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ORIGINAL ARTICLE

Structural Lung Disease and Clinical Phenotype in Bronchiectasis Patients

The EMBARC CT Study

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Abstract

Rationale: Chest computed tomography (CT) scans are essential to diagnose and monitor bronchiectasis (BE). To date, few quantitative data are available about the nature and extent of structural lung abnormalities (SLAs) on CT scans of patients with BE.

Objectives: To investigate SLAs on CT scans of patients with BE and the relationship of SLAs to clinical features using the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) registry.

Methods: CT scans from patients with BE included in the EMBARC registry were analyzed using the validated Bronchiectasis Scoring Technique for CT (BEST-CT). The subscores of this instrument are expressed as percentages of total lung volume. The items scored are atelectasis/consolidation, BE with and without mucus plugging (MP), airway wall thickening, MP, ground-glass opacities, bullae, airways, and parenchyma. Four composite scores were calculated: total BE (i.e., BE with and without MP), total MP (i.e., BE with MP plus MP alone), total inflammatory changes (i.e., atelectasis/consolidation plus total MP plus ground-glass opacities), and total disease (i.e., all items but airways and parenchyma).

Measurements and Main Results: CT scans of 524 patients with BE were analyzed. Mean subscores were 4.6 (range, 2.3–7.7) for total BE, 4.2 (1.2–8.1) for total MP, 8.3 (3.5–16.7) for total inflammatory changes, and 14.9 (9.1–25.9) for total disease. BE associated with primary ciliary dyskinesia was associated with more SLAs, whereas chronic obstructive pulmonary disease was associated with fewer SLAs. Lower FEV_1, longer disease duration, *Pseudomonas aeruginosa* and nontuberculous mycobacterial infections, and severe exacerbations were all independently associated with worse SLAs.

Conclusions: The type and extent of SLAs in patients with BE are highly heterogeneous. Strong relationships between radiological disease and clinical features suggest that CT analysis may be a useful tool for clinical phenotyping.

Keywords: bronchiectasis; bronchial diseases; airway wall thickening; artificial intelligence; quantitative imaging analysis

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Bronchiectasis (BE) disease is a clinical syndrome characterized by cough, sputum production, and recurrent infectious exacerbations combined with the radiological appearance of abnormal dilation of the bronchi (1). BE disease may result from a variety of etiologies and is highly heterogeneous in its clinical, microbiological, and functional attributes. The irreversible dilation of bronchi is assumed to reflect accumulated structural airway damage and is associated with chronic inflammation, bacterial infection, impaired mucociliary clearance, and disease progression, known as the concept of the "vicious vortex" (2).

Assessment and management are based on clinical assessment of disease severity and disease activity. The frequency of exacerbations, extent of symptoms, and presence of airway infections such as *Pseudomonas aeruginosa* (*PsA*) can be used to identify patients at higher risk of future poor outcomes. Composite clinical scores such as the Bronchiectasis Severity Index combine a number of clinical factors to identify patients at higher risk of exacerbations, hospitalizations, and mortality.

BE is defined by the presence of radiological abnormalities, but, currently, the extent of radiological disease is not routinely considered when evaluating a patient's phenotype or assessing their risk.

The gold standard for the radiological diagnosis of BE is thin-section chest computed tomography (CT). The morphologic criteria for BE on CT are bronchial dilation relative to the accompanying pulmonary artery, lack of tapering of the bronchus, and identification of bronchi within 1 cm of the pleural surface, often accompanied by bronchial wall thickening and mucus plugging (MP) (3). However, in routine clinical practice, airway abnormalities are evaluated subjectively, and no quantification of BE or accompanying features is routinely performed.

For the quantitative analysis of airway and parenchymal abnormalities in BE disease, the Bronchiectasis Scoring Technique for CT (BEST-CT) was developed. BEST-CT is a scoring system that uses morphometric principles and has been shown to be effective in detecting and monitoring the extent of airway abnormalities as a percentage of the affected parenchyma. BEST-CT has been shown to be a reproducible system with which to quantify the severity and extent of the structural lung abnormalities (SLAs) in patients with granulomatous lymphocytic interstitial lung disease and those with BE chronically infected with *PsA* (4–6).

The EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) registry was established in 2015 (7) as a prospective, pan-European observational study of patients with BE (8). Because BEST-CT is currently the best-validated scoring method to quantify extent of radiological disease in BE, we hypothesized that radiological data would be associated with clinical phenotype. We conducted a substudy embedded within the EMBARC registry to incorporate quantitative CT analysis in more than 500 patients with the aim of establishing relationships between the radiological extent of disease and its etiology, severity, and phenotype.

Methods

Study Population

We collected clinical data and CT images and from patients enrolled in the EMBARC registry. Details of the EMBARC data collection protocol and baseline data from the EMBARC registry have been published previously (7, 8). The key inclusion criterion to be included in the registry is a primary clinical diagnosis of BE, per the judgment of the treatment center, consisting of *1*) a clinical history consistent with BE and *2*) a CT scan demonstrating BE. Key exclusion criteria for EMBARC registry are *1*) BE due to known cystic fibrosis (CF), *2*) age $<$18 years, and *3*) inability or unwillingness to provide informed consent. A complete list of inclusion and exclusion criteria was described previously (7). For the present substudy, eight BE centers in six countries were included: one each in Rotterdam, The Netherlands; Dundee, London, and Cambridge, United Kingdom; Sint-Niklaas, Belgium; Monza, Italy; Haifa, Israel; and Paris, France (Figure 1). Each center was asked to make a completely random subselection (50–100 patients) within their available cohort. In parallel to the primary BE registry, EMBARC has a European nontuberculous mycobacterial (NTM) BE substudy, which collects additional data from patients meeting the Infectious Diseases Society of America/American Thoracic Society criteria for active NTM infection (9). The NTM registry was used to enrich the cohort for patients with active NTM infection. This oversampling was performed to ensure sufficient statistical power to investigate this relevant clinical determinant (NTM) with a relatively low prevalence in European centers (10).

