Chest Computed Tomography Scores of Severity Are Associated with Future Lung Disease Progression in Children with Cystic Fibrosis

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Rationale: Most children with cystic fibrosis (CF) experience a slow decline in spirometry, although some children continue to be at risk for more significant lung disease progression. Chest computed tomography (CT) scans have been shown to be more sensitive to changes in lung disease than spirometry and may provide a means for predicting future lung disease progression.

Objectives: We hypothesized that Brody chest CT scan scores obtained in 2000 in a prospectively monitored cohort of children with CF would be associated with the most recent measures of lung disease severity.

Methods: Brody chest CT scan scores were calculated for 81 children enrolled in the Wisconsin CF Neonatal Screening Project. Multivariable linear regression was used to determine associations between Brody scores and the most recent (age 21 yr or June 30, 2010, whichever was later) measures of CF lung disease.

Measurements and Main Results: The mean observation time after the chest CT scan was 7.5 years. Brody chest CT scan scores were significantly associated with the most recent measures of spirometry ($P < 0.001$) and Wisconsin and Brasfield chest radiograph scores ($P < 0.001$). The strength of this association was much stronger than spirometry obtained near the time of the chest CT scan ($P < 0.01$) but not chest radiograph scores.

Conclusions: Chest CT scan scores are associated with future lung disease severity, and quantitative chest imaging (chest CT scan and chest radiograph scores) is more strongly associated with future lung disease severity than measures of spirometry. These findings may help clinicians identify patients at risk of future lung disease progression.

Keywords: chest x-ray; pulmonary function tests; FEV₁; quantitative chest radiography

With a greater proportion of children with cystic fibrosis (CF) having normal pulmonary function test (PFTs) (1) and very gradual decreases in FEV₁ (2), it has become difficult or impossible to use FEV₁ to identify those children at risk for more rapid lung disease progression. This is especially true in light of the study by Konstan and colleagues, which determined that the greatest risk factor for FEV₁ decline in children with CF was having an FEV₁ % predicted greater than 100% (3). Cross-sectional studies of children with CF have demonstrated that high-resolution chest computed tomography (CT) scans are

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Chest computed tomography (CT) scan scores are more sensitive than traditional spirometry in detecting changes in lung disease severity in children with cystic fibrosis (CF). Whether chest CT scan scores are associated with future lung disease progression is unknown.

What This Study Adds to the Field

Quantitative chest imaging (chest CT scan and chest radiography scores) are statistically significantly associated with future measures of lung disease severity. These scores may be used to identify children with CF at high risk of future lung disease progression.

more sensitive than traditional PFTs in detecting early signs of lung disease (4–6). Additionally, chest CT scan has been shown to be more sensitive to intercurrent changes in lung disease than PFTs (7–9). Given the sensitivity of chest CT scan in detecting early lung disease, chest CT scans may provide a tool for predicting future lung disease progression. In a recent study, Loeve and colleagues demonstrated that chest CT scans scored using the Brody scoring system (4) could predict the frequency of pulmonary exacerbation over the ensuing 2 years, independent of FEV₁ severity (10). Having more frequent pulmonary exacerbations is associated with subsequent FEV₁ decline (3, 11).

The Wisconsin CF Neonatal Screening Project (WI RCT) is a randomized control trial that was designed to assess the benefits to CF made possible through early diagnosis via newborn screening (12). In 2000, a chest CT scan was added to the protocol for 81 children who were still being followed systematically as a part of the WI RCT protocol (5). In the current study, we hypothesized that the Brody chest CT scan scores obtained in 2000, in a prospectively monitored cohort of children with CF, would be associated with the most recent assessment of lung disease severity for subjects followed in the WI RCT, and that the association would be stronger than for other measures of lung disease severity available in the WI RCT. Some of the results of these studies have been previously reported in the form of an abstract (13).

