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Bronchiectasis in Severe Asthma: Does It Make a Difference?

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Keywords
Asthma · Bronchiectasis · Computed tomography · Sputum culture · Phenotype

Abstract
Background: Asthma and bronchiectasis are 2 heterogeneous diseases that frequently coexist, particularly in severe asthma. Recognition of this co-diagnosis may importantly affect treatment decisions and outcome. Previous studies in asthma with bronchiectasis show inconsistent outcomes, probably due to the heterogeneity of the included asthma cohorts. ***Objectives:*** We hypothesized that bronchiectasis contributes to asthma severity and that patients with severe asthma and bronchiectasis present with distinct characteristics resulting in different treatable traits. In addition, we explored whether bronchiectasis in severe asthma is more common in a specific phenotype. ***Methods:*** This is a single-center study consecutively including patients with severe asthma from a tertiary referral center. Severe asthma was diagnosed according to the ATS/ERS guidelines. Asthma and infectious exacerbations were defined by the attending specialist as respiratory symptoms requiring treatment with systemic steroids or antibiotics, respectively. Two independent blinded radiologists evaluated each CT. ***Results:*** 19% of patients with severe asthma showed bronchiectasis on CT. Patients with bronchiectasis had a lower FEV1% predicted (p = 0.02) and FEV1/FVC (p = 0.004) and more infectious exacerbations (p = 0.003) compared to patients without bronchiectasis. Bronchiectasis is more common in patients with a longer duration of asthma, sensitization to *A. fumigatus* or a positive sputum culture. Sputum cultures of patients with severe asthma and bronchiectasis revealed more *P. aeruginosa*, *S. maltophilia*, *H. parainfluenzae,* and *A. fumigates* compared to the non-bronchiectasis group. The adult-onset, eosinophilic asthma phenotype showed the highest prevalence of bronchiectasis (29.4%). ***Conclusions:*** Patients with severe asthma and coexisting bronchiectasis were found to represent a distinct group, in terms of disease severity, microbiology, and asthma phenotype. Performing (HR)CT and sputum cultures can help to identify these patients. These results can possibly contribute to early recognition and targeted treatment of this patient group.

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Introduction

Only a small proportion of asthma patients (<4%) fulfil the criteria of severe asthma [1]. These patients are known to have a high risk of exacerbations, increased health-care utilization, and impaired quality of life [2]. One of the factors known to be associated with severe asthma is the existence of comorbidity [3]. Therefore, the workup of patients with uncontrolled asthma consists of optimal treatment of comorbidities before labelling asthma as severe and refractory.

Bronchiectasis (BE) is a common comorbidity in asthma. Currently, BE is often recognized late during disease in patients with severe asthma. However, treatment adjustments in severe asthma patients may be considered if BE is present, both for maintenance therapy as well as during exacerbations [4–7]. Therefore, for optimal personalized treatment, early diagnosis of BE in severe asthma is important.

Actual numbers about prevalence of BE in asthma vary among studies from <5% in overall asthma populations to 25–40% in uncontrolled or more severe asthma [3, 8–10]. This wide variability may be related to differences in study design or radiological methods used but probably is largely due to the heterogeneity of the included asthma cohorts. This heterogeneity may also underlie the different factors that are identified as associated with the BE coexistence in different asthma cohorts. Data on the presence of BE as comorbidity in truly refractory severe asthma and associated risk factors are scarce. Moreover, since some comorbidities may be more common in specific phenotypes of severe asthma [3], insight into the occurrence of BE in asthma phenotypes might be useful and might contribute to a better knowledge and characterization of BE in severe asthma.

Therefore, in the present study, we assessed the presence of BE in a well-defined group of patients with truly severe asthma and examined the clinical, functional, radiologic, inflammatory, and microbial characteristics associated with BE. In addition, we explored whether BE was more common in a specific severe asthma phenotype.

Materials and Methods

Patients

Patients (>18 years) with severe asthma were consecutively recruited from a tertiary severe asthma referral center in the Netherlands from 2008 to 2018. The diagnosis of asthma was objectively confirmed by a physician based on medical history and 1 or more of the following criteria: significant bronchodilator reversibility, defined as an increase in forced expiratory volume in 1 s (FEV1) of ≥12% and ≥200 mL after bronchodilator therapy or a provocative concentration of methacholine or histamine causing a 20% fall in FEV1 of ≤8 mg/mL or a worsening in FEV1 ≥12% predicted and 200 mL after tapering of medication.

