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Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease or bronchiectasis: A comparative cohort study

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Running head: RA-associated lung disease and serious infection

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ABSTRACT

Objective: To investigate the association between rheumatoid arthritis-associated lung disease (RA-LD) and serious infection risk.

Methods: We conducted a retrospective cohort study using the MGB Biobank (Boston, Massachusetts), comparing RA-LD to RA patients without lung disease (RA-no LD), matched by age, sex, and RA duration. RA-LD cases were verified by medical record review and chest imaging for clinically apparent RA-associated interstitial lung disease (RA-ILD) and/or RA-associated bronchiectasis (RA-BR). The primary outcome was serious infection. Incidence rates and propensity score-adjusted subdistribution hazard ratios (sdHR) were calculated using Fine and Gray models to account for competing risk of death.

Results: Among 221 RA-LD cases (151 RA-ILD and 70 RA-BR) and 980 RA-no LD comparators, RA-LD had a significantly higher serious infection risk compared to RA-no LD comparators (55.8 vs. 25.8 per 1,000 person-years, sdHR 1.60, 95%CI 1.20-2.12). The increased risk remained significant for RA-ILD cases (sdHR 1.79, 95%CI 1.33-2.41), but not for RA-BR (sdHR 1.19, 95%CI 0.72-1.97). Anatomic sites of infection that were more common in RA-LD included pulmonary, skin and soft tissue, and ear, nose and throat; RA-LD was associated with various pathogen types: virus, bacteria, fungus, and mycobacteria. Specific pathogens with higher frequency in RA-LD cases, particularly among RA-BR, included influenza virus, respiratory syncytial virus, *Staphylococcus*, *Pseudomonas*, and nontuberculous mycobacteria.

Conclusion: RA-LD, particularly RA-ILD, is associated with a significant increased

risk of serious infection across anatomic sites and diverse pathogen types. RA-BR is associated with increased pulmonary infections. Prospective studies and trials are needed to clarify optimal approaches to treat patients with RA-LD and reduce infection risk.

INTRODUCTION

Rheumatoid arthritis-associated lung disease (RA-LD), encompassing RA-associated-interstitial lung disease (RA-ILD) and RA-associated bronchiectasis (RA-BR), is increasingly recognized as a significant contributor to morbidity and mortality in patients with RA¹⁻⁴. Most previous studies have investigated RA as a whole, identifying about a 2-fold increased risk of serious infection compared to the general population^{5,6}. Previous research^{7,8} on RA-ILD and serious infection risk mostly lacked a comparison group of RA without lung disease (RA-no LD). Findings from a recent study⁹ indicated a 2.6-fold increased risk of hospitalized infection for RA-ILD vs. RA-no ILD patients. However, this study was limited to patients who had not achieved RA remission, and did not investigate types of infection. To date, the relationship between RA-BR and serious infection has not been investigated in studies incorporating a comparator group.

Immune dysregulation due to RA^{6,10} and immunosuppressive treatments¹¹⁻¹³ may increase serious infection risk in RA-LD patients. Additionally, the presence of lung disease can compromise the pulmonary reserve, complicating the clinical management of infections and negatively impacting the overall prognosis¹⁴. Understanding how lung disease contributes to the infection burden is essential for improving clinical outcomes and tailoring infection prevention strategies, such as encouraging vaccination, for patients with RA-LD.

Therefore, we aimed to investigate the relationship between RA-LD and serious

infection risk by leveraging data from the Massachusetts General Brigham (MGB) Biobank comparing RA-LD cases to RA-no LD comparators. Additionally, we separately investigated RA-ILD and RA-BR for serious infection risk. We hypothesized that patients with RA-LD would have a higher risk of serious infection than RA-no LD comparators. Beyond serious infection, we also investigated RA-LD and risk of anatomic sites of infection, pathogen types and specific pathogens.

METHODS

Study design and participants

This retrospective cohort study was conducted utilizing data from the MGB Biobank, which collected biospecimens, surveys, and linked to clinical data from the electronic health record (EHR) of more than 150,000 participants across multiple hospitals in the Greater Boston area since 2010¹⁵. Participant race and ethnicity were obtained from the EHR, from self-report obtained during registration to the health care system. This sub-study received approval from the MGB institutional review board (Protocol #2019P000264) and adheres to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Identification of RA

Patients with RA were initially identified through a validated algorithm that integrated diagnosis codes, laboratory results, and natural language processing of EHR data, achieving a 95% positive predictive value and 97% specificity for RA¹⁶.

We then performed medical record review to confirm that all participants met classification criteria for RA according to the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria¹⁷ and to obtain the clinical diagnosis date for all RA cases.

RA-LD cases

RA-LD cases were identified as clinically apparent RA-ILD and/or RA-BR, as described in previous studies^{18,19}. Potential cases were identified by billing code for ILD and/or BR, chest computed tomography (CT) imaging, or lung biopsy/procedure including autopsy. We then performed detailed medical record reviews to obtain clinical evidence for RA-ILD and/or RA-BR which was defined as a physician's clinical diagnosis of either condition, or the presence of characteristic symptoms such as cough, sputum production, and/or dyspnea, alongside ILD/BR findings noted on imaging²⁰. Imaging evidence was determined by CT scan findings scored independently by two thoracic radiologists using a previously described scoring system^{21,22}, with discrepancies resolved by consensus or a third radiologist. Further details of the scoring system can be found in the previous study¹⁹. We performed medical record review to determine the date of clinical diagnosis for RA-ILD or RA-BR.

Since ILD can cause traction BR, we considered patients with both ILD and BR to have RA-ILD. Thus, the RA-BR cases had isolated BR¹⁹ without any clinical or imaging evidence of ILD in the EHR or CT scans.

The primary analysis combined RA-ILD and RA-BR cases into a single RA-LD cohort. In secondary analyses, we investigated RA-ILD and isolated RA-BR strata separately.

Matched RA-no LD comparators

The pool of possible RA-no LD comparators consisted of the remaining patients that did not meet the criteria for RA-ILD and/or RA-BR so that they had no clinical or imaging evidence of ILD or BR.

Each RA-LD case was matched with up to five RA-no LD comparators based on calendar birth date (± 5 years), sex, and RA duration (± 5 years) at the index date, which was defined as the later of RA or ILD/BR diagnosis for RA-LD cases, and the corresponding matched date for RA-no LD comparators. RA-no LD comparators were also required to have at least one clinical encounter after the index date.

Serious infection

The primary outcome, specified a priori, was the first occurrence of any serious infection, defined as infections requiring hospitalization²³. All infections were identified using ICD-9 and ICD-10 codes during an inpatient stay (positive predictive value 90% in a previous validation study)²³⁻²⁶. The ICD codes are listed in

Supplementary Table 1. To verify whether coded pulmonary infections were RA-LD flares, we randomly selected 10 pneumonia patients and found all 10 had documented infectious pneumonia.

