HHS Public Access

Author manuscript

Pediatr Pulmonol. Author manuscript; available in PMC 2020 March 06.

Published in final edited form as:

Pediatr Pulmonol. 2018 October ; 53(10): 1369–1377. doi:10.1002/ppul.24144.

Quantitative chest computerized tomography and FEV_1 equally identify pulmonary exacerbation risk in children with cystic fibrosis

Don B. Sanders, MD[1,*], **Zhanhai Li, PhD**[2], **Katelyn Parker-McGill, MD, MPH**[3], **Philip Farrell, MD, PhD**[4], **Alan S. Brody, MD**[5]

[1]Department of Pediatrics, Riley Hospital for Children, School of Medicine, Indiana University, Indiana, IN

[2]Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI

[3]Medical College of Wisconsin, Milwaukee, WI

[4]Departments of Pediatrics and Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI

[5]Department of Radiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

SUMMARY

Background—Chest computerized tomography (CT) scores are associated with the frequency of future pulmonary exacerbations in people with cystic fibrosis (CF). However, cut-off values to identify children with mild lung disease with different risks for frequent future pulmonary exacerbations have not been identified.

Methods—Chest CT scans were assessed using the Brody score for participants of the Pulmozyme Early Intervention Trial (PEIT) and Wisconsin Randomized Clinical Trial of CF Newborn Screening (WI RCT). We determined the area under the receiver operating characteristic (ROC) curve for Brody scores and forced expiratory volume in 1 second (FEV_1) to compare with the frequency of pulmonary exacerbations up to 10 years later.

Results—There were 60 participants in the PEIT with mean (SD) age 10.6 (1.7) years at the time of the CT and 81 participants in the WI RCT with mean age 11.5 (3.0) years. The Brody score cut-off that best identified children at-risk for ≥0.3 annual pulmonary exacerbations was 3.6 in the PEIT and 2.1 in the WI RCT. There were no statistical differences between ROC curves for the Brody CT score and FEV_1 % predicted in either study ($p \geq 0.4$).

Conclusions—CT score cut-off values that identify children with CF with mild lung disease at different risks for frequent pulmonary exacerbations over an extended follow up period are similar

[*]During the conduct of this study, Dr. Sanders was a faculty member in the Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin, Madison, WI

Corresponding author: Don B. Sanders, MD, MS, Riley Hospital for Children, 705 Riley Hospital Drive, ROC 4270, Indianapolis, IN 46202, dbsand@iu.edu, Phone: 317-274-7208, Fax: 317-944-7247 .

Author's contributions: All authors contributed to the conception and design of the work, interpretation of data for the work, acquisition and/or analysis of data, drafting the work, and each provided final approval and agree to be accountable for all aspects of the work.

in separate cohorts. Brody scores and FEV_1 % predicted have similar abilities to identify these children, suggesting that FEV_1 % predicted alone may be adequate for predicting future frequency of pulmonary exacerbations.

Keywords

Bronchiectasis; FEV_1; Brody scores

INTRODUCTION

Computerized tomography (CT) scans of the chest are used in research and clinical practice to detect the severity of structural lung disease in people with cystic fibrosis (CF). Chest CT scores are sensitive to detect early, regional disease, and are more sensitive to progression of disease than traditional spirometry.[1–3] Chest CT scores are also predictive of the frequency of future pulmonary exacerbations up to 10 years later.[4–6] This predictive ability is important because pulmonary exacerbations are valuable clinical endpoints associated with lower quality of life, increased healthcare costs, more rapid progression of lung disease, and increased mortality.[7–11] Patients at high risk could be treated with additional CF therapies that have been shown to reduce the frequency of pulmonary exacerbations, and efforts could be made to increase adherence to CF therapies, as better adherence is associated with lower rates of pulmonary exacerbations.[12] Conversely, decreasing the burden of care for patients who are at low risk of having pulmonary exacerbations by decreasing the number of therapies would be helpful in reducing healthcare costs and improving adherence and quality of life.[13]

Cut-off values that can differentiate between children with CF who are at high- or low-risk for future pulmonary exacerbations have been described. Loeve *et al.* compared the rates of pulmonary exacerbations in the two years after a chest CT scan was obtained.[4] They found that subjects with bronchiectasis scores >7% of the maximum score were more likely to have at least one exacerbation during two years of follow up. They also found that the rate of pulmonary exacerbations was significantly higher for children with forced expiratory volume in 1 second (FEV_1) ≤78% predicted, but did not compare the predictive ability of chest CT scores to FEV_1. Another study from the same group found that subjects who had bronchiectasis scores >17.5% of the maximum score were more likely to have more than 3 exacerbations in a 6 year follow up period.[6] The cut off for FEV_1 obtained at the same time as the chest CT did not perform as well as bronchiectasis in identifying these patients.

These cut-points, however, will have limited clinical utility at this time, as children with CF today are unlikely to average 2 pulmonary exacerbations per year or to have bronchiectasis this severe.[14,15] Determining whether specific cut-off values in chest CT scores can identify a particular patient's risk of future pulmonary exacerbations in a cohort of healthier children with CF would provide a better assessment of the value of CT scanning in predicting future disease severity. Clinical decision making tools that identify patients with high risk for future morbidity or mortality have been successfully developed in other pulmonary disorders such as asthma, community acquired pneumonia, and COPD.[16–18] There are no widely used clinical prediction tools in CF. A recently developed tool for predicting future spirometry

does not include chest CT results.[19] Our hypothesis is that meaningful cut-off values in the Brody chest CT score can be identified that will identify children with CF at high- or low-risk for frequent future pulmonary exacerbations, and that the cut-off points will provide more predictive ability than FEV_1 % predicted. To address our hypothesis, we compared the rates of pulmonary exacerbations for up to 10 years after chest CT scans were obtained in two well-defined cohorts of children with CF.

