summaries and recorded in each pulmonary interval history form. For each hospitalization, the dates of admission and discharge, as well as the diagnosis/reason for admission, e.g., PEx, PA or MRSA eradications, other respiratory related reasons (e.g., rhinovirus/RSV infections, viral bronchiolitis, sinus surgery, etc), or GI/nutrition-related reasons (e.g., poor weight gain, gastrostomy tube placement, etc) were entered into the FIRST study database.

2.3 | Defining CF early-onset lung disease (CFELD)

Using the data described above, we developed the CFELD scoring system aimed at identifying early-onset CF lung disease. Specifically, we utilized cumulative longitudinal data from the first 3 years of life on 8 measures to derive an overall CFELD score for each subject, and then used the CFELD scores to classify subjects into five categories of lung disease: asymptomatic, minimal, mild, moderate, and severe. As described in detail in Table 2, each CFELD component was assigned 1, 2, or 3 points based on their frequency of occurrence in the first 3 years of life. The sum of the points from all 8 subscores constituted the overall CFELD score, which has a maximum attainable score of 15 points.

2.4 | Plasma inflammatory markers

In addition to clinical characteristics to assess lung disease onset longitudinally, we measured four cytokines commonly assessed in the CF population[29]: interleukin (IL)-6, IL-8, IL-10 and tumor necrosis factor (TNF)-α, in plasma collected concurrently with clinical blood draws without additional phlebotomy at approximately 4 months of age and annually thereafter. Cytokines were quantified using the MILLIPLEX® MAP human cytokine/chemokine magnetic bead panel in the Luminex analyzer MAGPIX®, (EMD Millipore, Millipore Sigma, Merck KGaA) according to the manufacturer's instructions.[30] Elevated cytokine levels were defined using values published from the Associated Regional and University Pathologists, Inc. (ARUP) Laboratories (https://ltd.aruplab.com/Tests/Pub/0051394) as follows: IL-6 > 2.5 pg/ml, IL-8 > 9.4 pg/ml, IL-10 > 5.3 pg/ml, and TNF-α> 14.5 pg/ml. High cytokines in the first 3 years of life was defined as the percent of time (equivalent to the percent of measurements with elevated values divided by the number of all measurements). This definition captured the entire history in the first 3 years of life because it utilized all longitudinal measurements of the cytokines for each individual, as opposed to a single value of the average of all values or any elevated value.

2.5 | Other relevant covariates

Information on CF-causing variants in the *CFTR* gene, gestational age, birth weight and length, and the occurrence of MI were collected from electronic medical records. Pancreatic functional status was assessed at 2, 4, 6, 8, 12 months of age and annually thereafter by fecal elastase-1 concentration. Children with CF were classified as pancreatic sufficient (PS) if their fecal elastase-1 levels were consistently >200 μg/g in the first 2 years of life.[31] Use of CFTR modulatory therapies was collected in the medication section of the pulmonary

interval history form at each CF center visit. For age ≤36 months, only ivacaftor (approved in for age 2–5 years in 2015 and for infants in 2019) and ivacaftor/lumacaftor (approved for age 2–5 years in 2018) are approved. Therefore, in the FIRST study cohort, only younger subjects born after 2015 were eligible for these two modulators.

Demographics were recorded by the research coordinators at enrollment. Race was termed as recommended by the NIH, i.e., White, Black or African-American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and More than One Race. Ethnicity was termed Hispanic or Latino and Not Hispanic or Latino. SES data such as those presented in Table 1 were collected at enrollment and annually via a parent questionnaire.

2.6 | Statistical analysis

Analysis of variance and the median test were used to compare means and medians, respectively. Chi-square test and Fisher's exact test (when sample size was <5 in any subgroup) were used to compare proportions. Correlations between respiratory measures and/or plasma cytokine concentrations were assessed by Pearson's correlation coefficient.

To identify factors significantly associated with CFELD scores through 3 years of age, multiple regression model was performed. To assess the likelihood of having early-onset CF lung disease, ordinal logistic regression analysis was performed using the five CFELD categories. All analyses were performed by using SAS (version 9.4).

3 | RESULTS

3.1 | Characteristics of the study population

The characteristics of the FIRST cohort were described recently[23] and are summarized in Table 1. *CFTR* genotypes classified by pathologic variants with and without F508del and the distribution of pancreatic phenotypes resembled the national CF population as reported in the 2020 CFF Patient Registry.[29] Our study cohort only had four non-White subjects: one Black and three identifying as *more than one race*.

