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Original Article

Bronchiectases at early chest computed tomography in children with cystic fibrosis are associated with increased risk of subsequent pulmonary exacerbations and chronic pseudomonas infection

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Abstract

Background: Children with cystic fibrosis (CF) are often *Pseudomonas aeruginosa* (PsA) free and exhibit normal spirometry between the ages of 5 and 7. It is reported that computed tomography (CT) is more sensitive than FEV1 as an instrument in the identification of pulmonary disease. It is not known whether CF-CT scores in childhood may be used to highlight children at risk of developing severe disease.
Aims: 1 — To assess the number of respiratory exacerbations (RTEs) during a follow-up period of 6 years and their correlation with the CF-CT scores in young CF children. 2 — To assess whether PsA-negative CF children with high chest CF-CT scores are more likely to develop chronic PsA lung infection.
Methods: 68 chest CT performed in patients without chronic PsA infection were scored. All patients (median age 7.8 years) had at least 4 clinical, functional and microbiologic assessments/year in the subsequent 6 years. RTE was defined as hospitalization and IV antibiotic treatment for respiratory symptoms.
Results: 86.8% patients had <3 RTEs in the 6 year follow-up period. The number of RTEs in the 6 years subsequent to the CT scan was correlated to the bronchiectasis CT score (BCTS) ($r = 0.612$; $p < 0.001$) and to FEV1 at baseline ($r = -0.495$, $p < 0.001$). A BCTS ≥ 17.5 identified patients with >3 RTEs during follow-up (sensitivity: 100%, specificity: 85%), while FEV1 did not. Only BCTS was significant in a logistic multivariate model (RR 1.15). BCTS was significantly lower and FEV1 higher in patients who did not develop chronic PsA infection by the end of the study.
Conclusion: In CF children free from chronic PsA, both CT scores and FEV1 values demonstrate significant correlation with disease severity in the subsequent 6 years but CT score has higher predictive value in the identification of patients at risk.

Keywords: Cystic fibrosis; Computed tomography; Respiratory exacerbations; *Pseudomonas aeruginosa*

1. Introduction

Cystic fibrosis (CF) lung disease is progressive and characterized by the development of bronchiectasis and regional air trapping, chronic lower-airway bacterial infection, respiratory tract exacerbations (RTEs) and progressive decrease in lung function. Traditionally, spirometry (i.e. forced expiratory volume in 1 s or FEV1) has been used to monitor disease progression.

Recent data show that chest CT can help us identify structural abnormalities in children who are too young to perform routine spirometry that gives reliable values [1–3].

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Despite some concerns about ionizing radiation exposure and other disadvantages, for example its high cost, chest CT has become the gold standard for the diagnosis of bronchiectasis in CF and non-CF individuals [4,5]. The role of chest CT in monitoring the progression of CF lung disease has been extensively studied in the last few years, thanks to standardization of quantitative CF scoring systems [6]. A comparison between the CF-CT score, which is an upgraded version of the Brody CT scoring system, and other surrogate clinical endpoints in CF [7–9] shows that the high sensitivity of the bronchiectasis subscore is of more utility in diagnosis and tracking of early lung disease compared to FEV1 [2,10].

Longitudinal studies are needed to establish whether early-age CF-CT scores identify those patients who will then develop severe lung disease during adolescence or young adulthood.

Disease progression in CF is related to RTEs and chronic lung *Pseudomonas aeruginosa* (PsA) infection [11]. RTE is an accepted outcome in CF [12,13], although there is no consensus on its definition [14]. Up to this date however only two studies [7,15] have examined the correlation between chest CT scores and later RTEs in these patients; the follow-up period in both was 2 years. In addition, it is not clear whether the presence of bronchiectasis precedes PsA infection and thus whether it is an early determinant of lung disease progression.

The first aim of our study was to examine the association between chest CT scores and RTE over a longer period to establish whether they can identify those patients who are at risk of deteriorating. To our knowledge, there are no studies which describe the correlation between chest CT scores and RTEs over an extended follow-up in children with CF who are PsA free.