MATERIALS AND METHODS

Study cohorts

Longitudinal data were obtained for two distinct cohorts of children with CF. The first cohort includes children in the Pulmozyme Early Intervention Trial (PEIT).[20] The inclusion criteria for the PEIT were: children with CF, ages 6–10 years, with forced vital capacity (FVC) ≥85% predicted, the ability to perform reproducible pulmonary function tests, no dornase alpha use for 6 months prior to enrollment, and no pulmonary exacerbations within 60 days prior to enrollment. Chest CT scans were obtained in 1999–2000 for 60 of the subjects in the PEIT at 15 participating centers during periods of clinical stability at the end of the 2-year study and scored using the Brody scoring system.[21] Spirometry was performed on the same day as the chest CT. Data from the time of the chest CT through the last available data entry or 2009, whichever came first, was obtained from the CF Foundation Patient Registry (CFFPR) and linked to the original chest CT data. The CFFPR is a well-described database that contains detailed data on demographics at every encounter for people with CF in the U.S.[22] Pulmonary exacerbations treated with IV antibiotics (at home or in the hospital) for an increase in respiratory signs and symptoms were recorded in the CFFPR.

The second cohort includes subjects in the well described Wisconsin Randomized Clinical Trial of CF Newborn Screening (WI RCT).[23] 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. Children in both groups were diagnosed with CF with a sweat chloride level ≥60 mEq/L and were seen every 3 months and prospectively followed in the study through age 21, or 6/30/2010, whichever was earlier.[23] Cultures of respiratory secretions were obtained quarterly. Spirometry was obtained at least every 6 months with strict quality control measures.[24] A chest CT was added in 2000 for patients who continued to receive care in the protocol and who gave additional informed consent, as described previously.[25] We recorded the FEV_1 % predicted obtained closest to the chest CT (within one year prior). As in the PEIT study, pulmonary exacerbations treated with IV antibiotics for an increase in respiratory signs and symptoms were recorded for 10 years or through 6/30/2010, whichever came earlier.

Chest CT protocols

In the PEIT study, CT scans were obtained according to a protocol that used 1 mm thick slices and a 1 second scan time. Inspiratory images were obtained at 10-mm intervals and 4 expiratory images were obtained at: 0.5 cm above the aortic arch, the carina, at the inferior margin of the hilum, and 1 cm above the diaphragm. CT scans were scored independently by

two thoracic radiologists using the Brody scoring system.[21] In the WI RCT study, after the recent history, physical examination, and spirometry were reviewed to determine they were at their baseline health status, a chest CT was performed. The CT scan (Lightspeed; GE Medical Systems, Milwaukee) protocol used 1.25-mm thick slices with inspiratory images at 10 mm intervals and expiratory images at 20 mm intervals. Hard-copy images were scored independently by three radiologists (ASB and two others) using the Brody scoring system.[25]

In both studies, the radiologists were blinded to the patient identities, severity of lung disease, and randomization group. The Brody scoring system has been reported as a total score with a maximum possible value of 207[21] and as a score representing the average severity of each of the six lobes, including the lingula as a separate lobe, with a maximum of 40.5.[26] For this analysis, we report Brody scores using the latter method.

Statistical Analysis

We used descriptive statistics to describe both of the cohorts at the time of the chest CT and at the most recent follow up point. In the US, approximately 1 in 3 children with CF are treated with IV antibiotics for a pulmonary exacerbation each year.[27] For our initial analysis, we compared children who had an annual rate above the median rate of pulmonary exacerbations of 0.3 pulmonary exacerbations per year to children who had fewer pulmonary exacerbations. The risk of pulmonary exacerbations treated with IV antibiotics increases with age,[9] but not in a uniform fashion, so for this analysis we averaged the total number of pulmonary exacerbations over the observation period. All analyses were performed separately for the PEIT and WI RCT cohorts to assess the generalizability of our results. To determine the cut-off points which best discriminate between these rates of pulmonary exacerbations, we obtained the area under the receiver operating characteristic (ROC) curve (AUC), and values for sensitivity and specificity were calculated. A comparison of AUCs was performed using the chi-square test of Wald statistics comparing the Brody CT score and bronchiectasis subscores to FEV_1 % predicted. We then determined the annual rate of pulmonary exacerbations per year and compared children at high-risk (defined as the top quartile of pulmonary exacerbations) and low-risk (defined as the bottom quartile of pulmonary exacerbations) to the children in the remaining three quartiles in both PEIT and WI RCT study cohorts. Statistical significance was defined as a two-sided p-value < 0.05. The current study was approved by the IRBs at the University of Cincinnati and University of Wisconsin.

RESULTS

The demographics and characteristics of the children in the PEIT and WI RCT cohorts were similar (Table 1). At the time of the CT, which occurred between 1999 and 2000 for both cohorts, there were more children in the PEIT study who were pancreatic insufficient ($p = 0.016$) and infected with *Staphylococcus aureus* ($p = 0.009$); mean FEV_1 % predicted was higher than in the WI RCT cohort ($p = 0.003$). One patient in the PEIT study was positive for methicillin resistant *S. aureus* at the time of the chest CT; there were none in the WI RCT cohort. In the PEIT study, the mean (SD) Brody chest CT score was 3.8 (1.9) out of a possible 40.5. The mean (SD) bronchiectasis subscore was 0.6 (0.8) out of a possible 12. In

the WI RCT study, the mean (SD) Brody chest CT score was 3.1 (2.9), and the mean (SD) bronchiectasis subscore was 1.0 (1.2). Each of these scores indicates generally mild, but abnormal, values.

