Demographic, Lifestyle, and Serologic Risk Factors for Rheumatoid Arthritis-Associated Bronchiectasis: Role of RA-related Autoantibodies

Gregory McDermott MD[1,6] (ORCID ID: 0000-0002-9750-5448), Ritu Gill MD[2,6], Staci Gagne MD[3,6], Suzanne Byrne MD[3,6], Weixing Huang MSPH[1], Xiaosong Wang MS[1], Lauren C. Prisco BA[1], Alessandra Zaccardelli MS[1], Lily W. Martin BS[1], Lucy Masto[1], Vanessa L. Kronzer MD MSCI[5] (ORCID ID: 0000-0002-7489-3134), Nancy Shadick MD MPH[1,6], Paul F. Dellaripa MD[1,6], Tracy J. Doyle MD MPH[4,6], Jeffrey A. Sparks MD MMSc[1,6] (ORCID ID: 0000-0002-5556-4618)

[1] Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston, MA, USA

[2] Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, USA

[3] Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA

[4] Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA

[5] Division of Rheumatology, Mayo Clinic, Rochester, MN

[6] Harvard Medical School, Boston, MA, USA

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Corresponding Author:
Jeffrey A. Sparks, MD, MMSc
Division of Rheumatology, Inflammation, and Immunity
Brigham and Women's Hospital
60 Fenwood Road, #6016U
Boston, MA 02115
617-525-1040
jsparks@bwh.harvard.edu
@jeffsparks
ORCiD : 0000-0002-5556-4618

ABSTRACT

Objective: To investigate demographic, lifestyle, and serologic risk factors for isolated rheumatoid arthritis-associated bronchiectasis (RA-BR) not due to interstitial lung disease (ILD).

Methods: We performed a case-control study using RA patients from the Mass General Brigham Biobank. We reviewed the records of all RA patients meeting 2010 ACR/EULAR criteria with CT chest imaging to identify RA-BR cases and controls with RA and RA-related lung disease. For each patient, the CT chest imaging performed closest to enrollment was independently reviewed by two 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 of 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 1.84-8.53), positive rheumatoid factor (OR 4.40 95%CI 2.14-9.07), and positive anti-CCP (OR 3.47 95%CI 1.65-7.31). Higher-titer RA-related autoantibodies were associated with higher odds of RA-BR.

Conclusions: Seropositivity, older age at RA diagnosis, and lower BMI at RA onset were associated with isolated bronchiectasis in RA not due to 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.

INTRODUCTION

Bronchiectasis is an extra-articular 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 (abbreviated RA-BR) is associated with increased morbidity and mortality compared to the general population and RA patients without bronchiectasis.(3–5) Recent studies have noted a high burden of clinical and subclinical bronchiectasis in RA patients, with radiologic prevalence as high as 30% when high-resolution CT (HRCT) 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 ("traction bronchiectasis") or in isolation (termed here "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)

Due 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 meta-analysis noted prevalence of RA-BR ranging from 0.6-2.87% using clinical and from 6-58.1% using radiologic criteria.(7) Another recent meta-analysis noted that older age, longer RA duration, genetic factors (*CFTR* 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 RA patients selected from a large institutional biobank. We identified cases

with isolated RA-BR occurring in the absence of any interstitial lung disease and controls without RA-related lung disease using detailed medical record review and evaluation of chest computed tomography (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 Massachusetts General Brigham (MGB) Biobank, a large, multi-hospital, biospecimen and clinical data collection research program in the greater Boston, Massachusetts area.(11) Between its inception in 2010 and September 2021, n=123,717 patients enrolled in the MGB Biobank. The MGB Institutional Review Board approved this sub-study protocol #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 n=2,017 adult RA cases in the MGB Biobank using a previously described algorithm incorporating diagnosis codes, laboratory results, and natural language processing with 95% positive predictive value at 97% specificity for RA defined by the 2010 American College of Rheumatology/European Alliance for Rheumatology Associations (ACR/EULAR) classification criteria.(12,13) Next, we extracted demographic data, clinical notes, CT chest imaging, radiology reports, RF and 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, two 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 two radiologists had discordant scores. The radiologists were blinded to clinical details and the other radiologists' interpretations. Further discussion of the scoring of ILA and bronchiectasis is provided in the **Supplemental Materials**.