Severe asthma was confirmed, after a systematic assessment with a multidisciplinary team, using the American Thoracic Society (ATS) and European Respiratory Society (ERS) guideline criteria [2]. Patients with a smoking history of ≥15 pack-years were excluded.

Determination of asthma phenotype was based on clinical and inflammatory parameters. Patients were divided into non-eosinophilic, early-onset atopic, or late-onset eosinophilic asthma subphenotypes. The non-eosinophilic phenotype was defined as blood eosinophils $<0.3 \times 10^9$ cells L^{-1} at baseline assessment. If patients had blood eosinophils $\geq 0.3 \times 10^9$ cells L^{-1} and an age of asthma onset ≥18 years, they were considered a late-onset eosinophilic phenotype [11]. The early-onset atopic phenotype was defined as the start of asthma at age <18 years and a positive atopic status (defined as a score of >0.35 kU L^{-1} for at least one of the common aeroallergens [non-aspergillus] tested). This study was performed in accordance with the Declaration of Helsinki, and ethics approval was waived by the Human Research Ethics Committee METC Zuidwest Holland (nr 18-058).

Design

In this single-center retrospective cohort study, all patients were seen by 1 of 2 asthma-specialized respiratory physicians and a respiratory nurse at first consultation. Data on demographics, medical history, comorbidity, health-care utilization, exacerbations, smoking history, and medication use were collected. The Charlson Comorbidity Index, a scoring system assessing presence of multiple comorbidities, was calculated for all patients [12].

The diagnosis of asthma exacerbations and infectious exacerbations was confirmed by the attending specialist. Asthma exacerbations were defined as episodes with worsening of asthma symptoms, requiring treatment with systemic steroids [13]. Infectious exacerbations were defined as respiratory symptoms requiring treatment with antibiotics.

Spirometry [14], fractional exhaled nitric oxide (FeNO) measurement [15], peripheral blood eosinophils, and allergy tests were performed during a stable state at the outpatient clinic. Peripheral blood counts were expressed as absolute numbers. Atopy was defined as a score of >0.35 kU/L for at least one of the specific aeroallergens tested. Specific IgE for *Aspergillus* was additionally tested. Allergic bronchopulmonary aspergillosis (ABPA) was diagnosed following diagnostic criteria proposed by the International Society for Human and Animal Mycology (ISHAM) working group for ABPA [16].

Criteria to select patients for performing a CT scan were set by the attending severe asthma specialist. Depending on symptoms and clinical presentation, additional diagnostic tests such as CT scan or sputum culture were performed. When diagnostic tests had already been performed by referring pulmonologists, these data were used in the assessment. If a patient had received multiple CT scans, the CT scan with the shortest time interval to primary assessment was chosen. However, patients with CT scans, showing BE, performed after primary assessment and during treatment with monoclonal antibodies were excluded (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000511459).

Table 1. Demographics of patients with severe asthma with and without BE

	Total cohort $n = 91$	Severe asthma with BE $n = 17$ (18.7%)	Severe asthma without BE $n = 74$ (81.3%)	p value
Age at primary assessment, year	51.27±15.97	60.82±8.72	49.14±16.46	**<0.001**
Duration of asthma, year	28.83±18.77	39.12±18.62	26.38±18.22	**0.01**
Age of asthma onset, year	22.91±19.92	21.71±18.03	23.28±20.47	0.77
Gender, *n* (%)				
Female	62 (68.1)	12 (70.6)	50 (76.6)	0.81
Male	29 (31.9)	5 (29.4)	24 (32.4)	
Smoking status, *n* (%)				
Never	60 (65.9)	10 (58.8)	50 (67.6)	0.49
Active	5 (5.5)	1 (5.9)	4 (5.4)	
Past	26 (28.6)	6 (35.3)	20 (27)	
Ethnicity, *n* (%)				
Caucasian	74 (81.3)	15 (88.2)	59 (79.7)	0.66
Non-Caucasian	17 (18.7)	2 (11.8)	15 (20.3)	
BMI, kg/m^2	27.68±5.64	26.88±5.04	27.86±5.79	0.98
Charlson Comorbidity Index	0.00 [0.00–1.00]	1.00 [1.00–2.50]	0.00 [0.00–1.00]	**<0.001**

Data are presented as mean ± SD, median [interquartile range] or *n* (%). $p < 0.05$ was considered significant.

