Bronchiectasis and asthma: Data from the European Bronchiectasis Registry (EMBARC)

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Background: Asthma is commonly reported in patients with a diagnosis of bronchiectasis.

Objective: The aim of this study was to evaluate whether patients with bronchiectasis and asthma (BE+A) had a different clinical phenotype and different outcomes compared with patients with bronchiectasis without concomitant asthma.

Methods: A prospective observational pan-European registry (European Multicentre Bronchiectasis Audit and Research Collaboration) enrolled patients across 28 countries. Adult patients with computed tomography–confirmed bronchiectasis were reviewed at baseline and annual follow-up visits using an electronic case report form. Asthma was diagnosed by the local investigator. Follow-up data were used to explore differences in exacerbation frequency between groups using a negative binomial regression model. Survival analysis used Cox proportional hazards regression.

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Results: Of 16,963 patients with bronchiectasis included for analysis, 5,267 (31.0%) had investigator-reported asthma. Patients with BE+A were younger, were more likely to be female and never smokers, and had a higher body mass index than patients with bronchiectasis without asthma. BE+A was associated with a higher prevalence of rhinosinusitis and nasal polyps as well as eosinophilia and *Aspergillus* sensitization. BE+A had similar microbiology but significantly lower severity of disease using the bronchiectasis severity index. Patients with BE+A were at increased risk of exacerbation after adjustment for disease severity and multiple confounders. Inhaled corticosteroid (ICS) use was associated with reduced mortality in patients with BE+A (adjusted hazard ratio 0.78, 95% CI 0.63-0.95) and reduced risk of hospitalization (rate ratio 0.67, 95% CI 0.67-0.86) compared with control subjects without asthma and not receiving ICSs.
Conclusions: BE+A was common and was associated with an increased risk of exacerbations and improved outcomes with ICS use. Unexpectedly we identified significantly lower mortality in patients with BE+A. (J Allergy Clin Immunol 2024;■■■:■■■-■■■.)

Key words: *Asthma, registry, eosinophils, exacerbations*

Asthma is characterized by the Global INitiative for Asthma as a heterogeneous disease that is usually characterized by chronic airway inflammation.[1,2] It is defined by "the history of respiratory symptoms (eg, wheeze, shortness of breath, chest tightness, and cough) that vary over time and in intensity, together with variable expiratory airflow limitation."[1] The most recent update of the Global INitiative for Asthma guidelines recognizes that asthma is an umbrella term, with multiple different subtypes of disease that have different mechanisms and inflammatory endotypes.[1] Bronchiectasis is a recognized complication of asthma and has been reported on high-resolution computed tomography (CT) scan in up to 50% of patients with severe asthma.[3-5] However, bronchiectasis is also regarded as a separate disease with a different definition and diagnostic criteria.[6] Diagnostic overlap is encountered because patients with a primary diagnosis of bronchiectasis have chronic airway inflammation and similar respiratory symptoms and may present with airflow obstruction.[7] Bronchiectasis has historically been regarded as a neutrophilic disorder, whereas asthma has been associated with predominantly eosinophilic inflammation.[8,9] The recognition of neutrophilic subtypes of asthma and eosinophilic subtypes of bronchiectasis further complicates the distinction between these conditions.[8,10] Allergic bronchopulmonary aspergillosis (ABPA) is a classic example of the way in which asthma and T_H2-driven inflammation can cause, or worsen, bronchiectasis, as ABPA is associated with thick tenacious sputum, exacerbations, and worsening lung function as well as radiologic bronchiectasis.[11] Patients with bronchiectasis without a diagnosis of asthma frequently have sensitization to environmental allergens and elevated markers of T_H2 inflammation, and these have been linked to an increased risk of exacerbations.[8,12]

Patients with underlying asthma are frequently excluded from bronchiectasis trials, and thus there is an absence of published data on the clinical characteristics and outcomes in this group. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) registry has prospectively enrolled a broad, representative population of patients with CT-confirmed bronchiectasis from across Europe.[13] Using the EMBARC registry, we investigated whether there are distinct clinical features and/or outcomes in patients bronchiectasis and asthma (BE+A) as well as the frequency of elevated eosinophils, IgE, and other biomarkers measured during routine clinical practice.

