Impact of seropositivity and disease-modifying antirheumatic drugs on pulmonary tuberculosis risk in rheumatoid arthritis

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Rheumatoid arthritis patients are prone to active pulmonary tuberculosis development, with rates affected by seropositivity and DMARDs. Focused tuberculosis screenings may need to be carried out in rheumatoid arthritis patients. https://bit.ly/4gWN2yN

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Abstract

Background It remains unclear whether active pulmonary tuberculosis risk is still high in rheumatoid arthritis patients in settings where tuberculosis infection screening is performed before the use of biologicals. Moreover, the impacts of seropositivity and disease-modifying antirheumatic drugs on active pulmonary tuberculosis risk should be elucidated.

Methods The incidence of active pulmonary tuberculosis was compared between patients with rheumatoid arthritis (n=59 577; 41 501 seropositive rheumatoid arthritis and 18 076 seronegative rheumatoid arthritis) and 1:5 age- and sex-matched controls without rheumatoid arthritis (n=297 885) enrolled between 2010 and 2017. The participants were followed until December 2019.

Results During a median follow-up duration of 4.4 years after a 1-year lag period (interquartile range 2.6–6.4 years; maximum 9 years), patients with rheumatoid arthritis showed a 3.2-fold (95% CI 2.91–3.55) higher active pulmonary tuberculosis risk than matched controls, even after adjusting for potential confounders. In an analysis of rheumatoid arthritis serological status, patients with seropositive rheumatoid arthritis and those with seronegative rheumatoid arthritis showed 3.20-fold (95% CI 2.86–3.58) and 2.54-fold (95% CI 2.13–3.04) increased risks, respectively, relative to matched controls. Furthermore, rheumatoid arthritis patients who were exposed to biological or targeted synthetic and disease-modifying antirheumatic drugs and those not exposed to the drugs showed 4.68-fold (95% CI 3.69–5.93) and 2.88-fold (95% CI 2.59–3.20) increased risks, respectively, relative to matched controls. In rheumatoid arthritis patients, active pulmonary tuberculosis risk factors included male sex, underweight and comorbidities such as diabetes mellitus.

Conclusion Rheumatoid arthritis patients are prone to active pulmonary tuberculosis development, with rates affected by seropositivity and disease-modifying antirheumatic drugs. Focused tuberculosis screenings may need to be carried out in rheumatoid arthritis patients based on our results.

Introduction

Rheumatoid arthritis (RA), the most common chronic autoimmune inflammatory disease, affects about 18 million people worldwide, with significant morbidity and mortality rates [1–4]. With recent advances in

RA treatment, including disease-modifying antirheumatic drugs (DMARDs) and several biological DMARDs (bDMARDs) [5], the treatment outcomes and prognosis of RA have improved. However, wider use of these immunosuppressive treatments has increased the risk of pulmonary infections, including active pulmonary tuberculosis (TB) disease [6–8]. Thus, TB infection (previously referred to as latent TB infection) screening and treatment are highly recommended to reduce active pulmonary TB risk in patients with RA before prescribing bDMARDs, especially tumour necrosis factor (TNF) inhibitors [9, 10].

In Korea, TB infection screening has been mandatorily performed in patients with RA since December 2004 (see Methods). Therefore, the association needs to be re-evaluated to confirm whether bDMARDs increase the active pulmonary TB risk in patients with RA in an era of routine TB infection screening and treatment, although an association between RA and active pulmonary TB risk has been relatively well established by previous studies [11–19].

In addition to the effect of TB infection treatment, many previous studies did not comprehensively adjust for several potential confounders that can affect the development of TB, which include body mass index (BMI), unhealthy behaviours (*e.g.* smoking, heavy alcohol consumption or sedentary lifestyle) and comorbidities (*e.g.* diabetes mellitus (DM) and COPD) [20, 21]. Furthermore, although RA is classified as seropositive RA (SPRA), which is characterised by positive serum rheumatoid factor and/or anti-citrullinated protein antibodies, and seronegative RA (SNRA), there are limited data on the impact of seropositivity on active pulmonary TB risk in patients with RA. Elucidating factors related to active pulmonary TB risk would be very beneficial in guiding focused TB screening in patients with RA.

Hence, this study aimed to evaluate the active pulmonary TB risk in patients with RA in the setting of mandatory TB infection screening and treatment before using bDMARDs. This study also aimed to assess the impact of seropositivity and DMARDs on the association between RA and active pulmonary TB risk and to elucidate other risk factors for active pulmonary TB development in patients with RA.

Methods

Definition of TB infection and active pulmonary TB disease prevention in Korea

In this study, TB infection was defined as a persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens, with no evidence of clinically manifested TB. This phenomenon was formerly referred to as latent TB infection; however, the World Health Organization recently discarded this term [22].