Radiology

HRCT was performed on a multidetector computed tomography scanner at a slice thickness of 1 mm from the lung apex to the diaphragm using 1 mm of collimation. CT scans were viewed using Philips Intellispace PACS 4.4 software (Best, the Netherlands). Two independent radiologists blinded to the other research findings evaluated each CT scan. Criteria for BE were defined in accordance with the radiological criteria [9]. The extension of BE was assessed according to modified Reiff et al [17] criteria, resulting in a score between 0 and 18. When the Reiff scores were >2 points different, the cases were re-evaluated by both radiologists and a definite consensus score was given.

Statistical Analysis

Differences between patients with and without BE were analysed using unpaired Student's t test, χ^2 tests, Fisher's exact tests, and nonparametric tests, where appropriate. Baseline characteristics of severe asthma patients without a chest CT were compared with patients with a CT scan performed without BE as a sensitivity analysis. Statistical analyses were carried out using SPSS software version 24 (IBM, Armonk, NY, USA). p values <0.05 were considered statistically significant.

Table 2. Radiologic characteristics of 17 severe asthma patients with BE

Location of BE		
Upper lobes	($n = 14$)	82%
Lingula or middle lobule	($n = 11$)	65%
Lower lobes	($n = 10$)	59%
Bilateral	($n = 11$)	65%
Quantity of lobes involved		
<3	($n = 8$)	47%
≥3	($n = 9$)	53%
Type of BE		
Cylindrical	($n = 7$)	41.2%
Varicose	($n = 10$)	58.8%
Cystic	($n = 6$)	35.3%
Modified Reiff score; mean ± SD	6.88±5.48	

Results

Of the 127 consecutively recruited patients with severe asthma, 22 patients were excluded because of a smoking history of ≥15 pack-years. Of the remaining 105 patients, 14 patients did not have a CT scan at all ($n = 12$) or did not have an adequate timing of the CT scan ($n = 2$) and were, therefore, excluded (online suppl. Fig. 1). The mean time interval between CT scan and primary assessment was 1 ± 1.44 years. There was no difference in baseline characteristics between patients with no clinical suspicion of BE and no CT performed and those with a CT scan confirming the absence of BE.

Most of the 91 patients included in the analysis were female (Table 1). They all used high doses of inhalation corticosteroids (>1,000 μg fluticasone equivalent), and 30% of the patients were on daily oral corticosteroids.

Seventeen out of these 91 (18.7%) patients showed BE with a mean total modified Reiff score of 6.88 ± 5.48. Most

Table 3. Asthma severity parameters in severe asthma patients with and without BE

	Severe asthma with BE $n = 17$ (18.7%)	Severe asthma without BE $n = 74$ (81.3%)	p value
Maintenance systemic corticosteroids at primary assessment, n (%)	6 (35.3)	22 (29.7)	0.68
Mean daily dose systemic corticosteroids, mg	8.33±2.58	9.32±6.08	0.71
Asthma exacerbations, courses of systemic steroids*, ‡	3.00 [2.00–4.50]	3.00 [2.00–4.00]	0.46
Infectious exacerbations, antibiotic courses‡	2.00 [0.00–3.00]	0.00 [0.00–1.00]	**0.003**
Number of hospitalizations‡	1.00 [0.00–2.00]	0.00 [0.00–1.00]	0.16
Post-bronchodilator FEV1% pred	63.94±16.86	76.18±19.95	**0.02**
Post-bronchodilator FEV1/FVC ratio	57.22±10.29	66.29±11.81	**0.004**

Data are presented as mean ± SD, median [interquartile range] or n (%). $p < 0.05$ was considered significant. FEV1, forced expiratory volume in 1 s; % pred, percentage of predicted value. * Minimum of 5 days 30 mg. ‡ In the previous year.

Table 4. Inflammatory parameters in severe asthma patients with and without BE

	Severe asthma with BE $n = 17$ (18.7%)	Severe asthma without BE $n = 74$ (81.3%)	p value
Blood eosinophils, $\times 10^9$/L	0.80 [0.44–1.34]	0.40 [0.25–0.80]	**0.03**
Total IgE, kU/L	199 [47.5–434.5]	215 [65–677]	0.41
Positive atopic status, n (%)	6 (35.3)	50 (67.6)	**0.02**
Sensitized (serum IgE) to Asp. Fumigatus, n (%)	9 (52.9)	14 (20.3)	**0.01**

Data are presented as mean ± SD, median [interquartile range] or n (%). $p < 0.05$ was considered significant.

of the BE were localized in the left upper lobe (70.6% of patients), and most patients had bilateral BE (64.70%). Most BE were of the varicose type (59%). In 90% of the patients, the CT scan showed bronchial wall thickening (Table 2).