Abbreviations used

ABPA:	Allergic bronchopulmonary aspergillosis
BE+A:	Bronchiectasis and asthma
BSI:	Bronchiectasis severity index
COPD:	Chronic obstructive pulmonary disease
CT:	Computed tomography
EMBARC:	European Multicentre Bronchiectasis Audit and Research Collaboration
ICS:	Inhaled corticosteroid
IRR:	Incident rate ratio

METHODS

The EMBARC registry is a prospective observational study of patients with a clinical history consistent with bronchiectasis confirmed by CT conducted across more than 28 countries worldwide.[14] The registry includes European and non-European countries. The study is approved by the ethical committee in the host country (United Kingdom) and by institutional review boards or ethics committees in all countries and regions in which the study is conducted. A detailed protocol of the study has been previously published, as have detailed baseline characteristics.[13,14]

Data collection

Patient enrollment began in January 2015, and patients enrolled up to April 2022 were included for the purposes of this analysis. Patient data were collected annually using a standardized case report form. Comprehensive clinical data incorporating demographics, comorbidities, medications, etiologic testing, microbiology, radiology, lung function, and disease history were recorded. Etiology was recorded by the local investigator and verified using data on results of etiologic testing. Data on clinically indicated sputum samples sent during clinical stability and exacerbation were collected, and patients were classified according to whether they had isolated specific bacteria in any sample in the previous 12 months. Spirometry was performed at baseline and at each follow-up visit according to American Thoracic Society/European Respiratory Society standards. For the primary analysis, predicted values and percentage of predicted values were calculated using European Community of Coal and Steel reference equations.[15] Radiologic severity was evaluated in the patient's most recent CT scan using the modified Reiff score as previously described.[16] Disease severity was evaluated using the bronchiectasis severity index (BSI) with a sensitivity analysis performed using the FACED score (including FEV_1, age, chronic colonization by *Pseudomonas aeruginosa*, radiologic extension [number of pulmonary lobes affected], and dyspnea).[17] Exacerbations were defined as use of antibiotics for acute respiratory symptoms and were recorded from a combination of patient history, hospital, and prescription records.[18] Symptoms

were evaluated using the Quality of Life Bronchiectasis questionnaire version 3.1 using validated translations.[19] European countries were grouped into regions according to the EuroVoc classification, with the United Kingdom considered separately due to high recruitment rates.

Asthma diagnosis and related biomarkers

Asthma diagnosis was recorded in 2 fields within the EMBARC dataset. Asthma could be reported as an etiology of bronchiectasis (in the opinion of the investigator) or as a comorbidity. The diagnosis of asthma was exclusively based on the clinical report of the investigator responsible for the case report form, and no specific tests were requested to confirm the diagnosis of asthma. For the purposes of analysis, the primary comparison was between patients with any diagnosis of asthma (etiology or comorbidity), but a comparison of patients with bronchiectasis as an etiology is also presented. Clinician-reported ABPA was also recorded and compared between patients with and without a diagnosis of asthma. Associated biomarkers were eosinophil counts, total IgE, and specific IgE to *Aspergillus*. Blood eosinophil counts were considered elevated when categorized above the local laboratory reference range. Total IgE was categorized as <150 IU/mL, 150 to 300 IU/mL, 300 to 500 IU/mL, 500 to 750 IU/mL, 750 to 999 IU/mL, 1000 to 2000 IU/mL, and >2000 IU/mL). Specific IgE to *Aspergillus* and *Aspergillus* skin test were recorded as elevated/positive or not elevated/negative in relation to the local laboratory reference ranges. ABPA was diagnosed using the International Society for Human and Animal Mycology criteria.[20]

Long-term clinical outcomes

Data are collected for up to 5 years on an annual basis for calculation of clinical outcomes. Since patient enrollment began in 2015, patients have up to 5 years of follow-up at the time of writing, although the dataset includes patients enrolled through to 2021/2022 who have not yet had a follow-up visit. Statistical analysis of relevant end points takes into account the duration of follow-up. Relevant clinical outcomes were survival, exacerbation frequency, and risk of hospitalization due to severe exacerbations.

Statistical analysis

Summary data are presented as median with interquartile range. Comparisons of 2 groups used the 2-sample *t* test with comparisons of more than 2 groups performed using ANOVA. Proportions were compared using the χ^2 test or Fisher exact test if any cell contained a value less than 10. Given the large sample size of the EMBARC registry, statistically significant differences may be observed where clinically significant differences are not evident. Therefore, throughout this article, *P* values are used only where they aid interpretation of the data as previously described.[13] In view of the number of comparisons performed, *P* values should be interpreted with caution. Exacerbation frequency and frequency of severe exacerbations requiring hospital admission over time were studied using a negative binomial regression model with time in study as an offset. Survival analysis was performed using Cox proportional hazards regression. Two forms of adjusted analysis were performed to investigate the impact of confounders on the relationship between concomitant asthma and outcomes. The adjusted analysis included covariates of sex and BSI score (which incorporates 9 clinical variables). The fully adjusted analysis incorporates individual covariates age, sex, smoking status, cardiovascular disease, diabetes, COPD, radiologic severity using the Reiff score, inhaled corticosteroid (ICS) use, long-acting β-agonist and macrolide use, *P aeruginosa* infection, and country. Variables were selected based on clinical relevance. IBM SPSS version 27 (IBM Corp, Armonk, NY) or GraphPad Prism version 9 (GraphPad Software, Boston, Mass) were used for all analyses.