METHODS

The design of the WI RCT is described in detail elsewhere (12). In summary, blood specimens of newborns born in Wisconsin between 1985 and 1994 were assigned either to an early CF diagnosis group or to a standard diagnosis group (12). Control patients were unblinded at 4 years of age (14). A sweat chloride level of greater than or equal to 60 mEq/L at one of Wisconsin's two CF centers was required to

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TABLE 1. COHORT CHARACTERISTICS AT THE TIME OF THE CHEST COMPUTED TOMOGRAPHY SCAN AND THE MOST RECENT DATA AS OF JUNE 30, 2010

Characteristic	Yr before Chest CT Scan	Most Recent Data	Mean (SD) Elapsed Time (yr)
Screened, %	48	—	—
Female sex, %	42	—	—
F508del/F508del, %	57	—	—
Pancreatic insufficiency, %	84	—	—
Meconium ileus, %	23	—	—
Brody chest CT scan score, median (range)	2.0 (0–12.8)	—	—
Age, yr, mean (SD)	11.5 (3)	19.0 (2.0)	7.5 (1.8)
FEV ₁ , % predicted, mean (SD), N = 76	91.1 (16.7)	86.8 (19.4)	5.9 (1.9)
FEF _{25–75} , % predicted, mean (SD), N = 73	85.4 (29.3)	70.5 (29.5)	5.9 (1.9)
RV/TLC, mean (SD), N = 70	30.2 (7.9)	30.0 (10.9)	5.6 (2.1)
WCXR, mean (SD), N = 71	15.4 (13.0)	24.9 (15.7)	5.3 (1.8)
BCXR, mean (SD), N = 71	18.8 (2.9)	17.8 (3.9)	5.3 (1.8)
Daily cough, %	46	64	7.5 (1.8)
Culture positive for <i>Pseudomonas aeruginosa</i> , %	48	52	7.5 (1.8)
Hospitalized in the last yr, %	9	24	7.5 (1.8)

Definition of abbreviations: BCXR = Brasfield chest X-ray score; CT = computed tomography; FEF_{25–75} = forced expiratory flow, midexpiratory phase; RV/TLC = residual volume/total lung capacity; WCXR = Wisconsin chest X-ray score.

Total N = 81, unless otherwise indicated.

establish the diagnosis. This investigation was approved by the institutional review boards at the University of Wisconsin and the Children's Hospital of Wisconsin.

Patients were seen every 3 months and assessed by an Evaluation and Treatment Protocol (12) developed in 1984 and reviewed regularly. Patients were prospectively followed in the study through age 21 years. Cultures of respiratory secretions were obtained quarterly (15). PFTs were generally begun when children reached 4 years of age, and were obtained at least every 6 months with strict quality-control measures (16). Chest radiographs obtained at the time of diagnosis and annually were scored using the Brasfield (BCXR) and Wisconsin (WCXR) scoring systems (17, 18). Parents reported cough frequency and sputum production at each visit.

A chest CT scan was added in 2000 for patients who continued to receive care in the protocol at the two CF centers and who gave additional informed consent, as described previously (5). Study participants obtained a chest CT scan at a study visit after the recent history, physical examination, and spirometry were reviewed to determine they were at their baseline health status. The chest CT scan (Lightspeed; GE Medical Systems, Milwaukee, WI) used a thin-section technique (1.25-mm section thickness) with inspiratory images at 10-mm intervals and expiratory images at 20-mm intervals. Hard-copy images were scored independently by three radiologists (A.S.B. and two others) using the Brody scoring system (19).

Statistical Analysis

Linear regression was used to determine associations between Brody scores and the most recent (age 21 years or June 30, 2010, whichever

was later) measures of CF lung disease. Data within 2 years of the chest CT scan were excluded. We performed multivariable regression, adjusting for baseline factors at the time of the chest CT scan (age at the time of the chest CT scan, sex, screen or control group, genotype [homozygous F508del versus all other combinations], pancreatic insufficiency, and meconium ileus) and potential confounding factors: FEV₁ and *Pseudomonas aeruginosa* infection at the time of the chest CT scan, and time between the CT scan and the most recent assessment, after a review of the literature to find factors associated with (1) lower pulmonary function, and/or (2) Brody scores (3, 20, 21). We repeated the analysis to determine the association between the Brody bronchiectasis subscores and the most recent lung disease measurements.

