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TITLE

A comprehensive approach to lung function in bronchiectasis

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CONFLICT OF INTEREST

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KEY WORDS

Bronchiectasis; Residual volume; Reversibility; Exacerbation; Plethysmography; Spirometry

ABSTRACT

Background: International guidelines recommend simple spirometry for bronchiectasis patients. However, pulmonary pathophysiology of bronchiectasis is very complex and still poorly understood. Our objective was to characterize lung function in bronchiectasis and identify specific functional sub-groups.

Methods: This was a multicenter, prospective, observational study enrolling consecutive adults with bronchiectasis during stable sate. Patients underwent body-plethysmography before and after acute bronchodilation testing, diffusing lung capacity (DL_{CO}) with a 3-year follow up. Air trapping and hyperinflation were a residual volume (RV)>120%predicted and a total lung capacity>120%predicted. Acute reversibility was: ΔFEV_1 ≥12% and 200 ml from baseline (FEV_{1rev}) and ΔRV ≥10% reduction from baseline (RV_{rev}). Sensitivity analyses included different reversibility cutoffs and excluded patients with concomitant asthma or chronic obstructive pulmonary disease.

Results: 187 patients were enrolled (median age: 68 years; 29.4% males). Pathophysiological abnormalities often overlapped and were distributed as follows: air trapping (70.2%), impaired DL_{CO} (55.7%), airflow obstruction (41.1%), hyperinflation (15.7%) and restriction (8.0%). 9.7% of patients had normal lung function. RV_{rev} (17.6%) was more frequent than FEV_{1rev} (4.3%). Similar proportions were found after multiple sensitivity analyses. Compared with non-reversible patients, patients with RV_{rev} had more severe obstruction (mean(SD) FEV_1%pred: 83.0% (24.4) vs 68.9% (26.2); P=0.02) and air trapping (RV%pred, 151.9% (26.6) vs 166.2% (39.9); P=0.028).

Conclusions: Spirometry alone does not encompass the variety of pathophysiological characteristics in bronchiectasis. Air trapping and diffusion impairment, not airflow obstruction, represent the most common functional abnormalities. RV_{rev} is related to worse lung function and might be considered in bronchiectasis' workup and for patients' functional stratification.

INTRODUCTION

Bronchiectasis is characterized by irreversibly damaged and dilated bronchi in the context of recurrent respiratory symptoms, such as productive cough, and episodes of infective exacerbations [1]. Lung function abnormalities in bronchiectasis patients are usually ascribed to the extent and severity of bronchial derangement as well as the presence of other predisposing factors, including smoking status or the co-existence of other respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD). In 1952 Whitwell suggested that the development of bronchiectasis is promoted by an early involvement of lymphoid follicles in small airways, which gradually leads to the obstruction of more distal airways [2]. Accordingly, bronchiectasis has been always described as a chronic obstructive disease in most of the medical textbooks and the forced expiratory volume in one second (FEV_1) has been employed to evaluate functional impairment in both daily practice and clinical research [3,4]. Furthermore, the FEV_1 has been included in both severity scores, the Bronchiectasis Severity Index and the FACED score, recently developed and validated for their use in bronchiectasis patients [5,6].

The 2010 British Thoracic Society (BTS) guidelines recommend simple spirometry to investigate functional abnormalities in adults with bronchiectasis, leaving the measurement of lung volumes and gas transfer factor (KCO) only in specific cases of airflow obstruction such as COPD or emphysema [7]. However, recent literature suggested that bronchiectasis patients might show a variety of pathophysiological abnormalities, including restrictive or mixed patterns, isolated air trapping or even normal lung function [8-11]. Moreover, functional measurements other than FEV_1, such as the degree of hyperinflation

Abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; DLCO = lung diffusion capacity; ERS = European Respiratory Society; FEV_1 = Forced Expiratory Volume in 1 second; FEV1/VC = Tiffeneau index; FRC = functional residual capacity; IC = inspiratory Capacity; ICS = inhaled corticosteroids; LABA = long acting beta-2 agonists; LAMA = long acting muscarinic antagonists; LLN = lower limit of normal; RV = Residual Volume; sRaw = total specific airway resistances; TLC = total lung capacity; VA = alveolar volume; VC = slow vital capacity

and lung diffusion capacity, seem to be independent predictors of mortality [12]. Notably, although distal airways proved to be crucial in the genesis of obstruction in bronchiectasis, responsiveness to bronchodilators has always been evaluated considering improvements in FEV_1 [13-15], which represents a rough indicator of small airways response in chronic obstructive diseases [16,17]. On the contrary, acute changes in static volumes and airway resistances demonstrated a higher sensitivity as markers of bronchodilation and have a close association with symptoms [16-20]. In light of these clinical and research gaps, we designed a multicenter epidemiological prospective study with the following objectives: the primary aim was to investigate the different pulmonary pathophysiological characteristics in adults with bronchiectasis according to a comprehensive evaluation of plethysmography and lung diffusion capacity (DL_{CO}); secondary aims were to explore the presence and role of air trapping reversibility and to identify different functional sub-groups in patients with bronchiectasis.

Some of the results of this study have been previously reported in the form of an abstract [21].

MATERIALS AND METHODS

Study design

This was a multicenter, prospective, observational study of adult outpatients attending the bronchiectasis outpatient clinic at the IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico in Milan and the San Gerardo Hospital in Monza, Italy, from January 2013 to December 2014. Standard operating procedures for the outpatient care of bronchiectasis patients in both centers included the assessment of body-plethysmography before and after the bronchodilation test, together with DL_{CO}. Consecutive patients aged ≥18 years with clinically significant bronchiectasis diagnosed on high-resolution computed

tomography (HRCT) scan in stable state were recruited. Inclusion criteria were: a) a clinical history consistent with bronchiectasis (cough, chronic sputum production and/or recurrent respiratory infections); b) at least one chest HRCT demonstrating bronchiectasis affecting one or more lobes; c) clinical stability, defined as the absence of hospitalization or bronchiectasis exacerbations that required use of systemic corticosteroids or antibiotics up to 3 months before the study enrollment. Exclusion criteria were the following: a) inability to give the inform consent; b) inability to perform repeatable lung function maneuvers; c) a confirmed diagnosis of cystic fibrosis; d) traction bronchiectasis in a context of pulmonary fibrosis; e) pregnancy at the time of recruitment; f) history of drug abuse; g) impaired cognitive function (Mini-Mental State Examination score <26) or psychiatric illness; h) known unstable arrhythmia.