Clinical Parameters

The following data were collected from the EMBARC registry: demographic characteristics, previous medical history, comorbidities, spirometry, hospital admissions in the 1 year before inclusion in the study, microbiology, and severity of disease as reflected by the Bronchiectasis Severity Index (BSI) and FACED score

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

At a Glance Commentary

Scientific Knowledge on the Subject: The evaluation of bronchiectasis (BE) disease, even though it is characterized by the presence of radiological abnormalities, currently lacks a measure of the extent of radiological disease in evaluating patient phenotypes, disease activity, and the risk of poor outcomes. Current clinical practice assesses radiological abnormalities subjectively without quantifying BE or accompanying features. In this study within the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) registry, we analyzed computed tomography (CT) scans with the quantitative Bronchiectasis Scoring Technique for CT from more than 500 patients to investigate the relationships between specific radiological abnormalities and BE disease etiology, severity, and phenotype.

What This Study Adds to the Field: Our analysis found great heterogeneity in the nature and extent of structural lung abnormalities with prominent inflammatory features. Lower FEV_1% predicted, presence of *Pseudomonas aeruginosa* and nontuberculous mycobacteria, severe exacerbations, and BE disease etiology were all strongly correlated with the extent of distinct radiological abnormalities on chest CT scans. The quantitative Bronchiectasis Scoring Technique for CT outcomes can be used to phenotype BE disease in patients and determine the relationship between clinical characteristics and radiological disease manifestations.

(FEV_1% predicted, age, chronic colonization by *PsA*, radiological extent of disease, and dyspnea) (11, 12).

The underlying etiology of BE is recorded in the EMBARC registry based on testing recommendations by European Respiratory Society guidelines. Ten different etiology groups were defined based on the available categories in the registry and the sample sizes per group: *1*) idiopathic BE; *2*) allergic bronchopulmonary aspergillosis (ABPA); *3*) asthma; *4*) primary/secondary immunodeficiency; *5*) connective tissue disease, rheumatoid arthritis, and inflammatory bowel disease; *6*) chronic obstructive pulmonary disease (COPD); *7*) NTM infection; *8*) other disease (e.g., Mounier-Kuhn syndrome, yellow nail syndrome, Young's syndrome, CF transmembrane conductance regulator–related disorders, aspiration, and gastroesophageal reflux disease); *9*) postinfectious BE (including after tuberculosis); and *10*) primary ciliary dyskinesia (PCD). Additionally, this study investigated whether patients had a codiagnosis of asthma and/or COPD in addition to the recorded primary etiology of the BE.

In the EMBARC registry, patients were categorized by duration of BE disease into five groups (0–5 years, 5–10 years, 10–15 years, 15–20 years, and ⩾20 years). Hospital admissions due to pulmonary exacerbations in the previous year were categorized as none, one, or two or more. Furthermore, patients were categorized by normal or increased (⩾300 cells/ml) blood eosinophil count (13).

CT Collection

The Erasmus MC LungAnalysis core laboratory (Rotterdam, The Netherlands) provided participating centers with a procedure to verify the pseudonymity of CT images and facilitated safe data transfer of pseudonymized CT scans from the participating hospitals to LungAnalysis. CT scans were included in this study if they fulfilled the following requirements: *1*) correct digital format (i.e., correct DICOM headers), *2*) sufficient inspiratory lung volume as defined by a round shape of the trachea and the presence of lung parenchyma between the heart and sternum, *3*) complete display of the lungs, *4*) no artifacts beyond mild artifacts with minimal effect on the visualization of the lungs (Figure 1). Moreover, for each patient, the centers selected the chest CT scan that was performed closest to the time of enrollment in the EMBARC cohort (with a maximum interval of ±4 years, i.e., 1,460 d).

BEST-CT Scoring

BEST-CT is a morphometric scoring system based on the same principles as the extensively validated Perth-Rotterdam Annotated Grid Morphometric Analysis for Cystic Fibrosis (PRAGMA-CF) (14). In short, a grid is placed on 10 equally spaced axial chest CT slices between the lung apex and base, based on the PRAGMA-CF scoring method (14, 15). Each grid box is annotated by a trained and certified observer for the presence of SLAs (5). Each grid cell that contains ⩾50% coverage of the lung is scored using the following hierarchical system (highest to lowest priority): *1*) atelectasis/consolidation (ATCON), *2*) BE with MP (BEMP), *3*) BE without MP (BEwMP), *4*) airway wall thickening (AWT), *5*) MP without BE, *6*) ground-glass opacities (GGOs), *7*) bullae, *8*) airways (i.e., those that are not dilated), and *9*) parenchyma (i.e., those without annotated abnormalities) (Figure 1).

