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Demographic, Lifestyle, and Serologic Risk Factors for Rheumatoid Arthritis (RA)–associated Bronchiectasis: Role of RA-related Autoantibodies

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ABSTRACT. ***Objective.*** To investigate demographic, lifestyle, and serologic risk factors for isolated rheumatoid arthritis (RA)–associated bronchiectasis (RA-BR) that is not a result of interstitial lung disease (ILD).

Methods. We performed a case-control study using patients with RA from the Mass General Brigham Biobank. We reviewed the records of all patients with RA meeting the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria with computed tomography (CT) chest imaging to identify RA-BR cases and controls with RA and RA-related lung disease. For each patient, the CT chest imaging that was performed closest to enrollment was independently reviewed by 2 radiologists for the presence of RA-related lung diseases. Cases had clinical and radiologic evidence of RA-BR without interstitial lung abnormalities on imaging. Controls had RA and no evidence of bronchiectasis or ILD. We examined the associations between demographic, lifestyle, and serologic factors with RA-BR using multivariable logistic regression.

Results. We identified 57 cases of isolated RA-BR and 360 RA controls without RA-related lung disease. In multivariable models, RA-BR was associated with older age at RA onset (OR 1.37 per 10 years, 95% CI 1.02–1.82), lower BMI at RA diagnosis (OR 0.94 per kg/m^2, 95% CI 0.89–0.99), seropositive RA (OR 3.96, 95% CI 1.84–8.53), positive rheumatoid factor (OR 4.40, 95% CI 2.14–9.07), and positive anticyclic citrullinated peptide (OR 3.47, 95% CI 1.65–7.31). Higher titers of RA-related autoantibodies were associated with higher odds of RA-BR.

Conclusion. Seropositivity, older age at RA diagnosis, and lower BMI at RA onset were associated with isolated bronchiectasis in RA that was not a result of ILD. These findings expand the list of potential risk factors for RA-BR and suggest a pathogenic link between airway inflammation and RA-related autoantibodies.

Key Indexing Terms: bronchiectasis, rheumatoid arthritis, risk factors

Bronchiectasis is an extraarticular disease manifestation associated with rheumatoid arthritis (RA) characterized by bronchial dilation, inflammation, and recurrent infection leading to airway damage and distortion.[1,2] RA-associated bronchiectasis (RA-BR) is associated with increased morbidity and mortality compared to the general population and patients with

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RA who do not have bronchiectasis.[3,4,5] Recent studies have noted a high burden of clinical and subclinical bronchiectasis in patients with RA, with radiologic prevalence as high as 30% when high-resolution computed tomography (CT) scans were performed for research purposes on patients with newly diagnosed RA.[6]

Despite recognition of this important disease manifestation, there have been limited investigations into risk factors associated with RA-BR development. This research has been further complicated by significant variability in the clinical presentation of RA-BR as well as study design.[7,8] RA-BR may occur in combination with interstitial lung disease (ILD; ie, "traction bronchiectasis") or in isolation (termed here as "isolated RA-BR").[9] Whether isolated RA-BR represents a distinct clinical entity is largely unknown, as there have been few studies explicitly focusing on this disease.[4,10]

Owing, in part, to these challenges, there is significant heterogeneity in study methods, diagnostic criteria, and research populations for prior RA-BR research. This has resulted in conflicting findings with respect to RA-BR prevalence and risk factors. One recent metaanalysis noted prevalence of RA-BR ranging from 0.6% to 2.87% using clinical criteria and from 6% to 58.1% using radiologic criteria.[7] Another recent metaanalysis noted that older age, longer RA duration, genetic factors (ie, cystic fibrosis [CF] transmembrane conductance regulator mutations and HLA variants), and undetectable levels of mannose-binding lectin were associated with RA-BR while highlighting relatively high prevalence and significant variability in study design.[8]

We aimed to identify risk factors for isolated RA-BR by performing a case-control study using a sample of patients with RA selected from a large institutional biobank. We identified cases with isolated RA-BR occurring in the absence of any ILD as well as controls without RA-related lung disease; to identify cases and controls, we used detailed medical record review and evaluation of chest CT images by thoracic radiologists with specific clinical and research experience in RA-related lung diseases.