This study was conducted in accordance with the amended Declaration of Helsinki and it was reviewed and approved by the Ethical Committees of both hospitals. Each recruited patient gave a written, informed consent.

Data collection and microbiological analysis

At the time of enrollment, all patients underwent the same comprehensive diagnostic work-up as recommended by the 2010 BTS guidelines [7]. Demographics, comorbidities, disease severity, respiratory symptoms, microbiology, radiological, and laboratory findings in stable state, long-term treatments and outcomes (including exacerbations, hospitalizations, and mortality) during a three-year follow-up were recorded. Etiology of bronchiectasis was evaluated as previously described [22]. Disease severity was evaluated through the BSI [5]. Details on radiological and clinical scoring are reported in the data supplement.

Pulmonary function tests

Lung function tests were performed according to current American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations [18,23,24]. Static, dynamic lung volumes and total specific airway resistances were assessed by means of a constant-volume body plethysmograph (PowerCube-Body Box; Ganshorn Medizin Electronic; Niederlauer, Germany). Airflow obstruction and a restrictive ventilatory defect were defined according to lower limit of normal (LLN) criteria [18]. ATS/ERS criteria were adopted to grade obstruction severity [18]. A mixed obstructive-restrictive pattern was considered as the concomitant presence of a FEV_1/ slow vital capacity (VC)<LLN and a total lung capacity (TLC)<LLN [18]. The presence of air trapping was defined as a residual volume (RV)>120%predicted value [16,25]. Hyperinflation was defined as a TLC>120%predicted value [26]. Bronchodilation responsiveness was assessed according to the latest recommendations [18] and was tested both in terms of reversibility of FEV_1 and RV. Briefly, plethysmographic measurements were repeated 15 minutes after administration of 4 doses of salbutamol metered dose inhaler 100 mcg with a spacer applied. Due to the lack of consensus, different cutoff levels were applied in two different subsets of patients: 1) patients with airflow obstruction, considering a significant airflow reversibility: a) an increase in FEV_1 ≥12% and ≥200 mL from the baseline value [18] and b) an increase of ≥400 mL from the baseline value as suggested by the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) guidelines [27]; 2) patients with air trapping, in which a significant air trapping reversibility was considered as: a) a decrease in RV ≥ 10% from the baseline value or b) an absolute reduction of ≥300 mL from the baseline value as previously suggested [17,28]. Lung diffusion capacity for carbon monoxide (DL_{CO}), KCO and alveolar volume (VA) were measured with the single breath maneuver (GA2002CO, Ganshorn Medizin Electronic; Niederlauer, Germany), assessing the VA by means of the inert gas dilution technique [24]. For every patient, the VA measurements were normalized with plethysmographic TLC as suggested by Hughes et al

[29]. The presence of ventilation inhomogeneity was considered as a VA/TLC <0.8 according to Santus et al [30] and Neder et al [31]. All bronchodilators and/or inhaled corticosteroids (ICS) were withdrawn 24 hours before the lung function testing. According to the standard operating procedures, all patients were asked to perform pulmonary physiotherapy before performing pulmonary function testing. During follow up, patients continued their chronic bronchodilator/anti-inflammatory treatment based on normal clinical practice and on the clinical judgment of the attending physician that was blind to the scope of the study.

Functional stratification and sub-groups

A functional stratification was postulated a priori to define different pathophysiological entities associated with bronchiectasis. To identify the bronchiectasis sub-groups, four main criteria were adopted and sequentially applied: presence of 1) air trapping, 2) airflow obstruction, 3) acute bronchodilator reversibility if criteria 1 and 2 were present, and 4) restriction. Patients, thus, had to fall within the following sub-groups: A) normal plethysmography, B) acutely non-reversible obstruction – i.e. non-reversible air trapping or airflow obstruction, C) reversible air trapping, D) reversible airflow, E) restriction and, in case restriction co-existed with the characteristics of group B, C and D, the resulting sub-group was considered having a F) mixed functional abnormality. More details on functional sub-groups is provided in the online data supplement.

Study outcomes

All-cause mortality was analysed as primary outcome and defined as death for any cause from the first visit to completion of a 3-year follow-up. Secondary outcomes included exacerbations and three year all-cause mortality. For a detailed definition of exacerbation,

please see the online supplement. Severe exacerbations were defined as unscheduled hospitalizations or emergency department visits for severe bronchiectasis exacerbations or complications and were recorded from patient histories and verified using administrative databases, according to the BTS guidelines [7].

Statistical analysis

Data were analyzed with SPSS 21.0 for Windows 10 (SPSS Inc., Chicago, IL, USA). Predicted normal lung function values were from Quanjer [32]. For consistency reasons, in the present study the Global Lung Function Initiative 2012 predictive equations [33] were not adopted, considered the unavailability of predictive equations for VC (here used for the definition of airflow obstruction) and all the plethysmographic parameters. Continuous variables are expressed as median (interquartile range – IQR) or means (standard deviation - SD), according to their parametric distribution assessed with the Shapiro-Wilk test. Comparisons between groups were performed by means of Kruskal Wallis test, ANOVA, Mann-U-Whitney or unpaired t-test as appropriate. The model included effects for period, carryover, treatment, time and the interaction of treatment and time and a random subject effect. Linear regressions were computed with the least mean square method. Tests were two-sided and statistical significance was taken at $p<0.05$.

Sensitivity analysis

To investigate whether the coexistence of COPD or asthma could represent a confounding factor that would impact on the distribution and classification of lung function parameters, the primary analyses were repeated excluding patients with a concomitant diagnosis of asthma or COPD. Furthermore, to assess the possible centre-related difference in the prevalence of lung function abnormalities, patients were also divided in the two cohorts of provenience and thus analysed accordingly.