RESULTS

Of 16,963 patients with bronchiectasis included for analysis, 5,267 patients (31.0%) had investigator-reported asthma. The patients with clinician-reported asthma were significantly younger (median age, 66 vs 68 years), were more likely to be female (63% vs 60%), were more likely to be never smokers (59% vs 51%), and had a higher body mass index than patients without asthma (body mass index, 25.8 vs 24.4) (Table I). Comorbidities were markedly different with a higher frequency of rhinosinusitis and nasal polyps reported in patients with BE+A. Patients with BE+A had similar lung function but received a number of treatments more frequently; these included, as expected, a higher use of ICSs and bronchodilators, but also a higher usage of airway clearance, macrolide antibiotics, and any prophylactic antibiotics compared with patients with bronchiectasis without asthma (Table I). Similar results were observed when limiting the control population to subjects with idiopathic bronchiectasis without asthma (see Table E1 in this article's Online Repository at www.jacionline.org).

In terms of treatments, 19.7% of patients with a recorded diagnosis of asthma were not taking a regular ICS. Only 387 (7.3%) patients were taking ICSs without an additional treatment. The remaining patients were taking ICSs with at least 1 additional controller medication. There were 410 (7.8%) patients taking oral corticosteroids long term and 58 (1.1%) patients taking monoclonal antibodies at baseline.

Asthma was recorded as the underlying cause of bronchiectasis in 1165 patients (6.9%). Table E2 (in the Online Repository at www.jacionline.org) shows the comparisons between asthma-related bronchiectasis, idiopathic bronchiectasis, and bronchiectasis due to other causes.

Severity of disease in BE+A

Patients with concomitant asthma had similar etiologies to patients without asthma. Fig 1, *A*, shows the distribution of etiologies. Idiopathic and postinfective disease was the most common etiology regardless of whether or not patients had concomitant asthma.

Microbiology was also highly similar between the groups (Fig 1, *B*), with no significant difference in the frequency of *P aeruginosa* detection, but a higher frequency of *Haemophilus influenzae* ($P < .0001$), *Moraxella catarrhalis* ($P < .0001$), and *Streptococcus pneumoniae* ($P < .0001$) in patients with asthma. Using the Quality of Life-Bronchiectasis questionnaire, patients with concomitant asthma had more severe respiratory symptoms (mean difference 5.2 points, 95% CI 4.3-6.1, $P < .0001$). The above characteristics suggested that patients with asthma may

TABLE I. Baseline characteristics of patients included in the EMBARC registry according to the presence of coexisting asthma