The second aim of our study was to investigate, in the cohort of young PsA-negative CF patients, whether CT scores and FEV1 could be used to identify those patients who are more likely to develop chronic PsA infection before adolescence. We investigated the abovementioned associations in a cohort of patients who all had 6 years of clinical, functional and microbiological follow-up after the first chest CT.

2. Methods

2.1. Study population

This retrospective analysis includes all eligible patients with a confirmed diagnosis of CF who had a chest CT scan during the period from January 2004 to April 2007 and who were subsequently followed in the Verona CF Regional Centre (Italy). Since 2004, starting from when they can reliably do pulmonary function tests, all of our patients have a routine chest CT scan every 2 to 3 years. We included only those CT scans performed as part of an annual check up when patients were clinically stable.

Eligible children 1) were aged ≥ 4 and ≤ 11 years, 2) had been diagnosed with CF (sweat chloride ≥ 60 mmol/l and/or two known CF mutations), and 3) were monitored for 6 years in our center, with at least quarterly clinical, spirometric and microbiological assessments every year throughout the period. We excluded: 1) patients for whom we had incomplete follow-up data and 2) patients who had a lung transplant before the end of the follow-up. The hospital review board approved the study protocol, and parents' written informed consent was obtained.

2.2. Follow-up assessments

Patients were seen every three months and assessed according to the European CF Society Standards of Care [16]. Clinical data were extracted from electronic patient records.

2.3. Chest CT scans

A single 4-detector row CT scanner (Somatom Plus 4, Siemens, Berlin, Germany) was used. The CT scans were obtained in the supine position using the following scan parameters: 80–120 kVp, 15–24 mAs, pitch of 1, with automatic tube current modulation. The lung parenchyma was evaluated using the following HRCT reconstruction parameters: 1 mm slice thickness at 3 to 10 mm intervals from apex to base during voluntary end inspiration breath-holds in cooperative patients. The calculated Dose Length Product or DLP range (DLP = volume CTDI * scan length) for the CT scans was 22–113 mGy * cm (estimated mSv range: 0.34–1.74).

2.4. CT scoring

All CTs were scored using a CF-CT scoring system (Brody II), proposed by Brody and colleagues [6]. Bronchiectasis, mucus plugging, airway wall thickening and parenchyma scores were calculated for each patient; air trapping was not evaluated. The maximum total CT score (243) is the sum of maximum values for each parameter (bronchiectasis, mucus plugging, airway wall thickening, opacities, air trapping) for every single lung lobe, considering the lingula as a separate lobe. Excluding air trapping, the maximum theoretical value is 216. For statistical analysis, only partial subscores were considered and expressed as a percentage of the maximum possible score (0–100).

All 73 scans were anonymized, randomized and scored using a modified Brody score [6] by two suitably qualified, independent observers (S.V. and M.L.). Mean CT scores were used for analysis.

2.5. Spirometry, respiratory cultures and exacerbations

All spirometry measurements were obtained using a single water bell spirometer (Biomedin, Padova, Italy). Forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and forced expiratory flow between 25 and 75% of FVC (FEF 25–75) were expressed as percentages of predicted values and as Z scores. Reference equations for children by Zapletal and Samanek [17] were used.

Deep throat or sputum cultures were obtained at least every three months. The prevalence of PsA infection was assessed

during lifetime, in the year preceding the CT scan and in the last year of the study period. Infection was defined according to the Leeds criteria [18]: 1) never; PsA never cultured from sputum or pharyngeal samples; 2) free; no growth of PsA found in the previous 12 months, having previously been PsA culture positive; 3) intermittent; when 50% or fewer of the samples were positive for PsA; and 4) chronic; when sputum or pharyngeal samples were positive for PsA in more than 50% of the cultures in a 12 month period. The presence of *Staphylococcus aureus* (methicillin sensible — MSSA- and methicillin resistant — MRSA) was assessed at the time of the CT and at the end of follow-up. A MSSA infection was defined chronic when sputum or pharyngeal samples were positive for PsA in more than 50% of the cultures in a 12 month period. The presence of other bacteria was also recorded at the time of the CT.