As per the Korean College of Rheumatology recommendations, since 2004, all Korean RA patients who are to begin biologicals undergo screening for TB infection by interferon-γ release assay or tuberculin skin test beforehand. While patients with negative TB infection results are permitted to receive biologicals immediately, those with positive results should undergo TB infection treatment for at least 3 weeks before receiving biologicals [23–25].

Data source and setting

The National Health Insurance Service (NHIS) is a single insurance provider universally covering 97% of the Korean population; the remaining 3% are Medicaid beneficiaries. The NHIS database includes demographics, diagnoses based on the International Classification of Disease 10th revision (ICD-10), healthcare usage and prescriptions. The NHIS also provides a biannual health screening programme for all individuals >40 years of age, which includes anthropometric measurements (*e.g.* height, weight and blood pressure), questionnaires on health behaviours (*e.g.* smoking status, alcohol drinking and physical activity) and laboratory test results (*e.g.* fasting glucose and lipid levels) [26–28].

Our study protocol was approved by the Institutional Review Board of Samsung Medical Center (application no. SMC 2022–06-141), in compliance with the Declaration of Helsinki. Because the data used in the study were previously collected and made public in an anonymised state, the need for written informed consent was waived.

Main exposure

The main exposure of this study was RA. Briefly, RA was diagnosed based on the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria, which included 1) joint involvement (score 0–5), 2) serology (rheumatoid factor or anti-cyclic citrullinated peptide antibody; score 0–3), 3) acute-phase reactants (C-reactive protein or erythrocyte sediment rate; score 0–1) and 4) symptom duration (score 0–1) [29]. A combined score of ⩾6 points fulfils the requirements for definite RA, so RA diagnosis does not necessarily require positive serology in all patients. Regarding the definition of RA in this study, SPRA was defined as a combination of the ICD-10 diagnosis code M05, the Rare and

Intractable Disease (RID) code V223 and the use of RA-related medication. SNRA was defined as a combination of the ICD-10 code M06 (excluding M06.1 (adult-onset Still's disease) and M06.4 (inflammatory polyarthropathy)) and the use of RA-related medication. RA-related medication use included the prescription of any DMARDs, such as conventional synthetic DMARDs, bDMARDs and targeted synthetic DMARDs (tsDMARDs), for ⩾180 days (supplementary table S1).

Because the RID programme, operated by the NHIS, provides financial support for patients with various rare and intractable diseases, the validity of an SPRA diagnosis is strictly reviewed by the health insurance review and assessment service; a positive test result for rheumatoid factor or anti-cyclic citrullinated peptide antibody and a certificate from a physician stating that patients satisfy the classification criteria for RA are required [30, 31]. Accordingly, patients with RA diagnostic codes with a prescription for biologicals or any DMARD can be considered accurate cases of RA. The current definition has been widely used in previous studies [30–32].

Study participants

Among patients newly diagnosed with RA between 2010 and 2017 (n=119 788), we enrolled those who participated in a national health screening examination within 2 years of RA diagnosis (n=64 457) and for whom covariates (*e.g.* BMI, lifestyle habits, economic status) were available. The index date was when the diagnosis code of RA was first registered. After excluding participants with autoimmune diseases other than RA (n=213), those with missing health checkup variables (n=2321), those <20 years of age (n=6), those with a previous history of TB (n=742), those who developed TB or died within 1 year after the index date (n=715) and those who were ineligible for matching (n=883), we finally enrolled 59 577 patients deemed eligible for 1:5 age and sex matching.

For the control group, we identified an initial control pool of 1 207 831 individuals without RA diagnosis matched by age, sex and index year (1:10 matching). The index year for the matched controls was when each corresponding RA patient received an RA diagnosis. After applying the above exclusion criteria, we performed 1:5 age and sex matching to identify the final non-RA control group (n=297 885) (figure 1).

Outcomes

The primary outcome was newly diagnosed active pulmonary TB, which was defined by ICD-10 codes for TB (A15–A19) and the specific NHIS codes for TB (V206, V246 and V000) [33]. Because additional insurance benefit is provided to all patients with the specific NHIS codes for TB (the copayment by these patients is 0–10% of total costs), the validity of the specific codes is strictly reviewed [20, 27, 34, 35]. Study participants were followed from 1 year after the index date (1-year lag period) until the occurrence of outcome, death or 31 December 2019, whichever came first.