To determine associations between the other lung disease measures available within 1 year before the chest CT scan in 2000 and the most recent FEV₁ and WCXR, we added each lung disease measure in 2000 individually to the multivariable regression model that included only the baseline factors. For lung disease measures in 2000 that were significantly associated with the most recent FEV₁ or WCXR, we used an F test to compare the strength of association between chest CT scan and the most recent FEV₁ and WCXR, adjusting for baseline factors.

RESULTS

At the time of the chest CT scan, 98 of the original 132 patients were still being followed. Of these 98, 9 did not give consent for the chest CT scan, and 8 either did not come to their chest CT scan appointment or had chest CT images that were not acceptable due to motion artifact. The 81 patients who obtained a chest

TABLE 2. UNADJUSTED AND ADJUSTED LINEAR REGRESSION PARAMETERS (SE) FOR THE GROUP MEAN DIFFERENCE IN THE MOST RECENT LUNG DISEASE MEASURES ASSOCIATED WITH A UNIT CHANGE IN BRODY CHEST COMPUTED TOMOGRAPHY SCAN SCORE

Lung Disease Measure	Unadjusted Model (SE)	P Value	Fully Adjusted Model (SE)	P Value
FEV ₁ , % predicted	−4.3 (0.7)	<0.001	−3.1 (0.7)	<0.001
FEF _{25–75} , % predicted	−5.9 (1.1)	<0.001	−4.3 (1.2)	0.001
RV/TLC	2.5 (0.4)	<0.001	2.6 (0.4)	<0.001
WCXR	3.5 (0.5)	<0.001	3.7 (0.6)	<0.001
BCXR	−0.9 (0.1)	<0.001	−1.1 (0.1)	<0.001
<i>Pseudomonas aeruginosa</i>	0.06 (0.02)	0.002	0.04 (0.02)	0.1
Hospitalization in the yr of the most recent data	0.03 (0.02)	0.09	0.06 (0.02)	0.02

Definition of abbreviations: BCXR = Brasfield chest X-ray score; FEF_{25–75} = forced expiratory flow, midexpiratory phase; RV/TLC = residual volume/total lung capacity; WCXR = Wisconsin chest X-ray score.

The following variables were included in the final adjusted model: FEV₁ % predicted, *P. aeruginosa* endobronchial infection, and age at the time of the chest CT scan; the time between the chest CT scan and the most recent lung disease measure; patient group (screened or control); sex; genotype (homozygous F508del vs. all others); pancreatic status; and meconium ileus status.

Figure 1. Scatterplot and regression line of the most recent FEV₁ % predicted and Brody chest computed tomography (CT) scan score in 2000.

CT scan were similar to the original WI RCT cohort (*see* Table E1 in the online supplement). After obtaining the chest CT scan, 10 patients did not obtain additional chest X-rays as a part of the original study protocol. The mean values for the lung disease surrogates generally revealed mild abnormalities at the time of the chest CT scan (Table 1), with the exception of WCXR (mean 15.4) and BCXR (mean 18.8). These mean values indicate the presence of irreversible abnormalities, based on criteria of a WCXR score greater than 5 and BCXR score less than 21 (22). The median Brody chest CT scan score was 2.0 (range 0–12.8) out of a possible score of 36. The mean Brody scores were not different between the control group (3.6) and the screened group (2.7, $P = 0.2$).