3.2 | Prevalence of each CFELD manifestation

The most frequent clinical manifestation of CF lung disease in the FIRST cohort during their first 3 years of life was MD-reported PEx episodes, followed by PEx hospitalizations and positive PA cultures (Figure 1). A total of 405 MD-reported PEx episodes were documented in the first 3 years of life, among them, 96% were treated with antibiotics. The most frequent symptom reported during PEx episodes was increased cough (95%), followed by runny/stuffy nose (69%), increased sputum (33%), decreased appetite (29%), fever >100 degrees Fahrenheit (21%), decreased activity (14%), and shortness of breath (10%). Parent-reported chronic cough occurred in approximately 60% of the FIRST cohort by age 3 years. Combining all respiratory hospitalizations (Figure 1B), a total of 266 hospitalization episodes were documented in 2469 pulmonary interval history forms (11%) in the first 3 years of life. Only 10% of subjects did not exhibit any pulmonary manifestations.

3.3 | Correlations of PEx episodes and chronic cough with respiratory hospitalizations

In addition to determining the prevalence of each of the eight CFELD manifestations, we also examined whether the five nonhospitalization measures (Figure 1A) were correlated with the number of respiratory hospitalizations. The number of MD-reported PEx episodes in the first 3 years of life and parent-reported cumulative cough scores, the outcome we used to identify chronic cough, were found to be highly associated with number of respiratory hospitalizations (Figure 2). On the other hand, PA + and MRSA + cultures were not correlated with respiratory hospitalizations, and concurrent PA + and SA + cultures were only weakly associated respiratory hospitalizations ($r = 0.17$, $p = 0.03$).

3.4 | Distribution of the CFELD scores

We next evaluated the spectrum of the CFELD scores. Although the maximum attainable CFELD score is 15 points, the highest CFELD score in the FIRST cohort was 12 (Figure 3). The prevalence of CFELD categories were 10% asymptomatic, 17% minimal, 29% mild, 33% moderate, and 12% severe. We consider the moderate and severe categories as representing an early-onset lung disease phenotype. The proportion of infants in the early-onset phenotype was 45%, and only 10% of infants were in the asymptomatic category, which we consider a delayed onset phenotype. The highest CFELD score for patients with PS was 9, consistent with a less severe pulmonary phenotype. In the early-onset phenotype, 100% of subjects had at least one occurrence of MD-reported PEx, and more than 50% were hospitalized for PEx at least once.

3.5 | CFELD phenotype distributions by age and pancreatic phenotype

The prevalence of CFELD early-onset phenotype increased by threefold from age 1 to 3 years (Figure 4A, moderate and severe categories). When stratified by pancreatic phenotype, almost half of infants with MI (neonatal presentation of PI) and PI had the early-onset phenotype. In contrast, nearly half of infants with PS had the delayed onset phenotype (Figure 4B).

3.6 | Predictors of CFELD scores and categories

Our final analysis applied multiple regression models to identify factors associated with CFELD scores and the five CFELD phenotypes. Because IL-8, IL-10 and TNF-α were highly correlated ($r > 0.56$ for all pairwise correlations), we chose to include IL-10 (lowest p value in the correlation analysis) and IL-6 (low correlations with all other 3 cytokines, $r < 0.20$ for all pairwise correlations) in Table 3.

Multiple regression model using the CFELD score as a continuous variable showed that PI subjects had a higher (worse) CFELD score compared to PS subjects (Table 3). Having GI/nutrition-related hospitalizations was also predictive of higher CFELD scores. Longer duration of CFTR modulator therapy was associated with lower CFELD scores. High plasma IL-6, which is a proinflammatory cytokine,[32] was associated with higher CFELD scores. In contrast, high plasma IL-10, which is anti-inflammatory cytokine,[33] was associated with lower CFELD scores. Regarding SES indicators, having Medicaid/public health insurance or daycare exposure was associated with higher CFELD scores, except the daycare effect had a borderline significant p value of 0.06.

In conjunction with the above, results from ordinal logistic regression analysis showed that having PI, having GI/nutrition-related hospitalizations, and having Medicaid/public health insurance increased the likelihood of being in the more severe CFELD categories. On the other hand, having elevated plasma IL-10 and longer duration of CFTR modulator therapy decreased the likelihood of being in the more severe CFELD categories.