Data were missing for a very small percentage of the overall cohort. Data were available in the CFFPR for all participants in the PEIT study for 5 years after the chest CT, and for 55 subjects up to 10 years later. One patient died prior to 2009. Overall, the mean (SD) observation time after the chest CT was 9.8 (0.7) years. For the WI RCT study, the mean observation time between the chest CT scan and the most recent observation was 7.5 years. No patients died before the end of the study period. The decline in FEV_1 % predicted was greater for the participants of the PEIT study (−2.2% predicted per year) than for the participants of the WI RCT study (−0.6% predicted per year), $p < 0.001$. More participants in the PEIT study acquired *Pseudomonas aeruginosa* during the follow up period than in the WI RCT study, $p = 0.0015$ (Table 1). During the observation period, the range of pulmonary exacerbations treated with IV antibiotics and recorded in the CFFPR was 0 to 63 for participants in the PEIT study and 0 to 50 for participants in the WI RCT study (Figure 1). The median annual rate of pulmonary exacerbations was 0.35 for participants in the PEIT study and 0.30 for participants in the WI RCT study.

The mean Brody chest CT scores, bronchiectasis subscores, and FEV_1 % predicted were all statistically significantly different between children with ≥0.3 pulmonary exacerbations or <0.3 pulmonary exacerbations per year in both the PEIT and WI RCT studies, and when combining the two studies (Table 2). Results were similar when using medians instead of means (data not shown). The differences in the mean FEV_1 % predicted (~12% predicted), Brody CT score (~ 2 points), and bronchiectasis subscore (~0.7 points) between the pulmonary exacerbation groups were similar in the PEIT and WI RCT cohorts. The optimal cut-off points to differentiate between the frequencies of future pulmonary exacerbations were similar in the PEIT and WI RCT cohorts for FEV_1 % predicted (94.1–101.6), the Brody chest CT score (2.1–3.6), and bronchiectasis subscore (0.3–0.4) (Table 3). The AUCs were also similar between the two studies for each of the lung disease measures. FEV_1 % predicted had a higher AUC in the PEIT study than in the WI RCT study. The AUCs were not substantially affected when we adjusted for *P. aeruginosa*, BMI below the 10^{th} percentile, or Medicaid insurance status at the time of the CT in bivariate analyses (data not shown). There were no statistical differences between the ROC curves for the Brody CT score and FEV_1 % predicted in the PEIT study ($p = 0.6$), WI RCT study ($p = 0.4$), or the combined studies ($p = 0.8$) (Figure 2). The differences between the bronchiectasis subscore and FEV_1 % predicted were also not statistically significantly different (data not shown).

The sensitivities and specificities for each of these measures of lung disease were similar between the two studies (Table 4); only FEV_1 % predicted was more sensitive and specific in the PEIT study in comparison to the WI RCT study. Combining the cohorts did not improve sensitivity or specificity. We also tested whether combining the cut-off values for FEV_1 % predicted and the Brody score changed the sensitivity and specificity. In both cohorts, the sensitivity for identifying children at risk of frequent future pulmonary exacerbations increased, but the specificity decreased (Table 4). The corresponding mean (95% CI) AUC in the PEIT study, 0.85 (0.75, 0.94), was increased in comparison to the

AUC for FEV_1 % predicted alone, 0.79 (0.68, 0.90), but the difference was not statistically significant (p = 0.18). Similarly in the WI RCT study, the AUC for FEV_1 % predicted combined with the Brody score was 0.75 (0.63, 0.86), compared to 0.67 (0.55, 0.79) for FEV_1 % predicted alone, p = 0.14.

We repeated our analyses by comparing the children with the highest and lowest quartiles of pulmonary exacerbation rates in each cohort (Table 5). In general, the optimal cut-off points, AUCs, sensitivities, and specificities to differentiate between the frequencies of future pulmonary exacerbations were similar when comparing children above and below the median and lowest quartile rate of pulmonary exacerbations. Children with the highest quartile rate of pulmonary exacerbations (>1 per year) had slightly lower FEV_1 % predicted and higher Brody CT scores. The Brody CT score had slightly better AUCs than FEV_1 % predicted for identifying the children with the highest quartile rate of pulmonary exacerbations. There were no statistical differences between the ROC curves for the Brody CT score or FEV_1 % predicted when combining the two studies when we changed the annual rate of pulmonary exacerbations to 0.4 per year (p = 0.5) or 0.5 per year (p = 0.7).

DISCUSSION

This study identifies cut-off values in the Brody CT score that distinguish between children with essentially normal values for FEV_1 % predicted who went on to have different rates of pulmonary exacerbations up to 10 years later in two separate cohorts of children with CF. Neither Brody CT scores nor bronchiectasis subscores distinguished between the two groups of children better than FEV_1 % predicted obtained at the same time as the chest CT. This was true whether the CT score was used alone, or in combination with FEV_1 % predicted. By defining cut-off values that are similar in different cohorts of children with CF with mild lung disease on spirometry and chest CT, our results add to our understanding of CT scores as surrogate endpoints. Most importantly, our results suggest that the risk of future pulmonary exacerbations treated with IV antibiotics is not negligible even among the majority of children with CF today who have normal spirometry and minimal structural lung disease.

Predictive ability of chest CT scores

Similar to previous studies, we have demonstrated an association between chest CT scores and future risk or frequency of pulmonary exacerbation,[3,4,6,28] though we did not find an optimal cut-point that could meaningfully distinguish patients at high- or low-risk of future pulmonary exacerbations. In the study by Botoluzzi and colleagues, the optimal cut point to identify patients with more than 3 exacerbations over 6 years of follow up was a bronchiectasis score of 17.5%.[6] In the study by Loeve *et al.,* bronchiectasis subscores >7% identified children with ≥0.5 annual pulmonary exacerbations in a 2-year follow up period.[4] Our results build on these previous studies by demonstrating the link in healthier children with less bronchiectasis and fewer pulmonary exacerbations, and over a longer follow up period. Expressed as a percentage, the best cut-point for the bronchiectasis subscore in our studies were lower at 2.5% and 3.3%. Our results are further strengthened by using data

from two multi-center studies. Taken together, our results may be more generalizable to current cohorts of children with CF.

