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Imaging of Bronchial Pathology in Antibody Deficiency: Data from the European Chest CT Group

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Abstract

Studies of chest computed tomography (CT) in patients with primary antibody deficiency syndromes (ADS) suggest a broad range of bronchial pathology. However, there are as yet no multicentre studies to assess the variety of bronchial pathology in this patient group. One of the underlying reasons is the lack of a consensus methodology, a prerequisite to jointly document chest CT findings.

We aimed to establish an international platform for the evaluation of bronchial pathology as assessed by chest CT and to describe the range of bronchial pathologies in patients with antibody deficiency.

15 immunodeficiency centres from 9 countries evaluated chest CT scans of patients with ADS using a predefined list of potential findings including an extent score for bronchiectasis.

Data of 282 patients with ADS were collected. Patients with common variable immunodeficiency disorders (CVID) comprised the largest subgroup (232 patients, 82.3%). 80% of CVID patients had radiological evidence of bronchial pathology including bronchiectasis in 61%, bronchial wall thickening in 44% and mucus plugging in 29%. Bronchiectasis was detected in 44% of CVID patients aged less than 20 years. Cough was a better predictor for bronchiectasis than spirometry values. Delay of diagnosis as well as duration of disease correlated positively with presence of bronchiectasis.

The use of consensus diagnostic criteria and a pre-defined list of bronchial pathologies allows for comparison of chest CT data in multicentre studies. Our data suggest a high prevalence of bronchial pathology in CVID due to late diagnosis or duration of disease.

Key Words

Chest CT; CVID, Primary Antibody Deficiency, bronchiectasis; bronchial pathology

Introduction

Primary antibody deficiency syndromes (ADS) are a heterogeneous group of immune disorders characterised by subnormal immunoglobulin levels and/or the inability to mount specific antibody responses (1). Common variable immunodeficiency disorders (CVID) are the most frequent humoral immunodeficiency requiring immunoglobulin replacement therapy with an incidence of approximately 1:25,000 – 1:50,000 live births (2).

Agammaglobulinaemia, XLA (x-linked agammaglobulinaemia) together with other variants, forms the second largest group affecting 3 to 6 per million live births (3). Recurrent bacterial infections of the respiratory tract are a major part of morbidity in both conditions although the frequency and severity are reduced by immunoglobulin replacement therapy (2,4-10). Airway infections are predominantly caused by encapsulated bacteria and can lead to persistent structural lung disease such as bronchiectasis (11,12). Presence of bronchiectasis is strongly associated with mortality in CVID and XLA (13,14).

Early detection of the presence or progression of structural lung disease is essential to develop preventive or therapeutic strategies in this setting. Imaging techniques, in particular computed tomography (CT), are considered the gold standard for diagnosing structural lung disease (15,16).

Chest X-ray (CXR) and pulmonary function tests (PFT) including spirometry, gas transfer and body plethysmography are readily available and can be repeated frequently, due to lower or absent dose of ionising radiation compared to sequential CT imaging.

However, both methods lack sensitivity to detect structural lung disease in patients with antibody deficiency (11,17) or other conditions, such as cystic fibrosis (CF) (18).

A sizeable body of literature reports bronchial morbidity in patients with antibody deficiency based on chest CT findings (17,19). However, these studies were almost exclusively single centre studies and are not easily comparable, since they used differing reporting systems and nomenclatures (11,20,21). The performance of multicentre studies therefore demands consensus data definition, reporting and scanning methodology to afford internal validity.

The difficulties of providing a standardised evaluation of chest CT scans in antibody deficiencies may have contributed to the apparent paucity of clinical studies describing preventive or therapeutic interventions in this patient group (22).

The present study is the result of an international multicentre and multidisciplinary collaboration aiming to create a common platform of chest CT findings from patients with primary antibody deficiencies. Based on a large number of chest CT studies, the distribution, variety and extent of pulmonary pathology was assessed. Herein, we report the findings on bronchial pathology in conjunction with clinical data and pulmonary function testing. Based on these findings, we propose a method to document bronchial pathologies for multicentre use such as patient registries.

Methods

Development of a consensus list of CT findings

In the Chest CT in Antibody Deficiency Group, immunologists, radiologists and pulmonologists agreed a list of chest CT findings with the aim of collecting pathologies of potential relevance for patients with PAD. The list was based upon clinical experience and review of the literature. In order to use radiological terminology that is both widely accepted and defined by an image repository, the syllabus of the Fleischner Society (15) was used. A short form of definitions and exemplary images was provided to the participating centres (http://www.chest-ct-group.eu/imagerepository).

The Chest CT Group criteria scored 16 items (table 1, online repository), including 4 on bronchial pathologies. Bronchial wall thickening was defined as a diameter of a bronchial wall being larger than one third of the outer diameter of the accompanying bronchial artery, of more than a fifth of the outer diameter of the bronchus. Bronchiectasis was defined as an airway lumen larger in diameter than the outer diameter of the accompanying bronchial artery. Two items were scored only as present or absent (bronchial wall thickening, atelectasis). Mucus plugging was additionally scored for the distribution pattern (central or peripheral). Bronchiectasis was scored for distribution and extent, the latter comprising a simplified bronchiectasis score (0, 1, 2 or 3, $\geq$ 4 lobes affected or cystic changes in $\geq$ 2 lobes).

Chest CT scans and data collection

Chest CT scans were performed according to local guidelines of the participating centres and evaluated locally. All chest CTs were acquired at full inspiratory capacity by using a thin slice protocol of acquisition.

The diagnosis of the immunodeficiency was based on the diagnostic criteria of the European Society for Immunodeficiencies (ESID)(23). Only CT scans that were performed in patients with a stable clinical condition were included. The radiologists were requested to employ

chest CT scoring system provided by the Chest CT in Antibody Deficiency Group in addition to their local practice.

CT findings along with clinical data were documented with the ESID online registry (24). Some centres preferred to send the data with an anonymised chest CT documentation sheet (table I, online repository) to the study centre. All data were stored in a database in an anonymised fashion.

Clinical data collection

Similarly, clinical data were collected with a second documentation sheet with items identical to the ESID registry (table II, Clinical Data Sheet in the online repository). The clinical data sheet comprised data on lung function (spirometry, body plethysmography and carbon monoxide diffusion capacity), pattern of cough and use of antibiotics).

