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Prevalence and risk factors of bronchiectasis in rheumatoid arthritis: A systematic review and meta-analysis

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Abstract

Objectives: We performed a systematic review and meta-analysis for the prevalence and risk factors of rheumatoid arthritis-related bronchiectasis (RA-BR).

Methods: We queried PubMed and EMBASE databases to identify published literature related to prevalence and risk factors for RA-BR among patients with RA. Data extraction included study design, country, year, method of RA-BR detection, RA characteristics, numerator of RA-BR cases and denominator of patients with RA, and associations with RA-BR presence. We performed a meta-analysis using random or fixed effects models to estimate the prevalence of RA-BR among RA.

Results: Out of a total of 253 studies, we identified 41 total studies that reported on prevalence (n=34), risk factors (n=5), or both (n=2). The included studies had heterogeneous methods to identify RA-BR. Among the 36 studies reporting prevalence, 608 RA-BR cases were identified from a total of 8,569 patients with RA. In the meta-analysis, the pooled overall prevalence of RA-BR among RA was 18.7% (95%CI 13.7–24.3%) using random effects and 3.8% (95%CI 3.3–4.2%) using fixed effects. Among studies that used high-resolution chest computed tomography (HRCT) imaging, the prevalence of RA-BR was 22.6% (95%CI 16.8–29.0%) using random effects. When only considering retrospective studies (n=12), the pooled prevalence of RA-BR among RA was 15.5% (95%CI 7.5–25.5%); among prospective studies (n=24), the pooled prevalence was 20.7% (95% CI 14.7–27.4%). Risk factors for RA-BR included older age, longer RA duration, genetics (*CFTR* and *HLA*), and undetectable circulating mannose binding lectin (MBL) biomarker.

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Conclusion: In this systematic review and meta-analysis, the prevalence of RA-BR was nearly 20% among studies with HRCT imaging, suggesting that bronchiectasis may be a common extra-articular feature of RA. Relatively few factors have been associated with RA-BR. Future studies should standardize methods to identify RA-BR cases and investigate the natural history and clinical course given the relatively high prevalence among RA.

Keywords

rheumatoid arthritis; bronchiectasis; pulmonary

INTRODUCTION

Although rheumatoid arthritis (RA) is known to affect lung structure and function(1), the prevalence of overall lung involvement among patients with RA varies significantly across studies(2). Bronchiectasis (BR) is an established extra-articular manifestation of RA, which presents as irreversible damage to the bronchi along with widening and thickening resulting in exuberant mucus production(3, 4). BR in RA patients (hereafter termed as RA-BR) can lead to decreased quality of life as well as increased risk for infection and mortality(5–7). Mortality of RA-BR has been reported to be over 7-fold higher than the general population, and 5-fold higher than RA without BR(6). RA-BR also poses a large economic burden, as both conditions are lifelong(3). Therefore, it is important to gain a better understanding of the factors that may increase risk for developing RA-BR, as well as identifying how prevalent this condition is around the world. Investigating the burden of RA-BR may lead to a better understanding of pathogenesis and improved management. The prevalence and risk factors of RA-BR are unclear in previous studies.

To address these gaps in knowledge, we focused on summarizing the prevalence of RA-BR using a systematic review and performed a quantitative meta-analysis. Additionally, we investigated the risk factors for BR presence in RA patients through a systematic review.

1. METHODS

We performed a systematic review and meta-analysis of the prevalence and risk factors of RA-BR. We used the PRISMA-P 2015 checklist and pre-registered (ID#199080 on PROSPERO).

2.1 Search strategy and study selection

We queried PubMed and EMBASE databases. The search strategy was based on the PRISMA 2019 search strategy flow diagram. We searched for “rheumatoid arthritis; AND; bronchiectasis.” No further limits were set during this search to allow for all possible results. The inclusion and exclusion criteria were assessed for study eligibility by two independent abstractors. The search was conducted on July 15, 2020.

2.2 Eligibility criteria

The following specific inclusion criteria were applied during screening: (1) peer-reviewed original science; (2) reported at least 5 patients; (3) published in English; and (4) related to

both RA and BR. For the prevalence aim, we required that RA-BR be identified among a larger denominator of patients with RA. For the risk factors aim, we required that RA-BR be the outcome of interest among an RA population. The results were required to be statistically significant in the study. The following study characteristics were excluded during screening: (1) non-primary literature (i.e., review articles, editorials); (2) case reports or series involving fewer than 5 human patients; (3) published in a language other than English; (4) did not relate to both RA and BR; and (5) studies not involving humans (e.g., mouse models).

We initially screened article titles and abstracts to remove articles that obviously did not meet study criteria. After the initial screen, we conducted a full text review to verify inclusion and exclusion criteria for eligibility. All articles were reviewed independently by two individuals to verify inclusion and exclusion criteria were met. The data were extracted independently by two reviewers (LMW and LCP) into data extraction tools. A third individual (JAS) adjudicated disagreements.

2.3 Summary measures

The main objective of this review was to summarize and report on the prevalence and risk factors of RA-BR. The study population was defined as anyone with RA according to the study criteria. BR was defined according to each study criteria and needed to occur among patients with RA. None of the selected studies for review included interventions, due to a lack of interventional studies relating to this topic. All studies included were observational, and the outcome of interest was RA-BR.

The data measuring prevalence of RA-BR was extracted and confirmed by two separate reviewers. Relevant data that reported on the prevalence of BR in RA included sample size, RA disease duration, number of BR cases (numerator) among RA sample (denominator) and methods of diagnosis such as type and indication (clinical or research) of chest imaging. BR in RA cases among patients with RA-associated interstitial lung disease (RA-ILD) were also reported, if applicable. We then summarized the subset of studies that studied both bronchiectasis and ILD since RA-BR may have been secondary due to traction from ILD, rather than primary/isolated RA-BR, in these patients.

A quantitative meta-analysis was conducted using the R software package for the prevalence of RA-BR among RA cases using a random effects model for all studies meeting our initial inclusion criteria as the primary analysis. We also performed meta-analyses separately among retrospective and prospective study designs.

A series of sensitivity analyses were conducted for the meta-analyses. First, we repeated the primary analysis but used fixed effects instead of random effects. The rest of the sensitivity analyses used random effects and considered the combined, retrospective, and prospective studies, as applicable to the studies being removed. Second, we removed a large retrospective study by Shadick et al. due to having an uncertain denominator(8). Third, we removed two additional studies due to chest imaging not obtained on all patients(9, 10). Fourth, a prospective study was removed due to use of research chest radiographs instead of chest computed tomography (CT) scans(11). Fifth, we limited the analyses to studies that

only used high resolution (HRCT) scans as a chest imaging modality. Finally, we removed studies with fewer than 50 patients.

Risk factors were assessed among selected articles and data were extracted by two separate reviewers. We examined all exposures that the literature investigates as a potential risk factor for BR among patients with RA. Measures of assessing risk factors were recorded including risk factor type, population type, comparison group, odds ratio (OR), relative risk (RR), frequency, and proportions. Only statistically significant findings were included in the review.