METHODS

Setting and participants. We conducted a case-control study using the Mass General Brigham (MGB) Biobank, a large, multihospital, biospecimen and clinical data collection research program in the greater Boston, Massachusetts, area.[11] Between its inception in 2010 and September 2021, 123,717 patients enrolled in the MGB Biobank. The MGB Institutional Review Board approved this substudy protocol (no. 2019P003709). All study participants provided written informed consent.

Isolated RA-BR cases. We identified cases of isolated RA-BR using a combination of clinical record review and review of chest imaging by thoracic radiologists. We first identified 2017 adult RA cases in the MGB Biobank using a previously described algorithm. The algorithm incorporated diagnosis codes, laboratory results, and natural language processing with 95% positive predictive value at 97% specificity for RA, as defined by the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria.[12,13] Next, we extracted demographic data, clinical notes, CT chest imaging, radiology reports, rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) status, and pathology reports from the electronic health record (EHR) for all patients with RA who had chest CT imaging (n = 620). We reviewed each patient to identify cases of RA-related lung disease and confirm that all met the 2010 ACR/EULAR RA classification criteria.[14] Clinical evidence of bronchiectasis was defined as physician diagnosis of bronchiectasis recorded in clinical notes or characteristic symptoms of cough, sputum production, and/or dyspnea with bronchiectasis findings noted on clinical imaging. For each patient, 2 thoracic radiologists (RG, SG, or SB) independently scored the CT chest scan performed closest to MGB Biobank enrollment for the presence of bronchiectasis, RA-ILD, and interstitial lung abnormalities using a previously described scoring system.[15,16] A third radiologist provided a majority interpretation when the first 2 radiologists had discordant scores. The radiologists were blinded to clinical details and the other radiologists' interpretations. Further discussion of the scoring of ILD and bronchiectasis is provided in the Supplementary Material (available with the online version of this article).

We defined cases as having clinical evidence of bronchiectasis and no evidence of ILD. To differentiate isolated bronchiectasis from traction bronchiectasis as a result of ILD and other parenchymal lung disease, we required all cases to have no evidence of interstitial lung abnormalities or ILD on the thoracic radiologist reviews of their CT scans and no clinical evidence of ILD on medical record review. The index date was the date of the RA-BR case status, defined as the first imaging report, clinical note, or date of CT scan reviewed by thoracic radiologists to identify bronchiectasis, whichever came first.

We reviewed isolated RA-BR cases for other health conditions that predispose patients to bronchiectasis: allergic bronchopulmonary aspergillosis (ABPA), mycobacterial infections, mucociliary disease, primary immunodeficiency syndromes, alpha-1 antitrypsin deficiency, and CF.[17,18]

Controls with RA and no bronchiectasis or other lung disease. Controls were patients with RA in the MGB Biobank with no evidence of bronchiectasis or ILD. All controls were initially identified by the algorithm and were then confirmed by medical record review to meet the 2010 ACR/EULAR RA classification criteria.[14] They had no evidence of bronchiectasis or ILD by clinical review and no evidence of ILD, interstitial lung abnormalities, or bronchiectasis on consensus radiology review of their CT scans performed closest to MGB Biobank enrollment. The index date for controls was the date of the CT scan reviewed by thoracic radiologists confirming no lung disease.

Demographic, lifestyle, and serologic factors; medications; and pulmonary function testing. We chose known risk factors for other RA-related lung diseases as covariates, including sex, age, race, cigarette exposure, age at RA diagnosis, RA duration, and RA-related autoantibodies (ie, RF and anti-CCP).[19] We obtained demographic information on age and sex from the EHR, and we obtained information on race, smoking status, and smoking pack-years from health questionnaires performed at MGB Biobank enrollment. We obtained missing health questionnaire data from EHR review. We collected BMI measurements (calculated as weight in kilograms divided by height in meters squared) from the EHR at the date of RA onset. We determined RA diagnosis date and age at RA diagnosis from medical record review.