We defined cases as having clinical evidence of bronchiectasis and no evidence of ILD. To differentiate isolated bronchiectasis from traction bronchiectasis due to 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 scan and no clinical evidence of ILD on medical record review. The index date was the date of 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 cystic fibrosis.(17,18)

Controls with RA and no bronchiectasis or other lung disease

Controls were RA patients in the MGB Biobank with no evidence of bronchiectasis or ILD. All controls were initially identified by the algorithm 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 scan performed closest to MGB

Biobank enrollment. The index date for controls was the date of CT scan reviewed by thoracic radiologists confirming no lung disease.

Demographic, lifestyle, and serologic factors; medications; 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 (RF and anti-CCP).(19) We obtained demographic information on age and sex from the EHR and 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 body mass index (BMI) measurements 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 3x ULN) and high positive (>3x 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 one 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 **Supplemental Materials**.

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-squared tests and Fisher's exact tests to compare proportions and Wilcoxon rank sum tests with medians and interquartile ranges for continuous variables.

We examined the association of demographic, lifestyle, and RA serologic factors with isolated RA-associated bronchiectasis using logistic regression to calculate odds ratios (OR) and 95% confidence intervals (CI). The dependent variable was isolated RA-associated bronchiectasis case status. Independent variables included sex, White race (vs. other race), categorical smoking status (never [reference group]/past/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 impact 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 also 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 PFT parameters (% predicted of FEV_1 and 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 (n=10) RA-BR cases with ABPA, mycobacterial infection, or primary immunodeficiency. All analyses were pre-specified and used SAS version 9.4 (SAS Institute Inc., Cary, NC). A two-

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. Fifty of the 57 RA-BR cases (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: 87.7%, controls: 85.8%) and female (cases: 86.0%, controls: 76.4%). There were no significant differences between RA-BR cases and controls for smoking status (never: 42.1% vs. 45.8%; former 54.4% vs. 45.3%; current smokers 3.5% vs. 8.9%, p=0.25) or median pack-years (cases: 2.5; controls: 1.0 p=0.67).

Isolated RA-BR cases had lower median BMI at RA diagnosis (25.3 kg/m^2) compared to RA controls without RA-related lung disease (27.6 kg/m^2, p=0.003). A higher percentage of RA-BR cases were underweight (5.3% vs. 3.6%) or normal BMI (42.1% vs. 28.9%) and a lower percentage were obese (21.1% vs. 37.2%, p=0.08). RA-BR cases were more likely to be seropositive (84.2% vs 55.8%, p<0.0001), have positive RF (73.7% vs. 46.1%, p<0.0001), and have positive anti-CCP antibodies (57.9% vs. 40.8%, p=0.0001) than controls. There were no statistically significant differences in csDMARD (79.0% vs. 82.2%), bDMARD (61.4% vs. 50.8%), tsDMARD (3.5% vs. 6.11%), or TNFi use (56.1% vs. 43.6%) between cases and controls. A smaller proportion of RA-BR cases used abatacept prior to the index date compared

to controls without RA-related lung disease (3.5% vs. 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 OR for RA-BR of 1.37 (95%CI 1.02-1.82, p=0.04) per 10 years. There was a trend towards 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 OR 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 OR 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. Furthermore, high-positive RF conferred the highest odds for RA-BR (multivariable OR 5.44 95%CI 2.57-11.54, p<0.0001). We observed similar results for anti-CCP positive patients (multivariable OR for RA-BR 3.47 95%CI 1.65-7.31, p=0.001). High positive anti-CCP, defined as levels more than three times the ULN, had OR 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 **Supplemental Table S1**. 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 (ρ=-0.38, p=0.015), % predicted FVC (ρ=-0.32, p=0.045), and FEV_1/FVC (ρ=-0.32, p=0.045) (**Supplemental Figure S1).** There was a statistically significant correlation between higher anti-CCP titer and lower % predicted FVC values (ρ=-0.38, p=0.015), 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. Breakdown of these etiologies is listed in **Table 4**. None were diagnosed with cystic fibrosis 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 statistical significance (OR 0.96 95%CI 0.90-1.02 per kg/m^2, p=0.15). Full results are shown in **Supplemental Tables S2 and S3**.