RESULTS

Study sample

A total of 187 patients were enrolled, 63 patients from Milan and 124 from Monza, (median [IQR] age: 68 [59-73] years; 29.4% males). Anthropometric and clinical variables are presented in Table 1 and Table 2. Forty (42.2%) patients were either actual or former smokers and the most common comorbidities were gastroesophageal reflux disease (20.8%), COPD (18.7%) and asthma (12.3%). More than one third of the patients were chronically infected with at least one microorganism, and 22.5% had chronic *Pseudomonas aeruginosa* infection. A total of 88 (48.5%) patients were exposed to long-term bronchodilator therapy, and 52 out of 88 (59.1%) were treated with an ICS either in fixed dose combination or alone.

Functional characteristics in bronchiectasis

A summary of the pathophysiological characteristics of the study sample is shown in Figure 1. 58.9% of patients had a normal spirometry. 9.7% had both normal spirometry and plethysmography (Figure 1). Taking into account also plethysmography and DL_{CO}, the most frequently observed functional abnormality was air trapping (70.2%), followed by a reduction in DL_{CO} (55.7%), airflow obstruction (41.1%), hyperinflation (15.7%) and a restrictive ventilatory defect (8.0%) (Figure 1). Patients had often overlapping features, with 23.0% of the study sample having concomitantly airflow obstruction, air trapping and a DL_{CO} impairment, while 16.6% had air trapping and a reduced DL_{CO} (Figure 2). Hyperinflation was always associated with air trapping, with a mean(SD) RV/TLC of 130.5%pred (27.9%). 51.9% of patients with air trapping had a FEV_1/VC within normal values. A pure restrictive disease was found in only 5.5% of patients. Only two patients

had isolated airflow obstruction, but isolated air trapping or an impaired DL_{CO} were found in 15.5% and 11.6% of patients, respectively (Figure 2).

Airflow and air trapping reversibility to salbutamol

Overall, 137 (73.3%) patients underwent bronchodilation testing (Figure 3, Panel A). Significant reversibility of air trapping was found in 33 (17.6%) patients (26.4% of patients tested for reversibility) (Figure 3, Panel B). With the 300 ml reversibility cut-off for RV, patients with reversible air trapping were 25 (13.4%). Reversibility of airflow obstruction according to ATS/ERS criteria was found in 4 (3.2%) patients (5.7% of tested) while no patients satisfied the BTS/SIGN criterion [27] for airflow reversibility (Figure S1). Only one patient presented both airflow and air trapping reversibility and was considered as having reversible airflow obstruction (Figure 3, Panel B).

Functional sub-groups in bronchiectasis

The functional sub-groups identified with the four-step methodology are reported in Figure 4. Accordingly, 39 (20.8%) were classified in sub-group A (normal plethysmography), 91 (48.6%) in sub-group B (acutely non-reversible obstruction), 33 (17.6%) in sub-group C (reversible air trapping), 8 (4.3%) in sub-group D (reversible airflow) and 11 (5.9%) in sub-group E (restricted). Only patients characterised by reversible airflow showed signs of ventilation inhomogeneity at DL_{CO} (Figure 4). Patients' distribution following alternative criteria for bronchodilator responsiveness are detailed in the data supplement and in Figure S1.

Sensitivity analysis

The primary sensitivity analysis excluded a total of 54 patients: 34 with COPD, 17 with asthma and 3 with both asthma and COPD. The proportion of patients tested for

reversibility did not change compared with the whole sample (73.5% *vs.* 74.2%). The distribution of pathophysiological abnormalities and the proportion of the functional sub-groups did not change significantly compared to the whole study sample (data supplement and Figure S2). Particularly, the number of patients with positive reversibility to air trapping was comparable (15.0% *vs.* 17.6%, P = 0.421), as was the proportion of hyperinflated patients (15.6% *vs.* 15.7%, P ≈ 1.000) (Figure 2).

The secondary sensitivity analysis was carried out considering separately patients coming from the Milan and the Monza cohort. Compared with the whole study sample, no significant changes were found in the prevalence of lung function abnormalities and air trapping reversibility (Figure S3). Furthermore, according to the four-step functional algorithm, the proportion of each functional sub-group did not change when the largest cohort (Monza) was assessed (Figure S4 and online supplement). Taking in account the small changes provided by the sensitivity analyses, the univariate analysis was carried out in the whole study sample (N = 187).

Sub-group analysis

The comparison of baseline characteristics of functional sub-groups is presented in Table 3 and 4. As sub-groups D, E and F were the less numerically represented, they were not included in the main analysis. As expected, compared with groups B and C, group A had the best lung function. Compared with group B, group C had worse airflow obstruction (mean %predicted [SD] FEV_1: 68.9 [26.2] *vs*. 83.0 [24.4], P=0.02) and higher RV (166.2 [39.9] *vs.* 151.9 [26.6], P=0.028) and worse (median%predicted [IQR]) RV/TLC (130.4% [117.8-143.5] *vs*. 148.0 [121.3-156.9], P=0.029). Conversely, DL_{CO} tended to be higher in group C, with progressively lower values from group B to A. In average, DL_{CO} was reduced due to a prevalent reduction in KCO (Table 3). No difference was observed in terms of

HRCT scores, colonizing bacteria and BSI (Table 4). A trend towards a higher frequency of exacerbations per year of follow up from group A to group C was observed (ANOVA P=0.161), but no difference between groups in three-year mortality (Table 4).

A univariate analysis including also sub-groups D, E and F is reported in Table S1.

DISCUSSION

The major findings of the presents study can be summarised as follows: 1) Among adults with bronchiectasis, the majority of functional abnormalities is missed when the assessment is limited to simple spirometry; 2) Air trapping and DL_{CO} impairment are the most common lung function abnormalities (70.2% and 55.7%, respectively); 3) Reversibility of residual volume is present in more than one fourth of bronchiectasis patients with air trapping, while FEV_1 reversibility is less frequently observed; 4) Dichotomous lung function criteria can be adopted to identify and divide bronchiectasis in specific pathophysiological patterns.