Secondary outcomes

In secondary analyses, we also investigated risk for any infection, infection by care setting (inpatient or outpatient), anatomic sites of infection, and pathogens. Anatomic sites included pulmonary, skin and soft tissue, ear, nose, and throat (ENT), urinary tract, musculoskeletal, gastrointestinal (GI), and others (including infections of the eye, nervous system, prosthetic devices, implants, grafts, sepsis, systemic inflammatory response syndrome [SIRS] of infectious origin, and septic shock). Types of pathogens included viral, bacterial, fungal, mycobacterial, and parasitic infections. Finally, we also investigated risk for specific pathogens. ICD codes are listed in **Supplementary Table 2**.

Covariates

Demographics were obtained from electronic query and included age at index date, race, and Hispanic ethnicity. The MGB Biobank survey was used to collect smoking status (never/past/current) and pack-years. For those that did not answer the survey, we performed medical record review to obtain missing smoking data. Comorbidities within 365 days prior to the index date, including diabetes, heart failure, myocardial infarction or stroke, cancer from solid tumor, leukemia, or lymphoma were assessed using the Charlson Comorbidity Index (CCI)^{27,28} based on ICD codes to quantify the overall comorbidity burden. We verified cancer at index date by medical record review since codes may not indicate active cancer. When calculating the CCI, we excluded chronic obstructive pulmonary disease (COPD) since we expected many RA-LD patients to have COPD codes and also excluded

connective tissue disease since all patients had RA.

We obtained RA characteristics, including RA duration at index date, serostatus, anti-cyclic citrullinated peptide antibodies (ACPA) status, rheumatoid factor (RF) status. Additionally, we collected the most recent erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) within 1 year before index date, along with the use of disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids. The specific DMARDs were categorized by mechanism of action and also classified as conventional synthetic DMARDs (csDMARDs), biologic DMARDs (bDMARDs), or targeted synthetic DMARDs (tsDMARDs). Lung disease characteristics included the presence of ILD, BR, both ILD and BR, ILD before RA, BR before RA, and subtypes of ILD encompassing usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), fibrotic ILD, organizing pneumonia (OP), and respiratory bronchiolitis (RB). Furthermore, data on healthcare utilization, and previous serious infection within 365 days before index date were collected. We conducted medical record review to identify missing serostatus data, and when no data were available, we performed multiple imputation by chained equations²⁹. Otherwise, no other covariates in the propensity score had missing data.

All patients were followed until the occurrence of either outcome, death, or their last clinical encounter (**Supplementary Figure 1**)

Statistical analysis

We compared the RA-LD and RA-no LD cohorts at baseline (defined as the

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index date) using chi-square or Fisher's exact tests for categorical variables and *t*-tests or Wilcoxon rank-sum tests for continuous variables, depending on the data distribution. Means and standard deviations (SD) were reported for normally distributed data, while medians and interquartile ranges (IQR) were used for skewed distributions. Incidence rates of serious infections (per 1,000 person-years) were calculated from baseline, with censoring events defined as either death or the last clinical encounter. To account for competing risk of death, we used a Fine and Gray model^{30,31} to estimate subdistribution hazard ratios (sdHR) with 95% confidence intervals (CIs) for the association between RA-LD and first serious infection. This analysis included both a two-level exposure model (comparing RA-LD to RA-no LD) and a three-level exposure model (comparing RA-ILD and RA-BR separately to RA-no LD). Models were adjusted for propensity scores that incorporated all baseline covariates that were imbalanced and included smoking status, pack-years, CCI score, serostatus, glucocorticoid use, csDMARDs, bDMARDs, serious infection within 365 days before index date, and healthcare utilization.

For secondary outcomes, we performed comparative analyses of anatomic sites of infection, infection by care setting (outpatient and inpatient), pathogens of infection, specific pathogens of infection between RA-LD cases and RA-no LD comparators. Proportions were compared using chi-square tests or Fisher's exact tests, as appropriate, to evaluate differences in infection characteristics. Additionally, we conducted the same analyses comparing RA-ILD and RA-BR cases separately to

RA-no LD comparators. Since these secondary analyses were considered exploratory and hypothesis-generating, no adjustments for multiple testing were made in this study.

We also performed multivariable logistic regression models among RA-LD, RA-ILD, and RA-BR patients separately to estimate odds ratios (ORs) and 95% CIs for the associations between RA treatments, selected baseline characteristics, and serious infection risk. The model adjusted for age, sex, smoking status, serostatus, and use of glucocorticoids, csDMARDs, bDMARDs, tsDMARDs, methotrexate, TNF inhibitors, and rituximab.

We considered a two-sided p value <0.05 as statistically significant. All analyses were performed in R version 2024.04.2+764.

Sensitivity analyses

To assess the robustness of our findings, we conducted three sensitivity analyses. First, we excluded all serious infections attributable to SARS-CoV-2 to evaluate whether our results were influenced by SARS-CoV-2-related infections. Second, to further address potential confounding, we re-estimated propensity scores by replacing the CCI with individual comorbidities, while retaining all other covariates in the original model. Third, we limited the follow-up period to a maximum of 10 years from the index date to address potential limitations in statistical power for detecting differences in serious infection risk at later time points.

RESULTS

Baseline characteristics of RA-LD cases and RA-no LD comparators

We analyzed 221 RA-LD cases and 980 RA-no LD comparators. Baseline characteristics are shown in **Table 1** and **Supplementary Table 3**. Since RA-LD cases and RA-no LD comparators were matched by age (mean age of 63.4 years in RA-LD vs. 61.6 years in RA-no LD), sex (75% female in RA-LD vs. 76% female in RA-no LD), and RA duration at the index date, these characteristics were similar across both groups.

The RA-LD cohort included 151 (68%) patients with RA-ILD and 70 (32%) with RA-BR (**Supplementary Table 3**). Regarding ILD subtypes, UIP was present in 73 (48%) and NSIP in 30 (20%). Of the 980 RA-no LD comparators, 242 (24.6%) were verified to have had a normal chest CT from research review of images. Among these, the median interval between the CT date and index date was 359 days (IQR: -1,339.5 to 1,550), 43.4% had their scan before the index date, and 56.6% after.