2.4 Risk of bias

To address risk of bias, two independent reviewers assessed studies for eligibility and extracted data. A third reviewer completed final assessments of studies and data extraction to assure all data included were accurate. All studies were categorized according to type of study design. We also quantified the type and presence of chest imaging and whether this was performed for clinical or research purposes.

3. RESULTS

3.1. Study selection

A total of 253 articles were identified through our database search. In the initial screen of titles and abstracts, we excluded 45 review articles and 105 extraneous articles (see Figure 1 for flow diagram). After screening the full text, we removed an additional 62 articles for the following reasons: did not report on RA-BR prevalence or risk factors among RA (n=42); less than 5 patients included (n=8); risk factors not statistically significant (n=3); and denominators did not consist of RA (n=9).

In total, we included 41 full-text articles: 34 articles were included only for prevalence, 5 articles included only for risk factors, and 2 articles were included for both prevalence and risk factors. There were 36 articles reporting both RA-BR numerators and RA denominators that were included in the quantitative meta-analysis of RA-BR prevalence.

3.2. RA-BR in retrospective studies

The data collected in each retrospective study relating to prevalence are in Table 1. Dates of publication ranged from 1994 to 2020 and were conducted in France (n=5), USA (n=2), Japan (n=1), China (n=1), and Saudi Arabia (n=1). Mean RA duration ranged from 3.5 to 21.2 years. Sample size ranged from 25 to 4,000 patients with RA. All studies except Allain et al. used clinical CT or HRCT to confirm BR diagnosis(2, 8, 9, 12–19). Three studies did not conduct imaging on all patients analyzed(8–10). One study(17) specified that 270 patients were excluded due to lack of imaging. Research review of imaging modality varied considerably among studies, including blinding from clinical data, experience of radiologist, number of radiologist reviewers. Three studies did not report on the methods of RA-BR identification(8, 15, 18). One study compared prevalence of BR in RA-ILD to RA-no-ILD(18).

3.3. RA-BR in prospective studies

The prospective studies relating to RA-BR prevalence are shown in Table 2. Dates of publication ranged from 1994 to 2020 and were conducted in countries such as France (n=4), Turkey (n=2), Brazil (n=2), and UK (n=3). Two papers reported on the same cohort of patients(20, 21). Mean RA duration in years ranged from less than 1 to 17.1. Four studies did not report RA duration(20–23). Sample size ranged from 20 to 332 total RA patients. All used research chest CT or HRCT to identify BR diagnosis except one study which used research chest radiograph(11). Review of imaging varied among studies, such as blinding of clinical data, experience of radiologist and number of radiologist reviewers, with three studies not reporting(20, 21, 24). Six studies included data on RA-ILD(1, 23, 25–28), with two comparing BR in RA-ILD to BR in RA-no-ILD(25, 26). One study only included RA-ILD patients in the denominator of the study sample(23). Eight studies only included RA patients that did not have respiratory symptoms or airway abnormalities prior to enrollment(26, 27, 29–34), and 16 studies included patients that either reported respiratory symptoms or there was a suspicion of pulmonary abnormalities(1, 11, 20–25, 28, 35–41).

3.4. RA-BR among patients with RA and other lung diseases

Some studies reported on BR among patients with RA-associated interstitial lung disease (RA-ILD). We identified 7 studies that studied the intersection of RA-BR and RA-ILD (Table 5).One retrospective study by Zhang et al. compared BR in RA-ILD patients to RA-no-ILD, and the prevalence was higher in RA-ILD (18.1%) compared to RA without ILD (10.5%)(18). Six prospective studies included data on BR in RA-ILD patients. McDonagh et al. reported that RA-BR prevalence was higher in RA-ILD (30.0%) compared to RA without ILD (20.0%)(26), while Matsumoto et al. reported that RA-BR prevalence was higher in RA without ILD (9.6%) compared to RA-ILD (0.0%)(25). An additional two patients from a cohort of 36 had traction BR secondary to ILD, and another study found 2 cases of RA-ILD among RA-BR patients(1, 28). Demir et al. stated that of 23 patients with suspected or confirmed RA-ILD, 9 (39%), had RA-BR(27). Overall lung involvement in RA patients ranged from 7–80%, with RA-ILD being the most common(2), which could impact the overall prevalence due to varying definitions of lung abnormalities across studies.

3.5. Prevalence of RA-BR among RA meta-analysis results

A series of meta-analyses were performed to determine the prevalence of BR among patients with RA in the reported literature. Forest plots of the included studies are shown in Figure 2 for all studies, Figure 3A for retrospective studies, and Figure 3B for prospective studies.

Among the 36 studies, 608 RA-BR cases were identified from a total of 8,569 patients with RA. In the primary analyses, the pooled overall prevalence of RA-BR in the random effects meta-analysis was 18.7% (95%CI 13.7–24.3%), Figure 2). Among retrospective studies (n=12) reporting RA-BR, the prevalence was 15.5% (95% CI 7.5–25.5%, Figure 3A). Among prospective studies (n=24), the prevalence of RA-BR in the meta-analysis was 20.7% (95% CI 14.7–27.4%, Figure 3B).

Prevalence was lowest in retrospective studies where RA-BR was identified through clinical care (e.g., two large retrospective studies that investigated 4,000 and 1,129 RA patients reported RA-BR prevalence of 0.6% and 2.7%, respectively(2, 8)).

3.6. Sensitivity analysis results

Sensitivity results of meta-analyses are shown in are shown in Table 3. In the meta-analysis using fixed effects, the prevalence of RA-ILD among RA was 3.8% (95%CI 3.3–4.2%). The remaining analyses used random effects as a variation of the primary analysis. After removing a large study with an uncertain denominator, the prevalence was 19.6% (95%CI 14.7–25.1%). After removing four studies(8–11) that did not obtain chest imaging on all patients or used of research chest radiograph instead of chest CT scans, the prevalence was 21.9% (95% CI 16.9–27.4%). When we restricted the analysis to include studies that only conducted HRCT scans (n=24), the prevalence was 22.6% (95% CI 16.8–29.0%). After limiting to studies that had fewer than 50 patients (n=23), the prevalence was 14.4% (95% CI 9.3–20.3%).

3.7. Risk factors for RA-BR

A total of seven studies included in our review found statistically significant risk factors for RA-BR presence among patients with RA(3, 30, 42–46), included in Table 4. Older age and African American ethnicity were the only statistically significant demographic risk factors reported(3, 30). Six genetic risk factors were reported among four studies including CFTR mutations and HLA genetic variants. Hillarby et al. reported that the proportion of *HLA-DQB1*0601* in RA-BR was 31%, compared to 4.0% in RA-no-BR (p=0.0001) and also found statistically significant differences in proportion among *HLA-DQA* and *HLA-DQB* variants(44). Toussirot et al. found the proportion of *HLA-DRB1**0401 to be higher among RA-BR patients (39%) compared to RA-no-BR (17%) (p<0.001)(45). Two studies found significant differences in *CFTR* for RA-BR risk(42,43). Undetectable circulating mannose binding lectin was the only biomarker reported to be associated with developing BR in RA patients (37.5%) when compared to RA-no-BR (8.9%) (p=0.005)(46). Additionally, biologic disease-modifying antirheumatic drug use was reported as having statistically lower odds of RA-BR compared no use(46).