The following composite BEST-CT scores were used to investigate the relation between clinical outcomes and CT findings:

- Total BE (%TBE) = %BEMP + %BEwMP
- Total MP (%TMP) = %BEMP + %MP
- Total inflammatory CT characteristics (%TInF) = %ATCON + %BEMP + %MP + %GGO
- Total disease (%DIS) = %ATCON + %TBE + %AWT + %MP + %GGO + %bullae

Intra- and Interobserver Reliability

Certification was obtained by completion of standardized training modules (CF-CT, PRAGMA-CF, and BEST-CT). The observer who scored all CT scans was a radiology resident with subspecialty training in thoracic radiology (A.L.P.P.). The second observer for the interobserver reliability was a certified LungAnalysis laboratory staff member (M.B.). To assess intraobserver variability of the BEST-CT scoring method, the main observer rescored 28 randomly selected CT scans 1 month after completion.

Statistical Analysis

Descriptive statistics of patient characteristics are displayed as medians with IQRs or as counts and percentages as appropriate. Intra- and interobserver agreement of CT scoring methods and intraclass correlation coefficients (ICCs) were calculated with

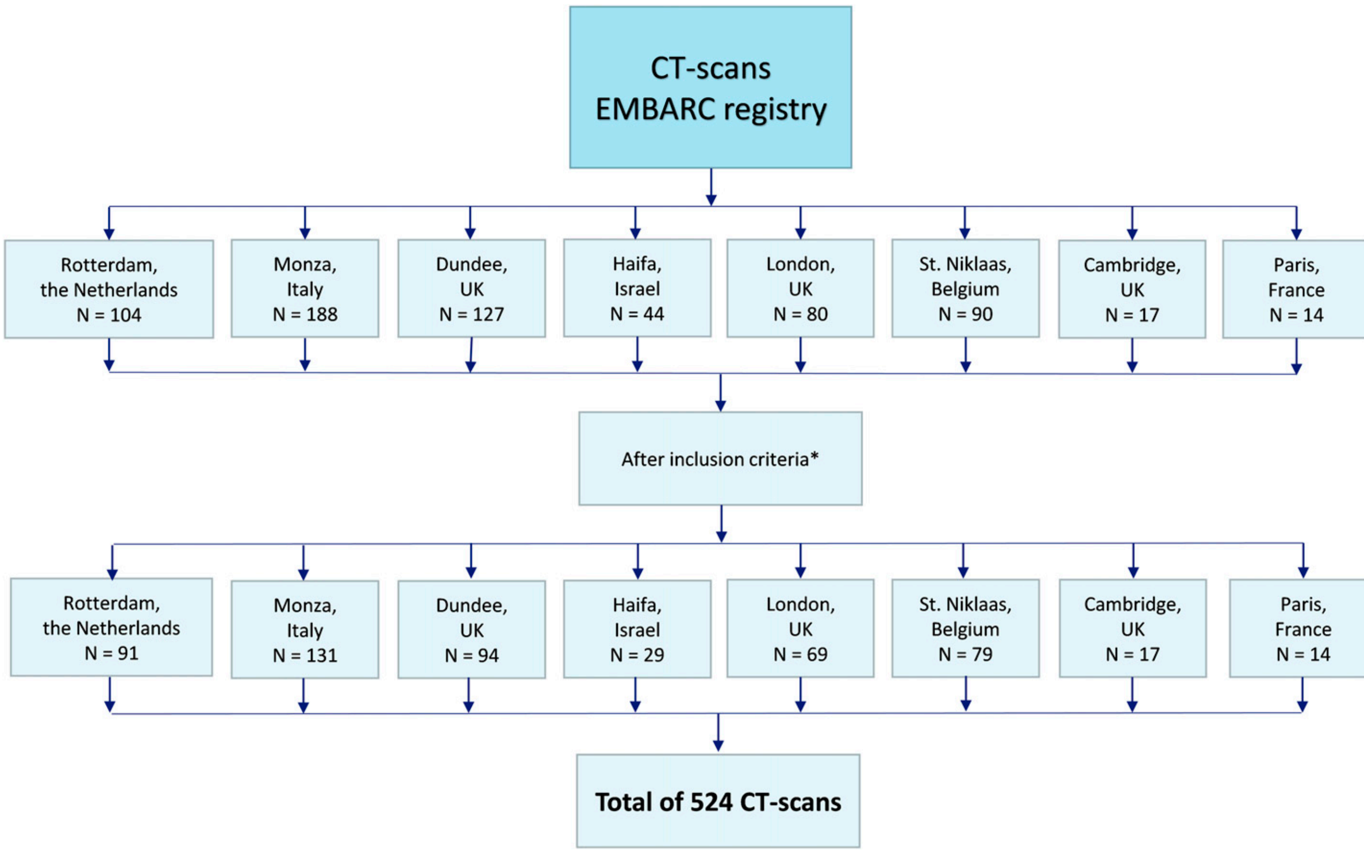

Figure 1. Flow chart of the selection of eligible computed tomography (CT) scans used for Bronchiectasis Scoring Technique for CT from the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) registry. *The inclusion criteria are: *1*) inspiratory chest CT series, *2*) continuous helical CT acquisition, *3*) slice thickness ⩽1.5 mm, *4*) imaging of the entire lung parenchyma, and *5*) no artifacts present beyond mild artifacts with minimal effect on visualization of the airways. Moreover, for each patient, the centers selected the chest CT scan that was performed closest to the time of enrollment in the EMBARC cohort (with a maximum interval of ±4 years, i.e., 1,460 d).

two-way mixed-effects models assessing the consistency of single measurements. ICC values lower than 0.50 were considered poor, 0.50–0.75 moderate, 0.75–0.90 good, and greater than 0.90 excellent (16).