Predictive ability of CT scores compared to FEV_1

Our results demonstrate a single CT score and FEV_1 measurement have predictive abilities in multiple cohorts comparable to the ability of FEV_1 to predict 2-year mortality.[29] In contrast to chest CT scores, more information is available on clinically important cut-off values for FEV_1 % predicted that would allow clinicians to identify children with CF who are at high risk for future adverse events. The lower limit of normal for FEV_1 % predicted has been defined according to age and sex for global populations,[30] and in comparison to other children with CF.[31] However, it is unclear what degree of abnormalities on chest CT is indicative of future morbidity and mortality. Although chest CT is much more sensitive than FEV_1 in detecting progression of early CF lung disease, in our study, FEV_1 % predicted was as effective as chest CT scores in identifying children at risk for frequent future pulmonary exacerbations. When we compared the optimal cut-points for identifying the 25% of patients with the least and most pulmonary exacerbations, neither the Brody CT score nor bronchiectasis subscore performed better than FEV_1 % predicted, though the Brody CT score tended to perform slightly better in identifying the children with the most pulmonary exacerbations. In contrast, CT scores generally performed better than FEV_1 in the studies by Bortoluzzi and Loeve.[4,6] Studies of potential predictors of disease progression are highly dependent on characteristics of the study cohort and frequency of the outcome measure (i.e., pulmonary exacerbations). There are many differences between our study and previous studies that may potentially explain the different results, including different patient populations with different severities of lung disease, study designs (single- vs multi-center, exacerbation frequency cut-point), and purpose for obtaining CT scans (clinical vs research). Given the high correlation between FEV_1 and the rate of pulmonary exacerbations,[9] it is not surprising that FEV_1 would be associated with future risk of pulmonary exacerbations. As FEV_1 increases for subsequent birth cohorts of children with CF, and as FEV_1 decline slows over time,[32] other evaluation methods that are more sensitive, e.g., CT scores, lung clearance index,[33] or magnetic resonance imaging,[34] may be needed to identify children at risk for adverse clinical outcomes. Further work is necessary to meaningfully use this predictive ability to adjust therapeutic regimens.

Risk of pulmonary exacerbations

We also note that pulmonary exacerbations occurred frequently during the follow up period in these two relatively healthy cohorts of children with CF. The proportion of children with at least one pulmonary exacerbation treated with IV antibiotics per year is between 20 and 30% for ages 5–13 years, and has not changed appreciably in at least 20 years.[27] Although the use of CFTR modulators decreases the frequency of pulmonary exacerbations, patients continue to be at-risk for loss of FEV_1 following these events.[35] It is imperative that we identify patients at-risk for pulmonary exacerbations to prevent the occurrence of these important patient-centered outcomes. Our analysis was not designed to address the ability of FEV_1 or chest CT to predict pulmonary exacerbations over a short time span, which can contribute substantially to progression of lung disease.[36] A history of pulmonary

exacerbations treated with IV antibiotics is highly predictive of future risk of pulmonary exacerbations.[37]

Limitations

The chest CT scans in the PEIT and WI RCT studies were obtained, on average, at about 10 years of age, so we are unable to comment on the generalizability of cut-off values in CT scores, either in terms of age, severity of FEV_1, or predictive ability. We did not assess chronic medication use in this analysis, although eligible patients not taking chronic medications are at increased risk for pulmonary exacerbations over a short time frame.[38] In order to attain a long follow up period, we studied outcomes after chest CT scans that were obtained in 1999–2000, before many of the current CF therapies were available. As with any study with a long follow up period, this could limit the generalizability of our findings and the ability to predict future events, especially as additional therapies become available. Given the long follow up period, it is not entirely surprising that the AUC values were only "acceptable," i.e., not "excellent" or "outstanding."[39] Ongoing studies that incorporate serial chest CT scans may provide additional information on the predictive ability of chest CT findings, especially in younger children with mild lung disease.[40,41]

Prior to 2012, pulmonary exacerbations treated without IV antibiotics were not recorded in the CFFPR, so our study cannot assess if spirometry or quantitative chest CT scores are associated with the future risk of these pulmonary exacerbations, which are likely more common in our study population made of young patients with high levels of lung function.[42] The Brody score is a research tool that is challenging to use in routine clinical care at this time to adjust therapeutic regimens.[43] Given the probability that quantitative chest imaging will be clinically valuable,[24,28] current efforts are ongoing to develop an automated scoring system.[44,45] However, currently there are no data that show that alterations in care based on routinely obtained CT scans result in improved outcomes.

Conclusions

We have defined cut-off points in Brody scores that discriminate between children with CF and mild lung disease at different risks for frequent future pulmonary exacerbations over an extended follow up period. Brody scores were relatively similar in separate cohorts of children with CF with normal FEV_1. Ongoing studies may be helpful in optimizing the use of chest CT scores for prediction of future disease progression in younger children with CF.

ACKNOWLEDGEMENTS

The authors would like to thank the Cystic Fibrosis Foundation for the use of CF Foundation Patient Registry data to conduct this study. Additionally, we would like to thank the patients, care providers, and clinic coordinators at CF Centers throughout the United States for their contributions to the CF Foundation Patient Registry.

Support: Cystic Fibrosis Foundation (SANDERS11A0) and Institute for Clinical and Translational Research (ICTR) through the NIH National Center for Advancing Translational Sciences (NCATS) grants UL1 TR000427 and KL2TR000428. The WI RCT was supported by National Institutes of Health grants DK 34108 and M01 RR03186 and Cystic Fibrosis Foundation grant A001-5-01.

Some of these results were presented at the 2013 North American Cystic Fibrosis Conference in Salt Lake City, Utah

Conflict of Interest: DBS has received grant support and honoraria from the CF Foundation; no compensation was provided in exchange for this manuscript. The other authors have no conflicts of interest to disclose.