Compared to patients without BE, severe asthma patients with BE were older at primary assessment 60.8 versus 49.1 years ($p < 0.001$), had a longer duration of asthma, 39.2 versus 26.4 years ($p = 0.01$), and reported more comorbidities (Table 1). Patients with BE showed more severe disease with more severe airway obstruction, more antibiotic cycles and a tendency to more hospitalizations compared to severe asthma patients without BE (Table 3).

Regarding the inflammatory biomarkers, high levels of blood eosinophil counts were found in both subgroups with significant higher levels in the BE group (0.80 vs. 0.40; $p = 0.028$) (Table 4). Severe asthma patients with BE were less frequently sensitized to the common aeroallergens tested, but showed a higher percentage of sensitization to *A. fumigatus* (53 vs. 20%). The diagnosis of ABPA was confirmed in 2/17 patients with BE and 3/74 patients without BE ($p = 0.23$).

Sputum culture was performed in 47/74 (64%) patients without BE and 17/17 (100%) patients with BE. A total of 88.2% of the patients with severe asthma and BE had 1 or more positive sputum cultures compared to 57.4% of the patients without BE ($p = 0.035$). Sputum cultures of patients with severe asthma and BE revealed more *P. aeruginosa*, *S. maltophilia*, *H. parainfluenzae,* and *A. fumigates* as compared to the non-bronchiectasis group (Fig. 1). When grouping the patients according to their asthma phenotypes, adult-onset eosinophilic asthma was the phenotype with the highest prevalence of BE (29.4%) compared to a prevalence of 12.5% in patients with early-onset atopic asthma and 9.5% in non-eosinophilic asthma (Fig. 2). The difference in prevalence of BE between these 3 asthma phenotypes was not statistically significant ($p = 0.178$).