To our knowledge, this is the first study showing a comprehensive functional assessment in adults with bronchiectasis, including plethysmography, DL_{CO} and lung volume reversibility. In 49.2% of patients, plethysmographic and DL_{CO} assessment detected lung function abnormalities that would have been missed with the sole spirometry, while only 9.7% of patients had no functional alterations at all. These data underline the need for a standardized comprehensive functional approach to identify pathophysiological features such as air trapping or impaired diffusing capacity that are common in bronchiectasis [12]. A series of radiological studies demonstrated that the major determinants of airflow obstruction and its decline over time were represented by signs of bronchiolitis and small airway disease, such as bronchial wall thickness and decreased attenuation on the expiratory CT [9,34]. Considering the significant role of small airways in bronchiectasis

[34,35], a simple approach limited to spirometry is not sufficient to detect hyperinflation and increased airway resistances, the presence of which may imply regional flow limitation, lung inhomogeneity and non-uniform distribution of closing pressures [16,36]. More recently, the lung clearance index (LCI) has been reported to be a non-invasive, reliable and reproducible method to investigate lung ventilation inhomogeneity in patients with stable non-cystic fibrosis bronchiectasis [37]; however LCI, unlike traditional lung function parameters, was found to be less sensitive to exacerbations or external interventions [38].

In the present study, DL_{CO} was uniformly impaired across the studied sample, and despite being an important factor for patients' outcomes [12], its relation with other functional variables in the natural history of bronchiectasis still represents an unsolved question.

Airway hyper-reactivity [39] and airflow reversibility have often been considered common in bronchiectasis, the latter ranging from 14% to 25% according to different studies [14,15,40]. Our findings are in line with those of Aksamit and colleagues [40] who recently found a significant acute bronchodilator response in terms of FEV_1 in 5% of cases out of a cohort of 963 bronchiectasis patients. Although the majority of patients with obstructive diseases such as COPD are defined as non-responsive with spirometry criteria, they can show important reductions in static volumes following administration of bronchodilators; such improvements, as opposed to changes in FEV_1, are significantly related with changes in dyspnoea and exercise tolerance [16,20,41]. In the present study we demonstrated that volume responsiveness occurs also in bronchiectasis, involving almost a third of the tested patients. Moreover, patients with reversible air trapping had more severe obstruction and higher baseline residual volume compared to non-reversible patients. This is in line with previous reports that studied FEV_1 reversibility both in bronchiectasis and COPD [15,16]. A low FEV_1 is associated with bronchiectasis exacerbations [42], however it remains unclear

if the worsening of respiratory symptoms during these events is related to an acute further reduction in FEV_1 or could be due to an increase in air trapping. To date, only one study investigated the association of bronchodilator response and bronchiectasis exacerbations, with inconclusive results [14]. Although limited in number, previous data showed that the association with asthma or COPD in patients with bronchiectasis has a great impact on patient related outcomes and translates in a difficult-to-control disease and more severe exacerbations [11,43,44]. However, the sensitivity analysis we performed confirmed that not only reversibility of air trapping is independent of the presence of other chronic obstructive diseases, but also that hyperinflation and air trapping are proper characteristics of bronchiectasis, indicating a pathological process involving both functional small airways disease and a loss of elastic recoil.

Small airways hyper-reactivity is related to bronchial inflammation and neutrophil-driven inflammation is associated with disease severity in bronchiectasis [45,46]. The recent identification of peripheral neutrophil elastase activity as a predictor of exacerbations and lung function decline in bronchiectasis [47] and the correlation we found with reversibility of air trapping and worse lung function further support the hypothesis that in bronchiectasis patients bronchial hyper-reactivity may be a hallmark of disease severity and may help to identify more fragile patients.

Notably, none of the functional sub-groups we identified differed in the chronic bronchodilator treatment. When, how and what kind of patients with bronchiectasis may benefit from bronchodilators or ICS therapy represents, so far, an unsolved issue. In the present study, the lack of difference in exacerbation rates between sub-groups may have been masked by not functionally-driven inhaled therapeutic approaches. Recent reviews and international guidelines report only very weak suggestions for long-term use of LABA or ICS in bronchiectasis [7,48,49]. Nonetheless in our study 30.8% of patients with normal

plethysmography was exposed to inhaled bronchodilators or ICS and 20.5% to ICS only. The synergy demonstrated between long acting bronchodilators and ICS and their role as modulators of the production of superoxide anions and leukotriene-B4 in neutrophilic inflammation [50,51] should represent an additional incentive for setting specifically designed randomized controlled trials in patients with bronchiectasis.

Some consideration should be made concerning the pragmatic approach we propose for the functional stratification of bronchiectasis patients. As it was previously shown, the degree of FEV_1 responsiveness to bronchodilators can vary over time [52] and during exposure to chronic inhaled treatment [15,52], and this might be true also for reversibility of air trapping. Moreover, we suggest that methacholine challenge should be performed in all patients with normal plethysmography at baseline but that symptoms compatible with bronchial hyper-reactivity.

The present pilot study is limited by the small sample size; this might be responsible for a limited representation of some functional patterns as patients with FEV_1 reversibility. The threshold of 10% chosen for the air trapping reversibility relies on data published in literature [17,28] as no consensus has been defined so far. The duration of the follow up period and the sample size didn't allow for further speculation on the role of air trapping responsiveness on exacerbations and mortality. Furthermore, the role of air trapping reversibility in patients without air trapping at baseline needs further investigation.

In conclusion, spirometry alone does not encompass the variety of pathophysiological characteristics in bronchiectasis. Plethysmography, DL_{CO} and reversibility testing are necessary for the definition and recognition of overlapping functional features in patients with bronchiectasis; waiting for larger randomized clinical trials on this topic, this functional assessment should lead to an individualized bronchodilator treatment and allow for an appropriate follow up.

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TABLES

Table 1. Demographics, comorbidities and chronic treatment of the study population.