We extracted RF and anti-CCP status from the EHR. RA-related autoantibodies were tested for clinical purposes, and the assay varied by calendar time and clinical laboratory. Therefore, we standardized each autoantibody to the upper limit of normal (ULN) of the assay. We further categorized patients as having low positive (> 1 to 3× ULN) and high positive (> 3× ULN) RF and anti-CCP. Although some patients had missing RF (cases: n = 4; controls: n = 8) or anti-CCP data (cases: n = 13; controls: n = 40), all patients had at least 1 autoantibody result. We defined "seropositive" as positivity for either RF or anti-CCP. There were no other missing data.

We obtained disease-modifying antirheumatic drug (DMARD) prescription information prior to index date and pulmonary function testing for cases from the EHR, as detailed in the Supplementary Material (available with the online version of this article).

Statistical analysis. We assessed baseline characteristics at RA diagnosis as well as ever vs never DMARD use, by class and individual medications,

prior to index date for isolated RA-BR cases and RA controls without RA-related lung disease. We used chi-square tests and Fisher exact tests to compare proportions, and Wilcoxon rank-sum tests with medians and IQRs for continuous variables.

We examined the association of demographic, lifestyle, and RA serologic factors with isolated RA-BR using logistic regression to calculate odds ratios (ORs) and 95% CIs. The dependent variable was isolated RA-BR case status. Independent variables included sex, White race (vs other race), categorical smoking status (never [reference group], past, or current), continuous pack-years, continuous BMI at RA diagnosis, age at RA diagnosis in years (per decade, continuous), RA duration in years at index date (continuous), and seropositive vs seronegative status.

To further assess the effect of RA-related autoantibodies on isolated RA-BR, we performed analyses for each RA-related autoantibody and by autoantibody titers. We constructed multivariable logistic regression models with isolated RA-BR case status as the dependent variable. We investigated RF and anti-CCP individually and performed an analysis categorizing patients into mutually exclusive groups by antibody level, excluding patients with missing data. Multivariable models were adjusted for demographic factors and known risk factors for other RA-related lung diseases, including age at RA diagnosis, sex, race, RA duration at index date, smoking status, continuous pack-years, and BMI at RA onset. We investigated the association of RA autoantibody titer with pulmonary function test (PFT) variables (% predicted of forced expiratory volume in the first second [FEV_1] and forced vital capacity [FVC] as well as FEV_1/FVC ratio) among RA-BR cases by plotting the continuous results and calculating Spearman correlation coefficients with *P* values.

To assess the robustness of our findings, we performed a sensitivity analysis excluding 10 RA-BR cases with ABPA, mycobacterial infection, or primary immunodeficiency. All analyses were prespecified and used SAS statistical software, version 9.4 (SAS Institute). A 2-sided P value < 0.05 was considered statistically significant, without adjustment for multiple comparisons.

RESULTS

Characteristics and medication use of RA-BR cases and controls. We identified 57 cases of isolated RA-BR cases and 360 RA controls without RA-related lung disease. Out of 57 RA-BR cases, 50 (88%) had been evaluated by pulmonology and all were symptomatic with bronchiectasis findings on imaging. Characteristics of cases and controls are listed in Table 1. The majority were White (cases: 50/57, 87.7%; controls: 309/360, 85.8%) and female (cases: 49/57, 86.0%; controls: 275/360, 76.4%). There were no significant differences between RA-BR cases and controls for smoking status (never smoked: 24/57, 42.1% vs 165/360, 45.8%; former smokers: 31/57, 54.4% vs 163/360, 45.3%; current smokers: 2/57, 3.5% vs 32/360, 8.9%; $P = 0.25$) or median pack-years (cases: 2.5, IQR 0.0–15.5; controls: 1.0, IQR 0.0–15.6; $P = 0.67$).

