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Correlation between clinical-functional parameters and number of lobes involved in non-cystic fibrosis bronchiectasis

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ABSTRACT

Background: Currently, the prognosis of bronchiectasis is based on different prognostic indicators, like BSI and FACED score, founded on clinical-demographic, functional and radiological criteria. Both scoring systems include the number of lobes involved in bronchiectasis, which represents an adverse prognostic index. Our study aimed to investigate the prognostic role of the clinical-functional parameters and the number of involved lobes ratio in adult bronchiectasis.

Methods: The study was conducted on 52 patients diagnosed with non-cystic fibrosis bronchiectasis (NCFB) between 2015 and 2017 who attended the Pneumology Unit of Monaldi Hospital in Naples, Italy. Correlations between clinical-functional parameters (BMI, smoking history, number of exacerbations in the previous year, spirometry, DL_{CO}, ABG test, and 6MWT) and number of involved lobes were investigated.

Results: At baseline, the number of exacerbations in the previous year had a statistically significant association with the number of involved lobes. Furthermore, at baseline, the radiological criterion was also negatively associated with some functional parameters (FEV_1/FVC ratio e $FEF_{25-75\%}$). Statistical significance was lost during the follow up, demonstrating the effectiveness of the therapy.

Conclusions: Imaging extension represents a promising biomarker of disease severity as well as a helpful follow up tool for non-Cystic Fibrosis bronchiectasis (NCFB).

Key words: Bronchiectasis; HRCT; lobe; pulmonary function tests; exacerbations; NCFB.

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Introduction

The term "bronchiectasis" indicates a permanent and irreversible dilation of the bronchial wall, associated with the occurrence of cough, dyspnoea, daily production of sputum, and recurrent respiratory infections [1]. Intraluminal neutrophils, having come into contact with the aetiological agent, produce inflammatory mediators, destroying elastin, cartilage, and muscles of the large airways, with consequent irreversible bronchodilation. Besides, macrophages and lymphocytes form infiltrates in the inflamed airways. Repeated damage causes a thickening of the bronchial walls, formation of mucus plugs, and the presence of varying degrees of hyperinflation [2]. It has a huge social-health impact, caused mainly by frequent hospitalizations and mortality [3,4]. The overall prevalence of bronchiectasis in the Italian population, according to data provided by general practitioners (GPs), is 163 per 100,000, whereas annual incidence is 16.3 per 100,000 person-years [5]. Both prevalence and incidence increase with age, with the highest rates reported in patients aged >75 [5].

The aetiology of non-cystic fibrosis bronchiectasis (NCFB) differs between childhood and adulthood. The localized forms are mostly secondary to chronic obstructive factors, represented in the child by the accidental aspiration of a foreign body. In adults, localized forms of NCFB are caused by infections or tumour pathology, generally benign. Both age groups may be subjected to obstruction due to the inflammatory-infectious hypertrophy of the peri-interbronchial lymph nodes.

In the aetiology of diffuse forms, the alteration of the pulmonary defence mechanisms prevails due to primary immunodeficiency, detected in the dysgammaglobulinemia, or by altered mucociliary clearance due to ciliary dyskinesia, systemic disorders (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, inflammatory bowel disease) or alteration of the rheological characteristics of secretions and facilitated bacterial adhesiveness, as observed in cystic fibrosis (CF) [6]. However, very often, NCFB remains idiopathic (40-50%).

Mucus removal and local defence mechanisms against microorganisms are essential in keeping the lungs free from infections [2]. When these mechanisms are impaired, exacerbations worsen inflammation, resulting in fibrosis and dilation of the bronchial wall. Therefore, there is a progressive decrease in respiratory function, confirmed by spirometry. Usually, FEV_1 declines according to the disease's progression, and thus it might be preferred for monitoring bronchiectasis [7]. Likewise, both arterial blood gas analysis (ABGs) and diffusing capacity of the lung for CO (DL_{CO}) may be abnormal due to these alterations.

The 6-minute walking test (6MWT) is a sub-maximal, simple exercise test used to assess the respiratory system's functional responses during physical effort, representing a helpful index of the aerobic capacity of bronchiectasis patients [8]. Of course, early diagnosis allows for quick and targeted treatment that improves the long-term prognosis.