Variables	**Study group**
n.	187
Demographics	
Median (IQR) age, years	68 (59-73)
Either smokers or former smokers, n (%)	79 (42.2)
Comorbidity	
GERD, n (%)	39 (20.8)
COPD, n (%)	34* (16.6)
Asthma, n (%)	23* (12.3)
Connective tissue disease, n (%)	21 (11.2)
Myocardial infarction, n (%)	7 (3.7)
Peripheral vascular disease, n (%)	5 (2.7)
Moderate-severe liver disease, n (%)	5 (2.7)
Moderate-severe chronic kidney disease, n (%)	5 (2.7)
Congestive heart failure, n (%)	4 (2.1)
Mild liver disease, n (%)	2 (1.1)
Cerebrovascular accident, n (%)	1 (0.5)
Leukemia, n (%)	2 (1.1)
Treatment	
Macrolide, n (%)	14 (7.5)
Inhaled antibiotic treatment, n (%)	7 (3.7)
Chronic bronchodilator therapy	
LABA, n (%)	6 (3.2)
LAMA, n (%)	24 (12.8)
LABA/LAMA FDC or LAMA + LABA, n (%)	6 (3.2)
ICS, n (%)	6 (3.2)
LABA/ICS FDC	13 (10.5)
LABA/LAMA/ICS	33 (17.6)
Theophylline, n (%)	3 (1.6)

n: number; IQR: interquartile range 25-75; GERD: gastro-oesophageal reflux disease; COPD: chronic Obstructive Pulmonary Disease; LABA: long acting β-2 agonists; LAMA: long acting muscarinic agonists; ICS: inhaled corticosteroids; FDC: fixed dose combination; * = the prevalence reported refers to the single cases. Among patients with COPD and asthma, 3 patients had a concomitant diagnosis of COPD and asthma (see results in the text).

Table 2. Clinical, radiological and microbiological status of the study population.

Variables	**Study group**
n.	187
Disease severity	
Median (IQR) BSI score,	6 (4-9)
BSI score Risk Class, n (%)	
Mild	38 (30.6)
Moderate	49 (39.5)
Severe	37 (29.8)
Radiological status	
Median (IQR) Reiff score	6 (4-6)
Mean (SD) Bhalla score	18.6 (10.5)
Clinical status	
Chronic cough, n (%)	63 (33.7)
Daily Sputum, n (%)	114 (61.0)
Sputum colour, n (%)	
Mucous	30 (24.2)
Mucous-Purulent	34 (27.4)
Purulent	11 (5.9)
Haemoptysis, n (%)	31 (16.6)
MRC, median (IQR)	1 (0-1)
MRC 4-5, n (%)	17 (9.1)
Long-term oxygen therapy, n (%)	14 (7.5)
Median (IQR) exacerbations in the previous year	2 (1-3)
At least one hospitalization in the previous year, n (%)	41 (21.9)
Microbiology	
Chronic infection with at least one pathogen, n (%)	72 (38.5)
P. aeruginosa, n (%)	42 (22.5)
H. influenzae, n (%)	17 (9.1)
S. aureus, n (%)	15 (8.0)
MRSA, n (%)	3 (1.6)
MSSA, n (%)	12 (6.4)
K. pneumoniae, n (%)	7 (3.7)
S. pneumoniae, n (%)	4 (2.1)
Enterobacteriaceae, n (%)	2 (1.1)
Other bacteria, n (%)	2 (1.6)
Patient related outcomes	
Mean (SD) SGRQ	31.6 (20.2)
Median (IQR) one-year follow-up exacerbations	1 (0-2)
Median (IQR) three-year follow-up exacerbations	2 (0-4)
One-year mortality, n (%)	3 (1.6)
Three-year mortality, n (%)	7 (3.7)

n: number; IQR: interquartile range 25-75; BSI: Bronchiectasis Severity Index; MRC: medical research council; FEV_1: forced expiratory volume in the first second; MSSA:

methicillin-sensitive *Staphilococcus aureus*; MRSA: methicillin-resistant *Staphilococcus aureus*.

Table 3. Lung function characteristics of the most represented functional groups identified by the lung function flow-chart.

	Normal plethysmography (A) N = 39, 20.8%	**Acutely non-reversible obstruction (B)** N = 91, 48.6%	**Reversible air trapping (C)** N = 33, 17.6%	**P**	**P (B) vs (C)**
Anthropometric					
Males (%)	12 (30.8)	24 (26.4)	7 (21.2)	0.956[b]	0.784[b]
Age, years (IQR)	68.0 (58.5-73)	67.0 (60-73)	67.0 (57.5-74)	0.863[a]	0.801[d]
BMI, Kg/m^2 (IQR)	25.9 (20.4-28.6)	22.8 (19.8-26.3)	23.4 (19.7-27.4)	0.163[a]	0.592[d]
Lung function					
FEV1, %pred (SD)	94.7 (15.7)	83.0 (24.4)	68.9 (26.2)	**0.001[c]**	**0.020[e]**
FEV1<50%pred, n (%)	0 (0.0)	9 (9.9)	9 (27.3)	**<0.001[b]**	<0.001[b]
FEV1<35%ped, n (%)	0 (0.0)	5 (5.5)	3 (9.1)	0.149[b]	0.954[b]
VC, %pred (SD)	88.8 (15.6)	86.5 (20.0)	78.5 (21.6)	0.240[c]	0.128[e]
FEV1/VC, %pred (IQR)	101.0 (96.2-107.0)	91.8 (79.0-97.6)	85.1 (76.2-92.2)	**<0.001[a]**	**0.047[d]**
Obstructed, n (%)	0 (0)	51 (56.0)	21 (63.6)	**<0.001**	0.129[b]
sRaw, %pred (IQR)	107.8 (78.6-121.3)	144.0 (120.9-187.4)	193.7 (134.4-249.0)	**<0.001[a]**	0.102[d]
FRC, %pred (SD)	104.2 (11.1)	126.4 (12.3)	135.8 (9.6)	**<0,001[a]**	**0.041[e]**
TLC, %pred (SD)	97.6 (8.6)	112.1 (11.5)	111.8 (8.7)	**<0.001[c]**	0.665[e]
TLC>120%pred, n (%)	0 (0.0)	26 (23.7)	4 (12.1)	**0.018**[b]	0.289[b]
RV, %pred (SD)	110.0 (8.7)	151.9 (26.6)	166.2 (39.9)	**<0.001[c]**	**0.033[e]**
RV>120%pred, n (%)	0 (0.0)	86 (94.5)	25 (75.7)	**<0.001**[b]	**0.014[b]**
RV/TLC, %pred (IQR)	109 (103.1-116.1)	130.4 (117.8-143.5)	148.0 (121.3-156.9)	**<0.001[a]**	**0.029[d]**
DL_{CO}, %pred (SD)	70.7 (18.1)	72.3 (23.8)	77.2 (20.2)	0.906[c]	0.759[e]
DL_{CO}<80%pred, n (%)	20 (51.3)	60 (65.9)	19 (57.6)	0.496[b]	0.647[b]
KCO, %pred (IQR)	56.2 (47.7-67.8)	54.6 (44.7-65.4)	65.6 (43.7-70.1)	0.531[a]	0.274[d]
VA%, pred (SD)	94.3 (12.4)	100.7 (18.2)	94.8 (20.1)	0.467[c]	0.392[e]
VA/TLC, %pred (IQR)	0.94 (0.89-0.99)	0.89 (0.81-0.99)	0.92 (0.67-0.94)	0.088[a]	0.558[d]