Covariates

BMI was calculated by dividing the patient weight in kilograms by the square of their height in metres and was categorised into the following four groups as recommended for Asian people: <18.5 $kg \cdot m^{-2}$ (underweight), 18.5–22.9 $kg \cdot m^{-2}$ (normal), 23.0–24.9 $kg \cdot m^{-2}$ (overweight) and ⩾25.0 $kg \cdot m^{-2}$ (obese) [36]. Smoking was classified into five categories based on current and past smoking status and total smoking amount (pack-years): never-smoker, ex-smoker with <20 pack-years, ex-smoker with ⩾20 pack-years, current smoker with <20 pack-years and current smoker with ⩾20 pack-years [37]. Alcohol drinking was classified into three levels according to daily alcohol intake: none, <30 $mg \cdot day^{-1}$ (mild) and ⩾30 $mg \cdot day^{-1}$ (heavy). Regular exercise was defined as moderate physical activity for ⩾30 min performed ⩾5 times per week or vigorous physical activity for ⩾20 min performed ⩾3 times per week [38]. Low income was defined as the lowest quartile of health insurance premiums based on household income. Among comorbidities, DM, hypertension, hyperlipidaemia and chronic kidney disease were defined using ICD-10 codes and the prescription of relevant medication for the year before the index date or using the results of a health-screening examination, as previously described [20, 34, 38–42]. Chronic airway diseases included asthma (ICD-10 diagnosis codes J45–J46) and COPD (J41–44), which were assessed during the year prior to the index date [20, 34, 39, 40].

Statistical analysis

The incidence rate of TB was calculated by dividing the number of TB cases by the total follow-up duration (1000 person-years). A cumulative incidence plot was used to compare the incidence of TB between patients with RA and matched controls or among SPRA patients, SNRA patients and matched controls; a log-rank test was used to identify significant differences between groups. The hazard of TB development in RA was estimated with the use of Cox proportional hazards regression analyses and is presented as hazard ratio (HR) with 95% confidence interval (CI). The multivariable analysis was adjusted for age, sex, low

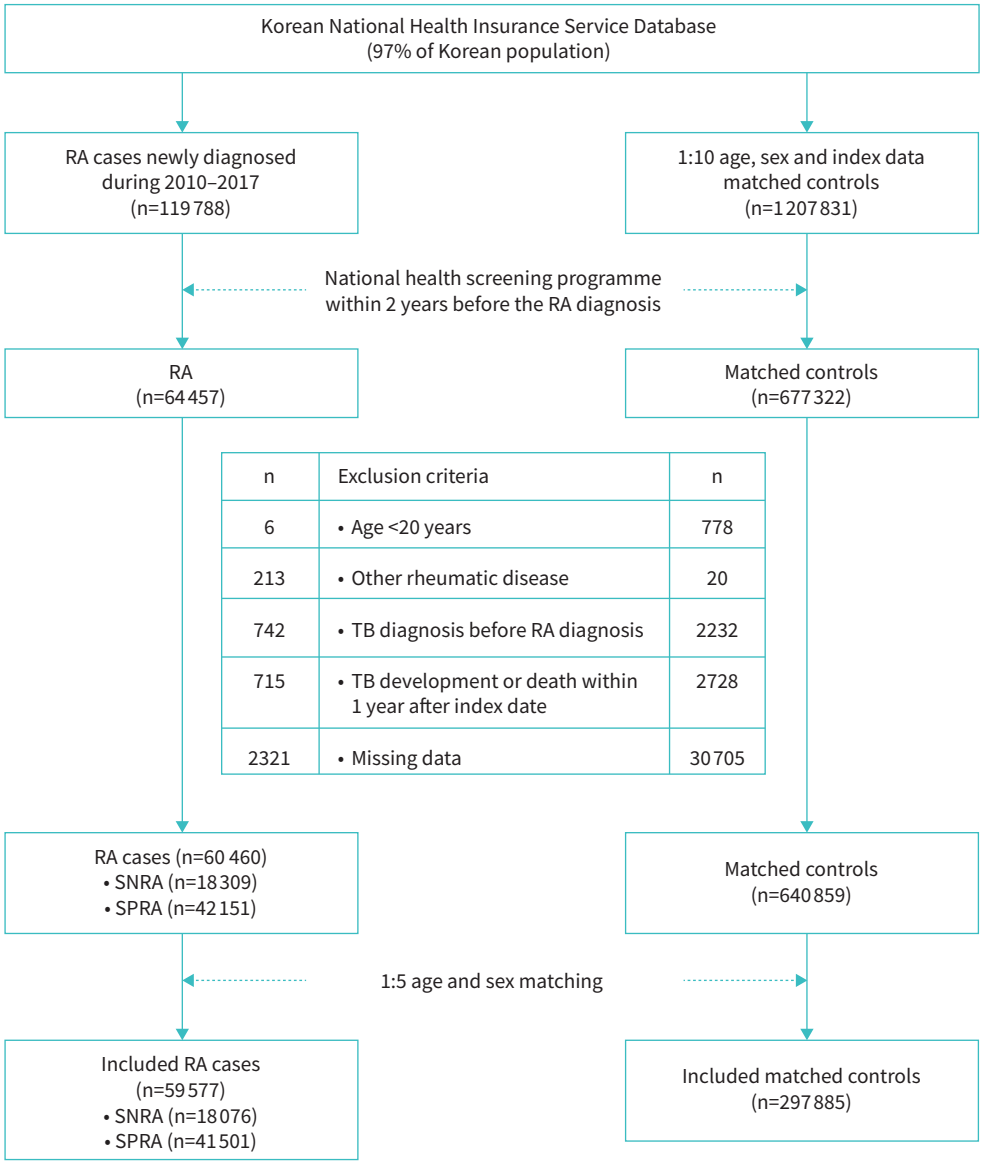

FIGURE 1 Flow chart of study population. RA: rheumatoid arthritis; SNRA: seronegative rheumatoid arthritis; SPRA: seronegative rheumatoid arthritis; TB: tuberculosis.