Variables	Bronchiectasis with asthma (n = 5,267)	Bronchiectasis without asthma (n = 11,696)	*P* value
Demographics			
Age (y), median (IQR)	66 (55-73)	68 (58-75)	< .0001
Sex, female, no. (%)	3,316 (63.0)	7,019 (60.0)	< .0001
Race, no. (%)			
White	4,830 (91.7)	10,625 (90.8)	< .0001
Asian	130 (2.5)	233 (2.0)	
Black	56 (1.1)	79 (0.7)	
Mixed/other	68 (1.3)	218 (1.9)	
Not reported	183 (3.5)	541 (4.6)	
BMI, median (IQR)	25.8 (22.7-29.8)	24.4 (21.4-28.1)	< .0001
Smoking status, no. (%)			
Never smokers	3,105 (59.0)	5,991 (51.2)	< .0001
Ex-smokers	1,929 (36.6)	4,856 (41.5)	
Current smokers	233 (4.4)	849 (7.3)	
Comorbidity, no. (%)			
Cardiovascular disorders	1,541 (29.3)	3,968 (33.9)	< .0001
Stroke	192 (3.6)	408 (3.5)	.61
Diabetes	591 (11.2)	1,133 (9.7)	.002
Chronic renal failure	153 (2.9)	514 (4.4)	< .0001
Rhinosinusitis	1,433 (27.2)	2,044 (17.5)	< .0001
Nasal polyps	661 (12.5)	562 (4.8)	< .0001
COPD	1,165 (22.1)	3,159 (27.0)	< .0001
Osteoporosis	801 (15.2)	1,427 (12.2)	< .0001
Depression	785 (16.6)	1,502 (12.8)	< .0001
GERD	2,363 (44.8)	4,232 (36.2)	< .0001
Solid tumor	482 (9.2)	1,381 (11.8)	< .0001
Lung function, median (IQR)			
FEV_1 (L)	1.78 (1.26-2.37)	1.79 (1.26-2.38)	.92
FEV_1 (% predicted)	75.7 (55.8-95.0)	77.4 (56.1-97.6)	.57
FVC (L)	2.69 (2.08-3.42)	2.63 (2.03-3.31)	< .0001
FVC (% predicted)	92.4 (75.9-107.6)	90.8 (72.7-107.8)	< .0001
GOLD FEV_1 categories, no. (%)			
>80% predicted	2,041 (38.8)	4,510 (38.6)	< .0001
50%-79% predicted	1,796 (34.1)	3,549 (30.3)	
30%-49% predicted	744 (14.1)	1,561 (13.3)	
<30% predicted	162 (3.1)	448 (3.8)	
Missing	524 (9.9)	1,638 (14.0)	
Clinical status			
Sputum volume (mL/day), median (IQR)	7 (0-20)	6 (0-20)	.056
mMRC Dyspnoea Scale, no. (%)			
0	1,181 (22.4)	3,250 (27.8)	< .0001
1	1,774 (33.7)	3,787 (32.4)	
2	1,245 (23.6)	2,410 (20.6)	
3	703 (13.3)	1,488 (12.7)	
4	301 (5.7)	589 (5.0)	
Treatment, no. (%)			
Regular airway clearance	3,002 (57.0)	5,737 (49.1)	< .0001
Long-term macrolide treatment	1,068 (20.3)	1,872 (16.0)	< .0001
Inhaled antibiotic treatment	375 (7.1)	935 (8.0)	.048
Other oral antibiotic prophylaxis	312 (5.9)	482 (4.1)	< .0001
Inhaled corticosteroids	4,231 (80.3)	4,469 (38.2)	< .0001
Long-acting β-agonist	3,899 (74.0)	4,733 (40.5)	< .0001
Long-acting muscarinic antagonist	1,605 (30.5)	3,102 (26.5)	< .0001
Long-term oxygen therapy	220 (4.2)	780 (6.7)	< .0001
Noninvasive ventilation	113 (2.1)	237 (2.0)	.61
Oral theophylline	261 (5.0)	222 (1.9)	< .0001
Leukotriene receptor antagonist	844 (16.0)	163 (1.4)	< .0001
Oral corticosteroids	410 (7.8)	380 (3.2)	< .0001
Monoclonal antibodies	58 (1.1)	10 (0.09)	< .0001

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease; *FVC*, forced vital capacity; *GERD*, gastroesophageal reflux disease; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease; *IQR*, interquartile range; *mMRC*, modified Medical Research Council.