The mean observation time between the chest CT scan and the most recent observation was 7.5 years. During that time period, there was progression of all lung disease surrogates, with the exception of residual volume/total lung capacity (RV/TLC). There was a significant association between chest CT scan score in 2000 and the most recent measure of all lung disease surrogates in an unadjusted model (Table 2 and Figures 1–4), indicating that chest CT scan score severity is associated with future lung disease progression over the subsequent 2 to 10 years. The association was strongest for FEV₁ % predicted; forced expiratory flow, midexpiratory phase (FEF_{25–75}) % predicted; and WCXR score. The associations between the chest CT scan score and the most recent lung disease surrogates remained statistically significant when the multivariable model was used (Table 2). For example, using the fully adjusted model,

Figure 2. Scatterplot and regression line of the most recent Wisconsin chest X-ray score (WCXR) and Brody chest computed tomography (CT) scan score in 2000.

Figure 3. Scatterplot and regression line of the most recent forced expiratory flow, midexpiratory phase (FEF_{25–75}) % predicted and Brody chest computed tomography (CT) scan score in 2000.

for every one point increase in Brody chest CT scan score, the most recent FEV₁ % predicted was a mean of 3.1 % predicted lower ($P < 0.001$).

The mean Brody bronchiectasis subscore was 1.0, with a range of 0 to 5.0. The association between the Brody bronchiectasis subscore and the most recent lung disease surrogates was even stronger than the Brody score (Table 3). Using the same multivariable regression models as above, the Brody bronchiectasis subscores remained highly significantly associated with the most recent lung disease surrogate measurements, indicating that the extent and distribution of bronchiectasis (as measured by the Brody bronchiectasis subscore) is associated with future lung disease progression.

Tables 4 and 5 detail the associations between the lung disease measures in 2000 and the most recent FEV₁ and WCXR. In addition to the chest CT scan score, WCXR, BCXR, FEV₁ % predicted, FEF_{25–75} % predicted, and RV/TLC in 2000 were significantly associated with the most recent FEV₁ % predicted (Table 4) and WCXR (Table 5). The chest CT scan score in 2000 was more strongly associated with the most recent FEV₁ % predicted than either the 2000 FEV₁ % predicted ($P = 0.002$) or FEF_{25–75} % predicted ($P < 0.001$) (Table 4). Similarly, the chest CT scan score in 2000 was more strongly associated with the most recent WCXR than either FEV₁ % predicted ($P < 0.001$), FEF_{25–75} % predicted ($P < 0.001$), or RV/TLC ($P < 0.001$) in 2000 (Table 5). On the other hand, WCXR and BCXR in 2000 were statistically significantly associated with the most recent FEV₁ % predicted ($P < 0.001$ for each) and WCXR

Figure 4. Scatterplot and regression line of the most recent residual volume/total lung capacity (RV/TLC) and Brody chest computed tomography (CT) scan score in 2000.

TABLE 3. UNADJUSTED AND ADJUSTED LINEAR REGRESSION PARAMETERS (SE) FOR THE GROUP MEAN DIFFERENCE IN THE MOST RECENT LUNG DISEASE MEASURES ASSOCIATED WITH A UNIT CHANGE IN BRODY CHEST COMPUTED TOMOGRAPHY SCAN BRONCHIECTASIS SUBSCORE

Lung Disease Measure	Unadjusted Model (SE)	P Value	Fully Adjusted Model (SE)	P Value
FEV ₁ , % predicted	-10.5 (1.7)	<0.001	-7.9 (1.7)	<0.001
FEF ₂₅₋₇₅ , % predicted	-14.3 (2.7)	<0.001	-10.4 (3.0)	0.001
RV/TLC	6.0 (0.9)	<0.001	5.9 (1.0)	<0.001
WCXR	9.2 (1.1)	<0.001	9.2 (1.2)	<0.001
BCXR	-2.4 (0.2)	<0.001	-2.5 (0.3)	<0.001
<i>Pseudomonas aeruginosa</i>	0.1 (0.04)	0.003	0.1 (0.1)	0.1
Hospitalization in the yr of the most recent data	0.07 (0.04)	0.06	0.2 (0.1)	0.009

For definition of abbreviations, see Table 2.