To investigate the association between the four different BEST-CT composite scores (%TBE, %MP, %TinF, and %DIS) and clinical parameters (age, sex, duration of disease, FEV_1% predicted, microbiology, smoking status, hospital admissions, etiology, codiagnosis of asthma and/or COPD, eosinophil count, and BSI and FACED scores), we used multivariable linear regression. For categories, we also performed an *F*-test for overall effects. All statistical analysis was done using SPSS software (version 27.0; SPSS Inc.) and R (version 4.0.5, 2005; R Foundation for Statistical Computing). Correction for multiple testing was not performed. Statistically significant results were defined at a *P* value of less than 0.05.

Results

CT Scan Collection and Study Population

In total, 664 CT scans were collected from the eight participating centers. Of these, 140 were excluded (as illustrated in Figure 1). Hence, 524 inspiratory scans were analyzed using the BEST-CT method. The median time between the CT scan and enrollment in the EMBARC registry was 210 days (IQR, 80–560 days). Patient characteristics and etiologies of BE disease are shown in Table 1. A total of 63% of patients were female ($n = 329$), and the median patient age was 66 years (IQR, 55–74 years). In the majority of cases, BE was attributed to an idiopathic and postinfectious etiology: 37% ($n = 193$) and 14% ($n = 76$), respectively (Table 1). A total of 35% of patients had an infection with *PsA*, and 19% had active NTM infection.

Spectrum of Chest CT Outcomes

Table 2 presents the median and IQR of each component score and the composite scores %TBE, %TMP, %TinF, and %DIS. The prevalence of patients with any cells scored positive on that particular component is also reflected in the table. Although most of the scans showed components of BE (BEMP and/or BEwMP) and infection/inflammation (BEMP, MP, ATCON, and/or GGO), there was a wide spread in the extent to which these abnormalities were present. The %TBE ranged from 0% (in 20 patients) to 23%, %MP from 0% to 59%, %TinF from 0% to 60%, and %DIS from 0% to 88%. Outcomes of the CT scans per patient are shown in a stacked-bar graph of all component scores, demonstrating the heterogeneity of the extent of the different types of SLAs across all patients (Figure 2).

Table 1. Patient Characteristics at the Time of Enrollment

Characteristic	Value
No. of analyzed CT scans	524
Age, yr	66 (55–74)
Sex	
Male	135 (37%)
Female	329 (63%)
BMI, kg/m^2 (*n* = 95 missing)	23.4 (20.5–27.6)
Site	
Rotterdam, The Netherlands	91 (17%)
Sint-Niklaas, Belgium	79 (15%)
London, UK	69 (13%)
Dundee, UK	94 (18%)
Cambridge, UK	17 (3%)
Haifa, Israel	29 (6%)
Monza, Italy	131 (25%)
Paris, France	14 (3%)
History of bronchiectasis (*n* = 29 missing)	
<5 yr	237 (48%)
5–9 yr	87 (18%)
10–14 yr	55 (11%)
15–20 yr	30 (6%)
>20 yr	86 (17%)
Underlying etiology	
Idiopathic	193 (37%)
Postinfective	76 (14%)
Other diseases*	52 (10%)
ABPA	35 (7%)
Primary/secondary immunodeficiency	35 (7%)
NTM	32 (6%)
COPD	29 (5%)
Primary ciliary dyskinesia	26 (5%)
CTD/RA/IBD	25 (5%)
Asthma	20 (4%)
Codiagnosis of asthma and/or COPD	212 (40.5%)
Asthma	138 (26%)
COPD	95 (18%)
Hospital admissions in previous year†	
0	396 (76%)
1	100 (19%)
⩾2	28 (5%)
Spirometry	
FEV_1, % predicted	79% (64–98%)
FVC, % predicted	93% (77–109%)
Smoking status	
Never	293 (56%)
Former	181 (35%)
Current	50 (9%)
Pseudomonas aeruginosa infection	185 (35%)
NTM infection (*n* = 8 missing)	98 (19%)

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CTD = connective tissue disease; IBD = inflammatory bowel disease; NTM = nontuberculous mycobacteria; RA = rheumatoid arthritis.
Data presented as median (IQR) where applicable.
*Other diseases include cystic fibrosis transmembrane conductance regulator–related disorders, aspiration, and gastroesophageal reflux disease.
†Hospitalization in the previous year is associated with the patient's enrollment in EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration).

BEST-CT and Clinical Characteristics

Table 3 shows the results of the multiple regression analysis for BEST-CT composite scores (%TBE, %TMP, %TinF, and %DIS) with the clinical characteristics. Several clinical characteristics were significantly associated with the BEST-CT composite scores. Older patients and those with a longer duration of disease (especially a duration of 15–20 years) had significantly more radiological changes on the CT scan for all composite scores ($P < 0.01$) except %TMP versus age ($P = 0.17$).

Overall, BE etiology was significantly associated with all BEST-CT composite scores ($P < 0.01$). Patients with NTM specified as the etiology of their BE had significantly higher %TinF and %DIS scores. PCD was significantly associated with more %TMP and %TinF. ABPA and postinfectious etiologies of BE, on the contrary, were significantly associated with a higher %TBE. However, patients with primary and/or secondary immunodeficiency or COPD as the underlying cause of BE had significantly lower %TBE. A codiagnosis of asthma and/or COPD was also negatively associated with %TBE. The sample size was large enough to allow us to statistically check for interaction between the variables of sex and asthma/COPD codiagnosis. These additional analyses did not show any evidence of differences in the effect size between male and female participants on %TBE or any of the other composite outcome scores (data not shown).