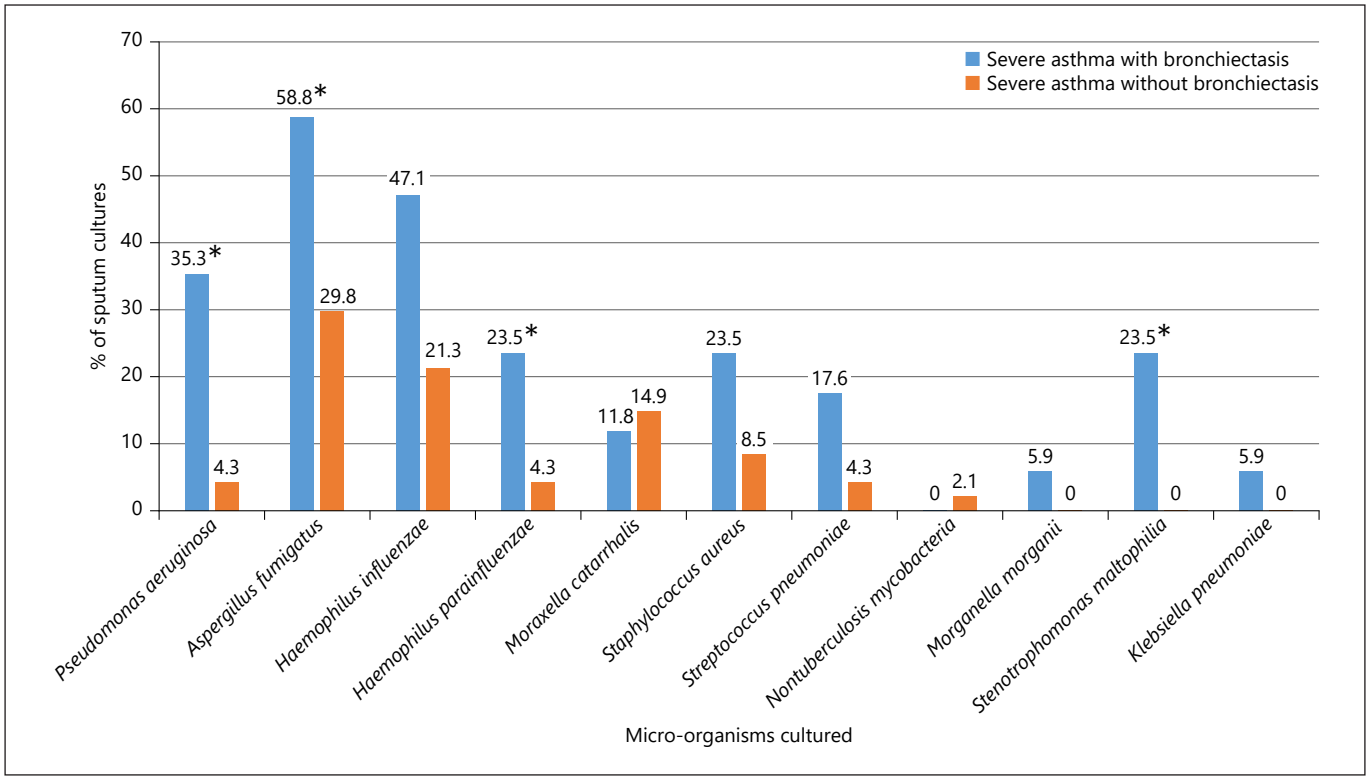

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Fig. 1. Microorganisms isolated in sputum cultures of patients with severe asthma with and without bronchiectasis. * Significant difference between patients with and without bronchiectasis.

Discussion

In an extensively characterized, well-defined severe asthma cohort, the presence of BE is more common in patients with a longer duration of asthma, older age at presentation, and sensitization to *A. fumigatus*. Coexistence of BE in severe asthma is associated with more airway obstruction and a higher amount of blood eosinophils. In addition, these patients show more infectious exacerbations and positive sputum cultures with different pathogens compared to patients with severe asthma without BE. Interestingly, this is the first study to suggest that BE might be more prevalent in a specific inflammatory phenotype of severe asthma, namely, late-onset eosinophilic asthma.

The association between asthma and BE has been studied before. However, previous studies in patients with asthma and BE have included less well-described populations with a less stringent or not up-to-date selection of severe asthma patients or have included past smokers [18–20]. Recently, a prospective study in 398 patients with uncontrolled asthma also found asthma severity to

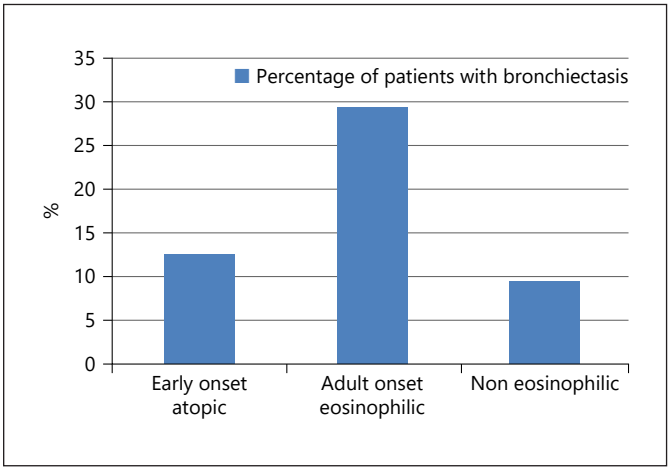

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Fig. 2. Prevalence of bronchiectasis distributed by the different asthma phenotypes (p = 0.178). Phenotypes were defined as follows: eosinophilic: blood eosinophils $\geq 0.3 \times 10^9$/L; adult onset: age ≥18 years at diagnosis; atopy: specific IgE >0.35 kU. L-1 for at least one of the common aero allergens (non-aspergillus) tested. 1 patient not classified.