Compared to RA-no LD comparators, RA-LD cases were more likely to have a history of smoking (57% vs. 46%, $p=0.009$), higher pack-years (median pack-years 5 vs. 0, $p<0.001$), and higher CCI scores ($p<0.001$). Additionally, RA-LD cases were also more likely to be seropositive (81% vs. 63%, $p<0.001$) and to use glucocorticoids (51% vs. 36%, $p<0.001$), methotrexate (38% vs. 31%, $p=0.048$), and bDMARDs (37% vs. 29%, $p=0.02$). RA-LD cases had higher proportions of a history of prior serious infection (5% vs. 2%, $p=0.02$) within the year before index date, and

increased healthcare utilization, as indicated by more frequent inpatient admissions (21% vs. 11%, $p<0.001$) and clinic visits in the previous year (median 11 vs. 6, $p<0.001$).

Overall serious infection risk

The competing risk model showed patients with RA-LD had a significantly higher incidence rate of first serious infection compared to RA-no LD comparators (**Table 2** and **Figure 1A**; 55.8 vs. 25.8 per 1,000 person-years, adjusted sdHR 1.60, 95%CI 1.20-2.12).

When analyzed separately, patients with RA-ILD exhibited an increased risk of serious infection compared to RA-no LD comparators (**Table 2** and **Figure 1B**; 58.9 vs. 25.8 per 1,000 person-years, adjusted sdHR 1.79, 95%CI 1.33-2.41).

Conversely, no significant difference was observed for patients with RA-BR compared to RA-no LD comparators (48.5 vs. 25.8 per 1,000 person-years, adjusted sdHR 1.19, 95%CI 0.72-1.97).

Risk by anatomic site of infection

RA-LD cases experienced a greater proportion of any infection compared to RA-no LD comparators (**Table 3**; 75% vs. 59%, $p<0.001$). Pulmonary infections were particularly common in the RA-LD cohort (54% vs. 24%, $p<0.001$), in both outpatient (**Supplementary Table 4**; 47% vs. 19%, $p<0.001$) and inpatient (31% vs. 10%, $p<0.001$) settings. RA-LD cases also had more inpatient skin and soft tissue infections (13% vs. 7%, $p=0.006$), though no difference was found in any infection or

outpatient infections. ENT infections were more common in RA-LD cases (38% vs. 27%, $p=0.001$), including both outpatient (35% vs. 26%, $p=0.007$) and inpatient infections (7% vs. 2%, $p=0.002$). Urinary tract infections (UTI) were also more frequent in RA-LD patients (30% vs. 23%, $p=0.04$), with higher outpatient infections (27% vs. 20%, $p=0.03$). There were no differences for musculoskeletal, GI, or other infections, except for inpatient other infections (14% vs. 8%, $p=0.007$).

Risk by type of pathogen

The proportions of overall and outpatient viral infections were similar between RA-LD cases and RA-no LD comparators (**Table 4 and Supplementary Table 5**). However, inpatient viral infections were significantly more common among RA-LD cases (16% vs. 8%, $p<0.001$). Bacterial infections (27% vs. 16%, $p<0.001$), fungal infections (26% vs. 9%, $p<0.001$), and mycobacterial infections (6% vs. 1%, $p<0.001$) were higher in RA-LD cases than in RA-no LD comparators, in both outpatient and inpatient settings. Parasitic infections were rare in both groups.

Risk by specific pathogen

For specific viral infections, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was the most common documented infection, but there was no difference between RA-LD cases and RA-no LD comparators (**Table 5**; 27% vs. 27%, $p=0.94$). RA-LD cases exhibited significantly higher proportions of influenza virus (8% vs. 5%, $p=0.047$) and parainfluenza virus (1% vs. 0%, $p=0.006$), with notable differences in inpatient settings (5% vs. 2%, $p=0.001$ for influenza; 0.9% vs.

0%, $p=0.03$ for parainfluenza). Respiratory syncytial virus (RSV) was also more common in RA-LD cases (3% vs. 0.8%, $p=0.03$), especially in outpatient settings (2% vs. 0.3%, $p=0.007$). Cytomegalovirus (CMV) infections were significantly more common in RA-LD (3% vs. 0.5%, $p=0.007$) across both outpatient (**Supplementary Table 6**) and inpatient settings. Additionally, RA-LD patients had more inpatient herpes simplex virus infections (HSV; 3% vs. 1%, $p=0.03$). No significant differences were observed for other viral infections, including varicella-zoster virus (VZV), human papillomavirus (HPV), and hepatitis viruses.

Regarding bacterial infections, RA-LD cases demonstrated significantly higher proportions of *Staphylococcus* infections (12% vs. 6%, $p=0.002$), *Pseudomonas* infections (7% vs. 1%, $p<0.001$), *Escherichia coli* (7% vs. 2%, $p=0.002$), *Hemophilus influenzae* (2% vs. 0.4%, $p=0.01$), and *Treponema pallidum* infections (0.9% vs. 0%, $p=0.03$). Notably, marked differences were observed in inpatient *Staphylococcus* infections (11% vs. 5%, $p<0.001$), both outpatient (4% vs. 0.3%, $p<0.001$) and inpatient *Pseudomonas* infections (5% vs 1%, $p=0.002$), and inpatient *Escherichia coli* infections (7% vs. 2%, $p<0.001$). Furthermore, a higher proportion of outpatient *Klebsiella pneumoniae* infections (1% vs. 0%, $p=0.006$) occurred in patients with RA-LD. In contrast, no significant differences were found for other bacterial pathogens that included *Clostridium difficile*, *Salmonella typhi*, and *Streptococcus pneumoniae*.

For mycobacterial infections, RA-LD patients had more nontuberculous mycobacteria infections (NTM; 5% vs. 0.7%, $p<0.001$) compared to RA-no LD

comparators in both inpatient (2% vs. 0%, $p=0.001$) and outpatient (4% vs. 0.7%, $p=0.002$) settings. However, no significant difference was observed for mycobacterium tuberculosis (MTB) infections. Regarding fungal infections, RA-LD cases were more likely to be infected with *Candida albicans* (22% vs. 8%, $p<0.001$), *Aspergillus* (5% vs. 0.3%, $p<0.001$), and pneumocystis (3% vs. 0.2%, $p<0.001$) compared to RA-no LD comparators. In contrast, no significant differences were found for any parasitic infections across both cohorts.

Secondary analyses for anatomic site of infection

Compared to RA-no LD comparators, RA-ILD cases exhibited greater proportions of any infections (77% vs. 59%, $p<0.001$), pulmonary infections (53% vs. 24%, $p<0.001$), and ENT infections (40% vs. 27%, $p=0.003$) in both settings (**Supplementary Tables 7, 8**). They also had more inpatient skin and soft tissue infections (13% vs. 7%, $p=0.02$), any UTI (32% vs. 23%, $p=0.03$), inpatient UTI (14% vs. 8%, $p=0.02$), and inpatient other infections (15% vs. 8%, $p=0.003$). No differences were observed for musculoskeletal or GI infections. Patients with RA-BR also showed an increased proportion of any infections (71% vs. 59%, $p=0.049$) and pulmonary infections (56% vs. 24%, $p<0.001$) in both settings, and more inpatient ENT infections (7% vs. 2%, $p=0.02$) compared to RA-no LD comparators.