For patients with active NTM infection, all composite scores were significantly higher (P values varying between 0.02 and <0.01). In patients with a positive *PsA* isolation, %TBE ($P < 0.01$) and %TMP ($P = 0.02$) scores were significantly increased.

All BEST-CT composite scores showed an inverse association with FEV_1% predicted values ($P < 0.01$). Both clinical severity scores (BSI and FACED) had a strong positive association with %TBE, %TMP, %TinF, and %DIS ($P < 0.01$).

The %TinF and %DIS scores were associated with hospital admissions for a severe exacerbation; in particular, one hospital admission was significantly correlated with these two composite scores ($P < 0.01$), and there was a trend toward correlation for two or more admissions ($P = 0.06$). This association can be affected by the timing of the questionnaire assessment, which could be before or after date of the CT scan. A univariate sensitivity analysis of this variable in the two groups (CT before questionnaire vs. vice versa) did suggest that the association may be driven mostly by the patients who completed the questionnaire before or on the date of the CT scan (data not shown).

No significant associations were found between smoking history or increased blood eosinophil counts and any of the composite BEST-CT outcomes.

Table 2. Component and Composite BEST-CT Scores

Score	Median	IQR	Prevalence
Component scores			
%ATCON	1.89	0.71–4.42	95%
%BEMP	0.48	0.00–1.77	74%
%BEwMP	3.68	1.47–6.13	95%
%AWT	0.41	0.00–2.10	58%
%MP	3.31	0.45–9.35	87%
%GGO	0.00	0.00–0.16	34%
%BUL	0.00*	0.00–0.00	18%
%A	0.00	0.00–0.29	31%
%P	85.10	73.89–90.35	100%
Composite scores			
%TBE	4.69	2.32–7.66	96%
%TMP	4.21	1.12–10.91	89%
%TinF	8.31	3.54–16.68	99%
%DIS	14.88	9.19–25.86	99%

Definition of abbreviations: A = airway; ATCON = atelectasis and/or consolidation; AWT = airway wall thickening; BEMP = bronchiectasis with mucus plugging; BEST-CT = Bronchiectasis Scoring Technique for Computed Tomography; BEwMP = bronchiectasis without mucus plugging; BUL = bullae; DIS = total disease; GGO = ground-glass opacities; MP = mucus plugging; P = parenchyma (without annotated abnormalities); TBE = total bronchiectasis; TinF = total inflammatory features; TMP = total mucus plugging.
All BEST-CT subscores are expressed as a percentage of total lung volume. This table presents data from patients with a BEST-CT component and composite score greater than zero. The third column lists the prevalence of patients with any cells scored positive for that particular component score. The order of components follows the hierarchical order by which the components are scored.
*Because bullae were present on relatively few CT scans ($n = 93$), the median and IQR are 0.00.

Reproducibility

ICCs of the BEST-CT method are presented in Table E1 in the online supplement. For the BEST-CT method, ICC scores within the main observer were all excellent except in the case of GGO, which was poor as a result of the very low prevalence of GGO detection.

Discussion

BE is a highly heterogeneous disease with a wide variety of etiologies and clinical, microbiological, inflammatory, and functional attributes. We used the BEST-CT scoring method to systematically describe the abnormalities on chest CT scans of a diverse cohort of 524 patients in the EMBARC BE registry and found great heterogeneity in the nature and extent of SLAs. Notably, the total volume of abnormalities varied greatly, ranging from 5% to nearly 90%. Several clinical characteristics were significantly associated with distinct BEST-CT composite scores.

The two most frequently found lung abnormalities were: *1*) BE without MP and *2*) MP. BE is generally viewed as the result of previous long-term airway inflammation, leading to irreversible structural damage. The presence of MP, on the contrary, is general evidence of active ongoing inflammation. Indeed, MP made the largest contribution to the inflammatory composite score %TInf. It is important to note that the scans included in this analysis were performed during diagnosis and routine follow-up of stable disease. MP can lead to airflow obstruction and impaired lung function, as clearly shown in our data. The accumulation of mucus in the airways is an important part of the aforementioned vicious vortex, increasing the susceptibility to more infections, exacerbations, and further progression of structural lung damage. Importantly, mucus plugs that occlude medium-sized to large airways have been independently associated with lung function and even mortality in COPD, which is another entity among the muco-obstructive lung diseases (17). The significant association we observed between %TInf, in particular, and the number of exacerbations defined by hospital admission supports the notion that this subgroup of patients with BE exhibits a higher level of disease activity and possible clinical sequelae (18). Thus, the radiologic phenotype of BE could help identify these patients and may have consequences for clinical care. Addressing mucus clearance is considered a crucial part of current BE management plans (19, 20). Although previous studies have indeed suggested a crucial role of inflammation in BE, the radiological evidence of MP in the present large cohort of patients with stable BE adds substantial support to this viewpoint (21).

Our study further highlights the significance of infection as a crucial component of the pathophysiology of BE. Patients with a *PsA* isolation had more BE as well as evidence of a greater degree of small airway disease, indicated by more MP. These findings align with previous studies that have demonstrated a correlation between *PsA* colonization in patients with BE and an increased risk of exacerbations, as well as more pronounced SLAs observed on CT scans (11, 12, 22, 23).

