

Quantitative chest computerized tomography and FEV₁ equally identify pulmonary exacerbation risk in children with cystic fibrosis

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SUMMARY (250 words)

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 (FEV₁) 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 FEV₁ % 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 in separate cohorts. Brody scores and FEV₁ % predicted have similar abilities to identify these children, suggesting that FEV₁ % predicted alone may be adequate for predicting future frequency of pulmonary exacerbations.

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) $\leq 78\%$ 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 FEV₁ % 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) $\geq 85\%$ 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 FEV₁ % 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 WIRCT 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 207²¹ 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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. FEV₁ % 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 10th 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % predicted combined with the Brody score was 0.75 (0.63, 0.86), compared to 0.67 (0.55, 0.79) for FEV₁ % 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 FEV₁ % predicted and higher Brody CT scores. The Brody CT score had slightly better AUCs than FEV₁ % 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 FEV₁ % 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 FEV₁ % 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 FEV₁ % predicted obtained at the same time as the chest CT. This was true whether the CT score was used alone, or in combination with FEV₁ % 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,^{3,4,6,31} 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 FEV₁

Our results demonstrate a single CT score and FEV₁ measurement have predictive abilities in multiple cohorts comparable to the ability of FEV₁ to predict 2-year mortality.²⁸ In contrast to chest CT scores, more information is available on clinically important cut-off values for FEV₁ % 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 FEV₁ % predicted has been defined according to age and sex for global populations,³² and in comparison to other children with CF.³³ 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 FEV₁ in detecting progression of early CF lung disease, in our study, FEV₁ % 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 FEV₁ % 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 FEV₁ 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 FEV₁ and the rate of pulmonary exacerbations,⁹ it is not surprising that FEV₁ would be associated with future risk of pulmonary exacerbations. As FEV₁ increases for subsequent birth cohorts of children with CF, and as FEV₁ decline slows over time,³⁴ other evaluation methods that are more sensitive, e.g., CT scores, lung clearance index,³⁵ or magnetic resonance

imaging,³⁶ 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 FEV₁ following these events.³⁷ 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 FEV₁ or chest CT to predict pulmonary exacerbations over a short time span, which can contribute substantially to progression of lung disease.^{38,39} A history of pulmonary exacerbations treated with IV antibiotics is highly predictive of future risk of pulmonary exacerbations.⁴⁰

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 FEV₁, 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.⁴¹ 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.”⁴² 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.^{43,44}

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.⁴⁵ The Brody score is a research tool that is challenging to use in routine clinical care at this time to adjust therapeutic regimens.⁴⁶ Given the probability that quantitative chest imaging will be clinically valuable,^{24,31} current efforts are ongoing to develop an automated scoring system.^{47,48} 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 FEV₁. Ongoing studies may be helpful in optimizing the use of chest CT scores for prediction of future disease progression in younger children with CF.

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Figure Legends

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 FEV₁ % 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 <i>Pseudomonas aeruginosa</i>	30 (50)	39 (74)	39 (48)	33 (47)	69 (49)	72 (59)
Culture positive for mucoid <i>P.</i> <i>aeruginosa</i>	20 (33)	29 (55)	23 (28)	27 (39)	43 (31)	56 (46)
Culture positive for <i>Staphylococcus aureus</i>	40 (67)	24 (45)	36 (44)	41 (59)	76 (54)	65 (53)

Table 2. The difference in FEV₁ % 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		Difference, Mean (SD)	P-value	Annual frequency of pulmonary exacerbations		Difference, Mean (SD)	P-value	Annual frequency of pulmonary exacerbations		Difference, Mean (SD)	P-value
≤0.3	>0.3	≤0.3			>0.3	≤0.3			>0.3			
	N=30 (50%)	N=30 (50%)			N=34 (42%)	N=47 (58%)			N=64 (45%)	N=77 (55%)		
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
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
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 FEV₁ % predicted, chest CT score, and bronchiectasis score that differentiate between patients with ≤0.3 or >0.3 annual pulmonary exacerbations