income, smoking, alcohol drinking, regular exercise and BMI in Model 1. Variables included in Model 1 as well as DM, hypertension, dyslipidaemia, chronic kidney disease and chronic airway disease were adjusted in Model 2. Furthermore, the hazard of TB development in RA was also assessed according to seropositivity and exposure to bDMARDs or tsDMARDs. To evaluate factors associated with TB risk among patients with RA, we performed stratified analysis according to the variables in table 1. The stratified analysis used two multivariable models adjusted for seropositivity and exposure to DMARDs (bDMARDs or tsDMARDs), respectively, in addition to all variables included in a fully adjusted model of the Cox proportional hazards regression analyses. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and $p<0.05$ was considered statistically significant.

Results

Baseline characteristics

The median age of study participants (n=357 462) was 57 years (interquartile range 49–65 years) and 74.5% were female. Among the patients with RA included in this study, 41 501 (69.7%) had SPRA and

TABLE 1 Baseline characteristics of the study population

	Total	Controls	Patients with RA	p-value
Subjects (n)	357 462	297 885	59 577	
Female sex	266 172 (74.5)	221 810 (74.5)	44 362 (74.5)	0.99
Age (years)[#]	57 (49–65)	57 (49–65)	57 (49–65)	0.99
20–39	27 714 (7.8)	23 095 (7.8)	4619 (7.8)	
40–64	235 308 (65.8)	196 090 (65.8)	39 218 (65.8)	
⩾65	94 440 (26.4)	78 700 (26.4)	15 740 (26.4)	
Low income[¶]	81 981 (22.9)	68 367 (23.0)	13 614 (22.9)	0.597
Smoking				<0.001
Never	282 417 (79.0)	236 055 (79.2)	46 362 (77.8)	
Ex-smoker (<20 pack-years)	21 403 (6.0)	17 710 (6.0)	3693 (6.2)	
Ex-smoker (⩾20 pack-years)	13 109 (3.7)	10 445 (3.5)	2664 (4.5)	
Current smoker (<20 pack-years)	22 518 (6.3)	18 951 (6.4)	3567 (6.0)	
Current smoker (⩾20 pack-years)	18 015 (5.0)	14 724 (4.9)	3291 (5.5)	
Alcohol drinking				<0.001
None	249 350 (69.7)	205 029 (68.8)	44 321 (74.4)	
Mild (<30 g·day^{-1})	95 318 (26.7)	81 731 (27.4)	13 587 (22.8)	
Heavy (⩾30 g·day^{-1})	12 794 (3.6)	11 125 (3.8)	1669 (2.8)	
Regular exercise	69 858 (19.5)	59 227 (19.9)	10 631 (17.8)	<0.001
Body mass index (kg·m^{-2})	23.7±3.3	23.8±3.3	23.5±3.3	<0.001
<18.5	11 973 (3.4)	9367 (3.1)	2606 (4.4)	
18.5–22.9	142 356 (39.8)	117 211 (39.4)	25 145 (42.2)	
23–24.9	87 775 (24.6)	73 630 (24.7)	14 145 (23.7)	
⩾25	115 358 (32.2)	97 677 (32.8)	17 681 (29.7)	
Comorbidities				
Diabetes mellitus	44 077 (12.3)	36 614 (12.3)	7463 (12.5)	0.111
Hypertension	130 061 (36.4)	106 640 (35.8)	23 421 (39.3)	<0.001
Dyslipidaemia	111 093 (31.1)	92 047 (30.9)	19 046 (32.0)	<0.001
Chronic kidney disease	23 814 (6.7)	18 981 (6.4)	4833 (8.1)	<0.001
Chronic airway diseases[+]	59 468 (16.6)	44 885 (15.1)	14 583 (24.5)	<0.001
RA type				
Seropositive RA			41 501 (69.7)	
Seronegative RA			18 076 (30.3)	

Data are expressed as mean±SD or n (%), unless otherwise indicated. RA: rheumatoid arthritis. [#]: median (interquartile range); [¶]: low income refers to the bottom quartile of the income distribution; [+]: asthma and COPD.