4. DISCUSSION

In this systematic review and meta-analysis, the prevalence of RA-BR among RA was 18.7% among the 36 included studies, emphasizing that BR may be a common and underrecognized extra-articular feature of RA. However, given that most studies incorporated chest imaging, this may include subclinical involvement. Despite how common RA-BR may be, we only identified 7 studies that reported statistically significant risk factors for RA-BR, emphasizing the relative lack of literature regarding risk factors of BR in RA patients.

When studies were separated based on study design (prospective vs. retrospective) the prevalence was 15.5% vs. 20.7%, respectively. This difference could be attributed to the use of either research scans or clinical scans that results in overestimation of BR diagnosis.

Wiater et al. recently conducted a similar systematic review on RA-BR prevalence and reported similar results: prevalence of 21.1% overall; clinical prevalence was (2.69%) and prevalence among those with imaging was 24.9%(5). Our results extend these by performing additional sensitivity analyses and also systemically reviewing the current literature related to risk factors for RA-BR.

Our results also indicate heterogeneous study designs and methods related to identification and case definitions of RA-BR. Studies varied considerably related to key factors such as prospective vs. retrospective design, sample size, diagnostic tools, and demographic or clinical features of included patients. For example, prevalence ranged from 0.6% to 58.0% across all studies included, 0.6% to 52.0% in retrospective studies, and 1.9% to 58% in prospective studies. Smaller studies of both prospective and retrospective methods generally reported higher prevalence of RA-BR, while most larger studies reported lower prevalence with regards to our pooled prevalence of 18.7%. The prevalence largely varied among clinical and research scans, use of CT, HRCT, or radiographic methods. Additionally, many studies did not report on whether experienced chest radiologists were involved in the detection of RA-BR caes. The inclusion or exclusion of reported respiratory symptoms prior to BR diagnosis in RA patients may have resulted in either an underestimation of BR diagnosis or, for the latter, identification of subclinical BR. Secondary or co-existing pulmonary conditions such as RA-ILD are another possible explanation, and 7 included studies reported on this(1, 18, 23, 25–28), three of which found a higher prevalence of BR in RA-ILD patients compared to RA without known ILD(18, 26, 27). The significant variation in prevalence highlights the need for longitudinal studies with larger RA cohorts to investigate the prevalence rates of BR in RA patients, taking into account the current diagnostic methods for BR (chest CT vs. HRCT vs. clinical symptoms), RA disease duration, and population characteristics related to respiratory symptoms and pre-test clinical suspicion for pulmonary involvement. There are also may be a selection bias in prospective studies where patients may be more amenable to participate if they have respiratory symptoms. Conversely, healthy individuals may be more amenable to participate in research studies. Thus, the results of our prevalence studies should be interpreted with caution and more work is needed to establish the true clinical and subclinical prevalence. However, our results do emphasize that BR is under-recognized and under-studied. RA-BR may have important implications related to the growing literature implicating airways disease in RA pathogenesis(47–51). RA-BR are also known to have increased risk for infection mortality(6, 52–54). Therefore, our results emphasize the many gaps in the literature related to RA-BR that deserve future study.

There were only 7 studies that reported statistical associations of risk factors with presence of RA-BR among RA patients. Based on our findings, the strongest evidence for possible risk involved genetics, but three(43–45) of the four studies were conducted >20 years ago, which demonstrates the need for updated research focusing on larger sample size and standardized diagnostic methods. The 6 genetic risk factors linked to BR development were reported in four studies(42–45) which focused on *CFTR* and *HLA* variants. A strength of Hillarby et al. study was its larger sample size when compared to all other risk factor groups, but its method of BR diagnosis using either surgery or bronchography could create inconsistent reports of true BR(44). Puechal et al. had a fairly small sample size in both

studies looking at *CFTR* mutation, but its method of BR diagnosis was most reliable in comparison to the other studies of genetic risk factors in that it used HRCT scans reviewed by two independent reviewers(42). Additionally, Attar et al. confirmed BR diagnosis using HRCT scans reviewed by a senior radiologist when reporting on age and RA disease duration(30). Disease duration and age of RA patients were identified as risk factors in the study by Attar et al. where BR in RA patients had a greater mean RA disease duration by 3.65 years, as well as older mean age by 11.6 years(30). This emphasizes the need to focus on and categorize patient age and disease duration when reporting the etiology and prevalence of BR in RA. The two studies that found increased odds of BR in RA among patients with African American ethnicity (compared to European)(3) and no use of biologic DMARDs(46) should be investigated further. The former association may be surprising given the higher prevalence of *CFTR* mutations in those with European ancestry. The latter association could be due to possible reverse causation and RA since clinicians may avoid biologic DMARDs due to the risk of infection. The biomarker mannose binding lectin (MBL) was found to be undetectable in a greater proportion of RA-BR patients compared to RA-no-BR(46). MBL is a pattern recognition molecule of the innate immune system that binds to sugars on microbial surfaces to activate complement pathways, suggesting that innate immunity and complement system may be involved in RA-BR. However, this was a small single study so this finding should be replicated. Identification of other biomarkers are needed to elucidate the pathogenesis of RA-BR and develop screening strategies for clinical use.

Although our systematic review did not focus on non-statistically significant risk factors and followed strict inclusion criterion, it is important to mention some of the proposed risk factors in other studies. Smoking is known to increase the risk of RA as well as various obstructive lung diseases(7, 55), but there is no current evidence suggesting smoking as a risk factor for BR development in RA(44). On the contrary, Kaushik et al. reported a higher proportion of non-smokers in the RA-BR group compared to RA alone, and those with RA only had a higher smoking pack-year mean than those with RA-BR(55). Elevated inflammatory markers were also mentioned as a potential risk factor in two studies(30, 56), one of which found elevated CCP and RF antibodies in a higher proportion of RA-BR patients compared to RA-no-BR, but this was not statistically significant(56). Further research is needed to clarify the link between these risk factors and development of BR in RA patients.

The sample sizes and scans not conducted on all patients may influence the estimation of individual prevalence rates. For example, the largest study approximated the total RA patients studied as 4,000, but clinical CT was not conducted on all patients analyzed(8), which could explain why the prevalence was only 0.6%. As expected, the prevalence increased when we removed this study (to 19.6%) and again when we removed studies that did not conduct imaging on all patients (to 21.0%)(9, 10).