($P < 0.001$ for each). The strengths of the associations were not statistically significantly different between the most recent FEV₁ and the 2000 chest CT scan, WCXR, and BCXR scores ($P > 0.1$ comparing 2000 chest CT scan to 2000 WCXR or BCXR). Similarly, the strengths of the associations were not statistically significantly different between the most recent WCXR and the 2000 chest CT scan, WCXR, and BCXR scores ($P > 0.4$ comparing 2000 chest CT scan to 2000 WCXR or BCXR).

DISCUSSION

We found that Brody chest CT scan scores were significantly associated with measures of lung disease severity obtained, on average, 5 to 7 years later for subjects followed prospectively in the WI RCT. The strength of this association was generally much stronger than other measures of lung disease severity obtained near the time of the chest CT scan. Previous studies have shown chest CT scans are able to detect early structural abnormalities in children with CF and lung disease progression even in children who have normal PFTs (4, 5, 7–9). However, only a few studies have evaluated the association between chest CT scan scores and future lung disease severity. Cademartiri and colleagues (23) reviewed Bhalla scores of chest CT scans performed at their center between 1991 and 2001 to evaluate the association between chest CT scan scores and future

TABLE 4. THE ASSOCIATIONS BETWEEN MEASURES OF LUNG DISEASE SEVERITY IN 2000 AND THE MOST RECENT FEV₁ % PREDICTED

Measure at the Time of the Chest CT Scan	Parameter Estimate for Group Mean Difference in FEV ₁ (SE)	P Value	P Value (F test) Comparing CT Scan with Lung Disease Measure
CT scan	-4.5 (0.8)	<0.001	—
WCXR	-0.9 (0.2)	<0.001	0.1
BCXR	3.9 (0.9)	<0.001	0.4
FEV ₁ , % predicted	0.8 (0.1)	<0.001	0.002
FEF ₂₅₋₇₅ , % predicted	0.4 (0.1)	<0.001	<0.001
RV/TLC	-1.4 (0.3)	<0.001	0.1
<i>Pseudomonas aeruginosa</i>	-4.1 (5.0)	0.4	—
Hospitalization in 2000	-0.9 (8.5)	0.9	—

For definition of abbreviations, see Table 1.

Lung disease measures that were statistically significantly associated with the most recent FEV₁ were compared with the strength of association with the chest CT scan in 2000, adjusting for baseline variables in 2000.

TABLE 5. THE ASSOCIATIONS BETWEEN MEASURES OF LUNG DISEASE SEVERITY IN 2000 AND THE MOST RECENT WISCONSIN CHEST X-RAY SCORE

Measure at the Time of the Chest CT Scan	Parameter Estimate for Group Mean (SE) Difference in WCXR	P Value	P Value (F test) Comparing CT Scan with Lung Disease Measure
CT scan	3.9 (0.5)	<0.001	—
WCXR	0.9 (0.1)	<0.001	0.4
BCXR	-3.7 (0.5)	<0.001	0.9
FEV ₁ , % predicted	-0.4 (0.1)	<0.001	<0.001
FEF ₂₅₋₇₅ , % predicted	-0.1 (0.1)	0.03	<0.001
RV/TLC	0.9 (0.2)	<0.001	<0.001
<i>Pseudomonas aeruginosa</i>	3.9 (3.6)	0.3	—
Hospitalization in 2000	-6.9 (6.5)	0.3	—

For definition of abbreviations, see Table 1.

Lung disease measures that were statistically significantly associated with the most recent WCXR were compared with the strength of association with the chest CT scan in 2000, adjusting for baseline variables in 2000.

lung disease. There were 57 patients with two to three chest CT scans, performed at a mean age of 15 years (range 9 mo to 38 yr). Bhalla scores did not predict progression of PFTs. However, the strength of their evidence was weakened because the authors did not report actual Bhalla scores or PFT values, and correlations between chest CT scan scores and PFTs were only compared for PFTs expressed in liters, which does not take into account lung growth with age for children.