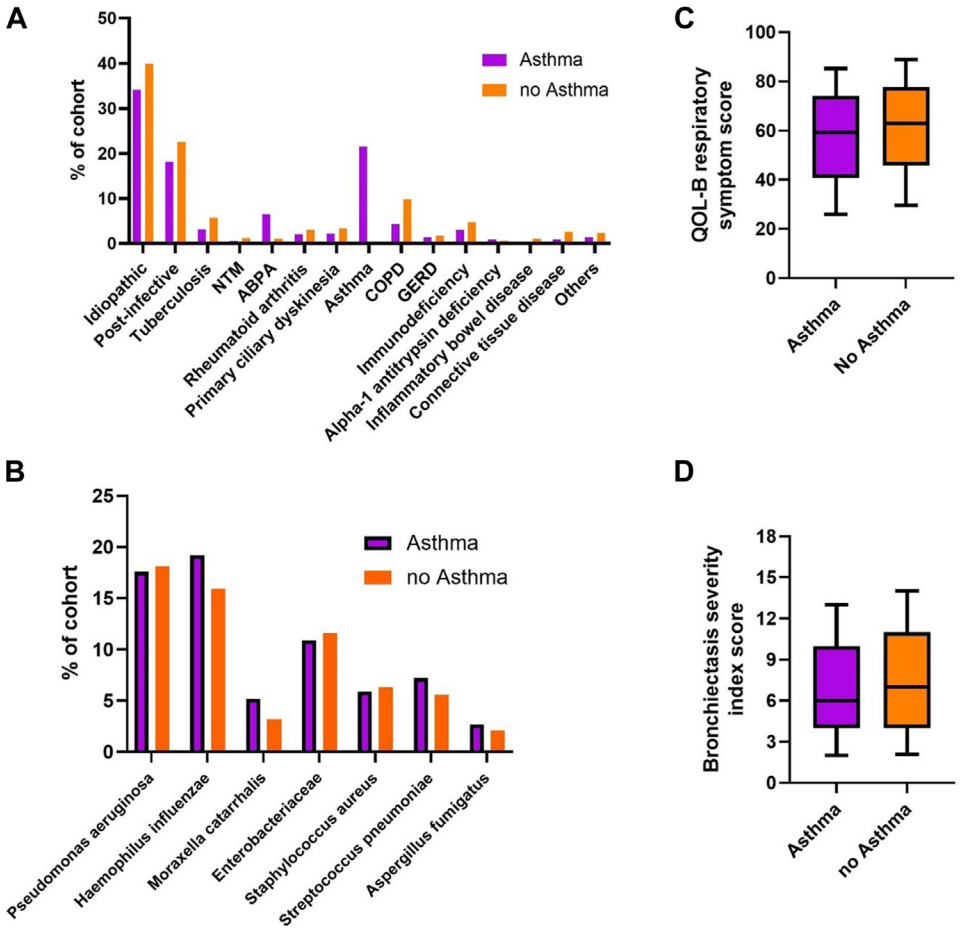

FIG 1. **(A)** Etiology in patients with and without asthma as a concomitant diagnosis. **(B)** Microbiology in patients with and without asthma as a coexisting diagnosis (microbiology refers to any isolation of this pathogen in sputum or bronchoalveolar lavage in the year before the first registry visit). **(C)** Respiratory symptoms measured using the Quality of Life-Bronchiectasis questionnaire. Data are shown as median with interquartile range *(boxes)* and 10% to 90% percentiles *(whiskers)*. **(D)** Bronchiectasis severity index. Data are shown as median with interquartile range *(boxes)* and 10% to 90% percentiles *(whiskers)*. *GERD,* Gastroesophageal disease; *NTM,* nontuberculous mycobacteria.

have more severe disease, as they are receiving more treatments and more often had rhinosinusitis and worse symptoms as well as lower Quality of Life-Bronchiectasis questionnaire scores. Nevertheless, this was not evident in the analysis of severity of disease using multidimensional scoring. In fact, the BSI score was significantly lower in patients with asthma compared with patients without coexisting asthma ($P < .0001$), suggesting lower disease severity (Fig 1, *D*).

The prevalence of asthma among patients with bronchiectasis across different European countries was variable, ranging from 8.6% in all patients with bronchiectasis in North Macedonia to 68.8% in the patients from Finland (Fig E1 in the Online Repository at www.jacionline.org). In general, the prevalence of asthma was higher in the United Kingdom (n = 3208, 39.3%) and Northern and Western Europe (n = 1046, 30.4%) compared with Southern (n = 811, 18.9%) and Central/Eastern Europe (n = 202, 19.0%) ($P < .0001$ comparing North/Western Europe vs Southern Europe and Eastern Europe, respectively).

ABPA and biologic data

Data were available for eosinophils for 3456 (65.6%) patients with asthma and 6025 (51.5%) patients without asthma, indicating that testing for these variables was highly skewed toward patients with asthma ($P < .0001$). Eosinophil counts above the local laboratory threshold was significantly more common in patients with asthma than in patients without asthma (20.5% vs 8.1%). Likewise, elevated IgE (23% vs 8%) and *Aspergillus* sensitization (30% vs 10%) were also more common in asthma. Nevertheless, elevated eosinophils, IgE, and *Aspergillus* sensitization were still commonly reported in patients without asthma (Table II).