As mentioned previously, most of the smaller studies had higher prevalence rates. After 13 studies with 50 or fewer patients were removed, the prevalence decreased to 14.4%(1, 14–16, 22, 26–29, 31, 34, 36, 41), representing a significant portion of the overall prevalence studies. The studies with some of the largest sample sizes in comparison to others,

reported a lower prevalence of RA-BR than our pooled prevalence. Duarte et al. reported a prevalence of 2.75% among 1,129 RA patients(2), and Matsumoto et al. reported a 9.6% prevalence among 332 RA patients(25). Due to differing study design methods and reporting of other variables, it is unclear whether and which factors could have impacted the results. For example, individual patient demographics, including RA disease duration and reported respiratory symptoms pose a limitation due to inconsistencies across included studies. Additionally, it was important to include any data on suspected RA-associated interstitial lung disease (RA-ILD) which could interfere with the accuracy of reported lung abnormalities, specifically relating to BR.

Recommended chest imaging modality for BR diagnosis is vital for accurate diagnosis, and 12 of the studies did not use HRCT scans(8–12, 14, 16, 19–21, 25, 41). When these studies were removed, prevalence increased to 22.6%. There was significant heterogeneity in the methods used to interpret imaging scans and identify RA-BR cases across all studies. Five of the studies did not report details on image interpretation.(8, 9, 18, 20, 21, 24). This emphasizes the need for a reliable and consistent method of BR diagnosis among RA patients.

4.1. Strengths and Limitations

Strengths of our systematic review and meta-analysis were the use of pre-specified inclusion and exclusion criteria as well as extensive research and review of all relevant published articles on BR and RA. Several sensitivity analyses were conducted to provide further support and clarity on what may or may not impact resultsA limitation included the inability to clearly identify the underlying causes of bronchiectasis. Bronchiectasis could be isolated or secondary to architectural distortion from fibrotic lung disease. Patients with isolated bronchiectasis may be more likely to require treatment aimed at primary airway dysfunction including mucociliary clearance, antibiotics, bronchodilators, and perhaps azithromycin. Bronchiectasis secondary to traction due to bronchiectasis may be less likely to be complicated by these issues so may be clinically distinct. Therefore, we summarized the specific studies that studied both RA and ILD. These findings highlight the need for more standardized assessments for bronchiectasis in RA, either isolated or due to traction from ILD, among other causes. We limited inclusion criteria to statistically significant risk factors, but it is possible overall trends could have been identified for risk factors that were not statistically significant in the individual studies. Another limitation is our use of 2 reviewers during the process of literature review, and may have resulted in risk of assessment bias. Additionally, after the search, we may have left out recently published relevant studies.

5. Conclusion

The prevalence of RA-BR in this systematic review and meta-analysis was 18.7%, emphasizing that bronchiectasis is a common extra-articular feature of RA. There were relatively few risk factors identified for RA-BR presence among RA, including older age, longer RA duration, genetics (*CFTR* and *HLA*), and undetectable MBL. Future studies should standardize methods to identify RA-BR cases and investigate the natural history and clinical course given the relatively high prevalence that we report.

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Declaration of Competing Interest

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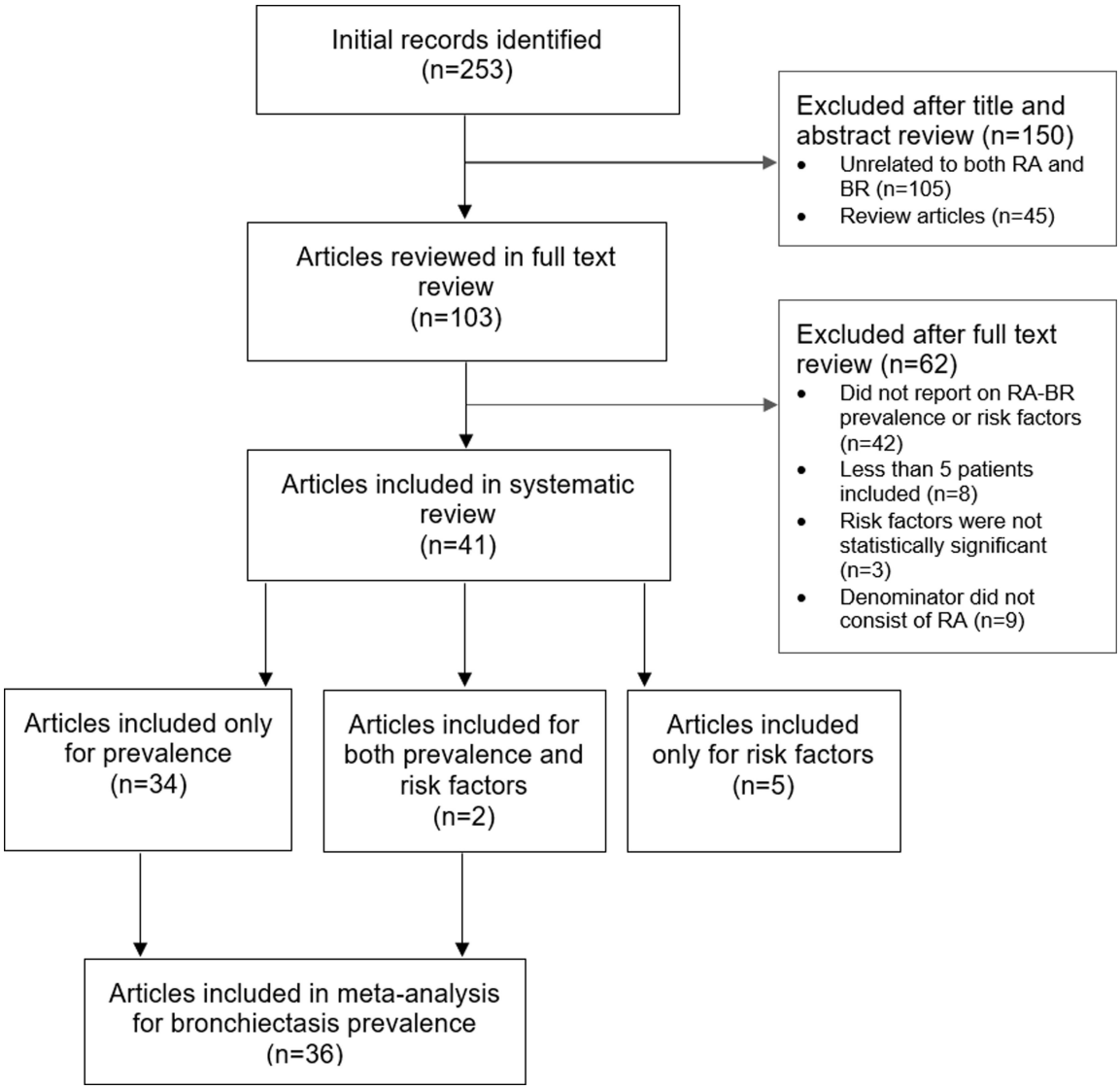


Fig. 1.

PRISMA flow diagram of studies assessed for bronchiectasis prevalence and risk factors among patients with rheumatoid arthritis.