18 076 (30.3%) had SNRA. Patients with RA were more likely to smoke, have lower BMI and have more frequent comorbidities, including hypertension, dyslipidaemia, chronic kidney disease and chronic airway disease, than matched controls (p<0.001 for all). Additionally, patients with RA were less likely to exercise regularly and to drink alcohol than matched controls (p<0.001 for both) (table 1).

Risk of active pulmonary TB according to the presence of RA and the RA serological status

A total of 1598 participants developed active pulmonary TB (including 619 patients with RA and 979 matched controls) during the follow-up period of 1 618 814 person-years, corresponding to a median of 4.4 years after the 1-year lag period (interquartile range 2.6–6.4 years; maximum 9 years); incidence rates were 2.3 per 1000 person-years in patients with RA and 0.7 per 1000 person-years in matched controls. Patients with RA showed a 3.21-fold (95% CI 2.91–3.55) greater risk of active pulmonary TB compared to matched controls; this association was consistent in the two adjusted models (Model 1: adjusted HR 3.15, 95% CI 2.85–3.49; Model 2: adjusted HR 3.02, 95% CI 2.73–3.35) (table 2). A significant difference was also apparent in the cumulative incidence probability of active pulmonary TB between patients with RA and matched controls (figure 2a).

In an analysis according to RA serological status in the fully adjusted Model 2, patients with SPRA and those with SNRA showed 3.20-fold (95% CI 2.86–3.58) and 2.54-fold (95% CI 2.13–3.04) increased risks, respectively, compared to matched controls. Compared to the SNRA group, the SPRA group had a greater active pulmonary TB risk (Model 2: adjusted HR 1.29, 95% CI 1.07–1.56) (table 2). An analysis of the cumulative incidence probability of active pulmonary TB was in line with these results (figure 2b).

TABLE 2 Risk of active pulmonary TB according to RA status and the serological status of RA patients

	Participants (n)	TB cases (n)	Duration (person-years)	Incident rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
By RA status							
Control	297 885	979	1 352 871	0.7	1 (Reference)	1 (Reference)	1 (Reference)
RA	59 577	619	265 943	2.3	3.21 (2.91–3.55)	3.15 (2.85–3.49)	3.02 (2.73–3.35)
By RA status and seropositivity							
Control	297 885	979	1 352 871	0.7	1 (Reference)	1 (Reference)	1 (Reference)
SNRA	41 501	142	79 241	1.8	2.47 (2.07–2.95)	2.66 (2.23–3.17)	2.54 (2.13–3.04)
SPRA	18 076	477	186 702	2.6	3.53 (3.16–3.94)	3.33 (2.99–3.72)	3.20 (2.86–3.58)
By seropositivity							
SNRA	18 076	142	79 241	1.8	1 (Reference)	1 (Reference)	1 (Reference)
SPRA	41 501	477	186 702	2.6	1.43 (1.19–1.73)	1.28 (1.06–1.55)	1.29 (1.07–1.56)

Model 1 was adjusted for age, sex, low income, smoking, alcohol drinking, regular exercise and body mass index. Model 2 was further adjusted for diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease and chronic airway disease. RA: rheumatoid arthritis; SNRA: seronegative rheumatoid arthritis; SPRA: seropositive rheumatoid arthritis; TB: tuberculosis.

Risk of active pulmonary TB according to the presence of RA and exposure to biologicals or tsDMARDs

Following analysis according to the presence of RA and drug exposure in the fully adjusted Model 2, bDMARD- or tsDMARD-exposed patients with RA and DMARD-naïve patients with RA showed 4.68-fold (95% CI 3.69–5.93) and 2.88-fold (95% CI 2.59–3.20) increased active pulmonary TB risks, respectively, compared to matched controls (table 3).

Factors associated with the risk of active pulmonary TB in patients with RA

Table 4 depicts factors associated with the risk of active pulmonary TB in patients with RA (n=59 577). In the adjusted model (Model 2), factors associated with active pulmonary TB risk among patients with RA included male sex (adjusted HR 2.04, 95% CI 1.62–2.58); age ⩾65 years (adjusted HR 2.93, 95% CI 1.92–4.46); underweight status (adjusted HR 1.76, 1.31–2.37); and the presence of comorbidities, including DM (adjusted HR 1.27, 95% CI 1.02–1.58), hypertension (adjusted HR 1.31, 95% CI 1.10–1.56) and chronic airway disease (adjusted HR 1.37, 95% CI 1.15–1.62). Additionally, seropositivity (Model 1: adjusted HR 1.33, 95% CI 1.10–1.61) and exposure to bDMARDs or tsDMARDs (Model 2: adjusted HR 1.55, 95% CI 1.21–1.97) were related to increased active pulmonary TB risk among patients with RA.