We recorded data about all hospitalizations for IV antibiotic treatment for respiratory symptoms in the 6 years following the baseline CT.

Only baseline CT scans were compared with baseline and follow-up parameters, including subsequent RTEs.

2.6. Statistical analysis

The interobserver agreement of the CT scores was calculated using an intraclass correlation coefficient (ICC). An ICC of >0.8 is generally considered to indicate very strong agreement. Descriptive statistics were calculated for each parameter (gender, age, spirometry measurements, colonization, RTEs): percentages were reported for discrete variables, while median, range, mean and standard deviations were calculated for the continuous variables.

Patient characteristics were compared using X^2 or Fisher's exact test (as appropriate) for discrete variables and the Kruskal–Wallis test for comparison of more than two groups for the continuous variables. The correlations between continuous variables were computed. The Pearson correlation coefficients were interpreted according to the Salkin scale: an r value between 0.8 and 1.0 (or −0.8 and −1.0) is defined as very strong, 0.6–0.8 as strong, 0.4–0.6 as moderate, 0.2–0.4 as weak and 0.0–0.2 as very weak or as no relationship [19].

CT scan scores and FEV1 results were grouped into quartiles. A receiver–operator characteristic (ROC) curve was plotted to find the CF-CT score value that was identified, with the highest sensitivity and specificity, those subjects who experienced 4 or more RTEs during the follow-up. The optimal cut-off points of parameters were selected according to the maximum Youden's index value (sensitivity + specificity-1). A logistic regression model was estimated to determine which variables were associated with the number of RTEs in a 6-year follow-up. Univariate analysis was performed for the following variables: FEV1%, age, BMI, BMI%, and BCTS. All variables having a $p < 0.1$ entered a multivariate logistic model.

A p value < 0.05 was considered statistically significant.

Version 11 of SPSS (SPSS Inc., Chicago, Illinois) and SAS (SAS Institute, Cary, NC, USA; Version 9.2) softwares were used for statistical analysis.

3. Results

3.1. Characteristics of the subjects

83 subjects had chest CT during the study period. 10 patients were eventually excluded as they did not meet the inclusion criteria (2 were lost during follow-up and follow-up data was incomplete for 8), therefore 73 subjects were eligible for the study. We performed the analysis excluding those patients who had already chronic PsA infection at the time of CT scan (n = 5) because this condition influences the disease severity and the prevalence of RTEs. Therefore we eventually included 68 patients in the study. Median age at CT was 7.8 years in the range 4.6–10.8, 36 (52.9%) were female. Subject characteristics are shown in Table 1.

All CT scans scored were of good quality and considered by an experienced radiologist to be adequate for evaluation.

3.2. RTEs

In the 6 years following the CT, 47.1% of the patients had no RTEs, 39.7% experienced from 1 to 3 and 13.2% had more than 3. The median number of RTEs in the follow-up period was 1 (range 0–15, interquartile range 0–2).

Table 1
Cohort characteristics at baseline (chest CT) and after 6 years.

Descriptives	Baseline (mean ± SD) (range)	6 years later
N included patients	68	68
Age, years	7.76 ± 1.57 (4.6–10.8)	–
Height, cm	127.9 ± 13.0 (103.9–164.1)	–
Weight, kg	29.5 ± 7.3 (15.2–50.9)	–
BMI, kg/m^2	16.8 ± 1.87 (13.1–22.5)	–
BMI percentile	44.3 ± 28.1	–
FEV1%	85.0 ± 16.0 (44.8–117)	85.7 ± 17.3 (46.1–118)
FVC % predicted	96.1 ± 12.9 (65.5–120.5)	95.6 ± 13.3 (67.3–127)
FEF 25–75% predicted	66.9 ± 27.9 (14.8–123.5)	65.4 ± 28.9 (17.5–138)
CF-CT bronchiectasis score	12.5 ± 10.1 (0–41.3)	–
CF-CT mucus plugging score	4.9 ± 7.8 (0–31.9)	–
CF-CT airway wall thickening score	11.3 ± 11.0 (0–40.7)	–
CF-CT parenchyma score	4.9 ± 4.3 (0–13)	–
Chronic MSSA infection	30 (44.1%)	25 (36.8%)
Chronic MRSA infection	0	6 (8.8%)
N pancreatic insufficiency	57	–
N Phe508del mutation homozygosis	19	–
Allergic bronchopulmonary aspergillosis	1	1
CF related diabetes	0	1