Isolated RA-BR cases had lower median BMI at RA diagnosis (25.3, IQR 22.7–28.5) compared to RA controls without RA-related lung disease (27.6, IQR 23.9–32.7; $P = 0.003$). A higher percentage of RA-BR cases had underweight (3/57, 5.3% vs 13/360, 3.6%) or normal BMI (24/57, 42.1% vs 104/360, 28.9%), and a lower percentage were obese (12/57, 21.1% vs 134/360, 37.2%; $P = 0.08$). RA-BR cases were more likely to be seropositive (48/57, 84.2% vs 201/360, 55.8%; $P < 0.0001$), have positive RF (42/57, 73.7% vs 166/360, 46.1%; $P < 0.0001$), and have positive anti-CCP antibodies (33/57, 57.9% vs 147/360, 40.8%; $P = 0.0001$) than controls. There were no statistically significant differences in conventional synthetic DMARD (45/57, 78.9% vs 296/360, 82.2%), biologic DMARD (35/57, 61.4% vs 183/360, 50.8%), targeted synthetic DMARD (2/57, 3.5% vs 22/360, 6.1%), or tumor necrosis factor (TNF) inhibitor use (32/57, 56.1% vs 157/360, 43.6%) between cases and controls. A smaller proportion of RA-BR cases used abatacept (ABA) prior to the index date compared to controls without RA-related lung disease (2/57, 3.5% vs 54/360, 15.0%; $P = 0.007$). No other individual medications examined were associated with RA-BR case status.

Risk factors for RA-BR. Multivariable models are detailed in Table 2. Higher BMI at RA diagnosis was inversely associated with isolated RA-BR (OR 0.94, 95% CI 0.89–0.99; $P = 0.02$) per kg/m^2. Older age at RA diagnosis had an OR for RA-BR of 1.37 (95% CI 1.02–1.82; $P = 0.04$) per 10 years. There was a trend toward increased odds of RA-BR with increasing duration of RA (OR 1.03, 95% CI 1.00–1.07), but this did not reach statistical significance ($P = 0.08$). Seropositive RA had an OR of 3.96 (95% CI 1.84–8.53, $P = 0.0004$) for RA-BR.

RA-related autoantibodies and RA-BR. In the analyses further examining the relationship between RA-related autoantibodies and RA-BR using multivariable logistic regression (Table 3), RF-positive patients had an OR of 4.40 (95% CI 2.14–9.07; $P < 0.0001$) for RA-BR after adjustment for age, sex, race, RA duration, smoking status, pack-years, and BMI. Further, high positive RF conferred the highest odds for RA-BR (OR 5.44, 95% CI 2.57–11.54; $P < 0.0001$). We observed similar results for anti-CCP–positive patients regarding RA-BR (OR 3.47, 95% CI 1.65–7.31; $P = 0.001$). High positive anti-CCP had an OR of 3.73 (95% CI 1.76–7.90; $P = 0.0006$) for RA-BR.

Pulmonary function testing. Summary PFT results for RA-BR cases are listed in Supplementary Table 1 (available with the online version of this article). PFT data were available for 45 out of 57 cases (79%). Too few controls had PFT data available close to the index date to analyze. Higher RF titers were significantly correlated with lower % predicted FEV_1 ($\rho = -0.38$, $P = 0.015$), % predicted FVC ($\rho = -0.32$, $P = 0.045$), and FEV_1/FVC ($\rho = -0.32$, $P = 0.045$; Supplementary Figure 1, available with the online version of this article). There was a statistically significant correlation between higher anti-CCP titer and lower % predicted FVC values ($\rho = -0.38$, $P = 0.025$), but not between anti-CCP titers and % predicted FEV_1 or FEV_1/FVC.