Patients who had a confirmed active NTM infection exhibited even more pronounced lung abnormalities on CT scans, with average differences between patients with versus without an NTM infection approximately two to three times greater than between patients with versus without a *PsA* infection. Even though *PsA* was not significantly associated with total inflammatory features, NTM was clearly and significantly associated. These findings corroborate previous research by Faverio and coworkers (24) that also demonstrated that active NTM infections are associated with a greater burden of SLAs compared with *PsA* infections. Interestingly, they did not find these structural abnormalities to be associated with increased disease severity and exacerbations, which contrasts with the trends indicated by our data. The presence of more bronchial wall thickening and BEwMP indicates chronic inflammation and actual remodeling of the bronchial walls, implying a more severe and chronic disease process in patients with NTM infections. Overall, our findings provide additional evidence that NTM isolates in patients with BE are associated with the more severe end of the spectrum of the disease, with evidence of chronic SLAs and active ongoing inflammation, promoting the importance of considering the specific microbial status when assessing disease severity and progression.

An essential part in the diagnostic workup and management of patients with BE is the identification of the underlying etiology and comorbidities (25–27). An

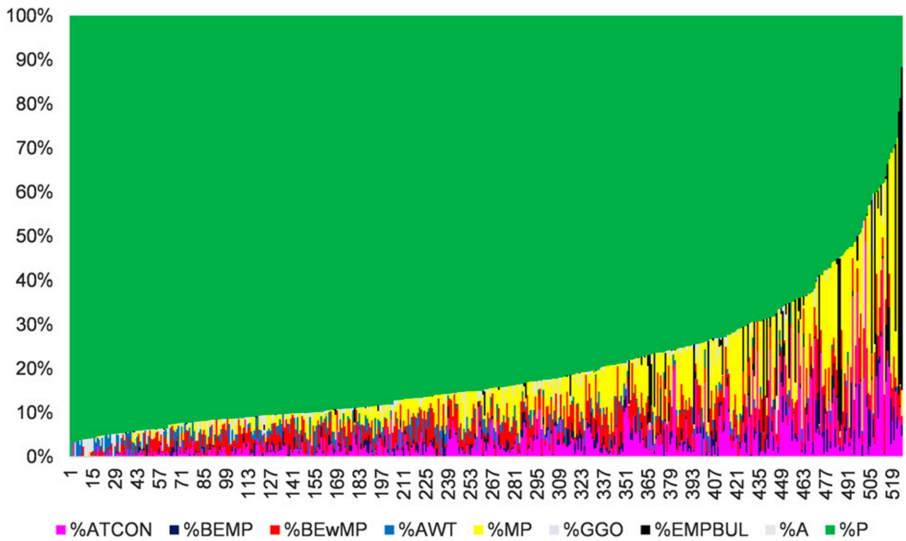

Figure 2. Visual distribution of the EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration) population. This stacked bar chart shows the results of Bronchiectasis Scoring Technique for Computed Tomography (CT) scoring of 524 chest CT scans. Each stacked bar represents the analysis results of one CT scan. Component scores are expressed as percentage of total lung volume and add up to 100% on the *y*-axis. The number of patients is represented on the *x*-axis. Subscores are listed in the order by which they are scored. Patients are sorted based on the total disease score (i.e., the sum of the percentages of atelectasis and/or consolidation, total bronchiectasis, airway wall thickening, mucus plugging, ground-glass opacities, and bullae). A = airway; ATCON = atelectasis and/or consolidation; AWT = airway wall thickening; BEMP = bronchiectasis with mucus plugging; BEwMP = bronchiectasis without mucus plugging; BUL = bullae; GGO = ground-glass opacities; MP = mucus plugging; P = parenchyma.

important finding of our study is the fact that different underlying etiologies were found to associate with some but not all BEST-CT composite scores.

Interestingly, patients with PCD as the cause of BE had significantly more MP and total inflammatory features. This finding is in agreement with a small observational study of Rademacher and coworkers that also showed that patients with PCD tend to have more atelectasis, MP, and a tree-in-bud pattern (28). These findings may be relevant for the selection of patients for more intensive mucus-clearance, antiinflammatory, and/or antibiotic strategies. In contrast to the participants with more signs of active inflammation, those participants with postinfectious etiology and ABPA showed no significant association with total MP or inflammatory scores. This supports the concept of a subgroup of patients with established BE due to a historic episode with infection and inflammation, but with no active ongoing inflammatory disease in the airways. Again, these findings could be important to recognize a phenotype of more stable BE that could, in theory, be managed safely with a less intensive treatment strategy. This is the first study that highlights the potential of CT imaging to identify specific radiologic phenotypes that could possibly be used to improve personalized treatment plans.

The finding that a codiagnosis of asthma and/or COPD is related to a significantly lesser extent of BE is important in light of research on BE and COPD and/or asthma overlap syndromes (29–31). A lower %TBE suggests that the symptoms of these patients could arise predominantly from their small airway disease rather than in the medium-sized and larger airways where BE is typically detected. The increased use of high-resolution CT may reveal previously unnoticed BE in asthma or COPD, with these patients then included as a subgroup with milder radiological abnormalities in the EMBARC registry (32). Whether these patients indeed have less relevant BE and a different response to treatment remains to be determined (31, 33). In a cohort of Czech patients with COPD, as many as 30.5% were found to have BE–COPD overlap syndrome, and a large subgroup of these patients did not have typical BE symptoms (34). Our data did not show any evidence of a difference in this association between male and female subjects. Finally, it can be appreciated that COPD and immunodeficiencies (primary and secondary) were, in fact, associated with fewer structural abnormalities, most notably significantly less total BE.