Variables with standard deviation (SD) are presented as mean values; parameters with inter-quartile range (IQR) are presented as median values; %pred: percent predicted value; TLC: total lung capacity; FRC: functional residual capacity; DL_{CO}: diffusing lung capacity for carbon monoxide; VA/TLC: alveolar volume to total lung capacity ratio; KCO: transfer factor; FVC: forced expiratory volume; VC: slow vital capacity; FEV1/VC: Tiffeneau index; RV: residual volume; RV/TLC: residual volume to total lung capacity ratio,

sRaw: total specific airway resistances. For other abbreviations please see text. [a] Kruskal Wallis test; [b] Chi Squared test; [c] ANOVA; [d] Mann-U-Whitney test; [e] unpaired t-test.

Table 4. Clincal characteristics of the most represented functional groups identified by the lung function flow-chart.

	Normal plethysmography (A) N = 39, 20.8%	**Acutely non-reversible obstruction (B)** N = 91, 48.6%	**Reversible air trapping (C)** N = 33, 17.6%	**P**	**P (B) vs (C)**
Radiology and clinic					
Bhalla score (IQR)	13.7 (7.5-18.0)	17.2 (10.0-25.0)	17.5 (13.0-23.0)	0.171[a]	0.806[d]
Reiff score (IQR)	4.7 (4-5.5)	5.4 (4.0-6.0)	5.7 (5.0-6.0)	0.129[a]	0.245[d]
BSI (IQR)	5.4 (4.0-7.0)	6.1 (4.0-10.0)	6.5 (5.0-9.0)	0.474[a]	0.527[d]
Colonized (any), n (%)	17 (43.6)	38 (41.7)	13 (39.4)	0.832[b]	0.594[b]
P. aeruginosa, n (%)	8 (20.5)	19 (20.9)	7 (21.2)	0.892[b]	0.638[b]
COPD, n (%)	5 (12.8)	17 (18.7)	5 (15.1)	0.800[b]	0.656[b]
Asthma, n (%)	2 (5.1)	10 (11.0)	7 (21.2)	0.050[b]	0.072[b]
GERD, n (%)	10 (25.6)	21 (19.1)	12 (36.3)	0.145[b]	**0.048[b]**
Cough, n (%)	16 (41.0)	44 (40.0)	15 (45.5)	0.826[b]	0.697[b]
Sputum, n (%)	20 (51.3)	55 (60.4)	21 (63.6)	0.253[b]	0.408[b]
Smokers, n (%)	14 (35.9)	42 (46.1)	14 (42.4)	0.896[b]	0.539[b]
Outcomes					
Exacerb/year, n (IQR)	0.3 (0.0-0.8)	0.5 (0.0-0.8)	0.8 (0.3-1.15)	0.148[a]	0.161[d]
Three-year mortality, n (%)	0 (0)	4 (6.5)	1 (5.0)	0.552[b]	0.908[b]
Bronchodilator therapy					
LABA, n (%)	1 (2.6)	3 (3.3)	2 (6.1)	0.597[b]	0.693[b]
LAMA, n (%)	2 (5.1)	15 (16.5)	4 (12.1)	0.261[b]	0.772[b]
LABA/LAMA, n (%)	1 (2.6)	3 (3.3)	2 (6.1)	0.597[b]	0.424[b]
ICS, n (%)	2 (5.1)	3 (3.3)	0 (0.0)	0.403[b]	0.324[b]
LABA/ICS, n (%)	4 (10.2)	14 (15.4)	4 (12.1)	0.814[b]	0.294[b]
LABA/ICS + LAMA, n (%)	2 (5.1)	13 (14.3)	8 (24.2)	**0.034[b]**	0.153[b]
ICS (any), n (%)	8 (20.5)	30 (33.0)	12 (36.4)	0.297[b]	0.127[b]
Inh. therapy (any), n (%)	12 (30.8)	51 (56.0)	20 (60.6)	**0.009[b]**	0.135[b]

Variables are presented as median values with inter-quartile range (IQR), if not otherwise reported. Colonized: patients colonized with any microorganism; *P. aeruginosa*: patients with chronic *P. aeruginosa* infection; inh. therapy: bronchodilator therapy; exacerb/year: median number of exacerbations per year during the follow up period; Mortality: number of patients deceased during the follow up period; LABA: long acting β2 agonists; LAMA: long

acting muscarinic antagonists: ICS: inhaled corticosteroids. For other abbreviations please see text. [b] Chi Squared test; [c] ANOVA; [d] Mann-U-Whitney test; [e] unpaired t-test.

FIGURE CAPTIONS

Figure 1. Distribution of the main pathophysiological characteristics according to spirometry, plethysmography and DL_{CO} measurements within the study population (N = 187). Striped areas represent the percentage of patients with normal spirometry within each group. The column in light blue indicates patients with spirometry, plethysmography and DL_{CO} within normal values.

Figure 2. Descriptive analysis of 187 bronchiectasis patients based on data from spirometry, plethysmography and DL_{CO}. For the definition of airflow obstruction, air trapping and restriction please see text. The percentage relative to the whole study population is reported in each area. FEV_1: forced expiratory volume in the first second; VC: slow vital capacity; RV: residual volume.

Figure 3. Distribution of patients tested with acute bronchodilation challenge whithin the study population (N = 187, Panel A) and prevalence of airflow and air trapping reversibility (striped areas) among tested patients (N = 137, Panel B). RV: residual volume; FEV_1: forced expiratory volume in one second.