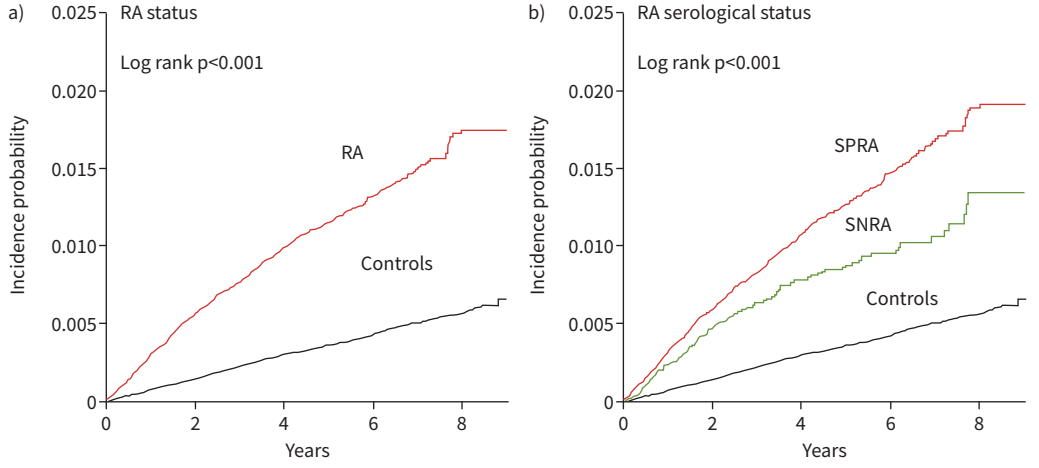

FIGURE 2 Cumulative incidence of active pulmonary tuberculosis according to a) rheumatoid arthritis (RA) status and b) serological status of RA. Year 0 indicates 1 year after RA diagnosis in participants with RA and 1 year after the time of being matched in matched controls. SNRA: seronegative rheumatoid arthritis; SPRA: seropositive rheumatoid arthritis.

TABLE 3 Risk of active pulmonary TB according to RA status and exposure to biological and targeted synthetic DMARDs

	Participants (n)	TB cases (n)	Duration (person-years)	Incident rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Control	297 885	979	1 352 871	0.7	1 (Reference)	1 (Reference)	1 (Reference)
DMARD[#]-naïve RA	54 738	544	242 895	2.2	3.09 (2.78–3.43)	3.00 (2.70–3.34)	2.88 (2.59–3.20)
DMARD[#]-exposed RA	4839	75	23 048	3.3	4.51 (3.57–5.71)	4.92 (3.89–6.23)	4.68 (3.69–5.93)

Model 1 was adjusted for age, sex, low income, smoking, alcohol drinking, regular exercise and body mass index. Model 2 was further adjusted for diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease and chronic airway disease. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; TB: tuberculosis. [#]: biological or targeted synthetic DMARDs.

Discussion

In this longitudinal nationwide study, patients with RA showed approximately three-fold greater risk of active pulmonary TB than matched controls, even after adjusting for potential confounders. The increased risk was more apparent in patients with SPRA than in those with SNRA compared to matched controls; additionally, the risk was more apparent in patients with RA exposed to bDMARDs or tsDMARDs than in those who had not been exposed to the drugs. Moreover, among patients with RA, factors associated with active pulmonary TB included male sex, older age, underweight status, seropositivity, tsDMARD or bDMARD exposure and comorbidities such as DM and chronic airway disease.

The present study confirmed that the risk of active pulmonary TB is higher among patients with RA than matched controls without RA while adjusting for various factors related to TB infection, which is in line with previous studies (summaries of the previous studies are provided in supplementary table S2) [11–16, 18, 19]. The augmented active pulmonary TB risk in RA is attributed to the immunological dysfunction caused by the disease itself as well as treatment with immunosuppressive agents [13, 18]. Notably, our study showed that active pulmonary TB risk continues to be increased in patients with RA, although approximately 20 years have passed since routine TB infection screening and treatment were initiated in Korea. This meaningful finding suggests that rheumatologists need to screen regularly for active pulmonary TB development in patients with RA, even in those who complete TB infection treatment.

Another notable finding of this study concerns the impact of seropositivity on active pulmonary TB risk in patients with RA. The increased active pulmonary TB risk was most evident in patients with SPRA, followed by those with SNRA and matched controls. Considering that disease activity is usually higher in SPRA than in SNRA, two potential mechanisms may explain our finding. First, greater disease activity in patients with SPRA may require more intensified immunosuppressive therapy compared to those with SNRA, which consequently hampers immune status and predisposes patients with SPRA to active pulmonary TB infection. Second, greater disease activity is more likely to be associated with a state of immune dysregulation and an increased risk of infection. Autoantibodies against the Fc receptor of IgG play a significant role in modulating immune responses in patients with seropositive RA [43]. These autoantibodies interfere with the normal functioning of immune cells, leading to an altered immune response. In the context of TB development, these autoantibodies may impair appropriate immune responses against *M. tuberculosis* infection. For example, these autoantibodies could interfere with the phagocytosis of *M. tuberculosis* by macrophages, reduce pro-inflammatory cytokines from immune cells, such as TNF-α, which are essential for controlling *M. tuberculosis* infection, and impair T-cell activation and proliferation [44–46]. Consequently, patients with SPRA who have these autoantibodies may be at a higher risk of developing active pulmonary TB because their immune system's capacity to control the infection is compromised. Hence, we need to consider seropositivity when screening for TB risk in patients with RA.