Since lung function data were only available as "percentage of predicted for height and weigth" in several centres, data were collected accordingly (not as absolute measurements). Cough lasting longer than 8 weeks was defined as chronic cough (25). Duration of disease was calculated as time interval from date of onset of disease specific symptoms to date of CT scan. The interval from date of diagnosis to CT scan was considered "duration of therapy" based on the assumption that a diagnosis of CVID or XLA is generally followed by a rapid initiation of immunoglobulin replacement therapy. "Delay of diagnosis" was the time from onset of symptoms to diagnosis.

Quality assurance, data processing and statistical analysis

Written informed consent was obtained for documentation within the ESID Registry (2). Data were transferred into a relational database (Microsoft Access V2010 Microsoft, Redmont, WA (USA)) and evaluated anonymously. The inter-rater reliability of the CT findings as documented in the chest CT pathology form was assessed by calculation of the intra-class correlation coefficient (ICC) between independent radiologists. Descriptive data were calculated as mean and standard deviation, or, if appropriate, as median and interquartile

range. Categorical data were reported as frequencies and percentages. Groups were compared using the t-test unless the data were not normally distributed. In this case, the following nonparametric methods were used. Categorical variables were analysed with Chi-Square tests. Correlations were calculated as Pearson's coefficient and with linear regression analysis. Explanation of variance was calculated using linear regression analysis. Dependence of variables on parametric data was assessed by logistic regression analysis. The influence of several variables was assessed by conditional forward and backward logistic and linear regression analysis. A p-value < 0.05 was considered statistically significant. Differences in prevalence of parameters between sexes were calculated by Mann Whitney U Test. All statistical analyses were performed with the Statistical Software Package for the Social Sciences (SPSS; V 24, IBM, Armonk, New York (USA)).

Results

Study Population

15 centres in 9 countries contributed chest CT findings of 282 patients (table III in online repository). Clinical data were available in 192 patients. Diagnoses were CVID (232 patients (82%)), XLA (28 patients (10%)), and other PAD (22 patients (8%). Data of the latter group are not included in this manuscript due to their lack of homogeneity.

Baseline characteristics of the CVID and XLA patient cohorts and data on clinical history are given in table 1. For age distribution see figure I in the online repository.

Quality assurance and data quality

The CT pathology documentation form was assessed for inter-rater reliability based on assessment by 4 radiologists of 21 randomly chosen CT studies. Rating was in good or very good agreement, as shown by intra-class correlation coefficients (ICC) (Calder et al. Paediatric Radiology 2014 44:1496–1506), ICC was 0.79 ($p < 0.001$) for atelectasis, 0.957 ($p < 0.001$) for mucus plugging, and 0.917 ($p < 0.001$) for bronchiectasis severity. Rating of bronchial wall thickening, however, was not reliable (ICC 0.332, p = n.s.).

In the main study, rating on the 4 items on bronchial pathologies was given in 94.9% (SD 2.1%) of the CT scans. The highest rate of missing data was present in the item termed "mucus plugging", with missing data in 7.8 % of the cases. Anthropometric data were available from 64%, spirometry from 62%, cough frequency from 64%, antibiotic treatment regimen from 72%, and body plethysmography from 28% of the patients.

Bronchial pathology in CVID

80% of the CVID patients had radiological evidence of some form of bronchial pathology. Bronchiectasis had the highest prevalence of all bronchial pathologies and was reported in 61% of the CVID cohort, followed by bronchial wall thickening (44%), atelectasis (32 %),

and mucus plugging (29%). Mucus plugging was more frequent in the periphery (20%) than in a distributed pattern (central and peripheral, 9%, figure 1). The prevalence of bronchial pathologies did not differ between sexes. Bronchiectasis was not associated with other bronchial pathology. Of the patients with bronchiectasis, 64% had no evidence of mucus plugging, 60% had no atelectasis, and 43% had no evidence of bronchial wall thickening.

Impact of age and duration of disease on bronchial pathology in CVID

The prevalence of bronchiectasis was lowest in the patient group undergoing CT at < 20 years at 44% and increased steadily with age to 79% in the age group ≥ 60 years (figure 2A). Extent of bronchiectasis showed an age related increase (R^2 =0.029; F=6.6; p=0.01, figure 2 B-D). Patients ≥ 60 years had the highest proportion of extensive disease (3 or more lobes affected and/or cystic changes) with 36% of this age group affected (figure 2D).

In contrast to bronchiectasis, prevalence of bronchial wall thickening, atelectasis and mucus plugging did not rise with age nor with duration of disease or of therapy. Bronchiectasis was associated with bronchial wall thickening, atelectasis and mucus plugging only in younger age groups (table IV in online repository).

In multiple regression analysis, duration of the disease was a predictor for the presence and extent of bronchiectasis, but age, sex and duration of therapy were not. Each year of disease was associated with an additional risk of bronchiectasis by 4.4% (p = 0.07) and an increase of the severity score by 0.025 (p<0.001) (Figure IV, online repository).

Patients with a longer delay of diagnosis had a higher extent of bronchiectasis, although this association was comparatively weak (F = 6.14, p = 0.015 in analysis of variance, figure 5).

Patients with advanced bronchiectasis tended to have higher trough IgG levels ($r_{pearson}$= 0.19, p = 0.048).

Bronchial Pathology in XLA

The prevalences of bronchiectasis, atelectasis and mucus plugging, but not of bronchial wall thickening, were higher in the XLA cohort as compared to the CVID cohort (Fig. 1a+b). The

extent of bronchiectasis was also more strongly related to age ($r_{Pearson}$ = 0.6, p < 0.001, Figure II in online repository) and to duration of disease ($r_{Pearson}$ = 0.7, p < 0.001) than in CVID patients. Again, duration of therapy correlated less strongly than age or duration of disease with the extent of bronchiectasis in XLA patients, but more so than in CVID patients ($r_{Pearson}$ = 0.55, p = 0.017). Bronchiectasis was also associated with bronchial wall thickening ($r_{Pearson}$ = 0.44, p = 0.018), but not to mucus plugging or atelectasis in this cohort.