Secondary analyses for type of pathogen

Compared to RA-no LD comparators, RA-ILD exhibited a higher proportion of inpatient viral infections (**Supplementary Table 9**; 17% vs. 8%, $p<0.001$). However,

RA-BR patients did not show a similar trend (14% vs. 8%, $p=0.06$). Both RA-ILD and RA-BR patients had more bacterial infections (28% vs. 16%, $p<0.001$; 26% vs. 16%, $p=0.03$) and fungal infections (28% vs. 9%, $p<0.001$; 23% vs. 9%, $p<0.001$).

Additionally, RA-BR patients exhibited a higher proportion of mycobacterial infections (13% vs. 1%, $p<0.001$) across both outpatient (**Supplementary Table 10**) and inpatient settings.

Secondary analyses for specific pathogen

Compared to RA-no LD comparators, RA-ILD patients had significantly more inpatient SARS-CoV-2 infections (**Supplementary Table 11**; 8% vs. 4%, $p=0.02$), inpatient VZV infections (3% vs. 1%, $p=0.04$), and any *Klebsiella pneumoniae* infections (3% vs. 0.8%, $p=0.02$). There were no significant differences in any influenza infections, any RSV infections, or NTM infections among RA-ILD cases. The remaining findings for RA-ILD vs. RA-no LD were consistent with those observed for RA-LD overall. RA-BR patients exhibited a higher proportion of inpatient influenza virus infections (7% vs. 2%, $p=0.008$) and outpatient RSV infections (**Supplementary Table 12**; 3% vs. 0.3%, $p=0.04$) compared to RA-no LD comparators. No notable differences were identified for *Escherichia coli* infections, *Klebsiella pneumoniae* infections, or *Treponema pallidum* infections. However, RA-BR patients had more *Pseudomonas* infections (10% vs. 1%, $p<0.001$), NTM infections (11% vs. 0.7%, $p<0.001$), *Candida albicans* infections (21% vs. 8%, $p<0.001$), and *Aspergillus* infections (3% vs. 0.3%, $p=0.04$) compared to RA-no LD

comparators.

Secondary analyses for treatment associated with serious infection risk

Glucocorticoids use was associated with increased risk of serious infection among RA-LD cases (**Supplementary Table 13**; adjusted OR 1.65, 95%CI 1.21-2.24) as well as RA-ILD (**Supplementary Table 14**; adjusted OR 1.58, 95%CI 1.14-2.18) and RA-BR (**Supplementary Table 15**; adjusted OR 1.60, 95%CI 1.14-2.25) cases. Rituximab use was also associated with increased serious infection risk in RA-LD (adjusted OR 2.55, 95%CI 1.03-6.33) and RA-BR patients (adjusted OR 3.38, 95%CI 1.38-9.10).

Sensitivity analyses

RA-LD remained associated with an increased risk of serious infection after excluding those attributable to SARS-CoV-2 (**Supplementary Table 16**; adjusted sdHR 1.62, 95%CI 1.22-2.16). Similarly, re-estimating the propensity scores using individual comorbidities instead of the CCI yielded comparable results (**Supplementary Table 17**; adjusted sdHR 1.62, 95%CI 1.65-2.18). Restricting the follow-up period to a maximum of 10 years from the index date did not materially change the results. RA-LD remained significantly associated with an increased risk of serious infection compared to RA-no LD (**Supplementary Table 18**; adjusted sdHR 1.75, 95%CI 1.29-2.37). In the three-level exposure model, RA-ILD continued to show a significantly elevated risk (adjusted sdHR 1.89, 95%CI 1.35-2.63), while the association for RA-BR remained non-significant, although the point estimate

increased slightly (adjusted sdHR 1.46, 95%CI 0.89-2.39).

DISCUSSION

This comparative cohort study found a nearly 2-fold increased risk of serious infection in RA-LD patients compared to RA-no LD comparators, with higher risk specific to the RA-ILD subgroup. Infection burden was evident across multiple anatomic sites, particularly pulmonary, skin and subcutaneous tissue, ENT, and urinary tract, and involved various pathogens, including viral, bacterial, fungal, and mycobacterial species. Additionally, RA-BR patients were found to be vulnerable to specific pathogens including NTM and other pulmonary infections across many pathogen types. These findings link RA-LD to an increased risk of serious infections, highlighting the need for tailored infection prevention strategies in this population.

Our study confirmed that RA-LD, particularly RA-ILD, is a significant risk factor for serious infection, consistent with prior studies⁷⁻⁹. Eri Sugano et al⁹ reported a 2.6-fold higher risk of hospitalized infections in RA-ILD patients, slightly higher than the 1.79-fold increased risk observed in our study. This difference may reflect variations in study populations, as they focused specifically on RA patients who had not achieved DAS28 remission to examine the impact of ILD on clinical remission. In addition to RA-ILD patients, our study also included RA-BR patients and classified infections by pathogen type, offering further specificity. The incidence rate of serious infection in RA-ILD patients was 58.9 per 1,000 person-years, similar to a previous study⁷ (74 per 1,000 person-years), but much lower than another⁸ (526 per 1,000

person-years), likely due to differences in outcome definitions. We defined serious infections as those requiring hospitalization, while the latter study defined them as infections requiring antibiotic therapy.

The varying risk of serious infections in RA-ILD (adjusted sdHR 1.79, 95% CI: 1.33-2.41) or RA-BR patients (adjusted sdHR 1.19, 95% CI: 0.72-1.97) compared to RA-no LD patients may reflect different immune and tissue-specific vulnerabilities. RA-ILD is marked by fibrosis, immune cell infiltration, and persistent inflammation, which can compromise pulmonary defense^{32,33}. Chronic inflammatory environment, along with increasing immunosuppressive burden^{11,13}, may impair both local and systemic immune responses³⁴, increasing infection susceptibility. Conversely, RA-BR primarily involves airway dilation with less fibrosis, and excessive natural killer cell activation may also contribute to its pathogenesis³⁵, potentially explaining the lack of elevated infection risk in RA-BR patients. However, this finding should be interpreted with caution. In the sensitivity analysis limited to 10 years of follow-up, the point estimate for serious infection in RA-BR increased with overlapping confidence intervals, suggesting potential power limitations. Despite this, RA-BR patients showed increased risks for many secondary outcomes including any infections and pulmonary infections in both inpatient and outpatient settings and were more susceptible to many pathogens like influenza, *Staphylococcus*, *Pseudomonas*, and NTM, highlighting the need for close monitoring and prioritization for vaccinations.