4 | DISCUSSION

During the past decade while early diagnosis of CF through NBS has been routine, it has become increasingly apparent that lung disease often develops during the first year of life,[4] thus confirming observations from autopsy studies[5–7] and chest CT imaging.[8–10] This early lung disease phenotype is also evidenced in the CFF Patient Registry database by a surprisingly high incidence of hospitalizations, i.e., about one-third of patients are hospitalized by 12 months of age based on the well-studied 6354 children with CF born in the United States between 2010 and 2018, diagnosed through NBS, and then enrolled in the CFF Patient Registry as reported by Martiniano et al.[4] Yet our ability in routine pulmonology practice to recognize what has been called “the relatively silent nature of early CF lung disease”[34] and to quantitate its severity have been limited. The usual objective measures of CF lung disease based on pulmonary function tests and imaging procedures have not applied well to young children except in highly controlled, labor intensive research settings.[20,21] Some studies have argued for using the multiple breath washout technique to determine LCI data serially.[20,21] However, a clinical practice guidelines committee convened by the CF Foundation concluded in 2016 that there was “insufficient evidence to recommend” this method for preschool children.[22] Also, based on published evidence, the committee only suggested “consideration of chest CT… every 2–3 years.” Thus, attempts over many decades to use pulmonary function tests to identify and quantitate early lung disease have had limited success in routine clinical practices while chest CT imaging has not provided a risk-free alternative for serial use at intervals that apply during the first few years of life. Yet during the era of CF NBS as these patients are being evaluated in CF specialty clinics every 1–3 months,[3] there is an abundance of rich clinical information being obtained routinely. An important challenge, in our judgment, has been how to interpret and apply this information. This gap underscores the need for a lung disease clinical evaluation method in preschool children with CF. The study reported herein achieved our goal of using readily available clinical information reflecting the most characteristic features of CF lung disease to develop the CFELD scoring system as a method to identify an early-onset phenotype and enable longitudinal quantitation of lung disease.

Our previous successes with creating and validating other lung disease scoring methods[24,25] and the abundance of systematic observations in the relatively large FIRST cohort proved invaluable. Refinement of the first CFELD iteration by relying on a panel of four experts allowed us to proceed with validation assessment, although the parental cough scoring component had been validated previously.[11] Our results confirm the reliability of parent-reported coughing. In addition, our comparison of hospitalizations, which we consider invaluable indicators of illnesses, with MD-reported PEx episodes was revealing as were the associations of CFELD score with pancreatic phenotype, CFTR modulator therapy, and SES indicators such as the type of health insurance coverage.

Limitations include a paucity of African-American and Hispanic CF patients and perhaps the methodology for constructing the CFELD score. Although CF is often considered a genetic disease of Caucasians, patients diagnosed through NBS during the past decade in the United States have been shown to include 20% non-White children[4]; however, we made special efforts to recruit minorities such as expanding enrollment opportunities to include the Chicago area with its more diverse population. Selection of the eight CFELD measures reflects our conclusions about the most characteristic features of CF.[10,17,20] Although selection of these characteristics is subjective and based on experienced clinicians' opinions rather than being entirely evidence driven, the application of multiattribute utility theory relies on consensus development from expert opinions.[24–27] These opinions were also relied upon for the arbitrary assignment of maximum points for each component. Two measures (PEx episodes and PEx hospitalizations) were assigned 3 points, in keeping with the indisputable importance of PEx in CF,[4,10,34] while three measures (positive PA culture, PA hospitalization, and cough) were assigned 2 points, and two measures (concurrent PA and SA positivity and other respiratory-illness hospitalizations) were only assigned 1 point. Another related limitation is that the CFELD scoring system has not been tested in another independent study population, but this can be done in a future project.

This study closes a gap because there has never been a clinical method applicable to identifying early-onset lung disease in young children with CF. It is interesting that about half the patients show moderate or severe lung disease indicative of an early-onset phenotype by the CFELD system and only 27% had minimal or no signs/symptoms of CF lung disease over the 3 years of observations. Our finding that the duration of CFTR modulator therapy was significantly associated with less severe CFELD scores also supports efforts to extend CFTR modulator therapy to young children. Increasing use of highly effective modulator therapy in the future would likely reduce CFELD scores, which would therefore provide another quantitative method of judging their impact on individual patients particularly in the moderate and severe categories. The 17% and 29% in the minimal and mild categories, respectively, have an uncertain or evolving phenotype. These patients, together with the 10% asymptomatic patients who we consider having a relatively delayed-onset phenotype, all need ongoing assessment.