Exacerbations

In the 12 months before the baseline visit, 4163 (24.5%) patients had 0 exacerbations, 3163 (18.6%) had 1 exacerbation, 3053 (18.0%) had 2 exacerbations, and 6584 (38.8%) had 3 or more exacerbations per year. There were 4483 (26.4%) patients

TABLE II. Testing for eosinophils, IgE, and IgE to *Aspergillus*

Parameter	Asthma with bronchiectasis	Bronchiectasis without asthma	*P* value
Any test performed	3456	6025	
Elevated peripheral eosinophil count, n/N (%)	574/2804 (20.5%)	433/5441 (8.0%)	< .0001
IgE groups	2755	5135	
<150	1837 (66.7%)	4361 (84.9%)	< .0001
150-300	279 (10.1%)	351 (6.8%)	
301-500	193 (7.0%)	169 (3.3%)	
501-750	122 (4.4%)	76 (1.5%)	
751-1000	71 (2.6%)	53 (1.0%)	
1000-2000	121 (4.4%)	68 (1.3%)	
>2000	132 (4.8%)	57 (1.1%)	
Raised specific IgE to *Aspergillus*	697/2337 (29.8%)	413/4028 (10.3%)	< .0001
Diagnostic criteria for ABPA at baseline	265 (7.7%)	103 (1.7%)	< .0001

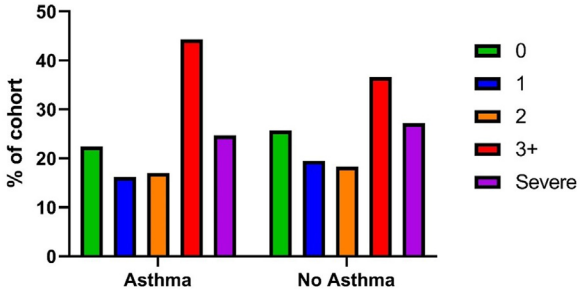

FIG 2. Proportion of patients experiencing exacerbations in the 12 months before the first registry visit.

with at least 1 hospitalization for severe exacerbations in the previous year. Patients with concomitant asthma were more likely to experience ≥3 exacerbations in the year before the study (44.3% vs 36.6%, $P < .0001$). The overall distribution of exacerbations is shown in Fig 2.

Long-term clinical outcomes

We analyzed the relationship between asthma and clinical outcomes in terms of exacerbations, hospitalization for severe exacerbations, and mortality over a maximum of 5 years of follow-up. In total, median follow-up time was similar between subjects with asthma and without asthma (median 1198 days vs 1114 days).

In the unadjusted analysis, asthma diagnosis was associated with a significantly increased risk of exacerbations and hospitalizations for severe exacerbations (Table III). These relationships persisted after adjustment for BSI and sex. Only the relationship between asthma and exacerbations remained significant after full adjustment, including clinical, demographic, and treatment parameters. In all analyses, patients with asthma had reduced mortality. The unadjusted analysis suggested a 27% lower hazard, which persisted with a hazard ratio of 0.77 (95% CI 0.65-0.93) in the fully adjusted analysis.

We analyzed whether the higher frequency of exacerbations could be explained by eosinophilia, IgE, or *Aspergillus* sensitization. Although *Aspergillus* sensitization was associated with exacerbations in the unadjusted analysis, this did not persist after multivariable adjustment. There was no significant relationship between elevated peripheral eosinophil count and exacerbations. There was a weak relationship between elevated IgE and increased exacerbations ($P = .03$) (Table E3 in the Online Repository at www.jacionline.org), which persisted after multivariate adjustment.

As ICS use is known to have a strong influence on outcomes for patients with asthma, the relationship between asthma and outcomes was analyzed in subgroups of patients based on ICS use at baseline. These results showed a clear association between asthma and reduced mortality in the fully adjusted analysis only if patients were also receiving ICSs (hazard ratio 0.78, 95% CI 0.63-0.95) (Table IV). ICS use in patients without asthma was associated with increased mortality in unadjusted analysis, but this relationship was not significant after adjustment. In the fully adjusted analysis, ICS use was associated with reduced risk of hospitalization in both patients with asthma (incident rate ratio [IRR] 0.67, 95% CI 0.67-0.86) and patients without asthma (IRR 0.87, 95% CI 0.77-0.98), while patients with asthma who were not treated with ICS were at increased risk of hospitalization (IRR 1.37, 95% CI 1.16-1.61). For all analyses, the patients without asthma and not treated with ICSs comprised the comparator group. There were no strong relationships between these groups and exacerbation rates in the fully adjusted analysis (Table IV).

DISCUSSION

Asthma is a common comorbidity in patients with bronchiectasis, but few large studies have explored the clinical implications of this overlap. Our data originate from the largest cohort of patients with asthma and bronchiectasis reported to date to our knowledge. Our findings suggest that patients with BE+A have worse symptoms and more frequent exacerbations compared with patients with bronchiectasis who do not have comorbid asthma. Asthma can be a cause of bronchiectasis, but in the majority of cases alternative causes, including idiopathic bronchiectasis, were reported, suggesting that asthma was considered a coexisting condition. The geographic variation we observed, with higher prevalence of coexisting asthma diagnosis in Northern Europe, is consistent with the known epidemiology of asthma, which is more common in Northern and Western Europe.[21] Nevertheless, another potential factor that could influence the prevalence of reported asthma could be the rate of tests being performed to investigate the presence of this condition across different countries.