DISCUSSION

In this case-control study of RA patients 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 literature on bronchiectasis in rheumatoid arthritis. 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 meta-analysis reporting a prevalence of clinical diagnosis of RA-BR from 0.6-2.87% and radiologic evidence of bronchiectasis in RA patients from 6-58.1%.(7) Another meta-analysis estimated a pooled overall prevalence of 18.7%, but also noted significant heterogeneity in study methods.(8)

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 upon a similar finding from a study of 35 patients with RA-BR that found an association between positive anti-CCP antibodies and bronchiectasis with OR 3.66, although this finding was not statistically significant, perhaps due to sample size limitations.(20) In contrast, another study noted a lower prevalence of anti-CCP positivity among isolated RA-BR patients compared to RA patients with 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 Demourelle et al. noted that subjects

without inflammatory arthritis but positive anti-CCP antibodies were more likely to have airway disease including bronchial wall thickening and bronchiectasis, compared to antibody negative controls.(28) Our study noted a correlation between higher RF titers and decreasing FEV1, FVC, and FEV1/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 anti-citrullinated antibodies may be produced in the lung and airways before articular RA onset(22,29–32) 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, who found increased levels of ACPA production in patients with bronchiectasis.(35)

Longer disease duration has also been associated with RA-BR in several studies, including a recent meta-analysis.(8,10,36) In our study, there was a trend towards 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 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 TNFi prior to index date than controls, but this did not reach statistical significance. A lower proportion of cases used abatacept, which was statistically significant. However, we were limited to pursue this further since only two RA-BR cases had used abatacept. Future studies with sufficient sample size 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.(37–40) An association between lower BMI and bronchiectasis may suggest that the lung plays a central role in promoting autoimmunity and a pro-inflammatory state, especially in normal and underweight individuals. Since BMI was measured at clinical RA onset 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 cystic fibrosis, some may have had undiagnosed or subclinical cystic fibrosis, 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.(9,44–47) We observed an association between RA-BR and longer RA duration, which has also been associated with RA-ILD.(47–49) 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 due to 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 with high confidence. We used a strict definition for isolated RA-BR designed to exclude cases of traction bronchiectasis due to ILD and 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. Furthermore, we performed detailed screening of controls to confirm that they had no clinical or radiologic evidence of bronchiectasis or interstitial lung disease. 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 abatacept, 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 impact 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 only detected 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 only analyzed 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 rheumatoid arthritis and emphasize the important and complex interactions between airway inflammation and rheumatoid arthritis.

REFERENCES

1. Barker AF. Bronchiectasis. N Engl J Med 2002;346:1383-93.
2. O'Donnell AE. Bronchiectasis. Chest 2008;134:815-23.
3. Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. Br J Rheumatol 1997;36:689-91.
4. De Soyza A, McDonnell MJ, Goeminne PC, et al. Bronchiectasis Rheumatoid Overlap Syndrome Is an Independent Risk Factor for Mortality in Patients With Bronchiectasis: A Multicenter Cohort Study. Chest 2017;151:1247-54.
5. Puéchal X, Génin E, Bienvenu T, Le Jeunne C, Dusser DJ. Poor survival in rheumatoid arthritis associated with bronchiectasis: a family-based cohort study. PLoS One 2014;9:e110066.
6. Wilsher M, Voight L, Milne D, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. Respir Med 2012;106:1441-6.
7. Wiater R, Håkansson KEJ, Ulrik CS. A causal relationship between rheumatoid arthritis and bronchiectasis? A systematic review and meta-analysis. Chron Respir Dis 2021;18.
8. Martin LW, Prisco LC, Huang W, et al. Prevalence and risk factors of bronchiectasis in rheumatoid arthritis: A systematic review and meta-analysis. Semin Arthritis Rheum 2021;51:1067-80.
9. Huang S, Doyle TJ, Hammer MM, et al. Rheumatoid arthritis-related lung disease detected on clinical chest computed tomography imaging: Prevalence, risk factors, and impact on mortality. Semin Arthritis Rheum 2020;50:1216-25.
10. Duarte AC, Porter JC, Leandro MJ. The lung in a cohort of rheumatoid arthritis patients-an overview of different types of involvement and treatment. Rheumatology (Oxford)

2019;58:2031-8.