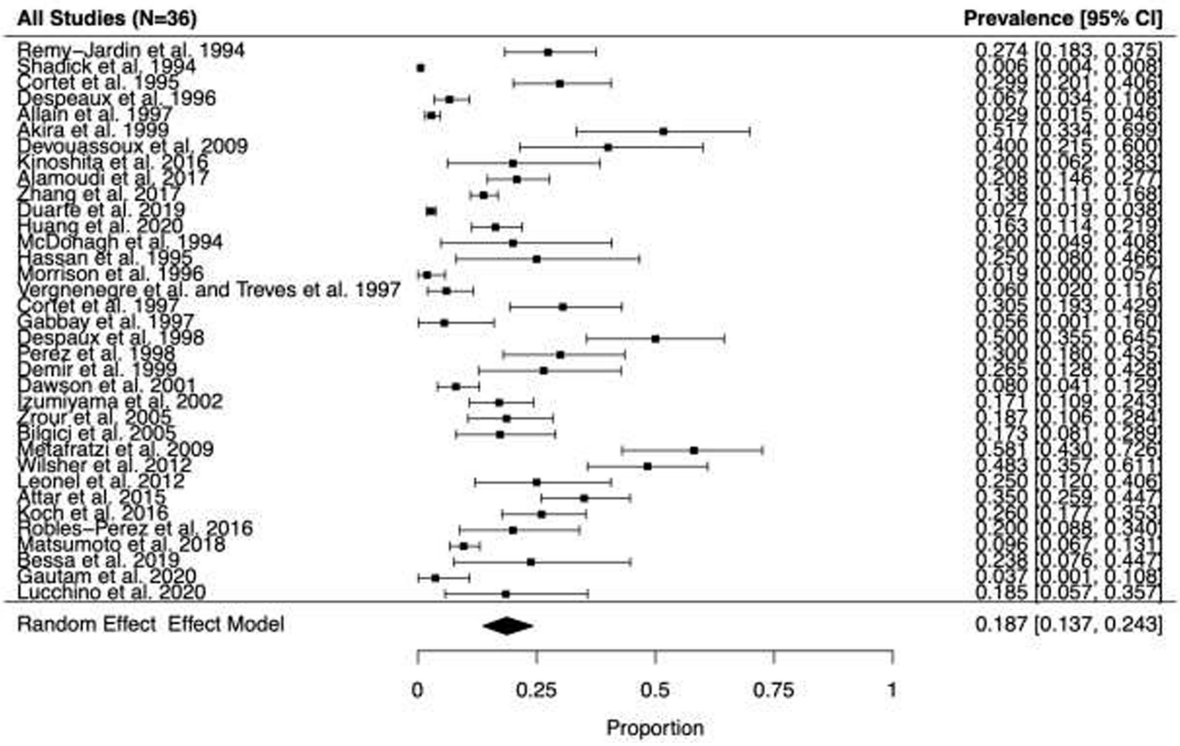
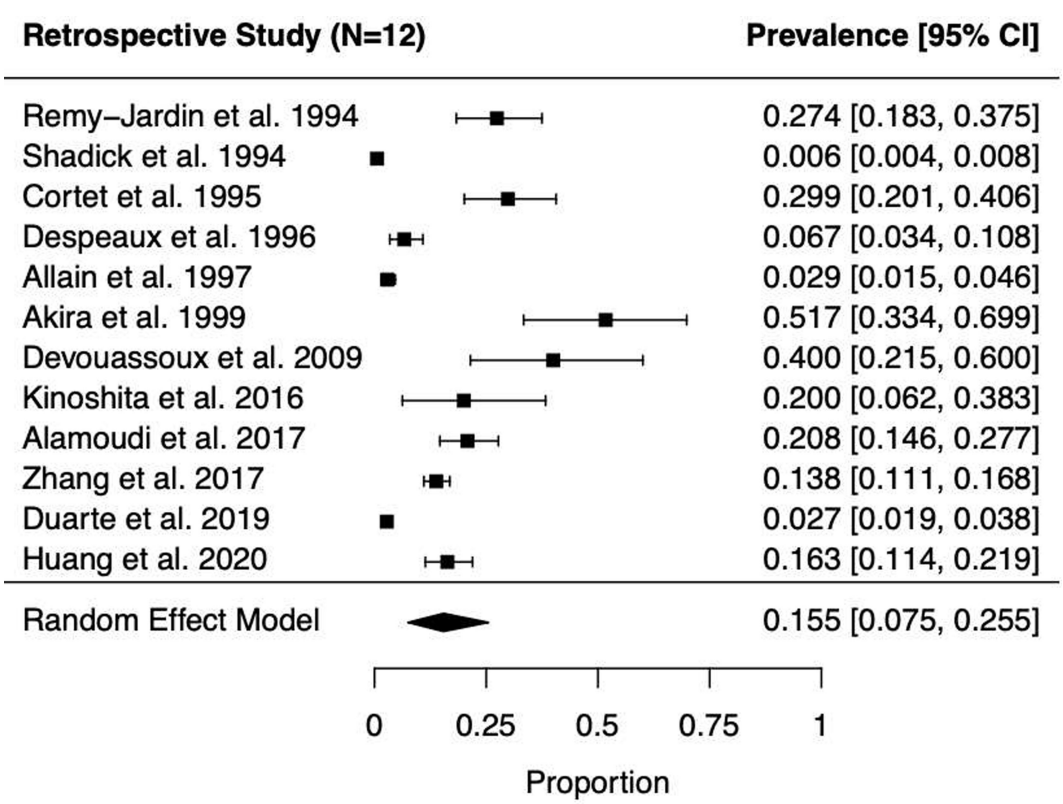


Fig. 2.

Forest plot and random effects meta-analysis for prevalence of bronchiectasis among patients with rheumatoid arthritis in all studies (n=36).