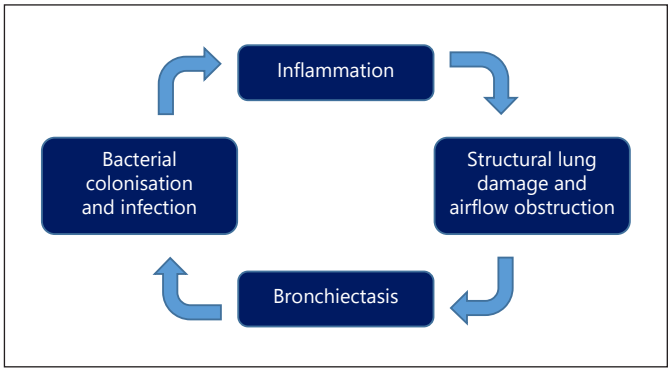

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Fig. 3. Airway inflammation and bronchiectasis.

be one of the factors associated with the presence of BE [18]. Contrary to our study, only 60% of the patients in this study were classified to have severe asthma, and no ERS/ATS criteria for the diagnosis of severe asthma were applied. Notably, no difference in positive sputum cultures was found in this study. This contrasts with our study and what would be expected in patients with clinically relevant BE. In addition, only significant differences in absolute FEV1 and FVC were found in this study and other comparable studies [18, 19]. We demonstrated that patients with severe asthma and BE have more severe airway obstruction, defined by FEV1 in percent of predicted and FEV1/FVC ratio, compared to patients without BE. This is an important finding as poor lung function is known to be associated with poor outcomes in asthma [21].

The prevalence of BE in severe asthma in the current study is 19%. This is lower than that reported in the existing literature (25–40%) [18–20, 22, 23]. One study describing qualitative analysis of HRCT findings in difficult-to-treat asthma found BE in 40% of the patients [24]. Another study found 47% of BE in severe asthma [19]. However, 50% of the patients in that study were smokers, and only 30% were treated according to Global Initiative for Asthma (GINA) step 5, which raises the question whether the inclusion of patients was based on truly severe asthma and COPD patients were excluded. This is important because the prevalence of BE in COPD is known to be higher than that in asthma [25–27]. CT scans performed in patients with BE in the current study showed no obvious signs of emphysema, which suggests COPD was adequately excluded. Differences in prevalence of BE in severe asthma and vice versa may also be country specific. Gao et al. [28] showed significant differences in risk factors for developing BE in different geographical regions. Our study is the first study evaluating patients with severe asthma and BE in The Netherlands.

In the present study, 90% of the patients with severe asthma showed bronchial wall thickening on CT scan. The mean duration of asthma at presentation was 29 years. This is similar to results in previous studies [8, 24] and may imply that a long duration of asthma and chronic inflammation finally will be accompanied by structural airway changes in nearly all patients with severe asthma (Fig. 3). In future diagnostic and treatment strategies for both asthma and COPD, radiologic imaging will be of increasing importance. CT scan in asthma and COPD can be applied not only for detection of coexistent BE but also for differential diagnosis, concomitant skeletal or cardiac diseases, and assessment of air trapping [29, 30]. In light of this, additional studies are needed to investigate if standard performance of CT scan and sputum cultures in patients with severe asthma is cost-effective or performing these tests should be considered on a case-by-case basis.

This study has some limitations. First, not all patients in this cohort underwent a CT scan and therefore had to be excluded. However, this was a small group (13%), and the baseline characteristics of this group did not differ substantially from patients that did not have BE. Therefore, a different outcome in this group is not expected.

Second, sputum culture was performed in 64% of the asthma patients without BE and 100% of the patients with severe asthma and BE. This can be explained by clinicians following current guidelines where sputum culture is part of the standard assessment of patients with BE, but not in patients with severe asthma. Nevertheless, this difference in sputum cultures performed makes it difficult to compare the microbiological data from both groups.

Finally, the difference in prevalence of BE between different asthma phenotypes was not statistically significant. Likely, this is a consequence of insufficient statistical power because of small sample size. Because our absolute percentages were highly suggestive, we suggest that analyzing the prevalence of BE by different asthma phenotypes in larger groups of patients, such as national or international (severe) asthma and BE registries, will be useful.

The strength of this study lies in the extensive characterization of patients, an objectively confirmed diagnosis of severe asthma and BE according to the current guidelines and exclusion of patients with a smoking history. Furthermore, all CT scans were re-evaluated and scored by 2 independent radiologists.

In this study, BE was more prevalent among severe asthma patients with the late-onset eosinophilic phenotype, and patients with severe asthma and BE had significant higher blood eosinophil counts. This is surprising taking into account that according to current insights, BE patients mainly show neutrophilic inflammation [31]. Blood eosinophil counts can be affected by treatment with maintenance corticosteroids and may be increased in ABPA, which is a common comorbidity in patients with severe asthma and BE. In this study, we consider it unlikely that the use of maintenance corticosteroids was of influence on the results, mainly the difference in eosinophil counts found. This is supported by the fact that there was no difference in treatment with maintenance corticosteroids and coexisting ABPA between both groups.