11. Karlson EW, Boutin NT, Hoffnagle AG, Allen NL. Building the partners healthcare biobank at partners personalized medicine: Informed consent, return of research results, recruitment lessons and operational considerations. J Pers Med 2016;6:1-11.

12. Liao KP, Cai T, Gainer V, et al. Electronic medical records for discovery research in rheumatoid arthritis. Arthritis Care Res 2010;62:1120-7.

13. Huang S, Huang J, Cai T, et al. Impact of ICD10 and secular changes on electronic medical record rheumatoid arthritis algorithms. Rheumatology (Oxford) 2020;59:3759-66.

14. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.

15. Washko GR, Lynch DA, Matsuoka S, et al. Identification of Early Interstitial Lung Disease in Smokers from the COPDGene Study. Acad Radiol 2010;17:48-53.

16. Doyle TJ, Dellaripa PF, Batra K, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. Chest 2014;146:41-50.

17. McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population: Effects of ethnicity on etiology and sputum culture. Chest 2012;142:159-67.

18. Araújo D, Shteinberg M, Aliberti S, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Eur Respir J 2017;50:3-6.

19. Huang S, Kronzer VL, Dellaripa PF, et al. Rheumatoid arthritis-associated interstitial lung disease: Current update on prevalence, risk factors, and pharmacologic treatment. Curr Treat options Rheumatol 2020;6:337-53.

20. Attar S, Alamoudi O, Aldabbag A. Prevalence and risk factors of asymptomatic bronchiectasis in patients with rheumatoid arthritis at a tertiary care center in Saudi

Arabia. Ann Thorac Med 2015;10:176-80.

21. Holers VM, Demoruelle MK, Kuhn KA, et al. Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Nat Rev Rheumatol 2018;14:542-57.

22. Ford JA, Liu X, Marshall AA, et al. Impact of Cyclic Citrullinated Peptide Antibody Level on Progression to Rheumatoid Arthritis in Clinically Tested Cyclic Citrullinated Peptide Antibody–Positive Patients Without Rheumatoid Arthritis. Arthritis Care Res 2019;71:1583-92.

23. Zaccardelli A, Liu X, Ford JA, et al. Asthma and elevation of anti-citrullinated protein antibodies prior to the onset of rheumatoid arthritis. Arthritis Res Ther 2019;21:1-12.

24. Huang S, He X, Doyle TJ, et al. Association of rheumatoid arthritis-related autoantibodies with pulmonary function test abnormalities in a rheumatoid arthritis registry. Clin Rheumatol 2019;38:3401-12.

25. Prisco L, Moll M, Wang J, et al. Relationship Between Rheumatoid Arthritis and Pulmonary Function Measures on Spirometry in the UK Biobank. Arthritis Rheumatol (Hoboken, NJ) 2021;73:1994-2002.

26. Sparks JA, Lin TC, Camargo CA, et al. Rheumatoid arthritis and risk of chronic obstructive pulmonary disease or asthma among women: A marginal structural model analysis in the Nurses' Health Study. Semin Arthritis Rheum 2018;47:639-48.

27. Zaccardelli A, Liu X, Ford JA, et al. Elevated Anti-Citrullinated Protein Antibodies Prior to Rheumatoid Arthritis Diagnosis and Risks for Chronic Obstructive Pulmonary Disease or Asthma. Arthritis Care Res (Hoboken) 2021;73:498-509.

28. Demoruelle MK, Weisman MH, Simonian PL, et al. Airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: Early injury or initiating site of autoimmunity? Arthritis Rheum 2012;64:1756-61.

29. Fischer A, Solomon JJ, Du Bois RM, et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. Respir Med 2012;106:1040-7.