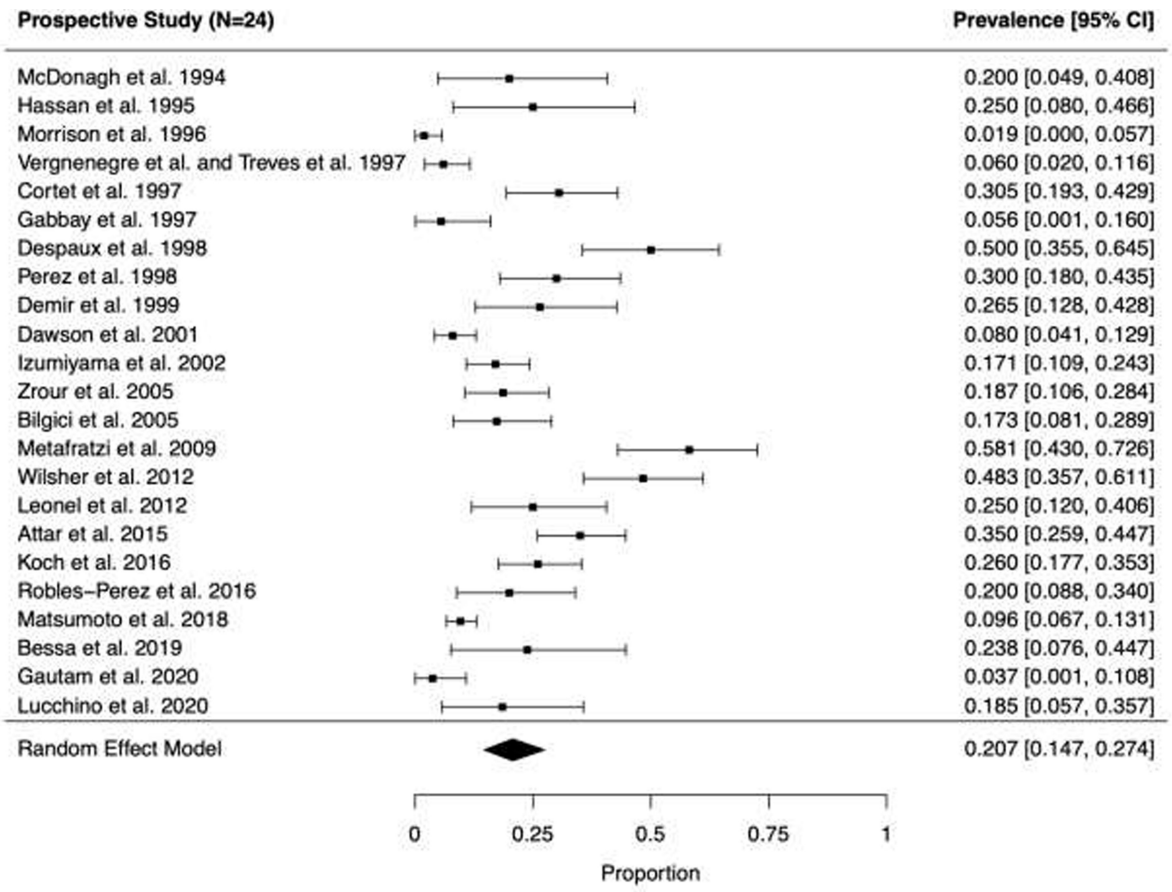


Fig. 3.

Forest plots and random effects meta-analyses of prevalence of bronchiectasis among patients with rheumatoid arthritis in (A, top panel) retrospective (n=12) and (B, bottom panel) prospective studies (n=24).

Table 1.

Retrospective studies reporting the prevalence of bronchiectasis among patients with rheumatoid arthritis (n=12).

Reference	Year	Country	RA duration, years	Patients with prevalent RA-BR (numerator)	Total RA patients studied, n (denominator)	Prevalence of RA-BR in RA (%)	Chest imaging modality used	Details on review of images and other notes
Remy-Jardin et al.	1994	France	Mean 12 (SD 8)	n=23	n=84	27.4%	Clinical CT	Two observers blinded to clinical history; Some of the total RA patients had suspected respiratory symptoms
Shadick et al.	1994	USA	Mean 6.4	n=23	n=4,000	0.6%	Clinical CT (not on all patients analyzed)	Not reported; Total RA patients studied is approximated
Cortet et al.	1995	France	Mean 12 (SD 8)	n=23	n=77	30.0%	Clinical HRCT	Two radiologists blinded to clinical history; Some of the total RA patients reported respiratory symptoms
Despeaux et al.	1996	France	Mean 11.1	n=12	n=180	6.7%	Clinical CT (not on all patients analyzed)	Not reported; Of the total patients studied, 100 had RA and 80 had BR, but 4/80 BR patients had RA and 8/100 RA patients had BR; Some of the total patients studied reported respiratory symptoms
Allain et al.	1997	France	Mean 8.12 (SD 7.85)	n=13	n=453	2.9%	Research chest radiographs (not on all patients analyzed)	Probable symptomatic RA-BR defined based on criteria from Walker WC, The lung in RA, MD Thesis, University of Edinburgh, 1966, which do not take CT findings into account; research chest CT performed for patients with chronic lower respiratory tract symptoms but no typical evidence of RA-BR on chest radiograph
Akira et al.	1999	Japan	Not reported	n=15	n=29	52.0%	Clinical CT	Two experienced chest radiologists blinded to clinical history; All patients included had respiratory symptoms
Devouassoux et al.	2009	France	Mean 7.8 (SD 8.2)	n=10	n=25	40.0%	Clinical HRCT	Research physicians (blinding unspecified); All patients included had respiratory symptoms
Kinoshita et al.	2016	Japan	Mean 5.0 (SD 3.9)	n=5	n=25	20.0%	Clinical CT	Two chest radiologists blinded to clinical history
Alamoudi et al.	2017	Saudi Arabia	Mean 3.5 (SD 4.6)	n=31	n=149	20.8%	Clinical HRCT	Two senior radiologists reviewed images (blinding unspecified); Some of the total RA patients reported respiratory symptoms (Excluded 270 patients from analysis due to no scan)
Zhang et al.	2017	China	Mean 8 (SD 9)	n=76	n=550	13.8%	Clinical HRCT	Not reported; Some of the total RA patients reported respiratory symptoms RA-BR prevalence was higher in RA-ILD (18.1%) compared to RA without ILD (10.5%)
Duarte et al.	2019	UK	Mean 14 (IQR 8–29 years)	n=31	n=1129	2.7%	Clinical HRCT	Expert thoracic radiologists reviewed in multidisciplinary meeting with radiologists, pulmonologists and rheumatologists (blinding unspecified); Most of the total RA patients reported respiratory symptoms

Reference	Year	Country	RA duration, years	Patients with prevalent RA-BR (numerator)	Total RA patients studied, n (denominator)	Prevalence of RA-BR in RA (%)	Chest imaging modality used	Details on review of images and other notes
Huang et al.	2020	USA	Mean 21.2 (SD 13.2)	n=31	n=190	16.3%	Clinical CT	Clinical report, cases verified by blinded review from two expert chest radiologists; Some of the total RA patients reported respiratory symptoms

CT, computed tomography; HRCT, high-resolution computed tomography; RA, rheumatoid arthritis; RA-BR, rheumatoid arthritis-associated bronchiectasis; SD, standard deviation.

Table 2.

Prospective studies reporting the prevalence of bronchiectasis among patients with rheumatoid arthritis (n=24).