Lung function

CVID patients showed mild obstructive lung disease in the older age groups without restriction, FEV_1 was 87.8 (19.6) % predicted in patients < 20 years and FEV_1 (FEV_1, figure 3A) 72.9 (26.3) % predicted in patients ≥ 60 years. There was a similar age dependent decline in maximal expiratory flow at 25% of vital capacity (MEF_{25}), and total lung capacity (TLC), but not of vital capacity (VC). However, explanation of variance of all parameters by age was weak (FEV_1: R^2 = 0.041, p = 0.016, F = 5.994; MEF_{25}: R^2 = 0.053, p = 0.01, F = 6.882; TLC: R^2 = 0.072, p = 0.028, F = 5.061). In XLA patients, advance of lung disease with age was more obvious. FEV_1 declined from 95.7 (8.7) % predicted in patients aged less than 20 years to 44.0 (23.2) %predicted in patients ≥ 40 years. Accordingly, linear regression analysis showed a stronger relation between age and decline in lung function parameters in XLA patients (vital capacity (VC): R^2 = 0.351, p = 0.005, F = 10.285; FEV_1: R^2 = 0.529, p < 0.001, F = 22.439; MEF_{25}: R^2 = 0.637, p = 0.002, F = 17.511; TLC: R^2 = 0.072, p = 0.028, F = 5.061).

CT findings and lung function

Presence of bronchial wall thickening, bronchiectasis or mucus plugging was associated with a lower FEV_1 in CVID patients (table V online repository, figure 3B). The combination of bronchiectasis and bronchial wall thickening showed a further decline (n = 54, FEV_1 of 69.3 (23.3) % % predicted). Patients with a severe lung disease as indicated by spirometry (FEV_1 < 40 % predicted) had a high prevalence of bronchiectasis (89%). However, normal FEV_1 (> 80 % predicted) did not preclude the presence of bronchiectasis . 59% of the patients with a

normal lung function had bronchiectasis (figure 3). Thus, spirometry was a poor predictor for presence (sensitivity: 48.9%) or absence of bronchiectasis (specificity: 68.8%, table IV online repository). Findings of bodyplethysmography and carbon monoxide diffusion capacity were not better associated with structural bronchial pathology.

Cough

The majority of CVID patients for whom clinical data were available (n = 147) had occasional (53.1%), or recurrent or chronic cough (34.7%). Prevalence of chronic cough increased with age and rose from 18% in the age group < 20 years to 38.5% in the age group ≥ 60 years ($R^2 = 0.054$, F = 8.315, p = 0.005). Quality of cough also changed with age; a higher proportion of patients had productive cough and frequency of cough with increasing age (79% in age group ≥ 60 years). In this age group all patient suffered from cough (fig. 4). Of the patients who coughed chronically, 75% had evidence of bronchiectasis. Nevertheless, 60% of the subjects with occasional cough also had bronchiectasis. Almost all patients with radiological evidence of bronchiectasis had some sort of cough (92.7%). These patients were twice as much likely to have productive rather than unproductive cough (66.7 vs. 33.3%). Patients with bronchiectasis and productive cough had a more compromised lung function test (mean FEV_1 = 71.9 (26.1) % predicted) than those with bronchiectasis and unproductive cough (mean FEV_1 = 86.2 (25.0) % [pred.], p = 0.033).

Use of antibiotics

Use of antibiotics varied considerably. Intermittent antibiotic therapy was more frequent (47.7%) than maintenance (26.8%) therapy in n = 163 CVID patients, for whom data were available. Usage varied also for patients with chronic cough (n = 51): intermittent 51.8% and maintenance 40.8% therapy and for patients with bronchiectasis (n = 95): intermittent 44.2%, and maintenance therapy 33.7%. Courses of antibiotic therapy were used more commonly as the proportion of patients with bronchiectasis rose: 51.2% of the patients who received no antibiotic therapy (n = 42) had bronchiectasis, 59.2% of the patients with intermittent therapy

(n = 71) had bronchiectasis, and 72.7% of the patients with mainentance antibiotic therapy (n = 44) had bronchiectasis. Our data did not discriminate between prophylactic and therapeutic use of antibiotics.

Discussion

The purpose of this study was to identify the range and extent of bronchial pathology as detected by chest CT in antibody deficient patients. A multicentre approach was used, as antibody deficiencies are a relatively rare condition. CT findings provide primarily qualitative data, which makes multicentre studies difficult to accomplish in the absence of pre-agreed criteria. With the Chest CT in Antibody Deficiency Group, we set up a catalogue of pathologies that were reported in the literature or seen in our own patients. In order to compile data that is comparable, we agreed upon common radiological terminology, set up an image repository, and agreed upon common definitions.

We found a high overall prevalence of bronchial pathology, with bronchial wall thickening and bronchiectasis present in 52% and 61% of the CVID patients, respectively. The present study is the first multicentre study to also assess extent of bronchiectasis in children and adults with antibody deficiency. While the prevalence of bronchiectasis increased with age, it was already present in our youngest age group (< 20 years) at 43%. Duration of disease, however, was the best predictor for presence and extent of bronchiectasis, with age and sex having no additional impact. Importantly, also delay of diagnosis correlated significantly with the extent of bronchiectasis. Atelectasis and mucus plugging were reported less frequently, but also at sizeable proportions of the patients.

As expected, the prevalence of bronchiectasis increased with age which did not apply to the bronchial wall thickening, atelectasis and mucus plugging. While bronchiectasis correlated to the other pathologies at younger age groups (table 4, online repository), in the older age groups bronchiectasis appeared to be more the accumulation of damage acquired in past and present inflammatory processes. Age as well as duration of disease accounted for more of the variation in bronchiectasis and lung function in XLA than in CVID. This may reflect the earlier and more homogeneous onset of immunodeficiency in XLA (8) compared with the predominantly adult onset of CVID (11), although differences in the pathogenesis of lung disease cannot be excluded.

Similar to prevalence and extent of bronchiectasis, spirometry values tended to be more pathological at higher age groups. Along with bronchiectasis, prevalence of chronic and productive cough increased with age, reaching 100%, in the oldest age group (> 60 years). Cough frequency correlated better to bronchiectasis than spirometry. XLA patients had more advanced bronchial disease in the older age groups when compared to the CVID cohort. This is consistent with data from an Italian cohort (26) who had a cumulative risk of developing structural lung disease of 92% by the age of 25 years, which was higher than in the Italian CVID cohort that had a prevalence of bronchiectasis of 54% at an average age of 41 years (27).