30. Demoruelle K, Weisman M, Harrington A, et al. Lung abnormalities in subjects with elevations of rheumatoid arthritis-related autoantibodies without arthritis by examination and imaging suggest the lung is an early and perhaps initiating site of inflammation in rheumatoid arthritis [abstract]. Ann Rheum Dis 2012;71:A25.

31. Nielen MMJ, Van Schaardenburg D, Reesink HW, et al. Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis: A Study of Serial Measurements in Blood Donors. Arthritis Rheum 2004;50:380-6.

32. Rantapää-Dahlqvist S, De Jong BAW, Berglin E, et al. Antibodies Against Cyclic Citrullinated Peptide and IgA Rheumatoid Factor Predict the Development of Rheumatoid Arthritis. Arthritis Rheum 2003;48:2741-9.

33. Willis VC, Demoruelle MK, Derber LA, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. Arthritis Rheum 2013;65:2545-54.

34. Joshua V, Loberg-Haarhaus M, Wähämaa H, et al. Citrulline Reactive B Cells are Present In the Lungs of Early Untreated RA [abstract]. Ann Rheum Dis 2019;78:1480.

35. Quirke AM, Perry E, Cartwright A, et al. Bronchiectasis is a model for chronic bacterial infection inducing autoimmunity in rheumatoid arthritis. Arthritis Rheumatol 2015;67:2335-42.

36. Hassen Zrour S, Touzi M, Bejia I, et al. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis: Prospective study in 75 patients. Jt Bone Spine 2005;72:41-7.

37. Lu B, Hiraki LT, Sparks JA, et al. Being overweight or obese and risk of developing

rheumatoid arthritis among women: A prospective cohort study. Ann Rheum Dis 2014;73:1914-22.

38. Dar L, Tiosano S, Watad A, et al. Are obesity and rheumatoid arthritis interrelated? Int J Clin Pract 2018;72:1-5.

39. Sandberg MEC, Bengtsson C, Källberg H, et al. Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. Ann Rheum Dis 2014;73:2029-33.

40. Kronzer VL, Huang W, Dellaripa PF, et al. Lifestyle and Clinical Risk Factors for Incident Rheumatoid Arthritis-associated Interstitial Lung Disease. J Rheumatol 2021;48:656-63.

41. Walsmith J, Roubenoff R. Cachexia in rheumatoid arthritis. Int J Cardiol 2002;85:89-99.

42. Masuko K. Rheumatoid Cachexia Revisited: A Metabolic Co-Morbidity in Rheumatoid Arthritis. Front Nutr 2014;1:1-7.

43. Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis: A review. Nutr Clin Pract 2013;28:676-83.

44. Juge P-A, Lee JS, Ebstein E, et al. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease . N Engl J Med 2018;379:2209-19.

45. Natalini JG, Baker JF, Singh N, et al. Autoantibody Seropositivity and Risk for Interstitial Lung Disease in a Prospective Male-Predominant Rheumatoid Arthritis Cohort of U.S. Veterans. Ann Am Thorac Soc 2021;18:598-605.

46. Xie S, Li S, Chen B, Zhu Q, Xu L, Li F. Serum anti-citrullinated protein antibodies and rheumatoid factor increase the risk of rheumatoid arthritis-related interstitial lung disease: a meta-analysis. Clin Rheumatol 2021;40:4533-43.

47. Samhouri BF, Vassallo R, Achenbach SJ, et al. The Incidence, Risk Factors, and Mortality of Clinical and Subclinical Rheumatoid Arthritis-associated Interstitial Lung

Disease: A Population-based Cohort. Arthritis Care Res (Hoboken) 2022;0-3.

48. Mohning MP, Amigues I, Demoruelle MK, et al. Duration of rheumatoid arthritis and the risk of developing interstitial lung disease. ERJ open Res 2021;7:00633-2020.