Patients with RA-LD have significantly more pulmonary infections, a finding

consistent across both RA-ILD and RA-BR subgroups when compared to RA-no LD patients. They also exhibited a greater risk of extrapulmonary infections, including ENT infections, serious skin and soft tissue infections, and both overall and outpatient UTIs. These findings underscore the broader impact of RA-related lung disease on infection susceptibility across multiple organs. Elevated pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor^{36,37} may promote systemic inflammation, impair immune cell function, and reduce the lung's ability to clear pathogens, increasing susceptibility to respiratory infections. Hypoxia associated with lung disease can exacerbate immune suppression, further weakening local and systemic immune responses^{38,39}. Systemic immune dysfunction driven by chronic inflammation impairs immune responses⁴⁰ at extrapulmonary sites, such as the skin and urinary tract, making these tissues more susceptible to infections. The use of immunosuppressive therapies, including steroids and DMARDs, can dysregulate both local and systemic immunity, increasing the risk of infections in various organs⁴¹. Chronic inflammation may also lead to microbial translocation⁴², where pathogens from the gut enter the bloodstream, further exacerbating extrapulmonary infections. These factors collectively enhance the susceptibility of RA-LD patients to infections across multiple organs.

Our study highlights the increased vulnerability of RA-LD patients to a range of viral, bacterial, fungal, and mycobacterial infections. While no significant difference was observed in SARS-CoV-2 infection occurrence between RA-LD and RA-no LD

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patients, this may reflect the increasing availability and uptake of COVID-19 vaccines^{43,44}. In contrast, RA-LD patients exhibited significantly more respiratory viral infections including influenza, parainfluenza, RSV, and CMV infections, as well as bacterial infections like *Staphylococcus*, *Pseudomonas*, *Klebsiella pneumoniae*, and *Escherichia coli*. These results suggested that lung disease in RA patients may impair respiratory defenses, making them more susceptible to these pathogens⁴⁵. Moreover, the increased proportions of fungal infections, including *Candida albicans*, *Aspergillus*, and pneumocystis, aligns with previous reports^{46,47} of heightened fungal susceptibility in immunocompromised populations. The higher incidence of NTM infections further underscores the increased risk for opportunistic pathogens in this group. The increased risk of NTM infections in RA-BR patients may suggest that NTM lung disease, often marked by nodules and bronchiectasis, could stem from underlying bronchiectasis, which predisposes patients to NTM infection and progression^{48,49}. Overall, these findings highlight the critical need for targeted infection prevention strategies, including enhanced vaccination and early treatment, for RA-LD patients.

In our study, we used CCI to assess comorbidity burden, given its wide use in infection risk studies. While the Rheumatic Disease Comorbidity Index (RDCI)^{28,50} captures RA-relevant conditions, it was developed for predicting functional outcomes and is less validated for infection. Adjustment for individual comorbidities rather than the CCI in the propensity score model supported the robustness of our findings.

However, the possibility of residual confounding due to unmeasured or misclassified conditions cannot be excluded.

This study has several strengths. First, we included both RA-ILD and RA-BR patients, and investigated the risk of serious infections, infection by anatomic sites, and pathogen types across both 2-level and 3-level exposure groups. To our knowledge, this is the first study comparing RA-BR patients to RA-no LD comparators, providing valuable insights into their infection risk. Second, we adjudicated all RA-LD cases through thorough medical record review, ensuring accurate exposure classification. Complete data on smoking status and pack-years, also obtained through medical record review, further strengthened our analysis. Additionally, we utilized data from the MGB Biobank, which enabled robust matching of RA-LD cases with RA-no LD comparators based on age, sex, and RA duration. Propensity score adjustment minimized selection bias and enhanced internal validity. Whatsmore, the long follow-up period strengthened the validity of our results, offering a comprehensive understanding of serious infection risk over time. Finally, our study quantified the risk of serious infection in RA-LD patients using a matched RA-no LD comparator group and investigated infection risk across anatomic sites and specific pathogens, revealing elevated rates of both pulmonary and extrapulmonary infections. These findings offer a more detailed understanding of infection vulnerability in RA-LD and may raise awareness for infection risk and need for mitigation. The quality of evidence in the 2022 ACR vaccine guideline⁵¹ for

rheumatic patients was generally low. Although the retrospective design of our study limits causal inference, our findings contribute real-world evidence that may inform future guidelines.

However, several limitations should be acknowledged. First, we lacked data on RA disease activity and lung disease severity, which may influence infection risk and cause residual confounding. Additionally, the EHR data are not reliable for capturing the actual doses of glucocorticoids. Therefore, we were unable to account for variations in dose or duration, which may introduce unmeasured confounding and should be considered when interpreting our findings. Second, we relied on diagnosis codes to identify infections, which has been validated²⁶ to be accurate for serious infections, but may not be as accurate in outpatient settings. Also, diagnosis codes may identify infections present during the inpatient stay without necessarily reflecting the primary reason for admission. While this method is commonly used in EHR-based studies, it may lead to misclassification of infection severity, particularly for conditions such as ENT infections. To minimize differential bias, we applied the same definition consistently across all comparison groups. We did perform a validation of pulmonary infections among RA-LD cases and this accurately identified infections, distinguishing them from RA-LD flares can be challenging. Third, the retrospective nature of the study limited the generalizability of the findings, as the data were from a single healthcare system. Therefore, the results may not be applicable to all populations, especially those outside of academic medical centers. Fourth, although

we used propensity score adjustment to account for imbalanced baseline characteristics, unmeasured confounders, such as vaccination status, may have influenced the associations observed. Further prospective studies are needed to validate our findings, better account for confounding variables, and improve generalizability. Fifth, as the site-specific infection analyses were exploratory in nature and involved multiple comparisons, we acknowledge the possibility of type I error and did not apply formal corrections for multiple testing. These findings should therefore be interpreted as hypothesis-generating and require validation in independent cohorts. Sixth, chest CT imaging was not uniformly available for all RA-no LD comparators, introducing the possibility of misclassification due to undiagnosed subclinical lung disease. We previously identified RA-no LD controls verified to have no parenchymal lung disease after research review of chest CT images^{18,19}. Nonetheless, the lack of systematic imaging may bias the comparison toward the null, and this should be considered when interpreting our findings. Another potential limitation is detection bias. Patients with RA-LD may undergo more frequent diagnostic testing due to increased clinical concern for respiratory complications. This heightened surveillance may lead to a greater likelihood of identifying infections, thereby increasing observed infection rates relative to RA-no LD comparators. Lastly, we adjusted for variables only at baseline. Post-baseline changes such as increased glucocorticoid use or vaccine uptake may have mediated findings that may contribute to the excess risk we report. In particular, RA-LD may

influence treatment decisions, making these exposures potential mediators rather than confounders. As a result, our ability to disentangle the effects of the underlying disease from treatment-related immunosuppression is limited. Future pharmacoepidemiologic studies using a target trial framework would be needed to investigate the effect of specific medications for RA-LD and serious infection risk.