Chest high-resolution computed tomography (HRCT) of the chest is currently the gold standard for correct diagnosis and staging of the lesions, assessing morphological aspects, localization, and extent of wall damage. Furthermore, it is useful to evaluate complications, such as emphysema and pulmonary hypertension. The latter condition can be identified early by measuring the pulmonary artery's cross-sectional area and comparing it to that of the aorta (AP/A ratio is strictly linked to the mean pulmonary artery pressure value) [9]. Emphysema can be identified by CT scans as low attenuation areas (LAA) with a different degree of vascular compartment involvement [9]. Also, thin slice reconstructions are preferred to detect lesions smaller than 5 mm and visualize the

"air-trapped" areas [9]. Upper lobe predominance is seen in sarcoidosis, aspergillosis, post-tuberculous scarring, and post-radiation fibrosis. Calcified hilar or mediastinal lymph nodes and calcified pulmonary granulomas suggest granulomatous infections, such as tuberculosis [6]. Anterior segment distribution (middle lobe and lingula) is generally observed in atypical mycobacterial disease, which usually involves two or more lobes and often affects middle-aged or elderly female patients [6]. Lower lobe distribution is most often seen in post-infectious bronchiectasis, chronic aspiration, immunodeficiencies, and primary ciliary dyskinesia [6].

The significant aetiological variability of bronchiectasis could explain the different extent of lesions in the lung lobes. Immunodeficiencies, genetic diseases, chronic colonization by multidrug-resistant strains of *Pseudomonas aeruginosa,* tuberculous and non-tuberculous mycobacterial infections are examples of conditions that predispose the onset of bronchiectasis [6]. These often have a severe prognosis due to the high number of annual exacerbations and the rapid deterioration of respiratory function towards lung failure, as confirmed by this study.

The analysis carried out in this study is focused on the relationship between clinical-functional parameters and imaging, examining the correlations among clinical data, lung function tests, and the number of lobes affected by bronchiectasis on chest HRCT. Functional data of interest were collected at baseline and at three and six months.

Methods

Study population

The study population included 52 adults diagnosed with NCFB referred to our Respiratory Medicine Unit at the Monaldi Hospital in Naples, Italy, between December 2015 and October 2017. Lung function testing and chest HRCT were available for all patients along with clinical data. The inclusion criteria were:

Age ≥ 18;
Chest HRCT confirmed diagnosis;
Exclusion of cystic fibrosis history.

Baseline clinical data

Fifty-two patients with an average age of 55.8 ± 17.3 years (21 to 81 years) were enrolled (Table 1). Main anamnestic data, including smoking habits and the recurrence of exacerbations in the previous year, were collected at enrolment. Thirty-two (61.5%) were females, twenty (38.5%) were male. There were seventeen former smokers (32.7%), six current smokers (11.5%), and twenty-eight non-smokers (55.8%).

Eleven patients (28.9%) reported no exacerbation in the previous year, thirty-tree patients (50%) reported one exacerbation, and eight (21.1%) reported more than one. Thirteen patients (25%) were affected by chronic infection of *Pseudomonas aeruginosa*.

Twenty patients (38.5%) were overweight (25.0 – 29.99 kg/cm^2), five (9.6%) had mild obesity (30.0 – 34.99 kg/cm^2), and two (3.8%) had moderate-severe obesity (> 35 kg/ cm^2).

Pulmonary function tests (PFTs)

The patients' pulmonary function was investigated through global spirometry, diffusing capacity of the lung for carbon monoxide (DL_{CO}), 6MWT, and ABGs. Functional data were collected at the first visit and subsequently at 3 and 6 months. Some controls are missing at T3 and T6 because the patients could not perform functional tests or did not show up for the outpatient visit.

Chest HRCT

All patients underwent chest high resolution computed tomography. Lingula was considered as a separate lobe [10].

The patients were grouped into two subsets according to imaging criteria: the first group included twenty-nine patients (55.8%) with up to 2 involved lobes and the second group consisting of twenty-three patients (44.2%) with more than 2 affected lobes (3 to 6). This categorization was designed to make the two groups homogeneous, such that the two groups were quite numerically balanced.

Statistical analysis

Standard descriptive statistics were used to characterize the overall cohort and the two groups defined, based on the numbers of involved lobes. Numerical variables were described using mean ± standard deviation (SD) with range, and categorical factors were synthesized using absolute frequencies and percentages. Accordingly, between-group comparisons were based on the Student's t-test for unpaired samples and the Fisher exact test.