49. Yin Y, Liang D, Zhao L, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. PLoS One 2014;9:1-6.

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

Characteristic	Isolated RA-BR cases (n=57)	RA controls without lung disease (n=360)	p-value
Demographics			
Female sex (n, %)	49 (86.0%)	275 (76.4%)	0.11
White (n, %)	50 (87.7%)	309 (85.8%)	0.70
Lifestyle factors			
Smoking status (n, %)			
Never	24 (42.1%)	165 (45.8%)	0.25
Past	31 (54.4%)	163 (45.3%)	
Current	2 (3.5%)	32 (8.9%)	
Pack-years (median and IQR)	2.5 (0.0, 15.5)	1.0 (0.0, 15.6)	0.67
BMI category at RA diagnosis (n, %)			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 and IQR)	25.3 (22.7, 28.5)	27.6 (23.9, 32.7)	**0.003**
RA factors			
Age at RA diagnosis (years, median and IQR)	55.0 (44.2, 63.1)	52.1 (40.2, 60.5)	0.15
RA duration at index date* (years median (IQR))	9.9 (2.8, 19.0)	6.9 (1.6, 14.9)	0.10
Seropositive RA (n, %)	48 (84.2%)	201 (55.8%)	**<0.0001**
RF+ (n, %)	42 (73.7%)	166 (46.1%)	**<0.0001**
RF level (fold above ULN, median and IQR)	5.4 (1.5, 22.8)	1.0 (1.0, 6.2)	**<0.0001**
Anti-CCP+ (n, %)	33 (57.9%)	147 (40.8%)	**0.0001**
Anti-CCP level (-fold above ULN, median and IQR)	9.5 (0.9, 24.3)	0.8 (0.3, 11.7)	**0.0009**
Ever DMARD use prior to index date*			
csDMARD	45 (79.0%)	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	2 (3.5%)	22 (6.11%)	0.20

Anti-CCP = cyclic citrullinated peptide; BMI = body mass index; bDMARD = biologic disease modifying antirheumatic drug; csDMARD = conventional synthetic disease modifying antirheumatic drug; IQR = interquartile range; RA = rheumatoid arthritis; RA-BR = rheumatoid arthritis-associated bronchiectasis; RF = rheumatoid factor; TNF = tumor necrosis factor; tsDMARD = targeted synthetic disease modifying antirheumatic drug (e.g., Janus kinase inhibitors such as tofacitinib); ULN = upper limit of normal

*Index date was date of RA-BR detection for cases and date of chest CT scan reviewed by thoracic radiologists for research purposes for controls

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

Characteristic	Multivariable* OR for isolated RA-BR (95%CI)	p-value
Demographics		
Male	1.00 (Ref)	
Female	0.60 (0.26-1.37)	0.22
White	1.00 (Ref)	
Non-White	0.87 (0.35-2.15)	0.76
Lifestyle		
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**

*Mutually adjusted for all covariates listed.
BMI = body mass index; RA = rheumatoid arthritis; RA-BR = rheumatoid arthritis-associated bronchiectasis

Table 3: Associations of RA-related autoantibodies with isolated RA-bronchiectasis

RA-related autoantibody status*	Multivariable† OR for isolated RA-BR (95%CI)	p-value
RF negative	1.00 (Ref)	
RF positive (>1x ULN)	**4.40 (2.14-9.07)**	**<0.0001**
RF negative	1.00 (Ref)	
RF low-positive (>1-3x ULN)	1.95 (0.67-5.66)	0.22
RF high-positive (>3x ULN)	**5.44 (2.57-11.54)**	**<0.0001**
Anti-CCP negative	1.00 (Ref)	
CCP positive (>1x ULN)	**3.47 (1.65-7.31)**	**0.001**
Anti-CCP negative	1.00 (Ref)	
Anti-CCP low-positive (>1-3x ULN)	1.45 (0.29-7.32)	0.65
Anti-CCP high-positive (>3x ULN)	**3.73 (1.76-7.90)**	**0.0006**

* 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)
†Adjusted for age, sex, race, RA duration, smoking status, pack-years, and body mass index
anti-CCP = anti-cyclic citrullinated peptide; BR = bronchiectasis; CI = confidence interval; OR = odds ratio; RA = rheumatoid arthritis; RF = rheumatoid factor; ULN = upper limit of normal

Table 4: Other etiologies of bronchiectasis in RA-associated bronchiectasis cases

Etiology	n, % 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%)

* There were no cases with alpha-1 antitrypsin deficiency, cystic fibrosis, or eosinophilic granulomatosis with polyangiitis