In conclusion, RA-LD, particularly RA-ILD, was associated with a significantly increased risk of serious infection. Further, RA-LD was associated with infections across various anatomic sites, care settings, and pathogens. Findings may be explained by lung damage and/or more intense immunosuppression, so future prospective studies and clinical trials are needed to investigate the mechanisms underlying increased infection risk in patients with RA-LD, evaluate the impact of different RA treatments, and inform tailored prevention strategies beyond current guideline recommendations for this high-risk population.

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Table 1. Baseline characteristics of RA-LD cases and RA-no LD comparators

Characteristics	RA-LD cases	RA-no LD comparators
Total	221 (100)	980 (100)
Demographics		
Age, years (mean and SD)	63.4 (12.2)	61.6 (12.4)
Female sex, n (%)	165 (75)	743 (76)
Race		
Asian Americans	3 (1)	13 (1)
Black Americans	14 (6)	54 (6)
Declined/Missing	5 (2)	23 (2)
Other	8 (4)	37 (4)
White Americans	191 (86)	853 (87)
Hispanic Americans	2 (0.9)	8 (0.8)
Smoking		
Smoking status, n (%)		
Never	80 (36)	465 (47)
Past	126 (57)	454 (46)
Current	15 (7)	61 (6)
Pack-years, median (IQR)	5 (0-22.5)	0 (0-12.1)
Comorbidities		
Charlson Comorbidity Index (median and IQR)	0 (0-1)	0 (0-0)
Diabetes	9 (4)	49 (5)
Heart failure	15 (7)	31 (3)
Cardiovascular disease	20 (9)	44 (4)
Solid tumor cancer	7 (3)	6 (0.6)
Leukemia or lymphoma	17 (8)	36 (4)
RA characteristics		
RA duration, years (median and IQR)	9.0 (0.7-18.9)	6.4 (1.8-15.0)
Seropositive	180 (81)	618 (63)
RA medications		
Glucocorticoids, n (%)	113 (51)	355 (36)
Any DMARDs, n (%)	136 (62)	542 (55)
csDMARDs, n (%)	108 (49)	411 (42)
Methotrexate	84 (38)	305 (31)
Hydroxychloroquine	27 (12)	131 (13)
Sulfasalazine	7 (3)	38 (4)
bDMARDs, n (%)	82 (37)	283 (29)
TNFi	59 (27)	211 (22)
Abatacept	5 (2)	38 (4)

Rituximab	10 (5)	23 (2)
Tocilizumab	7 (3)	23 (2)
tsDMARDs, n (%)	5 (2)	23 (2)
Tofacitinib	4(2)	20 (2)
Serious infection within 365 days prior to index date, n (%)	10 (5)	18 (2)

Health care utilization

Any hospitalization within 365 days before index, n (%)	47 (21)	107 (11)
Number of outpatient visits within 365 days before index, Median (IQR)	11 (4-23)	6 (2-15)

bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DMARDs, disease-modifying antirheumatic drugs; IQR, interquartile range; RA-LD, rheumatoid arthritis-associated lung disease; RA-no LD, rheumatoid arthritis without lung disease; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs

Table 2. Subdistribution hazard ratios for first serious infection accounting for competing risk of death, comparing RA-LD cases and RA-no LD comparators.

Comparisons	Serious infection events, n	Person-years	Incidence rate per 1,000 person-years	Multivariable* sdHR (95%CI)
2-level				
Exposure				
RA-no LD	204	7,909.1	25.8	1.0 (Ref)
RA-LD	85	1,522.9	55.8	1.60 (1.20-2.12)
3-level				
Exposure				
RA-no LD	204	7,909.1	25.8	1.0 (Ref)
RA-BR	22	453.7	48.5	1.19 (0.72-1.97)
RA-ILD	63	1,069.2	58.9	1.79 (1.33-2.41)

*RA-LD cases and RA-no LD comparators were matched by calendar date of birth, sex, and RA duration at index date of RA-LD diagnosis.

Adjusted for propensity score that included smoking status, pack-years, Charlson Comorbidity Index score, serostatus, glucocorticoids, csDMARDs, bDMARDs, previous serious infection, and health care utilization.

bDMARDs, biological disease-modifying antirheumatic drugs; CI, confidence interval; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; RA-BR, rheumatoid arthritis-associated bronchiectasis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; RA-LD, rheumatoid arthritis-associated lung disease; RA-no LD, rheumatoid arthritis without lung disease; sdHR, subdistribution hazard ratio

Table 3. Anatomic site of overall and inpatient infections, comparing RA-LD cases and RA-no LD comparators.

Characteristics	RA-LD cases (n=221)	RA-no LD comparators (n=980)	p-value
Any infections	166 (75)	583 (59)	<0.001
Inpatient	85 (38)	204 (21)	<0.001
Pulmonary infections	119 (54)	232 (24)	<0.001
Inpatient	68 (31)	102 (10)	<0.001
Skin and soft tissue infections	85 (38)	332 (34)	0.20
Inpatient	28 (13)	69 (7)	0.006
ENT infections	85 (38)	268 (27)	0.001
Inpatient	15 (7)	23 (2)	0.002
Urinary tract infections	66 (30)	229 (23)	0.04
Inpatient	25 (11)	78 (8)	0.11
Musculoskeletal infections	18 (8)	49 (5)	0.07
Inpatient	11 (5)	28 (3)	0.14
GI infections	14 (6)	56 (6)	0.72
Inpatient	9 (4)	26 (3)	0.27
Other infections*	42 (19)	144 (15)	0.11
Inpatient	30 (14)	77 (8)	0.007

*Other infections included infections of the eye, nervous system, prosthetic devices, implants, and grafts, sepsis, SIRS of infectious origin, and septic shock

ENT, ear, nose, and throat; GI, gastrointestinal; RA-LD, rheumatoid arthritis-associated lung disease; RA-no LD, rheumatoid arthritis without lung disease; SIRS, systemic inflammatory response syndrome

Table 4. Pathogen type of overall and inpatient infections, comparing RA-LD cases and RA-no LD comparators.