REFERENCES

1. de Jong P, Nakano Y, Lequin M, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. Eur Respir J. 2004;23(1):93–97. [PubMed: 14738238]
2. de Jong P, Lindblad A, Rubin L, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. Thorax. 2006;61(1):80–85. [PubMed: 16244089]
3. Brody A, Sucharew H, Campbell J, et al. Computed tomography correlates with pulmonary exacerbations in children with cystic fibrosis. Am J Respir Crit Care Med. 2005;172(9):1128–1132. [PubMed: 16100015]
4. Loeve M, Gerbrands K, Hop WC, Rosenfeld M, Hartmann IC, Tiddens HA. Bronchiectasis and pulmonary exacerbations in children and young adults with cystic fibrosis. Chest. 2011;140(1):178–185. [PubMed: 21148242]
5. Sanders DB, Li Z, Brody AS. Chest computed tomography predicts the frequency of pulmonary exacerbations in children with cystic fibrosis. Ann Am Thorac Soc. 2015;12(1):64–69. [PubMed: 25474182]
6. Bortoluzzi CF, Volpi S, D'Orazio C, et al. Bronchiectases at early chest computed tomography in children with cystic fibrosis are associated with increased risk of subsequent pulmonary exacerbations and chronic pseudomonas infection. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2014;13(5):564–571. [PubMed: 24726420]
7. Britto M, Kotagal U, Hornung R, Atherton H, Tsevat J, Wilmott R. Impact of recent pulmonary exacerbations on quality of life in patients with cystic fibrosis. Chest. 2002;121(1):64–72. [PubMed: 11796433]
8. Briesacher BA, Quittner AL, Fouayzi H, Zhang J, Swensen A. Nationwide trends in the medical care costs of privately insured patients with cystic fibrosis (CF), 2001–2007. Pediatr Pulmonol. 2011;46(8):770–776. [PubMed: 21465674]
9. Goss C, Burns J. Exacerbations in cystic fibrosis. 1: Epidemiology and pathogenesis. Thorax. 2007;62(4):360–367. [PubMed: 17387214]
10. Liou T, Adler F, Fitzsimmons S, Cahill B, Hibbs J, Marshall B. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153(4):345–352. [PubMed: 11207152]
11. Levy JF, Rosenberg MA, Farrell PM. Innovative assessment of inpatient and pulmonary drug costs for children with cystic fibrosis. Pediatr Pulmonol. 2016;51(12):1295–1303. [PubMed: 27740724]
12. Eakin MN, Bilderback A, Boyle MP, Mogayzel PJ, Riekert KA. Longitudinal association between medication adherence and lung health in people with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2011;10(4):258–264. [PubMed: 21458391]
13. Sawicki GS, Ren CL, Konstan MW, et al. Treatment complexity in cystic fibrosis: Trends over time and associations with site-specific outcomes. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2013;12(5):461–467. [PubMed: 23352205]
14. Ramsey KA, Rosenow T, Turkovic L, et al. Lung Clearance Index and Structural Lung Disease on Computed Tomography in Early Cystic Fibrosis. Am J Respir Crit Care Med. 2015;193(1):60–67.
15. Tepper LA, Ciet P, Caudri D, Quittner AL, Utens EM, Tiddens HA. Validating chest MRI to detect and monitor cystic fibrosis lung disease in a pediatric cohort. Pediatr Pulmonol. 2016;51(1):34–41. [PubMed: 26436668]
16. Forno E, Fuhlbrigge A, Soto-Quiros ME, et al. Risk factors and predictive clinical scores for asthma exacerbations in childhood. Chest. 2010;138(5):1156–1165. [PubMed: 20472862]
17. Chalmers JD, Singanayagam A, Akram AR, et al. Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. Thorax. 2010;65(10):878–883. [PubMed: 20729231]

18. Lange P, Marott JL, Vestbo J, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med. 2012;186(10):975–981. [PubMed: 22997207]
19. VanDevanter DR, Wagener JS, Pasta DJ, et al. Pulmonary outcome prediction (POP) tools for cystic fibrosis patients. Pediatr Pulmonol. 2010;45(12):1156–1166. [PubMed: 20717915]
20. Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatr. 2001;139(6):813–820. [PubMed: 11743506]
21. Brody A, Klein J, Molina P, Quan J, Bean J, Wilmott R. High-resolution computed tomography in young patients with cystic fibrosis: distribution of abnormalities and correlation with pulmonary function tests. J Pediatr. 2004;145(1):32–38. [PubMed: 15238903]
22. Knapp EA, Fink AK, Goss CH, et al. The Cystic Fibrosis Foundation Patient Registry. Design and Methods of a National Observational Disease Registry. Ann Am Thorac Soc. 2016;13(7):1173–1179. [PubMed: 27078236]
23. Farrell PM. Improving the health of patients with cystic fibrosis through newborn screening. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Adv Pediatr. 2000;47:79–115. [PubMed: 10959441]
24. Farrell P, Li Z, Kosorok M, et al. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. Pediatr Pulmonol. 2003;36(3):230–240. [PubMed: 12910585]
25. Farrell P, Collins J, Broderick L, et al. Association between mucoid Pseudomonas infection and bronchiectasis in children with cystic fibrosis. Radiology. 2009;252(2):534–543. [PubMed: 19703887]
26. Brody AS, Kosorok MR, Li Z, et al. Reproducibility of a scoring system for computed tomography scanning in cystic fibrosis. J Thorac Imaging. 2006;21(1):14–21. [PubMed: 16538150]
27. Cystic Fibrosis Foundation. Patient Registry 2015 Annual Report. Bethesda, 2016.
28. Sanders D, Li Z, Brody A. Brody chest CT scores of severity are associated with FEV1 and pulmonary exacerbations 10 years later. Pediatr Pulmonol. 2012;47(S35):377.
29. Mayer-Hamblett N, Rosenfeld M, Emerson J, Goss C, Aitken M. Developing cystic fibrosis lung transplant referral criteria using predictors of 2-year mortality. Am J Respir Crit Care Med. 2002;166(12 Pt 1):1550–1555. [PubMed: 12406843]
30. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–1343. [PubMed: 22743675]
31. Kulich M, Rosenfeld M, Campbell J, et al. Disease-specific reference equations for lung function in patients with cystic fibrosis. Am J Respir Crit Care Med. 2005;172(7):885–891. [PubMed: 15976373]
32. Que C, Cullinan P, Geddes D. Improving rate of decline of FEV1 in young adults with cystic fibrosis. Thorax. 2006;61(2):155–157. [PubMed: 16384880]
33. Gustafsson P, De Jong P, Tiddens H, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. Thorax. 2008;63(2):129–134. [PubMed: 17675316]
34. Thomen RP, Walkup LL, Roach DJ, Cleveland ZI, Clancy JP, Woods JC. Hyperpolarized 129Xe for investigation of mild cystic fibrosis lung disease in pediatric patients. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2017;16(2):275–282. [PubMed: 27477942]
35. Flume PA, Wainwright CE, Elizabeth Tullis D, et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2018;17(1):83–88. [PubMed: 28651844]
36. Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2012;40(1):61–66. [PubMed: 22135280]
37. Sanders DB, Zhao Q, Li Z, Farrell PM. Poor recovery from cystic fibrosis pulmonary exacerbations is associated with poor long-term outcomes. Pediatr Pulmonol. 2017;52(10):1268–1275. [PubMed: 28881091]