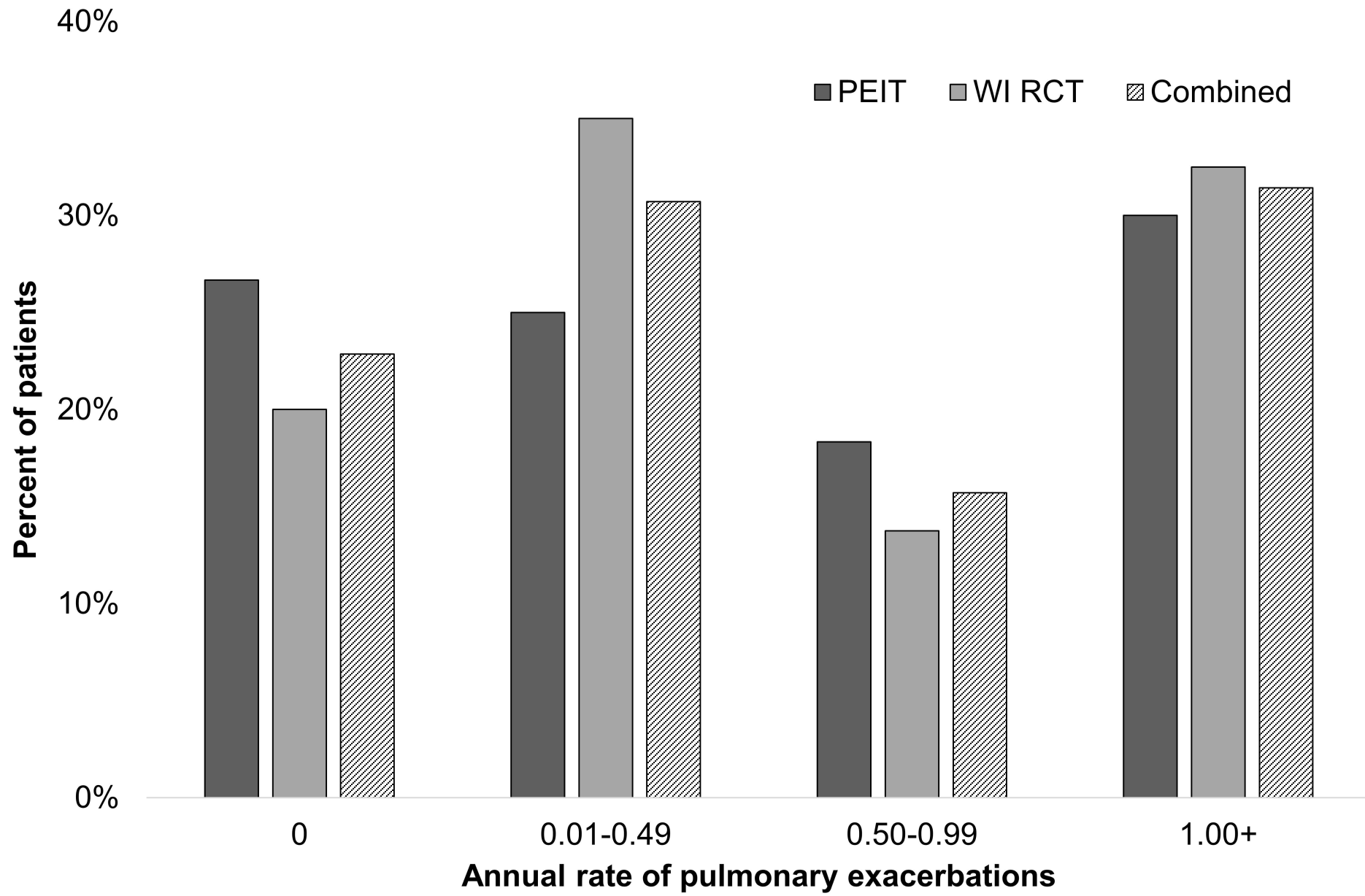
Lung disease measure	PEIT Study cohort		WI RCT Study cohort		Combined	
	Optimal cut-off	Mean (95% CI) AUC	Optimal cut-off	Mean (95% CI) AUC	Optimal cut-off	Mean (95% CI) AUC
FEV ₁ % predicted	101.6	0.79 (0.68, 0.90)	94.1	0.67 (0.55, 0.79)	95.9	0.72 (0.64, 0.80)
Brody CT score	3.6	0.75 (0.62, 0.88)	1.9	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, FEV₁ % predicted, and chest CT score combined with FEV₁ % predicted for differentiating between patients with ≤0.3 and >0.3 annual future pulmonary exacerbations