Abbreviations: BMI: body mass index; CT: computed tomography; FEV1: forced expiratory volume in 1 s; FEF 25–75: forced expiratory flow between 25 and 75% of FVC; FVC: forced vital capacity; MSSA: methicillin-sensible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*.

Table 2
Characteristics of patients according to the number of RTEs.

RTEs in 6 years	0 (N = 32)	1–3 (N = 27)	>3 (N = 9)
Age (years, SD)	7.65 (1.38)	7.63 (1.80)	8.51 (1.45)
BMI percentile, mean (SD)	49.10 (28.27)	39.58 (27.16)	41.63 (30.30)
FEV1% at CT, mean (SD)	92.81 (12.32)	80.40 (15.69)	70.97 (14.28)
FEF 25–75% at CT, mean (SD)	79.29 (22.42)	57.88 (22.99)	40.98 (18.93)
BCTS (mean, SD)	7.52 (5.66)	14.10 (10.61)	25.68 (8.09)

Abbreviations: see Table 1.

3.3. Chest CT scores

Interobserver agreement was strong for bronchiectasis CT score (BCTS) (ICC > 0.95) but, consistently with previously reported data [7], weak for mucus plugging (0.40), and airway wall thickening (0.00). ICC for parenchyma scores was 0.92. Only the BCTS was considered for analysis.

A high correlation coefficient was found between the BCTS and the number of RTEs in the following 6 years ($r = 0.612$, $p < 0.001$); the correlation coefficients between FEV1% or FEF 25–75% at baseline and RTEs were lower but still significant ($r = -0.495$ and -0.493 respectively, $p < 0.001$). The correlations between BCTS and initial FEV1% or FEF 25–75% and between BCTS and FEV1% or FEF 25–75% at the end of follow-up were low ($r = -0.37$ and -0.43 respectively, $p < 0.05$ for FEV1%; and $r = -0.32$ and -0.36 respectively, $p < 0.05$ for FEF 25–75%).

Patients with the highest BCTS and lowest FEV1% values had the highest rates of RTEs. Patients with >3 RTEs had significantly higher BCTS compared to those with 1 to 3 or no RTEs over the follow-up period (mean 25.7 ± 8.1, 14.1 ± 10.6 and 7.5 ± 5.7 respectively, $p < 0.001$). Descriptive data for these groups are presented in Table 2.

Fig. 1 shows the ROC curves for BCTS and FEV1 and their best cut-offs. A BCTS ≥ 17.5 identified patients with >3 RTEs with a sensitivity of 100% and a specificity of 85% (Youden's index = 0.85). The best cut off for FEV1% (88.7) with a 100% sensitivity had a very low specificity (50.8%) (Youden's index = 0.49).

Among the variables analyzed (age, BMI, BMI%, FEV1, BCTS), FEV1 and BCTS resulted significant in univariate analysis; this result was confirmed in the multivariate model only for BCTS. For every one unit increase in CT score, the odds ratio of having more than 3 RTEs increases by 15% (OR 1.15; 95% C.I.: 1.06–1.25, $p = 0.0009$).