Our study has several limitations. First, our study is cross-sectional, which does not allow for causal conclusions. Second, the selection of participating centers from the EMBARC network might not be fully representative of all European patients with BE. Even though patient selection within centers was random, minimizing selection bias, the retrospective collection of CT scans performed with nonstandardized scan protocols, non–lung volume–controlled scanning, and different scanner models could lead to misclassification of CT scores. Any inconsistencies in scan quality, however, are likely nondifferential, suggesting our reported associations might be understated. A further limitation is the median time interval of approximately 7 months between the CT scans and enrollment in the EMBARC registry, meaning scans might not align precisely with clinical data timing. This is of particular importance when interpreting the association with clinical characteristics that can vary over time, particularly hospital admissions in the previous year and FEV_1. Indeed, the association between the number of admissions and CT outcomes did appear to be stronger in participants whose clinical data assessment was before or on the date of the CT scan. Although this could suggest that recurrent exacerbations precede the structural lung changes rather than the other way around, we do not have the statistical power or the required longitudinal data to substantiate this claim. Notably, 4% of study participants did not show BE via the BEST-CT score. These patients still can have subtle BE. With the BEST-CT scoring method, 10 random but evenly spaced chest CT slices between the lung apex and base are assessed, so small areas of BE outside of these 10 slices may have been missed. It should, however, also be noted that scoring of BE relies on visual and therefore somewhat subjective estimation by observers. A cutoff ratio between airway and artery diameter of 1.5 or higher is generally recommended for airway widening, and visual estimation is even less sensitive to milder signs of AWT. Future research might use automated, artificial intelligence–driven scoring for accuracy. CT scans annotated as part of this project can aid in developing such automated algorithms

Table 3. Multiple Regression Analysis of BEST-CT

	%TBE Estimate	*P* Value	%TMP Estimate	*P* Value	%TinF Estimate	*P* Value	%DIS Estimate	*P* Value
Model 1								
Age	0.01 (0.00)	0.0018*	0.00 (0.00)	0.17	0.02 (0.00)	<0.0001*	0.02 (0.00)	<0.0001*
Female sex	−0.03 (0.09)	0.72	0.15 (0.15)	0.30	−0.02 (0.14)	0.88	−0.02 (0.14)	0.85
Duration of disease to enrollment		<0.0001*†		<0.0001*†		<0.0001*†		<0.0001*†
0–5 yr	Reference		Reference		Reference		Reference	
5–9 yr	0.19 (0.12)	0.10	0.05 (0.19)	0.80	−0.17 (0.18)	0.35	−0.12 (0.18)	0.51
10-14 yr	0.27 (0.14)	0.06	0.17 (0.23)	0.45	0.11 (0.22)	0.60	0.16 (0.22)	0.46
15-20 yr	0.63 (0.19)	0.0008*	1.12 (0.30)	0.0003*	1.09 (0.29)	0.0002	0.87 (0.29)	0.003*
>20 yr	0.29 (0.13)	0.02*	0.07 (0.20)	0.74	0.07 (0.20)	0.72	0.08 (0.19)	0.68
FEV_1, % predicted	−0.68 (0.16)	0.0007*	−2.37 (0.27)	<0.0001*	−2.60 (0.26)	<0.0001*	−2.46 (0.26)	<0.0001*
Microbiology								
Pseudomonas aeruginosa isolation	0.28 (0.09)	0.002*	0.34 (0.15)	0.02*	0.14 (0.14)	0.31	0.13 (0.14)	0.34
NTM isolation	0.34 (0.12)	0.006*	0.65 (0.20)	0.001*	0.43 (0.19)	0.02*	0.45 (0.19)	0.02*
Smoking status		0.34†		0.82†		0.28†		0.19†
Never	Reference		Reference		Reference		Reference	
Former	0.01 (0.09)	0.89	0.05 (0.15)	0.74	0.12 (0.15)	0.41	0.20 (0.14)	0.17
Current	−0.30 (0.16)	0.06	−0.11 (0.25)	0.66	−0.20 (0.24)	0.42	−0.00 (0.24)	0.99
Hospital admissions		0.50†		0.70†		0.008*†		0.002*†
0	Reference		Reference		Reference		Reference	
1	0.10 (0.10)	0.33	0.12 (0.17)	0.48	0.48 (0.17)	0.004*	0.53 (0.16)	0.001*
⩾2	0.00 (0.19)	0.99	0.23 (0.30)	0.44	0.54 (0.29)	0.06	0.54 (0.29)	0.06
Etiology		<0.0001†*		<0.0001*†		<0.0001*†		0.0003*†
Idiopathic	Reference		Reference		Reference		Reference	
ABPA	0.40 (0.18)	0.03*	0.15 (0.30)	0.62	0.25 (0.28)	0.38	0.29 (0.29)	0.31
Asthma	0.10 (0.23)	0.66	−0.52 (0.37)	0.16	−0.53 (0.35)	0.13	−0.57 (0.35)	0.10
Primary/secondary immunodeficiency	−0.40 (0.17)	0.02*	−0.33 (0.28)	0.24	−0.44 (0.27)	0.10	−0.29 (0.27)	0.29
CTD/RA/IBD	0.10 (0.19)	0.58	−0.15 (0.31)	0.63	0.00 (0.29)	0.98	0.28 (0.30)	0.35
COPD	−0.40 (0.20)	0.05*	−0.56 (0.33)	0.09	−0.46 (0.31)	0.15	−0.11 (0.31)	0.72
NTM	−0.03 (0.21)	0.89	0.53 (0.33)	0.11	0.69 (0.32)	0.03*	0.66 (0.31)	0.04*
Other diseases	−0.05 (0.15)	0.74	−0.04 (0.23)	0.86	0.43 (0.23)	0.06	0.38 (0.22)	0.08
Postinfective	−0.37 (0.12)	0.003*	0.25 (0.20)	0.21	0.15 (0.19)	0.44	−0.03 (0.19)	0.85
PCD	0.26 (0.20)	0.20	0.78 (0.33)	0.02*	0.69 (0.32)	0.03*	0.48 (0.31)	0.12
Codiagnosis of asthma and/or COPD	−0.24 (0.10)	0.01*	−0.19 (0.16)	0.25	−0.26 (0.53)	0.09	−0.26 (0.15)	0.08
Increased blood eosinophil count	−0.00 (0.14)	0.99	0.16 (0.23)	0.47	0.54 (0.29)	0.44	−0.09 (0.21)	0.68
Model 2								
BSI (*n* = 5 missing)	0.05 (0.00)	<0.0001*	0.10 (0.02)	<0.0001*	0.14 (0.02)	<0.0001*	0.13 (0.02)	<0.0001*
Model 3								
FACED (*n* = 2 missing)	0.17 (0.03)	<0.0001*	0.32 (0.04)	<0.0001*	0.42 (0.04)	<0.0001*	0.41 (0.04)	<0.0001*