Establishing a novel lung disease scoring system as a clinical method of evaluating the severity of CF lung disease in young children provides a new tool for clinical research in young children with CF. But more investigations will be needed to determine if our ultimate goal to identify patients at an increased risk for developing early-onset CF lung disease can be achieved across CF centers. This is increasingly important as new therapies become available to the very young population and will ideally be started before irreversible lung disease develops, i.e., bronchiectasis ensues.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

Abbreviations:

CF	cystic fibrosis
CFELD	cystic fibrosis early-onset lung disease
FIRST	feeding infants right… from the start
MI	meconium ileus
MRSA	methicillin-resistant *Staphylococcus aureus*
PA	pseudomonas aeruginosa
PE	pulmonary exacerbation
PI	pancreatic insufficiency
PS	pancreatic sufficiency
SA	*Staphylococcus aureus*

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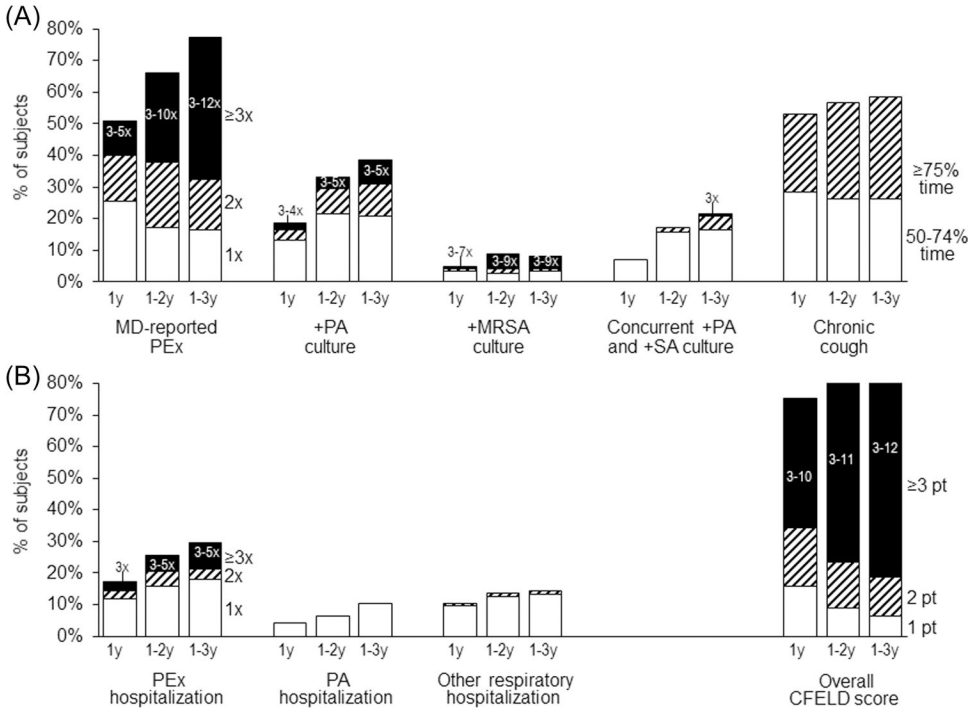

FIGURE 1.

Prevalence of the eight clinical manifestations (five nonhospitalization measures in (A) and three hospitalization measures in (B) used to construct the CF early-onset lung disease (CFELD) scoring system in the first year of life (1y), cumulative over 1–2 years (1–2y), and cumulative over 1–3 years (1–3y) in the FIRST cohort. The percentages of subjects who had one occurrence (1×), two occurrences (2×) and three or more occurrences (≥3×) in each manifestation are shown as open, hatched and black bars, respectively. The number inside the top black bar indicates the range of the frequency of occurrence for that manifestation. Chronic cough was defined by using cumulative cough scores indicative of having greater than occasional cough by parental report for more than 50% of time as explained in Table 2. CF, cystic fibrosis; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation.