Our data show a rate of bronchiectasis in CVID patients (61%) in the same range as reported with the as yet largest CVID cohort of Italian patients (54%) (27). In smaller chest CT studies, bronchiectasis rates varied between 29 and 78% (summarised in (17)). A meta-analysis of other studies summarised data from 587 CVID patients published in 26 studies. The authors reported an overall prevalence of 73% of pulmonary pathologies, mainly bronchiectasis and bronchial wall thickening.

The present study has several limitations:

First, it was not designed as a cross-sectional cohort study to assess the prevalence of particular pathologies. The participating centres varied in their policies to perform chest CT between clinical grounds and routine use. Since some centres performed chest CTs only on clinical grounds, the study is likely to overestimate prevalence and extent. The relatively high prevalence of bronchiectasis in children and adolescents (43% in the age group < 20 years) may be partly explained by the fact, that the majority of the CT studies in this age group was performed in a centre that performed CT on clinical grounds.

Second, we employed no training or quality control measures for our raters. Although we used an internationally accepted vocabulary (15), published an image repository on our website, we cannot be sure that all raters shared similar levels of expertise. Appreciating this, we designed the list of CT findings of this study to be as simple as possible, indicating merely presence or absence for most pathologies. A study on inter-rater reliability with our list of CT

findings showed very high rates of inter-rater agreement for all findings, in particular for the bronchiectasis score. Rating of bronchial wall thickening, however, was unreliable which is well recognized in the literature (28).

Despite these limitations, our data may nevertheless be meaningful. Our CVID study cohort has an age and sex distribution that is close to the distribution of the ESID registry. Also, the size of the compiled cohort is larger than previous reports in the literature.

Bronchiectasis is the finding most frequently reported in previous studies. Our data on the prevalence of bronchiectasis (61%) are in the same range compared to the as yet largest CVID cohort study (54%) (27). The latter study is likely to give the most accurate estimate on prevalence of bronchiectasis for it was based on regular chest CT scans. Other studies based on smaller cohorts reported bronchiectasis rates between 29 and 78% (summarised in (17)).

Chest CT scans identified a high proportion of respiratory pathology which did not appear to be identified by symptoms or lung function. This applied in particular to patients with low grade bronchiectasis in which spirometry tended to be normal (figure III in online repository). Also, the decline in FEV_1 with age was relatively small in our cohort, compared to other conditions with chronic lung disease, such as primary ciliary dyskinesia (PCD) (29,30). However, spirometry appeared to better discriminate between prevalence or absence of bronchiectasis in our patient group than reported in PCD or CF (31,32). While a sensitivity of 49% and a specificity of 68.8% for detection and exclusion of bronchiectasis are far from satisfactory, the use of spirometry in routine management in patients with ADS may be at least as adviseable as in PCD or CF. Although spirometry may not detect mild bronchiectasis, it is likely to be a meaningful parameter for advanced stage of bronchial disease. In addition, any decline in spirometry in a given patient, even within the normal range, may indicate progressing lung damage and hence should prompt further evaluation. The higher susceptibility to irradiation damage in some subgroups of CVID also supports the notion to regularly monitor pulmonary disease without use of ionising radiation. Particular attention should be paid to children and adolescents. Although bronchiectasis may be overestimated in this age group, the true prevalence of bronchiectasis is likely to be high enough to warrant

high priority for prevention of development of structural lung disease. Spirometry needs to be complemented by more sensitive functional tests. The multiple breath washout technique may be particularly promising for detecting bronchiectasis, as shown in CF and other conditions (31).

One important finding of this study is the observation that patients with a delay of diagnosis correlated with advanced formation of bronchiectasis in CVID. This finding argues that awareness of primary immunodeficiencies and early diagnosis may be particularly beneficial.

Prevalence and extent of bronchiectasis also increased with the years of disease, suggesting a repeated or continuous burden of bronchial inflammation throughout the course of disease.

Cough turned out to be more closely related to bronchial disease than parameters of spirometry. Again, patient selection may have biased this surprisingly high proportion of patients with clinical evidence of lung disease. However, cough and other clinical parameters, e.g. sputum volume, colour, frequency of chest exacerbations, or frequency of antibiotic therapy, may be valuable tools in future interventional trials. Our findings also argue that we do need better monitoring strategies for development of pulmonary pathologies before chronic or productive cough develops.

Therapeutic regimens for antibiotic treatment of CVID patients with bronchiectasis, pathologic spirometry or productive cough differ substantially in the present study as in others (9,11). Chapel et al. found no clear evidence that bronchiectasis can be prevented by prophylactic maintenance antibiotic therapy. Bondioni et al. recommended early detection of pulmonary changes to adjust antibiotic therapy (21,33,34).

Evidence for the benefit of antibiotic therapy or other interventions to prevent or ameliorate progress of bronchiectatic lung disease in other conditions is conflicting. Among the reasons for the lack of efficacy trials in immunodeficiency is the difficult choice of outcome parameters. FEV_1 and other lung function parameters show relatively little changes over time rendering them less sensitive than desirable. Magnetic resonance imaging (MRI) has made substantial progress in the detection of pulmonary pathology but is less widely available (35).

Chest CT is still considered the gold standard for detection of structural bronchial pathology (17) and sensitive for changes over time (21).

Our bronchiectasis score was designed for use in routine care without prior training of the raters. This score is clearly too crude to specifically assess progress of bronchiectasis. More detailed extent scores for bronchiectasis in CVID were applied in 2 single centre studies (20,21,36), demonstrating that progress of lung disease is detectable by chest CT at intervals as short as 5 years.

Given the size and the relevance of pulmonary morbidity in primary antibody deficiencies, the present study argues to optimise the use of chest CT. First, there is a need for a detailed score on bronchial and other pulmonary pathologies for interventional trials (37). Second, chest CT scans which are performed as part of routine care in primary antibody deficiencies should be documented in a uniform manner in a patient registry along other clinical and immunological data. Documentation should provide more quantitative data than the one used in the present study, but still be compatible with routine care. The Chest CT Group has elaborated a proposal for severity graded documentation of bronchial pathology (table VI, online repository). Since this will be more prone to variation between different raters, we plan to implement quality control measures that include rating of test images.

In summary, chest CT is a highly sensitive method for assessment of structural abnormalities of the bronchial airways. If it is complemented by lung function and clinical parameters, it can provide essential information on the progress and nature of lung disease in patients with antibody deficiencies. However, rating of CT findings for cohorts requires a consensus as to how the findings are documented. The present study shows how a multidisciplinary and multicentre approach can come into operation and affords a rationale how to shape future steps towards a better management of lung disease in antibody deficiency.