Sensitivity analysis. To examine whether findings may be explained by other known etiologies of bronchiectasis, we performed medical record review on all RA-BR cases to assess for potential other causes of bronchiectasis. Of the 57 RA-BR cases, 10 (17.5%) had known etiologies of bronchiectasis. A breakdown of these etiologies is listed in Table 4. None were diagnosed with CF or alpha-1 antitrypsin deficiency. We repeated our multivariable analysis after excluding these 10 cases. Results were similar to the main analysis, with strong associations between RA-BR and RF (OR 4.58, 95% CI 2.07–10.15; $P = 0.0002$) and anti-CCP positivity (OR 4.42, 95% CI 1.89–10.33; $P = 0.0006$). The association between lower BMI at RA diagnosis and RA-BR did not reach the threshold for

Table 1. Characteristics of isolated RA-associated bronchiectasis cases and controls.

	Isolated RA-BR Cases, n = 57	RA Controls Without Lung Disease, n = 360	*P*
Demographics			
Female sex	49 (86.0)	275 (76.4)	0.11
White race	50 (87.7)	309 (85.8)	0.70
Lifestyle factors			
Smoking status			0.25
Never	24 (42.1)	165 (45.8)	
Past	31 (54.4)	163 (45.3)	
Current	2 (3.5)	32 (8.9)	
Pack-years, median (IQR)	2.5 (0.0–15.5)	1.0 (0.0–15.6)	0.67
BMI category at RA diagnosis			0.08
Underweight	3 (5.3)	13 (3.6)	
Normal	24 (42.1)	104 (28.9)	
Overweight	18 (31.6)	109 (30.3)	
Obese	12 (21.1)	134 (37.2)	
BMI at RA diagnosis, kg/m^2, median (IQR)	25.3 (22.7–28.5)	27.6 (23.9–32.7)	**0.003**
RA factors			
Age at RA diagnosis, yrs, median (IQR)	55.0 (44.2–63.1)	52.1 (40.2–60.5)	0.15
RA duration at index date[a], yrs, median (IQR)	9.9 (2.8–19.0)	6.9 (1.6–14.9)	0.10
Seropositive RA	48 (84.2)	201 (55.8)	**< 0.0001**
RF positive	42 (73.7)	166 (46.1)	**< 0.0001**
RF level (fold above ULN), median (IQR)	5.4 (1.5–22.8)	1.0 (1.0–6.2)	**< 0.0001**
Anti-CCP positive	33 (57.9)	147 (40.8)	**0.0001**
Anti-CCP level (fold above ULN), median (IQR)	9.5 (0.9–24.3)	0.8 (0.3–11.7)	**0.0009**
Ever DMARD use prior to index date[a]			
csDMARD	45 (78.9)	296 (82.2)	0.55
Methotrexate	40 (70.2)	236 (65.6)	0.49
Hydroxychloroquine	25 (43.9)	159 (44.2)	0.97
Sulfasalazine	8 (14.0)	58 (16.1)	0.69
Leflunomide	5 (8.8)	39 (10.8)	0.64
bDMARD	35 (61.4)	183 (50.8)	0.14
TNF inhibitor	32 (56.1)	157 (43.6)	0.08
Abatacept	2 (3.5)	54 (15.0)	**0.007**
Rituximab	5 (8.8)	30 (8.3)	0.91
Tocilizumab	3 (5.3)	22 (6.1)	0.24
tsDMARD[b]	2 (3.5)	22 (6.1)	0.20

Data are in n (%) unless otherwise indicated. [a] Index date was the date of RA-BR detection for cases and date of chest computed tomography scan reviewed by thoracic radiologists for research purposes for controls. [b] An example of a tsDMARD is Janus kinase inhibitors such as tofacitinib. Values in bold are statistically significant. anti-CCP: anticyclic citrullinated peptide; bDMARD: biologic DMARD; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; RA-BR: rheumatoid arthritis–associated bronchiectasis; RF: rheumatoid factor; tsDMARD: targeted synthetic DMARD; ULN: upper limit of normal.

statistical significance (OR 0.96, 95% CI 0.90–1.02 per kg/m^2; $P = 0.15$). Full results are shown in Supplementary Tables 2 and 3 (available with the online version of this article).