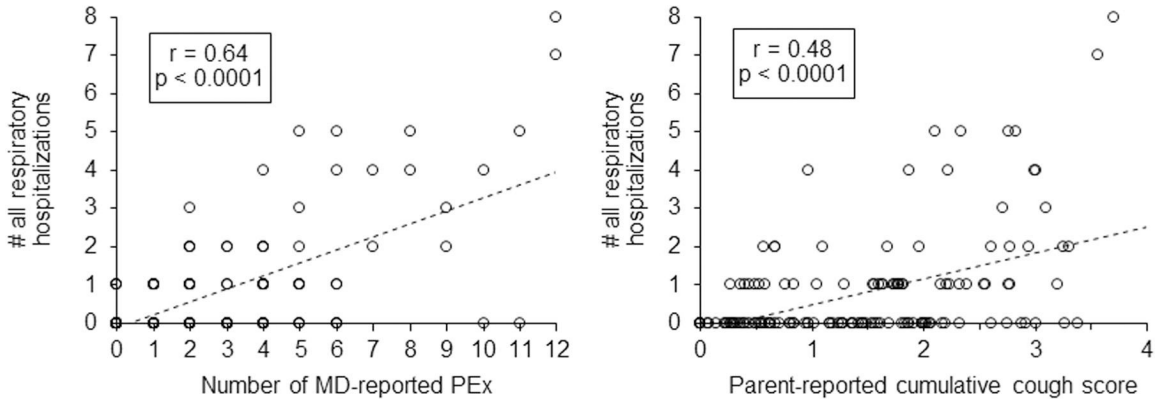

FIGURE 2.

Correlations between MD-reported pulmonary exacerbations (PEx) and parent-reported cumulative cough scores in the first 3 years of life in the FIRST cohort. Pearson's correlation coefficient (*r*) and *p* value are provided in each panel

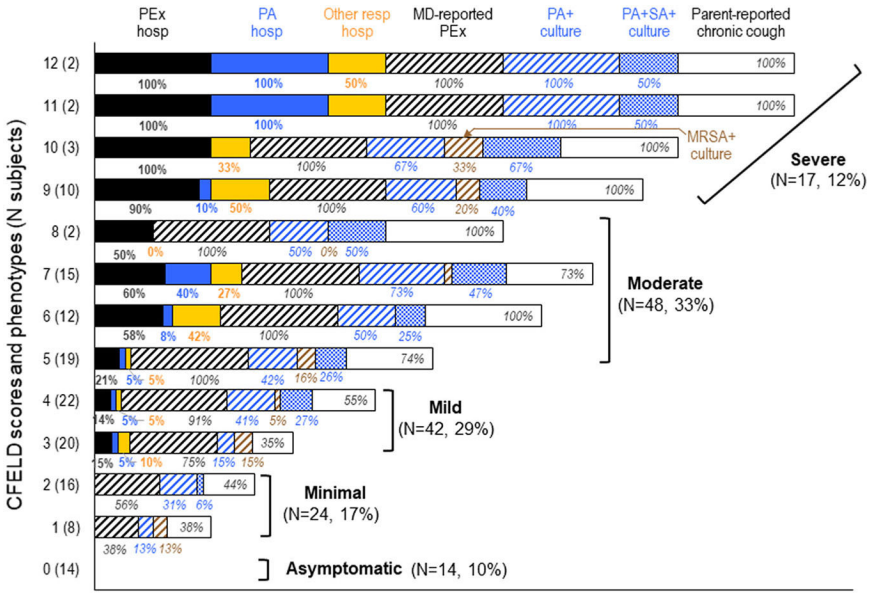

FIGURE 3.

Distribution of the CF early-onset lung disease (CFELD) scores and classification of the five CFELD phenotypes cumulative over the first 3 years of life: asymptomatic, minimal, mild, moderate and severe. For each CFELD score ranging from 0 to 12, the percentage of subjects that experienced at least one occurrence in each of the 8 CFELD components cumulatively by 3 years of age are visualized by horizontally stacked bars with the corresponding percentage shown underneath each bar. Chronic cough was defined by using cumulative cough scores indicative of having greater than occasional cough by parental report for more than 50% of time as explained in Table 2. CF, cystic fibrosis; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; PEx, pulmonary exacerbation