Conflict of interest statement

The authors declared that they have no conflict of interest.

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Tables

Table 1

Table 1: Characteristics of the study population, sorted by the two main diagnosis groups.

	CVID	**XLA**
n	232	28
Female, n	113 (49%)	0
Age, mean (SD; range) [years]	36.6 (17.6; 1.6-79.3)	25.1 (15.7, 4.0-53.1)
Children and adolescents < 18 years, n	46 (20%)	16 (53%)
Duration of disease, mean (SD; range) [years]	17.3 (13.5)	15.6 (11.6)
Delay of diagnosis, mean (SD; range) [years]	6.5 (8.3; 0 – 48.8)	2.8 (4.7; 0 – 17.3)
Duration of therapy, mean (SD; range) [years]	10.8 (9.8; 0 – 42.0)	11.3 (7.8; 0.9 – 29.7)
IgG trough levels, mean (SD) [g/L]	7.0 (3.0)	7.9 (2.1)

Abbreviations: CVID: common variable immunodeficiency disorders, XLA: X-linked agammaglobulinaemia; SD: standard deviation

Figures

Figure 1

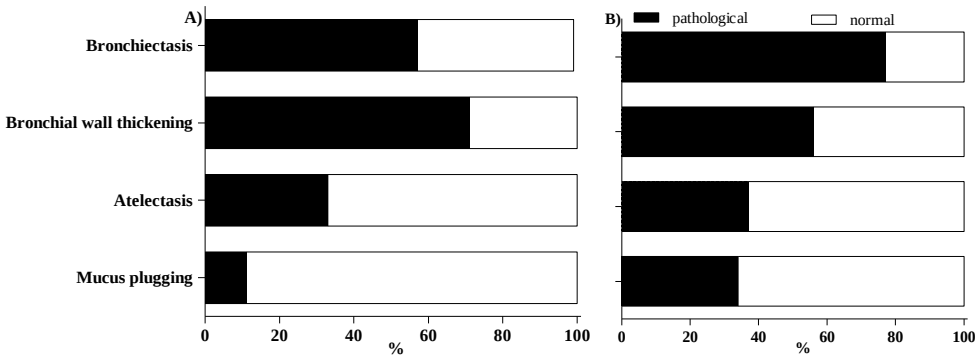

Fig.1.: Prevalence of bronchial pathology in patients with CVID (A) and XLA (B).

Figure 2

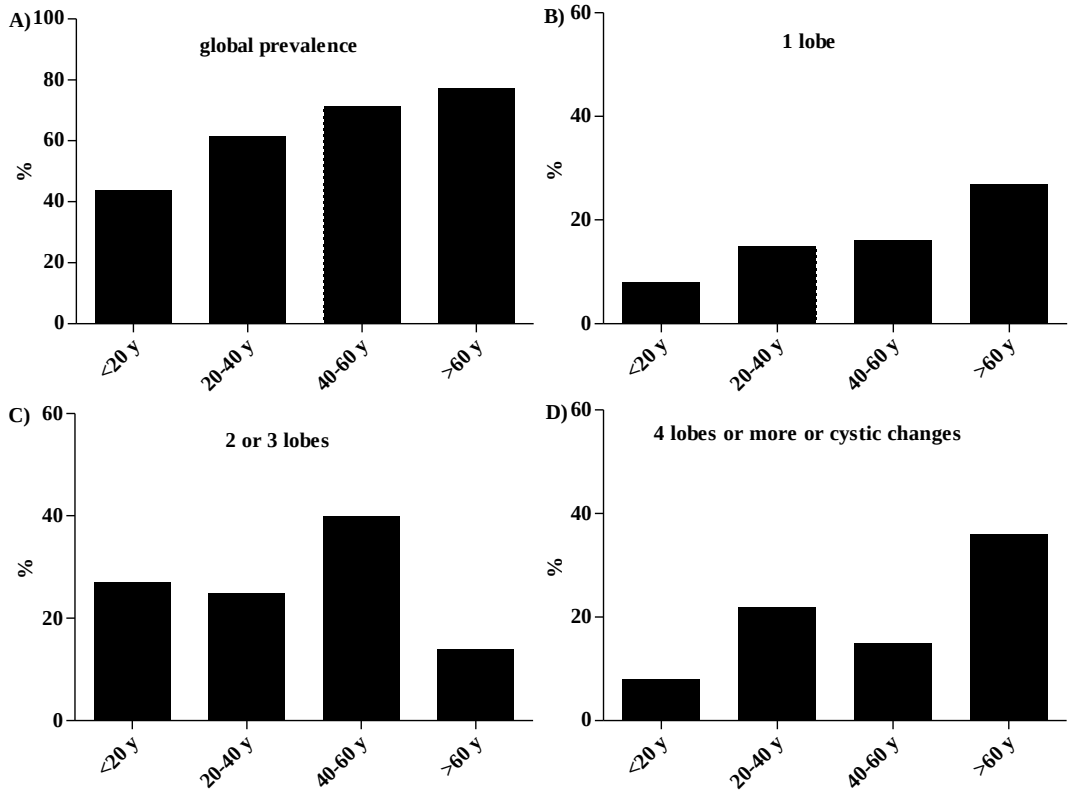

Fig.2: Prevalence, extent and age distribution of bronchiectasis in 232 CVID patients.

A: Global prevalence (any bronchiectasis), B: 1 lobe affected, C: 2 or 3 lobes affected, and D: 4 or more lobes affected or cystic changes. Lingula counted as a separate lobe. The extent score correlated significantly with age ($r_{Pearson} = 0.171$, $p = 0.01$).