In a recent study, Loeve and colleagues demonstrated that Brody bronchiectasis subscores predict pulmonary exacerbation frequency over the ensuing 2 years, independent of FEV₁ (10). Subjects with a Brody chest CT scan score worse than the median had more than five times as many pulmonary exacerbations as subjects with a Brody score less than 1. When we examined bronchiectasis subscores, we found that the strength of association with the most recent lung disease measures was even stronger than for the overall Brody chest CT scan score. The long-term significance of bronchiectasis in CF seems clear from Loeve and colleagues' data and our data reported herein. Although there has been limited research on specific respiratory pathogens and their association with bronchiectasis, observations we published recently (5) revealed that *P. aeruginosa* infections correlated closely with development of this irreversible, structural lesion. The apparent role of mucoid *P. aeruginosa* as a determinant of bronchiectasis is consistent with its pathobiology, that is, its protective biofilm resistant to antibiotics (24) and many toxins and virulence factors (25).

Clinically, the implication of our findings, as well as those of Loeve and colleagues, is that chest CT scan scores may be used to identify children with CF who are at significant risk of lung disease progression. These findings are especially helpful because the slow rates of change of traditional spirometry (4, 7, 26) make using spirometry to monitor progression of lung disease severity in children difficult. Moreover, the patients at most risk of a greater subsequent decline in FEV₁ are those with the highest FEV₁ (27). It is unknown what the chest CT scan appearance is in these children with supranormal FEV₁. Patients with high FEV₁ and chest CT scan abnormalities may in fact be at greater risk of lung disease progression. Additional studies that use spirometry and chest CT scan scores may be useful to determine if targeting these patients for aggressive treatment decreases the rate of disease progression.

Although chest CT scan scores were more strongly associated with future lung disease severity than spirometry, we found that

quantitative chest radiography (Wisconsin and Brasfield chest radiograph scores) were as strongly associated with future lung disease severity as the chest CT scan score. We (28) and others (29, 30) have previously demonstrated the sensitivity of quantitative chest imaging in monitoring lung disease progression in children with CF. Although further study is needed, it may be that quantitative chest imaging has a role in detecting bronchiectasis and may provide similar insight into future lung disease progression as chest CT scan, but without exposing patients to larger doses of ionizing radiation with chest CT scan (31).

Our study is limited in several ways. First, there was a wide range of follow up times after the chest CT scan: 2 to 10 years. Patients in the study began ageing out of the Wisconsin Neonatal Screening Project in 2005, when the oldest patients turned 21. This raises the possibility that the association we are identifying is between the chest CT scan and the lung disease measures obtained only a short time afterward. However, the strength of association remained when we adjusted for the time between the chest CT scan and the most recent measure of lung disease severity. Also, when we stratified the data by the median follow-up time, the parameter estimates were similar (data not shown). We are unable to make meaningful comparisons between the strengths of association with future lung disease progression between chest CT scan, infection with *P. aeruginosa*, and pulmonary exacerbation frequency because of the large standard errors for *P. aeruginosa* and pulmonary exacerbation frequency (Table 4). We did take into account the effects of infection with *P. aeruginosa* by adjusting for the presence of *P. aeruginosa* in our final model. We had relatively few patients hospitalized for a pulmonary exacerbation (9% of the cohort in 2000 and 24% in the year of the most recent data). Finally, these data were obtained from two CF centers with protocol-managed patients who generally had mild disease and who, before the chest CT scan in 2000, did not receive many of the standard treatments available to patients with CF today. However, given that patients with CF continue to have improvements in PFTs, these data should continue to be applicable.

We have shown that chest CT scan scores are associated with future lung disease severity, and that quantitative chest imaging (chest CT scan and chest radiograph scores) is more strongly associated with future lung disease severity than measures of spirometry. These findings may help clinicians identify patients at risk of future lung disease progression. More studies are needed that include chest imaging and spirometry, and over a longer time frame, to better understand the risk of lung disease progression in children with CF.

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