38. Sawicki GS, Ayyagari R, Zhang J, et al. A pulmonary exacerbation risk score among cystic fibrosis patients not receiving recommended care. Pediatr Pulmonol. 2013;48(10):954–961. [PubMed: 23255309]

39. Hosmer DW, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed Hoboken, New Jersey: John Wiley & Sons, Inc; 2013.

40. Sly PD, Gangell CL, Chen L, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med. 2013;368(21):1963–1970. [PubMed: 23692169]

41. Mott LS, Park J, Murray CP, et al. Progression of early structural lung disease in young children with cystic fibrosis assessed using CT. Thorax. 2012;67(6):509–516. [PubMed: 22201161]

42. Wagener JS, Rasouliyan L, VanDevanter DR, et al. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2013;48(7):666–673. [PubMed: 22888106]

43. Calder AD, Bush A, Brody AS, Owens CM. Scoring of chest CT in children with cystic fibrosis: state of the art. Pediatr Radiol. 2014;44(12):1496–1506. [PubMed: 25164326]

44. DeBoer EM, Swiercz W, Heltshe SL, et al. Automated CT scan scores of bronchiectasis and air trapping in cystic fibrosis. Chest. 2014;145(3):593–603. [PubMed: 24114359]

45. Rosenow T, Oudraad MC, Murray CP, et al. PRAGMA-CF. A Quantitative Structural Lung Disease Computed Tomography Outcome in Young Children with Cystic Fibrosis. Am J Respir Crit Care Med. 2015;191(10):1158–1165. [PubMed: 25756857]

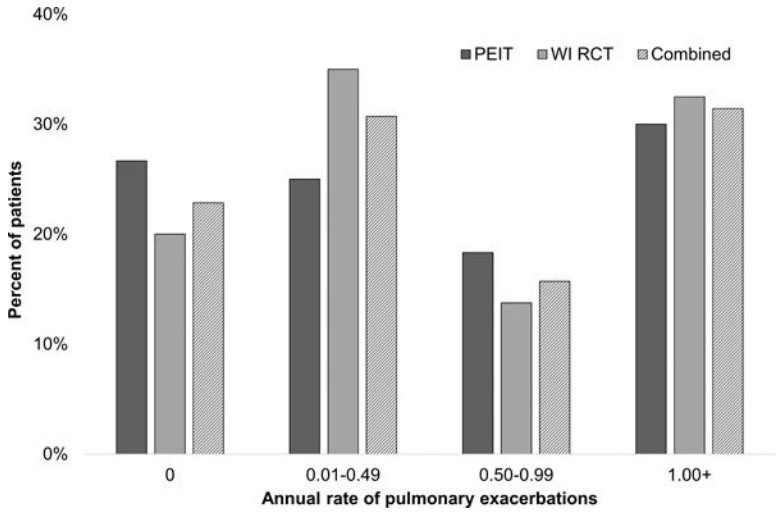
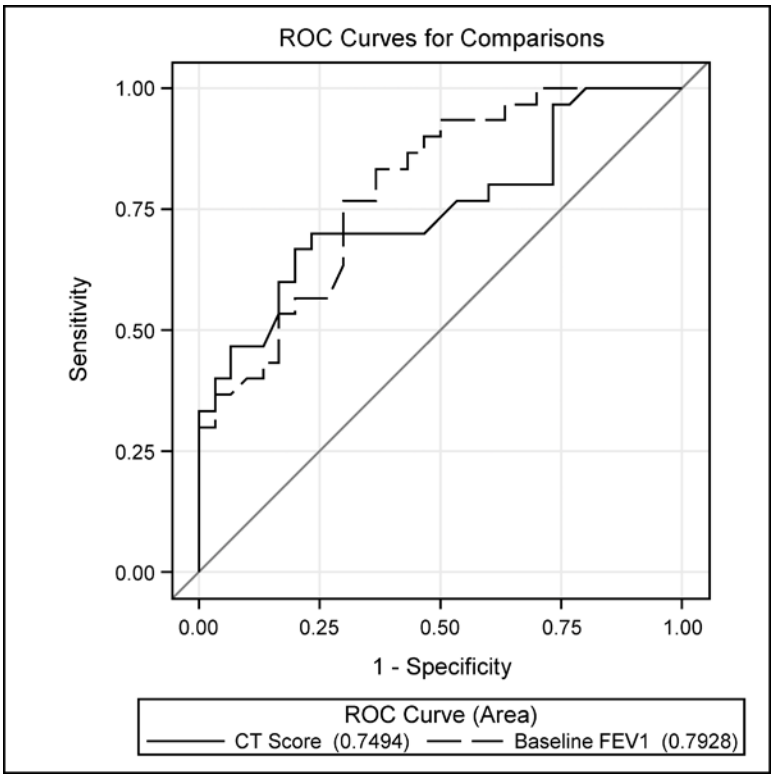
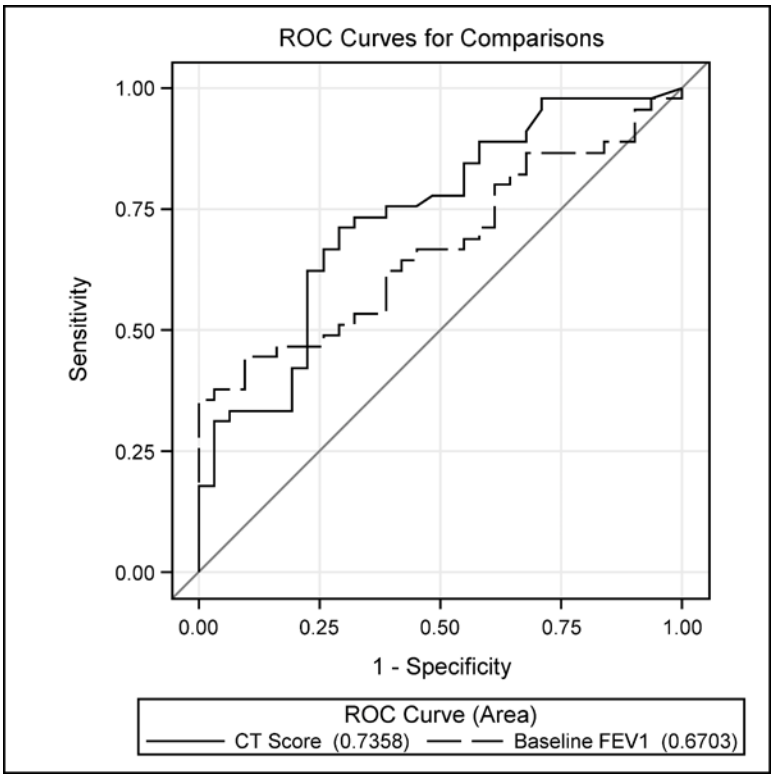