As expected, in the present study, patients with RA exposed to bDMARDs or tsDMARDs and those who were not exposed to these drugs, respectively, showed 4.7-fold and 2.9-fold greater active pulmonary TB risks than matched controls without RA. In agreement with our findings, previous studies also reported more pronounced active pulmonary TB risk in patients with RA who had received bDMARDs or tsDMARDs compared to those who had received conventional DMARDs [13, 17, 47–51], which is summarised in supplementary table S3. Although different bDMARDs, such as infliximab and etanercept, carry different active pulmonary TB risks in patients with RA [48, 49], our study was not designed to compare active pulmonary TB risk among patients on each drug. Notably, our results demonstrated that

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TABLE 4 Factors associated with active pulmonary TB risk in patients with RA (n=59 577)

	Participants	TB cases	Duration (person-years)	Incident rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Sex							
Female	44 362	383	201 943	1.9	1 (Reference)	1 (Reference)	1 (Reference)
Male	15 215	236	64 000	3.7	**1.92 (1.63–2.26)**	**2.09 (1.66–2.64)**	**2.04 (1.62–2.58)**
Age							
20–39 years	4619	27	21 671	1.3	1 (Reference)	1 (Reference)	1 (Reference)
40–64 years	39 218	329	180 233	1.8	1.46 (0.99–2.16)	1.47 (0.98–2.19)	**1.59 (1.06–2.38)**
⩾65 years	15 740	263	64 039	4.1	**3.23 (2.17–4.80)**	**2.62 (1.72–3.99)**	**2.93 (1.92–4.46)**
Low income							
No	45 963	479	207 164	2.3	1 (Reference)	1 (Reference)	1 (Reference)
Yes	13 614	140	58 779	2.4	1.02 (0.85–1.23)	1.06 (0.88–1.28)	1.07 (0.89–1.29)
Smoking							
Never	46 362	440	210 162	2.1	1 (Reference)	1 (Reference)	1 (Reference)
Ex-smoker (<20 pack-years)	3693	35	15 569	2.3	1.06 (0.75–1.50)	0.73 (0.49–1.06)	0.72 (0.49–1.06)
Ex-smoker (⩾20 pack-years)	2664	41	10 778	3.8	**1.79 (1.30–2.46)**	0.89 (0.61–1.29)	0.90 (0.62–1.31)
Current (<20 pack-years)	3567	39	15 356	2.5	1.20 (0.87–1.67)	0.98 (0.68–1.40)	0.98 (0.68–1.40)
Current (⩾20 pack-years)	3291	64	14 078	4.6	**2.15 (1.66–2.80)**	1.16 (0.83–1.60)	1.18 (0.85–1.63)
Alcohol drinking							
No	44 321	472	199 242	2.4	1 (Reference)	1 (Reference)	1 (Reference)
Mild (<30 g·day^{-1})	13 587	128	59 577	2.2	0.90 (0.74–1.10)	0.87 (0.70–1.07)	0.87 (0.70–1.07)
Heavy (⩾30 g·day^{-1})	1669	19	7124	2.7	1.12 (0.71–1.77)	0.79 (0.49–1.28)	0.79 (0.49–1.28)
Regular exercise							
No	48 946	518	219 173	2.4	1 (Reference)	1 (Reference)	1 (Reference)
Yes	10 631	101	46 770	2.2	0.91 (0.74–1.13)	0.89 (0.72–1.10)	0.89 (0.71–1.10)
Body mass index (kg·m^{-2})							
<18.5	2606	51	11 286	4.5	**1.67 (1.24–2.25)**	**1.76 (1.30–2.37)**	**1.76 (1.31–2.37)**
18.5–23	25 145	305	113 479	2.7	1 (Reference)	1 (Reference)	1 (Reference)
23–25	14 145	129	63 548	2.0	**0.76 (0.61–0.93)**	**0.67 (0.55–0.83)**	**0.67 (0.54–0.82)**
⩾25	17 681	134	77 630	1.7	**0.64 (0.52–0.78)**	**0.54 (0.44–0.66)**	**0.53 (0.43–0.65)**
Diabetes mellitus							
No	52 114	510	235 458	2.2	1 (Reference)	1 (Reference)	1 (Reference)
Yes	7463	109	30 485	3.6	**1.63 (1.32–2.00)**	**1.27 (1.02–1.59)**	**1.27 (1.02–1.58)**
Hypertension							
No	36 156	316	163 957	1.9	1 (Reference)	1 (Reference)	1 (Reference)
Yes	23 421	303	101 986	3.0	**1.53 (1.31–1.79)**	**1.31 (1.10–1.57)**	**1.31 (1.10–1.56)**
Dyslipidaemia							
No	40 531	423	186 135	2.3	1 (Reference)	1 (Reference)	1 (Reference)
Yes	19 046	196	79 807	2.5	1.06 (0.90–1.26)	0.95 (0.79–1.14)	0.94 (0.79–1.13)
Chronic kidney disease							
No	54 744	552	244 764	2.3	1 (Reference)	1 (Reference)	1 (Reference)
Yes	4833	67	21 179	3.2	**1.40 (1.09–1.81)**	1.10 (0.84–1.42)	1.09 (0.84–1.42)
Chronic airway diseases							
No	44 994	418	203 947	2.1	1 (Reference)	1 (Reference)	1 (Reference)
Yes	14 583	201	61 996	3.2	**1.57 (1.32–1.85)**	**1.37 (1.16–1.63)**	**1.37 (1.15–1.62)**