TABLE III. Relationship between asthma and clinical outcomes in bronchiectasis patients

Outcome	Unadjusted	Adjusted*	Fully adjusted†
Exacerbations	1.24 (1.18-1.29)	1.26 (1.21-1.32)	1.07 (1.02-1.12)
Hospitalizations	1.09 (1.02-1.16)	1.18 (1.10-1.27)	1.07 (0.99-1.16)
Mortality	0.71 (0.62-0.82)	0.75 (0.66-0.86)	0.77 (0.67-0.89)

Exacerbation and hospitalization frequency were analyzed using a negative binomial model, with data presented as rate ratios with 95% CIs. Mortality was analyzed using the Cox proportional hazards regression model, with data presented as hazard ratios with 95% CIs.
*Adjusted for BSI and sex.
†Adjusted for age, sex, smoking, cardiovascular disease, diabetes, COPD, radiologic severity, ICS use, long-acting β-agonists, macrolide use, *P aeruginosa* infection, and country.

TABLE IV. Relationship between reported asthma and clinical outcomes during follow-up

	Unadjusted	Adjusted*	Fully adjusted†
Mortality			
Asthma/ICS use	0.87 (0.73-1.03)	0.76 (0.64-0.90)	0.78 (0.63-0.95)
Asthma/no ICS use	1.09 (0.82-1.44)	1.00 (0.76-1.33)	1.08 (0.81-1.43)
No asthma/ICS use	1.63 (1.41-1.89)	1.12 (0.97-1.30)	1.00 (0.84-1.22)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)
Hospitalizations			
Asthma/ICS use	1.02 (0.92-1.12)	0.92 (0.83-1.02)	0.67 (0.67-0.86)
Asthma/no ICS use	1.53 (1.31-1.78)	1.32 (1.12-1.56)	1.37 (1.16-1.61)
No asthma/ICS use	1.56 (1.42-1.72)	1.01 (0.91-1.02)	0.87 (0.77-0.98)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)
Exacerbations			
Asthma/ICS use	1.24 (1.17-1.32)	1.10 (0.99-1.23)	1.00 (0.92-1.09)
Asthma/no ICS use	1.16 (1.04-1.29)	1.19 (1.11-1.27)	1.08 (0.97-1.21)
No asthma/ICS use	1.38 (1.29-1.47)	1.16 (1.09-1.24)	1.02 (0.94-1.10)
No asthma/no ICS use	1.00 (reference)	1.00 (reference)	1.00 (reference)

Mortality was analyzed using the Cox proportional hazards regression model, with data presented as hazard ratios with 95% CIs. Hospitalization and exacerbation frequency were analyzed using a negative binomial model, with data presented as rate ratios with 95% CIs.
*Adjusted for BSI and sex.
†Adjusted for age, sex, smoking, cardiovascular disease, diabetes, COPD, radiologic severity, long-acting β-agonists, macrolide use, *P aeruginosa* infection, and country.

Patients with BE+A experienced more frequent exacerbations during follow-up, even after adjustment for multiple potential confounders including country and treatments, but patients with asthma who were receiving ICSs, which are known to prevent exacerbations of asthma, were at reduced risk of severe exacerbations. Patients with asthma who were not treated with ICSs were at increased risk of severe exacerbations requiring hospitalization. ICSs are strongly recommended for asthma, but are not recommended in patients with bronchiectasis without asthma. Our data support the European Respiratory Society guideline recommendation to use ICSs in patients with asthma who also have bronchiectasis.[22] Nevertheless, we observed that a high percentage of patients with bronchiectasis were receiving ICSs in our registry in the absence of asthma or COPD. The reasons for this are unclear and require further study; possibilities include the overlap in symptoms between asthma, COPD, and bronchiectasis leading to confusion among clinicians. Another possibility is that the lack of other evidence-based treatments for bronchiectasis leads clinicians to try a readily available treatment due to a lack of alternative options to manage exacerbations and symptoms. We noted that long-term oral corticosteroid use was higher in patients with coexisting asthma, which may also impact the outcomes of these patients.