Figure 3

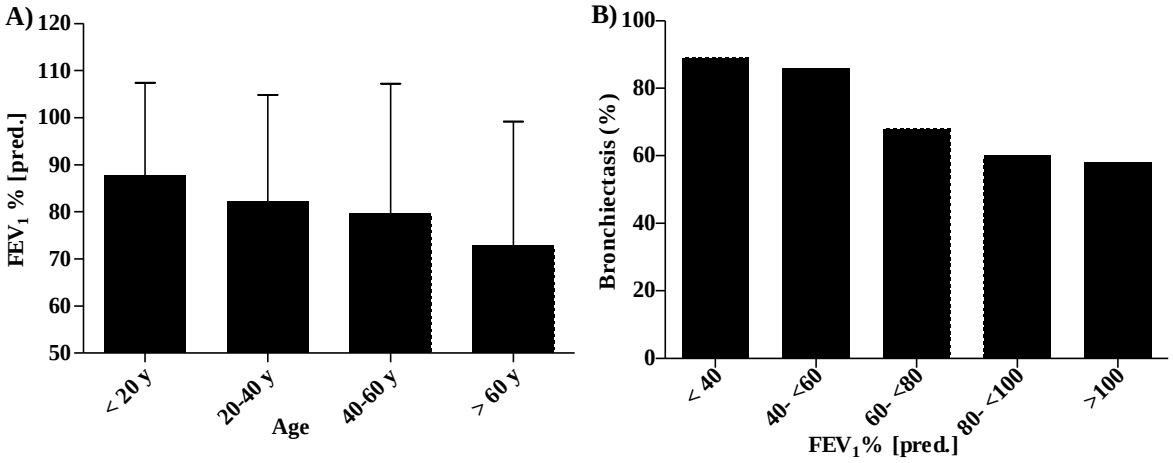

Fig. 3. A: Mean (SD) forced expiratory volume in 1 second as percentage of predicted value (FEV_1 % [pred.]) in 232 CVID patients stratified in age groups. FEV_1 % predicted declined significantly with age ($r_{Pearson}$ = -0.203, p = 0.016). B: Prevalence of bronchiectasis stratified by age groups. Prevalence and extent of bronchiectasis increased with deteriorating FEV_1 ($r_{Pearson}$ = -.22, p = 0.009 and ($r_{Pearson}$ = -.322, p < 0.001 for prevalence and extent of bronchiectasis with FEV_1 % predicted.

Figure 4

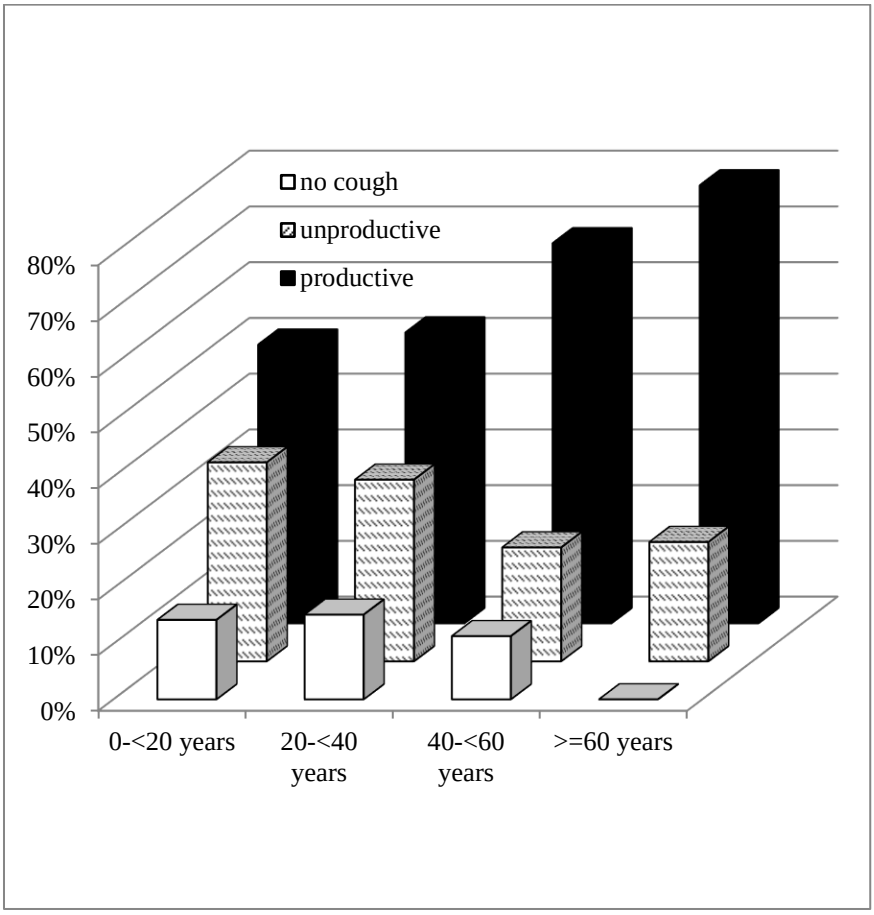

Fig.4. Prevalence of productive and unproductive cough of 120 CVID patients stratified in age groups. Productive cough was more frequent with age ($r_{Pearson}$ = 0.222, p = 0.012).