3.4. P. aeruginosa lung infection and CT score

In this cohort, 18 patients had no PsA cultured in their lifetime including up to the end of follow-up (group A). 38 patients, who had PsA cultured at least once in their lifetime, were PsA free or intermittent in the year before performing chest CT and were still PsA free or intermittent at the end of follow-up (group B), while 12 free or intermittent in the year before chest CT became PsA chronic in the 6-year follow-up (group C). We found that BCTS at baseline was significantly different in the three groups, being higher in group C than group B and higher in group B than in group A (mean 20.1 ± 9.3, 12.9 ± 10.8 and 6.6 ± 6.6 respectively; $p = 0.0003$). FEV1% and FEF 25–75% at the time of CT scans were significantly different in the three groups although higher in group A and group B and lower in group C (Table 3 and Fig. 2).

3.5. Other microorganisms

We also analyzed the presence of co-infection with MSSA, MRSA and other microorganisms. At the time of the CT, none of the 68 patients had MRSA, while 3 (16.7%) patients in group A, 19 (50%) in group B and 8 (66.7%) [8] in group C had chronic MSSA. At the end of follow-up, in group A 7 (38.9%)

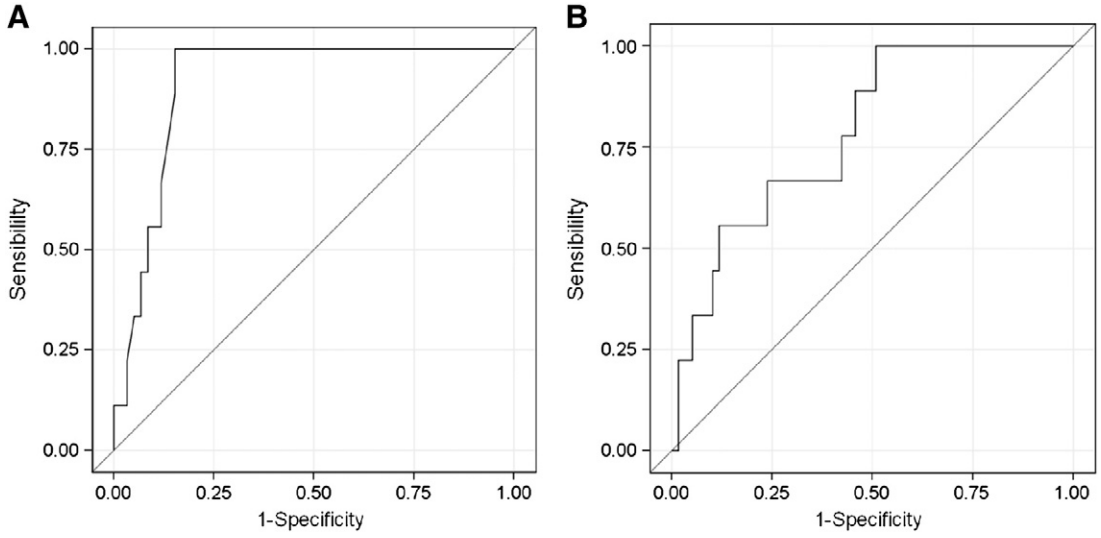

Fig. 1. ROC curves for bronchiectasis CT score (A) and FEV1 (B) identifying patients who had >3 RTEs in 6 years. The closer the apex of the curve toward the upper left corner, the greater the discriminatory ability of the test. The straight, diagonal line represents Area Under Curve (AUC) = 0.5 (no discriminative value). AUC for bronchiectasis CT score is 0.914 (cut off 17.5%: sensitivity 100%, specificity 85%). AUC for FEV1 is 0.785 (cut off 88.7%: sensitivity 100%, specificity 50.8%).

Table 3
Kruskal Wallis test comparing group A (never PsA), B (PsA free or intermittent within the study) and C (free or intermittent PsA at baseline with chronic infection at end of follow-up).