Longitudinal changes of functional data were assessed using Linear Mixed Models with time (baseline, 3, and 6 months), the number of lobes (1-2 *vs* 3-6), and their interaction as the only predictors. Results of LMMs were expressed as the difference in the Estimated Marginal Means (EMMs) with the corresponding 95% Confidence Intervals (95% CIs). Statistical significance was set at $p < 0.05$; all statistical analyses were conducted using the R Platform, v. 4.0.1 [11].

Results

Association between clinical data and number of lobes

According to the numbers of involved lobes (Table 1), all the patients were classified into two groups: no significant differences were found at baseline in the two groups concerning age, gender, BMI, and smoking habit. Patients with more than two involved lobes were characterized by more exacerbations in the last year (p=0.014).

Longitudinal change of functional and tomographic parameters

Plethysmography showed that all patients had lung hyperinflation (Motley Index >30% predicted). The pulmonary function tests

(PFTs) were performed according to the American Thoracic Society / European Respiratory Society guidelines [12].

Greater bronchiectasis involvement was found in the lower lobes (23.5% in the left lobe and 19.7% in the right lobe) and in the middle lobe (22.0%). The lingula was affected in 14.4% of cases, the left upper lobe in 9.8%, the right in 10.6%. These data are based on often multi-lobar involvement.

Regarding ABG analysis, only 4 (9.5%) patients experienced hypoxemia, and there was only one patient with severe hypoxemia. However, twelve patients had altered $PaCO_2$ values: eight (19.0%) showed an increase, generally associated with a bronchial or bronchiolar obstruction; four (9.5%) patients had hypocapnia, a sign of hyperventilation more related to a restrictive or mixed pattern.

At baseline, patients with more than two lobes involved in bronchiectasis showed significantly lower levels of FEV_1/FVC ratio (-8.16; 95% CI: -16.18 to -0.14) and FEF_{25-75}% (-20.8; 95% CI: -40.8 to -0.8) (Table 2). No other significant differences were observed, at baseline, in the other functional and tomographic parameters. FEF_{25-75}% remained significantly lower in the second evaluation (-25.13; 95% CI: -45.57 to -4.59), and afterward, mainly due to the decline observed in subjects with less than two involved lobes, the two groups become comparable. No other differences were observed between the two groups during the whole follow up.

Discussion

The current literature faces two main challenges in the management of bronchiectasis:
- Identifying patients with a high symptomatic burden, at risk of frequent exacerbations or rapid decline in lung function, who may benefit from faster aggressive treatment and closer follow up in reference centres, to reduce possible complications [13];
- Identifying low-risk patients who could benefit from non-specialist follow up or less aggressive treatment regimens to reduce health costs and improve patient satisfaction [13].

The incidence of the disease has undergone a notable increase in recent years. Bronchiectasis is no longer considered a rare condition as it was in the past (16.3:100,000 people per year), possibly due to better quality imaging techniques and more frequent use of HRCT to detect emphysema in COPD patients. The importance of HRCT in the diagnosis and monitoring of bronchiectasis is evident. This is also indicated by the high number of patients (55.8%)

Table 1. Clinical features and number of lobes involved in bronchiectasis. Values expressed as n (%) or as mean ± SD.

Parameters	All patients	1-2 lobes	3-6 lobes	p	Statistical significance
Age, years	52. 55.8 ± 17.3 (21 - 81)	29 60 ± 16.1 (21 - 81)	2353 ± 17.4 (21 - 81)	0.141	Not significant
Gender					
Female	32 (61.5)	16 (55.2)	16 (69.6)	0.39	Not significant
Male	20 (38.5)	13 (44.8)	7 (30.4)		
BMI, kg/m^2	25.8 ± 4.4 (18.4 - 42.8)	25.2 ± 3.4 (18.9 - 33.7)	27 ± 6 (18.4 − 42.8)	0.221	Not significant
Smoking				0.608	Not significant
Former smokers	17 (32.7)	11 (37.9)	6 (26.1)		
Non-smokers	29 (55.8)	14 (48.3)	15 (65.2)		
Smokers	6 (11.5)	4 (13.8)	2 (8.7)		
Exacerbations* (number)				0.014	Significant
0	11 (28.9)	7 (31.8)	4 (25)		
1	19 (50)	14 (63.6)	5 (31.2)		
>1	8 (21.1)	1 (4.5)	7 (43.8)		

BMI, body mass index; *exacerbation in the previous year.

with limited pulmonary involvement (1-2 lobes).