Characteristics	RA-LD cases (n=221)	RA-no LD comparators (n=980)	p-value
Viral infections	95 (43)	372 (38)	0.17
Inpatient	36 (16)	77 (8)	<0.001
Bacterial infections	60 (27)	152 (16)	<0.001
Inpatient	42 (19)	93 (9)	<0.001
Fungal infections	58 (26)	84 (9)	<0.001
Inpatient	25 (11)	30 (3)	<0.001
Mycobacterial infections	14 (6)	13 (1)	<0.001
Inpatient	5 (2)	1 (0.1)	0.001
Parasitic infections	2 (0.9)	3 (0.3)	0.23
Inpatient	0 (0)	1 (0.1)	1.00

RA-LD, rheumatoid arthritis-associated lung disease; RA-no LD, rheumatoid arthritis without lung disease

Table 5. Specific pathogens of overall and inpatient infections, comparing RA-LD cases and RA-no LD comparators.

Characteristics	RA-LD cases (n=221)	RA-no LD comparators (n=980)	p-value
Viral infections			
SARS-CoV-2	59 (27)	264 (27)	0.94
Inpatient	14 (6)	38 (4)	0.10
Varicella-zoster virus	19 (9)	64 (7)	0.27
Inpatient	6 (3)	10 (1)	0.09
Influenza virus	18 (8)	47 (5)	0.047
Inpatient	12 (5)	15 (2)	0.001
Herpes simplex virus	16 (7)	58 (6)	0.46
Inpatient	7 (3)	11 (1)	0.03
Respiratory syncytial virus	6 (3)	8 (0.8)	0.03
Inpatient	3 (1)	7 (0.7)	0.40
Cytomegalovirus	6 (3)	5 (0.5)	0.007
Inpatient	6 (3)	1 (0.1)	<0.001
Hepatitis C virus	3 (1)	7 (0.7)	0.40
Inpatient	3 (1)	5 (0.5)	0.17
Parainfluenza	3 (1)	0 (0)	0.006
Inpatient	2 (0.9)	0 (0)	0.03
Human papillomavirus	2 (0.9)	6 (0.6)	0.64
Inpatient	0 (0)	1 (0.1)	1.00
Adenovirus	1 (0.5)	2 (0.2)	0.46
Inpatient	0 (0)	1 (0.1)	1.00
Hepatitis A virus	1 (0.5)	4 (0.4)	1.00
Hepatitis B virus	1 (0.5)	1 (0.1)	0.33
Norovirus	1 (0.5)	1 (0.1)	0.33
Inpatient	1 (0.5)	0 (0)	0.18
Mumps	1 (0.5)	0 (0)	0.18
Inpatient	1 (0.5)	0 (0)	0.18
Epstein-Barr virus	1 (0.5)	0 (0)	0.18
Human immunodeficiency virus	0 (0)	1 (0.1)	1.00
Coxsackievirus	0 (0)	2 (0.2)	1.00
Inpatient	0 (0)	2 (0.2)	1.00
Bacterial infections			
<i>Staphylococcus</i>	26 (12)	57 (6)	0.002
Inpatient	24 (11)	46 (5)	<0.001
<i>Pseudomonas</i>	15 (7)	14 (1)	<0.001
Inpatient	11 (5)	13 (1)	0.002
<i>Escherichia coli</i>	15 (7)	22 (2)	0.002
Inpatient	15 (7)	20 (2)	<0.001

<i>Clostridium difficile</i>	8 (4)	22 (2)	0.24
Inpatient	5 (2)	12 (1)	0.22
Lyme disease	6 (3)	25 (3)	0.82
<i>Klebsiella pneumoniae</i>	5 (2)	8 (0.8)	0.07
Inpatient	4 (2)	8 (0.8)	0.25
<i>Hemophilus influenzae</i>	5 (2)	4 (0.4)	0.01
Inpatient	3 (1)	3 (0.3)	0.08
<i>Streptococcus pneumoniae</i>	3 (1)	6 (0.6)	0.22
Inpatient	2 (0.9)	5 (0.5)	0.62
Other <i>Streptococcus</i>	12 (5)	37 (4)	0.26
Inpatient	10 (5)	29 (3)	0.29
Listeria	2 (0.9)	7 (0.7)	0.67
<i>Treponema pallidum</i>	2 (0.9)	0 (0)	0.03
Inpatient	2 (0.9)	0 (0)	0.03
<i>Mycoplasma</i>	1 (0.5)	1 (0.1)	0.33
Inpatient	1 (0.5)	1 (0.1)	0.33
<i>Corynebacterium diphtheriae</i>	1 (0.5)	0 (0)	0.18
Inpatient	1 (0.5)	0 (0)	0.18
<i>Neisseria gonorrhoeae</i>	1 (0.5)	1 (0.1)	0.33
Inpatient	1 (0.5)	1 (0.1)	0.33
Legionella	0 (0)	2 (0.2)	1.00
Inpatient	0 (0)	2 (0.2)	1.00
<i>Rickettsia</i>	0 (0)	1 (0.1)	1.00
<i>Salmonella typhi</i>	0 (0)	1 (0.1)	1.00
<i>Neisseria meningitidis</i>	0 (0)	1 (0.1)	1.00
Mycobacterial infections			
Nontuberculous mycobacteria	11 (5)	7 (0.7)	<0.001
Inpatient	4 (2)	0 (0)	0.001
<i>Mycobacterium tuberculosis</i>	4 (2)	6 (0.6)	0.09
Inpatient	1 (0.5)	1 (0.1)	0.33
Fungal infections			
<i>Candida albicans</i>	49 (22)	83 (8)	<0.001
Inpatient	19 (9)	27 (3)	<0.001
<i>Aspergillus</i>	10 (5)	3 (0.3)	<0.001
Inpatient	7 (3)	2 (0.2)	<0.001
Pneumocystosis	7 (3)	2 (0.2)	<0.001
Inpatient	5 (2)	2 (0.2)	0.003
<i>Paracoccidioides brasiliensis</i>	1 (0.5)	0 (0)	0.18
Inpatient	1 (0.5)	0 (0)	0.18
Parasitic infections			
Amoeba	1 (0.5)	1 (0.1)	0.33
<i>Toxoplasma gondii</i>	1 (0.5)	0 (0)	0.18

Trichomoniasis	0 (0)	2 (0.2)	1.00
Inpatient	0 (0)	1 (0.1)	1.00

RA-LD, rheumatoid arthritis-associated lung disease; RA-no LD, rheumatoid arthritis without lung disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

FIGURE LEGEND

Figure 1. A. Cumulative incidence of first serious infection, comparing rheumatoid arthritis-associated lung disease (RA-LD) cases and RA-no LD comparators. **B.** Cumulative incidence of first serious infection, comparing RA-associated interstitial lung disease (RA-ILD) cases, RA-associated bronchiectasis (RA-BR) cases, and RA-no LD comparators.