	PsA infection			
	Group A	Group B	Group C	p
Bronchiectasis CT score%				
Median (range)	4.9 (0.0–26.9)	11.4 (0–41.3)	21.2 (5.6–33.9)	0.0003
Mean (SD)	6.6 (6.6)	13.0 (10.2)	20.1 (9.3)	
N obs.	18	38	12	
FEV1% at CT				
Median (range)	88.9 (71–114)	90 (44.8–117)	73.0 (52.8–82.8)	0.0019
Mean (SD)	90.7 (11.8)	86.5 (17.1)	71.7 (9.8)	
N obs.	18	38	12	
FEF 25–75% at CT				
Median (range)	74.3 (30.7–123.5)	69.8 (26–118)	42.3 (14.8–79.3)	0.0084
Mean (SD)	72.4 (27.8)	69.8 (24.4)	43.6 (17.2)	
N obs. [a]	16	33	11	
Age at CT, years				
Median (range)	6.7 (4.6–9.9)	7.9 (5.2–10.8)	8.5 (5.1–10.8)	0.1325
Mean (SD)	7.2 (1.7)	7.9 (1.4)	8.3 (1.7)	
N obs.	1 8	3 8	12	
Height, cm				
Median (range)	121.8 (104.8–164.1)	128.2 (103.9–145.9)	132.1 (109.9–148)	0.4
Mean (SD)	125.7 (15.2)	127.9 (12.4)	131.3 (11.6)	
N obs.	18	38	12	
Weight, kg				
Median (range)	27.5 (15.2–48.3)	29.5 (16.6–42.9)	29.6 (20.1–50.9)	0.7
Mean (SD)	28.3 (8.5)	29.5 (6.5)	31.4 (8.2)	
N obs.	18	38	12	
BMI, kg/m^2				
Median (range)	16.4 (13.1–20.3)	16.6 (13.9–20.7)	15.8 (14.8–22.5)	0.5
Mean (SD)	16.4 (1.9)	16.8 (1.7)	17.2 (2.3)	
N obs.	18	38	12	
BMI%				
Median (range)	38.9 (1.2–96.9)	45.6 (3.6–92.7)	26.9 (10.2–94.7)	0.97
Mean (SD)	42.8 (28.9)	45.5 (27.9)	43.1 (29.7)	
N obs.	18	38	12	

Abbreviations: See Table 1.
[a] In 8 patients <7.5 years old at the time of CT, FEF 25–75% was not reported in the database because they were not fully cooperative with the test.

patients had MSSA and 2 (11.1%) MRSA; in group B 15 (39.5%) had MSSA and 2 (5.3%) MRSA; and in group C, 3 (25.0%) had MSSA and 2 (16.7%) had MRSA. The differences between the groups were significant at the time of the CT (p =0.01) but not at the end of the follow-up (p = 0.7).

There were no significant differences in the overall number of patients colonized by other microorganisms between the 3 groups (Table 4).

4. Discussion

We analyzed a cohort of CF patients without PsA chronic infection, aged between 4 and 11 years old who had a routine baseline chest CT scan and were then followed for the subsequent 6 years. Our data showed that: a) a chest CT, performed in a stable clinical condition at this age, highlights patients at high risk of RTEs, while FEV1 is less predictive; BMI and age do not show significant value; b) PsA-free children with higher CT scores and lower FEV1 and FEF 25–75 values seem to be more susceptible to developing chronic PsA airway infection; c) patients who have never been infected with PsA have the lowest BCTS; and d) MSSA and MRSA infections do not show a significantly higher prevalence in the group of patients who had chronic PsA at the end of the follow-up. The prevalence of other bacteria does not differ in patients who never had PsA and in those who became chronically infected.

Bronchiectasis and chronic PsA infection are the two most important determinants in CF lung disease progression and are associated with increased morbidity and early mortality [11,20]. Chest CT provides a direct and sensitive means of measuring early structural changes in the lung of patients affected by CF [5]. Moreover it has been reported that CT scans highlight lung disease earlier than FEV1% [2,10]. This was better defined in a logistic model: in children free from chronic PsA, BCTS highlights patients at higher risk while FEV1 did not, and these results are independent from other variables such as age, BMI and other comorbidities (CF related diabetes, allergic bronchopulmonary aspergillosis).