Figure 5

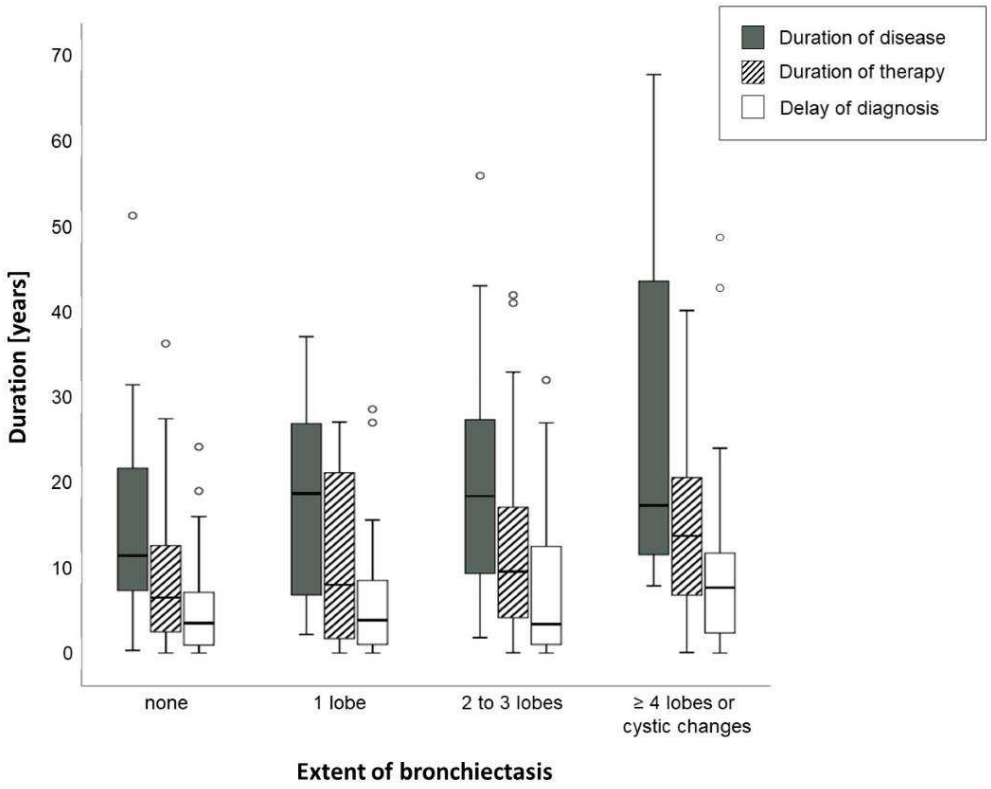

Fig.5: Severity of bronchiectasis in relation to duration of disease, duration of medical attention following diagnosis of CVID ("duration of therapy", and delay of diagnosis. Boxplots indicate median and interquartiles, whiskers range. Open dots show outliers. Delay of diagnosis correlates significantly with severity of bronchiectasis (p=0.03)

Online Repository

Table I

Documentation sheet for chest CT findings, section bronchial pathology.

Bronchial Pathology	
Bronchial wall thickening	☐ no ☐ yes
Bronchiectasis	☐ none ☐ one lobe ☐ two or three lobes ☐ four lobes or more or cystic changes in two or more lobes
Mucus plugging	☐ none ☐ central ☐ peripheral
Atelectasis	☐ no ☐ yes

Table II

Clinical data sheet

Chest CT in Antibody Deficiency Group

Clinical Data Sheet

Patient initials	Date of birth	Institution	Diagnosis	Date of CT study

General data

Sex	☐ male ☐ female
Weight	_____ kg
Length	_____ cm

Lung function: Spirometry

Date of test (most closely by date of CT)	___/___/_____ (MM/ DD / YYYY)
VC Vital capacity	_____ Liter _____ % predicted
FEV_1 Forced expiratory volume in 1 second	_____ Liter _____ % predicted
MEF25 Maximal expiratory flow at 25% of forced VC	_____ Liter / second _____ % predicted

Lung function: Body plethysmography

Date of test (most closely by date of CT)	___/___/_____ (MM/ DD / YYYY)
R_{eff} Effective airway resistance	_____ kPa*s/L _____ % predicted
RV Residual volume	_____ Liter _____ % predicted
TLC Total lung capacity	_____ Liter _____ % predicted

Lung function: CO diffusion

DL(CO)c CO diffsion capacity corrected for Hb	_____ ☐ mL/min/mmHG ☐ mmol/min/kPa

Clinical data at date of CT

Cough	☐ never ☐ occasional ☐ daily (< 8 weeks) ☐ chronic (> 8 weeks) ☐ unknown
Quality of cough	☐ unproductive ☐ productive
Antibiotic treatment	☐ none ☐ intermittent ☐ maintenance (permanent) ☐ unknown

Comments

_____

_____

_____

_____

Please enter data in ESID Registry or fax it to	**Ulrich Baumann** **++49-511-532-9125** **baumann.ulrich@mh-hannover.de**

Date	Name of clinician (in capital letters)	Signature

Table III

Contributing centres	CVID	XLA	Other Diagnoses
London (UK), Royal Free Hospital	41	6	8
Rotterdam (NL), Erasmus MC Sophia Children's Hosp.	38	0	0
Rome (I), Università degli Studi, La Sapienza	26	1	0
London (UK), Royal Brompton Hospital	21	0	0
Brno (CZ), Masaryk University, St Anne´s University	20	2	2
Cambridge (UK), Addenbrook´s NHS Trust	13	0	0
London (UK), Great Ormond Street Hospital	13	11	0
Brescia (I), Dept. of Paediatrics, University of Brescia	10	0	0
Naples (I), Federico II University	10	0	0
Cairo (ET), Paediatric University Hospital	9	0	3
Madrid (ES), Hospital 12 octubre	9	0	0
Hanover (D), Paediatric Pulmonology, Medical School	9	5	7
Melbourne (AUS), Alfred Hospital	7	3	2
Oxford (UK), John Radcliffe Hospital	5	0	0
Bruxelles (B), Cliniques Universitaires, Hôpital Erasme	1	0	0
Total	232	28	22

Table IV

Age dependent correlation of bronchiectasis with other bronchial pathology in 232 CVID patients.

	Bronchiectasis correlates with					
	Bronchial Wall Thickening (n=103)		**Atelectasis (n=74)**		**Mucus Plugging (n=67)**	
Age Group	$r_{Pearson}$	p	$r_{Pearson}$	p	$r_{Pearson}$	p
< 20	0.325	0.029	0.337	0.020	0.421	0.007
20 - < 40	0.595	< 0.001	0.283	0.019	0.447	<0.001
40 - < 60	0.309	0.006		n.s.		n.s.
≥ 60		n.s.		n.s.		n.s.
All Age Groups	0.363	< 0.001	0.250	< 0.001	0.322	< 0.001

621 **Table V**

622 **Contigency table of lung function and bronchiectasis.** A FEV_1 < 80 % predicted is

623 considered as pathological. Presence or absence of bronchiectasis as defined by chest CT.

Sensitivity of FEV_1 <80% % predicted to assess all cases of bronchiectasis	0.489
Specificity of FEV_1 >80% % predicted for no bronchiectasis	0.688
Positive predictive value	0.750
False negative rate (miss rate)	0.511
False positive rate (fallout)	0.313
Negative predictive value	0.413

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Table VI

Revised score for bronchial pathologies of the Chest CT in ADS group. For definitions of the various items see www.chest-ct-group.eu.