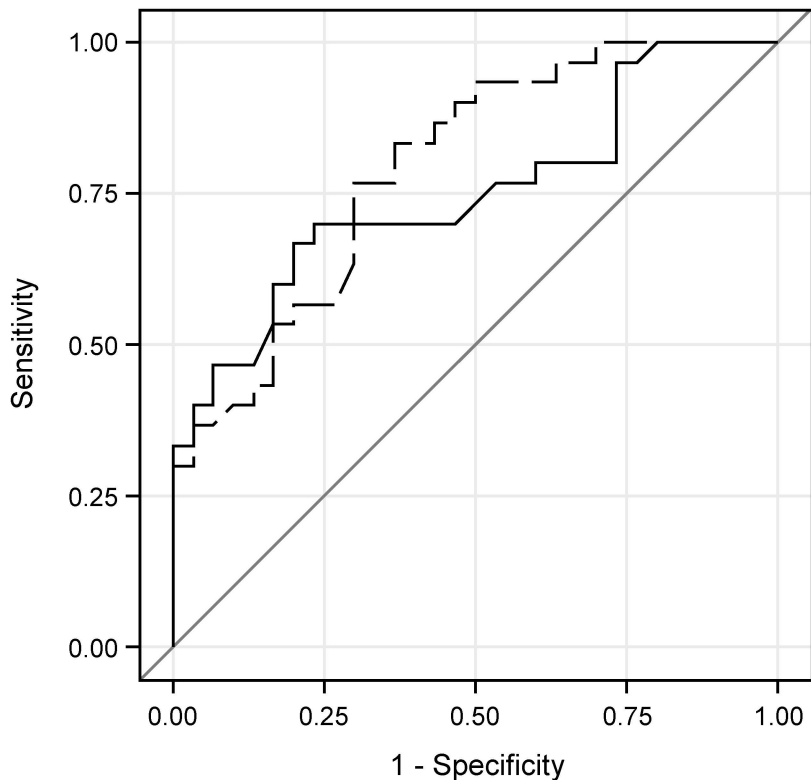
Lung disease measure	PEIT Study cohort		WI RCT Study cohort		Combined	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
FEV ₁ % predicted	0.77(.61,.93)	0.70(.53,.87)	0.62(.47,.77)	0.61(.43,.79)	0.61(.49,.73)	0.69(.57,.81)
Brody CT score	0.70(.53,.87)	0.77(.61,.93)	0.68(.54,.82)	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 FEV₁ % 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