Another crucial observation concerns the correlation between the number of lobes and functional parameters (FEV_1/FVC ratio and $FEF_{25-75\%}$). As previously described, at baseline, it resulted statistically significant; on the contrary, in the following steps (at T3 and T6 for FEV_1/FVC ratio, at T6 for $FEF_{25-75}\%$), the values became insignificant between the two groups (involvement of 1-2 lobes and 3-6 lobes). This result could be motivated by the response to treatment, influencing both inflammation and hypersecretion.

Comparing the study results with many papers described in literature, there is great heterogeneity regarding the relationship between radiology and clinical-functional aspects of bronchiectasis. In particular, a Chinese study published in 2016 showed the absence of correlation between the extent of bronchiectasis and age, smoking history, BMI, exacerbations in the previous year, FEV_1/FVC ratio and predicted FEV_1% in a patient cohort suffering from post-COPD bronchiectasis [14].

In contrast, in 2014, a Korean study found a negative correla-

tion between the extent of bronchiectasis and BMI in moderate to severe disease [15]. Patients experienced weight loss as the disease progressed.

The following year, an Italian team carried out a study on neutrophilic bronchial inflammation in NCFB patients. As a result, predicted FEV_1% was negatively correlated with the number of pulmonary lobes involved in the disease [16].

According to another paper published in 2019, which included bronchiectasis patients performing pulmonary rehabilitation, disease progression seems to be associated with a reduction in exercise capacity [17,18]. The 6-minute walk distance correlated with the extent of bronchiectasis on CT scan and was found by McDonnell *et al.* to reflect disease severity measured by the Bronchiectasis Severity Index (BSI) [18]. Patients with severe disease walked an average of 83 m less than patients with moderate disease and 198 m less than those with mild disease [17].

The BSI was set up and validated for bronchiectasis by Chalmers *et al.* in 2014 [17] .This is a 9-item scale that includes a radiological severity parameter [19]. This is evaluated with the

Table 2. Pulmonary function tests (PFTs) and number of lobes involved in bronchiectasis. Values expressed as mean ± SD.