Supporting Information

Supplementary Figure 1: Study design	1
Supplementary Table 1: List of ICD-9 and ICD-10 codes used to identify serious infections by anatomic site	2-5
Supplementary Table 2. List of ICD-9 and ICD-10 codes used to identify infections by pathogen type.....	6-18
Supplementary Table 3. Additional characteristics of the RA-LD cases and RA-no LD comparators.....	19-20
Supplementary Table 4. Anatomic site of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators	21
Supplementary Table 5. Pathogen type of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators	22
Supplementary Table 6. Specific pathogens of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators	23-24
Supplementary Table 7. Anatomic site of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.....	25
Supplementary Table 8. Anatomic site of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators	26
Supplementary Table 9. Pathogen types of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators	27
Supplementary Table 10. Pathogen types of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.....	28
Supplementary Table 11. Specific pathogens of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.....	29-32
Supplementary Table 12. Specific pathogens of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.....	33-34

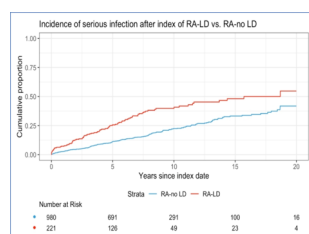
Supplementary Table 13. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-LD patients.....	35
Supplementary Table 14. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-ILD patients....	36
Supplementary Table 15. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-BR patients	37
Supplementary Table 16. Subdistribution hazard ratios for first serious infection accounting for competing risk of death, comparing RA-LD cases and RA-no LD comparators after excluding inpatient SARS-CoV-2 infections	38
Supplementary Table 17. Subdistribution hazard ratios for first serious infection accounting for competing risk of death, comparing RA-LD cases and RA-no LD comparators adjusting for propensity scores that included individual comorbidities instead of Charlson Comorbidity Index	39
Supplementary Table 18. Subdistribution hazard ratios for first serious infection accounting for competing risk of death, comparing RA-LD cases and RA-no LD comparators with follow-up limited to 10 years	40
Supplementary Table 1. List of ICD-9 and ICD-10 codes used to identify serious infections by anatomic site.	
Supplementary Table 2. List of ICD-9 and ICD-10 codes used to identify infections by pathogen type.	
Supplementary Table 3. Additional characteristics of the RA-LD cases and RA-no LD comparators.	
Supplementary Table 4. Anatomic site of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators.	
Supplementary Table 5. Pathogen type of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators.	
Supplementary Table 6. Specific pathogens of <u>outpatient infections</u> , comparing RA-LD cases and RA-no LD comparators.	
Supplementary Table 7. Anatomic site of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 8. Anatomic site of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 9. Pathogen types of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 10. Pathogen types of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 11. Specific pathogens of overall and inpatient infections, comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 12. Specific pathogens of <u>outpatient infections</u> , comparing RA-ILD cases, RA-BR cases, and RA-no LD comparators.	
Supplementary Table 13. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-LD patients.	
Supplementary Table 14. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-ILD patients.	

Supplementary Table 15. Associations between RA treatments and clinical characteristics at index date and risk of serious infection among RA-BR patients.

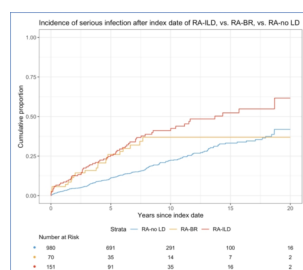
Supplementary Table 16. Subdistribution hazard ratios for first serious infection accounting for competing risk of death, comparing RA-LD cases and RA-no LD comparators after excluding inpatient SARS-CoV-2 infections.

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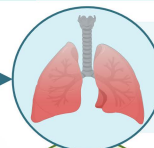
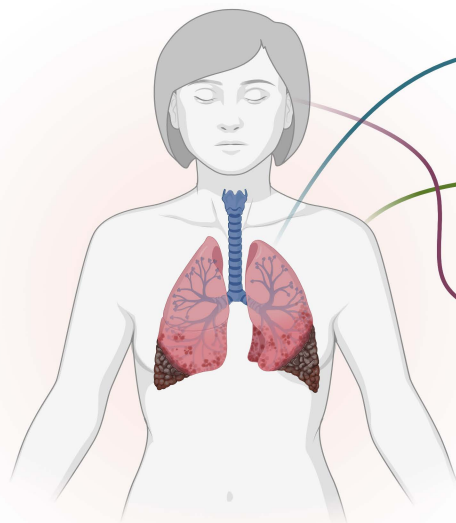
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Serious Infection Risk in RA-Associated Lung Disease

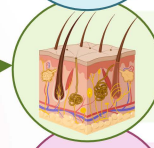
Cumulative Incidence of First Serious Infection

RA-LD:
Clinically-apparent RA-ILD and/or RA-BR

Most common anatomic sites of serious infection (RA-LD vs. RA-no LD)



Pulmonary
(31% vs. 10%, $p < 0.001$)



Skin and soft tissue
(13% vs. 7%, $p = 0.006$)



Ear, nose, and throat
(7% vs. 2%, $p = 0.002$)

Most common differences in pathogens (RA-LD vs. RA-no LD)



Staphylococcus (12% vs. 6%, $p = 0.002$)



Influenza virus (8% vs. 5%, $p = 0.047$)



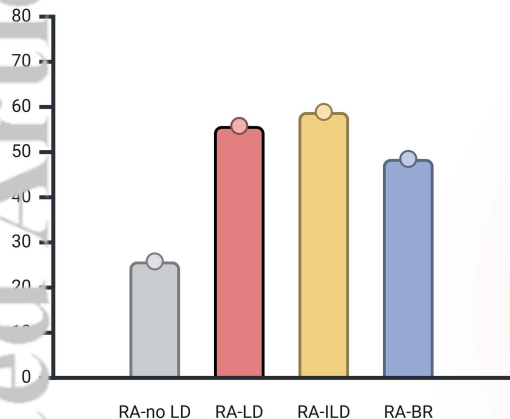
Pseudomonas (7% vs. 1%, $p < 0.001$)



Nontuberculous mycobacteria
(5% vs. 0.7%, $p < 0.001$)



Respiratory syncytial virus
(3% vs. 0.8%, $p = 0.03$)



RA-LD sdHR **1.60** (1.20–2.12)

RA-ILD sdHR **1.79** (1.33–2.41)

RA-BR sdHR **1.19** (0.72–1.97)

vs RA-no LD

Abbreviations: RA, rheumatoid arthritis; RA-BR, RA-associated bronchiectasis; RA-ILD, RA-associated interstitial lung disease; RA-LD, RA-associated lung disease; RA-no LD, RA without lung disease; sdHR, subdistribution hazard ratio

Zhang Q, et al. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease or bronchiectasis: a comparative cohort study. *Arthritis Rheumatol* 2025.