In this study we considered the number of RTEs as the main outcome since it is an accepted clinical endpoint in clinical trials in CF [12,13] and it is strongly related to the progression

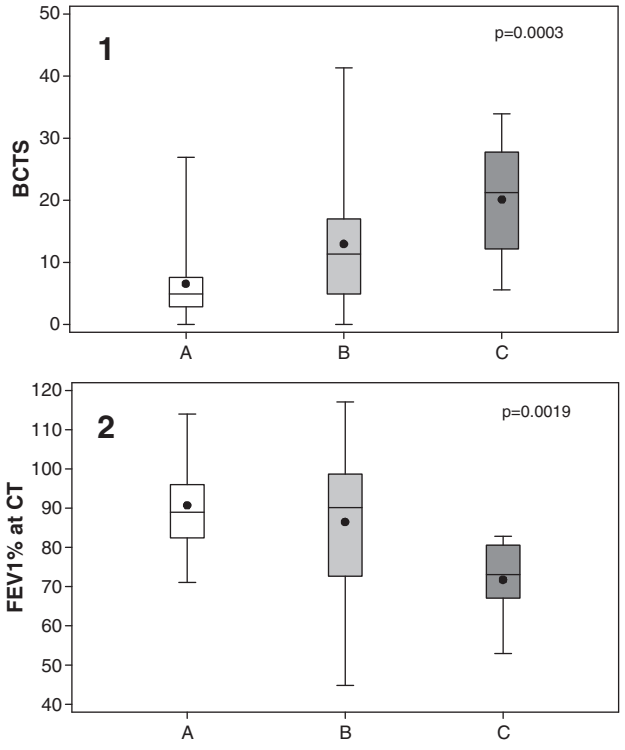

Fig. 2. Boxplots: bronchiectasis CT score [1] and FEV1 [2] in group A (never PsA), B (PsA free or intermittent within the study) and C (free or intermittent PsA with chronic infection at end of follow-up). Each box shows mean (dot), median (line), interquartile range (solid box), and extreme values. Bronchiectasis CT score at baseline was significantly higher in group C than in group B and higher in group B than in group A; FEV1 was significantly lower in group C. Abbreviations: BCTS bronchiectasis CT score.

of lung disease [21,22] although there is no clear consensus on its definition [14].

To our knowledge, there have been only three previous studies that demonstrate correlation between the number of RTEs and chest CT scores. Brody and colleagues [15] analyzed a cohort of 61 patients (age range 6–11 years) included in the Dornase alfa trial [23]: in a 2 year follow-up, patients with high CT scores suffered a greater number of RTEs. Considering the relationship between the changes in CT scores over two years and incidence of RTE, BCTS showed the highest correlation (r = 0.35). More recently, Loeve and colleagues [7] analyzed retrospectively the clinical data of 115 Dutch patients (aged from 5 to 20 years) in a 2-year follow-up after a baseline chest CT. A worse BCTS was shown to predict a higher rate of RTEs. The same correlation was confirmed in a recent study correlating CT score and quality of life in CF [9]. Our study expands therefore on previous observations but over a much longer follow-up period and with a different, clinically relevant cohort of young children without chronic PsA infection.

Previously, little correlation between chest CF-CT scores and FEV1 [2,6,10] has been described and this was confirmed in this study. BCTS carries the most weight in most scoring systems since it is more closely correlated with RTEs and FEV1% than the total score and other subscores [7,10,24]. Our study confirms that BCTS is more significant than other CT parameters. We could identify a BCTS threshold with good sensitivity and specificity for patients at higher risk. Our findings suggest that chest CT should be done early with CF children, before they can do spirometry testing. Along with infant lung function tests such as LCI [25], it could help to highlight patients at risk of RTE and rapidly progressive lung disease.