ROC Curves for Comparisons

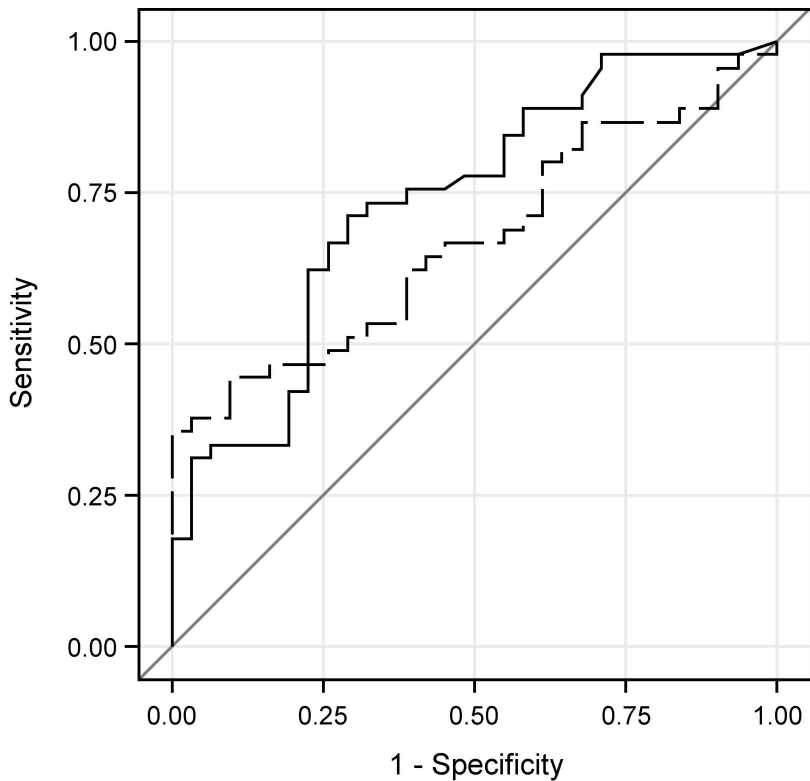


ROC Curve (Area)

— CT Score (0.7494)

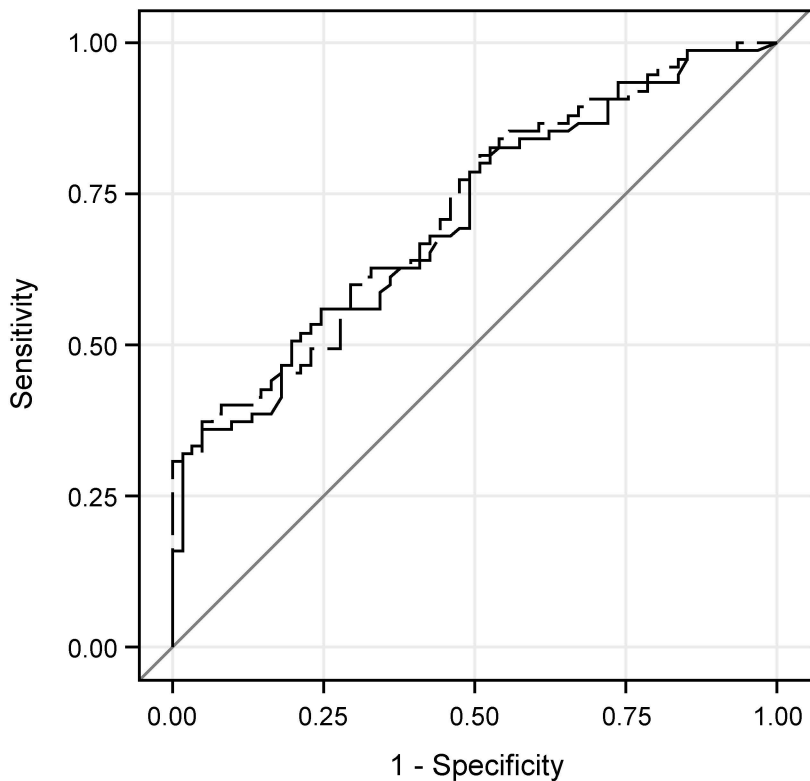
- - - Baseline FEV1 (0.7928)

ROC Curves for Comparisons



ROC Curve (Area)
—— CT Score (0.7358) - - - Baseline FEV1 (0.6703)

ROC Curves for Comparisons



ROC Curve (Area)
—— CT Score (0.7079) - - - Baseline FEV1 (0.7203)