Reference	Year	Country	RA duration, years (unless specified)	Patients with prevalent RA-BR (numerator)	Total RA patients studied, n (denominator)	Prevalence of RA-BR in RA (%)	Chest imaging modality used	Details on review of images and other notes
McDonagh et al.	1994	United Kingdom	Median 9 (range 1–27)	n=4	n=20	20.0%	Research HRCT	Two radiologists blinded to clinical history; all patients had no respiratory symptoms RA-BR prevalence was higher in RA-ILD (30.0%) compared to RA without ILD (20.0%)
Hassan et al.	1995	United Kingdom	Mean 9 (range 1–30)	n=5	n=20	20.0%	Research HRCT	One radiologist blinded to clinical history; all patients had no respiratory symptoms
Morrison et al.	1996	South Africa	Mean 12.4 (range 1–50)	n=2	n=104	1.9%	Research chest radiograph	Respiratory physician and radiologist blinded to clinical history; Some of the total RA patients studied reported respiratory symptoms
Vergnenegre et al. and Treves et al.	1997	France	Not reported	n=6	n=100	6.0%	Research CT	Not reported; RA-BR was suspected on clinical symptoms and radiological findings; Some of the total RA patients studied reported respiratory symptoms Each paper analyzed same patients.
Cortet et al.	1997	France	Mean 12 (SD 9.2)	n=18	n=59	30.5%	Research HRCT	Experienced radiologists blinded to clinical history; Some of the total RA patients studied reported respiratory symptoms Excluded 9 patients from analysis due to previous radiation therapy
Gabbay et al.	1997	Australia	Mean 13.2 (SD 8.6) months	n=2	n=36	6.0%	Research HRCT	Two radiologists blinded to clinical history; additional 2 patients had traction bronchiectasis secondary to ILD
Despaux et al.	1998	France	Mean 10.6 (range 2–29)	n=23	n=46	50.0%	Research HRCT	One radiologist blinded to clinical history; Some of the total RA patients studied reported respiratory symptoms
Perez et al.	1998	France	Mean 14.4 (SD 1.3)	n=15	n=50	30.0%	Research HRCT	Two observers blinded to clinical history; all patients had no airway abnormalities preceding the scan
Demir et al.	1999	Turkey	Mean 5.38 (SD 2.8)	n=9	n=34	26.0%	Research HRCT	One experienced radiologist blinded to clinical history; all patients had no known airways abnormalities before scan. Of 23 patients with suspected or confirmed RA-ILD, 9 (39%) had RA-BR.
Dawson et al.	2001	United Kingdom	Mean 12.7 (SD 8)	n=12	n=150	9.5%	Research HRCT	Two consultant radiologists blinded to clinical history; Some of the total RA patients studied reported respiratory symptoms
Izumiyama et al.	2002	Tokyo	Mean 10.2	n=21	n=123	17.1%	Research HRCT	Two trainee clinicians and one radiologist blinded to clinical history; patients with syndromes overlapping with other rheumatic diseases were not included; Some of the total RA patients studied reported respiratory symptoms Excluded 63 patients from analysis due to no scan

Reference	Year	Country	RA duration, years (unless specified)	Patients with prevalent RA-BR (numerator)	Total RA patients studied, n (denominator)	Prevalence of RA-BR in RA (%)	Chest imaging modality used	Details on review of images and other notes
Zrour et al.	2005	Tunisia	Mean 96 (SD 88) months	n=14	n=75	18.7%	Research HRCT	Not reported; Respiratory symptoms reported in 33% of total RA patients studied
Bilgici et al.	2005	Turkey	Mean 8.37 (SD 8.17)	n=9	n=52	17.0%	Research HRCT	Two radiologists (blinding unspecified); patients with history of airways abnormalities were not included Excluded 2 patients from analysis due to no pulmonary function tests
Metafratzi et al.	2009	Greece	Less than 1	n=25	n=43	58.0%	Research HRCT	Two observers blinded to clinical history; all patients had no known airways abnormalities before scan
Wilsher et al.	2012	New Zealand	Median 7 (range 1–12) months	n=29	n=60	48.0%	Research HRCT	Two experienced independent radiologists blinded to clinical history; Respiratory symptoms reported in 30% of total RA patients studied
Leonel et al.	2012	Mexico	Not reported	n=9	n=36	4.0%	Research HRCT	Two independent radiologists (blinding unspecified); All RA patients studied had clinical or radiological respiratory symptoms
Attar et al.	2015	Saudi Arabia	Mean 6.19 (SD 6.4)	n=35	n=100	35.0%	Research HRCT	One senior radiologist (blinding unspecified); all patients had no known previous airways abnormalities
Koch et al.	2016	Brazil	Mean 16.7 (SD 8.8)	n=25	n=96	26.0%	Research HRCT	Two radiologists alone or in consensus (blinding unspecified); Respiratory symptoms reported in 15.6% of the total RA patients studied
Robles-Perez et al.	2016	Spain	Median 12 months	n=8	n=40	20.0%	Research HRCT	Reviewed by expert lung radiologist (blinding unspecified); Respiratory symptoms reported in 70% of the total RA patients studied RA-ILD was found in 2 of the cases of RA-BR
Matsumoto et al.	2018	Japan	Mean 17.1 (SD 10.2)	n=32	n=332	9.6%	Research CT	Two experienced radiologists, one with 23 years' experience reading thoracic CTs and another randomly selected, both blinded to clinical history; Some of the total RA patients studied reported respiratory symptoms RA-BR prevalence was higher in RA without ILD (9.6%) compared to RA-ILD (0.0%)
Bessa et al.	2019	Brazil	Median 204 (IQR 114–252) months	n=5	n=21	23.8%	Research CT	Two readers with 5 and 21 years of experience in pulmonary imaging, blinded to clinical history; Respiratory symptoms reported in 52.4% of the total RA patients studied
Gautam et al.	2020	Pakistan	Not reported	n=2	n=54	3.7%	Research HRCT	Experienced radiologists (blinding unspecified); all patients had RA-associated ILD.
Lucchino et al.	2020	Italy	Mean 13.78 (SD 11.02) months	n=5	n=27	18.5%	Research HRCT	Two radiologists blinded to clinical history; patients required to have no serious comorbidities and no respiratory symptoms

CT, computed tomography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; RA, rheumatoid arthritis; RA-BR, rheumatoid arthritis-associated bronchiectasis; SD, standard deviation.

Table 3.

Sensitivity results of meta-analyses.

Analysis	Number of studies included	Prevalence estimate	95%CI
Combined			
Main analysis	36	0.187	[0.137, 0.243]
Main analysis with fixed effects	36	0.038	[0.033, 0.042]
Shadick et al. removed due to uncertain denominator	35	0.196	[0.147, 0.251]
Removed Shadick et al., Despeaux et al., and Allain et al. due to chest imaging not obtained on all patients	33	0.210	[0.159, 0.266]
Removed Shadick et al., Despeaux et al., and Allain et al. due to chest imaging not obtained on all patients, and Morrison et al. due to use of research chest radiograph instead of chest CT scans	32	0.219	[0.169, 0.274]
Inclusion of studies with only HRCT scans	24	0.226	[0.168, 0.290]
Studies removed with less than 50 patients	23	0.144	[0.093, 0.203]
Retrospective			
Main analysis	12	0.155	[0.075, 0.255]
Main analysis with fixed effects	12	0.021	[0.017, 0.025]
Shadick et al. removed due to uncertain denominator	11	0.177	[0.095, 0.277]
Removed Shadick et al., Despeaux et al., and Allain et al. due to chest imaging not obtained on all patients	9	0.218	[0.126, 0.327]
Inclusion of studies with only HRCT scans	5	0.183	[0.068, 0.335]
Studies removed with less than 50 patients	9	0.108	[0.046, 0.193]
Prospective			
Main analysis	24	0.207	[0.147, 0.274]
Main analysis with fixed effects	24	0.166	[0.148, 0.185]
Removed Morrison et al. due to use of research chest radiograph as a chest imaging modality instead of chest CT scans	23	0.220	[0.160, 0.286]
Inclusion of studies with only HRCT scans	19	0.241	[0.176, 0.312]
Studies removed with less than 50 patients	14	0.172	[0.103, 0.254]

Table 4.