Figure 1.

Annual rates of pulmonary exacerbations for the PEIT study, the WI RCT study, and the combined cohorts.





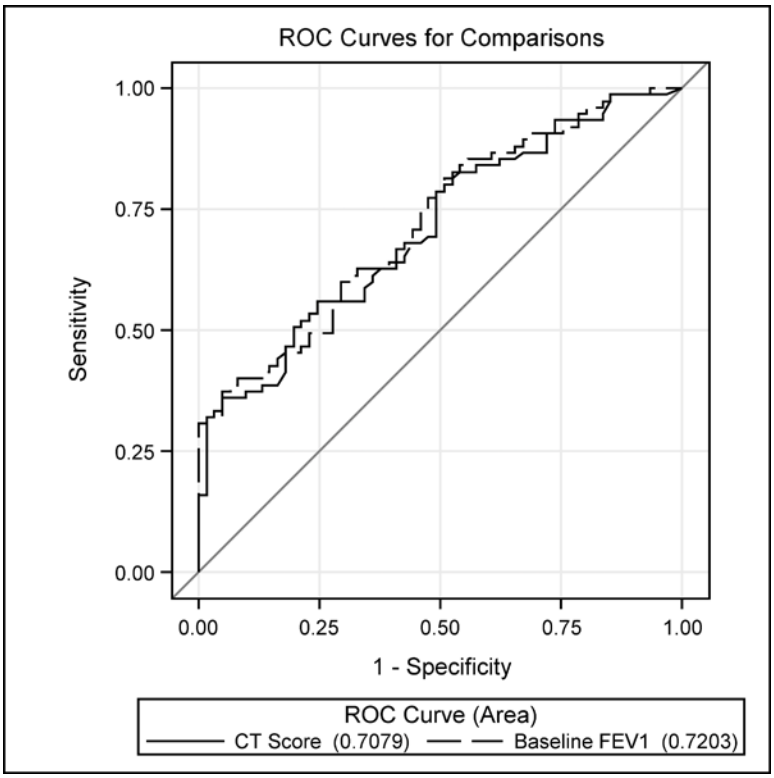


Figure 2.

ROC curves to discriminate between <0.3 and ≥0.3 annual future pulmonary exacerbations for chest CT score and FEV_1 % predicted in the PEIT study (**A**), WI RCT study (**B**), and combined cohorts (**C**).

Table 1.

Characteristics of the study cohorts.

Patient Characteristic	PEIT Study cohort, N = 60		WI RCT Study cohort, N = 81		Combined, N=141	
	At time of chest CT	At follow up	At time of chest CT	At follow up	At time of chest CT	At follow up
	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)	n (%) or mean (SD)
Female sex	24 (40)	21 (38)	34 (42)	34 (42)	58 (41)	55 (40)
Age, years	10.6 (1.7)	20.5 (1.7)	11.5 (3.0)	19.7 (1.6)	11.1 (2.5)	20.0 (1.7)
Homozygous F508del	30 (50)	26 (47)	46 (57)	46 (57)	76 (54)	72 (53)
Heterozygous F508del	23 (38)	22 (40)	31 (38)	31 (38)	54 (38)	53 (39)
Other mutations	7 (12)	7 (13)	4 (5)	4 (5)	11 (8)	11 (8)
Pancreatic insufficient	58 (97)	53 (96)	68 (84)	68 (84)	126 (89)	121 (89)
FEV_1 % predicted	99.2 (14.2)	77.1 (23.9)	91.1 (16.7)	86.4 (20.4)	94.6 (16.2)	82.6 (22.3)
Culture positive for *Pseudomonas aeruginosa*	30 (50)	39 (74)	39 (48)	33 (47)	69 (49)	72 (59)
Culture positive for mucoid *P. aeruginosa*	20 (33)	29 (55)	23 (28)	27 (39)	43 (31)	56 (46)
Culture positive for *Staphylococcus aureus*	40 (67)	24 (45)	36 (44)	41 (59)	76 (54)	65 (53)

Table 2.