Eosinophilic inflammation is an important predictor of responsiveness to steroids and new treatments for severe asthma with monoclonal antibodies [32]. Our finding raises the question whether eosinophilic inflammation in severe asthma with BE is the same phenomenon and has the same therapeutic consequences as in severe asthma without BE.

Regarding the fast progress in development of new therapies for severe asthma and the development of more and better biomarkers for phenotyping of disease and optimizing therapy [33, 34], it is relevant to better understand how these findings should be applied with respect to patients with overlap of chronic airway diseases. Future research is needed to evaluate the effect of coexisting BE on responses to biological and other add-on treatment in severe asthma. This applies not only to maintenance treatment but also treatment of exacerbations should be more personalized in this group of patients. This is illustrated by a recent study of Stefan et al. [7]. They reported that antibiotic treatment for patients hospitalized with an asthma exacerbation may be associated with adverse outcomes. To the contrary, antibiotics are the mainstay of treatment of infectious exacerbations in BE. Therefore, characterization of exacerbations in patients with both severe asthma and BE is important in guiding treatment.

The results of this study may have implications for clinical care of patients with severe asthma. Some factors we found to be associated with BE coexistence, like poor pulmonary function and positive sputum culture with pseudomonas and sensitization for *A. fumigatus,* are known to be associated with poor outcomes in severe asthma [21, 23, 35]. This makes early recognition relevant. Moreover, both severe asthma and BE are associated with a substantial financial burden [36, 37]. Early recognition and appropriate treatment of BE in severe asthma patients may reduce health-care costs.

The strong association of BE with positive sputum cultures and antibiotic consumption, found in this study, is consistent with clinically relevant BE. Data on sputum cultures are often missing in earlier studies [20, 24], whereas in current guidelines, clinically significant disease in BE is defined as radiologic abnormalities associated with symptoms of persistent or recurrent infections [35]. BE severity in general is nowadays expressed by one of the available scoring systems [38, 39]. By the absence of Medical Research Council (MRC) dyspnoea scale results, we are not able to give exact severity scores; but based on the current results with respect to the extent of BE, microbiology, exacerbation frequency, and pulmonary function, a large percentage of our cohort appears to qualify as moderate or severe BE which importantly affects prognosis and morbidity.

Although the current guidelines stimulate analysis and reduction of comorbidities prior to making the diagnosis of severe asthma, HRCT and sputum cultures that could help to identify patients with BE as a comorbidity are not yet included in the standard assessment of severe asthma. Based on our results, performing sputum cultures and HRCT in every severe asthma patient during primary assessment could help in early recognition of BE.

In conclusion, patients with concurrent BE were found to represent a distinct group within patients with severe asthma, in terms of disease severity, asthma phenotype, and possible outcome. Increased awareness of this co-diagnosis may contribute to early recognition and targeted treatment of this patient group which will improve disease outcome.

Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki, and ethics approval was waived by the Human Research Ethics Committee METC Zuidwest Holland (nr 18-058). This study protocol was approved by the institute's committee on human research.

Conflict of Interest Statement

The authors who took part in this study declare that they have not received any financial support or other benefits from commercial sources for the work reported in this manuscript nor do they have any financial interest which could create a potential conflict of interest. All authors read and approved the final manuscript.

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Author Contributions

Sarah Bendien: conceptualization-lead, data curation-equal, formal analysis-lead, investigation-lead, methodology-lLead, and writing-original draft-lead. Stephanie van Loon-Kooij: data curation-lead, formal analysis-supporting, writing-review, and editing-supporting. Gerdien Kramer: data curation-supporting, investigation-supporting, software-supporting, writing-review, and editing-supporting. Willemijn Huijgen: data curation-supporting, software-supporting, writing-original draft-supporting, writing-review, and editing-supporting, Josje Altenburg: writing-original draft-supporting, writing-review, and editing-supporting. Anneke ten Brinke: conceptualization-supporting, methodology-supporting, supervision-supporting, writing-original draft-supporting, writing-review, and editing-supporting. Anke-Hilse Maitland-van der Zee: conceptualization-supporting, formal analysis-supporting, investigation-supporting, methodology-supporting, supervision-lead, writing-original draft-supporting, writing-review, and editing-supporting.

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