Bronchial Pathology							
Airway wall thickening							
Number of lobes affected (lingula counts as a lobe)	⓪	①	②	③	④	⑤	⑥
Most severely affected bronchia: Extent as in % of accompanying vessel		< 33%		33-66%		>66%	
Bronchiectasis							
Number of lobes affected	⓪	①	②	③	④	⑤	⑥
Most severely affected bronchia: Extent as in % of accompanying vessel		< 33%		33-66%		>66%	
Mucus plugging (large airways)							
Number of lobes affected	⓪	①	②	③	④	⑤	⑥
Mucus plugging (small airways – tree in bud)							
Number of lobes affected	⓪	①	②	③	④	⑤	⑥
Atelectasis (volume loss > 50%)							
Number of lobes affected	⓪	①	②	③	④	⑤	⑥

Figure I

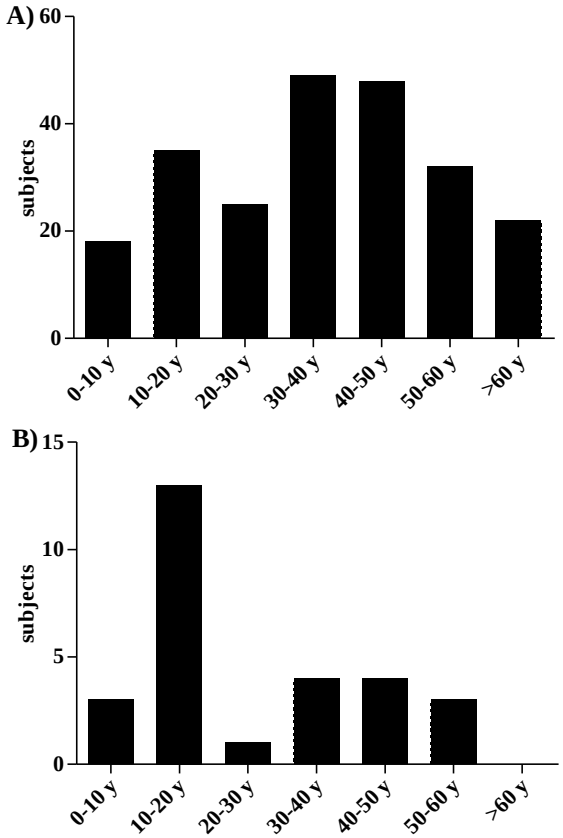
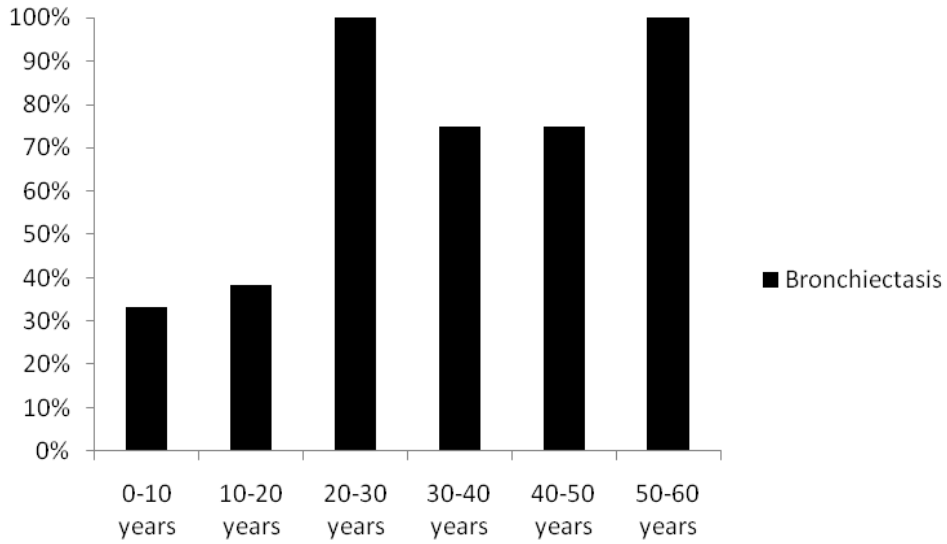


Fig. I: Age distribution of the cohort with CVID (A) and XLA (B)

635 **Figure II**



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637 **Fig. II: Prevalence of bronchiectasis in 28 patients with XLA.**

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Figure III

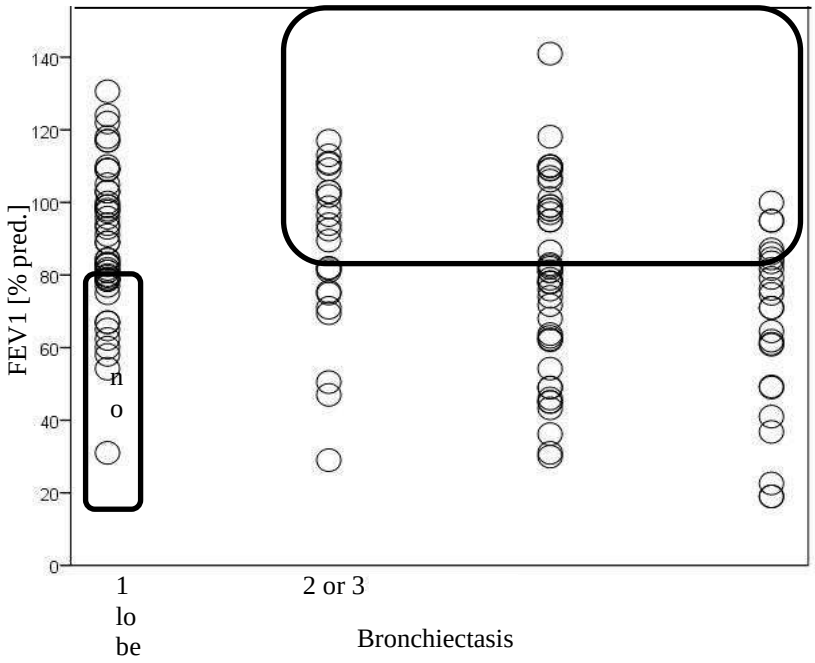

Fig. III. Individual levels of FEV_1 % predicted of 143 CVID patients in relation to extent of bronchiectasis. Upper right box: patients with bronchiectasis with normal lung function (FEV_1>80% % predicted: 47 (58.8%) out of the 80 patients with normal lung function. Lower left box: patients with no bronchiectasis, but with abnormal lung function (FEV_1<80% % predicted): 15 (25%) out of 60. The correlation between the extent score of bronchiectasis and FEV_1 was significant, but weak, in linear regression analysis ($F = 15.9$, $R^2 = 0.10$, $p < 0.001$).

Fig. IV: Correlation of prevalence of bronchiectasis with duration of disease. The cumulative prevalence of bronchiectasis in relation to the duration of disease. 1 year of disease is associated with an average increase of risk of bronchiectasis by 4.8% (p = 0.015).