Figure 4. Flow chart indicating the pathways suggested for the functional evaluation of patients with non-CF bronchiectasis. Four main steps are included. Air trapping is evaluated first. The second step is represented by the evaluation of airflow obstruction. The third step is reflects by the assessment of acute bronchodilation response, both in terms of volume (patients with air trapping) and in terms of FEV_1 (in patients that show airflow obstruction, ATS/ERS criteria). In patients with air trapping that do not show any reversibility at the residual volume, airflow reversibility should always be assessed. If both are absent, the patients belongs to the “acutely non-reversible obstruction” group. Finally,

the last step is represented by the evaluation of TLC. If a restrictive ventilatory defect is present, the patient has “mixed” functional characteristics. Different colors identify the component mainly responsible for the DL_{CO} impairment. Dashed ovals are groups not found within our study sample but that can theoretically exist. Numbers and percentages in each frame represent patients and their proportion in respect to the whole study sample. Pts: patients; FEV_1: forced expiratory volume in one second; RV: residual volume; TLC: total lung capacity; %pred: percent predicted value; DL_{CO}: diffusing lung capacity; LLN: lower limit of normal.

Figure 1_Revised
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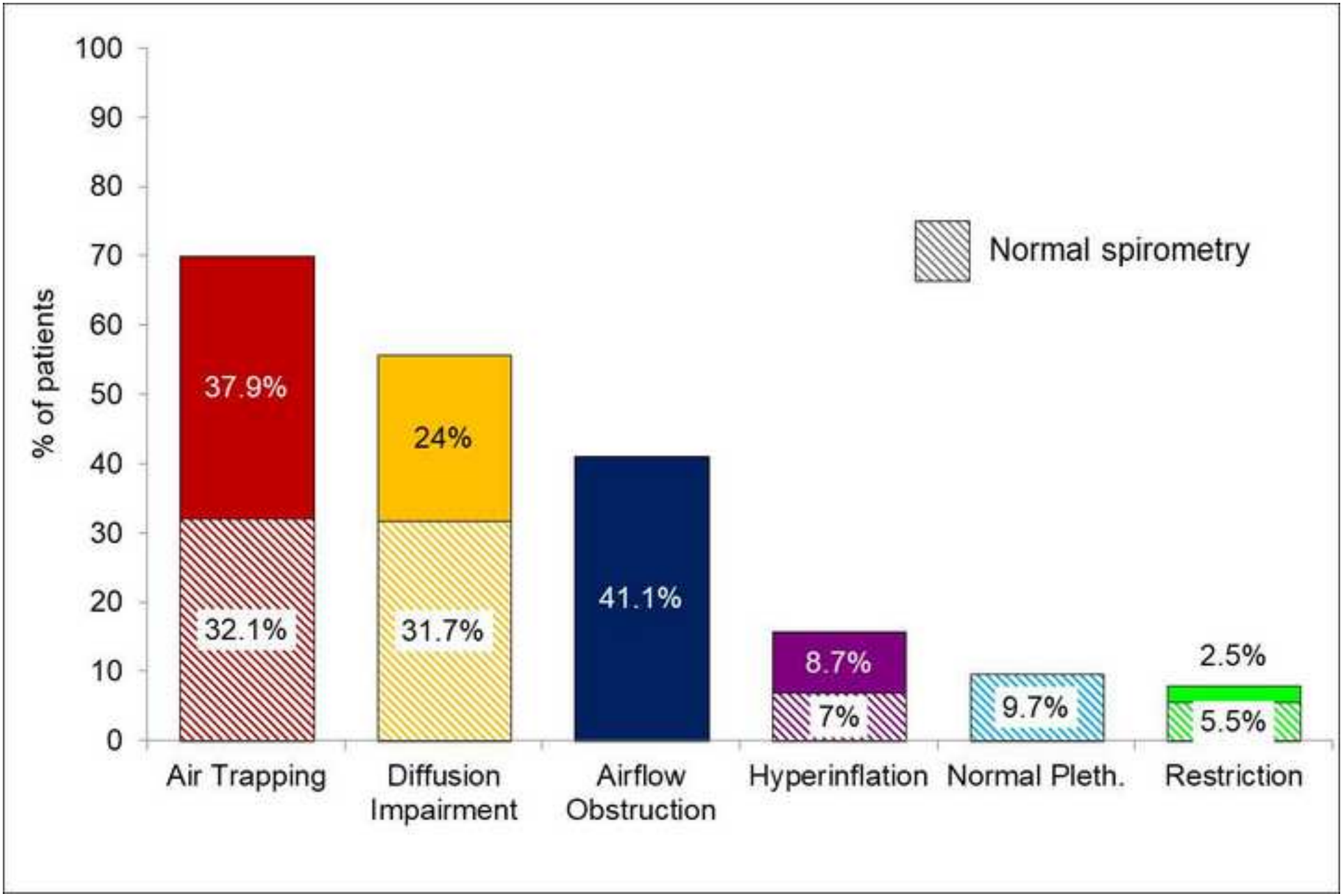