DISCUSSION

In this case-control study of patients with RA using a large institutional biobank, we identified seropositivity, older age at RA onset, and lower BMI as potential novel risk factors for RA-BR not caused by ILD. High positive RF and anti-CCP were strongly associated with RA-BR, suggesting a potential pathogenic link between RA-related autoantibodies and airway damage in bronchiectasis. Additionally, patients with RA-BR had lower BMI at RA diagnosis and were more frequently underweight or normal weight. These findings expand the understanding of demographic, clinical, and serologic risk factors for RA-BR and highlight the complex interplay between pulmonary and airway inflammation and RA.

This study adds to a growing body of literature on bronchiectasis in RA. Prior studies of RA-BR prevalence and risk factors have been complicated by significant heterogeneity in study design, diagnostic criteria, imaging techniques, and inclusion of patients with RA-ILD. Estimates of the prevalence of RA-BR have varied accordingly, with a recent metaanalysis reporting a prevalence of clinical diagnosis of RA-BR from 0.6% to 2.87% and radiologic evidence of bronchiectasis in patients with RA from 6% to 58.1%.[7] Another metaanalysis estimated a pooled overall prevalence of 18.7%, but also noted significant heterogeneity in study methods.[8]

Table 2. Associations of factors with isolated RA-associated bronchiectasis.

	Multivariable[a] OR for Isolated RA-BR (95% CI)	*P*
Demographics		
Sex		
Male	1.00 (Ref)	
Female	0.60 (0.26–1.37)	0.22
Race		
White	1.00 (Ref)	
Non-White	0.87 (0.35–2.15)	0.76
Lifestyle		
Smoking status		
Never smoker	1.00 (Ref)	
Past smoker	1.04 (0.50–2.14)	0.93
Current smoker	0.45 (0.09–2.35)	0.34
Smoking pack-years (per unit)	0.99 (0.98–1.01)	0.56
BMI at RA diagnosis (per kg/m^2)	**0.94 (0.89–0.99)**	**0.02**
RA factors		
Age at RA diagnosis (per 10 years)	**1.37 (1.02–1.82)**	**0.04**
RA duration at index date (per year)	1.03 (1.00–1.07)	0.08
Seronegative RA	1.00 (Ref)	
Seropositive RA	**3.96 (1.84–8.53)**	**0.0004**

[a] Mutually adjusted for all covariates listed. Values in bold are statistically significant. OR: odds ratio; RA: rheumatoid arthritis; RA-BR: rheumatoid arthritis-associated bronchiectasis.

Table 3. Associations of RA-related autoantibodies with isolated RA-BR.

RA-related Autoantibody Status[a]	Multivariable[b] OR for Isolated RA-BR (95% CI)	*P*
RF negative	1.00 (Ref)	
RF positive (> 1× ULN)	**4.40 (2.14–9.07)**	**< 0.0001**
RF negative	1.00 (Ref)	
RF low positive (> 1–3× ULN)	1.95 (0.67–5.66)	0.22
RF high positive (> 3× ULN)	**5.44 (2.57–11.54)**	**< 0.0001**
Anti-CCP negative	1.00 (Ref)	
Anti-CCP positive (> 1× ULN)	**3.47 (1.65–7.31)**	**0.001**
Anti-CCP negative	1.00 (Ref)	
Anti-CCP low positive (> 1–3× ULN)	1.45 (0.29–7.32)	0.65
Anti-CCP high positive (> 3× ULN)	**3.73 (1.76–7.90)**	**0.0006**

[a] RF analyses included 53 cases and 352 controls (n = 12 missing RF status); anti-CCP analyses included 44 cases and 320 controls (n = 53 missing anti-CCP status). [b] Adjusted for age, sex, race, RA duration, smoking status, pack-years, and BMI. Values in bold are statistically significant. anti-CCP: anticyclic citrullinated peptide; OR: odds ratio; RA: rheumatoid arthritis; RA-BR: rheumatoid arthritis–associated bronchiectasis; RF: rheumatoid factor; ULN: upper limit of normal.