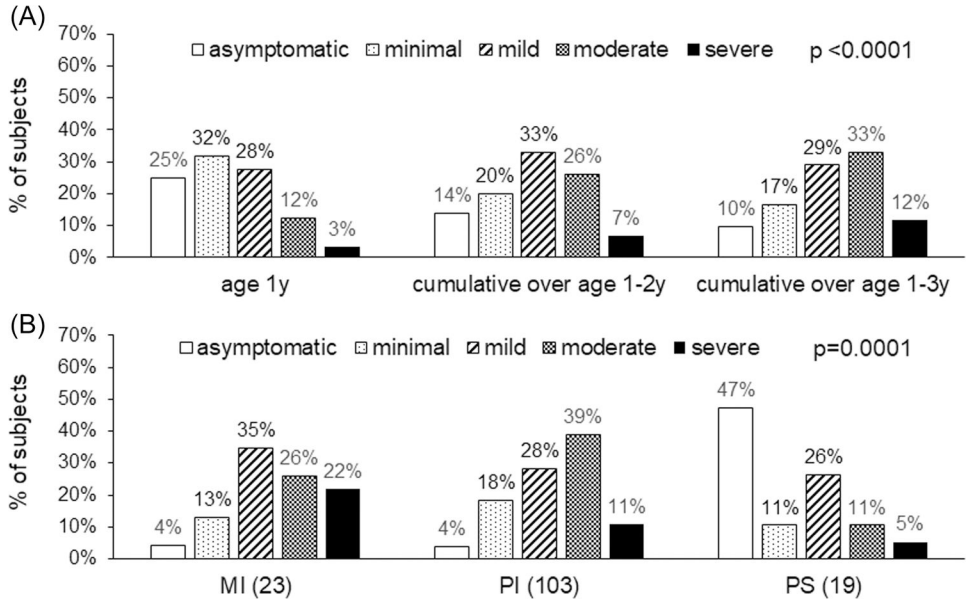

FIGURE 4.

Distributions of the CF early-onset lung disease (CFELD) categories by age in the first 3 years of life (A) and by pancreatic status (B) cumulative over the first 3 years of life in the FIRST cohort. CF, cystic fibrosis; MI, meconium ileus; PI, pancreatic insufficiency; PS, pancreatic sufficiency.

TABLE 1

Characteristics of the study population (N = 145)

CF characteristics	
Age at first CF center visit	
<1.0 months	114 (79%)[a]
1.0–1.8 months	25 (17%)
2.0–2.8 months	6 (4%)
Age at enrollment (months)	1.8 ± 1.1
CFTR genotype	
F508del/F508del	74 (51%)
F508del/other	59 (41%)
Other/other	12 (8%)
Pancreatic phenotype	
Meconium ileus[b]	23 (16%)
Pancreatic insufficiency	103 (72%)
Pancreatic sufficiency	19 (13%)
Birth weight (kg)	3.2 ±0.5 (1.9–4.4)
CFTR modulator therapy before 3 years of age	29 (20%)
Ivacaftor	11 (8%)
Age starting therapy (years)	1.9 ±0.7 (0.6–2.6)
Years of therapy	1.1 ±0.7 (0.4–2.4)
ivacaftor/lumacaftor	18 (12%)
Age starting therapy (years)	2.3 ±0.3 (1.8–2.8)
Years of therapy	0.8 ±0.3 (0.3–1.2)
Demographic and socioeconomic characteristics:	
Female sex	66 (46%)
Race: non-White	4 (3%)
Ethnicity: Hispanic	7 (5%)
Parental education: community college or above	
Mother and father	91 (63%)
Mother	11 (8%)
Father	12 (8%)
Neither	31 (21%)
Household annual income	
<$40,000	43 (30%)
$40,000−$79,000	48 (33%)
≥$80,000	54 (37%)
Daycare exposure before 3 years of age	62 (43%)
Age starting daycare (years)	0.9 ±0.8 (0.2–3.0)
Years of daycare exposure	1.9 ±1.1 (0.0–2.8)
Type of health Insurance	
Medicaid or other public insurance	54 (37%)

CF characteristics	
Private health insurance	91 (63%)
Having older sibling(s) with CF	20 (14%)
Exposure to passive smoke	8 (6%)

Abbreviation: CF, cystic fibrosis.

[a] Values are *N* (%) of subjects or mean ± *SD* (range).

[b] All were pancreatic insufficient.