	Timing	1-2 lobes	3-6 lobes	Difference (95% C.I.)	Statistical significance
FVC% (% predicted)	Baseline (43)	78.6 ± 31.7	76.2 ± 19.6	-2.34 (-18.93 to 14.25)	Not significant
	T3 (30)	79.5 ± 26	75 ± 17.9	2.5 (-14.72 to 20.03)	Not significant
	T6 (20)	78 ± 26	62 ± 15.1	-8.75 (-26.97 to 9.74)	Not significant
FEV_1% (% predicted)	Baseline (43)	75.3 ± 34.4	63.6 ± 20.7	-11.72 (-30.18 to 6.74)	Not significant
	T3 (30)	78.1 ± 30.8	61.6 ± 19.1	-9.79 (-28.5 to 9.01)	Not significant
	T6 (20)	76.8 ± 29.2	52.8 ± 18	-12.48 (-31.5 to 6.65)	Not significant
FEV_1/FVC ratio	Baseline (43)	76.6 ± 14.5	68.5 ± 13.4	-8.16 (-16.18 to -0.14)	Significant
	T3 (30)	77.4 ± 12.1	68 ± 12.5	-8.66 (-17.4 to 0.14)	Not significant
	T6 (20)	79.9 ± 12	74.1 ± 13.4	-0.74 (-10.26 to 8.99)	Not significant
$FEF_{25\%-75\%}$ (% predicted)	Baseline (43)	56.6 ± 38.3	35.8 ± 20	-20.8 (-40.8 to -0.8)	Significant
	T3 (30)	61.6 ± 33	31.5 ± 20.7	-25.13 (-45.57 to -4.59)	Significant
	T6 (20)	59.7 ± 30.4	34.2 ± 15.1	-20.41 (-41.42 to 0.7)	Not significant
DL_{CO}% (% predicted)	Baseline (30)	76.5 ± 24.6	68.4 ± 16.6	-8.15 (-22.82 to 6.52)	Not significant
	T3 (27)	73.9 ± 20.1	71.2 ± 22.4	-4.78 (-19.47 to 9.7)	Not significant
	T6 (16)	76 ± 20.8	64 ± 13.2	-9.52 (-26.22 to 7.29)	Not significant
TLC (% predicted)	Baseline (24)	150.3 ± 39.1	140.8 ± 49.2	-3.48 (-41.27 to 34.7)	0.861
	T3 (21)	137.5 ± 47.8	129.3 ± 41.2	-0.02 (-38.35 to 38.65)	0.999
	T6 (13)	138.8 ± 41.2	153.5 ± 30	-30.1 (-71.55 to 9.94)	0.171
MI	Baseline (24)	52.8 ± 11	49.3 ± 8.02	-3.15 (-12.37 to 6.24)	0.531
	T3 (21)	49 ± 10.7	53 ± 5.97	3.91 (-6.13 to 13.85)	0.471
	T6 (13)	57.2 ± 13.5	52.8 ± 8.22	-4.51 (-17.38 to 8.29)	0.520
RV% (% predicted)	Baseline (30)	83.6 ± 26.8	76.8 ± 28.6	-7.16 (-25.15 to 10.67)	Not significant
	T3 (27)	77.2 ± 23.4	68.1 ± 18.6	-8.62 (-26.45 to 9.42)	Not significant
	T6 (16)	88.8 ± 22.3	67 ± 14.1	-19.46 (-43.03 to 4.47)	Not significant
6MWT (m)	Baseline (18)	181 ± 196	100 ± 33.9	-74.23 (-197.02 to 49.21)	Not significant
	T3 (6)	121 ± 28	83.3 ± 34.3	-82.99 (-212.66 to 43.52)	Not significant
	T6 (4)	156 ± 44.1	86 ± 12	-119.71 (-252.38 to 10.36)	Not significant
PaO_2 (mmHg)	Baseline (41)	76 ± 14.8	73.5 ± 10.5	-2.48 (-10.09 to 5.13)	Not significant
	T3 (25)	76.6 ± 13.5	71.3 ± 12.4	-2.76 (-11.41 to 6.29)	Not significant
	T6 (15)	79.8 ± 5.82	70.3 ± 7.59	-4.43 (-14.81 to 6.46)	Not significant
SaO_2 (%)	Baseline (41)	96.6 ± 3.97	96.6 ± 2.68	-0.02 (-6.06 to 6.02)	Not significant
	T3 (25)	96.5 ± 2.43	96.3 ± 1.51	-0.23 (-8.06 to 7.61)	Not significant
	T6 (15)	97.6 ± 1.72	84.6 ± 34.2	-13.03 (-27.4 to +2.67)	Not significant
$PaCO_2$ (mmHg)	Baseline (41)	41.4 ± 8.23	41 ± 6.79	-0.39 (-4.82 to 4.04)	Not significant
	T3 (25)	39.8 ± 5.06	41.9 ± 8.81	1.12 (-3.67 to 5.84)	Not significant
	T6 (15)	39.5 ± 5.48	42.1 ± 8.06	-1.09 (-6.31 to 4.01)	Not significant

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25-75\%}$, forced expiratory flow at 25-75% of the vital capacity; DL_{CO}, diffusing capacity of the lung for carbon monoxide (CO); RV, residual volume; TLC, total lung capacity; MI, Motley index; 6MWT, six minute walking test; PaO2, partial pressure of oxygen; SaO_2, arterial oxygen saturation; $PaCO_2$, partial pressure of carbone monoxide (CO_2).

modified Reiff score, based on two tomographic parameters: the number of lobes affected by bronchiectasis and the degree of dilation (tubular = 1, varicose = 2, and cystic = 3). The maximum score is 18, and the minimum score is 1 [20].

Conclusions

HRCT is a key exam in NCFB diagnostics and monitoring. Its role in managing the NCFB is well established both in clinical practice and in the literature. The number of involved lobes seems to represent a useful prognostic index and an important follow up tool.

The study carried out showed a crucial correlation between imaging and the number of exacerbations in the previous year, as well as some functional parameters, FEV_1/FVC ratio and $FEF_{25-75\%}$. Regarding the latter, the lack of correlation in the follow up could be associated with an improvement of lung function due to the treatment. In fact, the main strategy in bronchiectasis consists of the prevention and treatment of exacerbations.

Further studies are needed with greater sample size. Furthermore, the prognostic role of $FEF_{25-75\%}$ could be investigated, considering its possible inclusion in the scoring systems currently used in the bronchiectasis staging, like the BSI.

However, the best tool to improve disease management is to strengthen GPs' awareness of bronchiectasis. With their collaboration, an early diagnosis will make the treatment faster and more targeted.

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