In light of this variability, there have been conflicting findings and relatively little research regarding RA-BR risk factors. Our finding of an association between anti-CCP positivity and RA-BR builds on a similar finding from a study of 35 patients with RA-BR; that study found an association between positive anti-CCP antibodies and bronchiectasis with an OR of 3.66, although this finding was not statistically significant, perhaps because of sample size limitations.[20] In contrast, another study noted a lower prevalence of anti-CCP positivity among isolated

Table 4. Other etiologies of bronchiectasis in RA-BR cases.

Etiology[a]	Instances Out of All RA-BR Cases, n = 57
History of tuberculosis	4 (7.0)
Allergic bronchopulmonary aspergillosis	2 (3.5)
History of nontuberculous mycobacterial infection	2 (3.5)
Primary immunodeficiency syndrome	1 (1.8)
Allergic bronchopulmonary aspergillosis and primary immunodeficiency	1 (1.8)

Data are in n (%). [a] There were no cases with alpha-1 antitrypsin deficiency, cystic fibrosis, or eosinophilic granulomatosis with polyangiitis. RA-BR: rheumatoid arthritis–associated bronchiectasis.

patients with RA-BR compared to patients with RA who had ILD, though this study did not include controls without RA-related lung disease.[10] Our findings associating RA-related autoantibodies and RA-BR should be replicated in other studies.

The association between bronchiectasis and RA indicates a possible pathogenic link between airway inflammation and RA. The "mucosal origins hypothesis" suggests that mucosal sites, including the lung, play a key role in generating RA-related autoantibodies.[21] This hypothesis is supported by several lines of evidence that posit a link between airway inflammation and autoantibodies.[22–27] A study by Demoruelle et al[28] noted that subjects without inflammatory arthritis but with positive anti-CCP antibodies were more likely to have airway disease, including bronchial wall thickening and bronchiectasis, compared to antibody-negative controls. Our study noted a correlation between higher RF titers and decreasing FEV_1, FVC, and FEV_1/FVC among RA-BR cases. This finding is consistent with studies demonstrating an association between autoantibodies and obstructive and restrictive PFT abnormalities in the RA population and also when comparing RA to the general population.[24,25] Prior research has demonstrated that RA-related autoantibodies and/or anticitrullinated protein antibodies (ACPA) may be produced in the lung and airways before articular RA onset[22,29,30,31,32] or in the early RA period.[33,34] A specific connection between bronchiectasis and autoantibody production was noted in a study by Quirke and colleagues,[35] who found increased levels of ACPA production in patients with bronchiectasis.

Longer disease duration has also been associated with RA-BR in several studies, including a recent metaanalysis.[8,10,36] In our study, there was a trend toward an association of longer RA duration with RA-BR. This was statistically significant in our sensitivity analysis excluding cases with other potential causes of bronchiectasis, but not in the main analysis. As known risk factors for bronchiectasis include acquired immunodeficiency syndromes and recurrent infections,[1] we investigated immunosuppressive medication use in our study, but we did not observe a significant association between RA-BR and most individual or classes of DMARDs. A slightly higher proportion of RA-BR cases used TNF inhibitor prior to index date than controls, but this did not reach statistical significance. A lower proportion of cases used ABA, which was statistically significant. However, we

were limited in pursuing this further since only 2 RA-BR cases had used ABA. Future studies with sufficient sample sizes are needed to investigate a possible association of DMARD use with RA-BR risk using pharmacoepidemiologic methods to account for possible confounding by indication.