Exacerbations in the EMBARC registry are defined by the use of antibiotics, which are universally recommended for patients with a primary bronchiectasis diagnosis at exacerbation. Asthma exacerbations may be treated with oral corticosteroids. A limitation of our analysis is that events exclusively treated with oral corticosteroids are not captured in the registry. Nevertheless, such events would likely be more often reported in patients with comorbid asthma and so would strengthen, rather than weaken, our finding of higher exacerbations in the BE+A group.

Large registries are not designed to identify the mechanisms of increased exacerbations. Our data suggest that the increased exacerbations are not the result of differences in microbiology or underlying etiology. Patients with worse symptoms have more exacerbations, and patients with BE+A had significantly worse symptom scores in our study suggesting this may be one explanation.[23] Asthma is typically treated with ICSs, bronchodilators and other anti-inflammatory medications, while bronchiectasis is treated most frequently with airway clearance and antibiotics.[22,24] We did not find that patients with asthma were less likely to receive airway clearance or antibiotics, but it is theoretically possible that diagnostic confusion between the 2 conditions leads to inappropriate use or underuse of medications. It is also possible that patients with asthma and characteristic signs and symptoms of asthma in the past can experience a shift in phenotype over time to develop symptoms and signs more characteristic of a primary diagnosis of bronchiectasis. Our data support the notion that regardless of how the combination of traits arises, treating the underlying asthmatic trait may still lead to improved clinical outcomes.

Our study has some limitations. Our population is >90% White, and so data may not be transferable to other populations. There is no single objective test for asthma, and so a major limitation of our analysis is that we cannot prove objectively whether the diagnosis of asthma was correct. We saw a higher frequency of eosinophilia and raised IgE in the patients with asthma, but these markers also occur in patients with bronchiectasis without asthma, and it is possible in some circumstances that these markers drive clinicians to diagnose asthma. Our findings are, however, consistent with reports of other studies globally in terms of the prevalence of clinician-report asthma. The US registry reported 29% of patients in the United States have BE+A,[25] and the recent phase 2 WILLOW trial also enrolled a cohort with 29% coexisting asthma.[26] The Korean[27] and Indian registries[28] both reported a frequency of 22%. As such, despite the limited diagnostic information, a similar proportion of patients are diagnosed with asthma in bronchiectasis cohorts worldwide. Neutrophilic subtypes of asthma and eosinophilic subtypes of bronchiectasis exist and have overlapping clinical features making diagnosis difficult. In most cases currently, a history of asthma excludes patients with bronchiectasis from participating in randomized clinical trials.[29,30] Our data suggest that the clinical features and outcomes of those patients are quite similar, including similar lung function, radiologic severity, and microbiology. Although there were statistically significant differences in some of these characteristics, the magnitude of difference was small and arguably not clinically relevant. As history of asthma is so common in this patient population that inclusion of these patients may be appropriate and make bronchiectasis trials more representative.

A surprising finding of our analysis was a strikingly lower mortality in patients with a history of asthma, which persisted despite adjustment for multiple confounders, including age, country, severity of disease, comorbidities, and treatments. The lower mortality rate is unexplained, particularly in view of the higher burden of symptoms and exacerbations in this group.[31,32] We also recently reported that patients with eosinophilic disease have a lower mortality rate.[33] One possible explanation is that while eosinophilic disease is responsive to ICSs and other treatments that are widely available, resulting in better clinical outcomes, no specific therapy is currently available for neutrophilic inflammation. This suggestion is supported by our finding that the mortality benefit was evident only in patients with BE+A treated with ICSs. However, in the absence of sufficient scientific evidence, we cannot exclude the existence of other unknown protective factors in the group of patients with BE+A. In contrast, previous work suggests that neutrophilic disease is associated with worse outcomes,[34] and this endotype is most commonly associated with diseases such as COPD and rheumatoid arthritis and chronic infection with organisms such as *P aeruginosa* and *H influenzae*.[35] While neutrophilic and eosinophilic diseases may coexist, they are often mutually exclusive, and therefore better outcomes in asthma may indicate the absence of other bronchiectasis endotypes associated with worse outcomes.

In summary, asthma is a common comorbidity of bronchiectasis associated with higher frequency of T_H2 inflammation and increased frequency of exacerbations. ICS use in patients with BE+A is associated with reduced mortality and risk of severe exacerbations. Patients with asthma-associated bronchiectasis should be considered a high-risk group requiring more careful follow-up and investigation.

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Key messages

- **The presence of asthma in patients with bronchiectasis is associated with less severe disease but increased exacerbations.**
- **ICS use in patients with BE+A reduces the risk of mortality and hospitalization.**

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