The difference in FEV_1 % predicted, chest CT score, and bronchiectasis score that differentiates between the frequencies of future pulmonary exacerbations

Lung disease measure	PEIT Study cohort				WI RCT Study cohort				Combined			
	Annual frequency of pulmonary exacerbations				Annual frequency of pulmonary exacerbations				Annual frequency of pulmonary exacerbations			
	≤0.3 N=30 (50%)	>0.3 N=30 (50%)	Difference, Mean (SD)	P-value	≤0.3 N=34 (42%)	>0.3 N=47 (58%)	Difference, Mean (SD)	P-value	≤0.3 N=64 (45%)	>0.3 N=77 (55%)	Difference, Mean (SD)	P-value
Mean (SD) FEV_1 % predicted	106.3 (11.1)	92.2 (13.6)	14.1 (12.4)	<0.001	97.2 (11.4)	86.7 (18.8)	10.5 (16.2)	0.003	101.7 (12.0)	88.9 (17.0)	12.8 (15.0)	<0.001
Mean (SD) Brody CT score	2.9 (1.1)	4.7 (2.2)	−1.8 (1.7)	<0.001	1.9 (1.9)	4.0 (3.2)	−2.1 (2.7)	<0.001	2.4 (1.6)	4.3 (2.9)	−1.9 (2.4)	<0.001
Mean (SD) Bronchiectasis score	0.3 (0.4)	0.9 (1.0)	−0.6 (0.8)	0.008	0.5 (0.7)	1.3 (1.4)	−0.8 (1.1)	<0.001	0.4 (0.6)	1.2 (1.2)	−0.7 (1.0)	<0.001

Table 3.

Optimum cut-off values and area under the curve (AUC) for FEV_1 % predicted, chest CT score, and bronchiectasis score that differentiate between patients with ≤0.3 or >0.3 annual pulmonary exacerbations

	PEIT Study cohort		WI RCT Study cohort		Combined	
Lung disease measure	**Optimal cut-off**	**Mean (95% CI) AUC**	**Optimal cut-off**	**Mean (95% CI) AUC**	**Optimal cut-off**	**Mean (95% CI) AUC**
FEV_1 % predicted	101.6	0.79 (0.68, 0.90)	94.1	0.67 (0.55, 0.79)	95.9	0.72 (0.64, 0.80)
Brody CT score	3.6	0.75 (0.62, 0.88)	1.9	0.74 (0.62, 0.85)	3.4	0.71 (0.62, 0.79)
Bronchiectasis score	0.4	0.69 (0.56, 0.83)	0.3	0.73 (0.62, 0.85)	0.4	0.72 (0.63, 0.80)

Table 4.

Sensitivities and specificities for chest CT score, bronchiectasis score, FEV_1 % predicted, and chest CT score combined with FEV_1 % predicted for differentiating between patients with ≤0.3 and >0.3 annual future pulmonary exacerbations

	PEIT Study cohort		WI RCT Study cohort		Combined	
Lung disease measure	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
FEV_1 % predicted	0.77(.61,.93)	0.70(.53,.87)	0.62(.47,.77)	0.61(.43,.79)	0.61(.49,.73)	0.69(.57,.81)
Brody CT score	0.70(.53,.87)	0.77(.61,.93)	0.68(.54,.82)	0.71(.54,.87)	0.55(.43,.66)	0.75(.64,.86)
Bronchiectasis score	0.60(.41,.79)	0.67(.49,.85)	0.72(.59,.86)	0.62(.45,.79)	0.61(.50,.72)	0.69(.57,.80)
FEV_1 % predicted + Brody CT score	0.90(.79,1)	0.53(.34,.72)	0.85(.75,.96)	0.50(.32,.68)	0.74(.64,.84)	0.55(.42,.67)

Table 5.

Optimum cut-off values, area under the curve (AUC), sensitivities, and specificities for FEV_1 % predicted, chest CT score, and bronchiectasis scores that differentiate between patients in the top and bottom quartile for annual rate of pulmonary exacerbations

	Bottom quartile (0 pulmonary exacerbations per year)						Top quartile (>1 pulmonary exacerbation per year)					
	FEV_1 % predicted		Brody CT score		Bronchiectasis subscore		FEV_1 % predicted		Brody CT score		Bronchiectasis subscore	
	PEIT	WI RCT	PEIT	WI RCT	PEIT	WI RCT	PEIT	WI RCT	PEIT	WI RCT	PEIT	WI RCT
Optimal cut-point	103.6	94.1	3.33	1.44	0.33	0.28	98.2	80.9	3.79	2.90	0.50	1.36
AUC (95% CI)	0.75 (0.62, 0.88)	0.74 (0.62, 0.86)	0.73 (0.60, 0.86)	0.72 (0.59, 0.85)	0.70 (0.55, 0.85)	0.73 (0.61, 0.86)	0.71 (0.58, 0.85)	0.64 (0.46, 0.81)	0.75 (0.62, 0.88)	0.80 (0.68, 0.92)	0.70 (0.53, 0.87)	0.76 (0.63, 0.90)
Sensitivity	0.75	0.78	0.81	0.65	0.81	0.70	0.73	0.57	0.73	0.81	0.67	0.67
Specificity	0.73	0.62	0.59	0.69	0.57	0.67	0.62	0.84	0.67	0.73	0.69	0.84