To our knowledge, this is the first investigation identifying an association between lower BMI at RA diagnosis and RA-BR. This contrasts with research that has identified obesity as a risk factor for RA, RA-ILD, and worse response to treatment in early RA.[37,38,39,40] An association between lower BMI and bronchiectasis may suggest that the lung plays a central role in promoting autoimmunity and a proinflammatory state, especially in normal and underweight individuals. Since BMI was measured at the onset of RA, and typically many years prior to the index date, it is unlikely that RA severity explains our findings. However, some patients who later develop RA may experience sarcopenia or RA cachexia before clinical diagnosis.[41,42] It is possible that nutritional deficiencies or metabolic factors play a role in propensity for RA-BR. While no RA-BR cases were known to have CF, some may have had undiagnosed or subclinical CF, a condition where patients are often underweight.[43] Future prospective studies should seek to replicate our observed association between low BMI and RA-BR.

Our study also provides insight into differences between RA-BR and RA-ILD risk factors. We found a strong association between autoantibodies and RA-BR, whereas an association between seropositive RA and RA-ILD has been conflicting.[9,44,45,46,47] We observed an association between RA-BR and longer RA duration, which has also been associated with RA-ILD.[47,48,49] Unlike consistent findings implicating smoking and RA-ILD, our study found no association between smoking status or pack-years and RA-BR.[40] This suggests that isolated RA-BR is not the result of lung damage from smoking and is a distinct entity from RA-ILD.[40] Finally, our finding associating lower BMI at RA diagnosis with RA-BR also contrasts with RA-ILD, where obesity has been reported as a risk factor in a prior study from our group[40] but not in a recent population-based study.[47] However, underweight has not been associated with RA-ILD. These findings highlight the need for additional research into risk factors across the spectrum of RA-related lung diseases.

Strengths of our study include using detailed clinical data and radiology review by thoracic radiologists to identify RA-BR cases and RA controls without RA-related lung disease. We used a strict definition for isolated RA-BR that was designed to exclude cases of traction bronchiectasis resulting from ILD and that required clinical and radiologic evidence of bronchiectasis occurring in the absence of interstitial lung abnormalities. Therefore, it is unlikely that clinical or subclinical ILD explains our findings. Further, we performed detailed screening of controls to confirm that they had no clinical or radiologic evidence of bronchiectasis or ILD. We were also able to evaluate multiple risk factors that have been established for other RA-related lung diseases, including cigarette smoking, obesity, and BMI.[40]

Our study has certain limitations. The cohort was obtained from a single healthcare system and included mostly White patients, which may limit generalizability. We focused on predictors of RA-BR that were present at RA diagnosis. Subsequent treatments and ongoing disease activity and severity may be mediators of RA-BR risk. We investigated medication use after RA diagnosis and prior to index date using EHR data. With the exception of ABA, we found no associations between DMARDs and RA-BR. Thus, it is unlikely that DMARD use after RA diagnosis explains the strong association we observed between seropositivity and RA-BR. The effects of disease activity, severity, and medications on RA-BR risk represent important avenues of future research. We adjusted for important covariates, including smoking, sex, and age at diagnosis, but residual confounding remains possible. While this is the largest study focused on identifying risk factors for isolated RA-BR, sample size was still limited. However, we were able to identify multiple novel risk factors with statistical significance. Our study focused on patients with clinical and radiologic evidence of bronchiectasis and did not investigate patients with subclinical disease that was detected only on imaging. Further studies to assess risk factors across the clinical spectrum of RA-BR are needed. Since we aimed to confirm case and control status on all patients, we analyzed only patients with available chest CT imaging. However, these were performed for clinical indications, which may introduce selection bias. Future prospective studies are needed to obtain chest CT imaging for research purposes to identify factors associated with RA-BR.

In conclusion, our study found that seropositivity, lower BMI at diagnosis, and older age at RA diagnosis were associated with RA-BR. These findings expand the list of potential risk factors for bronchiectasis in RA and emphasize the important and complex interactions between airway inflammation and RA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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