Demographics, genetics, biomarkers, and medications statistically associated with bronchiectasis among patients with rheumatoid arthritis (n=9 studies).

Reference	Year	Country	Study design	Risk factor group	Comparison group	Patients with RA-BR	Patients with RA-no-BR	Results	Notes
Demographics									
Attar et al.	2015	Saudi Arabia	Prospective cross-sectional	Older age (continuous variable)	N/A	n=35	n=65	Mean age of RA-BR: 58.6 years; Mean age of RA-no-BR: 47.0 years (p<0.001)	BR confirmed by senior radiologist evaluating HRCT scan
McShane et al.	2012	USA	Cross-sectional	African American	European American	n=12	N/A	Proportion of RA-BR in AA group: 28.6% Proportion of RA-BR in EA group: 6.2% (p<0.05)	All analyzed patients had BR. BR was confirmed by dedicated chest radiologist blinded to the study. RA was more likely to be the underlying etiology of BR for African Americans.
Rheumatoid arthritis characteristics									
Attar et al.	2015	Saudi Arabia	Prospective cross-sectional	Longer RA disease duration (continuous variable)	N/A	n=35	n=65	Mean disease duration RA-BR: 8.57 years Mean disease duration RA-no-BR: 4.92 years (p=0.006)	BR confirmed by senior radiologist evaluating HRCT scan
Genetics									
Puechal et al.	1999	France	Cross-sectional	*CFTR* mutation F508	No *CFTR* mutation F508	n=26	n=29	Proportion of *CFTR* mutation F508 in RA-BR group: 15.4%; Proportion of *CFTR* mutation F508 in RA-no-BR: 0% (p<0.05)	BR confirmed by two independent reviewers of HRCT scan
Hillarby et al.	1993	England	Prospective cross-sectional	*HLA-DQA1*0501*	No *HLA-DQA1*0501*	n=41	n=148	Proportion of *HLA-DQA1*0501* in RA-BR: 40%; Proportion of *HLA-DQA1* *0501 in RA-no-BR: 22% (p=0.039)	BR confirmed by surgery or bronchography
Hillarby et al.	1993	England	Prospective cross-sectional	*HLA-DQB1*0201*	No *HLA-DQB1*0201*	n=41	n=148	Proportion of *HLA-DQB1*0201* in RA-BR: 40%; Proportion of *HLA-DQB1*0201* in RA-no-BR: 22% (p=0.039)	BR confirmed by surgery or bronchography
Hillarby et al.	1993	England	Prospective cross-sectional	*HLA-DQB1*0601*	No *HLA-DQB1*0601*	n=41	n=148	Proportion of *HLA-DQB1*0601* in RA-BR: 31%; Proportion of *HLA-DQB1*0601* in RA-no-BR: 4.0% (p=0.0001)	BR confirmed by surgery or bronchography
Toussirot et al.	2000	France	Prospective cross-sectional	*HLA-DRB1*0401*	No *HLA-DRB1*0401*	n=15	n=25	Proportion of *HLA-DRB1*0401* in RA-BR: 39%; Proportion of *HLA-DRB1*0401* in RA-no-BR: 17%; (p<0.0001)	BR confirmed by CT scan

Reference	Year	Country	Study design	Risk factor group	Comparison group	Patients with RA-BR	Patients with RA-no-BR	Results	Notes
Puechal et al.	2010	France	Cross-sectional	*CFTR* mutation	No *CFTR* mutation	n=30	n=19	*CFTR* mutation: OR 5.30 for RA-BR ($p=5\times10^{-5}$)	BR confirmed by two independent reviewers of HRCT scan
Biomarkers									
Makin et al.	2019	Israel	Retrospective cohort	Undetectable mannose binding lectin (MBL)	Detectable MBL	n=17	n=114	Proportion of undetectable MBL in RA-BR: 37.5%; Proportion of undetectable MBL in RA-no-BR: 8.9% (p=0.005)	BR confirmed by evaluation of HRCT scan; MBL is a pattern recognition molecule of the innate immune system that binds to sugars on microbial surfaces to activate complement pathways
Medications									
Makin et al.	2019	Israel	Retrospective cohort	No bDMARD use	bDMARD use	n=16	n=115	Proportion of bDMARD use in RA-BR: 25%; Proportion of bDMARD use RA-no-BR: 75% (p=0.0002)	BR confirmed by evaluation of HRCT scan; finding could be due to reverse causation where clinicians were avoiding bDMARDs in patients with known RA-BR

bDMARD, biologic disease-modifying antirheumatic drug; BR, bronchiectasis; *CFTR*, cystic fibrosis transmembrane conductance regulator; *HLA*, human leukocyte antigen; MBL, mannose binding lectin; N/A, not applicable; RA, rheumatoid arthritis.

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Table 5.

Studies that evaluated the intersection of bronchiectasis and interstitial lung disease among patients with rheumatoid arthritis (n=7).

Reference	RA duration, years (unless specified)	Patients with prevalence RA-BR (numerator)	Total RA patients studied (denominator)	Prevalence of RA-BR in RA (%)	Comments
Gautam et al.	Not reported	n=2	n=54	3.7%	All patients had RA-ILD
Zhang et al.	Mean 8 (SD 9)	n=76	n=550	13.8%	RA-BR prevalence was higher in RA-ILD (18.1%) compared to RA without ILD (10.5%)
McDonagh et al.	Median 9 (range 1–27)	n=4	n=20	20.0%	RA-BR prevalence was higher in RA-ILD (30.0%) compared to RA without ILD (20.0%)
Gabbay et al.	Mean 13.2 (SD 8.6) months	n=2	n=36	6.0%	2 patients had traction bronchiectasis secondary to ILD
Demir et al.	Mean 5.38 (SD 2.8)	n=9	n=34	26.0%	Of 23 patients with suspected or confirmed RA-ILD, 9 (39%) had RA-BR.
Robles-Perez et al.	Median 12 months	n=8	n=40	20.0%	RA-ILD was found in 2 of the cases of RA-BR
Matsumoto et al.	Mean 17.1 (SD 10.2)	n=32	n=332	9.6%	RA-BR prevalence was higher in RA without ILD (9.6%) compared to RA-ILD (0.0%)

ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-BR, rheumatoid arthritis-associated bronchiectasis; SD, standard deviation.