We found that the pediatric CF patients who remained PsA free until the end of the follow-up had the lowest values of BCTS and the highest FEV1% mean values. Patients who were infection free or with intermittent infections with lower FEV1% and FEF 25–75% values and higher CF–CT scores at the age of 7 were also more at risk of becoming chronically infected in subsequent years. To our knowledge, very few studies have investigated the association between CT scores and PsA infection in CF lung. Robinson and colleagues [26] found significant differences in chest CT scores in different groups of children, according to their PsA status in the previous 19 months (PsA retrospectively ever detected vs never detected). Farrell and colleagues [27] showed that there was a correlation between chest CT scores and concomitant mucoid PsA infection but failed to demonstrate any correlation between chest CT scores and non-mucoid strains; we did not use such a distinction. A recent Australian study [28] suggests that bronchoalveolar lavage-directed antimicrobial therapy for RTEs is not effective in children in the first 5 years of life in reducing prevalence of future PsA infection or in lowering CT scores. None these studies however investigated, specifically and prospectively, PsA-free children to assess the risks of future infection.

Recent data suggest that simultaneous infection by PsA and MRSA could worsen lung disease [29]. In our cohort, none of the patients had MRSA at CT. At the end of the follow-up, 4 patients with previous chronic MSSA had chronic MRSA, 2 acquired intermittent MRSA infection; the prevalence was not significantly different in the 3 groups previously defined according to PsA status. However, the number of MSSA infected patients increases over 6 years in group A (never PsA) while it decreases in group B (PsA free or intermittent within the study) and in group C (free or intermittent at baseline with chronic infection at the end of follow-up). This could signify

Table 4
Colonization by other microorganisms at the time of CT scan in group A (never PsA), B (PsA free or intermittent within the study) and C (free or intermittent PsA at baseline with chronic infection at end of follow-up).

Colonization at CT	Group A (N = 18)	Group B (N = 38)	Group C (N = 12)	p
All	8 (44.4%)	27 (71.0%)	8 (66.6%)	0.15
H. parainfluenzae	7 (87.5%)	21 (77.7%)	3 (37.5%)	
H. influenzae	2	3	1	
Serratia species	–	2	2	
Alcaligenes xylosoxidans	–	2	–	
Stenotrophomonas maltophilia	–	2	1	
Candida	–	1	1	
>1 microorganism	1	4	0	

that MSSA is replaced by established PsA infections in more severe CF structural lung disease.

The prevalence of co-infection with other bacteria at the time of CT was not significantly different in these groups.

Our study has several limitations. First, data were collected retrospectively and RTE was defined according to a common shared definition (i.e. respiratory symptoms requiring IV treatment), which could exclude minor RTEs that require home treatment with oral antibiotics. Unlike the other studies, we did not consider the number of RTEs prior to the beginning of the follow-up. Furthermore air trapping score, which represents small airways involvement and is a relevant early marker of CF lung disease, was not computed because expiratory scans were not available in this young cohort. We did not include an analysis of CT scans at the end of the follow-up because scores were not available in all patients: this could have provided relevant information on radiologic progression of lung disease in the different PsA groups. We are planning to perform this analysis in future studies.

Finally, we did not analyze the differences between mucoid and non-mucoid PsA strains and data on colonization by microorganisms different from PsA and MSSA/MRSA at the end of the follow-up.

Although additional research is needed to fully understand the mechanisms at work, our findings offer evidence for the early identification in CF children of significant bronchiectasis through CT, even where there is no evidence of chronic PsA infection, and for considering such children at high risk and in need of tailored follow-up, timing and treatment options. Moreover, our data also support the view that lung damage precedes chronic PsA infection. Therefore, the clinical implications of this study are that chest CT scan should be recommended in children with CF, even when symptomless and before they start performing spirometry. Moreover, in those children with higher BCTS, it may be suggested to perform sputum cultures more frequently, as this could give more chances to treat earlier and more aggressively every PsA new infection. Further prospective multicenter longitudinal studies are necessary to confirm these outcomes.

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