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BEST-CT = Bronchiectasis Scoring Technique for Computed Tomography; BMI = body mass index; BSI = Bronchiectasis Severity Index; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CTD = connective tissue disease; FACED = FEV_1% predicted, age, chronic colonization by *Pseudomonas aeruginosa*, radiological extent of disease, and dyspnea; IBD = inflammatory bowel disease; NTM = nontuberculous mycobacteria; PCD = primary ciliary dyskinesia; RA = rheumatoid arthritis.

This table shows multivariable linear regression for patient characteristics versus composite BEST-CT scores. Multiple linear regression results are presented as estimates (standard error) and *P* values. A total of 498 patients (model 1) were analyzed in the main multiple linear regression analysis. However, BSI (model 2, *n* = 518) and FACED (model 3, *n* = 492) were put into different models (without their composite scores) to avoid colinearity. Model 1 (main model) consisted of age, duration of disease, sex, underlying etiology, codiagnosis of asthma and/or COPD, smoking status, FEV_1% predicted, *Pseudomonas aeruginosa* infection, NTM infection, hospital admissions, and blood eosinophil count. Model 2 consisted of age, duration of disease, sex, underlying etiology, codiagnosis of asthma and/or COPD, smoking status, blood eosinophil count, and BSI. Model 3 consisted of age, duration of disease, sex, underlying etiology, codiagnosis of asthma and/or COPD, NTM infection, smoking status, blood eosinophil count, and FACED score.

*F-test for overall effects. If the F-test for overall effect was significant, *P* values are reported for multiple linear regression.

†Multivariable linear regression. If the F-test for overall effect was significant, *P* values are reported for multiple linear regression.

using artificial intelligence. Another limitation is the combination of atelectasis and consolidation as one anomaly. It is known that these are two different CT characteristics. Because this was a retrospective study, not all patients were scanned with the use of contrast medium, making it sometimes challenging to distinguish between these two CT features. Finally, it should be noted that, because we investigated the associations between a range of possible predictor variables and structural lung outcomes, there is a chance of risk findings due to multiple testing. No formal correction for multiple testing was performed, which needs to be taken into account in the interpretation of our results.

This study is one of the largest to systematically study the relationship between a variety of radiological abnormalities and clinical phenotypes in a cohort of patients with BE (35). Historically, improved methods to classify and quantify radiological abnormalities like bone fractures and vascular lesions have deepened our understanding of the links between the disease, etiological factors, and patient subgroups (36, 37). For BE, developing objective ways to categorize and measure radiological lung changes can advance our understanding of inflammation and infection mechanisms, lung function impairment, disease progression monitoring, and therapy customization. In this study, we have shown associations between radiological manifestations and patient factors, increasing our understanding of the disease mechanisms in different patient subgroups. Moreover, we have demonstrated the value of a radiological scoring method in a large cohort of patients to demonstrate such associations. In the future, adoption of fully automated scoring systems may further facilitate these investigations. Automated assessment of all bronchi and accompanying arteries has been shown to be sensitive in the detection of airway widening and AWT in CF populations (38, 39), non–CF BE (35), and pediatric asthma. Analysis of the EMBARC cohort using automated analysis is ongoing.

In summary, we conclude that SLAs in patients with BE are heterogeneous and extensive with prominent inflammatory features. Lower FEV_1, *PsA* infection, NTM infection, severe exacerbations, and BE etiology were strongly correlated with the extent of SLAs on chest CT scans. The quantitative BEST-CT outcomes can be used to phenotype SLAs in patients with BE and uncover the relationship between patient characteristics and radiological disease manifestations. ■

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