Figure 2_Revised

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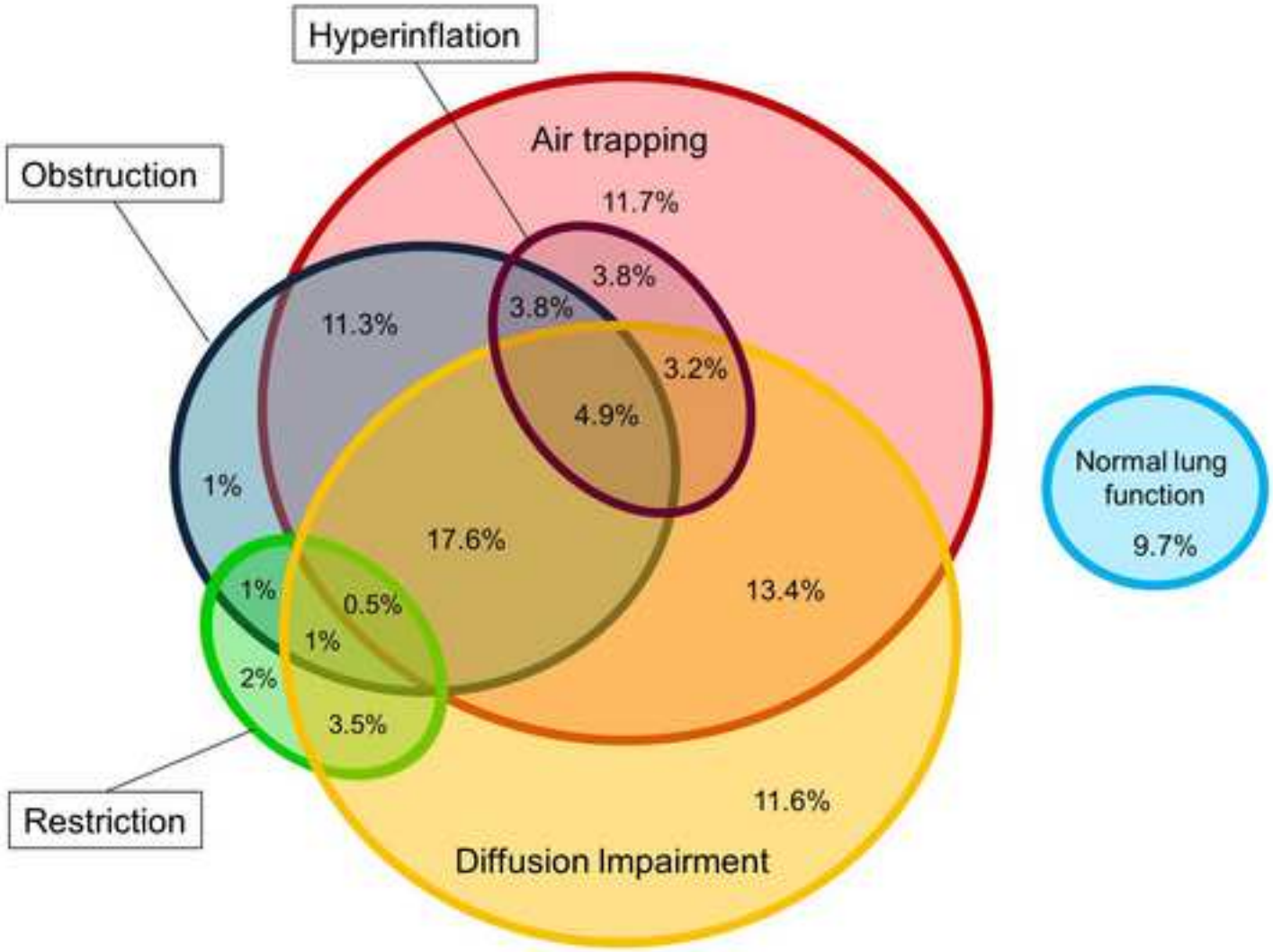

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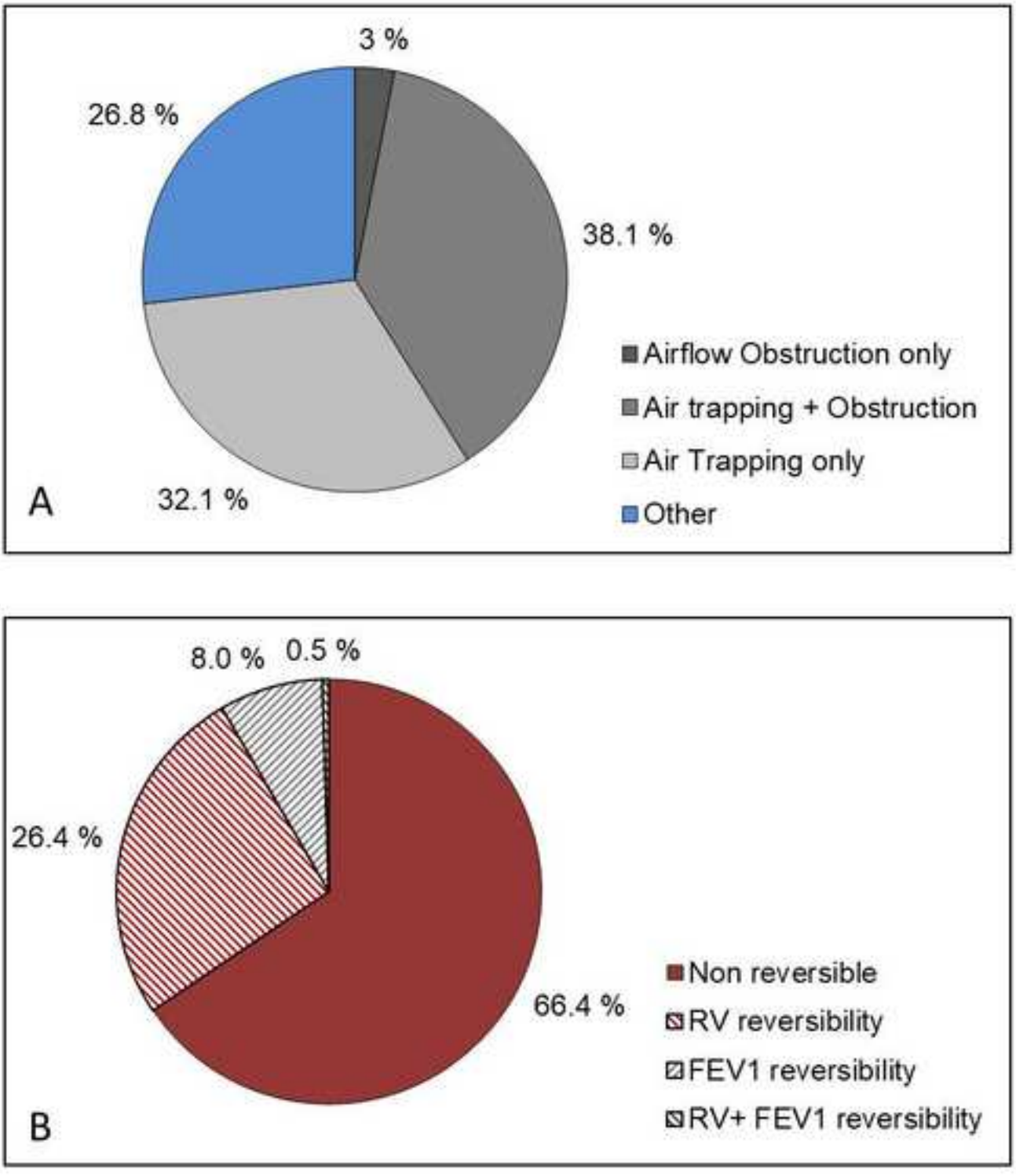

Figure 4_Revised

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