Continued

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TABLE 4 Continued

	Participants	TB cases	Duration (person-years)	Incident rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Seropositivity							
SNRA	18 076	142	79 241	1.8	1 (Reference)	1 (Reference)	
SPRA	41 501	477	186 702	2.6	**1.43 (1.19–1.73)**	**1.33 (1.10–1.61)**	
DMARD[#] exposure							
No	54 738	544	242 895	2.2	1 (Reference)		1 (Reference)
Yes	4839	75	23 048	3.3	**1.47 (1.16–1.87)**		**1.55 (1.21–1.97)**

Model 1 was adjusted for age, sex, low income, smoking, alcohol drinking, regular exercise, body mass index, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, chronic airway disease and seropositivity. Model 2 was adjusted for age, sex, low income, smoking, alcohol drinking, regular exercise, body mass index, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, chronic airway disease and exposure to biological or targeted synthetic DMARDs. Significant hazard ratios are indicated in bold. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; SNRA: seronegative rheumatoid arthritis; SPRA: seropositive rheumatoid arthritis; TB: tuberculosis. [#]: biological or targeted synthetic DMARDs.

treatment with bDMARDs or tsDMARDs is more likely than treatment with conventional DMARDs to predispose patients with RA to active pulmonary TB development in the clinical setting where routine TB infection screening and treatment are performed as per guidelines [52, 53].

In addition to seropositivity and bDMARD (or tsDMARD) use, this study revealed several factors associated with active pulmonary TB risk in patients with RA, including male sex; age >65 years; underweight status; and comorbidities such as DM, hypertension and chronic airway diseases (asthma and COPD). Our results are also in line with those of previous studies that investigated risk factors for TB development [20, 21, 54]. More precisely, focused screening of TB infection in the subset of RA patients who are more prone to active pulmonary TB would be an economical and reasonable strategy to lessen the infection risk compared to screening in all patients with RA. In this regard, our study results would be valuable in deciding the strategy of focused TB screening in RA patients. Notably, this strategy should be accompanied by the completeness of screening and adherence to preventive treatments in patients with RA.

This study has a strength in that it is a longitudinal nationwide study that evaluated active pulmonary TB risk in RA while comprehensively considering several confounders related to TB development and identified the group of patients with RA who would most benefit from TB screening. However, this study has a few limitations. First, there might be a selection bias given that we included relatively healthy individuals who underwent health screening examinations, which could result in a relatively low active pulmonary TB incidence. Second, given the nature of the population-based dataset, information on each participant's TB infection screening results and treatment completion was unavailable. Third, universal screening for TB infection in Korean RA patients may not necessarily indicate that they have received and completed treatment for TB infection. Fourth, because this study was conducted in a country with an intermediate TB burden, our results should be cautiously applied to other countries with different TB burdens.

In conclusion, patients with SPRA and SNRA showed approximately 3.2- and 2.5-fold greater risk of active pulmonary TB, respectively, compared with matched controls in clinical settings where routine TB infection screening and treatment are conducted. The apparent increased risk of active pulmonary TB in RA patients exposed to bDMARDs or tsDMARDs suggests that surveillance against active pulmonary TB should be continued, regardless of whether preventive treatment for TB infection has been completed. Based on our results, more precise TB screening should be considered in RA patients.

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Data availability: Data are available upon reasonable request.

Provenance: Submitted article, peer reviewed.

Ethics statement: Our study protocol was approved by the Institutional Review Board of Samsung Medical Center (application number SMC 2022-06-141), in compliance with the Declaration of Helsinki. Because the data used in the study were previously collected and made public in an anonymised state, the need for written informed consent was waived.

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