TABLE 2

Characteristics and criteria for the CF early-onset lung disease (CFELD) scoring system

		Criterion for each point (Number of occurrence[a])			
CFELD component	**Points assigned**	**0 point**	**1 point**	**2 points**	**3 points**
Hospitalization for PEx episodes	3	0	1	2	≥3
MD-reported PEx	3	0	1	2	≥3
Hospitalization for PA eradication	2	0	1	≥2	
Positive PA cultures	2	0	1	≥2	
Positive MRSA cultures	1	0	≥1		
Concurrent culture positivity for PA and SA	1	0	≥1		
Hospitalization for other respiratory-related reasons	1	0	≥1		
Severity of chronic cough (parent-reported cough score[b])	2	<1.5	1.5–1.74	≥1.75	
Maximum attainable CFELD score	15				

Abbreviations: CF, cystic fibrosis; MRSA, methicillin-resistant *Staphylococcus aureus;* PA, *Pseudomonas aeruginosa;* PEx, pulmonary exacerbation; SA, *Staphylococcus aureus.*

[a]For the hospitalization and positive culture components, the number of occurrences during the first year of life, cumulative over 1–2 years, and cumulative over 1–3 years, respectively, was assigned to 0, 1, 2, or 3 points as specified for each component listed above.

[b]Parent-reported cough severity was recorded as 0 (none), 1 (occasional), 2 (frequent), and 3 (constant). The raw cough scores at each visit were used to calculate a cumulative cough score (running average of all previous visits' scores) at age 1 year, cumulative over 1–2 years, and cumulative over 1–3 years, respectively. The severity of chronic cough was defined by a cumulative cough score indicating greater than occasional cough for <50% of the time (score of <1.5), 50–74% of the time (score of 1.5–1.74), or more than 75% of the time (score of ≥1.75).

TABLE 3

Factors associated with the risk of CF early-onset lung disease (CFELD) cumulative over the first 3 years of life

Multiple regression model	**Coefficient (mean ± SD)**	***p* value**
Outcome: CFELD score		
Predictors of interest[a]		
Pancreatic insufficiency vs. sufficiency	1.84 ±0.79	0.0216
F508del status		
None vs. homozygote	0.85 ± 0.96	0.3757
Heterozygote vs. homozygote	−0.50 ±0.52	0.3353
Age at first CF center visit (months)	−0.12 ±0.50	0.8045
# of GI/nutrition-related hospitalizations (0, 1, ≥2)	0.79 ± 0.32	0.0149
% time with high IL-6[b]	2.10 ±1.10	0.0585
% time with high IL-10[b]	−2.37 ± 1.06	0.0275
Years of CFTR modulator therapy before age 3 years	−1.20 ±0.58	0.0412
Parent education		
Community College or above vs. below	−0.45 ± 0.63	0.4780
Years of daycare exposure before age 3 years	0.40 ± 0.21	0.0629
Type of health insurance		
Medicaid or other public insurance vs. private	1.75 ±0.70	0.0132
Ordinal Logistic Regression Model	**Odds ratio (95% CI)**	***p* value**
Outcome: CFELD categories[c]		
Predictors of interest[a]		
Pancreatic insufficiency vs. sufficiency	6.02 (1.89–19.24)	0.0024
F508del status		
None vs. homozygote	1.57 (0.40–6.16)	0.5207
Heterozygote vs. homozygote	0.80 (0.38–1.67)	0.5473
Age at first CF center visit (months)	1.13 (0.56–2.28)	0.7384
GI/nutrition related hospitalizations (0, 1, >2)	1.78 (1.10–2.88)	0.0185
% Time with high IL-6[b]	3.76 (0.78–18.13)	0.0994
% Time with high IL-10[b]	0.12 (0.03–0.60)	0.0094
Years of CFTR modulator therapy before age 3 years	0.30 (0.13–0.70)	0.0055
Parent education		
Community College or above vs. below	0.49 (0.20–1.23)	0.1306
Years of daycare exposure before age 3 years	1.34 (0.99–1.81)	0.0612
Ordinal Logistic Regression Model	**Odds ratio (95% CI)**	***p* value**
Type of health insurance		
Medicaid or other public insurance vs. private	3.26 (1.19–8.96)	0.0103

Abbreviations: CF, cystic fibrosis; IL, interleukin.

[a]Additional covariates adjusted in the model: sex, race, ethnicity, household income level, older siblings with CF, exposure to passive smoke and study site.

[b]High cytokine was defined as the percent of time (equivalent to the percent of measurements with elevated values divided by the number of all measurements). This definition captured the entire history in the first 3 years of life because it utilized all longitudinal measurements of the cytokines for each individual as opposed to a single value of the average of all values or any elevated value.

[c]Five categories in the following order: asymptomatic, minimal, mild, moderate and severe. An odds ratio of greater than one indicates a greater likelihood of being in the more severe CFELD categories